Artigo de Revisão

v. 4 n. 3 (2023)
ISSN: 2675-8008
Revista Multidisciplinar em Saúde

ACESSO ABERTO

Data de Recebimento:
07/06/2023

Data de Aceite:
07/07/2023

Data de Publicação:
18/07/2023

Autor correspondente:
Rodrigo Cé,
biorodce@gmail.com

Citação:
SILVA, B. E. R. SILVA, J. R. CÉ, R. Exploring the efficacy of psychotropic drug combinations for covid-19 depression: a comprehensive review of literature. **Revista Multidisciplinar em Saúde**, v. 4, n. 2, 2023. https://doi.org/10.51161/integrar/rems/3807

[#] The manuscript's development witnessed equal contributions from both authors, Silva, B. E. R and Silva, J. R.

EXPLORING THE EFFICACY OF PSYCHOTROPIC DRUG COMBINATIONS FOR COVID-19 DEPRESSION: A COMPREHENSIVE REVIEW OF LITERATURE

Bruna Evandra Resende Silva[1]; Jardison Rocha Silva[2]; Rodrigo Cé [3*]

[1] Discente do Curso de Medicina, Universidade Federal do Sul da Bahia – UFSB, Teixeira de Freitas, BA, Brazil.

[2] Discente do Curso de Medicina, Universidade Federal do Piauí – UFPI, Teresina, PI, Brazil.

[3] Doutor em Ciências Farmacêuticas, Universidade Federal do Rio Grande do Sul – UFRGS, Porto Alegre, RS, Brazil.

ABSTRACT

Introduction: Psychotropic drugs have become increasingly significant during the COVID-19 pandemic due to their effectiveness in addressing neuropsychiatric symptoms. **Objectives:** This literature review aims to explore the effectiveness of combining vortioxetine, ketamine, bromazepam, and alprazolam in treating depression associated with COVID-19. **Methodology:** The study adopts a qualitative and quantitative research approach. Literature searches were conducted on scientific databases, including PUBMED, web of science, and electronic journals. Data were collected using keyword combinations related to vortioxetine, ketamine, bromazepam, and alprazolam in the treatment of depression during the COVID-19 pandemic. Selected articles were analyzed using thematic analysis. **Results and Discussion:** The mind-brain interface plays a crucial role in understanding psychological illnesses and their treatment. The COVID-19 pandemic has had a significant negative impact on mental health, leading to an increased utilization of psychotropic drugs. Vortioxetine, ketamine, bromazepam, and alprazolam have shown potential benefits in the treatment of depression associated with COVID-19. In additional, understanding the pharmacokinetic profiles and mechanisms of action of these drugs is essential for healthcare professionals to appropriately prescribe and monitor their use in patients. **Conclusion:** Combining vortioxetine, ketamine, bromazepam, and alprazolam may offer an effective treatment approach for depression associated with COVID-19. However, more research is required to determine the optimal dosages, potential risks, and long-term effects of this combination therapy.

Keyword: Vortioxetine; Ketamine; Bromazepam; Alprazolam; COVID-19.

RESUMO

Introdução: As drogas psicotrópicas tornaram-se cada vez mais significativas durante a pandemia de COVID-19 devido à sua eficácia no tratamento de sintomas neuropsiquiátricos. **Objetivos:** Esta revisão da literatura visa explorar a eficácia da combinação de vortioxetina, cetamina, bromazepam e alprazolam no tratamento da depressão associada ao COVID-19. **Metodologia:** O estudo adota uma abordagem de pesquisa qualitativa e quantitativa. Pesquisas bibliográficas foram realizadas em bancos de dados científicos, incluindo

DOI: 10.51161/integrar/rems/3807

PUBMED, web of science e revistas eletrônicas. Os dados foram coletados usando combinações de palavras-chave relacionadas a vortioxetina, cetamina, bromazepam e alprazolam no tratamento da depressão durante a pandemia de COVID-19. Os artigos selecionados foram analisados por meio da análise temática. **Resultados e Discussão:** A interface mente-cérebro desempenha um papel crucial na compreensão das doenças psicológicas e seu tratamento. A pandemia de COVID-19 teve um impacto negativo significativo na saúde mental, levando a um aumento da utilização de drogas psicotrópicas. A vortioxetina, cetamina, bromazepam e alprazolam mostraram benefícios potenciais no tratamento da depressão associada ao COVID-19. Além disso, entender os perfis farmacocinéticos e os mecanismos de ação desses medicamentos é essencial para que os profissionais de saúde prescrevam e monitorem adequadamente seu uso em pacientes. **Conclusão:** A combinação de vortioxetina, cetamina, bromazepam e alprazolam pode oferecer uma abordagem de tratamento eficaz para a depressão associada ao COVID-19. No entanto, mais pesquisas são necessárias para determinar as dosagens ideais, os riscos potenciais e os efeitos a longo prazo dessa terapia combinada.

Palavras-chave: Vortioxetina; Cetamina; Bromazepam; Alprazolam; COVID-19.

1 INTRODUÇÃO

Psychotropics are substances that exert an influence on the central nervous system, causing changes in behavior, mood, and cognition. These medications are classified into various groups, such as antidepressants, antipsychotics, anxiolytics, anticonvulsants, and mood stabilizers. Although they were already widely used before the SARS-CoV-2 pandemic, their significance has become even more evident during this time. They have demonstrated their effectiveness in addressing the neuropsychiatric symptoms resulting from the disease, as well as exhibiting antioxidative and anti-inflammatory effects (JANSEN VAN VUREN et al., 2021; JONES, MITRA, BHUIYAN, 2021; PRADO et al., 2017).

Vortioxetine, an antidepressant with multiple mechanisms of action, has demonstrated efficacy in improving cognitive and physical symptoms in individuals with depression (ORSOLINI et al., 2017). Additionally, vortioxetine possesses anti-inflammatory and immunomodulatory properties (TALMON et al., 2018). Ketamine, an anesthetic drug, exhibits antidepressant properties and is particularly effective in treating resistant cases of depression. It is known for its rapid onset of action and its ability to alleviate suicidal ideation (ZANOS & GOULD, 2018). Bromazepam and alprazolam, both high-potency benzodiazepines, are prescribed for short-term relief of excessive anxiety symptoms, mood disorders, schizophrenia, and other conditions (MACHADO et al., 2005; NASIR, 2020).

In this context, the purpose of this literature review is to explore the effectiveness of combining psychotropic drugs, including vortioxetine, ketamine, bromazepam, and alprazolam, in the treatment of depression associated with COVID-19. Vortioxetine functions as a selective serotonin reuptake inhibitor (SSRI), ketamine acts as an N-methyl-D-aspartate (NMDA) receptor antagonist, and bromazepam and alprazolam are benzodiazepines recognized for their anxiolytic properties. Furthermore, psychotropic drugs are commonly utilized to address mental illnesses by targeting chemical imbalances in the brain that contribute to the development of these disorders.

