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Treat Clinical Depression Using Antidepressants

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ABSTRACT

SSRIs are chemically distinct from traditional antidepressants such as tricyclic, tetracyclic, and monoamine oxidase inhibitors, but they share the same mechanism of action in that they selectively and potently inhibit serotonin neuronal reuptake while having no or very little effect on norepinephrine, acetylcholine, and histamine neuronal reuptake. As a result, when compared to other tricyclic and tetracyclic antidepressants, these drugs have fewer sedative, anticholinergic, and cardiovascular effects. Fluroxamine, fluroxamine, sertraline, indalpine, paroxetine, alproclate, femorxetine, and choroxamine are examples of SSRI drugs.

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INTRODUCTION

Depression is a mental illness that affects around 16% of the population at some point in their lives, and major depressive disorder is a prominent cause of disability around the world [1]. Depression is a common mental condition characterized by a sad mood, lack of interest or pleasure, feelings of guilt or low self-worth, sleep or hunger disturbances, low energy, and impaired focus. These issues can become chronic or recurring, causing significant limitations in an individual's ability to carry out his or her daily tasks [2]. It is the most frequent of the affective disorders (defined as mood disorders rather than mental or cognition abnormalities); it can range from a very mild condition bordering on normalcy to severe (psychotic) depression accompanied by hallucinations and delusions. Depression is a leading cause of disability and early death worldwide [3].

1. SYMPTOMS OF DEPRESSION

Not everyone who is depressed exhibits all of the symptoms. Some people have a few symptoms, while others have many symptoms, which are referred to as warning signals. The degree of symptoms varies from person to person [3].

1. Depressed mood most of the day, nearly every day (e.g., feels sad or empty) or observation made by others (e.g.,appears tearful).
2. Markedly diminished interest or pleasure in all, or almost all, activities most of day, nearly every day.
3. Significant weight loss when not dieting or weight gain (e.g., a change more than 5% of body weight in amonth) or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia every day.
5. Feeling of worthlessness or excessive or inappropriate guilt nearly every day.
6. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
7. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan for committing suicide.
8. Loss of libido [1]

1. CAUSES

- The precise etiology of depression is unknown. Many studies believe it is caused by chemical imbalances in the brain, which can be inherited or induced by life events. Some forms of depression appear to run in families; however, depression can occur in persons with no family history of the illness. Some people experience depression as a result of stressful life circumstances or occurrences. Typically, a number of things are at work. Depression can affect men and women of different ages, races, and socioeconomic backgrounds.

Depression can strike adolescents and teenagers as well. A variety of things can contribute to depression:

- Abuse of alcohol or drugs
- Life events or circumstances such as:
- Breaking up with a lover or girlfriend, failing a class, a family illness or death, or parents divorcing (for adolescents)
- Childhood occurrences such as abuse or neglect
- Divorce, death of a friend or relative, or job loss (for adults)
- Isolation from others (common in the elderly)
- Medical problems such as hypothyroidism (low thyroid activity), drugs (such as sedatives and blood pressure meds), cancer, serious illness, or continuous pain
- Sleeping issues [4].

2. TYPES OF DEPRESSION

- Major Depression
- Dysthymia
- Bipolar Disorder
- Seasonal Affective Disorder (SAD)[5]

Major Depression

One of the most prevalent psychiatric diseases is major depression (also known as unipolar depression) [6]. Major depression is a hereditary condition, with genetic effects playing a significant role. Individual environmental variables are also etiologically relevant. Major depression is a complex condition that is caused by a combination of hereditary and environmental factors [7]. A distinct change in mood, characterized by sadness or irritability, and accompanied by at least several psychophysiological changes, such as disturbances in sleep, appetite, or sexual desire; constipation; and loss of the ability to experience pleasure are required for the diagnosis of major depressive disorder [1]. Difficulty concentrating; suicidal thoughts on a regular basis [8].

Dysthymia

This is a mild, chronic depression that lasts for at least two years and is defined by chronic symptoms that do not impair but prevent one from feeling good about oneself. Many people with Dysthymia have major depressive episodes at some time in their lives [5].

