Pipeline, novel, and future treatments for unipolar depression

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ABSTRACT
In 2019, the World Health Organization (WHO) reported that approximately 280 million individuals were living with depression, including 23 million children and adolescents. Research indicates that individuals with depression experience impaired physical, social, and work functioning, directly impacting their quality of life. As a result, the need for accessibility to a wide range of antidepressant medications is crucial. This review is aimed to provide an overview of conventional antidepressant medications, evaluate the efficacy, safety, and tolerability of newly emerged drugs for unipolar depression treatment, and highlight promising medications in different stages of development, aiming to expand the therapeutic options available for depression.

Keywords: depression, conventional treatment, novel, future treatment

INTRODUCTION
According to World Health Organization (WHO), one in eight individuals suffers from a mental illness. In the case of major depressive disorder (MDD), in 2019, there were 280 million people living with this condition, encompassing 23 million children and adolescents [1]. Moreover, according to the WHO, clinical depression rates have increased by 25 percent worldwide as a result of the COVID-19 pandemic [2].

Based on DSM-5, MDD is a heterogeneous condition requiring individuals to experience five or more symptoms simultaneously for a continuous two-week period. One of these symptoms must be a depressed mood or loss of interest/pleasure. Other symptoms can include: depressed mood throughout the day; markedly diminished interest/pleasure in activities; weight loss/gain or changes in appetite nearly every day; cognitive and physical slowing; daily fatigue/loss of energy; feelings of worthlessness or excessive guilt; diminished ability to think/concentrate or indecisiveness; recurrent thoughts of death or suicidal ideation without/with a specific plan, occurring most days [3]. Most patients with depression struggle with the ongoing recurrence of depressive episodes, and individuals who experience chronic depression are at a significantly higher risk of suicide [4].

Research indicates that individuals suffering from depression experience challenges in their physical, social, and work functioning when compared to non-depressed individuals. The severity of depression directly influences their overall quality of life. However, measuring the intangible aspects of depression, such as emotional pain, suffering, and strain on relationships and daily activities, poses difficulties. These intangible burdens often lead to disruptions in daily life, breakdowns in family and marital relationships, and, in extreme cases, even homelessness. Unfortunately, estimates of the economic cost of depression typically fail to consider these intangible factors, resulting in underestimations of both the direct and indirect costs associated with depression. Consequently, the true economic impact of depression on society tends to be underestimated [5].

Considering that current treatments, such as cognitive-behavioral therapy and antidepressant medications, are not effective for all patients or may present significant side effects, the continuous emergence of new and innovative treatment for unipolar depression is essential to address this condition more effectively and improve patient outcomes.
In this review, our initial goal was to present traditional antidepressant medications. Subsequently, we aimed to introduce newly developed medications for the treatment of unipolar depression, along with evaluating their effectiveness, safety, and tolerability. Moreover, we sought to highlight medications currently in different stages of development that hold promise for expanding the repertoire of therapeutic options available for depression.

METHODS

To conduct this study, a comprehensive literature search was performed using the PubMed and Google Scholar databases. The search was conducted using the keywords “Pipeline treatment in Unipolar depression” and “Novel treatment in Unipolar depression” to identify relevant articles and studies. Additionally, the website https://clinicaltrials.gov/ was utilized to gather information on ongoing and completed clinical trials related to the identified therapeutic substances. After collecting the relevant information, articles were selected based on their relevance and applicability to the research topic.

Initially, in this study, we excluded traditional antidepressants. Subsequently, we highlighted the emergence of new antidepressants in recent years, as well as medications in various stages of research for unipolar depression. Toward the end of the article, we shed light on potential mechanisms that future treatments for unipolar depression could employ.