2 METHODOLOGY

The methodology of this literature research involves both qualitative and quantitative approaches, with a focus on the topic of “exploring the potential benefits and risks of combining vortioxetine, ketamine, bromazepam, and alprazolam in the treatment of depression during the COVID-19

pandemic." To this end, searches were conducted on various scientific data platforms, including the U.S. National Library of Medicine's Portal (PUBMED, web of science, Scientific Electronic Library Online (SCIELO, and electronic journals relevant to this topic for the qualitative research, while for the quantitative research, data were collected using keyword combinations such as "vortioxetine, vortioxetine and depression, vortioxetine and depression and COVID-19; ketamine, ketamine and depression, ketamine and depression and COVID-19; bromazepam, bromazepam and depression, bromazepam and depression and COVID-19; alprazolam, alprazolam and depression, alprazolam and depression and COVID-19". The selected articles underwent a screening process to ensure that they met the inclusion criteria, which involved examining the titles, abstracts, and full texts of each article. The articles that were deemed relevant and of high quality were then included in the study. The data were then analyzed using a thematic analysis approach, where the data were coded and grouped into themes based on their similarities and differences. The findings of the literature review and the qualitative survey were then integrated and analyzed to provide a comprehensive understanding of the potential benefits and risks of the combination of vortioxetine, ketamine, bromazepam, and alprazolam in the treatment of depression during the COVID-19 pandemic.

3 RESULTS AND DISCUSSION

3.1 The importance of the mind-brain interface in clinical contexts

The relationship between the brain and the mind is crucial in understanding psychological illnesses and their treatment. The brain is a complex network of neurons that communicate through electrical and chemical signals, while the mind is the subjective experience of thoughts, emotions, and perceptions resulting from these neural connections. Although once viewed as separate entities, the materialist perspective now recognizes their complementarity, where the brain sustains mental states, and the mind influences neuronal states to regulate them (GLANNON, 2015; SALONE et al., 2016).

The close interaction between the mental and neural levels means that changes or impairments in one can affect the other (FRIEDRICH, 2014. For example, environmental factors such as stress, emotions, and beliefs can trigger responses through the activation of specific brain systems, which can be adaptive or harmful. These responses are expressed through interactions with other body systems, such as the autonomic nervous system and the endocrine system (STECK & STECK, 2016).

Such factors can result in cognitive and mood impairments by triggering chemical reactions in the body that lead to brain hyperactivity (GLANNON, 2015. This process is linked to the development of psychological disorders. Thus, understanding the interface between the brain and the mind is crucial for developing effective treatments.

Recent studies have shown the potential of approaches such as brain-computer interface and neurofeedback therapy, which increase neural plasticity and reduce brain hyperactivity (GLANNON, 2015. Additionally, cognitive-behavioral therapy reframes emotions, and understanding neural circuits enables realistic expectations for pharmacological effects on the neuronal system (LEDOUX & PINHEIRO, 2016. These approaches represent significant advances in the field, allowing for more personalized and targeted interventions for the treatment of psychological illnesses.

3.2 Effects of the pandemic on mental health

The COVID-19 pandemic, which emerged towards the end of 2019, is a highly contagious disease that causes severe pneumonia and respiratory failure, resulting in numerous fatalities worldwide. In order to mitigate its impact, the World Health Organization has implemented measures such as the use of masks, strengthening healthcare systems, and social distancing. However, social isolation has had a significant negative impact on the mental health of people worldwide (JONES, MITRA, BHUIYAN, 2021).

The closure of schools and universities, which limited social contact with peers, has had a particularly adverse effect on children and adolescents. The sudden cessation of social interactions has resulted in the manifestation of psychopathological symptoms, physical health problems, and depression among parents who observe their children struggling in this context (NEARCHOU et al., 2020). The elderly population has faced even more complex repercussions due to the natural reduction in the circle of friends at their age and unfamiliarity with technology. This has led to problems such as irritability, cognitive decline, and panic disorder (BANERJEE, 2020; CHEN et al., 2021).

The psychological impact of the pandemic is not only related to the fear of contracting the disease, but also to the feelings of loneliness and stigma associated with infected individuals. These can lead to the development of post-traumatic disorders (CHEN et al., 2021). Moreover, the high number of deaths and the inability to bid farewell or seek comfort during the mourning process can trigger psychological vulnerabilities, such as depression, insomnia, and fear (AFONSO, 2020).

3.3 The influence of the pandemic on the utilization of psychotropic drugs

Psychotropic drugs (Fig.1) are defined by the World Health Organization (WHO) as substances that alter behavior, mood, and cognition by acting on the central nervous system. These drugs include antidepressants, tranquilizers, and hallucinogens that target psychological function. The use of psychotropic medications has increased significantly due to advances in psychiatric diagnoses, the emergence of new drugs, and new indications for existing medications. The COVID-19 pandemic has further exacerbated the need for psychotropic drugs, as it has negatively impacted the mental health of the general population (PRADO et al., 2017; BENISTAND et al., 2022).

Several studies conducted worldwide indicate an increase in the consumption of psychotropic drugs during the pandemic. In a study by Benistad et al. (2022), the authors demonstrated an increase in the delivery of psychotropic drugs in municipal pharmacies during the 18 months following the onset of the pandemic compared to the previous five years. In another study, patients with post-COVID-19 episodes treated with vortioxetine as part of an integrated therapeutic approach showed a significant reduction in the physical and cognitive symptoms of depression, along with a decrease in depressive symptoms and a substantial rate of clinical remission. Similar improvements were observed in anxiety, anhedonia, sleep, global functioning, quality of life, and inflammatory indices (DI NICOLA et al., 2023).

An unexpected result was the rise in the prevalence of antidepressant and antipsychotic use in most age groups and genders during the last quarter of 2020, with a higher increase observed in females and the elderly, consistent with a prior Canadian study on nursing home residents (AVERY et al., 2021). Notably, there was a similar proportionate increase in the delivery of antidepressants, anxiolytics, and hypnotics. Self-reported questionnaires or medical interview-based epidemiological surveys have already revealed the detrimental effects of the COVID-19 pandemic on mental health (YUAN et al., 2021; OZAMIZ-

ETXEBARRIA et al., 2020; MAZZA et al., 2020), and a surge in stress-related medication delivery has been shown following a traumatic or stressful event impacting the general population (MOTREFF et al., 2013; BARCELÓ et al., 2016). Numerous studies conducted since the onset of the pandemic have demonstrated a rise in anxiety, stress, and depression symptoms, directly linked to the health crisis (CÉNAT et al., 2020; LI et al., 2020; JIN et al., 2021).

