



CATOLICA
FACULDADE DE EDUCAÇÃO E PSICOLOGIA

PORTO

*IMPACT OF KETAMINE ASSISTED
PSYCHOTHERAPY IN ANXIETY AND DEPRESSION
SYMPTOMS: A QUASI-EXPERIMENTAL STUDY*

Dissertação apresentada à Universidade Católica Portuguesa para obtenção do
grau de mestre em Psicologia

Especialização em Psicologia da Justiça e do Comportamento Desviante

Matilde Pedrosa Sines Fernandes

Porto, julho de 2025



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Trabalho efetuado sob a orientação de
Professora Doutora Maria Carmo Carvalho

Porto, julho de 2025

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Com o aproximar do fim da minha vida académica, reflito sobre todos os fatores internos e externos que me fizeram ser capaz de terminar este percurso, principalmente nesta fase final. Acima de tudo, sinto um orgulho enorme de mim mesma pelo caminho que fiz e por toda a resiliência que fui capaz de manter até este momento.

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“Turn on, tune in, drop out.”

Timothy Leary, 1966

Declaração de responsabilidade - Uso de Inteligência Artificial (IA)

O presente trabalho foi realizado de forma integral por mim, sendo da minha total responsabilidade todos os aspetos relativos à sua redação. O uso de ferramentas de IA não comprometeram a originalidade desta dissertação. Nenhum conteúdo foi transcrito de forma integral, sendo que todos os contributos das ferramentas foram revistos e adaptados com base nos princípios da integridade académica.

Assumo a responsabilidade pelo uso de ferramentas de IA, nomeadamente do Chat GPT e do Perplexity, de forma consciente e responsável. Estas foram utilizadas como forma de apoio em algumas situações, nomeadamente na sugestão e revisão linguística da construção frásica de algumas secções, no apoio na pesquisa de referências bibliográficas e na geração de sinónimos e melhoria da coerência e síntese textual.

IMPACT OF KETAMINE ASSISTED PSYCHOTHERAPY IN ANXIETY AND DEPRESSION SYMPTOMS: A QUASI-EXPERIMENTAL STUDY

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Universidade Católica Portuguesa, Porto, Portugal

RESUMO

A ketamina, habitualmente utilizada como anestésico, tem demonstrado potencial terapêutico em doses subanestésicas no tratamento de perturbações mentais, como a depressão resistente ao tratamento (TRD) e a ansiedade. Quando integrada em contextos de psicoterapia, parece induzir efeitos antidepressivos e ansiolíticos.

Este estudo teve como objetivo avaliar a eficácia de um protocolo de psicoterapia assistida por ketamina (KAP) na redução de sintomas depressivos e ansiosos num contexto clínico naturalista, assim como avaliar o impacto de variáveis sociodemográficas na sua eficácia.

Foi realizado um estudo quase-experimental com um desenho pré-pós com 27 participantes de uma clínica de KAP em Barcelona. Os sintomas foram avaliados antes e depois da intervenção com o Inventário de Depressão de Beck-II (BDI-II) e a escala da Perturbação de Ansiedade Generalizada-7 (GAD-7).

Os resultados revelaram reduções estatisticamente significativas nos sintomas após KAP. Uma grande proporção dos participantes passou das categorias moderada (33,3% tanto no BDI-II como no GAD-7) ou grave (40,7% no BDI-II e 37% no GAD-7) para mínima (63% no BDI-II e 51,9% no GAD-7). As variáveis sociodemográficas não influenciaram os resultados, embora a gravidade inicial dos sintomas possa explicar parcialmente a redução observada.

Estes resultados apoiam as evidências sobre o potencial terapêutico da KAP. As limitações (pequena dimensão da amostra, ausência de um grupo de controlo e dependência de medidas de auto-relato) justificam a necessidade de investigação futura com amostras maiores, ensaios controlados e avaliações de acompanhamento.

Palavras-chave: Psicoterapia Assistida por Ketamina; Depressão; Ansiedade

ABSTRACT

Ketamine, commonly used as an anesthetic, has shown promising therapeutic potential in subanesthetic doses for treating mental health conditions such as treatment-resistant depression (TRD) and anxiety. When integrated with psychotherapy in a clinical context, it appears to induce antidepressant and anxiolytic effects.

This study aimed to evaluate the effectiveness of a Ketamine Assisted Psychotherapy (KAP) protocol in reducing depressive and anxiety symptoms in a naturalistic clinic setting, as well as to assess the impact of sociodemographic variables on its efficacy.

A quasi-experimental study with a pre-post design was carried out with 27 participants from a KAP clinic in Barcelona. Symptoms were assessed before and after the intervention with the Beck Depression Inventory-II (BDI-II) and the Generalized Anxiety Disorder-7 scale (GAD-7).

Findings revealed statistically significant reductions in symptom scores post-KAP. A large proportion of the patients shifted from moderate (33.3% on both BDI-II and GAD-7) or severe (40.7% for BDI-II and 37% for GAD-7) to minimal (63% for BDI-II and 51.9% for GAD-7) categories. Sociodemographic variables were not associated with the outcomes, although the baseline symptom severity may partially explain the reduction observed.

These results support existing evidence for the therapeutic potential of KAP. The limitations (small sample size, absence of control group and reliance on self report measures) justify the need for future research with larger samples, controlled trials and follow up assessments.

Keywords: Ketamine-Assisted Psychotherapy; Depression; Anxiety

Lista de abreviaturas

AMPA - amino-3-hydroxy-5-methyl-4-isoxazole propionic acid

BDI-II - Beck Depression Inventory-II

DMN - Default Mode Network

DMT - Dimethyltryptamine

EU - European Union

GAD-7 - Generalized Anxiety Disorder 7

KAP - Ketamine Assisted Psychotherapy

LSD - Lysergic Acid Diethylamide

NMDA - N-methyl-D-aspartate

OCD - Obsessive Compulsive Disorder

PAP - Psychedelic Assisted Psychotherapy

PTSD - Post Traumatic Stress Disorder

REBUS - Relaxed Beliefs Under Psychedelics

TRD - Treatment-Resistant Depression

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Introduction

The expansion of the digital world has led to a decline in social interactions, contributing to an increased individualism and isolation within communities (Fiorillo & Gorwood, 2020; Loades et al., 2020). These socio-cultural shifts have been giving space for the development and persistence of life-shortening and high cost treatment illnesses, such as depression and anxiety, significantly diminishing the quality of life of individuals (OECD, 2021; World Health Organization, 2022). These conditions not only have a profound individual and social impact, but are also commonly found in comorbidity with several other psychiatric diagnoses, such as post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and substance use disorders (Smith & Book, 2008; Breteler et al., 2020; Koopowitz et al., 2021). The rates of treatment resistance remain high, with conventional psychopharmacological interventions failing in up to one-third of patients with these conditions, producing several displeasing side effects (Cartwright et al., 2016; Mithoefer et al., 2016; Rong et al., 2018; Schenberg, 2018). Having this in consideration, different and innovative treatment strategies seem urgently needed.

Ketamine, a dissociative anesthetic with rapid-acting antidepressant effects, has emerged as a promising alternative for individuals unresponsive to conventional treatments (Ballard & Zarate, 2020; McIntyre et al., 2020; Ramos et al., 2022). The combination between the pharmacological neuroplasticity promoted by psychedelics and psychotherapy gave rise to Ketamine Assisted Psychotherapy (KAP), promoting meaningful psychedelic experiences that enhance emotional insight and interrupt maladaptive cognitive patterns, relieving the symptoms of several mental health issues (Wolfson & Vaid, 2024; Figueiredo et al., 2023; Mathai et al., 2022; Greenway et al., 2020).

However, much of the existing evidence comes from controlled clinical trials with limited ecological validity, often excluding patients with comorbidities or complex treatment histories and neglecting the importance of psychotherapy (Figueiredo et al., 2023; Walsh et al., 2021; Marsden & Torgerson, 2012; Lorenzo-Luaces et al., 2018). There is also a lack of evidence on how sociodemographic variables can affect the efficiency of KAP (Romeo et al., 2015; Wright & Kabbaj, 2018; Kim et al., 2021; Wolfson et al., 2023). Therefore, there is a need to examine the effectiveness of KAP in naturalistic settings, where real-world clinical dynamics, diverse populations, and variable treatment trajectories are present.

The present study aims to address this gap by evaluating the effectiveness of a KAP protocol in the relief of depressive and anxiety symptoms, in a naturalistic clinical context. Using standardized quantitative measures, this research explores the therapeutic potential of KAP as well as whether sociodemographic factors play a role in treatment outcomes. In doing so, it contributes to the ongoing effort to understand how psychedelic-assisted therapies can be effectively implemented in the mental health field.

Part I - Framework

The current mental health crisis is driven by a significant increase in psychiatric disorders, particularly after the Covid-19 pandemic (World Health Organization, 2022). Anxiety and depressive symptoms have emerged as the most prevalent forms of psychological suffering (Kalueff & Tuohimaa, 2004; World Health Organization, 2017; Kalin, 2020). In 2019, 14% of individuals in the EU reported experiencing anxiety disorders (OECD, 2021). Furthermore, 7.2% of EU citizens reported experiencing chronic depression, with Portugal recording the highest prevalence at 12.2% (Eurostat, 2021). In Spain, it is estimated that anxiety disorders affect around 12.6% of the population (Ministerio de Sanidad, 2023). In 2023, almost half (46%) of EU citizens experienced an emotional or psychosocial issue within the past 12 months, such as feeling anxious or depressed (European Commission, 2023). Social isolation (Loades et al., 2020), economic insecurity (OECD, 2021), the constant digital overload (Fiorillo & Gorwood, 2020) and the poor responses from mental health systems (World Health Organization, 2022) might be some of the explanatory factors for these numbers.

Anxiety and depressive symptoms seem to be recognized as core indicators of psychological distress and overall mental health (Wuthrich et al., 2015; Liu et al., 2018). They frequently occur comorbidly (Craske, 2012; Kessler et al., 2015; Forstner et al., 2019; Ironside et al., 2022) and growing evidence suggests these conditions share overlapping neurobiological mechanisms, reinforcing their conceptualisation as intertwined components of a psychopathological continuum, rather than isolated disorders (Pollack, 2005; Kalin, 2020; Koskinen & Hovatta, 2023). This co-occurrence is not only common, but clinically significant, as it tends to be associated with greater symptom severity, reduced treatment response and a higher rate of suicidal ideation (Pollack, 2005; Saris et al., 2017; Kalin, 2020; Chen, 2022; Ironside et al., 2022; Tanaka & Chen, 2023). It often leads to considerable deterioration in overall functioning, negatively impacting well-being, interpersonal

relationships, and participation in daily life (World Health Organization, 2022). Moreover, these conditions are life-shortening illnesses, and they generate a high social cost, particularly through decreased productivity, and pressure on public mental health services (Vollenweider & Kometer, 2010; OECD, 2021; World Health Organization, 2022).

Antidepressants are one of the most commonly employed interventions for addressing these conditions (Castro-Rodrigues, 2025). Their widespread use is partly attributed to their cost-effectiveness and their compatibility with the current biomedical model of health care (Johnson et al., 2017). However, these psychopharmacological interventions show several limitations (Hirschfeld, 2001; Kirsch, 2019; World Health Organization, 2022) and often fall short in adequately meeting patients' needs (Schenberg, 2018). Firstly, there's evidence for a significant increase in cases of disorders resistant to pharmacological interventions, namely treatment-resistant depression (TRD)¹ (Archer et al, 2018; Corriger & Pickering, 2019). In addition, these approaches usually require long periods (2 to 4 weeks) to show positive results, which may be insufficient in contexts that require rapid responses, such as cases of severe depression with suicidal ideation (Insel et al., 2013; Henssler et al., 2018; Leger & Unterwald, 2022). Although these conventional antidepressants lead to a reduction in depressive symptoms within a few weeks, often one-third of patients fail to return to normal functioning, even with multiple therapeutic interventions (Rong et al., 2018). Furthermore, the side effects of some of these medications are often exacerbated, sometimes quite unpleasant, and may outweigh the benefits for certain individuals (Cartwright et al., 2016; Mithoefer et al., 2016). Despite all of this, the use of antidepressants in Europe has doubled between 2000 and 2020 (Amrein et al, 2023). This scenario highlights the urgent need for a critical reflection on current approaches within the field of mental health.

