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ROLE OF ANTIDEPRESSANTS IN AMENDING THE CHEMICAL DISPARITY OF NEUROTRANSMITTERS IN PSYCHOSOMATIC DISORDERS.

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ABSTRACT:
This review summarizes the most common types of psychosomatic disorders including various types of depression based on their evolution, causes, symptoms and severity. The cellular and molecular mechanism behind the same in the areas of the brain, which are most susceptible to damage, both structurally and functionally (amygdala, the prefrontal cortex and the hippocampus) were keenly looked in to. Further, the therapeutic intervention through antidepressants was also been explored along with its three major categories in which they have been divided, their types, properties and mechanism of actions, especially towards the regulation of neurotransmitters in the brain has been highlighted. The behaviour of neurotransmitters in the presence of particular antidepressants is of grave importance in order to design an effective antidepressant drug, which could beat currently ineffective ones in the market and their potential forms have been studied and described. This review also provides an insight about the different approaches used for diagnosis using different types of biomarkers.

INTRODUCTION

One of the most probable cause of depression, found by researchers over the years, are chemical disparity or imbalance between the different neurotransmitters of the brain which are responsible for the regulation of numerous physical and emotional processes such as cognitive and mental performance, emotional status and pain response. Almost all functions in life are controlled by these varied neurotransmitters. Interactions between neurotransmitters, hormones, and other brain chemicals have a profound influence on overall health and well-being of humans, consequently, balanced mental phenomenon leads to attain higher concentration and focus, we feel more directed, motivated, and vibrant. But unfortunately, if neurotransmitter levels are inadequate these energizing and motivating signals are absent then we feel more stressed, sluggish, and out-of-control. Similarly, clinically depression can be treated with antidepressants coupled with counselling. [1,2] However, not all patients respond to antidepressant treatment and the therapeutic effects take a number of weeks to manifest and these effects are often accompanied by unwanted side-effects [3]. The development of more specific and faster-acting treatments requires the understanding of the mechanisms involved in the development of anxiety and depression. Therefore, insight about the various types and mechanism of this disorder is essential. The term psychosomatic disorders are often used more frequently with psychiatric problem, such as depression, anxiety or another disturbance that manifests itself as seemingly unrelated physical symptoms. To make a diagnosis of a psychosomatic disorder, there must be no other medical explanation for the observed symptoms. In simpler words, they are believed to be physical diseases that have a mental component derived from the stress and strain of everyday living. Most common ones are stress, anxiety and depression. [4]

Depression and its common types:

Depression can be reflected from the symptoms that may range from being milder ones with feeling of sadness or lows to the severe and most complicated ones like suicidal tendencies. The reason and cause behind this phenomenon is not

completely understood yet, but it is being suggested through various researches that its occurrence is based on combination of various biological, genetic, environmental and psychological factors [5] and depending on the same causative factors, it can be categorised into many types.

Listed below are the most common depression types observed in people, their causes and severity.

1. Major Depressive Disorder (MDD)

It is also known as clinical depression or unipolar depression and is among the commonest type of depression. MDD is characterized by feelings of extreme sadness, hopelessness, emptiness, disturbed eating and sleeping habits and anhedonia accompanied by thoughts of self-harm and suicide [6]. As exhibited by various studies that these types of depression are easy to treat through antidepressants and psychotherapy sessions with a counsellor.

2. Persistent Depressive Disorder (PDD)

It was formerly known as “dysthymia” and is a chronic form of depression that lasts for a minimum of two years. It may range from mild and moderate to serious as far as the symptoms for dysthymia are concerned and is marked by feelings of low self-esteem, changes in sleep cycle (either sleeping too little- insomnia, or sleeping too much), changes in appetite and lack of energy even while performing the most basic of activities. A sufferer may work adequately but not optimally. Thus, it is not easily recognizable [7, 8]. It can be treated by psycho-therapy, antidepressant drugs, or a combination of both.

3. Bipolar Disorder

It is characterized by mood swings that range from extreme highs to extreme lows and also called as ‘Maniac’ disease. A person may experience periods of extreme, elevated energy (mania) sometimes, marked by euphoria, wherein the person shows an increased level of self-esteem and confidence, indulgence in risky and self-destructive behaviour [9]. A period of major depression (extreme low) either precedes or succeeds the mania. Bipolar disorders are mostly found in middle aged men and women, and both the sexes have shown to be equally affected by this form of depression. It usually worsens if medications are not taken properly. Drugs that serve as mood stabilizers offer the best form of treatment for bipolar [10].

4. Seasonal Affective Disorder (SAD)

SAD is a major depression associated with symptoms that are influenced by the change of seasons, and is said to affect the normal circadian rhythm of the human body. Although the hormone serotonin has also been found to be responsible for inducing this type of depression. It is more commonly observed during the winter season due to absence of sunlight [11]. Sunlight regulates the circadian rhythm upon entering through our eyes, and its absence leads to a disruption of the rhythm causing a depression. It is generally treatable with light therapy, while medication is always the option [12].

