



Antidepressant: An Overview

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Abstract

Depression is the largest cause of disability in the world and a substantial contributor to the global illness burden. According to the National Health Interview Survey, individuals aged 18-29 had the highest percentage of persons experiencing any symptoms of depression, followed by those aged 45-64 and 65 and older, and finally those aged 30-44. Women are more likely than men to suffer from serious depressive disorders (8.7 percent compared to 5.3 percent of adult males). Depression is characterized by drastic changes in one's life, childhood trauma, a hectic schedule, stress, brain structure (risk is higher in the frontal lobe of the brain), a variety of medical histories, a larger intake of alcohol, and drug addiction, to name a

few. Because the medications used to treat severe depressive disorders have deadly adverse effects, the 3 R's, or Right Choice of Medication at Right Time in Right Dose or Quantity, are critical in achieving mental health. Despite the lack of a calming effect, SSRIs appear to be more helpful than TCAs in the treatment of depression with anxiety.

Keywords

Types, TCAs, SSRIs, SNRIs, Side effects, Treatment.

Introduction

A condition of sadness can be used to define depression. It is also known as a psychoneurotic disorder, which is characterized by mental and functional activity, sorrow, reduced activity, difficulties

thinking, loss of focus, disturbances in hunger, sleeping, and feelings of dejection, hopelessness, and the development of suicidal thoughts[1]. Clinical depression is a mental health disease characterized by pathological mood abnormalities. Depression is a major issue in low and middle-income countries. Depression kills 1.52 times more persons than the general population. It has a significant impact on the physical and emotional health of individuals, families, and society, as well as causing socioeconomic hardship[1]. Patients with depression may also have other psychiatric or anxiety issues. Endocrinopathies (hypothyroidism, hypoparathyroidism, Cushing's disease, and Addison disease), Subcortical dementia, frontal lobe disease, concealed tumors, brain stroke, right hemisphere stroke, and brain infection are all examples of depression[2]. Antidepressants are a class of drugs used to treat depression and other mental illnesses. They affect neurotransmitters such as serotonin, norepinephrine, dopamine, epinephrine, 5-hydroxytryptamine, and two catecholamines, causing changes in brain chemistry and altering mood and feelings[3,4]. Antidepressants have a wide range of side effects, so the right antidepressant should be chosen based on the symptoms of depression, the patient's health, previous experience, previous response & other drug therapy, pharmacological profile, drug interaction potential, adverse drug reaction profiles, evidence base, and other factors[3,5]. In comparison to TCAs, selective serotonin reuptake inhibitors (SSRIs) are the first choice of drug for depression because of their tolerability, acceptability, and safety profile. However, supportive therapies such as acupuncture, aromatherapy, chiropractic treatment, herbal remedies, meditation, massage therapy, exercise, and music therapy are also used [4,5].

Types of depression [6]

1. Major depressive disorder
2. Persistent depressive disorder
3. Bipolar depression
4. Postpartum depression
5. Premenstrual Dysphoric disorders
6. Seasonal affective disorders
7. Atypical depression

Symptoms of Depression [7-10]

Every symptom of depression or mania is not experienced by everyone who is depressed or manic. Some people may only have a few symptoms, while others may have several. Furthermore, the degree of symptoms may differ from person to person.

Depression is defined as: i. a persistent sad, anxious, or empty mood; ii. feelings of hopelessness, pessimism; iii. feelings of guilt, worthlessness, or helplessness; iv. a loss of interest or pleasure in hobbies and activities that you once enjoyed, including sex; v. a loss of interest or pleasure in hobbies and activities that you once enjoyed, including sex; v. a loss of interest or pleasure in hobbies and v. insomnia, early morning awakenings or oversleeping, vi. hunger and or weight loss or increase, vii. diminished energy, weariness, slowing down, viii. suicidal thoughts or attempts, ix. agitation, impatience, x. difficulty concentrating, remembering, or making decisions, xi. persistent medical symptoms that do not respond to therapy, such as headaches, intestinal problems, or chronic pain.

Pathophysiology of Depression

There are no biomarkers or imaging abnormalities that can be used to determine the pathophysiology of depression over time. A post-mortem examination of the brain reveals no significant structural or neurochemical abnormalities. The vast majority of currently available drugs were developed

through trial and error. The “amine hypothesis” underpins the majority of current theories[11].The most fundamental hypothesis for mood disorder is that it is caused by changes in biogenic amine levels. According to the theory, sadness is caused by a functional deficiency of catecholamines, notably norepinephrine (NE), whereas mania is produced by a functional excess of catecholamines at the brain's key synapses. Changes in the levels of biogenic amines in the brain, such as NE, dopamine (DA), and epinephrine, indolamine, serotonin, 5-hydroxytryptamine (5-HT), and two catecholamines, have been linked to the incidence of depression[12-14].

