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A review of the current research progress of drugs for depression

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Abstract. Depression is one of the most prevalent mental disorders encountered in clinical practice, with an increasing prevalence year on year, resulting in a significant burden to both individuals and society. The precise aetiology of depression remains uncertain, and the prevailing treatment modality is pharmacological. The clinical use of first-generation antidepressants, such as monoamine oxidase inhibitors and tricyclic antidepressants, is constrained by their adverse effects, including cardiovascular and liver toxicity. Subsequently, a fourth category of antidepressant medications emerged, exhibiting a reduced incidence of adverse effects in comparison to tricyclic antidepressants. The current standard of care for depression employs a range of antidepressant medications, including novel agents. It is important to note that antidepressant drugs have certain side effects and that the pathogenesis of depression remains an area of ongoing investigation. The urgent need for the development of more effective antidepressant drugs with fewer side effects is clear. This article presents a review of the research progress made in the field of antidepressant drugs, to provide a basis for the development of new antidepressant drugs.

Keywords: Depression, Monoamine oxidase inhibitors, Tricyclic antidepressants.

1. Introduction

Depression is one of the most prevalent mental disorders in clinical practice. Its defining characteristics include depressed mood, diminished interest or pleasure, and a lack of self-esteem or self-efficacy [1]. When left untreated, depression can have a profound impact on an individual's daily functioning and overall quality of life. Globally, the prevalence of depression is increasing year by year, representing a significant burden on both individuals and society. According to statistics from the World Health Organization (WHO), approximately 322 million individuals worldwide are affected by depression. Depression is projected to become the leading cause of non-fatal health loss by 2030, surpassing other major health concerns [2]. The precise etiology of depression remains unclear. However, research indicates that depression is the consequence of a complex interplay between environmental and genetic factors. Other hypotheses include monoamine neurotransmitters and Hypothalamic-pituitary-adrenal (HPA) axis dysfunction hypothesis, among others. The monoamine hypothesis postulates that a deficiency of monoamine neurotransmitters, including serotonin, dopamine and norepinephrine, is the underlying cause of clinical depression (Figure 1). Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis represents a significant pathophysiological mechanism underlying depression. A number of hormones, including those secreted by the adrenal glands, the thyroid, and estrogen, play a role in

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regulating the HPA axis [3]. The current treatment of depression is primarily focused on the inhibition of monoamine reuptake, thereby enhancing the bioavailability of monoamines within the central nervous system. This has led to the development of monoamine oxidase inhibitors, including phenothiazine and fluoxetine, among others. Tricyclic antidepressants, such as clomipramine and amitriptyline, have also been employed in this context. In light of the aforementioned adverse effects, Traditional antidepressants, newer antidepressants and drugs in clinical trials are presented, and their therapeutic mechanisms, efficacy and side effects are discussed. The article introduced traditional antidepressants, newer antidepressants, and clinical-stage medications, exploring their therapeutic mechanisms and efficacy, as well as side effects. Research is underway to develop alternative pharmaceuticals that exhibit reduced toxicity and enhanced efficacy.