5. Premenstrual Dysphoric Disorder (PMDD)

It is a severe form of PMS or Premenstrual Syndrome that is responsible for triggering depression, sadness, irritability, fatigue, anxiety etc. PMDD is exclusive to women [13]. It can be treated by antidepressants accompanied by lifestyle changes.

6. Postpartum Depression (PPD)

Postpartum depression, also known as perinatal depression, occurs at the time of pregnancy or up to the first 12 months after the birth of the baby [14]. It affects one in every seven women at/after or around the time of their delivery and is believed to be a result of hormonal changes in the female’s body during her pregnancy. PPD is characterized by feelings of intense, often devastating thoughts of self-harm and of harm to the baby, sadness, extreme anxiety and sleeplessness which interfere with the person’s routine activities and performance on a daily basis. PPD requires treatment with antidepressants [15].

7. Depressive Psychosis

This form of depression is characterized by symptoms same as that of major depression, along with the patient experiencing hallucinations and delusions such that he/ she tends to lose touch with reality [16]. These conditions make the person see, hear and believe in what is absolutely untrue or a mere product of their imagination. [17, 18] Depressive psychosis is treated with a medication that combines treatment of the patient with both

antidepressants and antipsychotic drugs. The treatments for almost all forms of depression require treatment with antidepressant drugs, if not in the initial stages then towards the completion of the treatment. Thus, be it sooner or later, it is evident that pharmacological handling of the cases becomes absolutely essential while dealing with the cure of depression [19].

Areas of the brain affected by depression:

Research has shown that stress and resulting depression leads to changes in the structural configuration of the brain. These changes however, are reversible upon treatment with antidepressants and pharmacotherapy. There are 3 main regions that are most affected by depression- the amygdala, the prefrontal cortex (area of the cerebral cortex covering the front part of the frontal lobe) and the hippocampus as shown in figure 1. [20]

1. Amygdala

The amygdala is that portion of the brain which is responsible for facilitating emotional responses like pleasure, sexual arousal, anger and fear [21]. When seen under magnetic resonance imaging, the amygdala was found to be either volumetrically enlarged or diminished in persons suffering with major depression as compared to healthy persons. This increase in size is also accompanied by an increase in its normal activity [22].

2. Prefrontal cortex

This region of the brain controls the personality expression, social behaviour, cognition and decision making abilities of a person. Recent neuroimaging researches have established a relation between depression and the abnormal functioning of the medial prefrontal cortex [23].

3. Hippocampus

Decreased hippocampal volumes (up to 13%) have been reported in persons suffering from depression. It is the area in the brain that is responsible for processing long term memory and recollection of the older memories [24]. An impaired hippocampus is often found in neurodegenerative diseases. The most probable reason for this is the action of stress hormones impairing the growth of neurons [25].

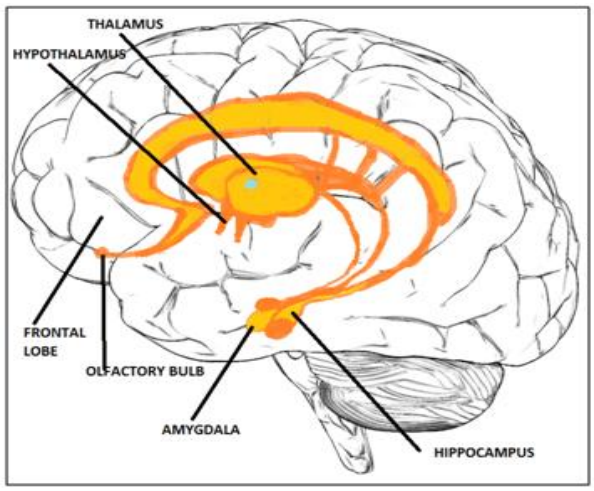


Figure 1: Areas of the brain affected by depression

Diagnosis of Depression by indicating Stress Biomarkers

Biomarkers are considered to be most effective tool for assessment of stress. They are either categorised as Metabolic, Neuroendocrine or Immune system markers.

A) Metabolic markers

For chronic stress, metabolic changes can be used as biomarkers since they are easily quantifiable. Some parameters which can quantify the change in metabolism and can be used as markers of chronic stress such as - Albumin, Waist-Hip ratio and Glycosylated haemoglobin [26]. Even the cholesterol levels cab be considered as biomarker parameter as the normal range of serum cholesterol (120-250 mg/dL) start getting replaced by decreased serum cholesterol levels under chronic stress. Low cholesterol levels in serum have also been observed in people who suffered from accidents, people showing aggressive behaviour and in patients that suffers from depression [27]. Also the albumin levels can be reduced by chronic stress, via various inflammatory or neuroendocrine mediators - either by increasing the rate of degradation, or by reducing the rate of synthesis. For chronically stressed individuals, waist-hip ratio is observed to be higher.