RESULTS

Traditional treatment for unipolar depression

The first antidepressant discovered was iproniazid, a monoamine oxidase inhibitor (MAOI), which was initially used for the treatment of tuberculosis in 1950. During this time, it was observed that some patients experienced extreme euphoria and hyperactivity while taking it. In the same year, then tricyclic antidepressant agents (TCAs) were discovered. Shortly after, the role of serotonin in MDD was identified, leading to the development of current first-line therapies such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). However, classic antidepressants have notable drawbacks, including adverse effects and delayed onset of efficacy. It is worth mentioning that more than a third of patients do not respond to traditional antidepressant treatment, which categorizes them as having treatment-resistant depression (TRD) [6].

The novel emerged and approved treatment for unipolar depression

A prevalent challenge in the field of depression treatment is the occurrence of TRD in a considerable proportion of patients (60-70%), resulting in a low rate of achieving full remission. TRD encompasses an inadequate response to a single trial of antidepressant pharmacological treatment.
sant treatment (in terms of dosage, duration, and adherence), while greater resistance is characterized by the failure of two monotherapy trials or one or more augmentation trials. Research has indicated that an extended pathway to complete remission requires a higher number of treatment attempts, thereby increasing the risk of developing resistance. In this review, we will provide a summary of newly emerged antidepressants that have shown potential in facilitating a more rapid response, aiming to prevent the emergence of TRD [7].

**Esketamine**, is a drug approved by U.S. Food and Drug Administration (FDA) in 2019 with the brand name Spravato [8]. It is the S-enantiomer of racemic ketamine and acts as a non-selective, non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors. Esketamine exhibits approximately three to four times greater affinity for NMDA receptors compared to the R-enantiomer, making it effective even at lower doses [9].

Suicide-related morbidity and mortality are significant public health concerns among individuals diagnosed with MDD. Studies indicate that approximately 10% to 20% of patients with MDD will attempt suicide at some point during their lifetime [10,11], with an estimated lifetime risk of 3.4% for completed suicide [12]. Thus, esketamine has shown a rapid, robust, and clinically meaningful reduction in depressive symptoms in phase II/III studies involving treatment-resistant depression [13]. In a proof-of-concept study with depressed patients at imminent risk for suicide, esketamine nasal spray showed promising results, suggesting its potential in the urgent care of individuals with MDD who have active suicidal ideation [14].

Advantages of esketamine include its short- and medium-term effectiveness, superior tolerability compared to racemic ketamine, once-weekly intranasal administration, and the ability for emergency treatment to rapidly alleviate acute depression symptoms. However, disadvantages include higher costs, the need for monitoring tolerability, and limited accessibility due to special prescription requirements.

**Auvelity** combines an NMDA receptor antagonist dextromethorphan (45 mg) with a norepinephrine-dopamine reuptake inhibitor buPROPion (105 mg), additionally, it increases serotonin levels by blocking its reuptake and enhancing its action in the dorsal raphe through sigma-1 agonism [15]. It has been approved by the FDA on 18th August 2022 for treating MDD in adults. This oral medication is the first and only approved treatment for MDD that offers a rapid onset of action. It has been clinically proven to demonstrate statistically significant antidepressant efficacy within one week, as compared to a placebo [16]. Due to the rapid metabolism of dextromethorphan by cytochrome P450 2D6 (CYP2D6), achieving therapeutic levels of dextromethorphan through oral administration alone is challenging. To address this issue, Bupropion, a CYP2D6 inhibitor, is combined with dextromethorphan in Auvelity. This innovative medication combines the mechanisms of action from various antidepressant therapies into a single treatment approach [17].

**Cariprazine**, approved as an Adjunctive Treatment for MDD by FDA on 16 December 2022, is an oral atypical antipsychotic. While the exact mechanism of action is unknown, Cariprazine is believed to work through partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors, as well as antagonist activity at serotonin 5-HT2A receptors. Pharmacodynamic studies have shown that Cariprazine acts as a partial agonist at dopamine D3, dopamine D2, and serotonin 5-HT1A receptors, with a higher affinity for dopamine D3 receptors. It also acts as an antagonist at serotonin 5-HT2B and 5-HT2A receptors and binds to histamine H1 receptors. Cariprazine has a lower affinity for serotonin 5-HT2C and α1A-adrenergic receptors and negligible affinity for cholinergic muscarinic receptors. In a Phase III study with 751 participants, Cariprazine at doses ranging from 1-3 mg/day demonstrated significant efficacy compared to placebo, but higher doses did not show the same level of efficacy [18].

