

New Pharmacological Therapeutic Approaches for Depressive Disorders: A Systematic Review

Taysa Leite de Aquino¹, Jaiany Rodrigues Libório¹, Ana Luiza Menezes Santana Bezerra¹, Giovana Macêdo Egídio Cavalcante¹, Dara Fernanda Brito Duarte¹, Ana Luíza de Aguiar Rocha Martin^{1,2}, Juliane dos Anjos de Paula¹ and Modesto Leite Rolim Neto^{1,3*}

¹School of Medicine of Juazeiro do Norte - FMJ/Estácio, Juazeiro do Norte, Ceará, Brazil

²Centro Universitário Dr. Leão Sampaio, UNILEAO, Juazeiro do Norte, Ceará, Brazil

³School of Medicine, Universidade Federal do Cariri - UFCA, Barbalha Ceara, Brazil

*Corresponding author: Neto MLR, School of Medicine, Universidade Federal do Cariri (UFCA), Rua Divino Salvador, 284, Rosário, Barbalha, Ceará 63180000, Brazil, Tel: (+55 88) 999042979; E-mail: modesto.neto@ufca.edu.br

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Abstract

Introduction: Depression, being the most disabling disease in the world and presenting high morbidity and mortality, requires an effective treatment to ensure the maintenance of the patients' quality of life. About a third of patients do not respond adequately to antidepressant treatment. New pharmacological therapies are being approached in order to reduce the unfavorable outcomes resulting from this pathology.

Objective: To develop a systematic review of the literature on the new possibilities of pharmacological treatments for depression in the last four years.

Method: A systematic review was carried out following the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). We have included studies on the effectiveness of new pharmacological therapies in patients with major depressive disorder and treatment-resistant depression.

Results: In the treatment of the major depressive disorder (MDD), the use of brexpiprazole 1 mg/day in addition to the usual antidepressant treatment (ADT) resulted in significant improvement in the main symptoms. Already referring to treatments for treatment-resistant depression (TRD): nasal esketamine proved beneficial in the short term, intravenous (IV) ketamine also appears as an effective therapy.

Conclusion: The use of brexpiprazole 1 mg/day associated with an antidepressant, and the use of lactobacilli represent a new option for those with MDD. In addition, both ketamine, riluzole, and cariprazine appear as new hopes for those who have not yet achieved remission of the depressive disorder with the use of more than two antidepressants.

Keywords: *New treatment; Pharmacological; Depressive disorder*

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1. Introduction

The World Health Organization (WHO) already predicted, according to the pace of diagnosis and the characteristics of the disease, that in 2020 depression would become the most disabling disease in the world. Currently, depression is responsible for the reduction of up to ten years of life expectancy, is the main cause of disability, has high rates of morbidity and mortality, being responsible, therefore, for an extremely negative direct impact on the quality of life of more than 322 million of people around the world, confirming and exceeding WHO estimates [1,2].

Facing a disease with unfavorable outcomes, treatment becomes essential to maintain the patients' quality of life. However, a third of individuals diagnosed with depression do not respond adequately to the first-choice treatments, including monoamine reuptake inhibitors [3]. In addition, these drugs take between three to seven weeks to start their antidepressant effects and up to 12 weeks to achieve maximum effect, as well having side effects in most users. In many situations, the combination of two or more of these drugs is not able to cease the patient's depressive symptoms, raising him to the diagnosis of treatment-resistant depression [1,4]. In this sense, the need for more effective treatments, with a faster onset of action, better dosage, and fewer side effects has increased in recent years and new therapeutic approaches for depressed patients have emerged aiming to reduce the unfavorable outcomes resulting from this pathology.

However, the proposed therapies face difficulties due to the long time spent and the high costs for the development of a new drug. This path takes, on average, 14 years. However, with the study of new approaches to products that are already consolidated in the market and the reuse of drugs, this time reduces to less than half, around six years [5]. Currently, many drugs are in the process of analysis and face difficulties such as the short observation time, the need for further studies related to the neurobiological mechanisms involved in the pharmacodynamics of the proposed drugs; or even the difficulties with the selection of the requirements for the study, which is often small and restricted to a region. However, both a long-term analysis and an understanding of the mechanism of action of the drug associated with the physiological processes of depression and the heterogeneity of the study group are extremely useful to understand and attest to the effectiveness of new therapies [1,4].