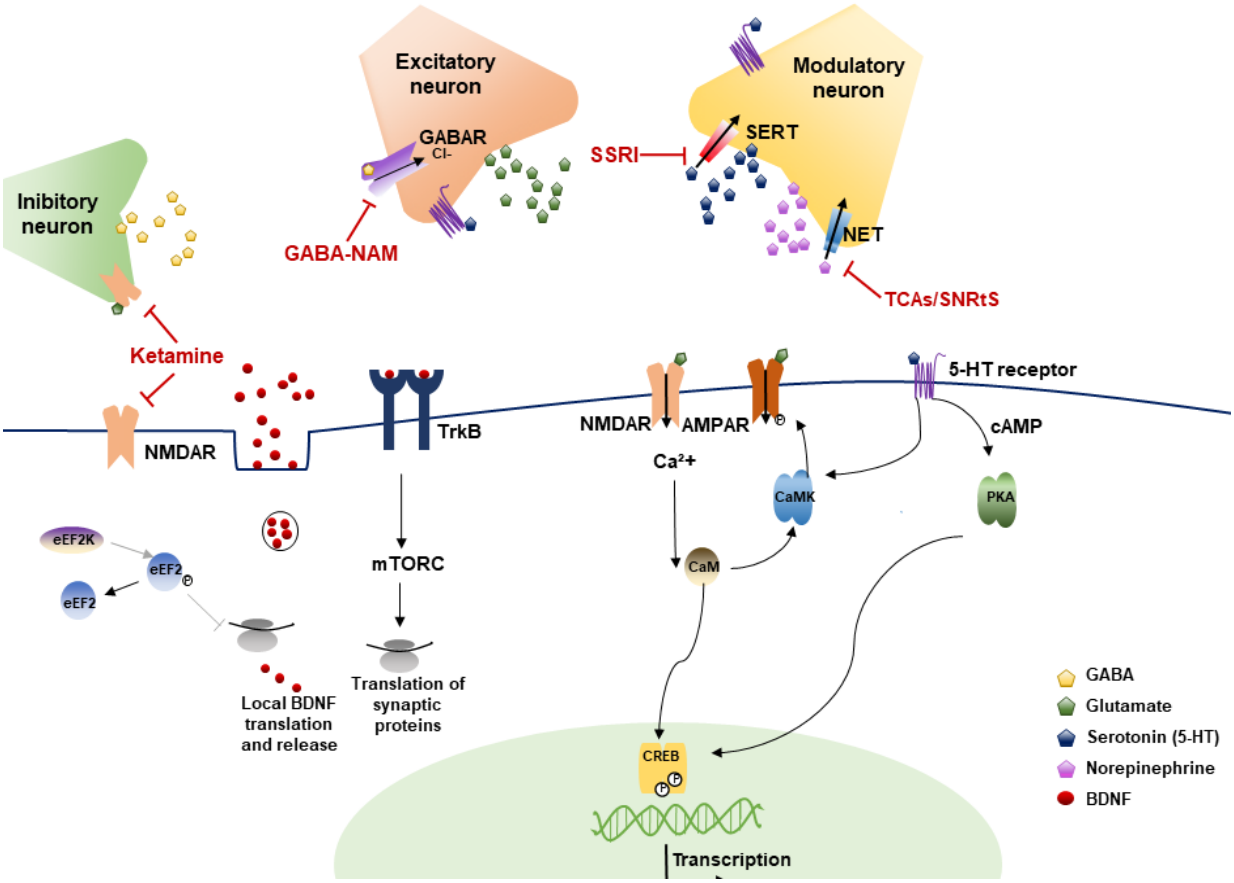


Figure 1. The schematic depicts the proposed mechanisms of action for antidepressants at the synapse level. To simplify, serotonin and norepinephrine are represented together. Ketamine is believed to work through two mechanisms, both of which are illustrated. The first mechanism involves blocking extrasynaptic NMDA receptors, which leads to the repression of eEF2 kinase and dephosphorylation of eEF2. This disinhibits the translation of BDNF, facilitating its synthesis. The second mechanism entails blocking NMDA receptors on inhibitory neurons, resulting in increased excitation, release of BDNF, and activation of mTOR via a TrkB-dependent signaling cascade. GABA-NAMs function as negative allosteric modulators of GABA receptors containing the alpha5 subunit. This modulation increases excitation and promotes activity-dependent synaptic strengthening. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) work by blocking the reuptake of serotonin, thereby elevating its synaptic concentration. This increased concentration leads to enhanced activation of serotonin receptors, promoting the activation of CaMK and PKA signaling pathways. Ultimately, this process leads to increased synaptic strength through transcriptional and post-translational modifications. For a more in-depth understanding of the antidepressant mechanism of action, additional information can be found in the publication (LEGATES, KVARTA, THOMPSON, 2019) “Neuropsychopharmacology” (2019) 44:140–154, accessible at https://doi.org/10.1038/s41386-018-0156-z.

3.4 Pharmacological targets as the focus of psychotropic drug perspectives: vortioxetine, ketamine, bromazepam, and alprazolam

3.4.1 Vortioxetine

Vortioxetine (Tab.1) is a type of multimodal antidepressant that works by inhibiting transmitter reuptake and interacting with different 5-HT receptor sites (ZOHAR et al., 2015). Vortioxetine has a complex mechanism of action as a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and an inhibitor of the serotonin transporter (SANCHEZ et al., 2015). By blocking 5-HT3 and 5-HT7 receptors, it is believed to activate the glutamatergic system in the rat frontal cortex. A study has found that vortioxetine has better efficacy in treating visuospatial memory and depression-like behavior in aged mice compared to fluoxetine (LI et al., 2015). Clinical studies have shown that vortioxetine has antidepressant properties and positive effects on cognitive function, such as memory and executive functioning, which is consistent with its pharmacodynamic profile (THASE et al., 2016).

After oral administration, Vortioxetine is slowly absorbed with an absolute bioavailability of 75%, and its pharmacokinetics are not influenced by food intake. It reaches maximum plasma concentration at 7-11 hours and has a half-life of 57 hours (AL-SUKHNI et al., 2015). Vortioxetine primarily undergoes renal excretion, and its main metabolite is pharmacologically inactive (AL-SUKHNI et al., 2015; ALVAREZ et al., 2014). As an inhibitor of serotonin transporters (SERT), vortioxetine exhibits a high affinity for SERTs (ANDERSEN et al., 2015) and 5HT3 receptors. However, it should be noted that low doses of vortioxetine will inhibit these receptors, while higher doses are required to occupy all of them (ALVAREZ et al., 2014). Nausea, headache, and dizziness were the most frequently reported adverse events that emerged during treatment with vortioxetine (D'AGOSTINO et al., 2015).

