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Novel Therapeutic Strategies for Depression

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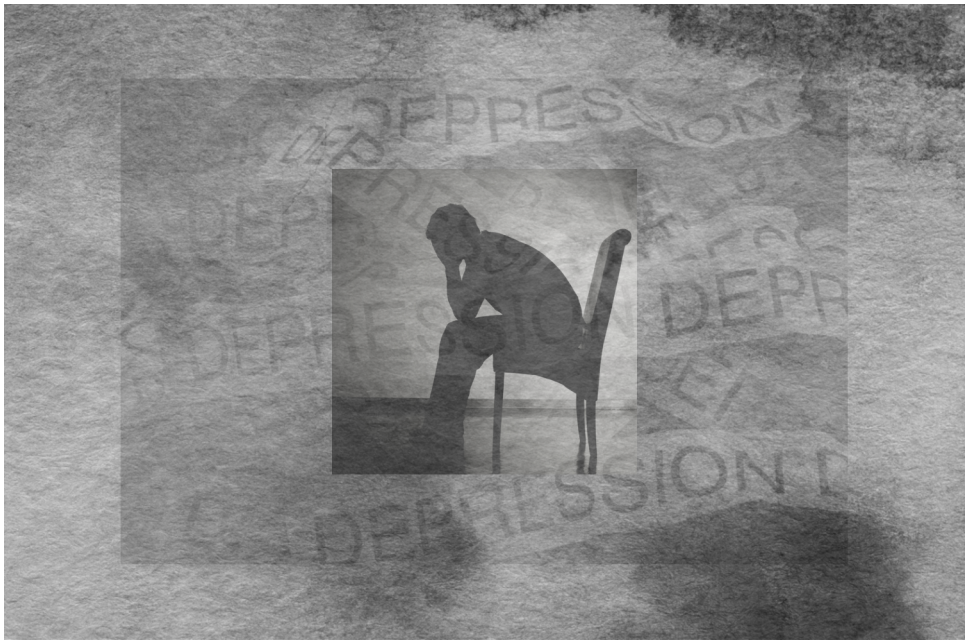

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Abstract

Depression is a complex neurological disorder that has many potential causes and treatment approaches. Though there are many conventional antidepressants available in the market, it is becoming increasingly difficult to rely on them as many patients may experience a lack of effectiveness or tolerance to these antidepressants. While current antidepressants increase serotonin and norepinephrine concentrations through reuptake inhibition, novel forms of antidepressants rely on the direct manipulation of receptors, thereby also improving neuroplasticity, which has emerged as a promising approach to treating depressive symptoms. In this literature review, various forms of novel antidepressants are analyzed. The mechanisms studied are Psilocybin's long-term success, Ketamine's rapid action, hormonal treatments' direct targeted approach, and natural products' reduction of neurotoxic side effects. Understanding how these powerful mechanisms work may allow for the research and creation of more effective antidepressants in the future.

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1. Introduction

Within the last few years, Major Depressive Disorder (MDD) has become one of the world's leading health problems. Within the last year, there were over 45,000 deaths, about one death every 11 minutes, by suicide, making it one of the leading causes of death in the United States[1]. Since MDD causes significant impairment in daily life, effective antidepressant treatments are necessary. Many current antidepressants focus on increasing serotonin, norepinephrine, or dopamine in patients with moderate to severe depressive symptoms through reuptake inhibition[2]. However, these conventional forms of antidepressant therapies are often ineffective in patients because there are many types of depression, including stress-induced, anxious depression, and treatment-resistant depression[3]. This complexity makes it difficult to find therapies that work for each patient. Furthermore, there is a lot of uncertainty regarding the long-term effects of conventional antidepressants and the potentially toxic side effects.

There have been recent attempts at implementing novel therapeutic strategies for depression that are more effective than conventional treatments. In this literature review, we will analyze Ketamine as a short-term therapeutic option[4], Psilocybin as a long-term therapeutic option[5], other psychedelic-related drugs[6], natural depression remedies[7], as well as hormonal treatments for depression[8]. All these novel strategies target depression differently through inhibition and modulation of specific receptors, neurotransmitters, and other biomarkers to significantly reduce suicide ideation and depressive symptoms. These novel antidepressants are researched because of their promising clinical tests and diverse mechanisms. Because these antidepressants have different mechanisms of treating depression, it is important to analyze which mechanisms are the most powerful in contributing to the most successful antidepressant, as it can be the baseline for the research and creation of more effective antidepressants in the future. The success of these novel antidepressants is measured based on their ability to prolong the therapeutic effect, increase neuroplasticity, and reduce neural toxicity.

2. Pathophysiology of Depression

Currently, many neurobiological theories exist for the pathophysiology of MDD. However, it has been difficult to choose one unified theory due to the clinical and etiological heterogeneity of the disorder[9]. For example, depressive pathophysiology can change significantly over the course of the illness, and all theories of depression are only relevant to some depressed patients in the population. As each patient is likely unique, it is critical to tailor treatment approaches specifically. This review will discuss a few of the current theories with the strongest empirical foundation, as each can be useful in developing novel therapies.

The monoamine deficiency theory posits that the underlying pathophysiological basis of depression is a depletion of the neurotransmitters—serotonin, norepinephrine, or dopamine—in the central nervous system[9]. Depletion of these neurotransmitters happens when presynaptic cells take the neurotransmitters back up before it reaches the receptor or when too little of a specific neurotransmitter is produced. These neurotransmitters are part of the monoaminergic systems, which are involved in important brain functions such as mood regulation, reward processing, circadian rhythm, and attention. In clinical trials, almost every compound that inhibits monoamine reuptake has been an effective antidepressant. This observation is what led to the development of the monoamine deficiency theory. Although antidepressants that target the monoamine systems can be initially effective, full, and partial resistance to these drugs and delayed onset of action occurs. These limitations suggest that dysfunctions of monoaminergic neurotransmitter systems in MDD represent effects of other abnormalities[9]. The monoamine deficiency theory remains the clinically most relevant theory, and new findings on dopamine have shown further potential in producing novel therapeutic strategies for depression.

The GABAergic hypothesis of MDD suggests that alterations in GABAergic transmission represent fundamentally important aspects of the etiological sequelae of MDD that are reversed by monoaminergic antidepressant drug action[10]. GABA is a neurotransmitter predominantly responsible for mediating neural inhibition in the brain. Magnetic resonance imaging

studies have shown that in acute depression, there are consistent reductions in total GABA concentrations in the prefrontal and occipital cortex. This observation may be due to acute stress effects or reduction in the density and size of GABAergic interneurons. However, there is also contradictory evidence of the GABA hypothesis[9].

Circadian abnormalities have been hypothesized to be etiologically associated with MDD. The circadian rhythm is part of the body clock that helps regulate body fatigue through day and night[11]. Disruptions to sleep and daytime fatigue is a criterion for depression, which suggests a subgroup of depression patients may have impaired circadian rhythms. In clinical studies, adjustments to the circadian cycle have been shown to have specific effects on subsequent mood and can even have antidepressant effects. Based on these findings, this hypothesis suggests that shortened REM latency, the association between phase advance of the sleep-wake cycle and phase advances in nocturnal cortisol secretion, and the effect of antidepressants on circadian rhythms are etiologically associated with MDD[9]. However, more research is required into the molecular explanation.