Given this situation and taking into account that 20% to 30% of individuals with major depressive disorder (MDD) develop treatment-resistant depression (TRD) [5], we aim to develop a systematic review of the literature regarding the new possibilities of pharmacological treatments for depression based on the acronym PICO: **P**: study population - people with depressive disorder according to DSM V 296.21, 296.22, 296.23 and 296.24; **I**: intervention - to demonstrate the effectiveness of new pharmacological therapies for depression; **C**: control - individuals with MDD and TRD; **O**: outcome - new pharmacological approaches to depressive disorders.

This question has had a greater impact in recent years due to the need for new pharmacological treatments since the number of patients with TRD and MDD who respond inadequately to conventional treatment is increasing. Thus, this study aims to formulate a systematic review of the literature regarding new pharmacological treatments for depression.

2. Method

A systematic review was carried out, following the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).

2.1 Inclusion criteria

The inclusion criteria were studies published in English, Portuguese and Spanish, suitability for this review, methodological rigor applied, and full text available for free. Review articles, as well as comments on literature, editorials, communications, and letters to the editor, were excluded. We had no restrictions related to the study design, methodological quality, or language. The problem with the language was solved through a reasonable degree of comparability, which allowed us to systematically analyze the selected evidence, its critical evaluation process, and its success in including relevant studies in other languages.

We classified assessments according to their level of inclusion of studies in other languages. Reviews that excluded non-English studies with an explicit justification in the research question or research objectives were categorized as justified by R1 (that is, justified in English), while those that excluded non-English studies without justification were categorized as restricted to RR1 (that is, languages that are not restricted to English). Reviews that did not explicitly exclude studies that were not in English were categorized as RR1-open unless they successively included studies that were not in English, in which case they were RR1-inclusive. Finally, revisions that did not declare language criteria were considered to be RR1-open.

2.2 Literature search and article selection

To search for the studies, the following databases were used: PubMed, LILACS and Science Direct data, from 2018 to 2021c with the descriptors MeSH and DeSC: “Pharmacological Treatment” AND/OR “Tratamiento Farmacológico”, “New Treatments” AND/OR “Novos Tratamentos”, “Depressive Disorder” AND/OR “Transtorno Depressivo”.

2.3 Data extraction and methodological quality assessment

One researcher (MLRN) extracted the data, and another verified the extraction. Two researchers (ALARM and JAP) independently assessed the methodological quality of systematic reviews using the AMSTAR tool and qualitative studies using the CASP checklist (Critical Appraisal Skills Program - CASP, 2020). One researcher (ALARM) assessed the quality of cross-sectional studies using the JBI Prevalence or the JBI Cross-sectional analytical checklist and longitudinal studies using the JBI Cohort checklist (Johanna Briggs Institute).

2.4 Data presentation and analysis

We describe the interventions and results based on the information provided in the studies. When studies showed results of new pharmacological therapeutic approaches to depressive disorders in numbers without numbers, we extracted them using online software (<https://apps.automeris.io/wpd/>).

2.5 Data presentation and analysis

We summarize the results narratively. We describe the interventions and results based on the information provided in the studies. When the studies showed results regarding new pharmacological therapeutic approaches for depressive disorders in the last four years, we extracted them using online software (<https://apps.automeris.io/wpd/>). We classify the certainty of the evidence using the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluations).

3. Results

The data were collected independently by three reviewers (ALARM, JAP, ALMSB, and MLRN). If there was disagreement between the evaluators on the inclusion and exclusion criteria, a specific discussion was made about the article in question until a final consensus. The necessary information was collected from published articles (FIG. 1).