3.4.2 Ketamine

Ketamine (Tab.1) is a mixture of (S)-ketamine and (R)-ketamine and is widely used as an anesthetic agent, for analgesia, and to treat depression (JELEN, YONG, STONE, 2020). It acts on various receptors, including mu-opioid and serotonergic receptors, but its primary mechanism of action is as an antagonist of the N-methyl-D-Aspartate (NMDAR) receptor, resulting in increased excitatory glutamatergic transmission (ABDALLAH et al., 2015; NOGUEIRA, 2020). Ketamine also promotes the release of brain-derived neurotrophic factor (BNFG), which enhances neuronal maturation and synaptic plasticity (ABDALLAH et al., 2015).

Ketamine is usually given intravenously but can also be administered intramuscularly, rectally, and orally (GOODMAN & GILMAN, 2012). Its high liposolubility and low degree of plasma protein binding facilitate quick absorption and diffusion into highly vascularized organs like the brain (FLETCHER, 2002). Ketamine is metabolized in the liver through the cytochrome P450 system, producing two metabolites: norketamine and dehydronorketamine, with norketamine being the primary excreted metabolite in urine (GALES & MAXWELL, 2018; KATZUNG, 2017).

Ketamine interacts significantly with sedatives, hypnotics, and antidepressants and is often combined with propofol during procedural sedation and analgesia (PSA) to minimize adverse effects (ZAKI et al., 2022). However, ketamine may cause adverse effects such as increased heart rate, systemic blood pressure, and cardiac output due to central sympathetic stimulation and depression of the right myocardium (KATZUNG,

2017). In the nervous system, ketamine induces a cataleptic state characterized by salivation, spontaneous limb movements, nystagmus with pupil dilation, and an overall increase in muscle tone (GOODMAN & GILMAN, 2012).

3.4.3 Bromazepam

Bromazepam (Tab.1) is a benzodiazepine drug used widely to treat psychiatric conditions such as anxiety, insomnia, and psychomotor disorders (DAVIES, 2007). Its mechanism of action involves interacting with GABA-A receptors, reducing brain activity in the central nervous system, resulting in a feeling of relaxation and tranquility (RUDOLPH & KNOFLACH, 2011). This drug counters the increase in glutamatergic transmission associated with anxiety disorders by providing GABAergic inhibition, which changes the membrane potential and increases the conductance of the postsynaptic membrane (NASIR, 2020).

After oral administration, bromazepam is rapidly absorbed, with a plasma peak reached after 1-3 hours. Due to its high solubility, it has a high binding capacity to plasma proteins and accumulates in adipose tissue. It undergoes metabolism in the liver through cytochrome P450, particularly CYP3A4, and is eliminated through the urinary route without generating active metabolites (DAVIES, 2007).

Bromazepam can interact with other drugs, such as antidepressants, anticonvulsants, non-barbiturate hypnotics, and alcohol, leading to potentiation of their effects. Drinking alcohol increases the activity of the GABA neurotransmitter, intensifying central nervous system depression, while drugs that affect cytochrome P450 interfere with bromazepam's metabolism, potentially amplifying adverse effects (SANTOS, 2022). Common adverse effects of bromazepam include drowsiness, mental confusion, dizziness, diplopia, mild respiratory depression, and ataxia (SANTOS, 2022; MEYLER, 2016).

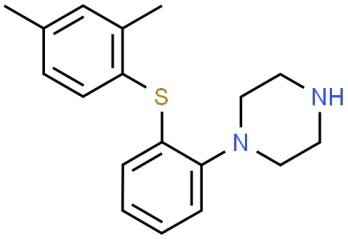
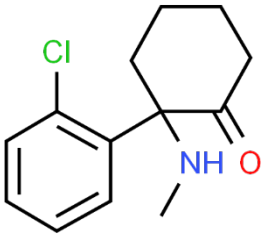
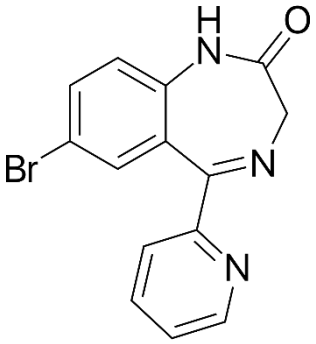
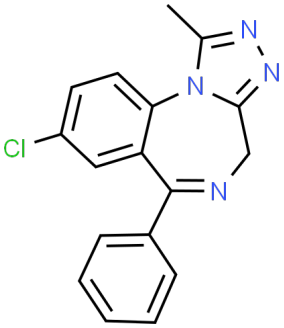
3.4.4 Alprazolam

Alprazolam (Tab.1) is not only the most commonly prescribed benzodiazepine, but it is also the most commonly prescribed psychotropic medication in the United States. Alprazolam is a high-potency triazolobenzodiazepine that is approved by the US Food and Drug Administration (FDA) for treating anxiety and panic disorders. Its primary metabolites are 4 and α-hydroxyalprazolam, and it is metabolized by cytochrome P450 (CYP) 3A4 (AIT-DAOUD et al., 2018; GREENBLATT & WRIGHT, 1993).

Alprazolam is classified as a benzodiazepine, which is a class of psychoactive medications that bind to the GABA-A receptor. The benzodiazepine binding site is between the alpha-1 and gamma-2 subunits of this receptor. By enhancing the effects of gamma-aminobutyric acid (GABA), benzodiazepine binding sites appear to couple with GABA-A receptors. The major inhibitory neurotransmitter GABA mediates the calming or inhibitory effects of alprazolam on the human nervous system. A common GABA-A receptor in the CNS consists of two alpha-1 subunits, two beta-2 subunits, and one gamma-2 subunit (IBÁÑEZ et al., 2014; MASIULIS et al., 2019).

Alprazolam is rapidly absorbed after oral administration, with a peak plasma concentration at 1 to 2 hours. Oral alprazolam has an average bioavailability of 80 to 100%, and it can be administered with or without food (GEORGE & TRIPP, 2022). Common adverse effects for patients taking alprazolam include drowsiness, tiredness, dizziness, sleep problems (insomnia), memory problems, and poor balance or coordination (GUINA & MERRILL, 2018).

Table 1. The physicochemical properties of psychotropic drugs.

Active Principle	Chemical Structure	Chemical Formula	MolecularMass (g/mol)	Routes of Administration
Vortioxetine		$C_{18}H_{22}N_2S$	298.44	Oral
Ketamine		$C_{13}H_{16}CINO$	237.72	Intravenous, Intramuscular, Oral, Fecal.
Bromazepam		$C_{14}H_{10}BrN_30$	316.15	Oral
Alprazolam		$C_{17}H_{13}CIN_4$	308.76	Oral

Please note that the chemical structures of the compounds were obtained from the website www.chemspider.com through a free download.