3. Important Receptors Involved in Depressive Symptoms

The serotonin hypothesis has dominated the field of depression research for decades. There are multiple receptors that have been implicated, but serotonin-1A (5-HT1A) and serotonin-1B (5-HT1B) are among the most important receptors as deemed by recent and ongoing research projects[12].

The 5-HT serotonin receptor group has been broadly linked to both anxiety and depression disorders[13]. The 5-HT receptor is found throughout the central and peripheral nervous systems in the form of either a G protein-coupled receptor or a ligand-gated ion channel. It is acted upon by the chemical serotonin and then proceeds to promote either excitatory or inhibitory neurotransmission. After binding to serotonin presynaptically, the receptor modulates the release of neurotransmitters such as glutamate, GABA, and dopamine and hormones such as oxytocin, prolactin, and cortisol, leading to physiological changes affecting emotion and cognition[14]. Furthermore, a growing and diverse body of evidence support the

involvement of 5-HT1A, the main inhibitory serotonergic receptor, in both mental disorders. This important role of the serotonin receptor was initially discovered through studies of tryptophan depletion, as tryptophan is the molecular precursor to the 5-HT receptors[15]. Recent studies have focused on the direct role of 5-HT receptors. Studies have implicated dysregulation of 5-HT neurotransmission as a primary defect in mood and anxiety disorders[13,15]. Complementary research findings suggested that 5-HT may play a role in recovery from mood disorders via selective serotonin reuptake inhibitors (SSRIs) and other serotonergic agents[16]. The role of 5-HT receptors in depression has additionally been shown through human studies, 5-HT1A polymorphism research, preclinical pharmacological studies, and preclinical genetic approaches.

Beyond the 5-HT receptor, other receptors affecting brain chemistry have been indicated to improve outcomes for patients with MDD. NMDA antagonists, such as ketamine, have been associated with antidepressant effects in patients suffering from MDD[17]. The NMDA receptor is typically activated by glutamate, which causes an influx of calcium ions and subsequent membrane depolarization for an action potential[18]. However, antagonists have been proposed to antagonize NMDA receptors on GABAergic interneurons and broadly increase levels of glutamate, the major excitatory neurotransmitter in the nervous system. AMPA receptor activation functions in a similar manner, except calcium ions, are substituted for sodium ions which allows for faster action potentials. In recent studies, compounds that augment signaling through AMPA receptors have been found to promote antidepressant-like behavioral effects in animal models[19].

4. Molecular Mechanisms of Antidepressants

Most current antidepressant medications fall under the category of reuptake inhibitors, namely selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)[20]. These medications function by preventing neurotransmitters (serotonin and norepinephrine) from being reabsorbed back into neurons in the brain after they are released. The mechanism of these drugs is based on the monoamine hypothesis, which states that depression is caused by a lack of available monoamines. By blocking reuptake and increasing the extracellular

concentration of monoamines, these drugs are thought to enhance and restore connections between neurons, ultimately resulting in an improved mood in patients[21].

Current research in antidepressants, however, is not based on the monoamine hypothesis and reuptake inhibition mechanism, largely due to the inconsistent results and efficacy of the current antidepressant medications. Reuptake inhibitors do not directly target the glutamatergic system, which plays a significant role in the brain and is thought to be a vital system regarding depressive symptoms[20,21]. Glutamate is an important neurotransmitter of the glutamatergic system and is released in response to increased 5-HT_{2A} receptor activation[22]. While SSRIs and SNRIs indirectly interact with the 5-HT_{2A} receptor by increasing neurotransmitter concentrations, they do not impact receptor activation or functionality[22]. Reuptake inhibitors have instead been found to cause postsynaptic receptor downregulation, which explains the delayed effects that patients often experience with current antidepressants[23]. SSRIs have also been shown to disrupt K+ channels that are necessary for glutamate reuptake by astrocytes, which are glutamate transporters. Blunted glutamate reuptake has recently been found to be associated with MDD[23,24].

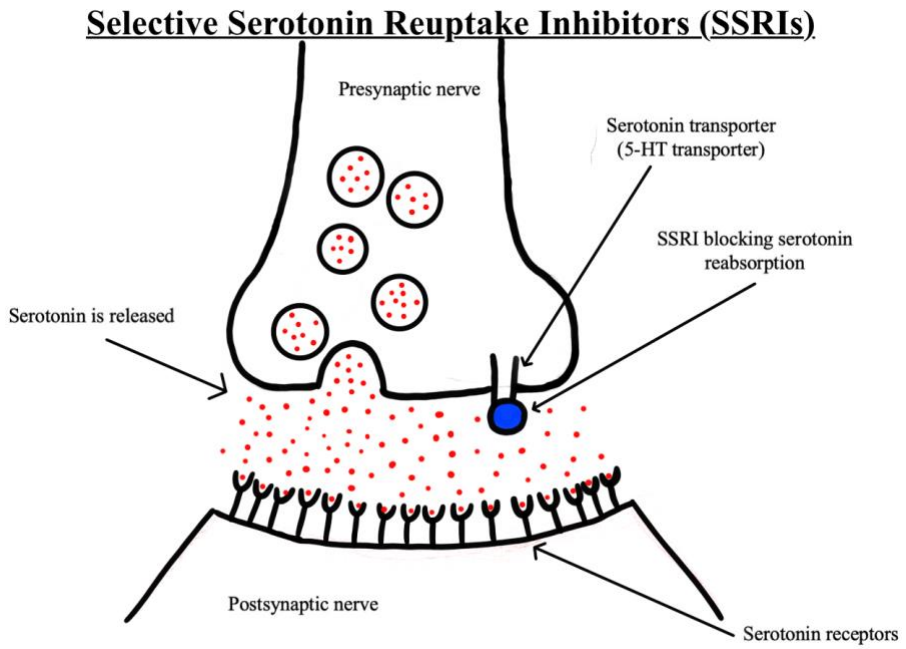

Figure 1: Mechanism of Selective Serotonin Reuptake Inhibitors (SSRIs). *When serotonin is released from a presynaptic cell into the synapse it can then bind to 5-HT receptors on the postsynaptic cell. This pathway, as mentioned before, is involved with important brain functions such as mood regulation, sleep, reward processing, and cardiac rhythm. Synaptic serotonin can also be reabsorbed by the presynaptic cell through 5-HT transporters, causing a decrease of serotonin available to bind to the postsynaptic 5-HT receptors. As seen in the figure above, SSRIs block the 5-HT transporter from reabsorbing serotonin, therefore increasing the concentration of serotonin in the synapse that can bind to postsynaptic 5-HT receptors.*

Novel antidepressant therapies currently being researched, such as ketamine and psilocybin, largely function as receptor agonists and antagonists. Receptor agonists activate a receptor to produce a response, which results in increased receptor functionality/activation. Psilocybin is an example of a receptor agonist, specifically activating 5-HT_{2A} receptors. Receptor antagonists are molecules that block receptors to prevent a response, which in turn can increase neurotransmitter concentrations in the synapses and increase the activity of different receptor-mediated pathways, as seen with ketamine and the NMDA receptor[25,26]. While treatments of this nature show promise in effectively treating depression both short- and long-term, much is still unknown regarding the long-term adverse effects and the overall efficacy of repeated exposure to these drugs. The specific concerns and research required for these drugs are discussed below.