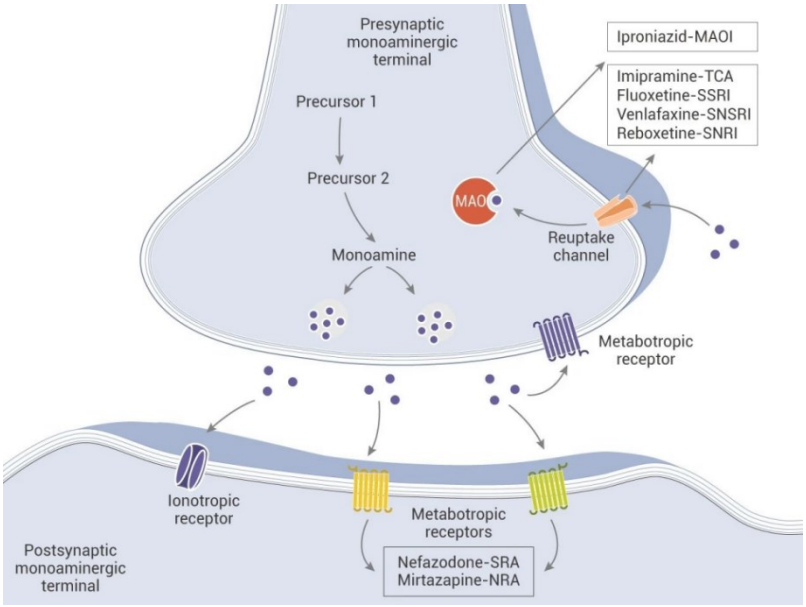

Figure 1. Monoamine neurotransmitter passing [4].

2. Traditional antidepressants

At present, the traditional antidepressants on the market are mainly divided into two types: monoamine oxidase inhibitors and tricyclic antidepressants.

2.1. Monoamine oxidase inhibitors (MAOIs)

There are two main types of MAO genes in humans: MAO-A and MAO-B differ in terms of their substrate affinity, inhibitor specificity, and tissue distribution [5]. Monoamine oxidase inhibitors (MAOIs) represent one of the earliest classes of antidepressant medications developed to alleviate depressive symptoms by modulating the chemical communication between neurotransmitters in the brain. As is the case with the majority of antidepressant medications, MAOI ultimately contributes to the onset of depressive brain chemical alterations. Monoamine oxidases are responsible for the clearance of neurotransmitters, including norepinephrine, serotonin, and dopamine, from the brain. MAOIs have the potential to impede this process, thereby enabling an increased number of neurotransmitters to function within the cells and circuits that are affected by depression. Monoamine oxidase inhibitors can be classified into two categories: early irreversible MAOIs and reversible MAOIs.

2.1.1. Irreversible monoamine oxidase inhibitors. In the early 1950s, researchers discovered that a hydrazide derivative of the anti-tuberculosis drug plinide had antidepressant effects on tuberculosis patients with depression [6]. This discovery marked the advent of MAOI as the first widely used, efficacious antidepressant medication. Subsequently, in 1957, Nathan Kline published the inaugural

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account of the neuropsychiatric effects of Ipnidzad, characterizing it as a "spiritual stimulant". In the year following the publication of the report, over 400,000 individuals diagnosed with depression were treated with the drug, known as iproniazid [7]. Following the discovery of its antidepressant properties, iplinide was also found to inhibit the enzyme MAO, which is involved in the catabolism of serotonin, norepinephrine, and dopamine. However, isoniazid was eventually removed from the market in the United States due to its hypertensive crisis and hepatotoxicity.

Phenothiazines are a group of nitrogenous and sulfur-containing heterocyclic compounds that were first synthesized in 1883 and subsequently became the first commercially available antipsychotic drugs in the United States during the 1950s [8]. The precise mechanism of action exhibited by benzthiazide remains unclear. It is understood, however, that benzthiazide exerts its effects primarily by inhibiting the selective activity of dopamine receptors and D2 receptors in the midlimb pathway. This inhibition can antagonize the hyperactivity of dopamine at synapses, thereby reducing the positive symptoms associated with schizophrenia, including delusions and hallucinations [9]. Consequently, the follow-up clinical trial is primarily employed for the treatment of schizophrenia.

2.1.2. Reversible monoamine oxidase inhibitors. MAO-B inhibitors have the capacity to selectively inhibit the breakdown of both endogenous and exogenous dopamine, thereby prolonging the action time of dopamine and consequently improving clinical symptoms. Additionally, preclinical studies have demonstrated that MAO-B inhibitors possess neuroprotective properties and can impede the advancement of the disease. Selegiline is an irreversible inhibitor of monoamine oxidase MAO-B. In animal studies, the antidepressant effects of selegiline have been shown to be related to the enhancement of hippocampal dopaminergic transmission and the prevention of synaptic plasticity damage [10].