3.5 Recent Scientific Trends and Growing Interest in Vortioxetine, Ketamine, Bromazepam, and Alprazolam: A PubMed Analysis

Additionally, we analyzed the scientific information on vortioxetine (Fig.2/A), ketamine (Fig.2/B), bromazepam (Fig.2/C) and (Fig.2/D) alprazolam that was published recently on the PUBMED platform. To achieve this, we generated graphs that display the number of scientific articles published on these substances over the past five years. Based on our findings, it can be concluded that the number of papers published in recent years on the selected topics has increased. This indicates a growing interest in exploring the therapeutic potential of these substances for various conditions, including depression and COVID-19. It is important to note that while the number of publications has increased, this does not necessarily imply that these substances are effective or safe for treating these conditions. Further research is needed to fully understand the potential benefits and risks of using these substances for therapeutic purposes. Nonetheless, the increase in scientific interest in these substances highlights the need for continued research to uncover their potential therapeutic value.

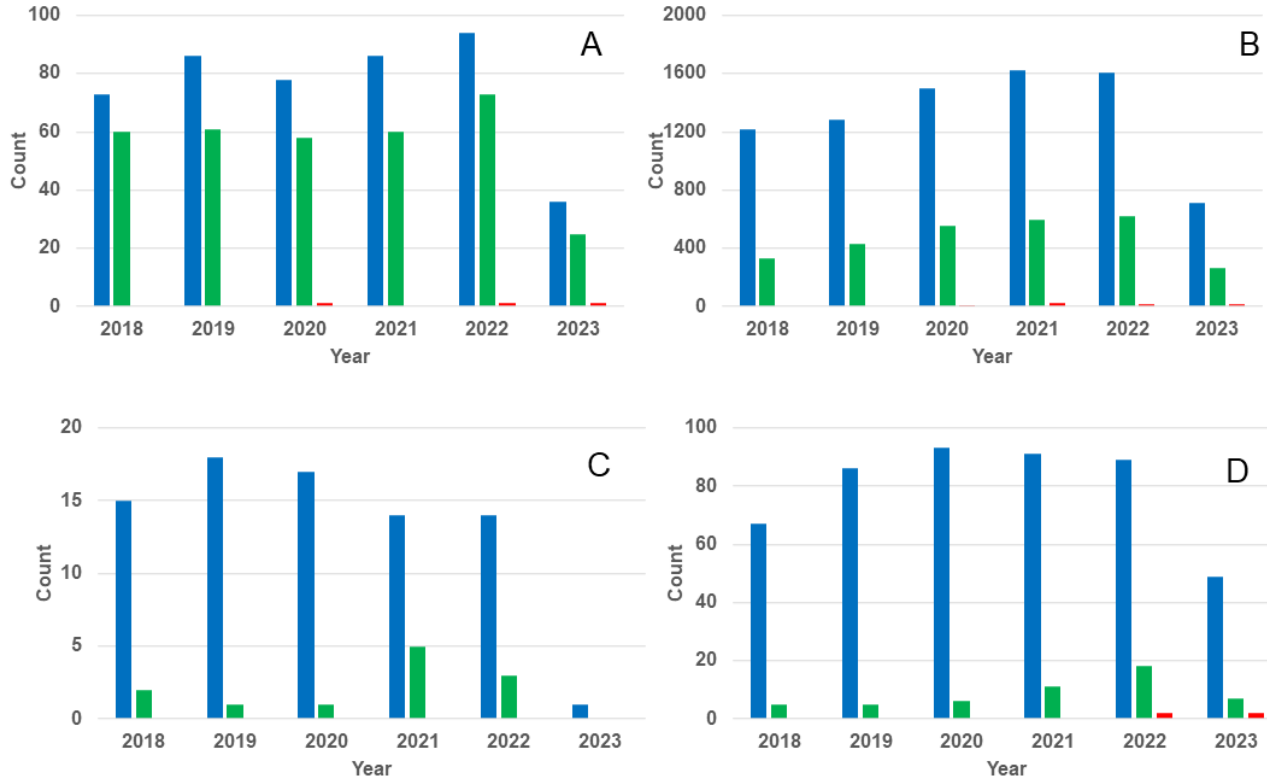


Figure 2. Quantity of documents released on PUBMED that include the keywords vortioxetine (A), ketamine (B), bromazepam (C) and (D) alprazolam. The search was conducted using specific keywords, including (vortioxetine) - with a total of 367 findings, (vortioxetine) AND (depression) - with 269 findings, and ((vortioxetine) AND (depression)) AND (COVID-19) - with only 3 findings (Fig. 2/A); (ketamine) - with a total of 6505 findings, (ketamine) AND (depression) - with 2311 findings, and ((ketamine) AND (depression)) AND (COVID-19) - with 44 findings (Fig. 2/B); (bromazepam) - with a total of 64 findings, (bromazepam) AND (depression) - with only 10 findings, and ((bromazepam) AND (depression)) AND (COVID-19) - with no findings (Fig. 2/C); (alprazolam) - with a total of 385 findings, (alprazolam) AND (depression) - with 45 findings, and ((alprazolam) AND (depression)) AND (COVID-19) - with only 3 findings (Fig.2/D). Note: The graphs use different colors to represent various findings related to the terms mentioned. Specifically, the blue color indicates findings related to “vortioxetine, ketamine, bromazepam,

and alprazolam." The green color represents findings related to "vortioxetine and depression, ketamine and depression, bromazepam and depression, and alprazolam and depression." Lastly, the red color is used to depict findings associated with "vortioxetine and depression and COVID-19, ketamine and depression and COVID-19, bromazepam and depression and COVID-19, and alprazolam and depression and COVID-19." Data was gathered up to May/2023.

3.6 Comprehensive Understanding of the Impact of Psychotropic Drugs

Vortioxetine is an antidepressant with multiple modes of action. It functions as an inhibitor of the serotonin (5HT) transporter, while also acting as an antagonist for the 5HT3A and 5HT7 receptors. Additionally, it acts as a partial agonist for the 5HT1A and 5HT1B receptors. This multimodal antidepressant, known as vortioxetine, has demonstrated efficacy in improving cognitive and physical symptoms in individuals with depression. It possesses a favorable safety and tolerability profile (ORSOLINI et al, 2017; CHRISTENSEN et al, 2018; TALMON et al 2018). Moreover, vortioxetine exhibits anti-inflammatory and immunomodulatory properties (TALMON et al 2018).

Some recent studies have explored the potential of Vortioxetine in the context of the Covid-19 pandemic. Vortioxetine has been shown to enhance physical and cognitive function in patients with depression, and it possesses anti-inflammatory and antioxidant properties. In a retrospective study conducted by Di Nicola (2023), the effects of vortioxetine were evaluated in 80 patients (44.4% men, aged 54±17.2 years) with post-COVID-19 major depressive episodes. These patients received vortioxetine as part of an integrated therapeutic approach. The study found that treatment with vortioxetine resulted in a significant reduction in the physical and cognitive manifestations of depression, accompanied by a decrease in depressive symptoms. Moreover, a substantial proportion of patients achieved clinical remission. Similar improvements were observed in anxiety, anhedonia, sleep quality, global functioning, quality of life, and inflammatory markers. Importantly, the use of vortioxetine was deemed safe and well-tolerated by the patients (DI NICOLA, 2023).

