Review

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Neuroplasticity and Mechanisms of Action of Acute and Chronic Treatment with Antidepressants at an Experimental Level

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Abstract: The neurobiology of depression establishes a close relationship between this psychiatric disorder and alterations in neuroplasticity associated with neuronal atrophy and a reduction in dendritic arborization in the prefrontal cortex and hippocampus. In this sense, the therapeutic effect of antidepressants is associated with changes in the brain associated with neuroplasticity, neurogenesis and synaptogenesis through the activation of intracellular signaling pathways associated with changes at the neurochemical and behavioral level in animal models used to study depression. Antidepressants increase the synaptic availability of monoamines (monoaminergic hypothesis) such as serotonin, noradrenaline and GABA by inhibiting their reuptake or degradation and activating intracellular signaling pathways such as the cAMP-CREB cascade, which regulates the expression of genes related to neuroplasticity and neurogenesis in various brain structures associated with depression. Although acute treatment alters the number of receptors, the therapeutic effect lasts 3-4 weeks and depends on the increase in the density of dendritic spines and the expression of proteins such as BDNF and GAP-43 in the hippocampus and cerebral cortex. This review focuses on the effects of acute and chronic treatment with monoaminergic antidepressants and new drugs and other pharmacological alternatives in preclinical studies with the aim of demonstrating their mechanism of action and relationship to neuroplasticity.

Keywords: neuroplasticity; antidepressants; acute and chronic treatment; depression; mechanisms of action; neurotrophic factors

1. Introduction

The therapeutic effect of antidepressants is based on complex mechanisms involving neuroplasticity that go beyond the traditional monoaminergic deficit hypothesis. Neuroplasticity is the adaptive ability of the brain to reorganise and form new connections under normal and pathological conditions [1]. Depression causes dendritic neuronal atrophy and a reduction in glial cells and dendritic arborization in neurons of the prefrontal cortex and hippocampus. In addition, an increase in dendritic branching of neurons of the cerebral amygdala was reported [2]. The neurotrophic hypothesis states that treatment with antidepressants promotes neu-roadaptive changes at the level of the brain, changes that counteract some of the characteristic symptoms of depression [3]. Chronic antidepressant treatment is known to promote complex mechanisms at the cellular, molecular and structural levels of neurons, via intracellular signalling pathways involved in survival and neuroplasticity. Chronic treatment with antidepressants stimulates the function of cAMP-responsive element binding protein (CREB), a transcription factor that regulates the expression of genes involved in neuroplasticity, cell survival and cognition [1].

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It promotes neurogenesis, dendritic arborization and synaptogenesis in the hippocampus and prefrontal cortex and reverses the pathological effects of stress and depression [4]. The cAMP-MAPK-CREB-BDNF cascade is involved in dendritic restructuring, neurogenesis and cell survival [5]. Chronic stress has been reported to decrease neuroprotective factors such as brain-derived neurotrophic factor (BDNF), which negatively affects neuroplasticity and increases neuronal atrophy. This phenomenon leads to a reduction in synaptic contacts and brain volume [2,6]. In contrast, other subcortical regions such as the amygdala show hypertrophy in the context of depression, possibly contributing to the anxiety and altered emotions characteristic of this disorder [7]. These findings underscore the critical importance of understanding the neurobiological mechanisms underlying depression as a basis for developing more effective and targeted therapeutic approaches that can counteract the observed brain changes.

Treatment alternatives have been tested at an experimental level with the aim of improving the efficacy and safety of treatments for depression. This research is of crucial importance, especially considering that response rates to existing treatments are only 50% [8]. In this sense, the effect of chronic treatment with antidepressants has been confirmed in animal models such as forced swimming, where the effect of relatively low doses of fluoxetine on behavioural hopelessness has been observed [9,10]. In addition, an increase in BDNF specifically in the hippocampus and prefrontal cortex of mice [11] and an increase in the expression of 5-HT1A and 5-HT2A receptors in the raphe, hippocampus and cerebral cortex of the rat [12] have been observed. However, acute treatment, especially at high doses administered 24, 5 and 1 hour before the forced swim test, has been shown to alter behavioural indicators of hopelessness in rats. These effects appear to be related to an increase in levels of neurotransmitters such as gamma-aminobutyric acid (GABA), dopamine (DA), noradrenaline (NA) and serotonin (5-HT), without necessarily causing plastic changes in brain structures that control emotional processing [13,14]. These findings on antidepressants have led to the exploration of new pharmacological strategies targeting non-monoaminergic mechanisms.

The aim of this review is to provide a comprehensive understanding of the different antidepressants used experimentally, to elucidate the mechanisms of action of the different antidepressants and to determine the differences between acute and chronic antidepressant treatment on an experimental level on neuroplasticity in the rodent brain. To prepare this review, we conducted a comprehensive bibliographic search in PubMed, Scopus and Web of Science using specific keywords such as antidepressants, acute treatment, chronic treatment, forced swimming, neuroplasticity and experimental depression. The search was refined to include only studies published since 2000. Inclusion criteria focused on research articles, reviews, abstracts and position statements examining the effects of different types of antidepressants at an experimental level during chronic and acute treatment, as well as their mechanism of action and changes in neuroplasticity. Exclusion criteria excluded those studies that had no antidepressant effect, did not have access to full text, or were not rigorously peer-reviewed.

Data extraction followed a structured approach, capturing critical information on study design, key findings and the relevance of each study to understanding the differences in antidepressant effect between acute and chronic administration and the potential mechanism of action of each effect. We assessed the quality and validity of the studies based on methodological rigor, reproducibility and peer-reviewed status. This approach ensured that only high quality studies were included, allowing a comprehensive synthesis of the current state of knowledge.