Considering these challenges, psychedelics have emerged as a focus of medical research (Azevedo et al., 2023). The last few decades have seen a “psychedelic renaissance”² (Sessa, 2013) and this field is once again acknowledging these substances as promising and viable tools for enhancing mental health (Estalagem, 2023). Research has been highlighting their potential to act as alternatives to antidepressants, anxiolytics and other medicines, due to their faster mechanism of action and reduced side effects (dos Santos et al., 2018).

¹ TRD requires a minimum of two different pharmacological treatment failures (Gaynes et al., 2019).

² Commonly used term between the psychedelic scientific community to refer to the resurgence of research on the potential therapeutic benefits of psychedelic compounds (Reiff et al., 2020). Although these substances have been studied since the 1950s, research came to a halt for several decades due to social and political restrictions, only resuming over the past decades (Estalagem et al., 2023).

However, despite growing evidence of its therapeutic benefits, the use of these substances is largely conditioned by their legal status (Azevedo, 2023; Ordem dos Psicólogos Portugueses, 2025). Ketamine is an exceptional situation, as it is a substance authorized for industrial or pharmaceutical purposes for human and veterinary use (Infarmed, 2024). For all these reasons, the use of ketamine assisted psychotherapy (KAP) for the treatment of resistant depression is common practice in various public and private mental health settings in Portugal and Spain, where the substance is used off-label³ (da Gama & Torres, 2023).

Ketamine is an anesthetic substance first synthesized in the 1960s and used in human and veterinary medicine (Drozd et al., 2022). It has emerged as a substitute anesthetic for phencyclidine due to its high safety profile (Dore et al., 2019; Castro-Rodrigues, 2025). This substance is classified as a psychedelic “dissociative anesthetic” due to its ability to “disconnect consciousness from the body and the environment” (Domino, 2010). When used in subanesthetic doses⁴ (Katalinic et al., 2013; Marguilho et al., 2023), its main effects are antidepressant and anxiolytic, induction of dissociative and psychedelic states and induction of neuroplasticity - a process that enhances communication between brain regions that are usually disconnected, making the brain more receptive to cognitive processing and psychotherapeutic content (Kolp, 2014; dos Santos et al., 2018; de Vos, 2021; Ballard & Zarate, 2020). Its main adverse effects include increased blood pressure, dizziness, blurred visions and nausea, but are often mild and transitory (Grady et al., 2017; Yavi et al., 2022).

The mechanisms underlying the ketamine action in symptom relief remain unclear, though several hypotheses have been proposed (Sanacora & Schatzberg, 2015; Drozd et al., 2022). Ketamine seems to mainly work by affecting the brain’s glutamate⁵ system, acting as an NMDA receptor antagonist (Kugaya & Sanacora, 2005; Kishimoto et al., 2016; Abdallah et al., 2018; Muscat et al., 2021). This mechanism reduces excessive excitatory signaling and promotes a compensatory increase in glutamate, which results in the activation of AMPA receptors, an effect considered crucial for the rapid antidepressant and anxiolytic response (Gerhard et al., 2016; Kang et al., 2022). These neurochemical changes are associated with increased neuroplasticity, enhanced functional connectivity and reduced activity in the Default Mode Network (DMN), a part of the brain typically active during self-referential

³ The off-label use of a substance refers to its legal prescription, but for a treatment that does not yet have scientific evidence to support its application (Zhang et al., 2016).

⁴ The anesthetic dose of ketamine in adults is approximately 1-2 mg/kg when applied intravenously and 8-10 mg/kg when applied intramuscularly (Elkomy et al., 2015; Marland et al., 2013).

⁵ Glutamate is the brain’s primary excitatory neurotransmitter, playing a crucial role in supporting key functions like learning and memory (Castro-Rodrigues, 2025).

thinking and introspection in individuals with depression (Duman et al., 2012; Scheidegger et al., 2012; Gillespie & Nemeroff, 2020). By temporarily disrupting these neural patterns that limit usual behavior, ketamine appears to offer an alternative way to promote cognitive and emotional flexibility, contributing to significant symptom relief in several mental health issues (Duman et al., 2012; Krystal et al., 2019; Watts & Luoma, 2020).

The evidence of ketamine in favor of improving symptoms of TRD and suicidal ideation is consistent and well-founded (Vollenweider & Kometer, 2010; McIntyre et al., 2020; Ramos et al., 2022). KAP seems to relieve anxiety (Taylor et al., 2018; Dore et al., 2019; Ramos et al., 2022; Walsh et al., 2022) and depression symptoms (Berman et al., 2000; Witt et al., 2019; Conley et al., 2021; Alnefeesi et al., 2022; Hull et al., 2022) as well as reducing suicidal ideation (Derakhshanian et al., 2021; Lascelles et al., 2021; Abbar et al., 2022; Walsh et al., 2022) for at least 6 weeks (Grunebaum et al., 2018). Price et al. (2022) found a 46% response rate and a 27% remission for depressive symptoms after KAP, which is consistent with the findings of McInnes et al (2022), that estimated a 60% probability of these effects being sustained for 8 weeks. Thus, when compared to other treatments commonly used for mood disorders (such as electroconvulsive therapy and benzodiazepines), ketamine seems to show superior outcomes in terms of symptom reduction and therapeutic efficacy (Anand et al., 2023; Grunebaum et al., 2018). It induces a fast-acting sustained antidepressant effect in cases of TRD, even with a single subanesthetic dose (Grunebaum et al. 2018; Zanos & Gould, 2018; McIntyre et al., 2020; Muscat et al. 2021; Wilkinson et al., 2021) and it seems to be more effective than esketamine⁶ (Nikolin et al., 2023).

Behind these mood disorders, ketamine also seems to relieve symptoms in obsessive-compulsive disorder (Rodriguez et al., 2016; Walsh et al., 2022), PTSD (Halstead et al., 2021; Shiroma et al., 2024; Wellington et al., 2025), and substance use disorders, including alcohol, cocaine, and opioids (Krupitsky et al., 2002; Dakwar et al., 2020; Grabski et al., 2022; Walsh et al., 2022). Additionally, it has been used effectively to manage depressive symptoms in palliative care settings (Irwin et al., 2013; Iglewicz et al., 2015), where rapid relief is fundamental.

⁶ Derivative from ketamine, which has already been approved for the treatment of TRD (Infarmed, 2022). It is already used in the form of a nasal spray in some clinical contexts in several EU countries and in the US. It differs from ketamine in the way it interacts with receptors in the brain, having a greater affinity for the NMDA receptor (Canuso et al., 2018; Singh et al., 2016). This characteristic makes it have a faster antidepressant effect, making it a promising therapeutic option for reducing depressive symptoms, including suicidal ideation (Corrigan & Pickering, 2019; Daly et al., 2018).

In the following days after the administration of ketamine in the therapeutic context, patients commonly report noticeable improvements in emotional regulation and overall mood. Specifically, reductions in agitation, anger, reactivity, and self-criticism, alongside increased calmness and self-compassion, have been consistently observed (Mihaljević et al., 2020; Lascelles et al., 2021; Mathai et al., 2022; Cornfield et al., 2024; Perepelkin et al., 2025). It is also described that patients who undergo KAP are able to enhance their functionality in their daily life, as well as an improved concentration and sleeping, which increases motivation and socialisation (Griffiths et al., 2021; Lascelles et al., 2021; Perepelkin et al., 2025). These domains are often weakened in individuals experiencing depression and anxiety. Consequently, these changes seem to be key indicators of alleviation of the symptoms of these conditions (Kupferberg & Hasler, 2023).

Besides the promising results of KAP, studies have shown relevant therapeutic benefits of other psychedelics in various mental health issues (Reiff, 2020; Mathai et al., 2022). Classic psychedelics⁷ (LSD, psilocybin, DMT...) have shown relief in depressive symptoms, as well as symptoms of OCD and anxiety (Carhart-Harris et al., 2012; dos Santos et al., 2016; Wheeler & Dyer, 2020). They have also shown to help treat addictive behaviors, namely with alcohol and tobacco (dos Santos, et al., 2018; Teixeira et al., 2022), along with reducing anxiety related to terminal illnesses (Nichols, 2016; Brecksema et al., 2020). Beyond the immediate relief of core symptoms, psychedelics including ketamine have been associated with broader psychological changes that appear to support sustained improvements in mental health. They seem to increase psychological flexibility, which is associated with an improved ability to regulate emotions, adapt to stress, and interrupt rigid cognitive and emotional patterns (Majić et al., 2015; Dore et al., 2019; Muscat et al., 2021). Additionally, these experiences are associated with personality changes, such as reductions in neuroticism and increases in openness, autonomy and self determination. Together, these skills and traits facilitate mental openness, cognitive reframing, and emotional insight, directly addressing core characteristics of both depression and anxiety (Johnson et al., 2017; Bouso et al., 2018; Noorani et al., 2018; Wheeler & Dyer, 2020; Teixeira et al., 2022; Figueiredo et al., 2023; Ordem dos Psicólogos Portugueses, 2025; Perepelkin et al., 2025).

⁷ Their mechanism of action is due to the activation of serotonin 5-HT_{2A} receptors (Nichols, 2016), simultaneously promoting neuroplasticity - which increases connectivity between habitually disconnected brain areas, facilitating receptivity to cognitive functions and psychotherapeutic content (de Vos, 2021; Carhart-Harris et al., 2012; Kolp, 2014) - and neurogenesis, i.e. the creation of new neurons (Garrido et al., 2023).

Even so, these benefits of ketamine are usually short-lived, lasting only a few days, which means that this combination with numerous sessions of psychotherapy is often needed to keep the improvements going (Drozdz et al., 2022). With this in mind, the biopsicosocial Psychedelic Assisted Psychotherapy (PAP) model and specifically KAP are beginning to rise in various clinics around the world and are being used as a therapeutic approaches to relieve symptoms of mental disorders in public and private settings, as well as in underground contexts. Currently, PAP follows the psychedelic model, which promotes short-term psychotherapy using higher doses of psychedelics in a controlled therapeutic context (Nielson & Gus, 2018). Its principle is based on the interaction between the effects of the substance and the subjective psychedelic experience, facilitating meaningful and transformative experiences within a structured therapeutic setting, capable of bringing about changes in the individual's "existential paradigm", leading to lasting therapeutic benefits (Hoffer, 1967; Richards, 2017; Nielson & Guss, 2018; Figueiredo et al., 2023).

The consistent therapeutic effects of ketamine and other psychedelics in alleviating depression and anxiety symptoms depend not only on their pharmacological properties, but also on several other factors, such as the *set*, the *setting*⁸, the therapeutic relationship, the psychological preparation of the patient and the integration of the benefits in a broader and holistic therapeutic process (Leary, 1961; Griffiths et al., 2006; Hartogsohn, 2016; Nichols, 2016; Hartogsohn, 2017; Figueiredo et al., 2023). So, ensuring a safe and supportive therapeutic environment is essential to maximizing positive outcomes and reducing the risk of adverse psychological responses (Bonny & Pahnke, 1972; Becker, 2014; Figueiredo et al., 2023; Kaelen et al., 2018; Mota et al., 2023). Notably, a study by Aust and collaborators (2019) reinforced the idea that ketamine-induced experiences of anxiety were related to less antidepressant responses to the substance, underlining the importance of the protocols, the safe setting and the development of a trustful therapeutic relationship.