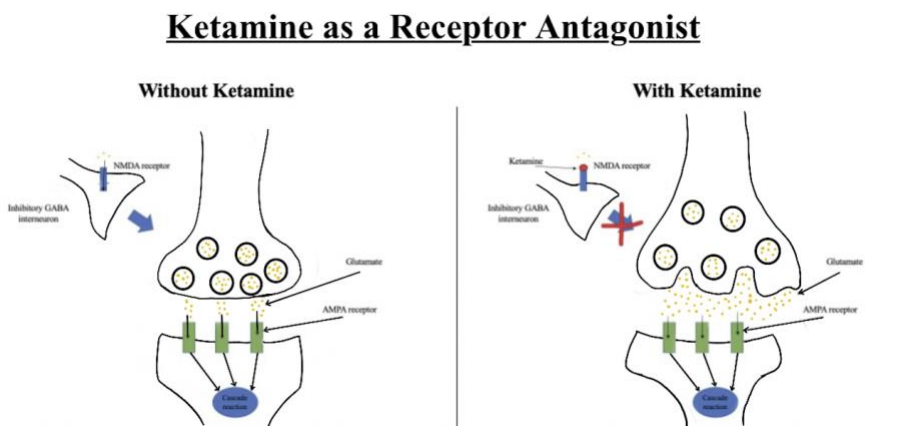

Figure 2: Ketamine as a Receptor Antagonist. *Ketamine functions as an NMDA receptor antagonist, blocking molecules, such as glutamate, from activating the receptor. When the NMDA receptor is activated on inhibitory GABA interneurons (left figure), it blocks the release of glutamate from nearby neurons and from activating AMPA receptors in postsynaptic neurons. Glutamate and the AMPA receptor are important components of the glutamatergic system, which is heavily linked with processes of mood regulation. When ketamine is present (right figure) it functions by blocking the NMDA receptor, therefore preventing the inhibitory effect of the GABA interneuron. This increases the amount of glutamate that is released into the synapse and preferentially activates the AMPA receptors, which causes a more rapid cascade reaction and antidepressant effect.*

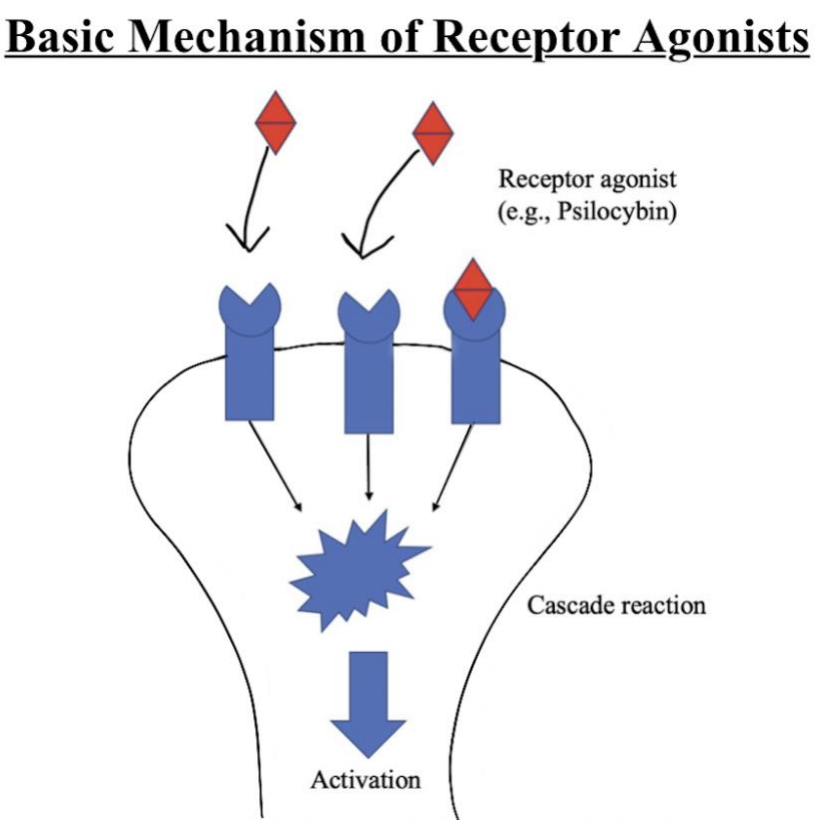

Figure 3: Basic Mechanism of Receptor Agonists. *Receptor agonists are molecules that can function like neurotransmitters and activate certain receptors, causing a cascade of reactions that ultimately lead to activation of other receptors or expression of specific genes and proteins. Psilocybin is an example of a receptor agonist, which is displayed as the red diamond in the figure above.*

5. Treatments of Interest and their Efficacy in Treating the Different Forms of Treatment-Resistant Depression

5.1. Ketamine as a Short-Term Therapeutic Option

There has been a lot of recent research utilizing ketamine as a short-term therapeutic option. Ketamine gained popularity with its efficacy for treatment-resistant depression. Due to its rapid onset and short duration of action, ketamine has a strong antidepressant effect. As mentioned earlier, ketamine is an NMDA receptor antagonist, therefore keeping glutamate levels higher. Ketamine affects glutamate levels, essentially targeting a neurotransmitter different from most common neurotransmitters targeted with conventional antidepressants[27]. Increased glutamate levels result in

lessened depressive effects as scientific research confirms the involvement of the glutamatergic system in the processes of mood regulation. In addition, the glutamatergic system is involved in neuroplasticity processes[28], such as the formation of synapses and the regulation of memory. However, other NMDA receptor antagonists do not have the same fast-acting effects, which suggests something else makes ketamine successful– ketamine metabolites[29], depending on its structure and chemistry. Ketamine also acts on the mTOR pathway[30], AMPA receptors and even the opioid receptors in the brain. The mTOR pathway is involved in cell proliferation, mortality, survival, and protein synthesis, resulting in the growth of new neural connections, and increasing neuroplasticity. Clinical trials have been done that show ketamine's rapid antidepressant effects. In one study, twenty-five males were given one dose of ketamine and its changing effects were measured over time, starting baseline at 1 h and 2 weeks after the last dose of ketamine, and 1 month after the last dose[31]. The table between the three pairs are shown below.

Hamilton Rating Depression Scale	Mean ± SD
Pair 1:	
Depression Baseline	23.40 ± 5.38
After 1 hr. of ketamine dose	21.20 ± 6.34
Pair 2:	
Depression Baseline	23.40 ± 5.38
After 2 weeks of ketamine dose	10.25 ± 6.40
Pair 3:	
Depression Baseline	23.40 ± 5.38
After 1 month of ketamine dose	10.45 +8.47

Table 1: Effect of ketamine treatment over time: Changes in the Hamilton Rating Scale for depression scores.