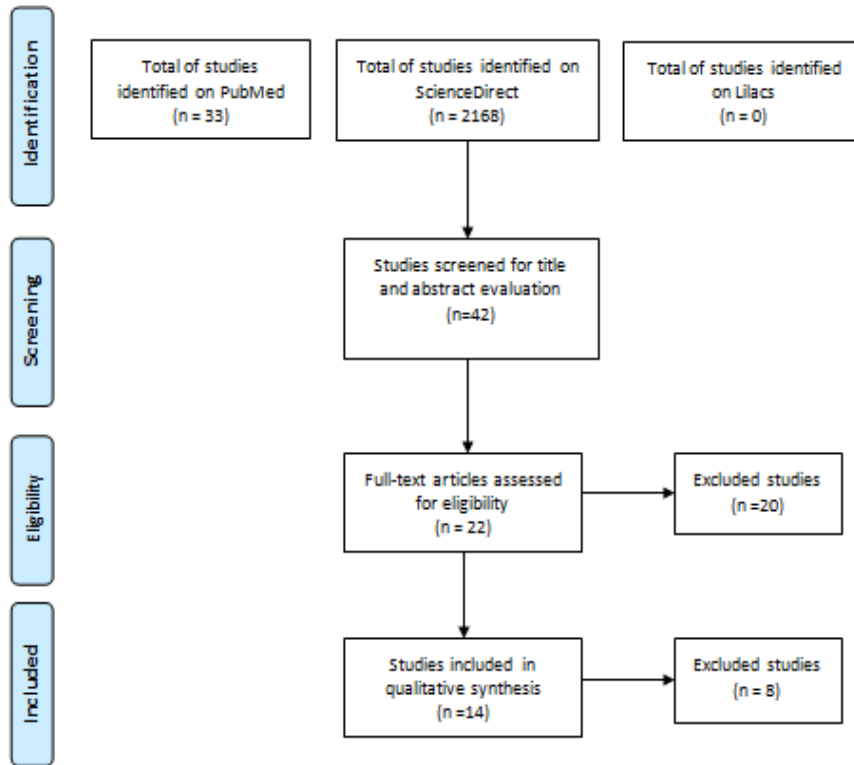


FIG. 1. **Bibliographic research flowchart.**

A total of 2,201 articles were found. Five independent researchers evaluated the titles and abstracts of the articles, 42 studies were pre-selected for presenting potential eligibility to the topic. In the end, 14 articles were considered relevant for the systematic review.

The articles included studies by Fabbri et. al. [5] - a study about potential new treatments for TRD; Griffiths et.al. [4] - a study about the evaluation of ketamine's antidepressant and adverse effects on TRD; Hudgens et. al. [1] - a study about the response of esketamine nasal spray in patients with TRD; Melo et. al. [6] - a study about the possible inferiority of esketamine compared to ketamine; Chahwan et. al [7] - a study about the probiotic's ability to act on depressive symptoms; Daly et.al. [2] - a study about antidepressant use associated with esketamine nasal spray in patients with TRD; Costi et. al. [8] - a study about lithium preventing severe depression after cessation of ketamine use; Fedgchin et. al. [9] - a study to evaluate esketamine nasal spray in TRD patients; Karakula-Juchnowicz et. al. [10] - a study about probiotic supplementation in patients with MDD; Sakurai et. al. [11] - a study about prolonged use of riluzole in patients with TRD; Zhuo et. al. [3] - a study about ketamine's ability to reverse depression and synaptic loss; Earley et. al. [12] - a study about the effect of cariprazine associated with ADT in patients with MDD; Hobart et. al. [13] - a study about the efficacy and safety of brexpiprazole in MDD; Nelson et. al. [14] - a study

about the effects of brexpiprazole associated with ADT in patients with MDD. The main characteristics of the selected studies were summarized in TABLE 1.

TABLE 1. Summary of authors, journals, locations, objectives, methodologies, results and main findings of the studies included for analysis in the systematic review based on the PRISMA method.

Author	Journal	Objective	Method	Results	Main Findings
Fabbri et. al. [5]	Progress in Neuro-Psychopharmacology and Biological Psychiatry	To identify new possible pharmacological options for TRD.	It was analyzed using a hypergeometric test if targets of already known genes were enriched in genes associated with TRD. This last one, after correcting the false discovery rate, was compared with genes associated with MDD that are shown to be enriched.	542 compounds enriched in genes associated with TRD (FDR $p < 0.05$) were identified, out of a total of 15,475. Significant effects included drugs that are already used today in TRD.	This study suggests new potential treatments for TRD. However, the research results are only exploratory, guiding the identification of promising drugs for this type of depression.

<p>Griffiths et.al. [4]</p>	<p>Journal of Affective Disorders Reports</p>	<p>To evaluate the antidepressant and adverse effects of ketamine in patients with TRD.</p>	<p>Interpretative phenomenological analysis (IPA) was used through semi-structured interviews with 13 patients with TRD.</p>	<p>Effects such as initial dissociative sensation, as well as improved perception, followed by improvement have been reported. With the associated reduction of suicidal ideals, increased motivation for daily activities, and others, and improved mood. All effects appeared as soon as the medication was infused.</p>	<p>Ketamine has beneficial effects on patients with TRD and represents hope for this group.</p>
<p>Hudgens et. al. [1]</p>	<p>Journal of Affective Disorders</p>	<p>To assess the response of patients with TRD to the use of esketamine nasal spray and an oral antidepressant.</p>	<p>Evaluation of two multicenter, randomized, double-blind, phase 3 studies using esketamine nasal spray combined with an oral antidepressant for four weeks compared to the placebo group.</p>	<p>Patients in the study who were treated with esketamine nasal spray + oral antidepressant had a reduction higher than or equal to 50% in MADRS compared to the placebo group.</p>	<p>The use of esketamine nasal spray associated with an oral antidepressant has significantly improved both the frequency and severity of symptoms in patients with TRD.</p>