Ketamine induces a dissociative state (Domino, 2010), which has long been considered an undesirable side effect by the traditional medical models (Castro-Rodrigues, 2025). However, these altered states of consciousness induced by ketamine appear to be features that should be integrated within the therapeutic process, as they may represent an important mechanism underlying its therapeutic potential on reducing depressive and anxiety

⁸ The *set* refers to the individual's inner state, their personality, their attitudes, as well as their preparation, expectations and intentions for the experience. The *setting* refers to the physical, social and cultural context in which the psychedelic experience will take place (Hartogsohn, 2017; Metzner & Leary, 1967)

symptoms (Vaid & Walker, 2022; Wolfson & Vaid, 2024). These experiences can positively transform one's self-perception and worldview and increase motivation for change (Becker, 2014; Dakwar et al., 2014; Dore et al., 2019; Rothberg et al., 2020; Drozd et al., 2022; Mathai et al., 2022; Wolfson & Vaid, 2024), being associated with clinically significant reductions in depressive and anxious symptomatology (McIntyre et al., 2020; Sumner et al., 2021; Alnefeesi et al., 2022; Hull et al., 2022).

Although existing literature supports the effectiveness of PAP in reducing anxiety and depression, the degree and nature of this therapeutic response may vary significantly depending on individual characteristics. Variables such as gender and age are known to influence intervention outcomes. Research consistently indicates that being female and within the 21 to 40 age range (Ahmed et al., 2020) is associated with a higher risk of experiencing depressive and anxiety symptoms (Jenkins et al., 2020; Farhane-Medina et al., 2022; Zhu et al., 2023). Thus, some evidence suggests that females may be more sensitive to ketamine's antidepressant effects (Franceschelli et al., 2015; Sarkar & Kabbaj, 2016; Wright & Kabbaj, 2018). When it comes to age, ketamine has been shown to be effective in adolescents, namely in reducing depressive symptoms and suicidal ideation (Kim et al., 2021; Wolfson et al., 2023). However, other studies report that neither sex or age influence ketamine efficacy (Romeo et al., 2015), indicating that the current evidence remains inconclusive.

Furthermore, there is also a high prevalence of white individuals among psychedelic studies, lacking cultural diversity among samples (Fogg et al., 2021; Rojas et al., 2024). This is particularly concerning given that people of color experience high rates of mood disorders (Michaels et al., 2022).

Considering all of this, this study seems particularly relevant given the high prevalence of depression and anxiety within contemporary communities. Furthermore, there is still a lack of evidence on how sociodemographic variables can affect the efficiency of KAP (Romeo et al., 2015; Wright & Kabbaj, 2018; Kim et al., 2021; Wolfson et al., 2023). This research intends to fill this gap, aiming to clarify whether and how these variables moderate the clinical outcomes.

Also, in the specific protocol of this clinic, the integrated approach between psychotherapeutic support and ketamine administration is being applied, reinforcing the notion that the therapeutic process extends beyond the pharmacological effect alone (Drozd et al., 2022). However, most studies neglect the role of psychotherapy as an active mediator

in the treatment process (Figueiredo et al., 2023). It is important to emphasize that, in addition to the administration of the substance, therapeutic follow-up is essential to observe symptom relief, and the combination of psychotherapy with ketamine might be more efficient than the two components alone (Rodriguez et al., 2016).

Nonetheless, there is still a lack of systematic, quantitative, naturalistic studies exploring the effects of KAP (Walsh et al., 2021; Mota et al., 2023), particularly within European clinical settings. Even though the efficacy and safety of ketamine has been well studied in controlled clinical trials, much of the available data comes from this research model conducted in laboratory environments (McIntyre et al., 2020; Raison et al., 2022). Therefore, it is essential to conduct real-world studies using standardized, objective tools to assess the efficacy of this therapeutic approach. Thus, these highly controlled studies usually exclude more complex clinical profiles and patients with comorbidities and suicidal ideation (Zorumski & Conway, 2017; Lorenzo-Luaces et al., 2018; McIntyre et al., 2020). In this context, the present study aims to contribute to the existing literature by offering a quantitative analysis of symptom alleviation in patients undergoing KAP at a naturalistic clinical setting in Barcelona, contributing to the robustness of the evidence on the impact and efficacy of ketamine in these diagnoses.

Part II - Methodology

The study employed a quasi-experimental quantitative procedure, using a pre-post design, in which 27 participants were evaluated at two different times, before (pre) and after (post) the intervention with KAP, using self-reported standardized measures of depression and anxiety symptoms (BDI-II and GAD-7). By using these validated tools, the study aims to collect both accurate and consistent data, providing objective evidence of the efficacy of the KAP. This approach minimizes bias and ensures that results are based on a uniform set of criteria, strengthening the generalization of the results. Additionally, a quantitative analysis allows for the exploration of relationships between certain demographic variables, such as patient characteristics (e.g., age, gender) and treatment outcomes (Kazdin, 2021). No control group was included, as this was a naturalistic study in a clinical setting in Barcelona.

The primary goal of this work was to evaluate the effectiveness of a KAP protocol in the relief of depressive and anxiety symptoms. More specific goals were: 1) To compare the levels of depressive symptoms reported on the BDI-II self-report scale before and after treatment with KAP; 2) To compare the levels of anxiety symptoms reported on the GAD-7

self-report scale before and after treatment with KAP; 3) To explore possible associations between sociodemographic variables (age, gender, nationality) and response to treatment.

In view of the above objectives, the following research questions were formulated:

- 1) Are there statistically significant differences in symptoms of depression before and after the KAP intervention?
- 2) Are there statistically significant differences in symptoms of anxiety before and after the KAP intervention?
- 3) Are there significant associations between sociodemographic variables and the response to treatment with KAP?

In addition, quantitative hypotheses were formed to be tested by inferential statistical analysis, being the following:

Research hypothesis 1: Participants will show a statistically significant reduction in depression levels after the KAP intervention.

Research hypothesis 2: Participants will show a statistically significant reduction in anxiety levels after the KAP intervention.

Research hypothesis 3: Participants of the female sex will present higher levels of symptoms reduction after KAP intervention.

Research hypothesis 4: Older participants will show lower treatment responses compared to younger participants following KAP.

Participants

For the purposes of collecting the sample used in this research, an intentional non-probability sampling was used. A quantitative analysis of the data previously collected, recorded and archived, in the scope of a KAP intervention performed from May 2023 until March 2025 at the clinic was used to describe participants' self-reported outcomes to evaluate the pre-post KAP intervention on the depression and anxiety symptoms.

The criteria for inclusion were: 1) Be over 18 years old; 2) Have completed the treatment in the clinic in Barcelona; 3) Have completed both questionnaires (BDI-II and GAD-7) before and after treatment.

Although clinical activity began around 2022, the systematic collection of quantitative measures using standardized psychometric instruments was not implemented from the beginning. It was only from May 2023 onward that a more consistent assessment protocol, including the BDI-II and GAD-7 questionnaires, was introduced. This marks the starting point for the present study, with data analyzed up to March 2025. During this time frame, a broader universe of $n=113$ participants was identified. However, many of these cases were excluded due to missing key data. Each case was reviewed individually, and participants were discarded if they had not completed both instruments at both assessment points (pre and post-treatment) or had missing responses in either scale. As a result, the final sample includes only those participants who completed all four required measures: the BDI-II and GAD-7 at both pre and post-treatment moments, which ensures the statistical reliability of within-subject comparisons.

Therefore, the quantitative sample consisted of the records of these participants who underwent KAP ($n=27$), which was retrieved following agreement with the clinic. The patients consented, in the beginning of the treatment, to give necessary data to a third party whenever a relevant request would be raised and to manage service requirements (Annex 1).

The quantitative sample consists of 27 participants, 13 (48.1%) female and 14 (51.9%) male. In terms of nationality, 7 (25.9%) are from Spain, 5 (18.5%) are from the United States of America, 4 (14.8%) are from Brazil, 3 are from France (11.1%) and the remaining 8 (29.6%) are from other countries (Greece, Germany, Sudan, Romania...). The participants' ages ranged from 23 to 68 ($M=41.42$; $SD=11.846$).

Instruments

The instruments used were the Beck Depression Inventory II (BDI-II) (both english and spanish version - Inventario de Depresión de Beck) (Annex 2 and 3), and the General Anxiety 7 (GAD-7) (both english and spanish version - Escala de Ansiedad Generalizada) (Annex 4 and 5). The BDI-II is a 21-item self-report scale that assesses the severity of depression symptoms (Beck et al., 1996). Those 21 items can be divided into two factors: somatic-affective symptoms (including the items of tiredness and fatigue, changes in sleeping patterns, loss of interest in sex, loss of pleasure, loss of interest in activities, low energy, irritability, agitation, sadness, concentration problems and changes in appetite) and cognitive symptoms (that include the components of selfcriticalness, past failure, worthlessness, punishment feelings, crying, pessimism, guilty feelings, suicidal thoughts or wishes and

self-dislike) (Arnau et al., 2001; Viljoen et al., 2003). Each item is rated on a 4-point scale from 0 to 3 and the test is scored by summing those scores for each of the 21 symptoms (Steer, 1999). Higher scores represent more frequent depressive symptoms. The defined cut-off points are: minimal depressive symptoms (0-13), mild (14-19), moderate (20-28) and severe (over 29) (Beck et al., 1996). The BDI-II has demonstrated excellent internal consistency (Cronbach's $\alpha > 0.90$) and strong convergent validity with other measures of depression, based on US and international samples (Beck et al., 1996; Wang & Gorenstein, 2013). The Spanish version of the BDI-II has also shown strong psychometric qualities, with high internal consistency ($\alpha = 0.89$) and good test-retest reliability (Sanz et al., 2003).

Concerning the GAD-7, this test is a brief self-report tool used to screen for generalized anxiety disorder by evaluating the frequency of anxiety symptoms over the past two weeks (Spitzer et al., 2006). It consists of 7 items and the patient must answer to what extent they feel nervous, anxious or on edge, not being able to stop or control worrying, worrying too much about different things, finding it hard to relax, being so restless that it's hard to sit still, getting easily upset or irritated and feeling afraid as if something might happen. Each item can be scored with 0 ("not at all"), 1 ("several days"), 2 ("more than half the days") or 3 ("nearly every day") (Williams, 2014). The cut-off points are: minimal anxiety symptoms (0-4), mild (5-9), moderate (10-14) and severe (15-21) (Spitzer et al., 2006). The original validation study reported excellent internal consistency ($\alpha = 0.92$) for identifying generalized anxiety disorder (Spitzer et al., 2006). Subsequent studies confirmed the scale's strong psychometric properties in both general and clinical populations (Löwe et al., 2008; Plummer et al., 2016). The Spanish adaptation of the GAD-7 also presents solid psychometric validity, with internal consistency of $\alpha = 0.93$ and strong correlations with other anxiety measures (García-Campayo et al., 2010).

Data collection procedures

Data was collected between May 2023 and March 2025, based on the clinical records of a specialized KAP clinic located in Barcelona.

In the clinic where the study took place, the clinical protocol followed four distinct phases (Australian Psychology Society, 2023): firstly, screening, where an anamnesis and mental state assessment is carried out, which is important for delimiting the patient's requests and decide if the client will benefit from this model of therapy (Ordem dos Psicólogos Portugueses, 2025). This is followed by preparation sessions, which are essential for building

a therapeutic relationship and clarifying intentions for the treatment. The third step is the dosing sessions, where the psychedelic substance is administered and the therapist guides the client through their altered state of consciousness. Finally, there is the integration phase, which aims to make sense of the insights that may have arisen in the experience, in order to integrate them into everyday life (Aixalà, 2022; Bathje et al., 2022; Frymann et al., 2022).

The BDI-II and GAD-7 instruments were completed by the participants at two points in time: at the beginning of the protocol during the preparation session and after the therapeutic sessions had finished. During these preparation sessions, other important documents are also handed out, including an informed consent form with all the secondary effects of ketamine described, as well as what is going to happen during the sessions, a cancellation policy, a prescription to collect the ketamine from the respective pharmacy and a data processing document, where clients allow their data to be used anonymously only for research purposes. Due to the intensity and unpredictability of a psychedelic experience, signing a clear, complete and detailed informed consent with all possible effects and risks is essential (Ordem dos Psicólogos Portugueses, 2025).