The Hamilton Depression Rating Scale is the most used administered depression scale, with a higher rating indicating higher depressive levels in a patient[31]. From the table, it is clear that the mean reduction of depression scores decreased, with the most notable change being at the two-week mark[31]. However, after one month of ketamine doses, the numbers do not drop– they stay roughly the same. This data indicates that ketamine's effects, though powerful and promising, are relatively short-term[31].

5.2. Psilocybin as a long-term treatment option

Psilocybin is a naturally occurring hallucinogen that has recently been identified as a potential long-term therapeutic option for depression. Psilocybin acts as a 5-HT_{2A} receptor agonist, activating the receptor that is involved with mood, emotions, thoughts, perceptions, etc. 32. By stimulating 5-HT_{2A} receptors on large glutamatergic pyramidal cells, psilocybin also increases the synaptic concentration of glutamate in the prefrontal cortex (PFC) [33]. Rather than blocking the reuptake of

neurotransmitters to increase synaptic concentrations like current antidepressant medications, psilocybin directly interacts and activates the 5-HT_{2A} receptor to induce changes in mood and thoughts[32]. In December 2016, a randomized, double-blind clinical trial involving psilocybin administration to patients with life-threatening cancer found that treatment with a high dose of psilocybin administered under supportive conditions reduced depressive symptoms in patients as quickly as 1 week, with effects lasting up to 3 months in 12 patients. There was also a decrease in depressed mood in some patients at a 6 month follow-up[34]. Numerous adverse effects were observed, but none were deemed life-threatening. No adverse effects were displayed in patients after the study was concluded[34]. The table below shows the results of this study, with numerous different outcome measures used to evaluate symptoms of depression, anxiety, and overall mood. Each of the outcome measures used is briefly explained in the table. This was a 9-month study performed with 56 participants randomly assigned to two groups either receiving high doses or low doses of psilocybin; while the results of this study are promising, there is a need for a larger and more diverse patient population to fully examine the effects of psilocybin as an antidepressant.

Measure	Group	Baseline	Post-session 1	Post-session 2	6 months
GRID-HAMD-17 (Depression)[a]	Low-Dose 1st	22.32	14.80	6.50	6.95
	High-Dose 1st	22.84	6.64	6.52	6.23
Beck Depression Inventory (BDI)[b]	Low-Dose 1st	18.40	12.92	8.17	8.00
	High-Dose 1st	17.77	7.00	5.80	6.17
HADS Depression[c]	Low-Dose 1st	9.48	6.04	4.57	4.64
	High-Dose 1st	9.81	3.92	4.28	3.46
HAM-A (Anxiety)[d]	Low-Dose 1st	25.68	16.64	8.92	7.95
	High-Dose 1st	25.73	8.48	7.52	7.04
STAI-Trait Anxiety[e]	Low-Dose 1st	47.46	40.48	35.48	36.83
	High-Dose 1st	47.73	34.64	34.28	35.32
POMS Total	Low-Dose 1st	51.72	42.48	21.09	23.50
Mood Disturbance[f]	High-Dose 1st	56.93	18.96	17.14	12.52
Brief Symptom Inventory (BSI)[g]	Low-Dose 1st	41.76	33.74	26.08	23.50
	High-Dose 1st	40.19	18.08	16.48	14.35
MQOL (Overall Quality of Life)[h]	Low-Dose 1st	5.69	6.17	6.90	6.88
	High-Dose 1st	5.32	7.14	7.46	7.65
MQOL (Meaningful Existence)[i]	Low-Dose 1st	6.03	6.10	7.30	7.29
	High-Dose 1st	5.43	7.23	7.30	7.62
LOT-R Optimism[j]	Low-Dose 1st	13.56	13.60	15.96	16.68
	High-Dose 1st	14.15	17.23	17.16	17.43

Table 2: Effects of Psilocybin. *Changes in 10 different outcome measures/scales after session 1, 2, and at a 6-month follow-up in two groups receiving different dosages of psilocybin.*

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a The GRID-HAMD-17 is a clinician-rated measure of depression, with lower scores correlating to fewer symptoms of depression[34].

b,c The BDI and HADS tests are self-rated measures of depression, with lower scores indicating fewer depressive symptoms[34].
d The HAM-A is a clinician-rated measure of anxiety, with lower scores signifying less anxiety in patients[34].
e The STAI test is a self-rated measure of anxiety, with lower scores signifying less anxiety[34].
f The POMS test is a self-rated mood measure, with lower scores indicating an overall better mood[34].
g The BSI score is a self-rated measure of psychiatric symptoms, with lower scores indicating fewer feelings of distress[34].
h, i The MQOL test is a self-rated measure of the overall quality of life, with higher scores indicating a better quality of life[34].
j The LOT-R test is a self-rated optimism measure, with higher scores correlating to more feelings of optimism[34].

Psilocybin also differs from current antidepressants in that limited exposure or administration of the drug has the potential for longer-lasting effects. Recent studies also show signs of high transient neuroplasticity after a single dose of psilocybin, which is a possible source of the longer-lasting effects associated with psilocybin[33,34]. Psilocybin targets inflammatory and oxidative stress pathways that lead to an increase in brain plasticity and cognitive flexibility, both of which are important gauges of neuroplasticity[33]. A study published in November 2021 also found that psilocybin increases the expression of genes related to neuroplasticity (c-Fos, Junb, Dusp1)[33,34]. This study refers to a clinical trial involving mice in which it finds that mice treated with psilocybin experienced increased density and strength of neural connections by 10 percent[33]. The same study published in 2021 also finds that suicidal behaviors are associated with neuroplastic dysfunction and that those that die from suicide have low levels of brain-derived neurotrophic factor (BDNF) in certain regions of the brain[33]. Psilocybin's ability to increase neuroplasticity in patients suggests that it could be used to treat patients at high risk of suicidal behaviors. However, more research is needed to fully evaluate its efficacy for these conditions.

While psilocybin has shown promise as a novel therapeutic option to treat depressive symptoms due to its prolonged effects on neuroplasticity, there is still much unknown. Many studies and trials performed involved small sample sizes, so their findings cannot be applied to a larger population[33]. There is a need for a trial involving administration in a clinical setting, which is not as ideal and accessible.

5.3. Psychedelic-related drugs

We have already seen an example of a popular, effective psychedelic-related drug– Psilocybin. Other drugs of similar properties will be discussed in this section. Ayahuasca is a psychoactive drink shown to have medicinal potential in treating psychological disorders. In recent clinical trials, the drug has been proven to decrease activity in the precuneus and medial prefrontal cortex[35]. These regions have also been implicated in the default mode network - a brain pathway most active during periods of introspection. Unsurprisingly, overstimulation of the default mode network has been associated with higher rates of depression and anxiety[36].

Ayahuasca combats stress-induced depression and anxiety through its composition of DMT and B-carboline[37]. DMT activates the Sig-1R receptor, which blocks neurodegeneration and regulates the production of protective antioxidants. B-carboline, meanwhile, has been shown to increase BDNF[38]. The drug ultimately leads to anti-inflammatory, neuroprotective, and potentially memory-boosting effects because of its focus on promoting nerve cell survival. Ayahuasca has added utility compared to traditional antidepressants due to its multifaceted approach to mental disorders: the drug has been shown to combat depression, anxiety, PTSD, and drug dependence[39,40]. Additionally, the psychedelic is faster-acting and lasts longer than other antidepressants that also target serotonin receptors [37].