<p>Correia-Melo et. al [6]</p>	<p>Journal of Affective Disorders</p>	<p>To test whether esketamine is not inferior to ketamine in terms of rapid induction of remission of depressive symptoms after a single intravenous dose in patients with TRD.</p>	<p>A randomized, double-blind, active-controlled, bicentre, non-inferiority clinical trial with two parallel groups. Participants in these groups (one of ketamine-0.5mg / kg and one of esketamine-0.25mg / kg).</p>	<p>Esketamine was not inferior to ketamine, analyzing the remission at 24hrs and 72hrs. However, in seven days, the remission rate in the ketamine group was higher. Regarding dissociative symptoms during infusion, there was no significant difference in the mean CADSS scores between ketamine and esketamine.</p>	<p>Esketamine was not inferior to ketamine for TRD 24 hours after intravenous administration. Both drugs caused improvement in depressive symptoms, with similar mild and self-limited adverse effects. Ketamine shows a tendency to have a longer-lasting antidepressant effect compared to esketamine, but the difference has not reached statistical significance and should be evaluated in future studies.</p>
<p>Chahwan et. al. [7]</p>	<p>Journal of Affective Disorders</p>	<p>To determine whether taking a probiotic supplement for eight weeks led to a reduction in depressive symptoms and to investigate any potential effects of it on cognitive reactivity to sad mood.</p>	<p>A randomized clinical trial using probiotics for eight weeks in patients from an initial triple-blind, placebo-controlled study in which 71 depressive participants were recruited using the Beck depression inventory and 20</p>	<p>Both the placebo group and those using the probiotic showed improvement in symptoms, suggesting non-specific therapeutic effects associated with weekly monitoring visits. However, participants in the probiotic group showed a higher significant reduction in cognitive reactivity compared to the placebo group, particularly in the subgroup of mild/moderate depression.</p>	<p>The use of probiotics can exert changes in the cognitive patterns that contribute to depression. The routine used in the preparation and daily consumption of the probiotic, to seek and improve depressive symptoms, had positive results in mood, regardless of the use of the probiotic or placebo.</p>

			non-depressed people for the control group.		
Daly et.al. [2]	JAMA Psychiatry	To evaluate the response of patients with TRD to the use of esketamine nasal spray and an oral antidepressant.	A randomized double-blind clinical trial. 455 individuals received treatment with esketamine nasal spray and an oral antidepressant. After 16 weeks of treatment, 297 patients showed remission or a stable response, participating in the phase of random drug withdrawal.	Of the 297 adults who entered the maintenance phase, 176 achieved stable remission, with 24 individuals in the esketamine and oral antidepressant group, and 39 in the placebo group relapsing. Of the 121 patients who entered in a stable response, 16 in the esketamine group and 34 in the placebo group experienced relapse. Treatment with esketamine nasal spray reduced the risk of recurrence by 51% in patients who obtained a stable remission and 70% in patients who obtained a stable response.	The association between esketamine nasal spray and an oral antidepressant had shown to be superior and with a lower relapse rate in the treatment of patients with TRD.