All the data was anonymized and used with the authorization of the institution and the consent of the participants, in accordance with the ethical principles of research in psychology and the data protection regulations.

Data analysis procedure

Quantitative analysis was performed with the support of IBM SPSS Statistics software (version 30.0). The analysis was structured in several steps to address both descriptive and inferential aspects of the data. First, descriptive statistics were carried out to characterize the study sample. This included calculating measures of central tendency and dispersion to summarize the data set (Martins, 2011). Relative frequencies for gender, age and nationality were also analyzed.

Then, to answer the specific investigation questions, inferential statistics were applied. As it is a pre-post design, the same group of subjects were compared at the level of two variables (depressive symptoms and anxiety symptoms) at two different moments (before and after the treatment). Normality of the score distributions was assessed using Kolmogorov-Smirnov tests, analyzing skewness, kurtosis, and visual inspection of histograms. An exploratory data analysis allows one to decide which type of statistical tests

(parametric or non-parametric) should be used to test the research hypotheses involving the present variables (Martins, 2011). Although slight deviations from normality were observed - particularly in post-treatment BDI-II scores - the sample size (n=27) was considered adequate for applying paired-samples t-tests, given the test's robustness to minor non-normality. Therefore, a test of differences for paired samples (t) was performed. It also showed the estimate of the effect using Cohen's d, allowing comparison with the effects found in other studies. To ensure the robustness of the results, Wilcoxon signed-rank tests were also performed as a non-parametric alternative. Finally, exploratory analyses using ANCOVA repeated measures were conducted to examine whether changes in symptom scores were associated with demographic variables such as age, sex, or nationality.

Part III - Results

A total number of 27 patients filled the self report symptom scales before and after de treatment. The sociodemographic characteristics of the participants are presented on table 1.

Table 1.

Sociodemographic characteristics of participants (n=27).

		n	%	M	SD
Gender	Male	14	51.9		
	Female	13	48.1		
Age range*	23-68			41.42	11.846
Nationality	Spain	7	25.9		
	USA	5	18.5		
	Brazil	4	14.8		
	France	3	11.1		
	Others (Greece, Germany, Romania...)	8	29.6		

*One missing value.

To complement the descriptive analysis, the following sections present the participant results on both scales as well as its distribution throughout cut-off categories.

Descriptive analysis of the depressive symptoms

Table 2 presents the mean scores and standard deviations for BDI-II in both moments (pre and post KAP). Table 3 was also included to graphically show the cut-off categories of the self report symptom scale, to understand the fluctuations in the patients.

Table 2.

Mean scores and standard deviations for BDI-II scores pre and post KAP.

	Mean (SD)
BDI-II pre treatment	27.22 (13.08)
BDI-II post treatment	12.56 (12.89)

The mean score on the BDI-II before the KAP intervention was M=27.22 (SD=13.08, indicating a moderate level of depressive symptomatology in the sample. After the treatment, the mean score dropped to M=12.56 (SD=12.89). This result shows a substantial reduction in self-reported depressive symptoms after the intervention, suggesting a clinically relevant improvement post-KAP.

Table 3.

BDI-II cut-off points and distribution of the participants through the categories.

Severity level	BDI-II Pre KAP n (%)	BDI-II Post KAP n (%)
Minimal (0-13)	4 (14.8%)	17 (63%)
Mild (14-19)	3 (11.1%)	2 (7.4%)
Moderate (20-28)	9 (33.3%)	3 (11.1%)
Severe (>29)	11 (40.7%)	5 (18.5%)

These results suggest a significant clinical improvement, with participants moving towards lower levels of depressive symptoms.

Descriptive analysis of the anxiety symptoms

Table 4 presents the mean scores and standard deviations for GAD-7 pre and post KAP. Table 5 graphically shows the cut-off categories of this symptom scale.

Table 4.

Mean scores and standard deviations for GAD-7 scores pre and post KAP.

	Mean (SD)
GAD-7 pre treatment	11.81 (5.49)
GAD-7 post treatment	5.41 (4.71)

Regarding anxiety symptoms, participants had a mean prior to treatment on the GAD-7 score of M=11.81 (SD=5.49), which corresponds to moderate anxiety levels. After completing the KAP protocol, the mean decreased to M =5.41 (SD=4.71), placing the sample within the mild range of anxiety severity. This notable reduction suggests that the intervention may have had a beneficial impact on anxiety symptoms as well (see Table 4).

Table 5.

GAD-7 cut-off points and distribution of the participants through the categories.

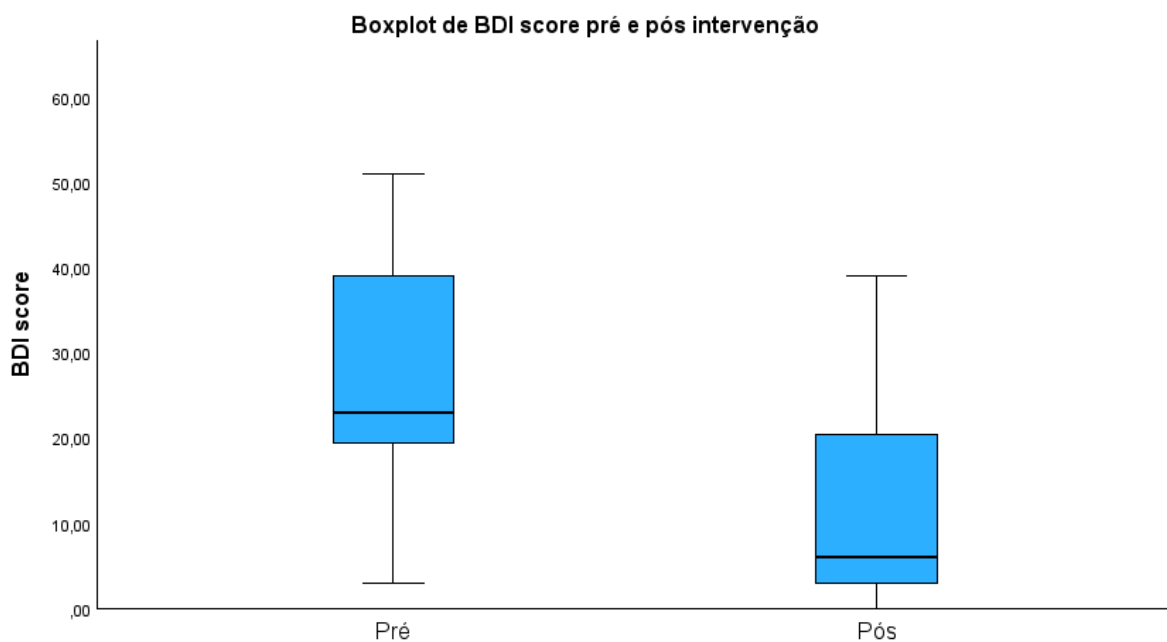
Severity level	GAD-7 Pre KAP n (%)	GAD-7 Post KAP n (%)
Minimal (0-4)	2 (7.4%)	14 (51.9%)
Mild (5-9)	6 (22.2%)	8 (29.6%)
Moderate (10-14)	9 (33.3%)	3 (11.1%)
Severe (15-21)	10 (37%)	2 (7.4%)

Regarding anxiety symptoms, before KAP, the majority of the patients were also located in the moderate (33.3%) and severe (37%) categories. After the intervention with ketamine, the majority (51.9%) of the participants had minimal symptoms, and only 7.4% remained in the severe category. These results reinforce the efficiency of KAP in the relief of anxiety symptomatology.

To complete the descriptive analysis, boxplots were used to show the distribution, symmetry and dispersion of the data, as well as to detect possible outliers (Figure 1 and 2). The boxplots illustrate the median, interquartile range, and extreme values, offering a visual summary of score distribution and asymmetry. Greater symmetry around the median suggests a distribution closer to normality.

Figure 1.

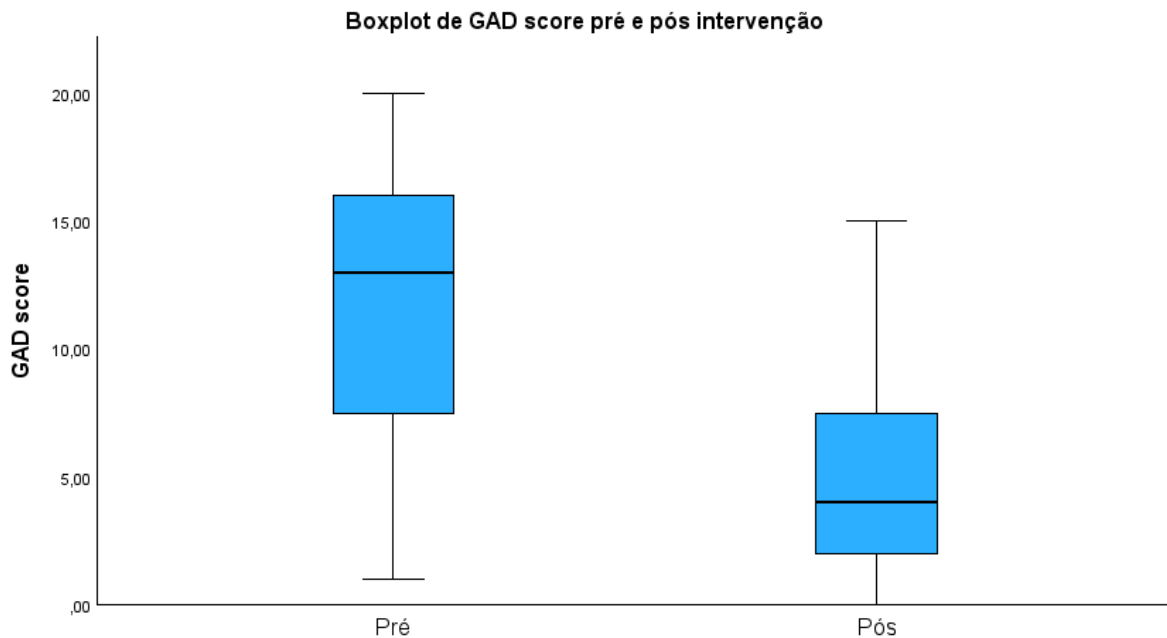
Boxplot of the BDI-II scores pre and post intervention.



Regarding the BDI-II scores, it is possible to observe a sharp reduction in median scores after the intervention with KAP. Before the intervention, the scores also demonstrated greater dispersion. This pattern suggests an overall improvement in the participants' self-reported depressive symptoms. The reduction in the interquartile range at post-treatment also suggests greater homogeneity in the distribution of scores after KAP.

Figure 2.

Boxplot of the GAD-7 scores pre and post intervention.



When it comes to the GAD-7 scores, the graphic analysis highlights a notable reduction in the median, suggesting a global improvement in the participants' self-reported anxiety symptoms. In the pre-intervention moment, it is possible to observe an extended interquartile range, indicating greater variability in the severity of anxiety symptoms. Post-intervention, there was a reduction in the interquartile range, reflecting less dispersion and lower levels of anxiety in most cases. Then, the visual comparison between the two moments suggest clinical improvement in the GAD-7 scores after treatment, and a more homogeneous distribution among the participants.

After carrying out the descriptive statistics and before employing the hypothesis tests, it was necessary to evaluate the normality assumptions for the variables under study. The normality of the variables was analyzed by checking the skewness and kurtosis values, divided by the respective standard error (SE). For Z values between -1.96 and 1.96, the variable is considered to have an approximately normal distribution (Marôco, 2011). A Kolmogorov-Smirnov test of normality was also performed. The results are presented on Table 6.