Ketamine, known for its antidepressant, non-barbiturate anesthetic, and anti-inflammatory properties, has been recognized for its effects even prior to the onset of the pandemic. Studies have already demonstrated its efficacy in the treatment of treatment-resistant depression, with notable improvements observed as early as 40 minutes after administration. Notably, research conducted by Murrough et al. in 2013 confirmed the superiority of ketamine over other drugs, such as midazolam, in reducing depressive symptoms. After the first 24 hours, the response rate was 64% for ketamine compared to only 28% for midazolam.

In the context of the COVID-19 pandemic, ketamine has been widely utilized for the treatment of resistant psychological disorders, often serving as a replacement for electroconvulsive therapy (SARMA et al., 2023). A case report by Meha, Suhasy, Rao in 2022 highlighted the efficacy of ketamine in alleviating severe depression with suicidal tendencies that developed post-COVID-19. The study demonstrated a significant decrease in the Montgomery Asberg Depression Rating Scale, corresponding to a remarkable 93.75% reduction after five ketamine infusions. Additionally, ketamine has emerged as the preferred drug for pneumonia cases associated with COVID-19 due to its antidepressant effects as well as its anesthetic properties, which minimize the need for other sedatives and improve hemodynamic stability and respiratory mechanics (WEINBROUM, 2021).

During the pandemic, there has been a notable increase in the consumption of antidepressants

and benzodiazepines. According to the Food and Drug Administration (FDA), in the United States alone, approximately 92 million prescriptions for benzodiazepines were issued in 2019 for the treatment of insomnia, anxiety, and epilepsy (SHAH et al., 2021). In 2020, the General Council of Faculties of Pharmacy reported a 14% rise in the use of antidepressants and anxiolytics compared to 2019 (REMÓN, MORALES, PALOMERO, 2022).

In terms of the specific drug under study, a survey conducted by Remón, Morales, Palomero (2022) revealed that among a sample of 80 individuals, bromazepam was the third most prescribed medication, accounting for 11.25% of prescriptions, with its usage predominantly among females. This finding is supported by Villalobos et al. (2023), whose research focused on psychotropic prescription dispensing in three pharmacies at the main headquarters of Hospital Clínica Bíblica in San José, identifying bromazepam as the most commonly consumed drug in 2019.

Regarding the effectiveness of the specific active ingredient, a study was conducted with 127 patients from Spain who used benzodiazepines, including bromazepam, during the COVID-19 pandemic. The sample consisted of 66.14% women and 33.86% men (with women representing two-thirds of BZD users). Among the ten studied benzodiazepines, lorazepam was the most frequently prescribed, accounting for 25.49% of all dispensing requests, followed by diazepam (14.38%), lormetazepam (14.38%), alprazolam (13.73%), and clorazepate (12.42%). Bromazepam and clonazepam had the lowest percentages of dispensing requests, with 8.50% and 5.88% respectively. Finally, the least prescribed benzodiazepines were ketazolam (1.96%), flurazepam (1.96%), and clobazam (1.31%), indicating their limited use as therapeutic options in the community (ARMAS et al., 2023).

In Brazil, limited literature exists regarding national analyses of the sales patterns of psychotropic drugs, although some studies have examined the prevalence and factors associated with depression or anxiety among health professionals, medical students, and public school teachers during the COVID-19 pandemic (DEL FIOL et al., 2023). In the United States, there has been an increase in cases of diagnosed depression and anxiety among adults, rising from 36% to 41% between August 2020 and February 2021, reflecting the impact of the pandemic on this population (VAHRATIAN et al., 2021). Similarly, visits to psychiatric clinics have also surged during the same period due to the pandemic (HOLLAND et al., 2021).

During the study period, clonazepam, alprazolam, zolpidem, and escitalopram were the most frequently sold psychotropic drugs in Brazil. Joinpoint regression analysis indicated an upward trend in sales for pregabalin, escitalopram, lithium, desvenlafaxine, citalopram, bupropion, and amitriptyline during the pandemic. Overall, there was an increase in the consumption of psychotropic drugs throughout the pandemic, with peak consumption occurring in April 2021, followed by a downward trend that coincided with a decrease in the number of deaths. Furthermore, the study highlighted that the drug alprazolam experienced a 39.03% increase in sales during the pandemic (DEL FIOL et al., 2023).

4 CONCLUSION

In conclusion, this comprehensive literature review examined the effectiveness of combining psychotropic medications for treating COVID-19-related depression. The drugs investigated, including vortioxetine, ketamine, bromazepam, and alprazolam, were found to be effective in managing depression alongside anxiety in patients. Nevertheless, additional research is essential to gain a more comprehensive understanding of their applications, benefits, and overall impact on individuals affected by COVID-19.

Conflict of interest:

The authors affirm that they have no conflicts of interest.

Acknowledgment:

We express our gratitude to the "PROJETO AVANÇAR+ CIENTÍFICO DA EDITORA INTEGRAR 2023.1" for providing the opportunity to undertake this scientific project. This initiative has allowed students to actively engage in scientific education and foster a deeper understanding of the subject matter.

5 REFERENCES

ABDALLAH, C. G.; SANACORA, G.; DUMAN, R. S.; KRYSTAL, J. H. Ketamine and rapid-acting antidepressants: a window into a new neurobiology for mood disorder therapeutics. **Annu Rev Med**. v. 66, p. 509-523, 2015.

AFONSO, P. O Impacto da Pandemia COVID-19 na Saúde Mental [The Impact of the COVID-19 Pandemic on Mental Health]. **Acta Med Port**, v. 33, n. 5, p. 356-357, maio 2020.

AIT-DAOUD, N.; HAMBY, A. S.; SHARMA, S.; BLEVINS, D. A Review of Alprazolam Use, Misuse, and Withdrawal. **J Addict Med**. v. 12, n. 1, p. 4-10, Jan/Feb 2018.

ALSHAMMARI, T. K. The Ketamine Antidepressant Story: New Insights. **Molecules**, v.25, n.23, p.5777, 2020.

ALVAREZ, E.; PEREZ, V.; ARTIGAS, F. Pharmacology and clinical potential of vortioxetine in the treatment of major depressive disorder. **Neuropsychiatr Dis Treat**. v. 10, p. 1297-1307, 2014.

AL-SUKHNI, M.; MARUSCHAK, N. A.; MCINTYRE, R. S. Vortioxetine: a review of efficacy, safety and tolerability with a focus on cognitive symptoms in major depressive disorder. **Expert Opin Drug Saf**. v. 14, p. 1291-1304, 2015.

ANDERSEN, J. et al. Binding of the multimodal antidepressant drug vortioxetine to the human serotonin transporter. **ACS Chem Neurosci**. v. 6, p. 1892-1900, 2015.