B) Immunological biomarkers

There are many circulating cytokines present in the systemic circulation and the change in their levels can be used as biomarker indications. The cytokines like IGF-1, IL-6, CRP and TNF-α get expressed due to unknown reasons in chronically

stressed individuals and indicates toward a humoral immunity oriented cytokine production [28]. As suggested by Sheng et al., IL-α or IL-1 act as stimulators for production of IL-6 and release of IL-1 was found to be a consequence of stress. The peripheral release of IL-6 following acute stress conditions can be prevented by an adequate HPA (hypothalamic pituitary adrenal) axis [29]. But due to the resistance to the immunosuppressant effects of glucocorticoids and the dysregulation of the HPA axis seen in chronic stress, there may be a decrease in the ability of the HPA to prevent peripheral inflammation which accounts for individuals that are suffering from chronic stress, showing increased systemic levels of IL-6. During chronic stress, the mRNA of TNF-α is higher which suggests *de-novo* synthesis rather than the release of preformed inducible proteins upon activation of lymphocytes and macrophages. As compared to control, the level of spontaneously produced TNF-α are also reported to be higher in people suffering from chronic stress [30, 31].

C) Neuroendocrine biomarker

The neuroendocrine system is the first to respond to a given stressor, therefore neuroendocrine factors are an effective biomarker for stress and it coordinates the response of many other physiologic systems to the stressor, including immune systems and cardiovascular, as well as energy production and/or utilization and behaviour, therefore bringing the body back to homeostasis [32]. The various neuroendocrine biomarkers are: Aldosterone, Adrenaline, Noradrenaline, Cortisol, Dopamine, and Dehydroepiandrosterone. The studies conducted on healthy adults suggests that chronic stressors that threaten physical integrity, are uncontrollable and they involve trauma that tend to result in a high flat diurnal profile of cortisol release, i.e. with lower than normal levels in the morning and higher than normal levels in the evening and controllable chronic stressors tend to produce higher than normal morning levels of cortisol [33].

Dehydroepiandrosterone (DHEA) is an androgen which is synthesized by the adrenal glands and functions as a HPA axis antagonist [34]. In healthy adults, the DHEA levels have been reported to fall during the hyper-responsive stage of the HPA axis, in response to chronic stressor. On the contrary, Adrenaline is released as a result of sympathetic nervous stimulation of the adrenal medulla, usually in response to stress [35]. Chronically stressed individuals have been reported to show low adrenaline responsivity due to habituation to constant adrenaline induced signalling. Elevation of adrenaline levels in healthy adults is caused due to acute stress, but this is due to increase in production. Because of this reason, it is difficult to attribute the rise in adrenaline levels to acute or chronic stressors. The neurotransmitter, Noradrenaline has widespread effects across multiple brain areas and it's been suggested that in adult humans, there is a decrease in the release of brain noradrenaline under chronic stress. Elevation in both plasma and brain noradrenaline levels have been reported to be caused by acute stress. Further, Dopamine levels are influenced by recreational drug use and later abstinence, obesity, exercise, feeding habits, exposure to chemicals like PCBs. Hence, it is not reliable to use dopamine alone as a biomarker of chronic stress. It can be one of the useful biomarkers for quantifying stress response, when used in conjunction with other markers as part of the allostatic load model [36]. Elevation in aldosterone secretion is caused by acute stress. Smoking, diet, etc. influence aldosterone levels, therefore the standalone use of aldosterone as a biomarker is unreliable.

Therapeutic approaches for Psychosomatic Disorders

1. **Cognitive–behavioural therapy**

It is the most commonly used form of treatment to manage the retaliation of an individual to stressful life events. The basic principle of treatment are psychological appraisals of stressful events and coping efforts related to these appraisals play a major role in determining the response to stress [36].

2. **Self-observation**

It helps individual to become more aware of how they respond to problematic situations. Patient has to keep record of how they responded to stressful events or challenges that occurred each day. The documentation should be made in three columns; antecedents, behaviours and consequences [37].

3. **Relaxation training**

These skills can be extremely useful in overseeing stress. The point at which the people figure out

how to unwind, their general level of autonomic arousal is decreased, just like their general muscle pressure. Those who can unwind are likewise more inclined to have the capacity to think more rationally and to be able to restructure negative cognitions when faced with stress [37].

4. **Hypnotherapy**

It is also referred to as hypnotherapy or hypnotic suggestion. It is a trance-like state in which a person has heightened focus, inner absorption and concentration. The patient under hypnosis, usually feels calm and relaxed, and they can concentrate intensely on a specific thought, memory, feeling or sensation while blocking out distractions. The patients under hypnosis are more open than usual to suggestions, and this can be used to modify the behaviour, perceptions, sensations and emotions [38].