Bipolar Disorder or Manic depression

Bipolar disorders can be divided into

- Bipolar I (manic depressive episodes)
- Bipolar II (hypomanic-depressive episodes or cyclothymia)

Bipolar disease appears to run in families and affects both men and women equally. Anomalies are related with distress and disruption, as well as an increased risk of suicide, particularly during depressive periods. In some situations, it can be a terrible long-term condition; in others, it has been linked to creativity, goal-setting, and positive outcomes [3].

Season Affective Disorder

This type of depression is caused by seasonal variations. Most cases begin in the fall or winter, or when the amount of sunlight decreases [5].

Melancholic Depression

Clinically, melancholic (or agitated) depression is clearly defined. It comprises of activating systems that serve arousal, vigilance, and attention while inhibiting systems that control eating, sleep, and sexual desires. In other words, melancholic sadness is characterized by anxiety and fear-inducing expectations. The individual feels imprisoned, unable to take positive action to improve the situation, and is frequently nervous, in a condition of continuous arousal [9].

Psychotic Depression

Psychotic depression is defined as a severe major depressive disease with psychotic features. This classification involves the normal criteria for major depressive episodes, plus hallucinogens or delusions that can be mood-congruent or mood-incongruent [10].

Atypical depression

In outpatients, atypical depression is the most common type of depression, although unlike melancholia, less is known regarding its comorbidity, course, and therapy. Aside from the well-defined constellation of symptoms that characterizes atypical depression (mood reactivity, hypersomnia, leaden paralysis, hyperphagia, and rejection sensitivity), particular axes have been identified.

Comorbid conditions I and II may distinguish atypical people from other depressive patients. Similarly, with atypical depression, the age of onset, duration of episodes, frequency of relapses and recurrences, and frequency of complete remission may differ [11].

Double depression

Depression can be difficult to cure, and those suffering with dual depression face a double battle. This condition is a combination of profound depression and dysthymia, a chronic depressive condition. A major depressive episode and dysthymia have comparable symptoms, but double depression has distinct characteristics that define it as a distinct illness. To alleviate double depression, both the major depressive episode and the underlying dysthymia must be resolved [12].

3. PATHOPHYSIOLOGY OF DEPRESSION

With the advent of reserpine in the early 1950s, it became clear that the medicine might cause depression in both hypertension and schizophrenia patients, as well as in normal persons. Pharmacologic research over the next few years indicated that the primary mechanism of action of reserpine was to prevent the storage of amine neurotransmitters like serotonin and norepinephrine in the vesicles of presynaptic nerve terminals. Reserpine caused depression and depleted amine neurotransmitter reserves;

thus, depression was thought to be related with decreased functional amine-dependent synaptic transmission. This concept served as the foundation for what became known as the amine of depression [6]. In severe retarded depressions, autonomic, metabolic, and electrophysiological problems follow a basic pattern; connection with varying somatic symptomatology is only partial, and delineation from other mental illnesses is hazy [13].

4. ANTIDEPRESSANTS

In the years following World War II, antidepressants were introduced alongside the first antibiotics, antihypertensive, and a variety of other medications as part of a therapeutic revolution. For the first time, an armamentarium of individual remedies for specific ailments, dubbed "magic bullets," were available. This development ushered in a revolution that has revolutionized our understanding of disease, health, and therapy [14]. These are medications that help improve mood in those suffering from depression. Almost all antidepressants influence monoaminergic transmission in the brain in some way, and many of them have additional features.

5. MECHANISTIC CLASSIFICATION OF ANTIDEPRESSANTS

1. **Tricyclic Antidepressants (TCAs)** Mixed (NA + 5-HT Amitriptyline, Amoxepine, Clomipramine, Dothepin, Doxepine, Imipramine, Trimipramine NE Favoring Desipramine, Nortriptyline, Maprotiline,Protriptyline
2. **Selective serotonin reuptake inhibitors (SSRIs)** Fluoxetine, Paroxetine, Fluvoxamine, Paroxetine, Sertraline,Venlafaxine
3. **Norepinephrine selective reuptake inhibitors (NSRIs, NaRIs)** Reboxetine
4. **Monoamine oxidase (MAO) inhibitors** Irreversible **MAO** inhibitors Phelezine, TranylcypromineReversible (**RIMA**s) Moclobemid
5. **Serotonergic agents** Nefadozone, Trazodone
6. **Other agents** Bupropion, Mirtazepine[15]