A recent clinical trial focused on ayahuasca's effects on treatment-resistant depression[35]. Twenty-nine patients with persistent, moderate-to-severe depressive symptoms received either a single dose of a placebo or ayahuasca. The results of the study indicated that when compared to the placebo, ayahuasca generated significant antidepressant effects. Statistical analyses proved that the effects were rapid, and the positive outcomes persisted for at least seven days. Although ayahuasca is especially promising as an antidepressant medicine due to its rapid effect in combating depressive symptoms, some other key features contribute to its potential. The drug has a rare capability of improving depression in patients resistant to traditional antidepressant therapies[35]. Additionally, ayahuasca's focus on the default mode network provides a direct focus on reducing the source of depressive

thoughts and instead increases blood flow to areas that regulate emotions and memory. Despite these encouraging findings, more studies must be conducted to prove ayahuasca's efficacy in other mood and behavioral disorders.

Lysergic Acid Diethylamide (LSD) is a classical hallucinogen more specifically characterized as an entheogen. Some of its characteristic mental effects include distortion of the sense of time and identity, visual hallucinations, and states of euphoria or dysphoria. Beyond these short-term effects on the brain, LSD may play an overlooked role in neurogenesis and possible long-term nervous system health. A recent clinical study indicates that the drug may help the brain grow cells and construct novel connections in brain regions that typically exhibit cell death in mental health disorders such as anxiety and depression[41]. The drug acts on the brain by interacting with the serotonin 5-HT2A receptor in an agonist capacity[42]. Thus, the drug is analogous to serotonin chemically, which has been associated with numerous brain-boosting and physiologically regulating benefits. Studies have implicated serotonin receptors specifically in promoting promnesic effects and regulating emotional behaviors[43]. Compared to other traditional antidepressant drugs that focus on inhibiting serotonin reuptake, LSD is both faster-acting and longer-lasting in the human body[44].

One current research trial presents that LSD promotes social behavior through mTORC1, a protein complex activating the translation of other proteins- in excitatory neurotransmission[45].LSD was shown to potential both AMPA and 5-HT2A synaptic responses in the mPFC (medial prefrontal cortex) and increase the phosphorylation of protein kinases Akt and mTOR in a rodent model. This effect on signaling in the mTOR pathway was hypothesized as the rationale behind the increase in prosocial behaviors like Ketamine. Another recent clinical trial utilized the administration of LSD and placebo to 20 healthy volunteers and subsequently measured the emotional behaviors of the participants 2 weeks after administration[46]. The results indicated that LSD was responsible for the heightened mood, optimism, and trait optimism of the participants. Another important ongoing clinical trial will measure the efficacy of LSD administration in patients suffering from MDD.

By targeting the 5-HT2A receptor, LSD functions as a serotonin-like chemical in an agonist role. This may be advantageous to other antidepressants due to its rapid and longer-lasting effects. LSD also affects the mTORC1 pathway, which has been implicated in increasing sociality. Although much research was conducted regarding LSD's therapeutic effects in the 1970s, government restrictions on psychedelic research have curtailed efforts in the past few decades[46]. The increasing rate of clinical trials, including psychedelics and LSD in psychiatric disorders, must continue to gather evidence of reproducibility and validity. Because of the prevalence of "bad trips" and the tendency of the drug to sometimes exacerbate existing psychiatric predispositions, trials testing the drug, in combination with therapy or trials focusing on micro-dosing the drug, may be an optimal focus[47].

5.4. Natural Products

Natural products encompass many possible treatment options, which all work to cure depression through different mechanisms. Most natural products act prophylactically and help to alleviate symptoms of depression while also benefiting internal organ functions[7]. Current natural products investigated as potential depression treatments include traditional Chinese medicine formula, herbs or their parts, and natural products that are either extracts or isolated compounds[7]. There are different types of natural products available for different types of depression, such as stress-induced depression, post-stroke depression, comorbidity depression, and more. Some products work well in conjunction with a good diet to prevent depression because some food components, such as omega-3 fatty acids and vitamin L1, can improve mood. Traditional herbal medicine has been used with multi-targets, multi-levels, and multi-ways[48].

Natural products differ from commonly prescribed antidepressants because they tend to originate from non-western medicine and focus on treating other mechanisms in the brain. For example, suppressing signaling pathways, treating internal heat depression, and protecting brain glial loss. Natural products also tend to be produced naturally, compared to most

antidepressants which are produced in a laboratory environment. Some natural products have fewer adverse effects compared to conventional depression medication and can also reduce medication load and undesirable side effects[49]. Natural products provide many compounds with antidepressant-like effects, and their therapeutic impacts have been highlighted for a long time. Apart from using as-is, natural products are also a great source for future antidepressant drug discovery.

There are in vitro, in vivo, nonclinical, and clinical/translational studies looking at the effectiveness of natural products in depression treatment. The potential of *Tetragonia tetragonioides* (TTK) was examined through a trial involving the animal model brain of depression[50]. Glial cells have a protective role within the CNS and PNS by helping to maintain homeostasis. Essentially, glial cells help to hold nerve cells in place so nerve cells can produce their appropriate function. Glial cells play a role in depression because the loss of glial functions has been shown to contribute to the pathophysiology of depression[50]. TTK is commonly called the New Zealand spinach and other local names. TTK is edible, both raw and cooked, and looks like a leafy plant[51]. In the research article, the team was able to protect glial loss (and hence loss of glial function) in the prefrontal cortex of a mouse brain by using TKK[52], demonstrating that TKK is a potential candidate for depression treatment. However, further research is necessary.

Xiaoyaosan, a mixture of dried plants and herbs, was shown to improve depressive-like behavior in rats[52]. Xiaoyaosan works by inhibiting immunoinflammatory activation and reducing the levels of inflammatory cytokines in the colon by suppressing the activation of the TLR4/NLRP3 inflammasome signaling pathway. Improvement in depression is likely due to the decrease in levels of various proteins, such as TLR4, TAK1, and IRAK1, which lead to a subsequent decrease in inflammatory cytokines, including IL-6, IL-1β, and TNF-α. Evidence shows that inflammatory cytokines contribute to the development of depression, and reducing the concentration of inflammatory cytokines alleviates depression symptoms[52,53].

Several natural products are effective in treating depression by reducing the likelihood of depression development, alleviating depressive symptoms, or accompanying conventional Western medicine. However, natural products are generally grouped under "alternative treatment," a treatment option used when Western medicine proves inadequate[54]. For natural products to gain more potential as novel therapeutic strategies, it is important for well-designed, more extensive clinical trials to be carried out. Only then more clinical trials using natural products can be carried out to prove the efficacy of natural products in depression treatment. Better integration of natural products in Western medicinal research is recommended.

5.5. Hormonal Treatment

Thyroid, gonadal, pineal gland, and adrenal axis hormones are the four hormonal groups that have garnered the most recent attention in depression research. Some hormones play a direct role in the nervous system by acting as neurotransmitters and affecting neuronal signaling[8]. Other hormones regulate the production of proteins that affect both brain cell structure and synaptic neurotransmission. Sex hormones have even been proven to stimulate neuroprotection.