Table 6.*Tests of normality Kolmogorov-Smirnov.*

	Asymmetry (SE)	Z value (Asymmetry)	Kurtosis (SE)	Z value (Kurtosis)	Sig.
BDI-II pre treatment	0.100 (0.448)	0.223	-0.987 (0.872)	-1.132	0.106
BDI-II post treatment	0.977 (0.448)	2.18	-0.419 (0.872)	-0.481	<.001
GAD-7 pre treatment	-0.380 (0.448)	-0.848	-0.861 (0.872)	-0.987	0.180
GAD-7 post treatment	0.850 (0.448)	1.897	-0.314 (0.872)	-0.360	0.188

Regarding these results, it was possible to observe that the BDI-II post treatment variable showed a Z value for asymmetry of 2.18, higher than the threshold of ± 1.96 , suggesting a violation of the normality assumption. Literature also shows that, if the $p < .005$, it is not possible to assume the normal distribution of the data. These distributions are possible to assess in the annex 6, 7, 8 and 9.

Consequently, as the variable BDI-II post-treatment was the only variable with this distribution, it was decided to apply parametric (test of differences for paired samples (t)) and non-parametric tests (Wilcoxon signed-rank tests) in a complementary way, ensuring the robustness of the statistical analysis, as recommended for data with mixed distributions, to verify the existence of statistically significant differences between the moments pre and post-intervention with KAP.

Parametric tests

Depressive symptoms (BDI-II)

The table 7 presents pre and post-treatment with ketamine measures of the BDI-II.

Table 7.

Paired sample t Test for the differences between pre and post-treatment for BDI-II (n=27).

	BDI-II pre treatment (N=27) Mean (DP)	BDI-II post treatment (N=27) Mean (DP)	t (26)
BDI-II total score	27.22 (13.08)	12.56 (12.89)	5.77***

*** $p < .001$

The average BDI-II score before the KAP treatment was $M=27.22$ ($SD=13.08$), while after the intervention it was $M=12.56$ ($SD=12.89$). This difference was analyzed using a t-test for paired samples, which revealed a statistically significant difference, $t(26) = 5.77$, $p < .001$, $d = 1.11$, indicating a significant reduction in depressive symptoms after the intervention with KAP with a very strong effect of the intervention in this symptomatology (Cohen, 1988). These findings are aligned with the proposal hypothesis, confirming that participants showed a statistically significant reduction in depression levels after the KAP intervention.

Anxiety symptoms (GAD-7)

The table 8 presents pre and post-treatment with ketamine measures of the GAD-7.

Table 8.

Paired sample t Test for the differences between pre and post-treatment for GAD-7 (n=27).

	GAD-7 pre treatment (N=27) Mean (DP)	GAD-7 post treatment (N=27) Mean (DP)	t (26)
GAD-7 total score	11.81 (5.49)	5.41 (4.71)	6.08***

*** $p < .001$

Regarding anxiety, the mean scores on the GAD-7 decreased from $M=11.81$ ($SD=5.49$) at pre-intervention to $M=5.41$ ($SD=4.71$) at post-intervention. The t-test for paired samples indicated a statistically significant difference, $t(26) = 6.08$, $p < .001$, $d = 1.17$, also

with a very strong effect of the intervention in these symptomatology (Cohen, 1988), confirming a significant reduction in anxiety symptoms, which is in line with the proposed hypothesis that participants would show a statistically significant reduction in anxiety levels after the KAP intervention.

Non-parametric tests

Depressive Symptoms (BDI-II)

In order to validate the results given the non-normality of the data, the Wilcoxon test was applied. Regarding the results of the BDI-II pre and post-intervention, they are presented in table 9.

Table 9.

Results of Wilcoxon Signed-Rank Test for BDI-II pre and post KAP (n=27).

	Median Pre-KAP (IQR)	Median Post-KAP (IQR)	Z	p
BDI-II	23.00 (21)	6.00 (18)	-4.002	<.001

They showed marginally significant differences between the scores before and after treatment, $Z = -4.002$, $p < .001$. This means that patients tend to reduce their self-reported symptoms of depression after treatment with KAP. Specifically, 24 participants showed a decrease in BDI-II scores, 1 remained unchanged and 2 showed worsening.

Anxiety Symptoms (GAD-7)

In the case of the GAD-7 results before and after treatment with KAP, these are presented in table 10.

Table 10.

Results of Wilcoxon Signed-Rank Test for GAD-7 pre and post KAP (n=27).

	Median Pre-KAP (IQR)	Median Post-KAP (IQR)	Z	p
GAD-7	13.00 (10)	4.00 (6)	-4.077	<.001

There were also marginally significant differences between the scores before and after treatment, $Z = -4.077$, $p < .001$. Participants tended to reduce their self-reported anxiety symptoms after treatment with KAP, with 24 participants recording an improvement and 3 a worsening of symptoms.

Analysis of the effects of sociodemographic variables

Lastly, in order to evaluate the influence of sociodemographic variables - gender, age and nationality - on the results obtained, an exploratory analysis using ANCOVA repeated measures was performed. The results regarding the BDI-II are presented on table 11.

Table 11.

Results of ANCOVA repeated measures to assess the effect of gender, age and nationality on the results of BDI-II pre and post intervention with KAP.

	df	Mean Square	F	Sig.	Partial Eta Squared
Time	1	100.944	1.239	0.278	0.053
Time * gender	1	200.545	2.462	0.131	0.101
Time * age	1	63.021	0.774	0.389	0.034
Time * nationality	1	58.631	0.720	0.405	0.032
Error (time)	22	81.455			

These results suggest that neither gender $F(1,22) = 2.462$, $p = 0.131$, $\eta^2 = 0.101$, the age $F(1, 22) = 0.774$, $p = 0.389$, $\eta^2 = .034$ nor the nationality $F(1, 22) = 0.720$, $p = 0.405$, $\eta^2 = .032$ proved to have a statistically significant effect on the variation in scores between the two moments ($p > .05$) on the results of the scale BDI-II and do not contribute significantly to explain variability on this test score. The results also indicated that the main effect of time was not statistically significant, $F(1, 22) = 1.239$, $p = 0.278$, $\eta^2 = 0.053$, indicating that, in this specific analysis, there was no significant overall reduction in depressive symptoms over time when considering these covariates.

The results regarding the GAD-7 are presented on table 12.

Table 12.

Results of ANCOVA repeated measures to assess the effect of gender, age and nationality on the results of GAD-7 pre and post intervention with KAP.

	df	Mean Square	F	Sig.	Partial Eta Squared
Time	1	25.963	1.834	0.189	0.077
Time * gender	1	24.712	1.745	0.200	0.074
Time * age	1	4.868	.344	0.564	0.015
Time * nationality	1	11.614	.820	0.375	0.036
Error (time)	22	14.159			

Likewise, a repeated measures ANCOVA was performed to analyze the effects of time on the GAD-7 scores, as well as possible interactions with sociodemographic variables. The main effect of time was not statistically significant, $F(1, 22) = 1.834$, $p = 0.189$, $\eta^2 = 0.077$, indicating that there was no significant reduction in anxiety symptoms over time.

Furthermore, none of the interactions between time and sociodemographic variables were significant. The interaction between time and gender resulted in $F(1, 22) = 1.745$, $p = 0.200$, $\eta^2 = 0.074$, the interaction with age showed $F(1, 22) = 0.344$, $p = 0.564$, $\eta^2 = 0.015$, and the interaction with nationality had $F(1, 22) = 0.820$, $p = 0.375$, $\eta^2 = 0.036$. These results suggest that the pattern of variation in anxiety scores was not significantly influenced by these variables over time, which allows us to reject the research hypothesis 3 (participants of the female sex will present higher levels of symptoms reduction after KAP intervention) and 4 (older participants will show lower treatment responses compared to younger participants following KAP).

Discussion

The present study aimed to evaluate the effectiveness of a KAP protocol in the relief of depressive and anxiety symptoms, using standardized self-report symptom scales, the BDI-II and the GAD-7, within a clinical sample. In the current work, patients reported a decrease in the symptomatology of both conditions after undergoing the treatment with ketamine, which aligns and confirms the hypothesis that KAP would promote substantial improvement in both depression and anxiety. The decrease in the pre-to-post means, associated with a reduction in the variability of the scores, suggests a consistent clinical response among the participants.

The effect sizes obtained in this study ($d=1.11$ [95% CI = 0.622, 1.586] for the depressive symptoms and $d=1.17$ [95% CI = 0.671, 1.655] for the anxiety symptoms) are notably strong, indicating large and clinically meaningful changes (Cohen, 1988; Brydges, 2019). These results are also supported by the substantial mean differences between the pre and post-KAP scores (for the BDI-II, values pre intervention were $M=27.22$ ($SD=13.08$), while after the intervention it was $M=12.56$ ($SD=12.89$); for the GAD-7, values were $M=11.81$ ($SD=5.49$) at pre-intervention and $M=5.41$ ($SD=4.71$) post-KAP).

The results of this study come in agreement with other studies in the literature. For example, in the study of Davis et al. (2021), individuals with major depressive disorder and PTSD showed less severity symptoms 2 hours and 1 day post one single-dose intravenous ketamine treatment, with an effect size of $d = 0.80$ and $d = 1.02$, respectively. The case study of Halstead et al. (2021) also showed a decrease in punctuation of BDI-II (from 40 to 27 points) after a 13-day KAP protocol. Moreover, Whinkin et al. (2023) reported a mean reduction of 6.71 points ($SD = 9.15$) on the GAD-7 in individuals with problematic substance use after several sessions with ketamine combined with psychotherapy.

These findings are consistent with the emerging literature on PAP, which has reported rapid and long-lasting effects of ketamine in certain mental health problems, like depression and anxiety (Berman et al., 2000; Taylor et al., 2018; Dore et al., 2019; Conley et al., 2021; Alnefesi et al., 2022; Ramos et al., 2022; Walsh et al., 2022). The homogeneity of post-treatment scores between individuals reinforces the applicability of this KAP protocol at different levels of symptom severity, corroborating studies that point to ketamine as an agent with great effect in relieving symptoms of resistant disorders (Zarate et al., 2006; Zanos & Gould, 2018; McIntyre et al., 2020; Muscat et al. 2021; Wilkinson et al., 2021).

Another finding lies in the fact that there were no significant effects of age, gender or nationality on post-treatment scores. These results suggest that the benefits of KAP in this study did not depend substantially on these individual demographic characteristics. This can support its applicability across diverse populations without the need for specific adjustments for these factors (Kessler et al., 2005), highlighting KAP's potential for broad therapeutic impact across different demographic groups.

As it took place in a naturalistic context, this work contributes to the scientific evidence by providing data where participants are not excluded on the basis of comorbidities or other variables often controlled in clinical trials, which increases the external validity of the results (Lorenzo-Luaces et al., 2018). Also, while some literature suggests that women may show greater responsiveness to ketamine's antidepressant effects (Wright & Kabbaj, 2018), and that younger individuals might benefit differently from psychedelic therapy (Ahmed et al., 2020; Kim et al., 2021), our findings did not replicate these effects. This might not be generalizable, as this finding can be limited to the small sample size. Other studies also report mixed or inconclusive findings on these demographic variables (Romeo et al., 2015), suggesting that more controlled research is needed to clarify their role. In fact, one of the increasingly prominent debates within the psychedelic scientific community concerns the conditioned understanding of the psychedelic research by the biomedical Western paradigms. This system neglects the important contributions of indigenous communities and other cultural groups whose historical, cultural, and ethnobotanical knowledge has played a foundational role in the use of psychoactive substances. Not including these groups and perspectives limits our understanding of this psychotherapeutic approach and raises ethical concerns regarding the inclusivity of research practices (George et al., 2020).

However, as the covariance analysis showed, the improvement in symptomatology may be strongly associated with the initial variability of the participants. This suggests that individual baseline factors (such as the severity of symptoms pre-KAP, duration of diagnosis, treatment history or personal expectations) could play a significant role in moderating the effectiveness of KAP. Participants with higher initial levels of depression or anxiety may have shown greater symptom reduction simply due to having more room for improvement, whereas those with milder symptoms might exhibit less dramatic changes. This highlights the importance of looking at each individual's starting point when interpreting results, since symptom improvement is not the same for everyone and can depend on several variables.