ARMAS, D. A. et al. Quality of life assessment in patients using benzodiazepines during the COVID-19 pandemic in a community pharmacy using EuroQol 5D-3L. **Pharmacy**, v. 11, n. 1, p. 19, 2023.

AVERY, A. R.; TSANG, S.; SETO, E. Y. W.; DUNCAN, G. E. Differences in Stress and Anxiety Among Women with and without Children in the Household During the Early Months of the COVID-19 Pandemic. **Front. Public Health**, v. 9, 688462, 2021.

BANERJEE, D. The impact of Covid-19 pandemic on elderly mental health. **Int J Geriatr Psychiatry**, v.35,n.12, p.1466-1467, dez. 2020.

BARCELÓ, M. A.; COLL-NEGRE, M.; COLL-DE-TUERO, G.; SAEZ, M. Effects of the financial crisis on psychotropic drug consumption in a cohort from a semi-urban region in Catalonia, Spain. **PLoS One**, v. 11, e0148594, 2016. BENISTAND, P. et al. Effect of the COVID-19 pandemic on the psychotropic drug consumption. **Front Psychiatry**. v. 13, 1020023, Dec 2022.

BRUNTON, L.L. GOODMAN & GILMAN: As Bases Farmacológicas da Terapêutica. 12ª ed. Rio de Janeiro**: McGraw-Hill**, 2012.

CÉNAT, J. M. et al. Prevalence of mental health problems in populations affected by the ebola virus disease: a systematic review and meta-analysis. **Psychiatry Res**., v. 289, 113033, 2020.
CHEN, P. J. et al. An overview of mental health during the COVID-19 pandemic. **Diagnosis (Berl)**, v.8, n.4, p.403-412, jul. 2021.

CHRISTENSEN, M. C.; FLOREA, I.; LINDSTEN, A.; BALDWIN, D. S. Efficacy of vortioxetine on the physical symptoms of major depressive disorder. **J. Psychopharmacol**., v. 32, n. 10, p. 1086–1097, 2018.

D'AGOSTINO, A.; ENGLISH, C. D.; REY, J. A. Vortioxetine (brintellix): a new serotonergic antidepressant. **P T**, v. 40, n. 1, p. 36-40, 2015.

DEL FIOL, F. S. et al. Sales trends of psychotropic drugs in the COVID-19 pandemic: A national database study in Brazil. **Front Pharmacol**. v.14, 1131357, Mar 2023.

DI NICOLA, M. et al. Vortioxetine improves physical and cognitive symptoms in patients with post-COVID-19 major depressive episodes. **Eur Neuropsychopharmacol**. v. 70, p.21-28, May 2023.

FRIEDRICH, E. V. C. et al. Mind over brain, brain over mind: cognitive causes and consequences of controlling brain activity. **Frontiers in Human Neuroscience**, v. 8, 2014.

GALES, A.; MAXWELL, S. Ketamine: Recent evidence and current uses. **ATOTW**, v. 381, p. 1-7, 2018.

GEORGE, T. T.; TRIPP, J. Alprazolam. In: StatPearls [Internet]. Treasure Island (FL): **StatPearls Publishing**; 2023 Jan-. Updated 2022 May 1.

GREENBLATT, D. J.; WRIGHT, C. E. Clinical pharmacokinetics of alprazolam. **Clin Pharmacokinet**. v. 24, p. 453–471, 1993.

GUINA, J.; MERRILL, B. Benzodiazepines I: Upping the Care on Downers: The Evidence of Risks, Benefits and Alternatives. **Journal of Clinical Medicine**, v. 7, p. 17, 2018.

HOLLAND, K. M. et al. Trends in US Emergency Department Visits for Mental Health, Overdose, and Violence Outcomes Before and During the COVID-19 Pandemic. **JAMA psychiatry**, v. 78, n. 4, p. 372-379, 2021.

IBÁÑEZ, J. et al. Effects of alprazolam on cortical activity and tremors in patients with essential tremor. **PloS one**, v. 9, n. 3, e93159, 2014.

JANSEN VAN VUREN, E. et al. The neuropsychiatric manifestations of COVID-19: Interactions with psychiatric illness and pharmacological treatment. **Biomed Pharmacother**, v. 135, p. 111200, 2021.

JELEN, L. A. et al. Ketamine: A tale of two enantiomers. **Journal of psychopharmacology (Oxford, England)**, v. 35, n. 2, p. 109-123, 2021.

JIN, Y. et al. Mass quarantine and mental health during COVID-19: A meta-analysis. **Journal of affective disorders**, v. 295, p. 1335-1346, 2021.

DAVIES, J. A. Bromazepam. In: Encyclopedia of Basic Pharmacology and Toxicology (Comprehensive Pharmacology Reference), **Elsevier**, p.1-3. 2007.

JONES, E. A. K et al. Impact of COVID-19 on Mental Health in Adolescents: A Systematic Review**.** **International Journal of Environmental Research and Public Health**, v. 18, n. 5, p. 2470, mar. 2021.

KATZUNG, B. G.; TREVOR, A. J. (Orgs.). Farmacologia Básica e Clínica. 13ª edição. Porto Alegre: **McGraw-Hill**, 2017. 1202 p.

LEGATES, T. A., KVARTA, M. D.; THOMPSON, S. M. Sex differences in antidepressant efficacy. **Neuropsychopharmacol,** v. 44, p. 140–154, 2019.

LEDOUX, J. E; PINE, D. S. Using Neuroscience to Help Understand Fear and Anxiety: A Two-System Framework. **The American journal of psychiatry**, v. 173, n. 11, p. 1083-1093, 2016.

LI, S et al. The impact of COVID-19 epidemic declaration on psychological consequences: a study on active weibo users. **International Journal of Environmental Research and Public Health**, v. 17, n. 6, p. 2032, 2020.

LI, Y et al. Reversal of age-associated cognitive deficits is accompanied by increased plasticity-related gene expression after chronic antidepressant administration in middle-aged mice. **Pharmacology, Biochemistry, and Behavior**, v. 135, p. 70–82, 2015.

MASIULIS, S. et al. GABAA receptor signalling mechanisms revealed by structural pharmacology. **Nature**, v. 565, n. 7740, p. 454-459, 2019.

MAZZA, C. et al. A Nationwide survey of psychological distress among Italian people during the COVID-19 pandemic: immediate psychological responses and associated factors. **International Journal of Environmental Research and Public Health**, v. 17, n. 9, p. 3165, 2020.

MACHADO, D. et al. Efeitos do Bromazepam observados pela eletroencefalografia quantitativa (EEGq) durante a prática de datilografia. **Arquivos De Neuropsiquiatria**, São Paulo, v. 63, n. 2b, p. 452–458, 2005.