5. **Biofeedback**

It is also referred to as applied psychophysiological feedback. It is the way toward showing automatic or subthreshold physiological procedures, as a rule by electronic instrumentation, and figuring out how to deliberately impact those procedures by rolling out improvements in cognition. This gives a noticeable and experiential exhibition of the mind-body association. It is likewise a therapeutic tool to encourage learning self-direction of autonomic functions for enhancing wellbeing [38].

6. **Pharmacotherapy**

Pharmacological treatment of psychosomatic disorders include antianxiety drugs (Benzodiazepines like Diazepam, Alprazolam etc.), antidepressants, Tricyclic antidepressants (Amitriptyline, Nortriptyline), Sedatives/hypnotics, monoaminoxidase inhibitors (Phenelzine, Isocarboxazid), Barbiturates. Out of them all, role of antidepressants are most important as it covers most of the chemical disparity caused due to the imbalance of various neurotransmitters[36,37].

Role of Antidepressants

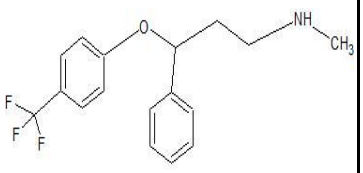
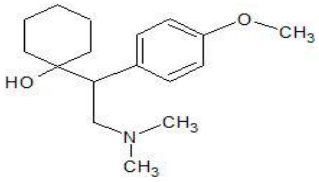
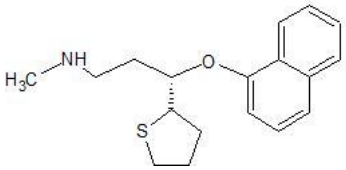
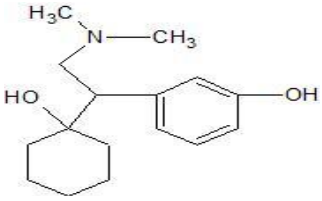
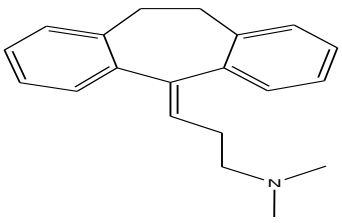
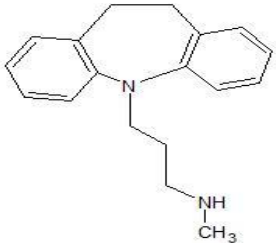
Antidepressants are psychiatric drugs which are available on prescription and are licensed to treat depression, and a few other physical and mental disorders including obsessive compulsive disorder (OCD), generalised anxiety disorder, chronic pain and post-traumatic stress disorder (PTSD) [37]. Disrupted communication between the brain and the body can have serious effects to one's health, both physically and mentally. Depression, anxiety and other mood disorders are thought to be directly related to imbalances with neurotransmitters [31]. Antidepressants are medications that help in relieving the symptoms of depression by correcting the chemical disparity of neurotransmitters in the brain which is believed to be responsible for the changes in mood and behaviour of the patient. People suffering from depression show disturbed, abnormal levels of certain brain chemicals, which in particular include the serotonin, dopamine and nor epinephrine. There exists a relationship between these three important monoamine neurotransmitters in the brain and specific symptoms of major depressive disorders. These symptoms are associated with an increase or decrease of specific neurotransmitters, which suggests that specific symptoms of depression could be assigned to specific neuro chemical mechanisms, and subsequently, specific antidepressant drugs could target symptom-specific neurotransmitters [38].

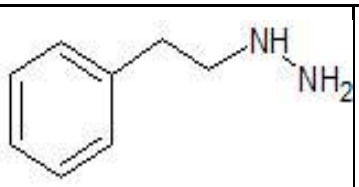
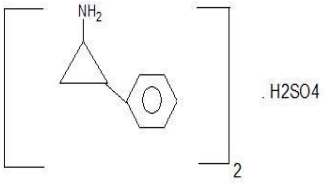
Antidepressant medications are believed to work, in part, by helping correct these brain chemical imbalances. These are known as the 'Big Three' neurotransmitters involved in depressions, however these are just a few of the neurotransmitters that function as messengers in the brain. Others include glutamate, GABA, and acetylcholine. [32,38]

Molecular mechanisms of action of antidepressants are much more diverse than that of antipsychotics. Classification of antidepressants based on their acute pharmacological actions is shown in Table 1. Antidepressants are amphiphilic molecules; so, they easy permeate through the cell membrane and may affect molecules on the outer and inner membrane surface, cytoplasmic elements and nuclear molecules. The neurotransmitter receptor hypothesis of antidepressant action explains the ultimate mechanism of their therapeutic action by receptor sensitivity changes. [38, 39]. There are five major classes of antidepressants used but the most common medications used at this time, includes the selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). The antidepressants can be further divided into 3 major categories:

a) Reuptake inhibitors - SSRIs, SNRIs, and NDRIs.
b) Cyclics (Tri and tetra- cyclic antidepressants) and SARIs.
c) Older antidepressants - Monoamine oxidase inhibitors (MAOIs)

Table 1: Classification of antidepressants with their examples, chemical composition and dosage.