6. MECHANISM OF ACTION OF ANTIDEPRESSANT

In the lack of a straightforward molecular hypothesis to account for antidepressant action, it is useful to explore for pharmacological effects shared by different medications, focusing on delayed adaptive changes that follow a similar time course to the therapeutic impact. This method has resulted in the observation that certain monoamine receptors, specifically 1 and 2 adrenoceptors, are persistently down-regulated after chronic antidepressant administration. In experimental animals, this is manifested as a decrease in the number of binding sites as well as a decrease in the functional response to agonists (e.g., stimulation of cAMP production by -adrenoceptor agonists). Because long-term antidepressant medication reduces endocrine responses to clonidine, a 2-adrenoceptor agonist, receptor down-regulation is likely to occur in people. Other receptors have been investigated as well; 1-adrenoceptors are not consistently affected, but 5-HT2-receptors are. The loss of -adrenoceptors as a factor in depression alleviation does not fit theory because -adrenoceptor antagonists are not antidepressants, despite being the most consistent change documented. Impaired presynaptic inhibition caused by 2-adrenoceptor downregulation, it is thought, may enhance monoamine release and consequently transmission. This idea is supported by the fact that certain newer antidepressants, such as mirtazapine, are antagonists at a variety of inhibitory presynaptic receptors, including 2-adrenoceptors [3].

MECHANISM OF ACTION

Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants, so named because of its distinctive three-ring nucleus, have been utilized in clinical trials for almost four decades. They are chemically and, to a lesser extent, pharmacologically similar to phenothiazines [6]. TCAs' primary immediate impact is to inhibit amine uptake by nerve terminals by competing for the binding site of the amine transporter. Although some TCAs appear to increase transmitter release indirectly by inhibiting presynaptic 2-adrenoceptors, amine synthesis, storage in synaptic vesicles, and release are not directly impacted. Most TCAs have a similar effect on noradrenaline and 5-HT uptake by brain synaptosomes but have a significantly lower effect on dopamine uptake. It has been proposed that treatment of motional symptoms occurs primarily from an increase in 5-HT-mediated transmission, whereas relief of biological symptoms results from an increase in noradrenergic transmission. The fact that the primary metabolites of TCAs have significant pharmacological action (in some cases stronger than the parent medication) and frequently differ from the parent drug in terms of noradrenaline/5-HT selectivity complicates interpretation [3].