2. Depression Overview

According to the World Health Organization, depression is a mental disorder characterized by a depressed mood or a lack of interest in activities for prolonged periods of time [15]. This debilitating emotional state is accompanied by symptoms such as cognitive impairment, hopelessness, despair, feelings of emptiness, changes in sleeping and eating patterns, difficulty concentrating and suicidal thoughts [16]. The effects of depression extend beyond the person affected and significantly affect their family, social and community relationships [15]. Depression is one of the leading causes of disability worldwide, affecting approximately 3.8 of the world's population, or around 280 million

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people [17–20]. Depression, particularly in patients with medical conditions, exacerbates the burden of disease and negatively impacts quality of life [21,22]. Building on this, the recent COVID-19 pandemic that emerged in 2020 has further exacerbated this situation, with factors such as childbirth and loss of loved ones contributing to increased rates of depression [23–25].

Neurobiological research on depression has shown a strong link between this psychiatric disorder and changes in neuroplasticity. These changes are particularly evident in neuronal atrophy and the reduction of dendritic branching in key brain structures such as the prefrontal cortex and hippocampus. A model has been proposed in which prolonged stress decreases neuroprotective factors such as BDNF, which negatively affects neuronal plasticity and increases neuronal atrophy. This process leads to a reduction in synaptic contacts and brain volume [2,26]. Conversely, other subcortical regions, such as the amygdala, exhibit hypertrophy associated with depression, which may contribute to the anxiety and altered emotions characteristic of this disorder [7]. These findings highlight the importance of understanding the neurobiological mechanisms underlying depression in order to develop more effective and targeted therapeutic approaches that can counteract the observed brain changes. The treatment of depression includes pharmacological and non-pharmacological options such as psychotherapy, but antidepressants can cause a number of adverse effects [27,28]. The low adherence to treatment and the occurrence of side effects have driven the search for therapeutic alternatives [29–31].

Preclinical research into treatment alternatives is being conducted with the aim of improving the efficacy and safety of depression treatments. This research is crucial, especially considering that response rates to existing treatments are only around 50% [32]. Therefore, research into antidepressant alternatives, such as herbal medicines, is crucial for improving treatment outcomes. Given the chronic nature of depression and the need to find both acute and long-term treatment solutions, the ongoing evaluation of these alternatives is critical to addressing the significant global burden of depression.

3. Mechanisms of Action of Antidepressants and Neuroplasticity

The main mechanism of action of antidepressants focuses on the synaptic availability of monoamines by inhibiting reuptake or degradation [33]. It is known that acute treatment has an effects on the number of receptors. The pharmacological response to chronic treatments in the clinic suggests neuroplasticity mechanisms necessary for the establishment of the therapeutic effect [34]. In addition, chronic administration of antidepressants leads to changes in the sensitivity of presynaptic and postsynaptic receptors [35]. These mechanisms usually focus on the restructuring of neuronal synapses, a process known as neuroplasticity of the neurotransmission systems involved, mainly 5-HT, NA and GABA. This process takes about 3 to 4 weeks [12], which explains the long latency period with which the therapeutic effects of drugs and substances with antidepressant activity can be observed.

The mechanism of action of drugs with antidepressant effects, such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs), have in common the enhancement of serotonergic neurotransmission [35], but their therapeutic effects are based on complex mechanisms (Shelton, 2000). Some of the mechanisms activate the adenylate cyclase-protein kinase A cascade and inhibit the phospholipase C-protein kinase C mechanisms that regulate gene expression. They also alter the expression levels of mRNAs of various receptors, neurotrophic factors and neuropeptides [36]. Crystallographic studies of G-protein-coupled receptors and neurotransmitter transporters have enabled us to understand the mechanism of antidepressants and to develop new drugs [37].

The molecular and cellular mechanisms by which antidepressants exert their effects are complex, i.e. they go beyond increasing the availability of monoamines in the synaptic space [38]. Acute administration of antidepressants can modulate the neuronal ERK/MAPK (extracellular signal-regulated kinase/mitogen-activated protein kinase) signalling pathway in the prefrontal cortex, which contributes to the restoration of neurogenesis and neuroplasticity [39]. Some antidepressants such as fluoxetine and ketamine have the ability to bind to the trkB receptor, a mechanism by which

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they could induce plastic changes at the brain level [40]. Chronic treatment, in turn, causes greater activation of the cAMP system, thereby increases the expression of transcription factors such as CREB, which regulate target genes such as BDNF [41]. In addition, it has been reported to increase neurogenesis in the adult hippocampus [40]. These changes in neuroplasticity strengthen synaptic connectivity and remodelling of neuronal circuits in the emotional circuitry [38].

Several studies have reported that fluoxetine ingestion induces long-lasting behavioral changes and neuroplasticity in the hippocampus and cortex in intact adult rodents [42,43]. In this sense, young rats (9 weeks old) treated with 10 mg/kg fluoxetine twice daily for three weeks showed greater motivation to explore novel environments in the Y-maze, with no effects on anhedonia and anxiety, assessed respectively with the sucrose test and the Elevated Plus Maze. However, an increase in the number of 5-bromodeoxyuridine-positive (BrdU+) cells, the density of dendritic spines in layer II/III pyramidal neurons of the medial prefrontal cortex, and the expression levels of BDNF/tropomyosin receptor kinase B (TrkB) were observed. These changes can persist for up to 20 days after the last fluoxetine dose [43].

Chronic treatment with fluoxetine has been shown to induce neuroplasticity in several brain regions of rodents. In the somatosensory cortex of rats, it increases c-fos expression and dendritic spine density [44]. In mice, administration of 10 mg/kg fluoxetine over a two-week period led to a reduction in hopelessness, anhedonia and anxiety. In addition, fluoxetine treatment decreased the deterioration of hippocampal neurons and the number of dendritic spines tended to increase, which is attributed to synaptic plasticity [45]. Similarly, in the chronic social isolation model in rats, administration of 5 mg/kg fluoxetine for three weeks was shown to reverse the behavioral effects induced by stress. On the other hand, the synaptosomal polysialic acid-neuronal cell adhesion molecule (plasticity-related molecule in the hippocampus) (PSA-NCAM), a molecular marker of plasticity, increases in the hippocampus of chronically isolated rats, an effect that is reversed by fluoxetine treatment [46]. However, the effects of fluoxetine in young rats are reported to differ from those in adults. As PSA-NCAM expression increases in several brain regions, the number of proliferating cells in the subventricular zone decreases [47].

