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An Overview On Depression And Antidepressants

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A B S T R A C T
The SSRIs differ chemically from conventional antidepressants like 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 impact on norepinephrine, acetylcholine, and histamine neuronal reuptake. Therefore, compared to other antidepressants of the tricyclic and tetracyclic class, these medications have less sedative, anticholinergic, and cardiovascular effects. The SSRI class of medications includes fluoxetine, fluroxamine, sertraline, indalpine, paroxetine, alproclate, femorxetine, and choroxamine.

Keywords: *Depression, Antidepressants, Tricyclic, Tetracyclic, And Monoamine Oxidase Inhibitors.*

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1.0 INTRODUCTION
Depression is a mental illness which affects around 16% of the population at some point in their lives and major depressive disorder is a leading cause of disability worldwide[1]. Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities[2]. It is the most common of the affective disorders (defined as disorders of mood rather than disturbances of thought or cognition); it may range from a very mild condition, bordering on normality, to severe (psychotic) depression accompanied by hallucinations and delusions. Worldwide, depression is a major cause of disability and premature death[3].

1.1 SYMPTOMS OF DEPRESSION
Not everyone who is depressed experiences every symptom. Some people experience a few symptoms and some many symptoms, also called warning signs. The severity of symptoms also varies with individuals[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 a month), 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 everyday.
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]

1.2 CAUSES
The exact cause of depression is not known. Many researchers believe it is caused by chemical imbalances in the brain, which may be hereditary or caused by events in a person's life. Some types of depression seem to run in families, but depression can also occur in people who have no family history of the illness. Stressful life changes or events can trigger depression in some people. Usually, a combination of factors is involved. Men and women of all ages, races, and economic levels can have depression. Depression can also occur in children and teenagers. A number of factors can play a role in depression:

- Alcohol or drug abuse
- Life events or situations, such as:
  - Breaking up with a boyfriend or girlfriend, failing a class, illness or death in the family, or parents divorcing (for adolescents)
  - Childhood events, such as abuse or neglect
  - Divorce, death of a friend or relative, or loss of a job (for adults)
  - Social isolation (common in the elderly)
- Medical conditions such as hypothyroidism (underactive thyroid), medications (such as sedatives and high blood pressure medications), cancer, major illness, or prolonged pain
- Sleeping problems[4].

1.3 TYPES OF DEPRESSION

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

Major Depression

Major depression (also called unipolar depression) is one of the most common psychiatric disorders[6]. Major depression is a familial disorder and its familiality mostly or entirely results from genetic influences. Environmental influences specific to an individual are also etiologically significant. Major depression is a complex disorder that does not result from either genetic or environmental influences alone but rather from both[7]. Diagnosis of major depressive disorder requires a distinct change of mood, characterized by sadness or irritability and accompanied by at least several psychophysiological changes, such as disturbances in sleep, appetite, or sexual desire; constipation; loss of the ability to experience[1]. Difficulty in concentrating ; recurrent thoughts of suicide[8].

Dysthymia

This is a mild, chronic depression that lasts for 2 years or longer and is characterized by chronic symptoms that do not disable but that keep one from feeling good about themselves. Many of those with Dysthymia also experience major depressive episodes at some point 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 disorders also appear to run families and effect men and women equally. Episodes of abnormality are associated with distress and disruption, and an elevated risk of suicide, especially during depressive episodes. In some cases it can be a devastating long-lasting disorder; in others it has also been associated with creativity, goal striving and positive achievements[3].

Season Affective Disorder

This is a depression that results from changes in the season. Most cases begin in the fall or winter, or when there is a decrease in sunlight[5].

Melancholic Depression

Melancholic (or agitated) depression is well characterized on clinical grounds. It consists of the activation of systems subserving arousal, vigilance, and attention, and the inhibition of systems controlling appetite, sleep and sexual desires. In other words, melancholic depression involves anxiety and fear-provoking expectations. The person feels imprisoned, unable to take any positive action to ameliorate the situation and is often anxious, in a state of chronic arousal[9].

Psychotic Depression

Psychotic depression is classified as major depressive disorder, severe, with psychotic symptoms. This classification requires the usual criteria for a major depressive episodes with the additional symptoms of hallucinogens or delusions, which can be either mood-congruent or incongruent[10].