<p>Costi et. al. [8]</p>	<p>Neuropsychopharmacology;</p>	<p>To analyze whether, after ketamine interruptions, participants randomized to lithium compared to placebo had less severe depression in two weeks.</p>	<p>Eligible participants after the first infusion of ketamine (IV) 0.5 mg/kg with antidepressant response improvement equal to or greater than 25% in the MADRS scale score were randomized in double-blind conditions to lithium or placebo.</p>	<p>Of the 77 participants assessed for eligibility, 42 with TRD met the inclusion criteria and received the test infusion with ketamine (IV), 35 participants who showed a response after 24 hours of the infusion were randomized and entered the double-blind lithium/placebo study. Of these, 34 continued in the study and were exposed to at least one dose of lithium or placebo, which did not differ in the continuation of the acute antidepressant response to ketamine.</p>	<p>Need for further studies to identify an effective strategy to prevent relapse of depression after an acute course of ketamine treatment.</p>
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<p>Fedgchin et al. [9]</p>	<p>International Journal of Neuropsychopharmacology</p>	<p>To evaluate the safety and efficacy of the esketamine nasal spray associated with an oral antidepressant in patients with TRD.</p>	<p>Multicenter, randomized, double-blind, active-controlled study with esketamine 84 mg/antidepressant, esketamine 56 mg/antidepressant, and antidepressant/placebo in 346 patients with moderate to severe depression and with no response to two or more antidepressants in the current episode of depression. MADRS was performed to assess primary and secondary efficacy.</p>	<p>There was no significant difference between esketamine 84 mg/antidepressant when compared to antidepressant/placebo. However, patients using esketamine 56 mg/antidepressant and esketamine 84 mg/antidepressant showed numerically significant secondary efficacy. On the last day of evaluation, the response was 54.1% in the 56mg esketamine/antidepressant group, 53.1% in the 84mg esketamine/antidepressant group, and 38.9% in the antidepressant/placebo group. The highest remission rate (38.8%) was in the 84mg esketamine/antidepressant group and the lowest (30.6%) in the antidepressant/placebo group.</p>	<p>Esketamine proved to be safe and tolerable in the short term, with no significant changes in these characteristics between doses.</p>
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<p>Karakula-Juchnowicz et al. [10]</p>	<p>Nutrition Journal</p>	<p>To demonstrate the effect of interventions on the gut-brain-microbiota axis in patients with MDD.</p>	<p>A randomized, 12-week, double-blind, placebo-controlled study with the aim of analyzing the effect of probiotic supplementation on the mental status of patients with MDD using a gluten-free and a non-gluten-free diet.</p>	<p>Proof of concept study. The use of probiotics associated with a gluten-free diet can alter the microbiota-gut-brain axis, which is connected to the pathophysiology of depression.</p>	<p>The microbiota influences the CNS. Therefore, the association of the probiotic with the gluten-free diet inhibits the inflammatory cascade of the pathophysiology of MDD, improving the psychiatric symptoms that are connected to the intestinal barrier.</p>
<p>Sakurai et. al [11]</p>	<p>Journal of Affective Disorders</p>	<p>To evaluate the long-term use of riluzole in patients with TRD.</p>	<p>12-week open-label extension phase of a randomized, double-blind, placebo-controlled study in 66 patients with TRD receiving riluzole. Using MADRS for evaluation</p>	<p>The response rate ($\geq 50\%$ reduction in MADRS scores) was 66.7% among responders in the acute phase and present in 24.1% among non-responders in the acute phase. The relapse rate (a MADRS score of ≥ 22 in patients who had previously achieved a response) was 8.3%.</p>	<p>Riluzole showed good long-term tolerability and may be beneficial for some patients with TRD, justifying a further evaluation.</p>

<p>Zhuo et al. [3]</p>	<p>Brain and Behavior</p>	<p>To test the ability of ketamine to quickly reverse depression and synaptic loss involved in the disease, as well as to evaluate the drug's action on the circadian rhythm of patients with treatment-resistant depression.</p>	<p>A randomized clinical study with 600 patients with treatment-resistant depression, which met criteria for the disease, such as MADRS > 20. It is the same scale used as one of the parameters for the results after 24 weeks of IV administration of placebo, control, or ketamine 0.5 mg/kg of weight at 11 am or 6 pm. Images of brain MRI, CT-Pet, Polysomnography, Electroencephalogram, Blood tests, and Scales of the disease were used</p>	<p>A single dose of ketamine was sufficient to achieve rapid and sustained antidepressant effects and to reduce the risk of suicide in patients with MDD. Besides, the current study intends to demonstrate the beneficial effect of ketamine in the circadian rhythm and what is the best time to take the medication so that this goal occurs more effectively. It also hopes to show the restoration and increase of synapses with the use of the drug.</p>	<p>As it is a pilot clinical study, it offers limitations, which cannot be compared to the revolutionary scope of the discoveries about the mechanisms of the effectiveness of ketamine in the treatment for resistant depression.</p>
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			to evaluate results.		
Earley et. al. [12]	Psychopharmacology Bulletin	To analyze the effects of cariprazine associated with an ADT, in adult patients with MDD who no longer respond effectively to them, using MADRS and the Sheehan Disability Scale (SDS).	Phase 3 study, double-blind, randomized, placebo-controlled study lasting 18-19 weeks that looked at the efficacy of adjunct cariprazine 1.5-4.5mg/d with ADT in patients diagnosed with MDD who did not	The use of cariprazine 1.5-4.5mg/day showed an improvement when compared to placebo both in the total SDS score and MADRS remission rates, in addition to the reduction of symptoms according to CGI-I (Global Clinical Impressions - Improvement). However, MADRS response rates did not increase with cariprazine vs. placebo.	Associating cariprazine with ADT, in adults with MDD who had an inadequate response to ADT, did not show a statistically significant improvement while compared to the use of placebos. However, the use of adjunct cariprazine has shown a reduction in the symptoms of MDD.