These results show that the effect of fluoxetine on neuroplasticity varies according to treatment duration, age and brain region, as the mechanism by which fluoxetine achieves the antidepressant effect is complex. Another study examined the effect of chronic treatment with fluoxetine on neurogenesis and the expression of growth-associated protein 43 (GAP43), a synaptic protein, in the hip pocampus of rats exposed to chronic unpredictable mild stress (CUMS), a behavioral model similar to depression. The results of this study showed that the treatment decreased immobility in the forced swim test and increased the expression of BrdU-positive cells and GAP-43 (a protein associated with neuronal plasticity). However, fluoxetine has a greater effect on neurite outgrowth than on neurogenesis [48].

On the other hand, the most commonly used tools in preclinical research to elucidate the mechanisms of action of drugs or molecules with antidepressant potential include the forced swim test, water uptake with sucrose or tail suspension, etc. These studies can be carried out with acute or chronic administration. Forced swimming, for example, is one of the most widely used and validated behavioral models for the study of drugs and substances with potential antidepressant effects, which assesses the hopelessness of the behavior. In this model, drugs or substances with antidepressant potential such as fluoxetine reduce immobility behavior and prolong the latency to the first immobility period, which is interpreted as an increase in the animal's motivation to escape from the stressful situation presented by the forced swim [9], a typical effect of clinically effective antidepressants. Furthermore, antidepressants that are ineffective when administered acutely have been shown to exert an antidepressant effects when administered chronically to experimental animals [49]. This chronic administration is necessary if the effects of stress on immobility and changes in neuroplasticity are to be reversed [45,49].

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4. Pharmacological Treatment of Depression

The pharmacological treatment of major depressive disorder (MDD) is based on the use of serotonergic drugs, despite their limited efficacy. Several mechanistically novel drugs have been developed in recent years, but many fail in clinical trials. Several hypotheses have been proposed to explain the pathophysiology of MDD, suggesting that physio-logical processes such as neuroplasticity, circadian rhythms and metabolism are potential targets [50].

Despite their limited efficacy, these antidepressants, especially SSRIs, are still the most important drugs for the pharmacological treatment of MDD. Approximately 35–50% of patients do not respond to treatment [51,52]. In addition, lethargy, sedation and sexual dysfunction are side effects of serotonergic antidepressants, making it difficult for patients to adhere to the required treatment regimens [53,54]. The time interval of at least two weeks to see an improvement in depressive symptoms when using currently available medications and the lack of response in treatment-resistant depressed patients are also issues that need to be addressed [55].

The monoaminergic hypothesis for depression, formulated in part on the basis of the antidepressant efficacy of serotonergic drugs, has not found sufficient support in the studies conducted to date [56]. Therefore, there is an urgent need to find new non-serotonergic drug targets with greater pharmacological efficacy and fewer side effects.

Early studies in MDD patients showed decreased levels of the monoamines 5-HT, DA and NE in the brain, leading to the so-called "monoaminergic hypothesis", that led to the development of several classes of antidepressants that primarily target the monoaminergic system [57,58]. MAOIs were the first compounds to show antidepressant activity by increasing the availability of monoamines in the synaptic cleft by preventing their degradation by monoamine oxidase (MAO) enzymes [50]. However, the use of MAOIs was restricted due to adverse effects and their reported toxicity [59,60].

Another class of drugs are the TCAs and tetracyclic antidepressants. TCAs such as imipramine cause an improvement in depressive state in some patients by inhibiting presynaptic NE and 5-HT reuptake transporters, leading to an increase in the concentration of NE and 5-HT in the synaptic cleft [50]. However, cyclic antidepressants can also act on other postsynaptic receptors (α-adrenergic, histaminergic and cholinergic). However, they are associated with adverse effects such as dizziness and memory impairment [60,61].

In the search for antidepressants with improved efficacy and effectiveness, pharmaceutical companies began researching ligands that selectively inhibit 5-HT reuptake. This led to the development of fluoxetine, the first SSRI approved by the Food and Drug Administration (FDA) [62]. Since then, other SSRIs have proven effective and are prescribed as first-line treatment for depression. SSRIs work by increasing the availability of 5-HT in the synaptic cleft, specifically by inhibiting 5-HT reuptake transporters. SSRIs have fewer side effects than TCAs, which typically include sexual dysfunction, insomnia and loss of appetite [58,60].

Another class of medications used to treat MDD are atypical antidepressants, which differ in their mechanism of action from other treatments and often act on multiple targets. 5-HT and NA reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, have been developed to selectively inhibit both the 5-HT and NA transporters [61]. There is evidence that SNRIs may be more effective than SSRIs in the treatment of MDD. Unfortunately, this effect seems to be specifically related to venlafaxine, which, however, has a higher discontinuation rate due to side effects [63–65].

Atypical or multimodal antidepressants act on other neurotransmitter systems. For example, bupropion is a DA and NA reuptake inhibitor that has a higher affinity for the DA reuptake transporter [66], while agomelatine is a melatonin receptor agonist and an inhibitor of certain serotonergic receptors [67]. Another class of antidepressants is referred to as "noradrenergic and serotonergic specific antidepressants" or NaSSAs. These drugs, represented mainly by mirtazapine, antagonize the a2-adrenergic receptor and inhibit certain serotonergic receptors [68]. Vortioxetine, one of the drugs recently approved by the FDA, inhibits 5-HT reuptake by inhibiting its transporter and has a high affinity for several types of 5-HT receptors [69]. The common side effects of atypical

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antidepressants are usually mild and include nausea, dry mouth, insomnia, nervousness, and low libido.