In the present study, diagnostic categories were not systematically distinguished, limiting the ability to assess how specific disorders may interact or contribute to comorbidity patterns. In addition to their strong association with one another, both depression and anxiety frequently co-occur with other mental health disorders and have a transversal influence on a wide range of other psychopathological diagnoses, such as PTSD, OCD and substance use disorders (Brady et al., 2013; Breteler et al., 2020; Koopowitz et al., 2021). This overlap is not unexpected, given that most of these disorders share several diagnostic criteria from the DSM-5 (American Psychiatric Association, 2013), including sleep disturbances, anhedonia, and difficulties with concentration (Nijdam et al., 2013). Clarifying these diagnostic profiles would allow for a better understanding of how KAP influences not only anxiety and depression, but also the broader clinical picture, including symptoms that overlap across multiple conditions. Since reducing anxious and depressive symptoms is often associated with clinical improvement in several of the conditions mentioned, such clarification could provide valuable insight into the mechanisms through which KAP contributes to psychological well-being (Ginzburg et al., 2010; Sharma et al., 2021).

With the increase of psychosocial disconnection, digital overburden and the poor responses from mental health systems provoking serious illnesses with high failure rate treatments (Vollenweider & Kometer, 2010; Fiorillo & Gorwood, 2020; Loades et al., 2020; World Health Organization, 2022), these alternative therapeutic approaches are urgently needed. The development of good mental health plays a crucial role at all stages of life, as it contributes to better educational achievement, greater productivity at work, and a more active and inclusive role in society (Council of the European Union, n.d.). PAP may represent a valuable option for populations that suffer with treatment resistant symptoms, offering them renewed possibilities (Vollenweider & Kometer, 2010; Erritzoe et al., 2024).

However, while the results of this study are promising, they also present several ethical concerns. There is a rising importance of integrating psychotherapeutic support into ketamine sessions and current evidence indicates that psychedelics may not be a viable treatment on their own. The current biomedical model tends to overemphasize the relief of symptomatology, often neglecting the emerging of other meaningful psychological processes that are crucial for the therapeutic potential of PAP in individuals (Griffiths et al., 2008; Watts & Luoma, 2020). The psychological benefits appears to emerge not from the pharmacological effect alone, but from the interaction of pharmacological factors, the therapeutic relationship, meaningful subjective experiences, and the integration phase blended with a more continuous

psychotherapeutic process (Vollenweider & Kometer, 2010; Mathai et al., 2022; Greenway et al., 2020; Watts & Luoma, 2020). This collaborative approach has the potential to enhance the therapeutic benefits, reducing the suffering of many individuals (Wolfson et al., 2023).

Also, despite the various hypotheses raised, the exact mechanisms of each component of PAP are still poorly understood and require further research (APS, 2023). Although the therapeutic potential of these substances is significant and brings new perspectives, their role should be seen as part of an ongoing evolution within the field of psychology and not as a radical paradigm shift (Aicher et al., 2024). It is especially important that scientific research maintains a balanced perspective on both the potential risks and benefits of psychedelics in general, avoiding the pitfalls of a reductionist vision and overlooking important factors that can negatively affect individuals that undergo these treatments (Ehrenkranz et al., 2024). This approach favors a more critical integration of these treatments into existing mental health systems, promoting continuous innovation in the field.

Moreover, implementing rigorous KAP safety protocols is crucial and these must be accompanied by clear ethical guidelines and qualified professional supervision to ensure its responsible and safe use (Phelps, 2017). Structured protocols should include thorough screening processes, psychological preparation, and post-session integration, which are essential in minimizing potential adverse effects. Administering ketamine within evidence-informed frameworks by trained professionals and under controlled conditions helps reduce certain risks such as emotional vulnerability, retraumatization or even therapist misconduct during vulnerable states (Morgan & Curran, 2012). Comprehensive informed consent is a key component of this process, as it ensures participants are fully aware of the nature of the treatment, the potential effects of altered states of consciousness, and the support structures available to them throughout the experience. Together, these measures foster a safer therapeutic environment and uphold the ethical standards necessary for the clinical use of psychedelics (Ordem dos Psicólogos Portugueses, 2025).

Conclusions

The present study aimed to evaluate the effects of KAP protocol on depressive and anxiety symptoms, using quantitative standardized measures in a naturalistic clinical context. Current results showed statistically and clinically significant reductions in measures of depressive and anxiety symptoms, which aligns with the recent findings of the literature and

contributes to scientific advances on the therapeutic potential of PAP as an integrative and innovative approach to mental health.

One of the main strengths of this study lies in its ecological validity typical of a naturalistic clinical setting. The dynamic of the intervention of KAP suggests that pharmacologically enhanced neuroplasticity may be most beneficial when accompanied by psychological processing and integration. This synergistic model appears to promote cognitive and emotional flexibility, promoting longer-lasting therapeutic effects (Griffiths et al., 2008; Vollenweider & Kometer, 2010).

Even though there were compliant results achieved and there are existing outcomes that prove the therapeutic potential of KAP, these must be interpreted with caution, since the study raises certain methodological limitations.

Firstly, it is not possible to establish causality with the present methodologic design. The present study does not feature a control group, which makes it subject to certain methodological biases, like regression to the mean and uncontrolled external events (Marsden & Torgerson, 2012). Performing research on a naturalistic setting brings other constraints, such as the absence of a control group, that inhibits the ability to isolate the effect of the intervention and comparisons with the potential effects of placebo or other uncontrolled variables. While the naturalistic clinical context enhances the ecological validity of the study, there are uncontrolled aspects that can compromise the uniformity of the intervention, such as a variability in the number of sessions during KAP, different therapeutic models applied during intervention, some patients taking antidepressants during treatment and the subjective experiences of the participants, typical of the psychedelic experiences. Therefore, even if an improvement is observed on the self report symptoms scores, it is not possible to claim with certainty that they are due to the KAP intervention.

Besides that, the participants did not fill the tests consistently over time, meaning that in some cases the post-intervention questionnaires were completed weeks or months after the end of treatment. This led to a substantial exclusion of participants due to missing data which may affect the reliability of the responses and introduce variability into the data collected.

The small sample size ($n=27$) and the non-probability intentional sampling procedure may have limited the statistical power of the results to contribute to the generalizability of the findings to wider populations, affecting external validity. The exclusion of cases with missing

data may also have generated selection bias, restricting the clinical variability of the participants included.

Also, although it was considered that this sample size ($n=27$) was adequate for applying paired-samples t-tests, even with slight deviations from normality, this assumption remains subject to debate. Some researchers argue that in small-sample studies, even minor violations of assumptions can impact the validity of results (Whitehead et al., 2016). Therefore, this factor contributes to a cautious interpretation of the findings.

Moreover, relying exclusively on self-reported measures brings certain biases, like social desirability and memory biases, as well as the impact of more transitory factors, such as the mood of the person on the day of the assessment.

Besides that, symptoms were only assessed immediately before and after the KAP sessions, not being possible to verify the maintenance of the symptom relief over time.

In addition, a relevant obstacle lies in the difficulty of isolating the specific therapeutic contributions of each component involved in the intervention: the psychotherapy and the ketamine administration. In the PAP models, psychedelics are followed by the integration sessions, that are structured psychological sessions, and the therapeutic outcomes are presumed to result from this dynamic interaction between the psychedelic substance and the psychotherapeutic process (Bathje et al., 2022; Drodz et al., 2022). The current study design does not allow a "substance-only" or "psychotherapy-only" comparison group, making it impossible to determine the impact of each component alone. Thus, there is not a way of knowing whether the symptom relief observed is due mainly from the rapid biochemical actions provided by ketamine, the psychotherapeutic support or the synergistic interaction between the two. This highlights an important debate in the literature: are we dealing with psychotherapy assisted by ketamine or ketamine assisted by psychotherapy? The evidence of the efficiency of KAP over the two components alone is still not clear (Rodriguez et al., 2016; Gomes & Novais, 2025) and there is still a need for more scientific evidence to understand the relationship between these two models.

For future research, several recommendations are brought up. Firstly, future studies should use another type of methodological design, such as experimental designs with random allocation of participants to intervention arms and different experimental conditions - ketamine alone, psychotherapy alone and KAP - allowing for a more precise assessment of

the specific contribution of each component to symptom relief and to reinforce the internal validity of the findings. Also, larger and more heterogeneous samples should be included, in order to contribute to the generalizability of the results and to understand if KAP can have potential across populations with diverse sociodemographic characteristics (Kessler et al., 2005). Including more diverse participants is important to make future research and treatment with KAP more culturally appropriate, especially considering that reported treatment outcomes may not be generalizable to all ethnic groups (Michaels et al., 2018; George et al., 2020). Future studies should also consider a more precise identification of participants' primary diagnoses and comorbid conditions. This could strengthen the interpretation of outcomes and inform more targeted therapeutic approaches. Data collection should also follow a more systematic and standardized protocol, ensuring greater temporal consistency between assessment moments. Future research should also account for the baseline characteristics when evaluating treatment outcomes, as they are essential for accurately interpreting therapeutic effects and identifying which profiles benefit most from KAP. Besides that, it is suggested the inclusion of different objective measures (e.g. scales applied by professionals) or qualitative measures, such as clinical interviews to explore the depth of the subjective experience of participants and how the interaction between ketamine and psychotherapy is experienced (Dore et al., 2019; Mathai et al., 2022). It would also be relevant to explore moderators of the therapeutic response, such as expectations or the living of subjective experiences, as well as to carry out longitudinal follow-ups to assess the maintenance over time of the effects observed. In the short term, it is known that ketamine can generate a rapid response (Berman et al., 2000; Drozd et al., 2022; Walsh et al., 2022), but without long follow-ups it is not possible to replicate these results over time.

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Annex

Annex 1 - Document of consent for the processing of personal data distributed in the preparation session.



Document of consent for the processing of personal data

Personal data:

Name:

Surname:

National ID or Passport number:

Representative on behalf (only if you are representing someone declared legally incompetent or is legally a minor):

Data Controller:

Identification name: ESPAI SYNAPTIC LAB S.L.

Reference adress: Carrer Galileu, 165, 3r 1a, 08028, Barcelona

Fiscal Identification Code: B42755876

e-mail: info@clinicasyntactica.com

By signing this document you consent to the processing of your data for the purposes detailed below by CLINICA SYNAPTICA.

According to the law written in arts.6.1.a), 7 & 8 of the EUROPEAN REGULATION (EU) 2016/679 approved by the EUROPEAN PARLIAMENT and the EUROPEAN COUNCIL in April, 27 of 2016, relative to the protection of the processing and use of any information provided by an identified and identifiable individual. As controller of the data provided, ESPAI SYNAPTIC LAB S.L. will incorporate this information to their filing systems for its processing.

For what reason and for whom will this information be processed?

CLINICA SYNAPTICA will process the data provided by consenting individuals in order to:

- Managing service requirements contracted online or in our clinic
- Sending required information to the patient, legal institutions or other previously consented recipient.
- To develop and provide commercial and proper maintenance and management of the service relation with the patient.

What the legitimacy of our data processing is?

The following legal basis provide a framework from which our enterprise may act:

- Contract or provide any service according to a commercial relation between the enterprise and an informed and consenting individual.

- Legitimate interest to send commercial information about our products and services.
- Legitimate interest to maintain established or future contact with the client or third party service and product providers.
- Legal obligations to share required information with Official Public Institutions for preventing tax evasion and third party requirements.
- Expressed consent from the recipient to elaborate profiles, contact application forms, information requirements and/or e-newsletter subscription.

To whom may your data be shared?