Atypical depression

Atypical depression is the most common form of depression in outpatients, but compared with melancholia, little is known about its comorbidity, course, and treatment. Beyond the well-characterized constellation of symptoms that define atypical depression (mood reactivity, hypersomnia, leaden paralysis, hyperphagia, and rejection sensitivity), specific axis

I and II comorbid conditions may differentiate atypical from other depressed patients. Similarly, age at onset, duration of episodes, frequency of relapses and recurrences, and frequency of complete remission in atypical depression may be different[11].

Double depression

Depression can be hard to treat, and those who have double depression have a double battle to fight. This condition involves a combination of major depression and a chronic depressive condition called dysthymia. A major depressive episode and dysthymia have similar symptoms but there are distinguishing features to double depression that make it its own special condition. Easing double depression requires both ending the major depressive episode and resolving the underlying dysthymia[12].

1.4 PATHOPHYSIOLOGY OF DEPRESSION

With the introduction of reserpine in the early 1950s, it became apparent that the drug could induce depression in patients being treated for hypertension and schizophrenia as well as in normal subjects. Within the next few years, pharmacologic studies revealed that the principal mechanism of action of reserpine was to inhibit the storage of amine neurotransmitters such as serotonin and norepinephrine in the vesicles of presynaptic nerve endings. Reserpine induced depression and depleted stores of amine neurotransmitters; therefore, it was reasoned, depression must be associated with decreased functional amine-dependent synaptic transmission. This idea provided the basis for what became known as the amine of depression[6]. Autonomic, biochemical and electrophysiological disturbances follow a general pattern in severe retarded depressions, correlation of these with the variable somatic symptomatology is only partial and demarcation from other psychiatric syndromes vague[13].

1.5 ANTIDEPRESSANTS

Antidepressants were introduced along with the first antibiotics, the first antihypertensive, and a range of other drugs in a therapeutic revolution that took place in the years just after World War II. For the first time, an armamentarium of specific treatments for specific diseases became available, an arsenal of magic bullets, as they were called. This development inaugurated a revolution that has transformed our ideas of disease, of health, and of treatment[14]. These are drugs which can elevate mood in depressive illness. Practically all antidepressants affect monoaminergic transmission in the brain in one way or the other and many of them have other associated properties.

1.6 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, Tranylcypromine
   Reversible (**RIMA**s) Moclobemid
   Serotonergic agents Nefadozone, Trazodone
5. **Other agents** Bupropion, Mirtazepine[15]

1.7 MECHANISM OF ACTION OF ANTIDEPRESSANT

In the absence of a simple mechanistic theory to account for antidepressant action, it is useful to look for pharmacological effects that the various drugs have in common, concentrating more on the slow adaptive changes that follow a similar time course to the therapeutic effect. This approach has led to the discovery that certain monoamine receptors, in particular β_1 and α_2-adrenoceptors, are consistently down-regulated following chronic antidepressant treatment. This can be demonstrated in experimental animals as a reduction in the number of binding sites, as well as by a reduction in the functional response to agonists (e.g. stimulation of cAMP formation by β-adrenoceptor agonists). Receptor down-regulation probably also occurs in humans, because endocrine responses to **clonidine**, an α_2-adrenoceptor agonist, are reduced by long-term antidepressant treatment. Other receptors have also been studied; α_1-adrenoceptors are not consistently affected, but 5-HT_2-receptors are also down-regulated. Loss of β-adrenoceptors as a factor in alleviating depression does not fit comfortably with theory, because β-adrenoceptor antagonists are not antidepressant, although it is the most consistent change reported. Impaired presynaptic inhibition secondary to down-regulation of α_2-adrenoceptors might, it is argued, facilitate monoamine release and thus facilitate transmission. Consistent with this possibility is the fact that some newer antidepressant drugs, such as **mirtazapine**, are antagonists at various inhibitory presynaptic receptors, including α_2-adrenoceptors[3].