**Brexanolone**, approved by the FDA in March of 2019, an exogenous analog of allopregnanolone, which is a major metabolite of progesterone, has shown promise in the treatment of postpartum depression (PPD). PPD is believed to be triggered by the decline of allopregnanolone levels and subsequent downregulation of γ-aminobutyric acid A (GABAA) receptors. Brexanolone acts as a positive allosteric modulator (PAM) of GABAA receptors, although the precise mechanism of action in treating PPD is not fully understood [19].

Brexanolone is administered intravenously, ensuring full absorption and 100% bioavailability. Adverse effects reported in the brexanolone treatment groups include dizziness, somnolence, headaches, nausea, rash, postural dizziness, dry mouth, hot flushes, pyrexia, sedation, sinus tachycardia, vertigo, infusion site pain, and fatigue. The most frequently reported adverse effects were dizziness and somnolence. Serious adverse events were experienced by 3% of the brexanolone group compared to 2% of the placebo group [19].

FDA black box warnings have been issued for brexanolone due to the risk of central nervous system depression, loss of consciousness, and the requirement of administration in a specialized care facility. Loss of consciousness occurred in 4% of patients in phase III trials, but all patients regained
consciousness within 15 minutes, with excessive sedation resolving within 90 minutes. Rapid effects of brexanolone were observed within 72 hours post-infusion start, but the maintenance of these effects at day 30 is inconsistent across trials [19].

It is worth noting that approximately 22% of participants in phase III trials were using antidepressants alongside brexanolone. The specific choice and dosage of other antidepressants may have influenced the long-term data and sustained effects of brexanolone. Combination use of brexanolone with current antidepressant therapy may provide both rapid and sustained relief of symptoms, but further studies are needed to assess this theory [19].

**The pipeline treatment for unipolar depression**

Medication in phase III clinical trials

**Esmethadone (REL-1017)**, developed by Relmada Therapeutics, is the (S)-enantiomer of methadone, also known as dextromethadone, acting like NMDA receptor channel blocker and new chemical entity (NCE). It is being evaluated in late-stage development for the treatment of MDD. It selectively targets hyperactive channels while maintaining physiological glutamatergic neurotransmission, and the (S)-enantiomer of methadone exhibits a low affinity for opioid receptors, which may reduce its abuse potential [20].

As of July 22, 2022, esmethadone is progressing toward a Phase III study for MDD. However, it did not achieve its primary endpoint, which was a statistically significant improvement in depression symptoms compared to placebo, as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) on Day 28. In the study, the REL-1017 treatment arm showed a reduction of 14.8 points on the MADRS on Day 28, while the placebo arm demonstrated a reduction of 13.9 points, indicating a higher-than-expected placebo response. Paradoxical results were observed in specific study sites, where placebo outperformed REL-1017. Relmada is currently investigating the nature of these findings [22].

**Zuranolone (SAGE-217, SAGE-NCE)**, is currently undergoing evaluation as a potential 14-day, rapid-acting, once-daily, oral medication for the treatment of MDD and PPD. It functions as an oral neuroactive steroid (NAS) that acts as a PAM of GABA-A receptors. The GABA system, a major inhibitory signaling pathway in the brain and central nervous system, plays a significant role in regulating brain function [23].