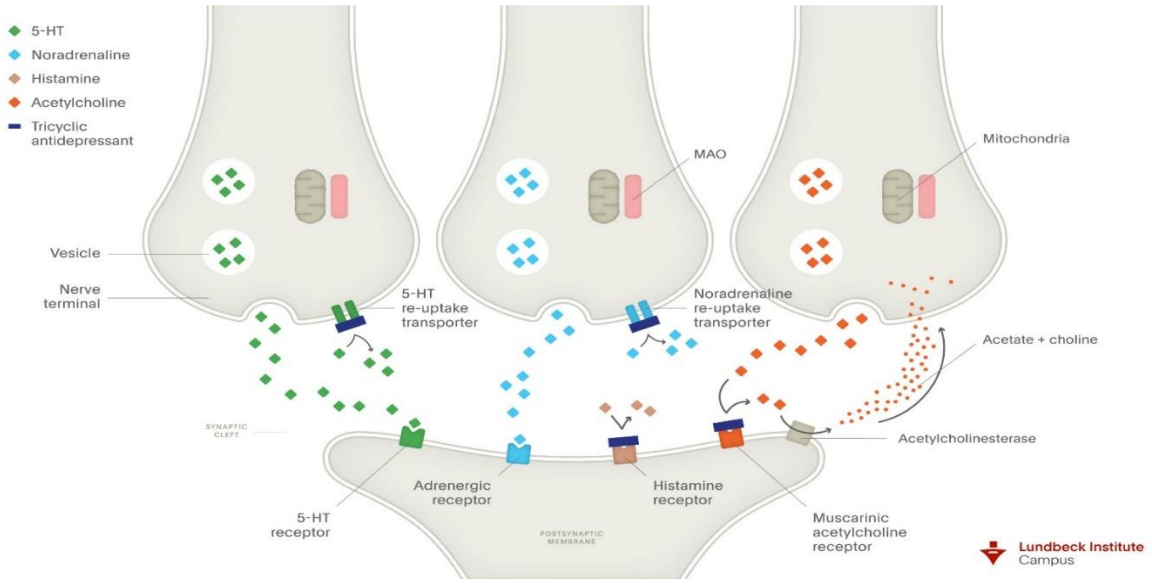

Fig. 1.1 Mechanism of Tricyclic Antidepressant

Selective serotonin reuptake inhibitors (SSRIs)

SERT (the reuptake transporter for 5-HT) is preferentially inhibited by selective serotonin reuptake inhibitors, which have little or no affinity for NE and dopamine transporters. These medicines bind to SERT with a strong and selective affinity, preventing 5-HT from binding to SERT and being absorbed into presynaptic cells. Excess 5-HT in the synaptic cleft indicates that the postsynaptic receptors are overactivated. Over time, this causes downregulation of pre- and postsynaptic receptors, a decrease in the quantity of 5-HT generated in the CNS, and a decrease in the number of SERTs expressed. Long-term SSRI administration produces SERT downregulation but not NET downregulation. [5].

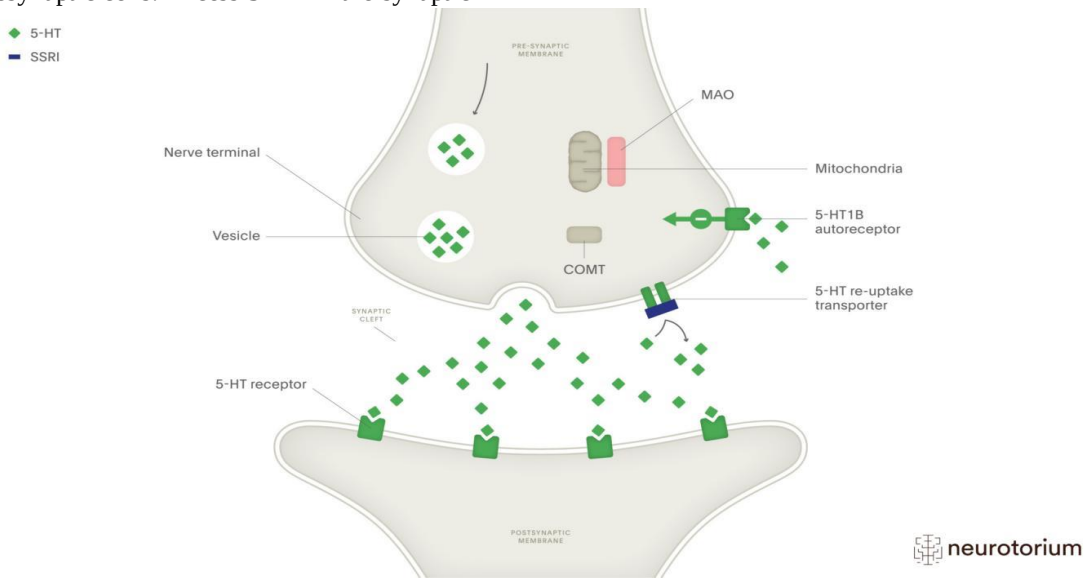

Fig. 1.2 Mechanism of Action of Selective serotonin reuptake inhibitors

Serotonin's increased synaptic availability stimulates a wide range of postsynaptic 5-HT receptor types. The stimulation of 5-HT3 receptors is thought to contribute to the usual unpleasant effects of this family of medications, such as nausea and vomiting, as well as sexual effects (delayed or impaired orgasm). 5-HT2C receptor stimulation may contribute to the agitation or restlessness caused by serotonin reuptake inhibitors [16].