Mechanism of Action of Antidepressant Agents [15,16]

1. Tricyclic Antidepressants

TCA operates on 5 separate neurotransmitter pathways to deliver Antidepressant effects. They impede the reuptake of serotonin & norepinephrine in presynaptic terminals, which leads to rise in levels of norepinephrine & serotonin in synaptic cleft. Antidepressant activity is aided by increases in the concentration of these neurotransmitters in the synapse.

e.g. Amitriptyline, Clomipramine, Imipramine, Nortriptyline, Reboxetine, doxepin.

2. Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO-A, MAO-B) is a mitochondrial enzyme involved in the oxidative deamination of biogenic amines like adrenaline, noradrenaline, dopamine, and 5-hydroxytryptamine. MAO inhibitors stop these neurotransmitters from being metabolized, allowing more brain chemicals to affect alterations in cells and circuits that have been damaged by depression.

e.g. Moclobemide, Phenelzine, Nialamide.

3. Selective Serotonin Reuptake Inhibitors

Serotonin is a chemical messenger (neurotransmitter) that helps neurons communicate. SSRIs prevent serotonin from being reabsorbed into neurons via the serotonin receptor transporter (SERT), allowing more serotonin to be accessible for improved message transmission. Because it only affects serotonin and no other neurotransmitters, the SSRI is selective.

e.g. Fluoxetine, Fluvoxamine, Paroxetine, Citalopram, Escitalopram, Dapoxetine.

4. Serotonin & Noradrenaline Reuptake Inhibitors

Both serotonin and norepinephrine neurotransmitters are blocked by SNRIs in the brain. SNRI has a dose-dependent effect. SSRIs, for example, have a low dose-behave. SSRI + NE reuptake inhibition at moderate doses; SSRI+NE reuptake inhibition+weak inhibition of dopamine reuptake inhibition at high doses.

e.g. Venlafaxine, Duloxetine.

5. Atypical Antidepressants

It works by changing changes in brain chemistry as well as changes in brain nerve cells, which helps to improve mood and alleviate depression. Neurotransmitters such as noradrenaline, dopamine, and serotonin are affected differently by atypical antidepressants.

e.g. Trazodone, Mianserin, Mirtazapine, Bupropion, Amineptine.

Side Effects [17-20]

1. Antimuscarinic Effects

Occurs as a result of TCAs, which alter mood-related brain chemicals.

Symptoms- Blurred vision, agitation, constipation, difficulty urinating, dry mouth, teeth decay, rise in

eye pressure, low blood pressure, hallucinations, rapid heartbeat, disrupted heart rhythm are some of the symptoms that can occur.

2. Decreased Alertness

Patients who use antidepressants for a long time are unable to concentrate, which has an impact on their driving and motor abilities.

3. Diabetes

Some antidepressants have an effect on lipid and cholesterol levels in the blood. Diabetes is more likely among adults over the age of 30 who have been taking SSRI or tricyclic antidepressants for a long time.

4. Hypertensive Reaction

Cheese, beer, wines, pickled meat, salmon, yeast extract, and other foods contain high levels of tyramine and dopa. These indirectly acting sympathomimetic amines escape degradation in intestinal walls and liver, reaching systemic circulation and releasing large amounts of noradrenaline from adrenergic nerve endings, resulting in symptoms such as hypertensive crisis (headache, palpitation, soreness, nausea, vomiting, tachycardia or bradycardia, dilated pupils, chest pain), cerebrovascular crisis (headache, palpitation, soreness, nausea, vomiting). As a result, these foods should not be consumed when taking MAO Inhibitors.

5. Risk of Malignancy

Antidepressant drugs induce fibrosarcomas and melanomas to grow faster and create mammary carcinoma. Tamoxifen reduces the chance of breast cancer recurrence. Both SSRIs and tamoxifen are processed by CYP2D6, but all SSRIs inhibit CYP2D6, reducing tamoxifen's effectiveness in breast cancer prevention.

6. Gastrointestinal Side Effects

Serotonin is a neurotransmitter which is involved in emotions, appetite, motor skill, and cognitive functioning. Serotonin effects on motor and sensory regulation of GIT. SSRI drugs work on serotonin levels or receptors and effects on GI motility.

SSRI - Nausea, vomiting.

SNRI - Nausea, diarrhoea, dyspepsia, GI bleeding, abdominal pain.

Fluvoxamine produces higher GI side effects than escitalopram.