Recently, some antidepressants have been launched, such as es-ketamine (Spravato) [70], a glutamatergic antagonist, the combination of dextrom-thorphan, an N-methyl-D-aspartate (NMDA) receptor antagonist, with bupropion (Auvelity) [71] and brexanolone (Zulresso), a positive allosteric modulator of GABAA [72]. Although these are new drugs for the treatment of MDD, they have been developed for specific indications, making it difficult to use them for specific types of depression. For example, Zulresso is only prescribed for postpartum depression; Spravato is only indicated for patients who do not respond to drug treatment for depression and may have sedation and cognitive impairment as side effects; and Auvelity has addiction potential, as dextromethorphan is known to have this problem. These new drugs can be seen as significant advances in the pharmacotherapy of MDD. However, they have limitations due to side effects, so the search for antidepressants with better effectiveness and efficacy for the treatment of MDD should continue [50]. The most commonly used antidepressants for the treatment of depression are listed in **Table 1.**

Table 1. Classes of antidepressants that are used to treat depression.

Class	Pharmacological target	Mechanism of action	Reference
Monoamine Oxidase Inhibitors (IMAO)			
Selegiline Fenelzina	Monoamine Oxidase Enzyme Type A and B.	Prevents the degradation of 5-hydroxytryptamine (5-HT); increases the availability of 5-HT in the synapses.	[59,60].
Tricyclic antidepressants (TCA)			
Amitriptyline Imipramine Nortriptyline	5-HT reuptake transporter and norepinephrine (NE) reuptake transporter.	Inhibits NE and 5-HT reuptake transporters; increases the availability of 5-HT and NE at the synapses; binds to postsynaptic noradrenaline, histamine and acetylcholine receptors.	[58,59].
Selective serotonin reuptake inhibitors (SSRIs)			
Fluoxetine Paroxetine Escitalopram Sertraline	5-HT reuptake transporters	In particular, they inhibit the reuptake of 5-HT, which increases the availability of serotonin in the synapse.	[58,60,64].
Specific noradrenergic and serotonergic antidepressants			
Mirtazapine Mianserin	α2 NE receptors and 5-HT receptors	α-2 NE receptor antagonists that cause an increased release of 5-HT and NE; they act as antagonists/agonists of several specific 5-HT receptors.	[68,73–75].
Norepinephrine and serotonin reuptake inhibitors			
Venlafaxine Duloxetine	5-HT receptors and NE uptake transporters	Inhibits the reuptake of 5-HT and NE and increases their availability in the synapses.	[75,76].
Atypical antidepressants			
Agomelatine			[76,77].

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Bupropion Vortioxetine	5-HT receptors, NE receptors and melatonin receptors	Bupropion acts as a DA and NE reuptake inhibitor; vortioxetine acts as an agonist/antagonist of several 5-HT and NE receptors; agomelatine activates melatonin receptors and antagonizes some 5-HT receptors.	
	New antidepressants		
Ketamine	Antagonist of the ionotropic glutamate receptor, NMDA 3A. Potentiator of the 5-hydroxytryptamine receptor 3A. Antagonist of the neuronal acetylcholine receptor subunit alpha-7. Inhibitor of nitric oxide synthase brain. Agonist and partial agonist of the dopamine D2 receptor. Agonist of the kappa-type opioid receptor. Antagonist of 5-hydroxytryptamine receptor 2 and 5-hydroxytryptamine receptor 1.	Ketamine interacts with N-methyl-D-aspartate (NMDA) receptors, opioid receptors, monoaminergic receptors, muscarinic receptors and voltage sensitive Ca ion channels. Unlike other general anaesthetic agents, ketamine does not interact with GABA receptors	[70,71].
Brexenolone	Positive allosteric modulator GABA(A) Receptor	Brexanolone is a neuroactive steroid that occurs naturally in the body (as natural allopregnanolone) when the female sex hormone progesterone is metabolized. This steroid compound is also thought to act as a barbitu-like positive allosteric modulator of synaptic and extrasynaptic GABAA receptors. In this way, brexanolone may enhance the activity of GABA at these receptors by opening the calcium channels of GABAA receptors more frequently and for longer periods of time. It is also thought that brexanolone triggers this effect on GABAA receptors at a binding site that differs from those of benzodiazepines.	[78–81].

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5. Effect of Acute Antidepressant Treatment on an Experimental Level

In preclinical studies, it is possible to observe the effect of high doses of antidepressants during acute administration, that is impossible to replicate in the clinic. There is evidence that acute treatment with antidepressants can have rapid effects on a subset of symptoms [82]. However, chronic administrations of two to four weeks are necessary to achieve a desired pharmacological effect according to the Hamilton scale [83].

Several studies have shown that a dose of 20 mg/kg fluoxetine administered 23.5, 5 and 1 hour before the forced swim test reduced immobility behavior in male rats in the Porsolt pond through effects on the 5-HT2C receptor [84]. On the other hand, [85] showed that fluoxetine at doses of 5 and 10 mg/kg reduced immobility and increased swimming behavior in ovariectomized female rats during treatment for 23.5, 5 and 1 h before the forced swim test. On the other hand, [14] reported that a dose of 10 mg/kg fluoxetine reduced immobility in female and male rats. However, low doses of 5 mg/kg fluoxetine do not have the same effect in male rats under the same dosing regimen [86]. Furthermore, antidepressants that are ineffective when administered acutely have been shown to produce antidepressant-like effects when administered chronically [49,86,87]. Such chronic administration in experimental sub-trials tends to be necessary to reverse the effects of stress on immobility [49,87].