Norepinephrine selective reuptake inhibitors (NSRIs/NaRIs)

Depression is thought to be associated with a decrease in communication and connection between neurons in the hippocampus. Neurotransmitters, which travel across the cells' thin synapses, allow neurons to communicate with one another. The majority of the neurotransmitter is reabsorbed by the presynaptic cell after connecting with receptors on a postsynaptic neuron, a process known as reuptake. Antidepressants increase the number of neurotransmitters active at the synapse, resulting in increased neuronal activity downstream. This stimulates neuronal development and synapse creation via an action on NMDA receptors, which has been proven in animal models to correlate with depression alleviation [17].

Monoamine oxidase (MAO) inhibitors

Monoamine oxidase is found in nearly all tissues and has two comparable molecular forms that are called for by different genes. MAO-A prefers 5-HT as a substrate and is the primary target of antidepressant MAOIs. MAO-B prefers phenylethylamine as a substrate, and both enzymes act on noradrenaline and dopamine. Selegiline preferentially inhibits type B [2].

2. CLINICAL USES OF ANTIDEPPERSANTS

The primary prescription for these medications is to treat depression, but clinical experience and controlled trials have proven a number of alternative uses [15].

Major depression

One of the most prevalent psychiatric diseases is major depression (also known as unipolar depression) [6]. Major depression is characterized by a sad mood, a loss of interest in typical activities, anorexia with significant weight loss, sleeplessness, exhaustion, and the inability to focus [5].

Bipolar depression

Bipolar disorders can be divided into

- Bipolar I (manic depressive episodes)
- Bipolar II (hypomanic-depressive episodes or cyclothymia)

Bipolar disease appears to run in families and affects both men and women equally. Anomalies are related with distress and disruption, as well as an increased risk of suicide, particularly during depressive periods. In some situations, it can be a terrible long-term condition; in others, it has been linked to creativity, goal-setting, and positive outcomes [18].

Atypical depression

In outpatients, atypical depression is the most common type of depression, although unlike melancholia, less is known regarding its comorbidity, course, and therapy. Aside from the well-known constellation of symptoms that characterizes atypical depression (mood reactivity, hypersomnia, leaden paralysis, hyperphagia, and rejection sensitivity), unique axis I and II comorbid disorders may distinguish atypical from other depressed patients [11].

Dysthymia

This is a mild, chronic depression that lasts for at least two years and is defined by chronic symptoms that do not impair but prevent one from feeling good about oneself. Many people who have dysthymia have major depressive episodes at some point in their lives [5].

Anxiety disorders

Anxiety is a natural response to stress. It can help you deal with a stressful scenario at work, study more for an exam, or stay focused on a crucial speech. In general, it aids in coping. However, anxiety becomes a crippling disorder when it becomes an excessive, unreasonable fear of ordinary circumstances [19].

Obsessive-compulsive and phobic states

Obsessive-compulsive disorder (OCD) is a severe and debilitating anxiety disease that affects approximately one out of every 40 adults, making it twice as frequent as schizophrenia and bipolar disorder and the fourth most common mental disorder. OCD appears all around the world and affects both men and women equally. OCD usually manifests itself gradually. Two-thirds of persons with OCD develop the disorder throughout adolescence or early adulthood [20].

Neuropathic pain

In clinical practice, chronic neuropathic pain is common. Patients suffering from diabetic polyneuropathy, HIV sensory neuropathy, post-stroke syndromes, and multiple sclerosis typically experience everyday discomfort that significantly reduces their quality of life. Chronic neuropathy pain is classified as either central or peripheral based on the location of the nervous system damage [21]. Pain is a common sign of neurological illness. Despite advancements in treatment, pain is frequently intractable to all therapeutic techniques [22].

CONCLUSION

The SSRIs are chemically distinct from traditional antidepressants such as tricyclic, tetracyclic, and monoamine oxidase inhibitors, but they share the common route of selective and potent inhibition of neuronal reuptake of serotonin while having no or very little effect on norepinephrine, acetylcholine, and histamine reuptake. As a result, these medicines have less sedative, anticholinergic, and cardiovascular effects than other tricyclic and tetracyclic antidepressants. Fluoxetine, fluroxamine, sertraline, indalpine, paroxetine, alproclate, femorxetine, and choroxamine are examples of SSRI medications

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