According to GlobalData, zuranolone is being studied in 25 clinical trials, with 16 completed, 7 ongoing, and 2 terminated. Results from the Phase III SKYLARk study demonstrated the superiority of a 15-day course of zuranolone compared to placebo in women with severe PPD. By day 3, women receiving zuranolone 50 mg daily exhibited a greater reduction in HAM-D (Hamilton Depression Rating Scale) scores compared to those receiving placebo (mean reduction: 9.5 vs. 6.1; P = 0.0008). The difference in mean HAM-D scores continued to increase steadily up to day 15. Even at day 45, women treated with zuranolone continued to exhibit a greater reduction in HAM-D scores compared to those receiving placebo. These findings highlight the potential effectiveness of zuranolone as a rapid-acting oral medication for the treatment of MDD and PPD [24].

However, in another Phase III study conducted on 581 participants, Zuranolone failed to demonstrate a significant effect at the 20 mg doses and showed a moderate effect at the 30 mg per day doses compared to the placebo [25].

**Toludesvenlafaxine (Ansofaxine, LY03005)** is a first-in-class triple monoaminergic reuptake inhibitor (TRI) that has reached clinical use. In China, a multicenter, double-blind, randomized, placebo-controlled Phase III clinical trial was carried out to evaluate the effectiveness and safety of ansofaxine, a potential triple reuptake inhibitor targeting serotonin, norepinephrine, and dopamine, in patients with MDD. A total of 588 eligible MDD patients were included in the study and randomly assigned in a 1:1 ratio to receive 8 weeks of treatment with ansofaxine 80 mg/day (n = 187), ansofaxine 160 mg/day (n = 186), or placebo (n = 185). Significant differences were observed in the mean changes of MADRS (Montgomery-Asberg Depression Rating Scale) total scores at week 8 between the two ansofaxine groups (80 mg: -20.0; 160 mg: -19.9) and the placebo group (-14.6; p < 0.0001).

The administration of ansofaxine at both doses was generally well-tolerated. These initial findings from the trial suggest that ansofaxine at both the 80 mg/day and 160 mg/day doses demonstrated effectiveness and safety in adult patients with MDD. The trial is registered under the ClinicalTrials.gov Identifier NCT04853407 [26].

**Rapastinel**, is an investigational intravenous (IV) formulation of a novel NMDA receptor partial agonist. The drug was discovered to have a rapid and...
long-lasting antidepressant effect in a phase II study, manifesting within 1 day [27].

The three crucial trials, namely RAP-MD-01, RAP-MD-02, and RAP-MD-03, involved patients with MDD who had a partial response to antidepressant therapy. These patients were randomly assigned to receive either a weekly bolus intravenous injection of rapastinel or a placebo along with an oral antidepressant therapy [27]. The results from the three acute studies indicated that the treatment groups receiving rapastinel did not show a significant difference compared to the placebo group in terms of the change in the MADRS total score, which was the primary endpoint. Furthermore, an interim analysis of a study assessing rapastinel for preventing relapse in MDD patients (RAP-MD-04) suggests that the primary and secondary endpoints of this trial will also not be achieved [27].

**Seltorexant (MIN-202),** is an advanced clinical development drug that acts as a selective antagonist of the human orexin-2 receptor. The orexin neuropeptide plays a role in regulating wakefulness, and inhibiting orexin receptor signaling promotes sleep. Seltorexant is being investigated as a potential treatment for depression, as it is believed to be effective in improving sleep. Additionally, it is being tested for its potential to treat agitation and aggression in individuals with Alzheimer’s disease (AD) [28].

Since 2009, Janssen has conducted over 20 Phase I studies on seltorexant. In individuals with insomnia, the drug has shown promising results, reducing the time it takes to fall asleep and increasing overall sleep duration [29]. Moreover, in patients with major depression and persistent insomnia, seltorexant has demonstrated the ability to alleviate core symptoms of depression and improve sleep quality [30].