Thyrotropin-releasing hormone, associated with the thyroid hormonal group, has been proven to stimulate locomotor activity, amongst other behavioral effects[55]. Additionally, thyrotropin is a pituitary hormone that stimulates the thyroid gland, and T4 and T3 are hormones secreted from the thyroid gland. Research studies have indicated that deficiency of these hormones in the central nervous system can result in fatigue, weight gain, and lack of energy-all common symptoms of depression[56]. The gonadal steroids estrogen and progesterone, beyond their neuroprotective effects, have been shown to affect brain regions involved in mood and behavior regulation[57]. Furthermore, Melatonin, the "sleep hormone," has been implicated in mediating the circadian rhythm. Given the common occurrence of sleep disturbance and irregular sleeping patterns in MDD, melatonin replacement therapies have been gaining popularity[58]. Additionally, a link between hypersecretion of corticotropin-releasing hormone (CRH) and depression has been established. Higher levels of this

hormone have been shown to reduce free cortisol levels and may be a therapeutic option for stress-induced depression[59].

Hormone therapy targets differ from traditional antidepressants as they focus on replacement therapies that increase levels of chemicals found naturally in the body[8]. Although hormone replacement therapies often have indirect effects on brain function and can thus result in unintended secondary effects, these therapies are much more targeted than novel drug treatments due to their natural prevalence in the human body. Furthermore, because such therapies often focus on the replacement of natural chemicals, they are much safer and likely to be approved for funding and distribution. In future research efforts, the three major endocrine systems—the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-thyroid (HPT) axis, and the hypothalamic-pituitary-gonadal axis—should be studied more to enable hormones as research targets in depression.

Treatment	Mechanism	Difference from current antidepressants	Pros	Cons
SSRIs & SNRIs	Reuptake inhibitors	These are most current antidepressant medications.	Improve communication and restore lost connections between neurons.	Delayed effects in patients. Do not target the glutamatergic system. Disrupt glutamate reuptake by astrocytes.
Ketamine	NMDAR antagonist Precents glutamate from activating it Potentiates AMPAR	Targets the glutamatergic system by directly blocking the NMDA receptor.	Fast-acting effects. Reduces suicide ideation. Promotes growth of new neural connections and neuroplasticity.	Short-term impact; effects last only about 1 week.
Psilocybin	Activates the 5-HT_{2A} receptor, which is involved with mood, emotions, thoughts, perceptions, etc.	Directly interacts and activates 5-HT_{2A} receptor to induce changes in mood and thoughts	Has shown signs of longer lasting effects. Some patients experienced improvements in just one week with no delayed effect. Has the potential to reduce suicidal behaviors and thoughts.	Has not been applied to a large population in clinical trials. Still a lot of unknown information regarding long-term adverse effects.
Ayahuasca	Decreases activity in the precuneus and medial prefrontal cortex. Inhibits default mode network activity to reduce stress-induced depression and anxiety. Blocks neurodegeneration and increases levels of BDNF.	Psychedelic effect is faster and more pronounced than the effects of current antidepressants.	Improvements in depression, anxiety, PTSD, and drug dependence. Rapid effect. Provides and alternative for those that are resistant to traditional therapies	Has more side effects than current drugs.
Lysergic Acid Diethylamide (LSD)	Activates the 5-HT_{2A} receptor, causing hallucinations and states of euphoria or dysphoria.	Directly interacts with the 5-HT_{2A} receptor as an agonist. Effects are more rapid and last longer than those of current drugs.	Rapid effect. Promotes cell growth and constructs new connections in brain regions that typically exhibit cell death with mental disorders. Improves optimism, mood, social behavior.	Government restrictions on psychedelic research. Can exacerbate existing psychiatric predispositions.
Natural Products	Act prophylactically and help alleviate depressive symptoms while also benefiting internal organ functions	Suppress signaling pathways and protect brain glial loss. Usually work through unconventional pathways/methods to treat depression.	Some have less adverse effects and reduce medication load. Can be used to accompany current drugs and therapies for depression.	Lack of research on their potential to treat depression. Misinformation online about natural products and their use. Unintended secondary effects.
Hormonal treatment	Adjust hormone levels to optimum levels to reduce depressive symptoms.	Hormone therapy targets are replacement therapies that increase levels of chemicals found naturally in the body.	Offers a targeted approach due to natural prevalence of hormones in the body.	Unintended secondary effects can occur.

Table 3: Summary Table that displays all forms of antidepressants discussed–both conventional and novel.

6. Practical Considerations

Ketamine and psilocybin are the most thoroughly researched and promising therapeutic options for treating depression. Before their widespread implementation, however, greater efforts must be undertaken to reduce stigmas and influence public perceptions surrounding psychedelic treatments. Governmental action is needed to ease medicinal restrictions on psychedelic, natural, and hormonal treatments for mental disorders[60]. Reputable scientific journals and agencies should continue to publish and advertise content displaying the efficacy of these novel treatments to change public perception. However, some concerns regarding these treatments are valid—as high doses of certain drugs may cause adverse side effects and set back research efforts[60]. Thus, researchers must continue to prove the reproducibility of their clinical trials and consider the implementation of natural products in conjunction with conventional drugs. Such a strategy may prove to make therapeutic options more accessible for patients and more likely to be approved for medicinal use.

7. Future Directions

Ketamine and Psilocybin have emerged as potential antidepressant therapeutic options through mechanisms that promote increased neuroplasticity. We have seen similar mechanisms in other psychedelic drugs, such as interaction with the 5-HT_{2A} receptor and signaling on the mTOR pathway[30,32]. By better understanding what specifically contributes to Psilocybin's long-term success, Ketamine's rapid action, hormonal treatments' direct targeted approach, and natural products' reduction of neurotoxic side effects, researchers can not only guide the development of novel antidepressants with similar properties, but we can even perhaps go into how to personalize antidepressants to meet individual needs. We can also expand this study of Depression to other neurological disorders as well, such as Post-Traumatic Stress Disorder, which could benefit from similar novel antidepressant mechanisms.

8. Conclusion

Research on antidepressant therapies has significantly advanced in recent years while taking on a new approach to treating depressive symptoms in patients. While current antidepressant medications increase concentrations of serotonin and norepinephrine through reuptake inhibition, new research focuses on the direct manipulation of receptors, specifically targeting and improving neuroplasticity, which has emerged as a promising approach to treating depressive symptoms. Ketamine has been shown to rapidly reduce depressive symptoms by targeting glutamate, promoting the formation of synapses and new neural connections. Psilocybin has also shown numerous signs of improving neuroplasticity in clinical trials, with the potential for longer-lasting effects. While ketamine and psilocybin are at the forefront of current antidepressant research, much information remains to be known about the impact of long-term and repeated exposure to these drugs, and larger clinical trials are necessary to evaluate their efficacy.