The most commonly used antidepressants in clinical practise are selective inhibitors such as 5-HT and NA inhibitors, MAOIs and TCAs, which represent the best pharmacological options. Nevertheless, a high percentage of patients do not achieve sustained remission due to adverse effects or the long time it takes for the therapeutic effects to kick in. It is therefore necessary to explore more effective and safer drugs with a faster onset of action. In this sense, two scenarios have been observed: i) the fact that in preclinical research, conventional antidepressants can produce different effects at effective or high acute doses, ranging from the emergence of anxiety-like behaviours or states [88] to antidepressant effects in preclinical models after 1 to 3 administrations within 24 hours, such as fluoxetine [13,14] and citalopram [88] in both sexes and different age groups [14].

These drugs have changed the paradigm of antidepressants, in which a long latency to therapeutic effect was considered an indispensable prerequisite, related to the establishment of slow-onset plastic changes in the various neural circuits that regulate motivated behavior and that are associated with changes in neurotrophin levels [89,90], which will be described later.

On the other hand, recent studies in both preclinical and clinical research have found new agents capable of producing antidepressant-like effects after a single administration and over a period of several hours [91–93]. These agents are substances previously known for other pharmacological properties, such as ketamine, which is used as an anesthetic and whose been discovered have been discovered at the clinical level [94], hallucinogens such as psilocybin and neurosteroids such as allopregnanolone, which have been shown to be effective in the treatment of depression over a period of 24 to 36 hours [95].

Other studies have reported that SSRI treatment increases synaptic 5-HT availability to a limited extent when administered acutely (2 to 4 administrations), due to inhibitory effects on release mediated by somatodendritic 5-HT1A receptors and terminal 5-HT1B autoreceptors [88], whose inhibitory effect on release is decreased after chronic treatment or by their antagonism [96]. It has been known for more than two decades that acute antidepressant treatment with 10 mg/kg fluoxetine induces changes in the expression of the c-fos gene that differ from the expression patterns of the same gene after chronic treatments and that help to explain the plastic changes of chronic treatment [97]. For example, acute intraperitoneal administration of 10 mg/kg imipramine can reverse immobility time in the forced swim test, with no observed effects on neurotrophin levels (NGF and BDNF) in the hippocampus and cerebral cortex [98]. Desipramine, reboxetine, bupropion and pagyline reduce immobility in the tail suspension model in intact mice in the same way as the SSRIs sertraline, fluoxetine and paroxetine, but not in NE- and epinephrine-deficient mice by disruption of the DO-beta-hydroxylase gene, in which only citalopram reduced immobility [99], emphasizing the importance of the noradrenergic system for the acute effects of the first group of drugs. While a single administration of citalopram (30 mg/kg) showed no effect, three administrations of citalopram (10

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mg/kg) intraperitoneally within 24 hours increased CREB phosphorylation in the hippocampus and decreased immobility time in the tail suspension test in mice, but not in CREBαΔ mutants, indicating its importance for the establishment of antidepressant effects. In addition, these three administrations succeeded in blocking the hypothermia response induced by the serotonergic agonist 8-OHDPAT, suggesting that within 24 hours the 5 HT1A and possibly 5HT7 autoreceptors were desensitized [88]. However, these effects were not observed when animals were exposed to another model of depression such as forced swimming with a single dose of citalopram (10 mg/kg, i.p.), but with selective 5 HT4 receptor agonists: RS 67333 (1.5 mg/kg, i.p.) and prucalopride (2.5 mg/kg, i.p.), which induce changes in CREB phosphorylation after only 3 days of treatment (Lucas et al, 2007), which underlines the potential of 5 HT4 receptor agonists as potential fast-acting antidepressants [100].

Ketamine is a non-competitive NMDA receptor antagonist that is primarily used as an anesthetic but also has antidepressant effects when administered acutely. Acute administration of ketamine has shown antidepressant effects in rat [101] and mouse models [102–104].

For example, in the forced swim test, high doses of imipramine (20 and 30 mg/kg) and ketamine (10 and 15 mg/kg weight) reduce immobility without altering lo-motor activity and increase energy metabolism by increasing creatine kinase activity in the striatum, cerebral cortex, prefrontal cortex and cerebellum [105]; but only the highest dose of ketamine increases BDNF and target of rapamycin (m TOR) protein in the hippocampus of rats [106]. The increase in BDNF was also observed in the prefrontal cortex of 14-month-old rats [107]. In addition, ketamine can reduce the levels of the interleukins IL-6 and IL-1β and increase the 5-HT/tryptophan ratio in the hippocampus [108]. In mice, acute administration of ketamine was also observed to increase the expression of the neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) in the dentate gyrus of the hippocampus, while blocking the signalling of this peptide attenuated the acute effects of ketamine in the tail suspension test, forced swimming, and sucrose consumption [109]. However, the antidepressant effects of ketamine are not always observed and depend on the dose, route of administration [102] and treatment protocol [110].

Ketamine promotes a cascade of cellular events that begin with the release of glu-tamate, activation of AMPA receptors that activate mTOR-mediated plasticity, BDNF, and the synthesis of synaptic proteins that facilitate plasticity in structures such as the prefrontal cortex [111,112] or increase the activity of immature neurons without increasing neurogenesis [113].

In male Wistar-Kyoto rats, which exhibit a depressive-like phenotype, simultaneous administration of treatment psychedelic substances psilocybin (1 mg/kg) and LSD (0.15 mg/kg) resulted in antidepressant-like effects in the forced swim test that appeared to last longer than the effects of ketamine [114]. Although both psilocybin and ketamine induce changes in the dopaminergic, serotonergic and GABAergic neurotransmission systems [115], a single administration of psilocybin in mice produces antidepressant-like effects in the forced swim test that are related to changes in the neuroplasticity of the hippocampus and prefrontal cortex in mice [116]. These plastic changes seem to be related to the higher affinity of these psychedelics to the TrkB receptors for BDNF [117]. It should not be overlooked that psilocin and psilo-cybin have no effect in the forced swim test in other cases, perhaps due to factors such as the genetic characteristics of the animals or the time after treatment at which the swim tests were carried out [118,119].