			respond to ADTs that were administered.		
Hobart et al. [13]	The Journal of Clinical Psychiatry	To demonstrate the efficacy of brexpiprazole 2 mg/day in combination with ADT in patients with MDD.	A randomized, placebo-controlled, double-blind study in which patients with inadequate response to ADT were selected. Brexpiprazole 2 mg/day was used and evaluated by MADRS.	The use of brexpiprazole 2 mg/day in association with ADT improved the total MADRS score compared to the placebo group. The treatment was well tolerated and without unexpected side effects.	This study showed evidence that brexpiprazole is effective and has good tolerability as an adjunctive treatment in MDD. The drug showed advantages over placebo mainly in patients with anxious distress.

<p>Nelson et al. [14]</p>	<p>Journal of Affective Disorders</p>	<p>To observe the effects of brexpiprazole associated with ADT on the main symptoms of MDD that were defined using MADRS items.</p>	<p>Post hoc analysis study for six weeks, randomized, double-blind, and placebo-controlled from two similarly designed Phase 3 studies. In the two studies, 980 patients were analyzed, between 18-65 years, that met the desired criteria. During the study phase, participants received ADT along with single-blind placebos.</p>	<p>The use of brexpiprazole associated with ADT had significant effects on the subscale of majority symptoms of MADRS compared to placebo at the end of six weeks. This drug proved to be more beneficial for essential symptoms than for individual non-essential symptoms.</p>	<p>Associating brexpiprazole with ADT showed a significant improvement in the main symptoms in MDD. The drug has been shown to exert its effects on MDD, treating the main symptoms of the disease.</p>
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3.1 Evaluation of the methodological quality of the included studies

The most common methodological deficiencies in all studies arose from insufficient reporting: samples, scenarios and recruitment procedures were often not fully described.

3.2 Mental health interventions

Ten studies reported the urgent need to implement interventions related to new pharmacological therapeutic approaches for depressive disorders. Four studies demonstrate the need for interventions for organizational adjustments through new pharmacological therapeutic approaches for depressive disorders in the last four years.

MDD is a complex, disabling mental illness and a highly prevalent health problem worldwide. Therefore, brexpiprazole and the probiotic Winclove's Ecologic® Barrier were seen as new viable treatments in addition to the usual therapy. Regarding TRD, it is a pathology classified from the therapeutic failure of at least two or three trials with antidepressants of adequate dose and duration. Thus, the new medications investigated for the treatment of TRD were nasal and IV esketamine and, IV ketamine, riluzole, and cariprazine, drugs with the potential to aid in TRD (FIG. 2).