MEHA, S. et al. Successful use of ketamine to treat severe depression with suicidality post-COVID-19–A case report. **Psychiatry Research Case Reports**, v. 2, n. 1, p. 100100, jan. 2023.

MEYLER'S SIDE EFFECTS OF DRUGS (SIXTEENTH EDITION). Bromazepam. **Elsevier**, 2016. p. 1052.

MOTREFF, Y. et al. Increase in psychotropic drug deliveries after the Xynthia Storm, France, 2010. **Prehospital and Disaster Medicine**, v. 28, n. 5, p. 428-433, 2013.

MURROUGH, J. W. et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. **American Journal of Psychiatry**, v. 170, n. 10, p. 1134-1142, 2013;

NASIR, M. et al. Glutamate Systems in DSM-5 Anxiety Disorders: Their Role and a Review of Glutamate and GABA Psychopharmacology. **Frontiers in Psychiatry**, v. 11, p. 548505, 2020.

NEARCHOU, F. et al. Exploring the Impact of COVID-19 on Mental Health Outcomes in Children and Adolescents: A Systematic Review. **International Journal of Environmental Research and Public Health**, v. 17, n. 22, p. 8479, nov. 2020.

ORSOLINI, L. et al. Current and Future Perspectives on the Major Depressive Disorder: Focus on the

New Multimodal Antidepressant Vortioxetine. **CNS & Neurological Disorders - Drug Targets**, v. 16, n. 1, p. 65-92, 2017.

OZAMIZ-ETXEBARRIA, N. et al. Psychological Symptoms during the Two Stages of Lockdown in Response to the COVID-19 Outbreak: An Investigation in a Sample of Citizens in Northern Spain. **Frontiers in Psychology**, v. 11, p. 1491, 2020.

PIRES, Flávia Luiza Nogueira. Uso da cetamina no tratamento da depressão: revisão de literatura. 2020. 49 f., il. Trabalho de Conclusão de Curso (Bacharelado em Farmácia) - **Universidade de Brasília**, Brasília, 2020.

PRADO, M. A. M. B.; FRANCISCO, P. M. S. B.; BARROS, M. B. A. Uso de medicamentos psicotrópicos em adultos e idosos residentes em Campinas, São Paulo: um estudo transversal de base populacional**. Epidemiologia e Serviços de Saúde**, v. 26, n. 4, p. 747-758, dez. 2017.

RAMOS, C. S. et al. The Therapeutic Effects of Ketamine in Mental Health Disorders: A Narrative Review. **Cureus**, v. 14, n. 3, p. 1-10, 2022.

REMÓN ÁLVAREZ-ARENAS, M. M.; MORALES GAMA, E.; PALOMERO GIL, M. del R. Abordaje farmacoterapéutico de la ansiedad desde la oficina de farmacia. **FarmaJournal**, v. 7, n. 1, p. 53–60, 2022.

RUDOLPH, U.; KNOFLACH, F. Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes. **Nature Reviews Drug Discovery,** v. 10, p. 685-697, 2011.

SALONE, A. et al. The Interface between Neuroscience and Neuro-Psychoanalysis: Focus on Brain Connectivity. **Frontiers in Human Neuroscience**, v. 10, 2016.

SANCHEZ, C.; ASIN, KE.; ARTIGAS, F. Vortioxetine, a novel antidepressant with multimodal activity: Review of preclinical and clinical data. **Pharmacology & Therapeutics**, v. 145, p. 43–57, 2015.

SANCHEZ, C.; ASIN, K. E.; ARTIGAS, F. Vortioxetine, a novel antidepressant with multimodal activity: Review of preclinical and clinical data. **Pharmacology & Therapeutics**, v. 145, p. 43–57, 2015.

SARMA, S. et al. Ketamine as an alternative to ECT in catatonia in elderly women with bipolar disorder: A case report. **Frontiers in Psychiatry**, v. 14, article 1138772, abr. 2023.

SHAH, K. et al. Benzodiazepine interaction with COVID-19 drugs. **Primary Care Companion for CNS Disorders**, v. 23, n. 6, 2021.

STECK, A.; STECK, B. Reflections on brain and mind. **Swiss Archives of Neurology, Psychiatry and Psychotherapy**, v. 167, n. 05, p. 155-163, 2016.

TALMON, M. et al. Vortioxetine exerts anti-inflammatory and immunomodulatory effects on human monocytes/macrophages. **British Journal of Pharmacology**, v. 175, n. 1, p. 113–124, 2018.

THASE, M. E. et al. A meta-analysis of randomized, placebo-controlled trials of vortioxetine for the treatment of major depressive disorder in adults. **European Neuropsychopharmacology**, v. 26, n. 6, p. 979–993, 2016.

VAHRATIAN, A. et al. Symptoms of Anxiety or Depressive Disorder and Use of Mental Health Care

Among Adults During the COVID-19 Pandemic - United States, August 2020-February 2021. **MMWR Morbidity and Mortality Weekly Report**, v. 70, n. 13, p. 490-494, apr. 2021.

VILLALOBOS-MADRIZ, J. A. et al. Prescribing trends in psychotropic medications among outpatients of a Latin American healthcare setting: a five-year retrospective study. **Cureus**, v. 15, n. 4, 2023.

WEINBROUM, A. A. Perspectives of ketamine use in COVID-19 patients. **Journal of Korean Medical Science**, v. 36, n. 4, Apr. 2021.

WORLD HEALTH ORGANIZATION (WHO). Mental Health and COVID-19: Early evidence of the pandemic's impact. **Scientific brief**, 2 March 2022.

YOSHIMURA, R. et al. Panic Disorder Induced by the Coronavirus Disease Pandemic in a Patient with Organic Mood Disorder Successfully Treated with Vortioxetine. **Case Reports in Psychiatry**, article 8870014, v. 2020, p. 1-3, Nov. 2020.

YUAN, K. et al. Prevalence of posttraumatic stress disorder after infectious disease pandemics in the twenty-first century, including COVID-19: a meta-analysis and systematic review. **Molecular Psychiatry**, v. 26, p. 4982–4998, 2021.

ZAKI, H. A. et al. An Analytical Comparison Between Ketamine Alone and a Combination of Ketamine and Propofol (Ketofol) for Procedural Sedation and Analgesia From an Emergency Perspective: A Systematic Review and Meta-Analysis. **Cureus**, v. 14, n. 7, article e27318, Jul. 2022.

ZANOS, P. et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. **Nature**, v. 533, n. 7604, p. 481–486, May 2016.

ZANOS, P.; GOULD, T. D. Mechanisms of ketamine action as an antidepressant. **Mol Psychiatry**, v. 23, n. 4, p. 801-811, 2018.

ZOHAIR, J. et al. A review of the current nomenclature for psychotropic agents and an introduction to the Neuroscience-based Nomenclature. **European Neuropsychopharmacology**, v. 25, n. 12, p. 2318–2325, Dec. 2015.