In 2019, the FDA approved brexenolone in an intravenous dosage form, the active ingredient of which is the neurosteroid allopregnanolone, for the treatment of postpartum depression. The decline in progesterone and neurosteroid levels in the postpartum period, which is seen as a kind of withdrawal from the effects of these substances, is considered to be part of the etiology of postpartum depression [120], an idea that had previously been proposed for the depression observed in premenstrual syndrome [121]. The antidepressant effect of allopregnanolone and other neurosteroids [122] has already been documented in preclinical studies in the forced swim model in mice [123] and in male [124] and female rats without ovarian hormones [125] from the first acute administration by modulating the activity of the GABA-A receptor. Apparently, the mechanism of brexenolone involves activation of the GABA-A receptor at synaptic and extrasynaptic levels, resulting in inhibition of circuits necessary for the treatment of postpartum depression [126]. These mechanisms also involve

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the BDNF signaling pathway, but seem to be independent of AMPA receptor activation [127]. The mechanisms of this work and their similarity to other agents of plant origin point to the possibility of new substances such as flavonoids, among which chrysin stands out [128].

The discovery of substances with mechanisms of action that provide virtually immediate antidepressant effects has led to the search for new substances such as reelin [129,130] with rapid action profiles that act by mimicking the mechanism of action of ketamine [92] or by novel mechanisms of action [131].

6. Effect of Chronic Antidepressant Treatment on an Experimental Level

Depression is one of the most common mental disorders, characterized by persistent sadness and lack of interest or pleasure in previously rewarding or enjoyable activities [132]. Unfortunately, evidence suggests that approximately 300 million people worldwide will suffer from depression in 2021, according to the Institute for Health Metrics and Evaluation [133].

SSRIs are widely used for the treatment and management of various mood disorders, especially depression [134]. Three SSRIs, including fluoxetine, sertraline, and es-citalopram, produce modest improvements (approximately 5–10%) in standardized depression scores in adolescent patients with moderate major depression without significantly increasing the risk of suicidal ideation or behavior [135].

It seems that SSRIs in chronic PTSD reduce basal levels of diurnal cortisol and cortisol reactivity to stress, leading to an improvement in mood [136]. As we know, the main mechanism of action of SSRIs is the blockade of the 5-HT transporter (SERT), which causes an increase of 5-HT in the synaptic cleft [137]. However, the therapeutic effects of SSRIs cannot be fully summarized in a simple inhibition of SERT [138]. Several studies have shown that SSRIs can alter the level of BDNF. For example, long-term treatment with fluoxetine increases BDNF expression in the hippocampus of depressed rats [90] and in the olfactory bulb of depressed mice [139]. Sertraline and escitalopram also increase BDNF levels, which improves depression [140]. On the other hand, clinical studies have also shown this effect [141].

Several studies have shown that antidepressant treatment affects neuroplasticity and increases neurogenesis, especially with antidepressants that act on 5-HT and NA in regions such as the hippocampus and cerebral cortex. This increase in the formation of new neurons is crucial for the recovery of cognitive and emotional function in patients with MDD [142]. Antidepressants also act by modifying synaptogenesis, i.e. the formation of new synapses between neurons, and have effects on neuronal growth factors such as BDNF, which play an important role in promoting neuroplasticity and neuronal survival and reversing the reduction in the volume of the hippocampus, a key structure of the limbic system in MDD [142].

Other studies have shown that chronic treatment with fluoxetine increases synaptic plasticity through effects on BDNF in the hippocampus and cortex. In addition, fluoxetine increases the volume of the hippocampus in people with MDD [143]. Similarly, antidepressants have been shown to increase levels of vascular endothe-lial growth factor (VEGF). This factor is crucial for promoting neurogenesis, angiogenesis and neuronal survival, as it promotes the formation of new neurons and synaptic connectivity [143]. For example, VEGF has been reported to regulate the effects of antidepressants such as lamotrigine, suggesting that this factor could serve as a biomarker to monitor response to antidepressant treatment [144].

On the other hand, other studies have shown that the insulin-like growth factor (IGF-1) plays an important role in the effect of antidepressants. In patients with MDD, it has been observed that serum levels of this factor are elevated, while they decrease again after the onset of the effect of SSRIs. IGF-1 has neuroprotective properties in the CNS and also promotes neurogenesis. IGF-1 influences the effect of antidepressants because it activates the MAP/ERK and PI3K signaling pathways, which are crucial for neuronal survival and synaptic plasticity [145].

The relationship between brain-derived neurotrophic factor (BDNF) and its receptor, TrkB (tropomyosin receptor kinase B), and antidepressants is an important area of research in the field of neuropharmacology. In this sense, a wide range of antidepressants such as SSRIs, dual

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antidepressants and naturally occurring products such as chrysin (7,8-dihydroxyflavone) have been reported to increase BDNF levels, favoring the binding of this neurotrophin to its receptor TrkB, which activates several intracellular signaling pathways such as MAPK/ERK and PI3K, essential for promoting plastic changes in the brain and maintaining neuronal survival under stress conditions [146]. **Figure 1** describes the mechanisms involved in acute and chronic antidepressant treatment that have been reported to date.

