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EFFECTIVENESS OF KETAMINE IN TREATMENT-RESISTANT DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: In relation to depression and its treatment, there are numerous medications that help in the treatment, whose mechanism of action is inhibiting selective serotonin reuptake or increasing the bioavailability of neurotransmitters in the central nervous system. However, a drug in the hypnotic class, ketamine increases the release of brain-derived neurotrophic factor, a protein that helps neurons develop synapses. Ketamine also affects glutamate transmission by blocking NMDA receptors. This makes ketamine have antidepressant effects in patients with treatment-resistant depression. It also increases the speed at which these patients respond to antidepressant medications. One study administered ketamine intravenously at subanesthetic doses found that it could rapidly reduce symptoms of treatment-resistant depression in patients. This is a systematic review study that was designed based on the criteria established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guide, considering the flow diagram and the PRISMA checklist. Ninety of the respondents who received the ketamine and oral antidepressant intervention showed an improvement. This review confirms that ketamine is beneficial in the treatment of patients with depressive disorder and generalized anxiety disorder. However, ketamine showed excellent results associated with antidepressants compared to other drugs, for example midazolam did not reduce 50% of the Montgomery-Asberg depression scale score.
Keywords: Ketamine; Depression; antidepressant.

INTRODUCTION

Depressive disorders include decreased energy, decreased appetite, insomnia, fatigue, loss of interest in previously pleasurable

activities, and reduced guilt when confronted. These symptoms often cause significant impairment and distress. Suffering with significant regularity causes significant negative effects on a person's life. This is because these symptoms require a definite decision. (BORGES et al., 2022).

Regarding depression and its treatment, there are numerous drugs that help in the treatment, whose mechanism of action is inhibiting selective serotonin reuptake (SSRI) or increasing the bioavailability of neurotransmitters in the central nervous system. (FLODEN et al., 2022 ; MOELLER et al., 2022). However, a drug in the hypnotic class, ketamine increases the release of brain-derived neurotrophic factor, a protein that helps neurons develop synapses. This chemical process is controlled by glutamate, an excitatory neurotransmitter. Ketamine also affects glutamate transmission by blocking NMDA receptors. This makes ketamine have antidepressant effects in patients with treatment-resistant depression. It also increases the speed at which these patients respond to antidepressant medications. A study administered intravenous ketamine at subanesthetic doses found that it could rapidly reduce symptoms of treatment-resistant depression in patients. (LIU et al., 2022).

The World Health Organization reported that approximately 5.8% of the Brazilian population is currently depressed. This number is greater than 11.5 million cases in all, which is the highest rate in the Americas, second only to the United States. The survey also showed that Ukraine, Australia and Estonia had higher rates of depression than any other American country; 6.3%, 5.9% and 5.9%, respectively, were the results of these countries, which are home to 17.4%, 14.1% and 14.1% of all cases in American depression surveys. The World Health Organization reports that the world's population has an overall prevalence of 4.4%. The lowest reported prevalence was 2.9% for the Solomon Islands and 3.7% for Guatemala. Showing an intense need to improve treatments in the field of mental health. (BRASIL., 2022).

Recently, research on the mental health of the general population is at the heart. However, this review aims to highlight this process, as it subsidizes the development of more effective actions and treatments aimed at communities. In this context, the aim of this study was to compile the literature on the impact of the treatment of depression using ketamine, to elucidate risk factors and possible interventions.

METHODOLOGY

This is a systematic review study that was designed based on the criteria established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guide, considering the flow diagram and the PRISMA checklist. Thus, from the guiding question: "Ketamine helps in the treatment of major depressive disorder?" the articles were searched.

Keywords were defined according to the PICOS model as follows:

1. Population: people with treatment-resistant depression;
2. Intervention: use of ketamine;
3. Comparative: control (placebo or midazolam);
4. Results (variables): improvement in the clinical picture of treatment-resistant depression;
5. Study design: clinical trial studies.

LITERATURE SEARCH

The survey of articles was carried out in the following databases: Medline/BVS and Medline/Pubmed. The following descriptors

and their combinations in Portuguese and English were used to search for articles: "Ketamine AND Antidepressants AND Treatment AND Depression // Ketamine AND Antidepressants AND Treatment AND Depression".