MECHANISM OF ACTION

Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants so called because of the characteristic three-ring nucleus have been used clinically for four decades. They closely resemble the phenothiazines chemically and, to a lesser extent, pharmacologically[6]. The main immediate effect of TCAs is to block the uptake of amines by nerve terminals, by competition for the binding site of the amine transporter. Synthesis of amines, storage in synaptic vesicles, and release are not directly affected, although some TCAs appear to increase transmitter release indirectly by blocking presynaptic α_2-adrenoceptors. Most TCAs inhibit noradrenaline and 5-HT uptake by brain synaptosomes to a similar degree but have much less effect on dopamine uptake. It has been suggested that improvement of motional symptoms reflects mainly an enhancement of 5-HT-mediated transmission, whereas relief of biological symptoms results from facilitation of noradrenergic transmission. Interpretation is made difficult by the fact that the major metabolites of TCAs have considerable pharmacological activity (in some cases greater than that of the parent drug) and often differ from the parent drug in respect of their noradrenaline/5-HT selectivity[3].

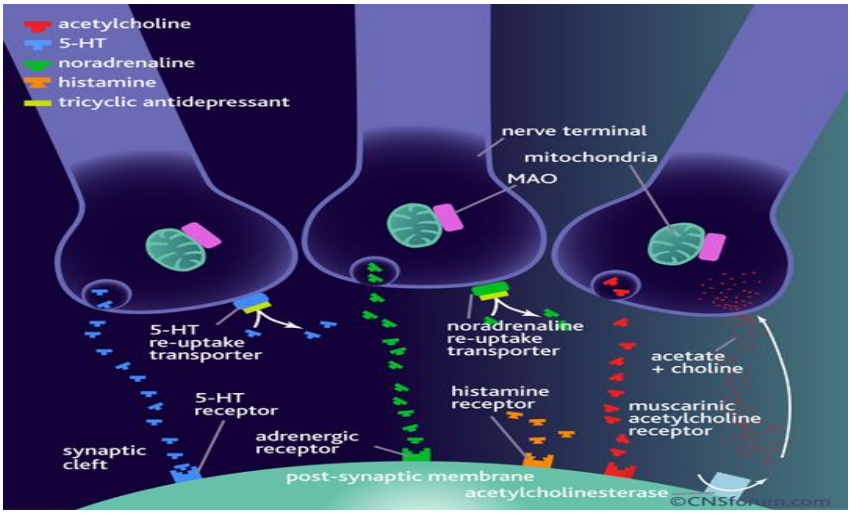

Fig. 1.1 Mechanisam of Tricyclic Antidepressant

Selective serotonin reuptake inhibitors(SSRIs)

The **selective serotonin reuptake inhibitors** preferentially act to inhibit SERT (the reuptake transporter for 5-HT) with minimal or no affinity for NE and dopamine transporters. These drugs have a high and selective affinity for SERT and, therefore, block 5-HT from binding to SERT and being absorbed into presynaptic cells. The excess 5-HT in the synaptic cleft means over activation of the postsynaptic receptors. Over an extended period of time, this causes down regulation of pre- and postsynaptic receptors, a reduction in the amount in the 5-HT produced in the CNS, and a reduction in the number of SERTs expressed. Long-term administration of SSRIs causes down regulation of the SERT, But not the NET[5].