Whenever a relevant and reasoned request would be raised, CLINICA SYNAPTICA will provide the consented data to a third party. In any case, the data would not be sold to a third party. External service providers (i.e., payment service or delivery service providers) that are contracted by CLINICA SYNAPTICA may use the data provided in order to adequately develop their commercial activities. Although, those providers cannot use for private interests or sell to any third party the data provided in this document. All service providers that work with CLINICA SYNAPTICA are required to use the information provided according to the same European Regulation in order to warrant personal data privacy.

In some cases, Supervisory Authorities can legally oblige to reveal personal information to the corresponding Official Institutions. Only strictly legally required information would be provided.

Personal data included in this document can be used by other members of the group of undertakings.

Which are and how could you exercise your rights?

You can exercise your rights by sending any request to the following e-mail: info@clinciasynaptica.com. You can request and exercise the following rights: right to access, right to rectify, right to delete, right to restrict the processing of, right to oppose, right of portability and right to not being subject to individual decisions made by the enterprise.

Additional Information

You can find additional information about the processing of your personal data in the following website: www.clinicasynaptica.com/politica-privacitat

By signing this document, you explicitly consent to CLINICA SYNAPTICA the processing of your personal data as previously described.

I have read the information provided and I agree to the processing of my personal data

I agree to the processing of my personal data to elaborate profiles.

(Check the previous statements)

Full Name:

Signature:



Annex 2 - Beck Depression Inventory-II (BDI-II)

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
 - 0 I do not feel sad.
 - 1 I feel sad
 - 2 I am sad all the time and I can't snap out of it.
 - 3 I am so sad and unhappy that I can't stand it.
2.
 - 0 I am not particularly discouraged about the future.
 - 1 I feel discouraged about the future.
 - 2 I feel I have nothing to look forward to.
 - 3 I feel the future is hopeless and that things cannot improve.
3.
 - 0 I do not feel like a failure.
 - 1 I feel I have failed more than the average person.
 - 2 As I look back on my life, all I can see is a lot of failures.
 - 3 I feel I am a complete failure as a person.
4.
 - 0 I get as much satisfaction out of things as I used to.
 - 1 I don't enjoy things the way I used to.
 - 2 I don't get real satisfaction out of anything anymore.
 - 3 I am dissatisfied or bored with everything.
5.
 - 0 I don't feel particularly guilty
 - 1 I feel guilty a good part of the time.
 - 2 I feel quite guilty most of the time.
 - 3 I feel guilty all of the time.
6.
 - 0 I don't feel I am being punished.
 - 1 I feel I may be punished.
 - 2 I expect to be punished.
 - 3 I feel I am being punished.
7.
 - 0 I don't feel disappointed in myself.
 - 1 I am disappointed in myself.
 - 2 I am disgusted with myself.
 - 3 I hate myself.
8.
 - 0 I don't feel I am any worse than anybody else.
 - 1 I am critical of myself for my weaknesses or mistakes.
 - 2 I blame myself all the time for my faults.
 - 3 I blame myself for everything bad that happens.
9.
 - 0 I don't have any thoughts of killing myself.
 - 1 I have thoughts of killing myself, but I would not carry them out.
 - 2 I would like to kill myself.
 - 3 I would kill myself if I had the chance.
10.
 - 0 I don't cry any more than usual.
 - 1 I cry more now than I used to.
 - 2 I cry all the time now.
 - 3 I used to be able to cry, but now I can't cry even though I want to.

11.
 0 I am no more irritated by things than I ever was.
 1 I am slightly more irritated now than usual.
 2 I am quite annoyed or irritated a good deal of the time.
 3 I feel irritated all the time.
12.
 0 I have not lost interest in other people.
 1 I am less interested in other people than I used to be.
 2 I have lost most of my interest in other people.
 3 I have lost all of my interest in other people.
13.
 0 I make decisions about as well as I ever could.
 1 I put off making decisions more than I used to.
 2 I have greater difficulty in making decisions more than I used to.
 3 I can't make decisions at all anymore.
14.
 0 I don't feel that I look any worse than I used to.
 1 I am worried that I am looking old or unattractive.
 2 I feel there are permanent changes in my appearance that make me look unattractive
 3 I believe that I look ugly.
15.
 0 I can work about as well as before.
 1 It takes an extra effort to get started at doing something.
 2 I have to push myself very hard to do anything.
 3 I can't do any work at all.
16.
 0 I can sleep as well as usual.
 1 I don't sleep as well as I used to.
 2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
 3 I wake up several hours earlier than I used to and cannot get back to sleep.
17.
 0 I don't get more tired than usual.
 1 I get tired more easily than I used to.
 2 I get tired from doing almost anything.
 3 I am too tired to do anything.
18.
 0 My appetite is no worse than usual.
 1 My appetite is not as good as it used to be.
 2 My appetite is much worse now.
 3 I have no appetite at all anymore.
19.
 0 I haven't lost much weight, if any, lately.
 1 I have lost more than five pounds.
 2 I have lost more than ten pounds.
 3 I have lost more than fifteen pounds.

- 20.
- 0 I am no more worried about my health than usual.
 - 1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
 - 2 I am very worried about physical problems and it's hard to think of much else.
 - 3 I am so worried about my physical problems that I cannot think of anything else.
- 21.
- 0 I have not noticed any recent change in my interest in sex.
 - 1 I am less interested in sex than I used to be.
 - 2 I have almost no interest in sex.
 - 3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score _____	Levels of Depression
1-10 _____	These ups and downs are considered normal
11-16 _____	Mild mood disturbance
17-20 _____	Borderline clinical depression
21-30 _____	Moderate depression
31-40 _____	Severe depression
over 40 _____	Extreme depression

http://www.med.navy.mil/sites/NMCP2/PatientServices/SleepClinicLab/Documents/Beck_Depression_Inventory.pdf

Annex 3 - Inventario de Depresión de Beck (BDI-2)

Inventario de Depresión de Beck (BDI-2)

Nombre:..... Estado Civil..... Edad:..... Sexo.....
Ocupación Educación:..... Fecha:.....

Instrucciones: Este cuestionario consta de 21 grupos de afirmaciones. Por favor, lea con atención cada uno de ellos cuidadosamente. Luego elija uno de cada grupo, el que mejor describa el modo como se ha sentido **las últimas dos semanas, incluyendo el día de hoy**. Marque con un círculo el número correspondiente al enunciado elegido. Si varios enunciados de un mismo grupo le parecen igualmente apropiados, marque el número más alto. Verifique que no haya elegido más de uno por grupo, incluyendo el ítem 16 (cambios en los hábitos de Sueño) y el ítem 18 (cambios en el apetito)

1. Tristeza

- 0 No me siento triste.
- 1 Me siento triste gran parte del tiempo
- 2 Me siento triste todo el tiempo.
- 3 Me siento tan triste o soy tan infeliz que no puedo soportarlo.

2. Pesimismo

- 0 No estoy desalentado respecto del mi futuro.
- 1 Me siento más desalentado respecto de mi futuro que lo que solía estarlo.
- 2 No espero que las cosas funcionen para mí.
- 3 Siento que no hay esperanza para mi futuro y que sólo puede empeorar.

3. Fracaso

- 0 No me siento como un fracasado.
- 1 He fracasado más de lo que hubiera debido.
- 2 Cuando miro hacia atrás, veo muchos fracasos.
- 3 Siento que como persona soy un fracaso total.

4. Pérdida de Placer

- 0 Obtengo tanto placer como siempre por las cosas de las que disfruto.
- 1 No disfruto tanto de las cosas como solía hacerlo.
- 2 Obtengo muy poco placer de las cosas que solía disfrutar.
- 3 No puedo obtener ningún placer de las cosas de las que solía disfrutar.

5. Sentimientos de Culpa

- 0 No me siento particularmente culpable.
- 1 Me siento culpable respecto de varias cosas que he hecho o que debería haber hecho.

- 2 Me siento bastante culpable la mayor parte del tiempo.
- 3 Me siento culpable todo el tiempo.

6. Sentimientos de Castigo

- 0 No siento que este siendo castigado
- 1 Siento que tal vez pueda ser castigado.
- 2 Espero ser castigado.
- 3 Siento que estoy siendo castigado.

7. Disconformidad con uno mismo.

- 0 Siento acerca de mí lo mismo que siempre.
- 1 He perdido la confianza en mí mismo.
- 2 Estoy decepcionado conmigo mismo.
- 3 No me gusta a mí mismo.

8. Autocrítica

- 0 No me critico ni me culpo más de lo habitual
- 1 Estoy más crítico conmigo mismo de lo que solía estarlo
- 2 Me critico a mí mismo por todos mis errores
- 3 Me culpo a mí mismo por todo lo malo que sucede.

9. Pensamientos o Deseos Suicidas

- 0 No tengo ningún pensamiento de matarme.
- 1 He tenido pensamientos de matarme, pero no lo haría
- 2 Querría matarme
- 3 Me mataría si tuviera la oportunidad de hacerlo.

10. Llanto

- 0 No lloro más de lo que solía hacerlo.
- 1 Lloro más de lo que solía hacerlo
- 2 Lloro por cualquier pequeñez.
- 3 Siento ganas de llorar pero no puedo.

11 Agitación

- 0 No estoy más inquieto o tenso que lo habitual.
- 1 Me siento más inquieto o tenso que lo habitual.
- 2 Estoy tan inquieto o agitado que me es difícil quedarme quieto
- 3 Estoy tan inquieto o agitado que tengo que estar siempre en movimiento o haciendo algo.

12 Pérdida de Interés

- 0 No he perdido el interés en otras actividades o personas.
- 1 Estoy menos interesado que antes en otras personas o cosas.
- 2 He perdido casi todo el interés en otras personas o cosas.
- 3. Me es difícil interesarme por algo.

13. Indecisión

- 0 Tomo mis propias decisiones tan bien como siempre.
- 1 Me resulta más difícil que de costumbre tomar decisiones
- 2 Encuentro mucha más dificultad que antes para tomar decisiones.
- 3 Tengo problemas para tomar cualquier decisión.

14. Desvalorización

- 0 No siento que yo no sea valioso
- 1 No me considero a mi mismo tan valioso y útil como solía considerarme
- 2 Me siento menos valioso cuando me comparo con otros.
- 3 Siento que no valgo nada.

15. Pérdida de Energía

- 0 Tengo tanta energía como siempre.
- 1. Tengo menos energía que la que solía tener.
- 2. No tengo suficiente energía para hacer demasiado
- 3. No tengo energía suficiente para hacer nada.

16. Cambios en los Hábitos de Sueño

- 0 No he experimentado ningún cambio en mis hábitos de sueño.
- 1^a. Duermo un poco más que lo habitual.
- 1b. Duermo un poco menos que lo habitual.
- 2a Duermo mucho más que lo habitual.
- 2b. Duermo mucho menos que lo habitual
- 3^a. Duermo la mayor parte del día
- 3b. Me despierto 1-2 horas más temprano y no puedo volver a dormirme

17. Irritabilidad

- 0 No estoy tan irritable que lo habitual.
- 1 Estoy más irritable que lo habitual.
- 2 Estoy mucho más irritable que lo habitual.
- 3 Estoy irritable todo el tiempo.

18. Cambios en el Apetito

- 0 No he experimentado ningún cambio en mi apetito.
- 1^a. Mi apetito es un poco menor que lo habitual.
- 1b. Mi apetito es un poco mayor que lo habitual.
- 2a. Mi apetito es mucho menor que antes.
- 2b. Mi apetito es mucho mayor que lo habitual
- 3^a. No tengo apetito en absoluto.
- 3b. Quiero comer todo el día.

19. Dificultad de Concentración

- 0 Puedo concentrarme tan bien como siempre.
- 1 No puedo concentrarme tan bien como habitualmente
- 2 Me es difícil mantener la mente en algo por mucho tiempo.
- 3 Encuentro que no puedo concentrarme en nada.