A Phase II trial revealed that the addition of seltorexant improved depressive symptoms in individuals who had previously shown a poor response to serotonin reuptake inhibitors. Notably, the drug exhibited the greatest efficacy in individuals with severe sleep disturbances at the beginning of the study [31]. Headache, sleepiness, and nausea were among the most commonly reported adverse effects.

Currently, two Phase III trials are underway, examining the effects of six weeks of seltorexant when added to antidepressant treatment in individuals with major depression and insomnia. These studies involve a total of 1,270 patients and are expected to conclude in 2023 [32,33].

**Buprenorphine/Samidorphan** is a µ-opioid-receptor partial agonist and κ-opioid-receptor antagonist with antidepressant activity. Two Phase III studies, namely FORWARD-4 and FORWARD-5, were conducted. These studies were multicenter, randomized, double-blind, and placebo-controlled, aiming to evaluate the efficacy and safety of ALKS 5461 as an adjunctive treatment for patients with MDD who had an inadequate response to standard antidepressant therapies. Both studies employed a sequential parallel-comparison design, which involves two treatment stages and two randomizations within a single study to mitigate the impact of the placebo response commonly observed in psychiatric trials. The most common adverse events observed in these studies included nausea, constipation, dizziness, vomiting, somnolence, fatigue, and sedation [34].

FORWARD-5 successfully met the primary endpoint, demonstrating that adjunctive BUP/SAM 2 mg/2 mg was superior to placebo in terms of the average difference in change from baseline to week 3 through the end of treatment in MADRS-6 and MADRS-10 (−1.5, P = 0.018; −1.9, P = 0.026, respectively). On the other hand, FORWARD-4 did not achieve the primary endpoint, as the change from baseline in MADRS-10 at week 5 versus placebo showed a result of −1.8 (P = 0.109). Nevertheless, separate analyses indicated significant treatment differences at other time points using traditional, regulatory-accepted endpoints such as the reduction in MADRS-10 at the end of treatment [35].

**Transdermal Estradiol and Micronized Progesterone,** is another combination of substances administered transdermally. Currently, a randomized clinical trial is underway involving 172 euthymic patients in the perimenopausal and early postmenopausal periods. The trial involves the administration of transdermal estradiol (0.1 mg/day) or a transdermal placebo over a duration of 12 months. In addition, oral micronized progesterone (200 mg/day for 12 days) is given every 3 months to women receiving active transdermal estradiol, while identical placebo pills are given to women receiving the placebo. After 12 months, it was observed that 32.3% of women receiving the placebo developed clinically significant depressive symptoms, whereas only 17.3% of women taking transdermal estradiol and intermittent micronized progesterone did so [36].

Medication in phase II clinical trials

**Onfasprodil (MIJ821),** being developed by Novartis, is currently in Phase II of clinical development for Major Depressive Disorder. According to GlobalData, Phase II drugs targeting MDD have a benchmark success rate of 39% for transitioning into Phase III [37].

MIJ821 is a negative allosteric modulator of the NMDAR subtype 2B. In phase II double-blind randomized controlled trial involving 70 patients with TRD, MIJ821 was administered via infusion on a weekly or bi-weekly basis for 6 weeks at doses of 0.16mg/kg and 0.32mg/kg. The treatment arms were compared with a weekly administration of 0.5 mg/kg of ketamine and a placebo, resulting in a total of 6
arms in the study (NCT03756129). Significantly greater reductions in the MADRS total score at 24 hours (primary outcome) were observed in the pooled MIJ821 0.16 mg/kg group (-15.51, p = 0.0013) and the pooled MIJ821 0.32 mg/kg group (-12.98, p = 0.0196) compared to the placebo group (-7.27). The intravenous ketamine group showed a MADRS score reduction of -12.9, but no direct comparison was made to MIJ821 or placebo. The antidepressant effects of MIJ821 were also significant at 48 hours but not sustained at 6 weeks. The study did not report the response rate based on MADRS. The most common adverse event associated with MIJ821 was amnesia (10.0%), and dissociation occurred in 5.0% of the pooled MIJ821 group. As of October 8, 2021, a phase II trial investigating MIJ821 in patients with MDD who have suicidal ideation with intent was still in the recruitment stage, according to ClinicalTrials.gov, (NCT04722666) [38].