Psychedelic-related drugs, such as ayahuasca and LSD, display the potential to treat depressive symptoms as well. Ayahuasca inhibits default mode network activity to reduce stress-induced depression and anxiety, while LSD functions similarly to psilocybin and promotes cell growth and connections to improve neuroplasticity. However, concerns over side effects and government restrictions have limited research on the psychedelic approach. Natural products have also been found to work well in conjunction with current antidepressant drugs and therapies due to reduced side effects and medication loads. While recent clinical trials show signs of antidepressant effects, there is still an overall lack of research surrounding these products and their potential to treat depression. Hormonal treatment, which has been used for years to treat a variety of disorders, has recently emerged as a potential antidepressant therapy. Replacement therapies involving thyroid, gonadal, pineal gland, and adrenal axis hormones specifically have shown signs of reducing depressive symptoms by adjusting the naturally occurring chemicals to their optimum levels. While hormonal treatment offers a targeted approach due to the knowledge surrounding hormones and their effect on the body, there are concerns about unintended secondary effects that can occur. Due to the relative inconsistency and inefficiency of current

antidepressants, many novel therapeutic strategies, and approaches to treat depression have emerged in recent years. Larger and more diverse clinical trials are needed for all the potential therapies discussed in this review to determine their efficacy in treating depression and whether they offer significant improvements compared to current reuptake inhibitors.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

1. Depression. National Institute of Mental Health. https://www.nimh.nih.gov/health/topics/depression. Accessed July 24, 2022.

2. Penn E, Tracy DK. The drugs don't work? antidepressants and the current and future pharmacological management of depression. *Ther Adv Psychopharmacol.* 2012;2(5):179-188. doi:10.1177/2045125312445469

3. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Prefer Adherence.* 2012;6:369-388. doi:10.2147/PPA.S29716

4. Szarmach J, Cubała WJ, Włodarczyk A, Wiglusz MS. Short-term ketamine administration in treatment-resistant depression: focus on cardiovascular safety. *Psychiatr Danub.* 2019;31(Suppl 3):585-590.

5. Johnson MW, Griffiths RR. Potential Therapeutic Effects of Psilocybin. *Neurotherapeutics*. 2017;14(3):734-740. doi:10.1007/s13311-017-0542-y

6. Tupper KW, Wood E, Yensen R, Johnson MW. Psychedelic medicine: a re-emerging therapeutic paradigm. *CMAJ.* 2015;187(14):1054-1059. doi:10.1503/cmaj.141124

7. Mischoulon D. Update and critique of natural remedies as antidepressant treatments. *Obstet Gynecol Clin North Am.* 2009;36(4):789-x. doi:10.1016/j.ogc.2009.10.005

8. Joffe RT. Hormone treatment of depression. *Dialogues Clin Neurosci.* 2011;13(1):127-138. doi:10.31887/DCNS.2011.13.1/rjoffe

9. Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians?. *World Psychiatry.* 2010;9(3):155-161. doi:10.1002/j.2051-5545.2010.tb00298.x

10. Luscher B, Shen Q, Sahir N. The GABAergic deficit hypothesis of major depressive disorder. *Mol Psychiatry.* 2011;16(4):383-406. doi:10.1038/mp.2010.120

11. National Institute of General Medical Sciences. *Circadian Rhythms.* www.nigms.nih.gov. Published September 9, 2021. https://www.nigms.nih.gov/education/fact-sheets/Pages/circadian-rhythms.aspx#:~:text=Circadian%20rhythms%20are%20physical%2C%20mental

12. Nautiyal KM, Hen R. Serotonin receptors in depression: from A to B. F1000Research. 2017;6:123. doi:10.12688/f1000research.9736.1

13. Garcia-Garcia AL, Newman-Tancredi A, Leonardo ED. P5-HT1A receptors in mood and anxiety: recent insights into autoreceptor versus heteroreceptor function. *Psychopharmacology*. 2013;231(4):623-636. doi:10.1007/s00213-013-3389-x

14. Frazer A, Hensler JG. Serotonin Receptors. Nih.gov. Published 2016. https://www.ncbi.nlm.nih.gov/books/NBK28234/

15. Jenkins T, Nguyen J, Polglaze K, Bertrand P. Influence of Tryptophan and Serotonin on Mood and Cognition with a Possible Role of the

Gut-Brain Axis. *Nutrients.* 2016;8(1):56. doi:10.3390/nu8010056

16. Dale E, Pehrson AL, Jeyarajah T, et al. Effects of serotonin in the hippocampus: how SSRIs and multimodal antidepressants might regulate pyramidal cell function. *CNS Spectrums.* 2015;21(2):143-161. doi:10.1017/s1092852915000425

17. Niciu MJ, Henter ID, Luckenbaugh DA, Zarate CA, Charney DS. Glutamate Receptor Antagonists as Fast-Acting Therapeutic Alternatives for the Treatment of Depression: Ketamine and Other Compounds. *Annual Review of Pharmacology and Toxicology.* 2014;54(1):119-139. doi:10.1146/annurev-pharmtox-011613-135950

18. Lüscher C, Malenka RC. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harb Perspect Biol.* 2012;4(6):a005710. Published 2012 Jun 1. doi:10.1101/cshperspect.a005710

19. Bleakman D, Alt A, Witkin J. AMPA Receptors in the Therapeutic Management of Depression. *CNS & Neurological Disorders - Drug Targets.* 2007;6(2):117-126. doi:10.2174/187152707780363258

20. Braund TA, Tillman G, Palmer DM, Gordon E, Rush AJ, Harris AW. Antidepressant side effects and their impact on treatment outcome in people with major depressive disorder: An ispot-D report. *Translational Psychiatry.* 2021;11(1). doi:10.1038/s41398-021-01533-1

21. Cellular and molecular mechanisms in the long-term action of antidepressants. *Remission in Depression.* 2008;10(4):385-400. doi:10.31887/dcns.2008.10.4/gracagni

22. Murnane KS. Serotonin 2A receptors are a stress response system. *Behavioural Pharmacology.* 2019;30:151-162. doi:10.1097/fbp.000000000000045

23. Hasselmann H. Ketamine as Antidepressant? Current State and Future Perspectives. *Current Neuropharmacology.* 2014;12(1):57-70. doi:10.2174/1570159x113119990043

24. Frizzo ME. Can a Selective Serotonin Reuptake Inhibitor Act as a Glutamatergic Modulator? *Current Therapeutic Research.* 2017;87:9-12. doi:10.1016/j.curtheres.2017.07.001

25. Newcomer JW, Farber NB, Olney JW. NMDA receptor function, memory, and brain aging. *Dialogues Clin Neurosci.* 2000;2(3):219-232. doi:10.31887/DCNS.2000.2.3/jnewcomer

26. Aleksandrova LR, Phillips AG, Wang YT. Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism. *J Psychiatry Neurosci.* 2017;42(4):222-229. doi:10.1503/jpn.160175

27. Kowalczyk M, Kowalczyk E, Kwiatkowski P, Łopusiewicz Ł, Sienkiewicz M, Talarowska M. Ketamine-New Possibilities in the Treatment of Depression: A Narrative Review. *Life (Basel).* 2021;11(11):1186. Published 2021 Nov 5. doi:10.3390/life11111186

28. D'Sa C, Duman RS. Antidepressants and neuroplasticity. *Bipolar Disord.* 2002;4(3):183-194. doi:10.1034/j.1399-5618.2002.01203.x