20. Cansancio o Fatiga

0 No estoy más cansado o fatigado que lo habitual.

1 Me fatigo o me canso más fácilmente que lo habitual.

2 Estoy demasiado fatigado o cansado para hacer muchas de las cosas que solía hacer.

3 Estoy demasiado fatigado o cansado para hacer la mayoría de las cosas que solía hacer.

21. Pérdida de Interés en el Sexo

0 No he notado ningún cambio reciente en mi interés por el sexo.

1 Estoy menos interesado en el sexo de lo que solía estarlo.

2 Estoy mucho menos interesado en el sexo.

3 He perdido completamente el interés en el sexo.

Puntaje Total:

Annex 4 – Generalized Anxiety Disorder 7 (GAD-7)

GAD-7

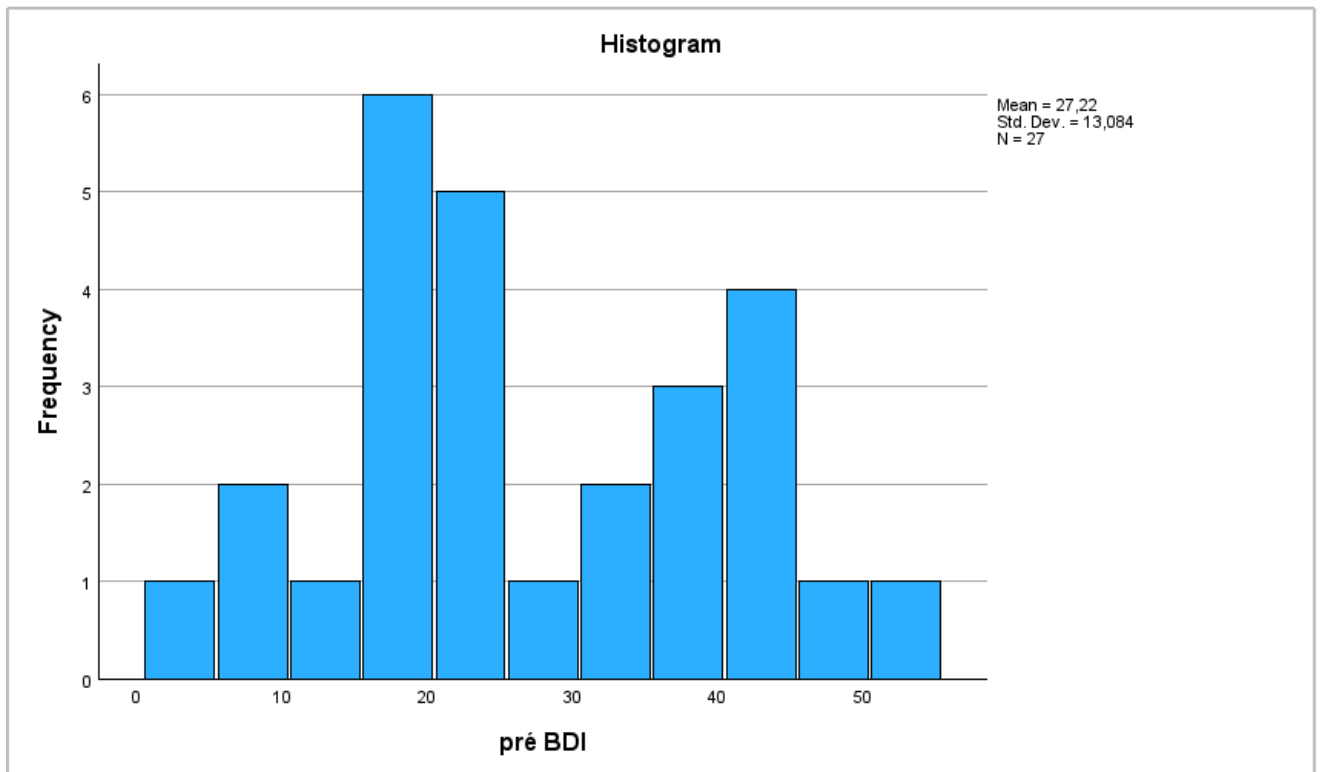
Over the <u>last 2 weeks</u> , how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	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

Annex 5 - Escala de Ansiedad Generalizada

GAD-7				
Durante las últimas 2 semanas, ¿qué tan seguido ha tenido molestias debido a los siguientes problemas?	Ningún día	Varios días	Más de la mitad de los días	Casi todos los días
<i>(Marque con un " " para indicar su respuesta)</i>				
1. Se ha sentido nervioso(a), ansioso(a) o con los nervios de punta	0	1	2	3
2. No ha sido capaz de parar o controlar su preocupación	0	1	2	3
3. Se ha preocupado demasiado por motivos diferentes	0	1	2	3
4. Ha tenido dificultad para relajarse	0	1	2	3
5. Se ha sentido tan inquieto(a) que no ha podido quedarse quieto(a)	0	1	2	3
6. Se ha molestado o irritado fácilmente	0	1	2	3
7. Ha tenido miedo de que algo terrible fuera a pasar	0	1	2	3
(For office coding: Total Score T ___ = ___ + ___ + ___)				

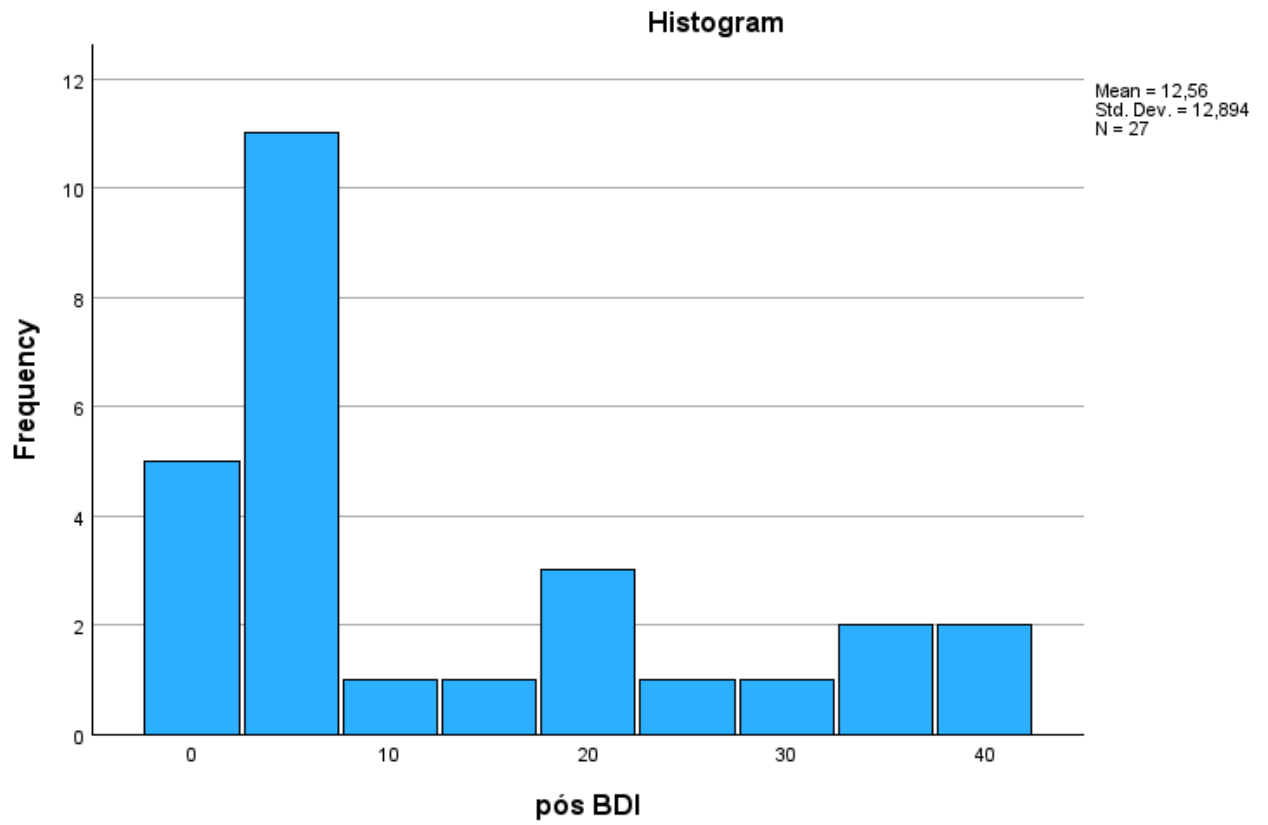
Annex 6 - Histogram of the normal distribution of the variable BDI-II pre-treatment.

pré BDI



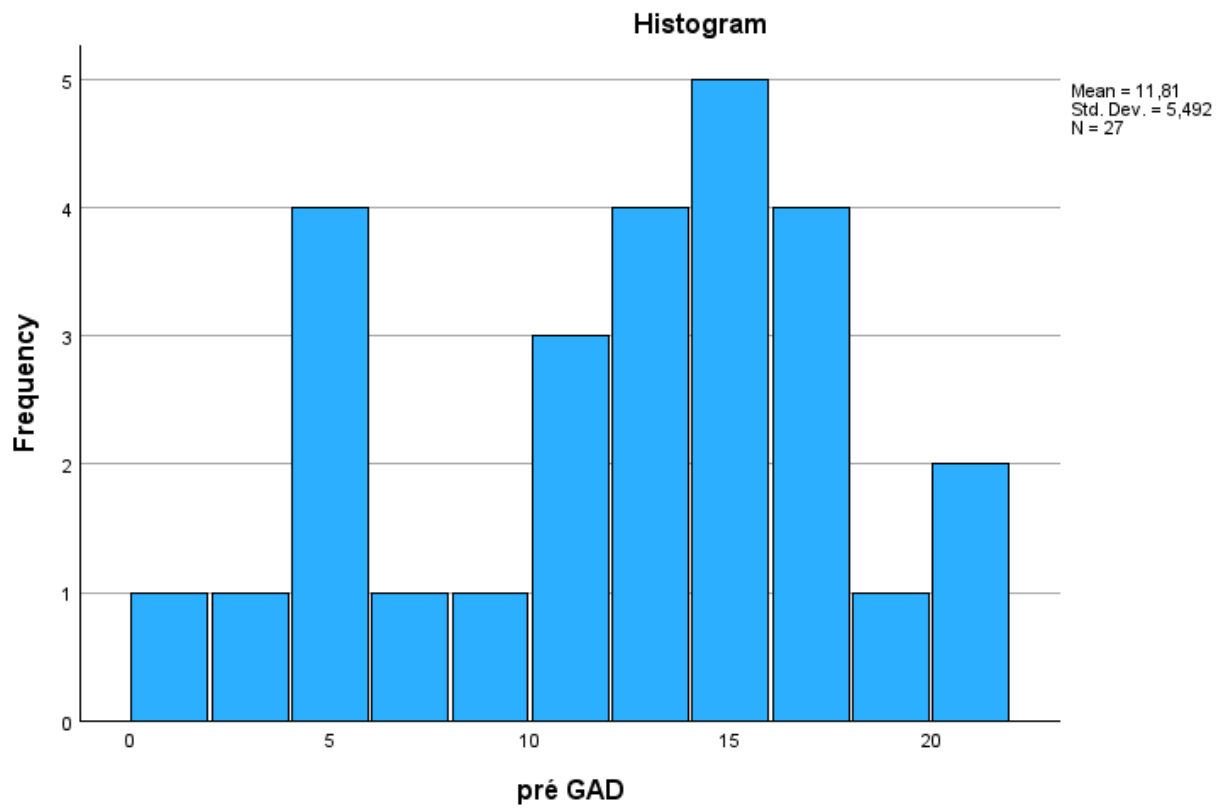
Annex 7 - Histogram of the normal distribution of the variable BDI-II post-treatment.

pós BDI



Annex 8 - Histogram of the normal distribution of the variable GAD-7 pre-treatment.

pré GAD



Annex 9 - Histogram of the normal distribution of the variable GAD-7 post-treatment.

pós GAD