Chemical compound	Brand name (label sold under)	Antidepressant type	Structure	Dosage (mg/day)
Fluoxetine	Prozac	SSRI (used to treat depression, panic attacks, obsessive compulsive disorder, a certain eating disorder (bulimia), and a severe form of premenstrual syndrome (premenstrual dysphoric disorder)		20- 60
Venlafaxine	Effexor XR	SNRI (used to treat major depressive disorder, anxiety, and panic disorder)		37.5- 75
Duloxetine	Cymbalta	SNRI (used for depression and chronic pain)		30
Desvenlafaxine	Pristiq	SNRI (used for depression and panic disorder)		50
Amitriptyline	Elavil	Tricyclic (improves mood and feelings of well-being, relieves anxiety and tension, helps you sleep better, and increases your energy level)		25
Desipramine	Norpramin	Tricyclic (helps to improve your mood, sleep, appetite, and energy level and may help restore your interest in daily living.		10

Phenelzine	Nardil	MAOI (used to treat symptoms of depression that may include feelings of sadness, fear, anxiety, or worry about physical health (hypochondria)		15
Tranylcypromine sulphate	Parnate	MAOI (improve your mood and feelings of well-being)		10

Reuptake inhibitors

They fall under the category of the type of drugs that are most commonly prescribed for treating depression. Reuptake can be defined as the phenomenon whereby the re absorption of a neurotransmitter takes place via a neurotransmitter transporter located along the plasma membrane of an axon terminal (the pre-synaptic neuron at a synapse) or via the glial cell after its function of transmitting a neural impulse has been performed. The function of a reuptake inhibitor is to prevent this from happening i.e., instead of getting reabsorbed, the neurotransmitter stays in the synapse (gap between the nerves) [39]. The reason these reuptake inhibitors are effective is because they aid in keeping the levels of neurotransmitters in the brain higher, which leads to improved communication between the nerve cells and which in turn leads to strengthening of the circuits inside the brain responsible for mood regulation[40]. Different kinds of reuptake inhibitors aim to act on different neurotransmitters. They can be subdivided as follows:

i) **Selective serotonin reuptake inhibitors (SSRIs)**

These are the most commonly prescribed antidepressants as they have been found to have very few side effects. Serotonin is known as the "feel-good chemical" because it produces a relaxed state of well-being. Serotonin works as a natural mood stabilizer, helping in regulating anxiety, reducing depression, healing wounds one keep up with one's routine activities like eating, sleeping, etc. It also helps one in performing one's routine activities like sleeping, eating, etc. [41]. Depression is associated with decreased levels of serotonin (along with the other brain chemicals). SSRIs help in maintaining high levels of serotonin in the brain by preventing its reabsorption. Some of the most common SSRI drugs in the market are Zoloft and Prozac [42].

In common terms the mechanism of action of serotonin is also known as SSRI; and three of the most common of them are paroxetine, sertraline and fluvoxamine have some of the selective effects on the serotonin reuptake pump. This mechanism (as shown in figure 2) initially causes an increase in the serotonin only at the cell body and the dendrites, not at axon terminals. The immediate consequence is to inhibit the rate of firing of serotonin neurons (and the release of serotonin) by an action at $5HT_{1A}$somatodendritic auto receptors. [41]

Longer-term exposure to serotonin eventually causes down regulation of these $5HT_{1A}$ auto receptors and disinhibition of serotonin release at axon terminals. A slightly late or delayed response has been seen in producing the increase in serotonin at the terminals is usually taken as the reason for the delayed onset of action of the SSRIs. The increased release of serotonin at the axons, in the presence of an inhibited serotonin reuptake pump, increases availability of serotonin to postsynaptic serotonin receptors [43]. These receptors may eventually down regulate. Postsynaptic serotonin receptors down regulation also occur during long-term treatment with tricyclic antidepressants and monoamine oxidase inhibitors. The chronic administration is also associated with a down regulation of postsynaptic b_1 adrenoceptors, but this has not been observed for citalopram, fluoxetine or fluvoxamine [44]. A common side effect of the other antidepressant includes nefazodone and venlafaxine, it may not be necessary for clinical efficacy.