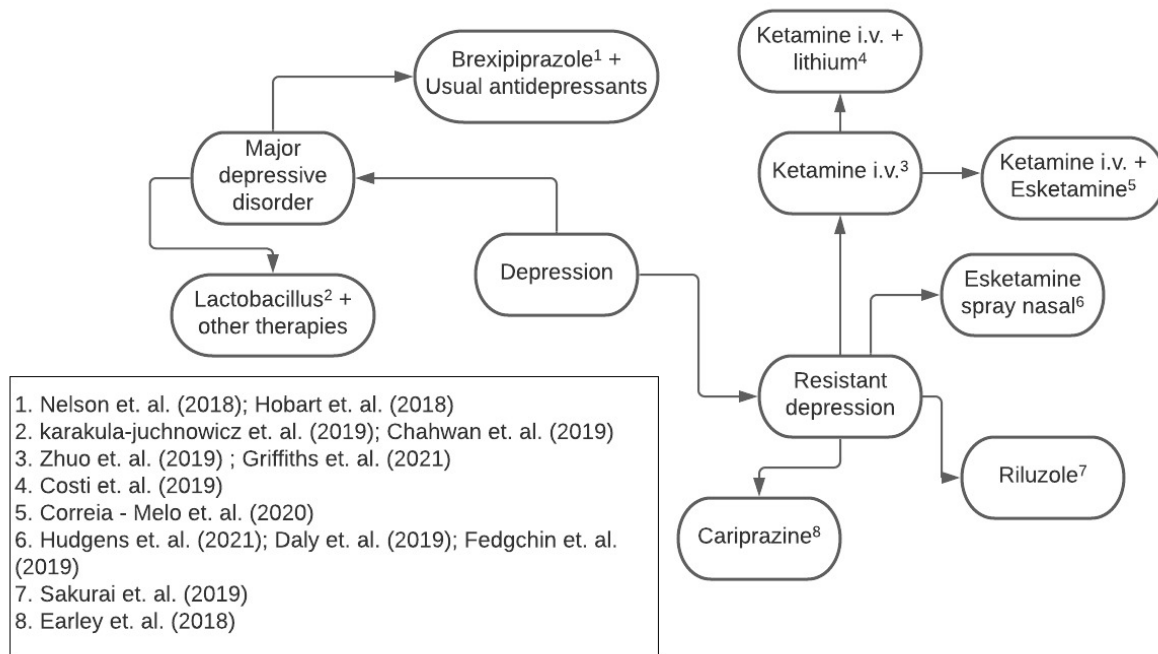


FIG. 2. Conceptual map of the depressive disorders and drugs studied.

4. Discussion

Patients diagnosed with MDD may not respond or poorly respond to the drugs used for this pathology [4]. When this happens, other therapeutic strategies should be considered as a change from the current antidepressant or association with a second pharmacological agent [14]. Given this, there was a need for studies with new agents, or the reuse of agents used therapeutically in other clinical conditions, for depression.

4.1 Major depressive disorder (MDD)

Brexpiprazole is a drug in the class of atypical antipsychotics that acts as a modulator of serotonin-dopamine activity, and that showed efficacy in the adjunctive treatment of MDD when in combination with antidepressants of different classes, in those patients who responded inadequately to ADT [13]. Brexpiprazole 1 mg/day, when associated with ADT for six weeks, showed a significant improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) score, positively impacting the symptoms of apparent and reported sadness, internal tension, tiredness, inability to feel, and thoughts pessimists [14].

The intestinal microbiota and its role in the gut-brain axis have been widely studied for several psychiatric pathologies including MDD. The main factors that generate the appearance of this depressive disorder are related to the inflammatory-immune

imbalance, and the modulation of this axis can be a promising therapeutic target for mental health [10]. The use for eight weeks of the probiotic Winlove's Ecologic® Barrier, which is composed of nine bacterial strains: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *B. lactis* W52, *L. acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19 e *L. lactis* W58, was used as a treatment in mild to moderate MDD. This medication in monotherapy was not effective in reducing depressive symptoms. However, when associated with Cognitive Behavioral Therapy, it can make changes in the patterns of cognitive reactivity concerning the sad mood associated with depression. Therefore, it can be effective when used to complement and potentiate the symptoms effects of other treatments for depressive disorders [7].

4.2 Treatment resistant depression (TRD)

Ketamine is a dissociative anesthetic that, in recent studies, is promising in the treatment of TRD. This drug represents new hope for those who, until then, have not responded with the combination of two or more antidepressants [3]. Esketamine, the S enantiomer of ketamine, is an antagonist of the N-methyl-d-aspartate (NMDA) receptor and was recently approved by the Food and Drug Administration (FDA), in the form of a nasal spray, as pharmacological therapy in TRD [1,2,4].

The choice of the ketamine S enantiomer concerning R is because it has greater affinity for the NMDA receptor than this one and, therefore, is considered more potent. The increase in the levels of glutamate in the synaptic cleft, provided by ketamine, consequently, increases the number of synapses, which are reduced in depression. Such action of ketamine through the glutamatergic pathway is already pointed out as well established by the most recent studies, representing one of the mechanisms responsible for the quick antidepressant responses of the drug, since such action reverses the chronic loss of synapses that occurs in the disease [3,5].

One study noted the change in MADRS scores in patients who had TRD. These patients started using a nasal spray containing 28 mg of esketamine, administered twice a week, associated with the daily use of a new oral antidepressant that had not yet been used and that was one of the options of choice: duloxetine, sertraline, escitalopram or venlafaxine from prolonged action, and were compared with the placebo group that received placebo nasal spray and oral antidepressant. There was a significant improvement with the use of esketamine nasal spray, defined as a reduction higher than or equal to 50%, or a reduction of 10 points, in MADRS, influencing both the severity of symptoms and their frequency [1,2].