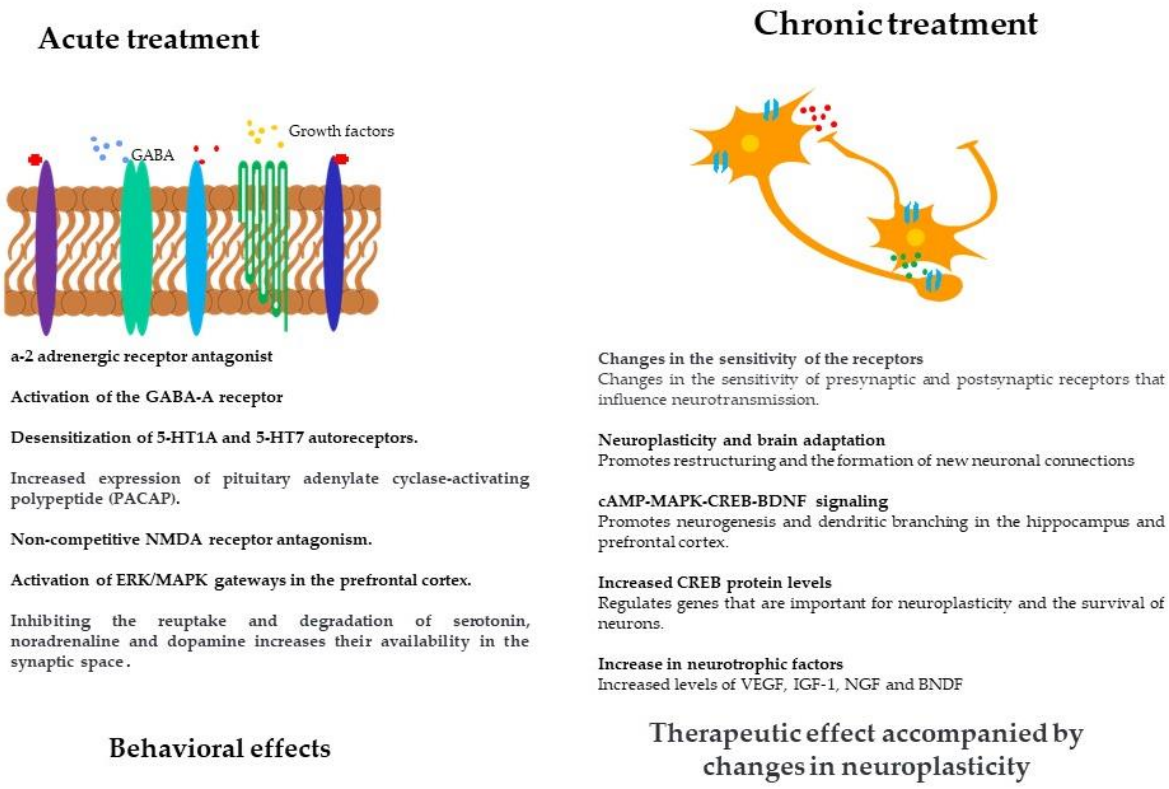

Figure 1. Proposed mechanisms that mediate the antidepressant effect experimentally.

Similarly, conventional antidepressants, which generally focus on the monoaminergic system, may alter the function of NMDA receptors that are important for long-term potentiation, which is essential for the regulation of processes such as memory and for changes in emotional and affective state. Ketamine, an NMDA receptor antagonist, has shown a rapid and long-lasting antidepressant effect, while riluzole, an inhibitor of glutamate release that also increases the expression of the glutamate transporter in the glia, helps to eliminate depressive symptoms [147]. The effects of drugs with antidepressant activity are described in **Table 2**.

Table 2. Effect of chronic treatment with antidepressants.

Drug	Dosage (route of administration, dose and duration of treatment)	Experimental subject	Experimental model	Identified effect	Mechanism	Reference

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Ketamine Letrozole	Ketamine 5 mg/kg. Letrozole 1 mg/kg. 7 days of treatment Intraperitoneal route of administration	Adult female and male rats of the Sprague-Dawley strain.	Forced Swim Test (FST)	Reduction of FST immobility in men with ketamine and reduction of FST immobility in women with letrozole. The combination of ketamine and letrozole reduces FST immobility in men.	It is assumed that they act via NMDA receptors and could modulate neurotrophic factors in the prefrontal cortex.	[148]
Levomilnacipran	30 mg/kg. 14 days of treatment Intraperitoneal administration route	Male Wistar rats.	Depression induced with lipopolysaccharides (LPS) 0.5 mg/kg for 2 weeks. Sucrose preference. FST. Open Field Test.	Levomilnacipran reduces immobility behavior in the FST. It reverses the increase in transcript levels of the proinflammatory cytokines IL-1β, INF-γ and TNF-α.	Levomilnacipran inhibits the activation of the TLR4/NF-κB and Ras/p38 signaling pathways and modulates the ERK/CREB/BDNF pathway.	[149]

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Fluoxetine	15 mg/kg/day. 6 weeks Intraperitoneal administration route	Male Wistar Rats	Chronic social isolation (CSIS) (6 weeks) Sucrose preference FST	Increased sucrose consumption. Reduction of immobility time in the FST	Expression of calcium/calmodulin-dependent protein kinase 1 (CaMKK1). Phosphorylation of the cAMP-responsive element-binding protein (CREB). Expression of BDNF.	[150]
Escitalopram Ibuprofen	Escitalopram 10 mg/kg Ibuprofen 40 mg/kg Combination of both 21 days of treatment Intraperitoneal administration route	Adult male Sprague-Dawley rats	Stress from restriction FST	Reduction of immobility in FST with individual and combined treatment. Reduction in corticosterone levels. Increase in BDNF and p11 levels.	Positive regulation of BDNF and p11	[151]

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Meloxicam Caffeic acid Sertraline	Meloxicam 3 mg/kg – 1mg/kg Caffeic acid 30 mg/kg – 10 mg/kg Sertraline 5mg/kg Meloxicam 1mg/kg + Caffeic acid 10mg/kg 21 days of treatment Intraperitoneal administration route	Adult male Sprague-Dawley rats	CUMS 6 weeks Open Field Test FST	All treatments reduced immobility in FST. Caffeic acid inhibits NA reduction and increases Trp and MHGP. Meloxicam inhibits NA reduction and increases Trp, MHGP and Tyr.	Inhibition of COX-2 and reduction of 5-HIAA.	[152]
Bryostatin-1 Imipramine	Bryostatin-1 (20 µg/m2) Intravenous administration by tail Imipramine (15 mg/kg) intraperitoneal administration 5.5 weeks of treatment	Male Wistar Rats	Open space swimming test Morris water maze Visible platform test.	Bryostatin-1 reduces immobility after 2 weeks of treatment. Bryostatin-1 restored the rats' ability in spatial learning and spatial memory recall.	Protein kinase C (PKC)ε activation	[153]