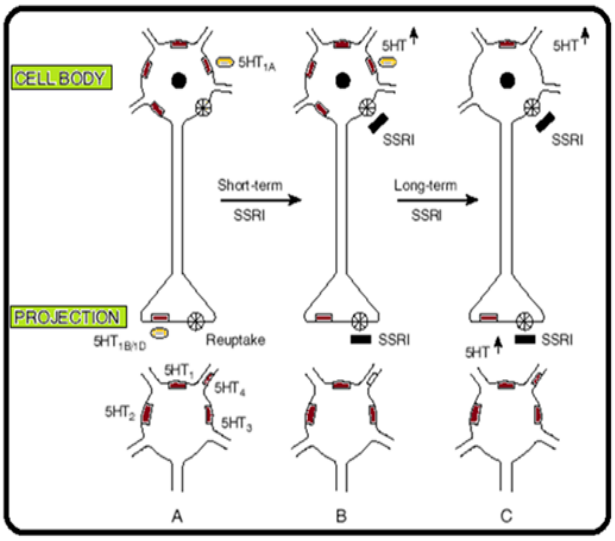


Figure 2: Mechanism of action of selective serotonin reuptake inhibitors

ii) **Serotonin and norepinephrine reuptake inhibitors (SNRIs)**

These types of drugs are used for the treatment of Major Depressive Disobedience disorder (MDD) and other anxiety related disorders, etc. Norepinephrine acts as both, a stress hormone and a neurotransmitter. Its release takes place in the blood stream when the body responds to a stressful condition. In such cases, norepinephrine also known as noradrenaline, influences and directs the way the brain reacts in such conditions [45]. It participates in regulating a person's mood by maintaining the energy and alertness levels. Low levels of norepinephrine are found in depression, hypotension and attention deficit hyperactivity disorder (ADHD) to name a few. SNRIs thus target two major neurotransmitters and function as dual reuptake inhibitors. For people who have unsuccessful SSRI treatment history, these dual acting antidepressants serve as an effective option. Examples include Effexor XR and Cymbalta [46].

iii) **Norepinephrine and dopamine reuptake inhibitors (NDRIs)**

The neurotransmitter dopamine is responsible for controlling the feelings of reward and pleasure, very low levels of the same are present in case of depression. Treatment with NDRIs helps in restoring the decreased levels of the chemical. Wellbutrin serves as a suitable example of an NDRI drug [47].

Cyclics (Tri and tetra- cyclic antidepressants) and SARIs

Cyclic antidepressants are a group of xenobiotic that are pharmacologically related to each other. They are used for the treatment of ADHD, neuralgic pain and depression. A cyclic antidepressant contains at least three rings in its chemical structure. Though beneficial for the treatment of depression, CAs- both tricyclics and tetracyclics, have been shown to pose a serious risk as a number of toxicity cases were reported related to the cardiovascular system and the CNS. Cyclic drugs have been modified over the years to increase the therapeutic value and decrease the toxicity levels [47, 48]. Amoxapine and Maprotiline are some of the examples of cyclic antidepressants. SARIs or Serotonin antagonist and reuptake inhibitors serve primarily as antidepressants, but are also used as hypnotics and anxiolytics. They serve two functions- inhibit the reuptake of serotonin, dopamine and/ or norepinephrine, and also antagonize serotonin receptors like 5-hydroxy-tryptamine (5-HT2A). This helps in redirecting the serotonin particles to receptors that aid in better functioning of nerve cells within mood circuits. Serzone is a common example [48, 49].

Older antidepressants - Monoamine oxidase inhibitors (MAOIs)

MAOIs belong to the oldest class of antidepressants. Their function is to block monoamine oxidase- the enzyme that is responsible for breaking down many neurotransmitters in the brain including serotonin and norepinephrine. Examples include Nardil and Marplan, to name a few [50].

REFERENCES:

1. T. Saarto and P. Wiffen, "Antidepressants for neuropathic pain", *Cochrane Database of Systematic Reviews*, 2007.
2. D. Gill and S. Hatcher, "Antidepressants for depression in medical illness", *Cochrane Database of Systematic Reviews*, 2000.
3. S. Ghaemi, E. Boiman and F. Goodwin, "Diagnosing Bipolar Disorder and the Effect of Antidepressants", *The Journal of Clinical Psychiatry*, vol. 61, no. 10, pp. 804-808, 2000.
4. J. Geddes, N. Freemantle, J. Mason, M. Eccles and J. Boynton, "Selective serotonin reuptake inhibitors (SSRIs) versus other antidepressants for depression", *The Cochrane Database of Systematic Reviews*, 1999.
5. V. Arango, M. Underwood, A. Gubbi and J. Mann, "Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral

prefrontal cortex of suicide victims", *Brain Research*, vol. 688, no. 1-2, pp. 121-133, 1995.