Psilocybe, a naturally occurring psychedelic compound found in the psychoactive psilocybe genus of mushrooms, acts as a serotonin 5-hydroxytryptamine type 2A (5-HT2A) receptor agonist.

In a phase II trial with a waiting list-controlled design, involving 27 patients with MDD, the primary endpoint was the change in Hamilton Depression Rating Scale 17 (HAMD17) scores at 1 week and 4 weeks after two psilocybin sessions. The psilocybin group received a dosage of 20 mg/70 kg in the first session and 30 mg/70 kg in the second session. The HAMD17 scores in the psilocybin group were significantly lower than those in the waiting-list group (8.0 ± 7.1 and 8.5 ± 5.7, respectively, both p-values < 0.001) at both time points (NCT03181529) [39].

In another double-blind, randomized clinical trial conducted with 52 participants diagnosed with major depressive disorder. The study took place at a psychiatric university hospital in Zurich, Switzerland, between April 2019 and October 2021. Participants were assigned to receive either a moderate dose of psilocybin or a placebo, along with psychological support. The trial’s primary endpoints were changes in depression severity measured by MADRS and BDI scores from baseline to 14 days after the intervention. The results showed that the group receiving psilocybin experienced a significant decrease in symptom severity, with a reduction of -13.0 points on the MADRS scale and -13.2 points on the BDI scale compared to baseline. These reductions were significantly larger than those observed in the placebo group. Furthermore, 54% of participants in the psilocybin condition met the remission criteria based on MADRS. Overall, the study indicated that a single moderate dose of psilocybin, combined with psychological support, led to significant improvements in depression symptoms in participants with MDD [40].

In a phase II trial (NCT037775200) involving individuals with treatment-resistant depression, the results indicated that a 25-mg dose of psilocybin led to significantly greater reductions in depression scores compared to a 1-mg dose over a 3-week period. However, it was noted that this higher dose was associated with adverse effects. Among the 233 participants in the trial, 77% experienced adverse events, including symptoms such as dizziness, headaches, and nausea, as reported by the investigators. These findings suggest that while the higher dose of psilocybin showed promising efficacy in reducing depression scores, it also came with a higher likelihood of experiencing adverse effects [41].

Nitrous oxide is an inhalational anesthetic commonly used in dentistry, emergency centers, and ambulatory surgery centers.

In a phase II crossover randomized controlled trial (RCT) involving 20 patients with TRD, inhalation of 50% nitrous oxide plus 50% oxygen for 1 hour was superior to placebo gas in improving the HAMD21 scores at 2 hours and 24 hours. The response rates at 24 hours were 20.0% in the nitrous oxide group and 5.0% in the placebo group, although this difference was not statistically significant. Common adverse events included nausea/vomiting, headache, numbness/paresthesia, and anxiety [42].

In another phase II crossover RCT with 24 patients with TRD, a single 1-hour inhalation of 50% and 25% nitrous oxide in oxygen did not show a significant reduction in HAMD21 scores compared to placebo gas at 2 hours, 24 hours, and week 1, but did at week 2. The response rates at 2 weeks were higher in the nitrous oxide groups compared to the placebo group, but the differences were not statistically significant. Adverse events reported 24 hours after inhalation included common cold/strep throat. Mild dissociative effects were reported during or immediately after inhalation, including feelings of disconnection, light-headedness, feeling high, and paranoia [43].

Results from another phase II study examining 1-hour inhalation of 50% nitrous oxide have not been reported yet, and an ongoing phase II RCT is investigating the effects of nitrous oxide at different concentrations [44].