29. Dimitrov IV, Harvey MG, Voss LJ, Sleigh

JW, Bickerdike MJ, Denny WA. Structure-Activity Relationships for the Anaesthetic and Analgaesic Properties of Aromatic Ring-Substituted Ketamine Esters. *Molecules.* 2020;25(12):2950. Published 2020 Jun 26. doi:10.3390/molecules25122950

30. Harraz MM, Tyagi R, Cortés P, Snyder SH. Antidepressant action of ketamine via mTOR is mediated by inhibition of nitrergic Rheb degradation. *Mol Psychiatry.* 2016;21(3):313-319. doi:10.1038/mp.2015.211

31. Mandal S, Sinha VK, Goyal N. Efficacy of ketamine therapy in the treatment of depression. *Indian J Psychiatry.* 2019;61(5):480-485. doi:10.4103/psychiatry.IndianJPsychiatry_484_18

32. Davis AK, So S, Lancelotta R, Barsuglia JP, Griffiths RR. 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety. *The American Journal of Drug and Alcohol Abuse.* 2019;45(2):161-169. doi:10.1080/00952990.2018.1545024

33. Strumila R, Nobile B, Korsakova L, et al. Psilocybin, a Naturally Occurring Indoleamine Compound, Could Be Useful to Prevent Suicidal Behaviors. *Pharmaceuticals.* 2021;14(12):1213. doi:10.3390/ph14121213

34. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*. 2016;30(12):1181-1197. doi:10.1177/0269881116675513

35. Palhano-Fontes F, Barreto D, Onias H, et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychological Medicine.* 2018;49(4):655-663. doi:10.1017/s0033291718001356

36. Hamilton JP, Farmer M, Fogelman P, Gotlib IH. Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. *Biological Psychiatry.* 2015;78(4):224-230. doi:10.1016/j.biopsych.2015.02.020

37. Jiménez-Garrido DF, Gómez-Sousa M, Ona G, et al. Effects of ayahuasca on mental health and quality of life in naïve users: A longitudinal and cross-sectional study combination. *Scientific Reports.* 2020;10(1). doi:10.1038/s41598-020-61169-x

38. Szilágyi A, Takács B, Szekeres R, et al. Therapeutic Properties of Ayahuasca Components in Ischemia/Reperfusion Injury of the Eye. *Biomedicines.* 2022;10(5):997. Published 2022 Apr 26. doi:10.3390/biomedicines10050997

39. Davis AK, Averill LA, Sepeda ND, Barsuglia JP, Amoroso T. Psychedelic Treatment for Trauma-Related Psychological and Cognitive Impairment Among US Special Operations Forces Veterans. *Chronic Stress.* 2020;4:247054702093956. doi:10.1177/2470547020939564

40. Loizaga-Velder A, Verres R. Therapeutic Effects of Ritual Ayahuasca Use in the Treatment of Substance Dependence—Qualitative Results. *Journal of Psychoactive Drugs.* 2014;46(1):63-72. doi:10.1080/02791072.2013.873157

41. Ly C, Greb AC, Cameron LP, et al.

Psychedelics Promote Structural and Functional Neural Plasticity. *Cell Reports.* 2018;23(11):3170-3182. doi:10.1016/j.celrep.2018.05.022

42. Fuentes JJ, Fonseca F, Elices M, Farré M, Torrens M. Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials. *Frontiers in Psychiatry.* 2020;10. doi:10.3389/fpsyt.2019.00943

43. Mueller F, Lenz C, Dolder PC, et al. Acute effects of LSD on amygdala activity during processing of fearful stimuli in healthy subjects. *Translational Psychiatry.* 2017;7(4):e1084-e1084. doi:10.1038/tp.2017.54

44. Hendricks PS, Thorne CB, Clark CB, Coombs DW, Johnson MW. Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. *Journal of Psychopharmacology.* 2015;29(3):280-288. doi:10.1177/0269881114565653

45. Gregorio DD, Popic J, Enns JP, et al. Lysergic acid diethylamide (LSD) promotes social behavior through mTORC1 in the excitatory neurotransmission. *Proceedings of the National Academy of Sciences.* 2021;118(5). doi:10.1073/pnas.2020705118

46. Carhart-Harris RL, Kaelen M, Bolstridge M, et al. The paradoxical psychological effects of lysergic acid diethylamide (LSD). *Psychological Medicine.* 2016;46(7):1379-1390. doi:10.1017/s0033291715002901

47. Liechti ME. Modern Clinical Research on LSD. *Neuropsychopharmacology.* 2017;42(11):2114-2127. doi:10.1038/npp.2017.86

48. Dai W, Feng K, Sun X, et al. Natural products for the treatment of stress-induced depression: Pharmacology, mechanism and traditional use. *Journal of Ethnopharmacology.* 2022;285:114692. doi:10.1016/j.jep.2021.114692

49. Noori T, Sureda A, Sobarzo-Sánchez E, Shirooie S. The Role of Natural Products in Treatment of Depressive Disorder. *Curr Neuropharmacol.* 2022;20(5):929-949. doi:10.2174/1570159X20666220103140834

50. Rajkowska G, Miguel-Hidalgo J. Gliogenesis and Glial Pathology in Depression. *CNS & Neurological Disorders - Drug Targets.* 2007;6(3):219-233. doi:10.2174/187152707780619326

51. Tetragonia tetragonioides (New Zealand spinach). www.cabi.org. https://www.cabi.org/isc/datasheet/52942

52. Ma K, Baloch Z, Mao F. Natural Products as a Source for New Leads in Depression Treatment. *Evidence-Based Complementary and Alternative Medicine.* 2022;2022:e9791434. doi:10.1155/2022/9791434

53. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience.* 2013;246:199-229. doi:10.1016/j.neuroscience.2013.04.060

54. Cleveland Clinic. Alternative Therapies for Depression | Cleveland Clinic. Cleveland Clinic. Published 2013. https://my.clevelandclinic.org/health/treatments/9303-depression-alternative-therapies

55. Hara J, Gerashchenko D, Wisor JP, Sakurai T, Xie X, Kilduff TS. Thyrotropin-Releasing Hormone Increases Behavioral Arousal through Modulation of Hypocretin/Orexin Neurons. *Journal of Neuroscience.* 2009;29(12):3705-3714. doi:10.1523/jneurosci.0431-09.2009

56. Shahid MA, Sandeep Sharma. Physiology, Thyroid Hormone. Nih.gov. Published March 23, 2019. https://www.ncbi.nlm.nih.gov/books/NBK500006/

57. McEwen BS, Akama KT, Spencer-Segal JL, Milner TA, Waters EM. Estrogen effects on the brain: actions beyond the hypothalamus via novel mechanisms. *Behavioral neuroscience.* 2012;126(1):4-16. doi:10.1037/a0026708

58. Tonon AC, Pilz LK, Markus RP, Hidalgo MP, Elisabetsky E. Melatonin and Depression: A Translational Perspective From Animal Models to Clinical Studies. *Frontiers in Psychiatry.* 2021;12. doi:10.3389/fpsyt.2021.638981
29. doi:10.1177/1179573520907397