MAO-A inhibitors are pharmaceutical agents that selectively inhibit MAO-A, primarily utilized for the management of depressive disorders. Their pharmacological action involves reversible and selective inhibition of MAO-A, prevention of the degradation of 5-HT and NE in the brain, and augmentation of the concentration of 5-HT and NE in the synaptic cleft of the brain. Sertraline/biamine chloride (moclobemide) is a selective monoamine oxidase (MAO-A) inhibitor that increases the concentration of norepinephrine (NE) and serotonin (5-HT) in synaptic spaces by inhibiting MAO-A, thereby reducing depressive symptoms. The efficacy of moclobemide in the treatment of depression has been corroborated by recent clinical trials and meta-analyses. Moclobemide has been demonstrated to exhibit comparable efficacy to tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and non-selective, irreversible MAO inhibitors [11]. The latest evidence corroborates and extends the therapeutic efficacy of the drug, while also minimizing the potential for adverse effects.

2.2. Tricyclic antidepressants (TCAs)

TCAs are among the most commonly prescribed drugs for the treatment of depression. They exert their therapeutic effect by inhibiting the reuptake of neurotransmitters, thereby increasing their concentration in the synaptic cleft and enhancing their action.

Clomipramine, a TCA, is currently the only antidepressant with evidence of clinically relevant inhibition of serotonin and norepinephrine reuptake (SNRI). The efficacy of chlorimipramine in the treatment of depression has been corroborated by clinical trials [12].

Amitriptyline, a prototypical tricyclic antidepressant, received approval from the US Food and Drug Administration for the management of major depression in 1961. Its principal mechanism of action is the increase in brain levels of norepinephrine and serotonin, which alleviates the symptoms of depression. The drug has been demonstrated to have a significant curative effect in the treatment of depression and other diseases. However, there is also a risk of cardiac toxicity, overuse or abuse, which may result in serious cardiac toxicity and even death [13].

In comparison to MAOIs, TCAs exhibit superior efficacy and allow for dosage adjustment. However, they also present a higher incidence of adverse effects, increased risk of overdose, and a greater propensity to interact with other pharmaceuticals.

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3. New antidepressants

In addition to monoamine oxidase inhibitors and tricyclic antidepressants, new antidepressant agents targeting alternative pathways are emerging as a promising alternative.

3.1. Selective serotonin reuptake inhibitors(SSRIs)

The currently recognized antidepressant treatment is referred to as a "first-line drug," and includes fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram. The initial five drugs were famously designated the "five golden flowers" of antidepressants. By inhibiting the synapses cells of the neurotransmitter serotonin reuptake in order to increase the extracellular can and postsynaptic receptor serotonin levels. Fluoxetine is indicated for patients who experience a lack of motivation and a lack of energy. It is preferred for patients who have a history of chronic cardiovascular disease. Sertraline is preferred for children with a history of chronic cardiovascular disease. Paroxetine is preferred for patients with higher levels of anxiety. Fluvoxamine is preferred for patients with depression and obsessive-compulsive symptoms. Citalopram and escitalopram are preferred for patients taking warfarin or multiple non-psychiatric drugs [14].

3.2. Selective serotonin. (5 - HT) and norepinephrine (NE) reuptake inhibitors (SNRIs)

The pharmacological action of SNRIs is primarily directed towards serotonin and norepinephrine, which can be described as a "dual channel" effect. Venlafaxine is the representative drug, exhibiting a dual channel role at high doses (150 mg/day or more) and a single channel function at low doses (75 mg/day), with a comparable therapeutic effect to SSRIs. In clinical practice, a considerable number of patients with depression present with a range of physical discomforts, including dizziness, headaches, palpitations, and chest tightness. SNRIs have been demonstrated to significantly improve depression accompanied by physical symptoms, particularly in the context of chronic pain [15].