6. P. Fitzgerald, A. Laird, J. Maller and Z. Daskalakis, "A meta-analytic study of changes in brain activation in depression", *Human Brain Mapping*, vol. 29, no. 6, pp. 683-695, 2008.

7. P. Koolschijn, N. van Haren, G. Lensvelt-Mulders, H. Hulshoff Pol and R. Kahn, "Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies", *Human Brain Mapping*, vol. 30, no. 11, pp. 3719-3735, 2009.

8. H. Manji, W. Drevets and D. Charney, "The cellular neurobiology of depression", *Nature Medicine*, vol. 7, no. 5, pp. 541-547, 2001.

9. D. Nutt, "Highlights of the International Consensus Statement on Major Depressive Disorder", *The Journal of Clinical Psychiatry*, vol. 72, no. 06, pp. 21, 2011.

10. H. van Praag and R. Plutchik, "Depression type and depression severity in relation to risk of violent suicide attempt", *Psychiatry Research*, vol. 12, no. 4, pp. 333-338, 1984.

11. C. Song, "The interaction between cytokines and neurotransmitters in depression and stress: possible mechanism of antidepressant treatments", *Human Psychopharmacology: Clinical and Experimental*, vol. 15, no. 3, pp. 199-211, 2000.

12. H. Jick, "Antidepressants and the Risk of Suicidal Behaviors", *JAMA*, vol. 292, no. 3, p. 338, 2004.

13. J. Moncrieff and I. Kirsch, "Efficacy of antidepressants in adults", *BMJ*, vol. 331, no. 7509, pp. 155-157, 2005.

14. A. Dranovsky and R. Hen, "Hippocampal Neurogenesis: Regulation by Stress and Antidepressants", *Biological Psychiatry*, vol. 59, no. 12, pp. 1136-1143, 2006.

15. L. Santarelli, "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants", *Science*, vol. 301, no. 5634, pp. 805-809, 2003.

16. A. Cipriani et al., "Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis", *The Lancet*, vol. 373, no. 9665, pp. 746-758, 2009.

17. P. Mottram, K. Wilson and J. Strobl, "Antidepressants for depressed elderly", *Cochrane Database of Systematic Reviews*, 2006.

18. E. Shimizu et al., "Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants", *Biological Psychiatry*, vol. 54, no. 1, pp. 70-75, 2003.

19. E. Dailly, F. Chenu, C. Renard and M. Bourin, "Dopamine, depression and antidepressants", *Fundamental and Clinical Pharmacology*, vol. 18, no. 6, pp. 601-607, 2004.

20. S. Ghaemi, D. Hsu, F. Soldani and F. Goodwin, "Antidepressants in bipolar disorder: the case for caution", *Bipolar Disorders*, vol. 5, no. 6, pp. 421-433, 2003.

21. A. Mayers and D. Baldwin, "Antidepressants and their effect on sleep", *Human Psychopharmacology: Clinical and Experimental*, vol. 20, no. 8, pp. 533-559, 2005.

22. H. Gijsman, J. Geddes, J. Rendell, W. Nolen and G. Goodwin, "Antidepressants for Bipolar Depression: A Systematic Review of Randomized, Controlled Trials", *American Journal of Psychiatry*, vol. 161, no. 9, pp. 1537-1547, 2004.

23. M. Kubera et al., "Stimulatory effect of antidepressants on the production of IL-6", *International Immunopharmacology*, vol. 4, no. 2, pp. 185-192, 2004.

24. J. Jureidini, C. Doecke, P. Mansfield, M. Haby, D. Menkes and A. Tonkin, "Efficacy and safety of antidepressants for children and adolescents", *BMJ*, vol. 328, no. 7444, pp. 879-883, 2004.

25. R. Dudas, R. Malouf, J. McCleery and T. Dening, "Antidepressants for treating depression in dementia", *Cochrane Database of Systematic Reviews*, 2018.

26. R. Shytle, A. Silver, R. Lukas, M. Newman, D. Sheehan and P. Sanberg, "Nicotinic acetylcholine receptors as targets for antidepressants", *Molecular Psychiatry*, vol. 7, no. 6, pp. 525-535, 2002.

27. G. Guaiana, C. Barbui and R. Abouhassan, "Antidepressants versus placebo for generalised anxiety disorder (GAD)", *Cochrane Database of Systematic Reviews*, 2018.

28. F. Guilherme Graeff and H. Zangrossi Jr., "The Dual Role of Serotonin in Defense and the Mode of Action of Antidepressants on Generalized Anxiety and Panic Disorders", *Central Nervous System Agents in Medicinal Chemistry*, vol. 10, no. 3, pp. 207-217, 2010.

29. S. Szabo and P. Blier, "Functional and pharmacological characterization of the modulatory role of serotonin on the firing activity of locus coeruleus norepinephrine neurons", *Brain Research*, vol. 922, no. 1, pp. 9-20, 2001.