7. Hepatotoxicity

It is caused by components of the metabolic process and the immune route. TCAs and other MAO inhibitors are more likely to cause liver damage than SSRIs like citalopram, escitalopram, paroxetine, and Fluvoxetine.

8. Dermatological Adverse Effects

Cutaneous adverse drug reaction occurs due to SSRIs. Vortioxetine received FDA approval for treatment of major depressive disorders in 2013. This drug acts as 5HT agonist, antagonist (5HT₃, 5HT₇, 5HT_{1D}) & 5HT transport inhibitor so that in Vivo non-clinical studies show that level of serotonin, dopamine, acetylcholine, histamine is increases into brain. Dermatological side effects disappear on discontinuation of antidepressants.

Symptoms - rashes on face, neck, dorsum of hands, itching, ecchymosis, pruritus of skin.

Alopecia, hyperpigmentation of skin, nails etc this is occurs due to fluvoxamine.

9. Cardio Vascular Effects

Because of less cardiovascular side effects, first-line antidepressants are safer than TCAs. Because MAO inhibitors commonly cause hypertension and tachycardia, their clinical use is limited. TCA

reduces systemic vascular resistance by blocking alpha adrenergic receptors, resulting in symptoms such as hypotension, orthostatic hypotension, sinus tachycardia (due to inhibition of cholinergic neurotransmission), impaired His-Purkinje Fibre conduction, slower conduction velocity, and a prolonged PR, QRS, QT interval.

Cardiovascular effects of SSRI include minimum effect on BP, PR interval, QRS duration, QTc interval. Sertraline & citalopram are safe & effective in patients with heart diseases. In people above 60 years, SNRI like venlafaxine causes orthostatic hypotension in more than 50% cases while mirtazapine causes it up to 7% Patients.

10. Serotonin Syndrome

Symptoms include headache, nausea, vomiting, diarrhoea, high temperature, shivering, sweating, high blood pressure, fast heart rate, tremors, muscle twitching, over reflexes, confusion, hallucinations, and coma in patients who are taking two or more medications that increase Serotonin levels in the brain, such as TCA, SSRI, SNRI, lithium-like drugs.

11. Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

TCAs, SSRIs, and SNRIs are to blame. Vasopressin is an antidiuretic hormone that regulates urine output. SIADH causes your body to produce too many antidiuretic hormones, causing your body to retain water and salt levels to drop, resulting in hyponatremia.

Symptoms -convulsions, confusion, hallucinations, coma, memory problems, difficulty to concentrate, drowsiness, death.

12. Hypomania

TCAs and MAO inhibitors in antidepressants cause hypomania. Hypomania is a heightened state of

mind that affects your mood, thoughts, and behavior, but it can also be an indication of bipolar disorder.

13. Sweating

This mechanism is in charge of maintaining body temperature. The impact of antidepressants on muscarinic receptors causes excessive perspiration in roughly 14% of patients. SSRIs, such as paroxetine, have an increased risk of causing excessive perspiration.

14. Sleep Disturbances

Normal sleep patterns are disrupted in depressed people because rapid eye movement (REM) and non-REM stages of the sleep cycle are both diminished. The influence on REM sleep is dependent on serotonin levels, and this effect disappears/rebounds when antidepressant medicines are stopped. MAO inhibitors and SSRIs are primarily to blame.

15. Weight Gain, Peripheral Edema & Metabolic Disturbances

Appetite, emotions, and motor skills are all affected by serotonin. Increased hunger, fluid retention, changes in glucose metabolism, histamine blockade, and hypothalamus dysfunction all contribute to weight gain. Weight reduction occurs during acute SSRI treatment, but long-term usage (more than 6 months) results in weight gain and an increased risk of obesity.

16. Sexual Dysfunction

The side effects of SSRI and SNRI medications are linked to a person's quality of life, physical, mental, and interpersonal interactions. SSRIs cause sexual dysfunction in around 50-70 percent of individuals, with paroxetine, Fluvoxamine, and sertraline posing

a larger risk. Men and women have various side effects.

In women - 1.delayed orgasm / inability to reach orgasm

2. Spontaneous orgasm

In men -1.reduced sexual desire

2. Failederection, delayed ejaculation

3. Lack of orgasm

4. Prolong erection.

Discontinuation of antidepressants, reduction in quantity of dosage, cognitive behavioural therapy, counseling therapy are used to overcome these side effects.

17. Fatal Toxicity

Fatal Toxicity Index' of older TCAs are most lethal than MAO inhibitors & newer antidepressants like SSRI & SNRI have lowest toxicity in overdose.

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