INCLUSION AND EXCLUSION CRITERIA

The selection of articles was guided by inclusion and exclusion criteria. The inclusion criteria defined for the selection of articles were: articles published in Portuguese, English; original articles in full that portray the theme related to the review and articles published and indexed in the aforementioned databases in the last 5 years.

The exclusion criteria defined for the selection of articles were non-original articles, dissertations and theses, articles that addressed the subject, but from a different point of view.

IDENTIFICATION AND SELECTION OF STUDIES

After applying the inclusion and exclusion criteria, the articles were identified. The screening of studies was carried out by reading and analyzing the titles and abstracts of all articles identified in each database, guided by the adopted inclusion and exclusion criteria. In the eligibility phase, after defining the articles to be included in each database, duplicate articles were excluded.

DATA EXTRACTION

Two independent researchers used custom spreadsheets to extract data from all included studies. After data extraction, data checking, if discrepancies arise, use a third investigator.

Data extracted from the article are: (1) Study design; (2) Number of initial participants who participated in the study; (3) Number and characteristics of participants completion of the intervention; (4) Results.

STATISTICAL ANALYSIS

Briefly, the outcome measures were calculated by n-sample difference, means and standard deviation. All analyzes were performed using the BioEstat software. Finally, we defined a significance level of P less than 0.05 as statistical significance.

RESULTS

STUDY SELECTION

A total of 3311 studies were identified according to our search strategy. Among them, presented two duplicate. After applying the adopted inclusion and exclusion criteria, 1001 studies in Medline/VHL reading and 1951 studies in Medline/Pubmed were excluded, with a total of 2952 articles. Then the titles and abstracts were read, 335 of the 359 references were excluded based on the eligibility criteria. Thus, 24 references were selected for full text evaluation. Finally, five articles were eligible for qualitative evaluation. The selection process for identifying eligible studies included in the meta-analysis, shown in figure 1.

The main characteristics of the included studies are described below. In the study by Daly et al.5 (2019), which was performed on 297 patients, with the mean and standard deviation of the age group: 46.3 (11.13), dividing them into two groups based on from the Montgomery-Asberg Depression Scale (MADRS) to be treated with nasal esketamine and placebo with oral antidepressants. Ninety of the respondents who received the ketamine and oral antidepressant intervention showed significant improvement compared to the control group, in addition to delaying relapses.

It is also worth considering, in line with the trial by Ionescu et al.3 (2021), which involved