30. J. Mendlewicz, P. Kriwin, P. Oswald, D. Souery, S. Alboni and N. Brunello, "Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study", *International Clinical Psychopharmacology*, vol. 21, no. 4, pp. 227-231, 2006.

31. F. Artigas, "Limitations to enhancing the speed of onset of antidepressants? are rapid action

antidepressants possible?", *Human Psychopharmacology: Clinical and Experimental*, vol. 16, no. 1, pp. 29-36, 2001.

32. L. Minguez et al., "Acute toxicity of 8 antidepressants: What are their modes of action?", *Chemosphere*, vol. 108, pp. 314-319, 2014.

33. T. Rein, "Is Autophagy Involved in the Diverse Effects of Antidepressants?", *Cells*, vol. 8, no. 1, p. 44, 2019.

34. S. Stahl, "Using neuroscience for naming psychotropic drugs", *CNS Spectrums*, vol. 21, no. 3, pp. 219-220, 2016.

35. A. Gramowski et al., "Functional screening of traditional antidepressants with primary cortical neuronal networks grown on multielectrode neurochips", *European Journal of Neuroscience*, vol. 24, no. 2, pp. 455-465, 2006.

36. L. Murrin, J. Sanders and D. Bylund, "Comparison of the maturation of the adrenergic and serotonergic neurotransmitter systems in the brain: Implications for differential drug effects on juveniles and adults", *Biochemical Pharmacology*, vol. 73, no. 8, pp. 1225-1236, 2007.

37. B. Eisensamer et al., "Antidepressants are functional antagonists at the serotonin type 3 (5-HT3) receptor", *Molecular Psychiatry*, vol. 8, no. 12, pp. 994-1007, 2003.

38. C. Schipke, A. Fesche, B. Haas, I. Heuser and O. Peters, "Astrocyte-derived proteins in the cerebrospinal fluid as biomarkers for the pathobiological staging of Alzheimer's disease", *Alzheimer's & Dementia*, vol. 8, no. 4, pp. P116-P117, 2012.

39. E. RICHELSON, "Synaptic Effects of Antidepressants", *Journal of Clinical Psychopharmacology*, vol. 16, no. 2, pp. 1S-7S, 1996.

40. E. Richelson and A. Nelson, "Antagonism by neuroleptics of neurotransmitter receptors of normal human brain in vitro", *European Journal of Pharmacology*, vol. 103, no. 3-4, pp. 197-204, 1984.

41. R. Hoehn-Saric, D. McLeod, F. Funderburk and P. Kowalski, "Somatic Symptoms and Physiologic Responses in Generalized Anxiety Disorderand Panic Disorder", *Archives of General Psychiatry*, vol. 61, no. 9, p. 913, 2004.

42. E. Richelson, "Pharmacology of antidepressants", *Mayo Clinic Proceedings*, vol. 76, no. 5, pp. 511-527, 2001.

43. A. Gelenberg et al., "Mirtazapine Substitution in SSRI-Induced Sexual Dysfunction", *The Journal of Clinical Psychiatry*, vol. 61, no. 5, pp. 356-360, 2000.

44. B. Leonard, "Impact of inflammation on neurotransmitter changes in major depression: An insight into the action of antidepressants", *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 48, pp. 261-267, 2014.

45. O. O'Leary, A. Bechtholt, J. Crowley, T. Hill, M. Page and I. Lucki, "Depletion of serotonin and catecholamines block the acute behavioral response to different classes of antidepressant drugs in the mouse tail suspension test", *Psychopharmacology*, vol. 192, no. 3, pp. 357-371, 2007.

46. G. Papakostas et al., "Somatic symptoms in treatment-resistant depression", *Psychiatry Research*, vol. 118, no. 1, pp. 39-45, 2003.

47. D. Taylor, J. Walden, A. Robins and P. Smith, "Role of the Neurotransmitter Reuptake-Blocking Activity of Antidepressants in Reversing Chloroquine Resistance in Vitro in Plasmodium falciparum", *Antimicrobial Agents and Chemotherapy*, vol. 44, no. 10, pp. 2689-2692, 2000.

48. C. Taylor, A. Fricker, L. Devi and I. Gomes, "Mechanisms of action of antidepressants: from neurotransmitter systems to signaling pathways", *Cellular Signalling*, vol. 17, no. 5, pp. 549-557, 2005.

49. P. Mao, "Potential Antidepressant Role of Neurotransmitter CART: Implications for Mental Disorders", *Depression Research and Treatment*, vol. 2011, pp. 1-11, 2011.

50. F. Coluzzi and C. Mattia, "Mechanism-Based Treatment in Chronic Neuropathic Pain: The Role of Antidepressants", *Current Pharmaceutical Design*, vol. 11, no. 23, pp. 2945-2960, 2005.