The adverse effects of pharmacological therapy were not significant and some patients experienced vertigo, headache, and dissociation as the most common changes [2,9]. Although pharmacological therapy with esketamine nasal spray has shown beneficial results in the short term, its long-term effects are still unclear, and it is necessary to evaluate the efficacy of the drug in this context [2]. Esketamine was also studied in its IV form to compare its effectiveness with that of IV ketamine. In this study, the rate of remission of depressive symptoms in 24 hours of IV esketamine 0.25 mg/kg was 24.1% and that of IV ketamine 0.5 mg/kg 29.1%, thus not lower than ketamine and presenting both efficacy, tolerability, and safety [6].

A phenomenological analysis was done with 13 patients with TRD who used IV ketamine, in an individual dose calculated according to height and weight. The doses administered ranged from 25 mg/40 ml to 75 mg/40 ml, all infused over 40 min, during three to 112 sessions. Interviews were conducted with these patients to assess the effects of the medication. For many

of them, feelings such as “happy and laughing”, “more willing to do activities”, “greater socialization and communication with others”, “feeling normal”, “with positive thoughts” and “reduced suicidal ideation” were reported [4].

Ketamine emerges as an effective therapy and able to work in different neurobiological pathways to provide its antidepressant actions. The drug can work in the circadian cycle, prolonging REM sleep time and increasing levels of brain-derived neurotrophic factor (BDNF) responsible for regulating slow-wave sleep. Thus, being able to redefine the changes in circadian rhythm caused by depression and improve synaptic plasticity is also affected by the disease [3,5].

The action of ketamine in modulating inflammation and the immune system as an inhibitor of glycogen synthase kinase 3 beta (GSK3B) that modulates the activity of proteins responsible for mood regulation, also seems to be responsible for the rapid antidepressant effects of ketamine [5]. Lithium, which is also an inhibitor of (GSK3), was the target of a randomized double-blind study that aimed to assess whether this drug was able to prolong the antidepressant effects of ketamine. The participants received IV ketamine and then, associated with lithium 600 to 1200 mg/day orally or with placebo for a week, and finally maintained with only lithium or placebo. However, no significant difference was seen between the groups. The addition of lithium did not, therefore, appear to have led to a reduction in MADRS scores compared to treatment with ketamine alone [8].

In addition to ketamines, other drugs are targets for studies for patients with TRD and patients with inadequate response to ADT. Studies conducted with riluzole and cariprazine in these patients used MADRS to assess primary efficacy. The mechanism of action of riluzole is believed to be the inhibition of presynaptic release of glutamate through the inactivation of voltage-gated sodium channels in glutamatergic nerve terminals, it is a drug used to treat Amyotrophic Lateral Sclerosis (ALS) and has been evaluated as long-term therapy in patients with TRD. Riluzole showed positive results, as it can promote a reduction higher than or equal to 50% in MADRS, despite not showing great differences concerning the placebo in terms of efficacy for the treatment of patients with TRD. The study realized with cariprazine, an atypical antipsychotic whose main mechanism of action is the partial agonist of dopamine D2 and D3 receptors, in patients with inadequate response to the usual treatment with antidepressants, did not show any significant changes in MADRS or a considerable decrease in depressive symptoms when faced with placebo. Consequently, further studies should be carried out to better understand these drugs in the treatment of depression [11,12].

5. Conclusion

Knowing that 20%-30% of patients with MDD develop TRD [5], the new therapies under study appear to improve the approach of these patients and prevent disease progression.

According to this systematic review, the use of brexpiprazole associated with antidepressants of different classes, as well as the use of Winclove's Ecologic® Barrier-type lactobacilli for eight weeks, showed short-term efficacy in the treatment of MDD. On the other hand, pharmacological options, such as ketamine, esketamine, riluzole, and cariprazine, appear as new possibilities for those who until then have not obtained remission of the depressive disorder with the use of more than two antidepressants. As assessed by Griffiths et. al. [4] and Fabbri et. al. [5], although the new pharmacological options addressed in our study have shown efficacy in the treatment of depressive disorders, we realize that there are still gaps in both the knowledge of the action

of drugs at the neurobiological level associated with the neurophysiology of the disease and the action of these drugs over the long term.

6. Conflict of Interest

The authors declare that they have no competing interests.

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