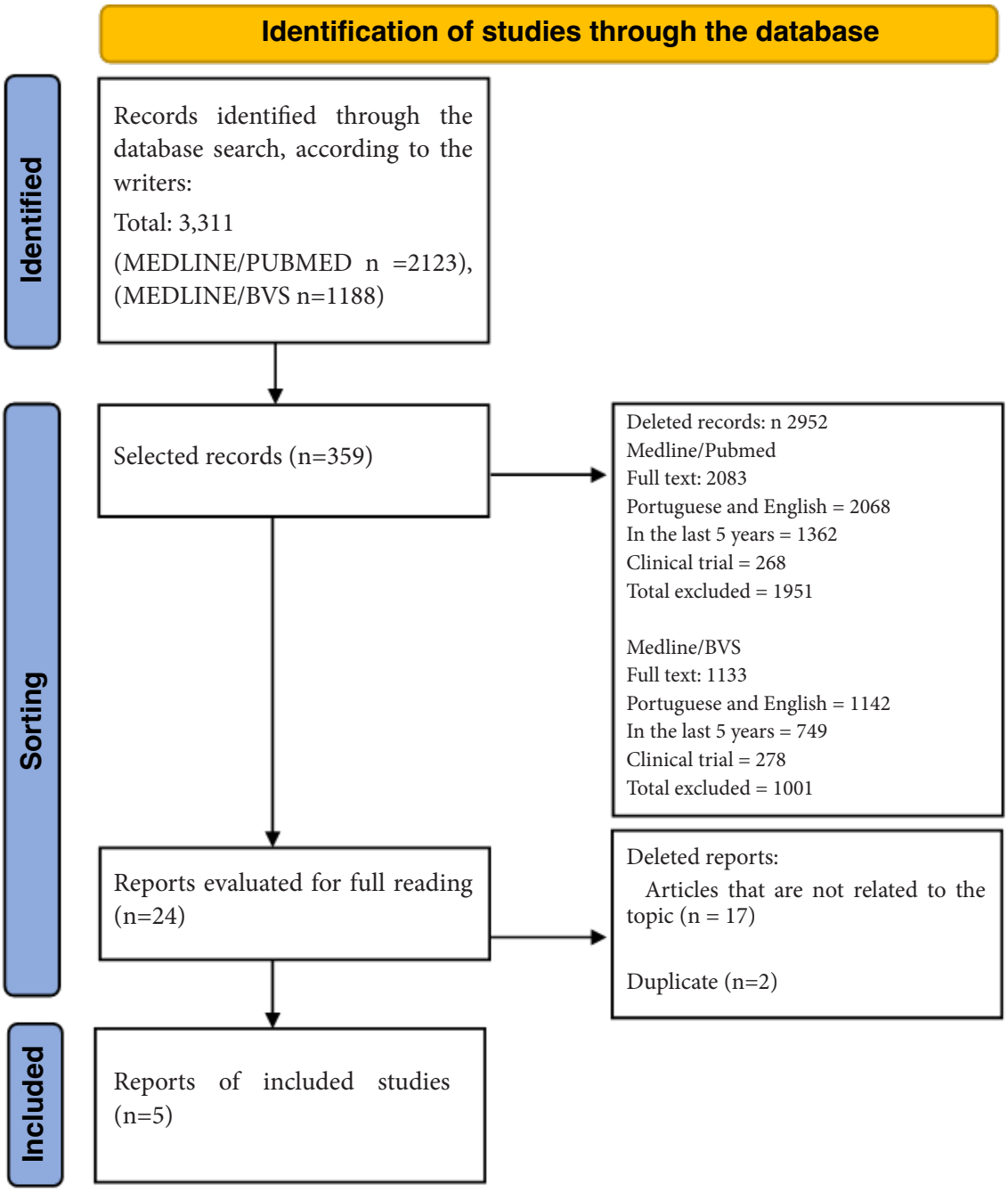

Figure 1: Flowchart for selection process, identification, screening, eligibility and included.

230 patients, equally divided between the groups that received nasal esketamine plus standard care and another in which placebo plus standard care was administered. Thus, esketamine plus standard care significantly improves depressive symptoms compared with placebo plus standard care, lowering Montgomery-Asberg Depression Scale (MADRS) scores.

Relatedly, it is noted that, according to Dwyer et al.4(2021), it was noticed that from ketamine infusions compared with administration of midazolam after the first 24 hours it significantly reduced the scores of the Montgomery depression scale -Asberg in 16 patients. Such, aged 13 to 17 years diagnosed with major depressive disorder received a single IV (intravenous) infusion of ketamine (0.5 mg/kg over 40 minutes) or midazolam (0.045 mg/kg over 40 minutes) after 2 weeks.

In addition, according to Phillips et al.2 (2019), which 43 people were selected for the study aged 18 to 65 years who were diagnosed with treatment-resistant depressive disorder. It is evident that in the 24-hour intervention after a single ketamine infusion, 11 participants (27%) met the antidepressant response criteria and 2 participants (5%) achieved remission. Single injection responders had a mean reduction in MADRS total score of 22.3 points (SD=5.3).

Finally, according to Popova et al.1 (2019), which included 223 patients who had treatment-resistant depression between 18 and 64 years of age, divided into two groups where one of the groups received placebo plus oral antidepressants and the other group is administered nasal esketamine plus oral antidepressants. It can be seen that after 28 days of treatment there was a significant improvement in depressive symptoms, in addition, a reduction in the Montgomery-Asberg depression scale scores compared to the control group.