3.3. Other new antidepressants

The noradrenergic and Serotonergic Antidepressants (NaSSA) prototype pharmaceutical agent is mirtazapine. In addition to its efficacy in improving sleep, the drug has the potential to enhance appetite, thereby addressing the issue of appetite loss in some patients [16]. Dopamine and norepinephrine reuptake inhibitors (NDRIs) are also one of the mechanisms of action for antidepressant drugs. As the representative drugs is Bupropion, which elevates mood to more normal levels. However, if the mood is excessively elevated, it may progress to mania. Bupropion carries the lowest risk of mania but the highest risk of depression.

In comparison to MAOIs and TCAs, the latest generation of antidepressants has a broader range of indications, which not only treat various forms of depression but also have applications in the management of a multitude of neurotic disorders. The medication has a lower incidence of adverse effects and these are generally mild. The medication is considered safe and well-tolerated for elderly patients and those with underlying physical illnesses. A long half-life allows for a more stable blood drug concentration, reducing the frequency of drug use. These drugs are typically used on a daily basis, which improves treatment adherence.

4. Clinical trials of pharmaceuticals

In addition to the aforementioned antidepressant drugs, there are several others that have been developed and are currently in use in clinical settings. However, many of these drugs are still in the experimental phase and have not yet been approved for use as antidepressants.

Brexanolone, an intravenous neurosteroid inhibitor, is a novel antidepressant under development as a positive allosteric modulator that modulates the function of gamma-aminobutyric acid (GABAA) receptors for the treatment of postpartum depression. A randomized, double-blind, placebo-controlled trial design was employed to randomly assign patients with postpartum depression to receive brexanolone or placebo and assess changes in depression over a 60-hour period. The results demonstrated a notable reduction in depressive symptoms among the brexanolone cohort in comparison

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to the placebo group. Furthermore, the study revealed that the brexanolone treatment group exhibited a low incidence of adverse events, with no instances of serious adverse events. The drug has provided a solution to the dearth of specific treatments for postpartum depression. The efficacy of traditional antidepressants in the treatment of postpartum depression is limited, whereas brexanolone, a novel treatment method, has the characteristics of rapid onset and is capable of alleviating the severe negative effects of postpartum depression on patients, infants and families to a greater extent than existing treatments [17].

AXS-05 is an oral N-methyl-D-aspartic acid (NMDA)receptor antagonist and agonist, sigma-1 by dextromethorphan (dextromethorphan) and ding bing nitrile (bropion). It has been demonstrated that this compound inhibits CYP2D6, thereby increasing its bioavailability. The efficacy and safety of AXS-05 in the treatment of major depressive disorder were also corroborated by the latest clinical trial, which was a 6-week randomized, double-blind, active-controlled phase 2 trial conducted in four centers in the United States from May 2018 to December 2018. The control group was tested using Ding Bing nitrile (bropion), an approved antidepressant drug. In comparison to the control group, the AXS-05 group exhibited a rapid and significant reduction in depressive symptoms, as evidenced by the results [18].

5. Conclusion

Depression represents a significant burden for patients in terms of their work and daily lives. Due to the presence of low mood and somatic symptoms, patients frequently experience difficulties in concentrating on their daily work and study, which in turn results in a decline in work efficiency and academic performance. Concurrently, social withdrawal and a lack of interest can engender feelings of solitude and helplessness, thereby exacerbating depressive symptoms. It is therefore imperative to develop more efficacious antidepressants with fewer side effects. Depression research has made significant progress in recent years, with the advent of new drugs such as Brexanolone and AXS-05, which demonstrate a substantial therapeutic advantage over existing treatments. These drugs have been demonstrated to have a significant impact on the alleviation of depressive symptoms, and also exhibit a rapid onset of action, thereby enhancing the efficacy of treatment and the quality of life of patients. The introduction of new drugs not only improves the efficacy of treatment, but also reduces the time and cost of treatment, alleviates the burden of depression on patients and their families, and improves the quality of life and work efficiency of patients. The future of depression drug research will continue to explore a multitude of avenues, with a view to deepening our understanding of the neurobiological mechanisms underlying depression, identifying new therapeutic targets and the development of more efficacious drugs.

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