Ayahuasca, a hallucinogenic botanical mixture used for healing and spiritual purposes in South America, combines N, N-dimethyltryptamine (DMT) with monoamine oxidase-inhibiting β-carbol ine alkaloids.

In a phase II double-blind, randomized controlled trial with 29 patients suffering from TRD, a single dose of ayahuasca demonstrated a significant improvement in the HAMD total score compared to placebo on day 7. The response rates at day 7 were also significantly different between the ayahuasca and placebo groups. Nausea and vomiting were common
side effects reported by participants [45]. No ongoing trials were registered as of August 22, 2021.

Local injections of botulinum toxin A (BTA), specifically in the facial muscles of the glabellar region, have been investigated for their potential antidepressant effects. This is thought to be due to the influence of facial expressions on emotional perception [46]. In a phase II crossover randomized controlled trial (DBRCT) involving patients with MDD, significant improvements were observed in the HAMD21 scores in patients who received BTA compared to those who received a placebo. The response rate was also significantly higher in the BTA group compared to the placebo group. Safety data were not reported in this study [47].

Another phase II DBRCT with female patients showed that 30 units of BTA had a marginally significant reduction in the MADRS scores compared to the placebo. Headache was a commonly reported adverse event in the BTA group, but there were no reports of dissociative symptoms, psychotic symptoms, or dependence [46].

The addition of BTA to ongoing antidepressant treatment demonstrated greater efficacy in reducing HAMD17 scores compared to placebo in another phase II DBRCT. Headache was again the main adverse event reported in the BTA group [48].

A phase IV DBRCT found that BTA had a higher response rate compared to placebo in patients with MDD. However, safety data for this study were not provided [49].

Future treatment

The development of drugs targeting NMDA and GABA-A receptors represents a promising advancement in the treatment of MDD. These drugs offer the potential for a faster response and may benefit a larger proportion of patients compared to monoamine-based therapies. In addition to NMDA and GABA-A receptors, other receptor targets of interest in MDD drug development include orexin, peroxisome proliferator-activated receptors, G-protein-coupled receptor 39, metabotropic glutamate receptors, galanin, and opioid receptors. Several biological processes, such as inflammation, oxidative stress, metabolic dysfunction, mitochondrial dysfunction, and neuroendocrine dysfunction, have also been implicated in the pathogenesis of MDD [50].

Although therapeutic compounds for most of these targets and processes are still in the early stages of development or yet to be identified, there are ongoing investigations into approved cyclooxygenase inhibitors, biological therapies, next-generation monoamine drugs, and atypical antipsychotics, considering their potential relevance to MDD and inflammation. As our understanding of the neurobiology of MDD continues to evolve, we can hope for the emergence of more promising treatments in the MDD treatment arsenal from ongoing drug development pipelines [50].

DISCUSSION

The article “Pipeline, novel, and future treatments for UNIPOLAR depression” highlights the prevalence of depression as a significant global issue affecting millions of people, including children and adolescents. It emphasizes the need for accessible and diverse antidepressant medications to effectively treat depression. Current treatments such as cognitive-behavioral therapy and conventional antidepressants may not be universally effective or may cause significant side effects. The article focuses on the development of new therapeutic options to enhance treatment efficacy and tolerability. Promising medications, including Esketamine, Auvelity, Cariprazine, and Brexanolone, are discussed, along with their demonstrated effectiveness in clinical studies. Additionally, emerging treatments such as Esmethadone, Zuranolone, Toludesvenlafaxine, Rapastinel, Seltorexant, and Buprenorphine/Samidorphan are highlighted as potential future options for depression treatment. The article also mentions other investigational treatments like onfasprodil, psilocybin, nitric oxide, and botulinum toxin A, which have shown positive results in phase II studies but require further research and clinical trials to confirm their efficacy and safety. Overall, the article provides insights into the diverse pipeline of antidepressant treatments, offering hope for a brighter future for patients with depression, including those who are treatment-resistant.

Conflict of interest: none declared

Financial support: none declared

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