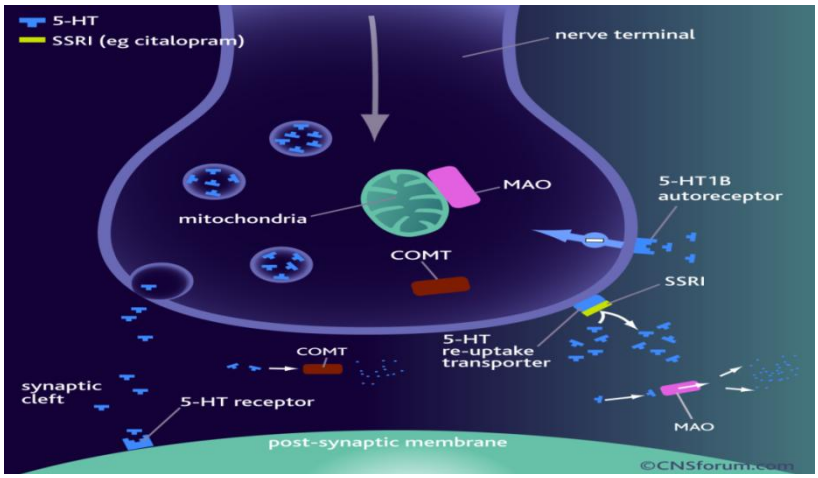

Fig. 1.2 Mechanism of Action of Selective serotonin reuptake inhibitors

Increased synaptic availability of serotonin stimulates a large number of postsynaptic 5-HT receptor types. Stimulation of 5-HT_3 receptors is suspected to contribute to common adverse effects haracteristic of this class of drugs, including gastrointestinal (nausea and vomiting) and sexual effects (delayed or impaired orgasm). Stimulation of 5-HT_{2C} receptors may contribute to the agitation or restlessness sometimes induced by serotonin reuptake inhibitors[16].

Norepinephrine selective reuptake inhibitors (NSRIs/NaRIs)

It has been theorized that depression corresponds with a reduction in communication and connectivity between neurons in the hippocampus. Neurons pass information to each other by means of neurotransmitters, which pass across the narrow synapses between the cells. After interacting with receptors on a postsynaptic neuron, most of the neurotransmitter is reabsorbed by the presynaptic cell in a process called reuptake. Antidepressants increase the number of neurotransmitters active in the synapse, thereby enhancing neuronal activity downstream. Via an effect on NMDA receptors, this causes neuronal growth and synapse formation which have been shown in animal models to correlate with the relief of depression[17].

Monoamine oxidase (MAO) inhibitors

Monoamine oxidase is found in nearly all tissues, and exists in two similar molecular forms coded by separate genes. MAO-A has a substrate preference for 5-HT and is the main target for the antidepressant MAOIs. MAO-B has a substrate preference for phenylethylamine, and both enzymes act on noradrenaline and dopamine. Type B is selectively inhibited by **selegiline**[2].

1.8 CLINICAL USES OF ANTIDEPPERSANTS

The major indication of these drugs is to treat the depression, but a number of the other uses have been established by clinical experience and controlled trails[15].

Major depression

Major depression (also called unipolar depression) is one of the most common psychiatric disorders[6]. Major depression generally presents as depressed mood, diminished interest in normal activities, and anorexia with significant weight loss, insomnia, fatigue and ability to concentrate[5].

Bipolar depression

Bipolar disorders can be divided into

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Anxiety disorders

Anxiety is a normal reaction to stress. It helps one deal with a tense situation in the office, study harder for an exam, keep focused on an important speech. In general, it helps one cope. But when anxiety becomes an excessive, irrational dread of everyday situations, it has become a disabling disorder[19].

Obsessive-compulsive and phobic states

Obsessive-compulsive disorder (OCD) is a severe and debilitating anxiety disorder afflicting about one adult in 40, making it twice as common as schizophrenia and bipolar disorder, and the fourth most common psychiatric disorder. OCD exists throughout the world and affects men and women at an equal rate. OCD usually begins gradually. Approximately two-thirds of the people with OCD develop the disorder in adolescence or early adulthood[20].

Neuropathic pain

Chronic neuropathic pain is common in clinical practice. Patients with conditions as diverse as diabetic polyneuropathy, human immunodeficiency virus (HIV) sensory neuropathy, post stroke syndromes, and multiple sclerosis frequently experience daily pain that greatly impairs their quality of life. Chronic neuropathy pain divides into two groups based on a central or peripheral location of the nervous system lesion[21]. Pain is a frequent symptom of neurological disease. Although there have been improvements in treatment, pain often remains unresponsive to all treatment modalities[22].

CONCLUSION

The SSRIs are chemically distinct from traditional antidepressants like tricyclic, tetracyclic and monoamine oxidase inhibitors, but share the common route of selective and potent inhibition of neuronal reuptake of serotonin, and have none or very little effect on neuronal reuptake of norepinephrine, acetylcholine and histamine. Thus, these drugs have less sedative, anticholinergic and cardiovascular effects than other antidepressants of tricyclic and tetracyclic class. Fluoxetine, fluroxamine, sertraline, indalpine, paroxetine, alproclate, femorxetine and choroxamine belong to SSRI group of drugs.

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