7. Pharmacological alternatives in the treatment of depression

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One of the limitations of pharmacological treatment of depression is the adverse effects. Therefore, the search for alternatives through other pharmacological approaches such as natural products, modulation of the inflammatory process and the microbiota is promising [154]. In this sense, the presence of saponins, terpenes and fla-vonoids in several herbal remedies has been demonstrated to have antidepressant effects through the inhibition of SERT, NA and DA [155]. On the other hand, it has been reported that plant molecules can regulate mood due to their antioxidant capacity. In this sense, rutin (quercetin-3-rutinoside) administered for 14 days at a dose of 80 mg/kg to rats with reserpine-induced depression was reported to prolong swimming time compared to the control group [156]. This effect is due to the antioxidant capacity of rutin and the decrease in acetylcholinesterase activity.

The combination of plant extracts with antidepressant activity in rats has shown a better effect when they were combined than when they were administered individually. In this regard, the combination of Bupleurum Chinese DC (Chaihu) and Paeonia lactiflora Pall (Baishao) administered at a dose of 7.5 mg/kg to rats with unpredictable chronic stress for 28 days showed an antidepressant effect by shortening the time of immobility and increasing sucrose preference. The metabolomics results suggest that the antidepressant effect of the combination of Chaihui and Baishao is due to its ability to activate multiple signaling pathways and metabolites. The MAPK and arachidonic acid signaling pathways are critical for neuroplasticity as they can influence synaptogenesis, inflammation and growth factor expression, essential mechanisms for reducing the characteristic symptoms of depression [157].

Another natural product that has shown antidepressant properties in rats subjected to the CUMS model is crocin (Crocus sativus Linn), a compound derived from saffron. Administration of crocin at a dose of 25 mg/kg over a four-week period was shown to increase sucrose consumption and locomotor activity and decrease immobility time in the forced swim test. In addition, metabolomics tools and network pharmacology were used to identify the major pathways of action of crocin, which include biosynthesis of tryptophan, phenylalanine, histidine, glycerolipids and steroid hormones. These results demonstrate the mechanism of action of crocin, which is an alternative treatment for depression [158]. In another study using the CUMS model in rats, the suspension of Ziziphi spinosae 100 mg/kg/day for 4 weeks was shown to have an antidepressant effect in the forced swim test and sucrose consumption. There is also an increase in serum levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5HIAA). Results that could modulate the serotonergic system as a possible mechanism of action [159].

Modulation of the inflammatory process represents an alternative to improving the symptoms of depression. In this sense, the antidepressant effect of the flavonoid quercetin was investigated in a model of LPS-induced depression in rats. Administration of 50 mg/kg quercetin over a 7-day period resulted in an increased in mobility time and grooming time and a decrease in proinflammatory mediators in the brain compared to the LPS-treated group. This suggests that quercetin has antidepressant properties via inhibition of neuroinflammation mediated by modulation of the microglial signaling pathway in the hippocampus and prefrontal cortex of the brain [160].

On the other hand, there are reports on the use of probiotics as a complementary alternative in the pharmacological treatment of depression. Probiotics can modulate the gut-brain axis, inflammation and the synthesis of various neurotransmitters. In this context, it was reported that 10-week treatment of adult male rats with a mixture of 8 strains of probiotics (a preparation called "Ecologic Barrier") at a dose of 4.5 grams, equivalent to 1.125 × 10^10 colony-forming units (CFU), reduced depressive behavior. This treatment reduced depressive behavior, improved the immune response, induced changes in the expression of genes related to HPA axis feedback, and increased the expression of genes related to neuroplasticity and neuroprotection, such as BDNF [161]. Similarly, treatment with probiotics in stressed rats restores gut flora, an effect that reduces behavioral variables indicative of depression and increases levels of NA and 5-HT and inhibits stress hormones such as adrenocorticotropic hormone (ACTH) and corticosterone [162]. In addition, probiotics have shown anxiolytic and antidepressant effects in stress-sensitive rat models that were also subjected to internal deprivation to induce additional stress. In addition, changes in the concentration of DA, 5-HT and

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their metabolites were detected in the hippocampus and striatum. These results suggest that treatment with probiotics alters gut flora and brain neurochemistry, an effect that is related to neuroplasticity and emotional state [163].

8. Conclusions

Depression is a complex mental disorder that affects millions of people worldwide. Its neurobiology is associated with structural and neurochemical changes in brain regions such as the hippocampus, the prefrontal cortex and the amygdala. Preclinical studies of antidepressants and their relationship to neuroplasticity are a very active area of research, reflecting the complexity of depression and contributing to understanding. These studies suggest that acute antidepressant treatments show immediate effects in behavioral models of depression such as forced swimming. However, the long-term effects of chronic treatment are crucial for the activation of intracellular signaling pathways related to neuroadaptive changes in the brain and thus for the establishment of therapeutic effect. These neuroadaptive changes are promoted by SSRIs and tricyclic antidepressants, which increase the bioavailability of various neurotransmitters at the synaptic level. In addition to traditional treatments, complementary alternatives should be considered, such as the use of probiotics and plant-based compounds, which have been shown to have an antidepressant effect and promote brain neuroplasticity. This review shows the effects of chronic antidepressant treatment at the preclinical level on neuroplasticity and its importance in establishing therapeutic efficacy against depression.

9. Future Directions

Research on the neurobiology of depression should continue to investigate non-monoaminergic mechanisms such as neuroinflammation, changes in the HPA axis and gut microbiome, and focus on mechanisms related to neuroplasticity. In this context, further preclinical research on the evaluation and efficacy of pharmacological alternatives will allow us to understand the mechanisms involved in the therapeutic effect of depression.

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