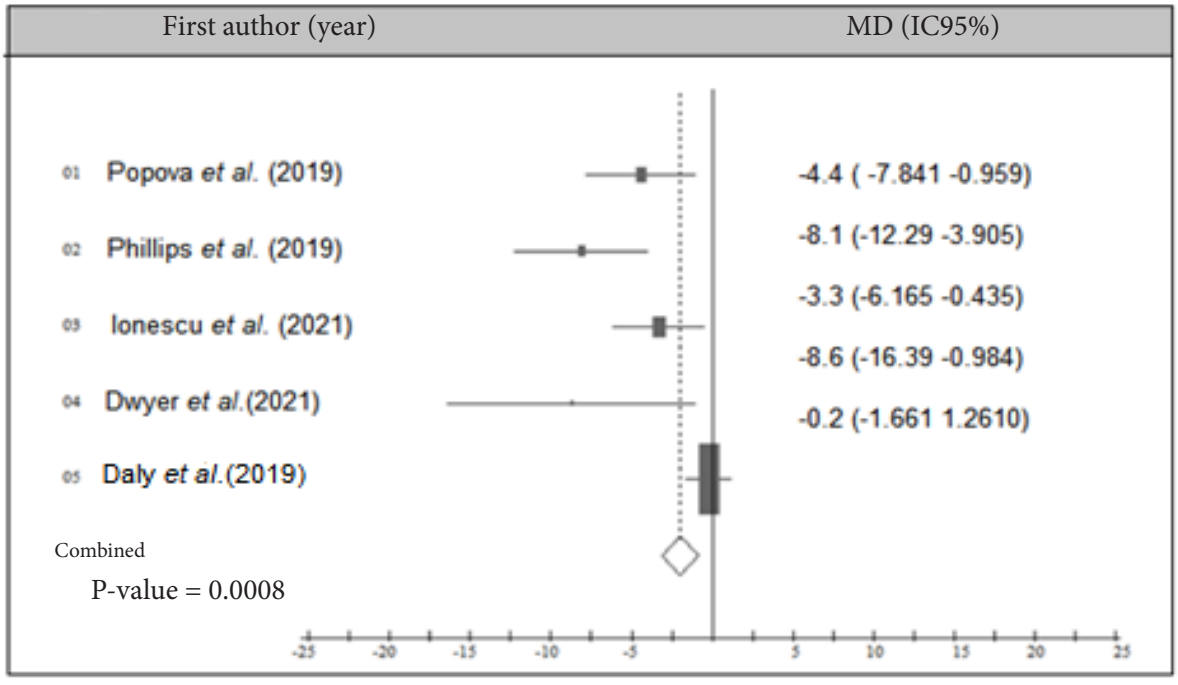

Figure 2 - Forest chart relationship between treatment of the ketamine group compared to the control group in patients with depression.

Use of nasal ketamine or esketamine influences the decrease in Montgomery-Asberg depression scale (MADRS) scores. It is clear that only the study [5] there was no difference between the pre and post intervention means, however, they were not significant, represented by the mean differences (MD) and confidence interval (-1,661 to 1,261), passing through the null line. However, the interventions adopted by the authors in the studies [1-4], had the desired result, presenting itself in relation to a reduction in the depressive condition with the use of the drug in 24 hours, with a statistical difference between the means with p-value = 0.0008 < significance level 0.05 (Figure 2). The combination of results, represented by the diamond is 95% CI = -3.1254 to -0.8193 and mean difference (MD w) = -1.9694.

DISCUSSION

This study aims to analyze through a meta-analysis of continuous fixed effects data that can highlight the most relevant aspects for the proposed theme. Therefore, from the beginning, it was important to show repeatedly that the group receiving ketamine had a positive response to resistant major depressive disorder. The results of several authors (1-4) showed a significant reduction in depressive symptoms in most patients, and these data were corroborated by the reduction in the score of the internationally recognized depression assessment scale, such as MADRS.

Regarding the dose of ketamine against depressive disorder, it can be observed that different doses of the drug have different clinical effects in patients. Even so, some authors have suggested that concentrations of 0.5 mg/kg produce potent antidepressant effects - and that the effect is stable - and concentrations below that do not produce consistent results. However, one study showed that a dose of 0.8 mg/kg was significantly better than a dose of 0.5 mg/kg in reducing symptoms of end-stage renal disease. Therefore, an analysis of long-term trials is needed to draw more accurate conclusions about the optimal therapeutic concentration of ketamine as an antidepressant.

Based on the dose of esketamine for the treatment of depression, it can be seen that different doses of the drug have different clinical effects in patients. Even so, some authors suggest that concentrations of 56 mg once daily produce potent antidepressant effects, while concentrations below that do not produce consistent results. However, patients using the 84 mg dose had significantly better clinical outcomes, so increasing the dose of nasal esketamine must be watched for efficacy and tolerability in each individual.

CONCLUSION

This review confirms that ketamine is beneficial in the treatment of patients with depressive disorder and generalized anxiety disorder. However, ketamine showed excellent results associated with antidepressants compared to other drugs, for example midazolam did not reduce 50% of the Montgomery-Asberg depression scale score. Therefore, the risk factors associated with this class of drugs need to be investigated more closely in order to obtain a possible effective intervention.

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