# ANTIDEPRESSANTS: A CRITICAL REVIEW

Shakila Sabir, Tehzeeb-ul-Nisa and M. Imran Qadir*

College of Pharmacy, GC University, Faisalabad, Pakistan

*Correspondence: mrimranqadir@hotmail.com

**Summary**

Depression is a psychological problem in which the victim experiences the feelings of sadness, frustration and loss. And these feelings retain for a long time. A group of psychiatric medication used to treat this condition is known as antidepressants. Many antidepressants are effective for eating disorder bulimia nervosa particularly fluoxetine. That is also effective for premenstrual dysphonic disorder. Imipramine and desipramine are useful for attention deficit hyperkinetic disorder. Atomoxetine is recently introduced for attention deficit hyperkinetic disorder. The most common unwanted adverse effects of antidepressants are sleepiness, additive effects with other sedative drugs, tremor, insomnia, blurred vision and difficulty with accomodation, raised intraocular pressure, bladder neck obstruction(may lead to urinary retention in older males), constipation, urinary hesitancy, confusion, postural hypotension(due to inhibition of α adrenorecptors), conduction defects, arrhythmias, aggravation of psychosis, withdrawal syndrome, seizures, weight gain, antimuscuranic (dry mouth), and sexual disturbances.

**Key words:** Antidepressants, tricyclic antidepressants, monoamine oxidase inhibitors

## Introduction

Depression is a psychological problem in which the victim experiences the feelings of sadness, frustration and loss. And these feelings retain for a long time. A group of psychiatric medication used to treat this condition is known as antidepressants. Despite extensive research to find a diagnostic test, the diagnosis of depression remains clinical. However there are some signs through which one can confirmed the depression e.g. depressed mood diminished pleasure or interest in activities, pronounced change in apatite or weight, alterations in sleep (insomnia and hypersomia), psycho meter agitation or retardation, fatigue or loss of energy inability to concentrate, indecisiveness and thought of death, dying or suicide. Depression is relatively common among patients with diagnosis of dementia and may be a risk factor for developing dementia. However there are some nonpsychiatric disorders that show the symptoms of fatigue, insomnia and difficulty in concentrating e.g. endocrinopathies, sub-cortical dementias, frontal lobe disease, right hemisphere disease, occuluttumors etc. [1-4]

## CLASSIFICATION ON THE BASIS OF MODE OF ACTION

In the past, when the fewer compounds were known, there were only two groups of drugs known as tricyclic antidepressants and monoamine oxidase inhibitors (Monoamine oxidase inhibitors). This style of grouping mixes the structural and functional characteristics. And now there is a broad range of antidepressants having totally different structures from each other, but there are only a few known functional (possibly therapeutic) effects of these compounds. So it is batter to classify the antidepressants on the basis of function instead of structure. [5-6]

**Monoamine Oxidase Inhibitors**
It includes phenelzine, tranycypromine and isocarboxazid.
**Norepinephrine Transport Blocker**
For example maprotiline, nortriptyline, protriptyline, reboxetine, amoxapine, desipramine and doxepin.
**Serotonin Transport Blocker**
Some examples of this group are fluvoxamine, lmipeamine, paroxetine, sertraline trimipramine, venlafaxine, amitriptyline, citalopram, clomipramine and fluoxetine.
**Dopamine Transport Blocker**
For example bupropion
**Serotonin 5-Hydroxy Triptamine (5-$HT_{2A}$) Receptor Blocker**
For example mirtazapine, nefazodone and trazodone

## MECHANISM OF ACTION OF ANTIDEPRESSANTS

**Physiological Process Takes Place at Synaptic Cleft**
As electrical signal arrives at the presynaptic nerve terminal, the presynaptic amine vesicles attach with the membrane of neuron and release the amine neurotransmitter in the presynaptic cleft. These amines attach to the postsynaptic receptors to activate the postsynaptic neuron. After detachment, these Amines may be removed by reuptake into the presynaptic neuron. Presynaptic amines are broken by the enzyme called monoamine oxidase.

**Action of Drugs**
According to the monoamine hypothesis, there is deficiency of noradrenaline and serotoninin depression. This is compensated by antidepressants. Actually these drugs cause to modify the amine storage, release or uptake. Specific serotonin reuptake inhibitors, as the name indicates, predominantly act on serotonin reuptaker and inhibit their action. And they have little effects on noradrenaline reuptake. TCAs act predominately on noradrenaline uptake but different TCAs have different action on serotonin reuptake. Desipramine and protiptyline have little potential to increase the level of serotonin whereas clomipramine have great potential to inhibit the serotonin reuptake than for noradrenaline reuptake. But venlafaxine have great effect on both. Mirtazapine also cause to increase the conc. of both neurotransmitter but by an autoinhibitory feedback system. Nefazodone principally has antagonist effects on postsynaptic serotonin receptors.
Monoamine oxidase inhibitors increase the level of these neurotransmitters by inhibiting their destruction by monoamine oxidase type A in the presynaptic terminal. The older Monoamine oxidase inhibitors, such as phenelzine and isocarboxide etc. attach these enzymes by covalent bond. So the enzymes are inhibited permanently and amine metabolic activity starts only when new enzymes are produced. And this process takes weeks. So these Monoamine

oxidase inhibitors are known as hit and run drugs. When the conc. of these neurotransmitter increase, they bind with postsynaptic receptors that ultimately lead to the change in second messenger system and cause to the gradual modification in cellular protein expression. Antidepressants increase the level of protein called cyclic AMP response-element binding protein (CREB). This protein is involved in the regulation of transcription of genes which effect on the survival of other protein including brain derived neurotiphic factor (BDNF). Dopamine transport blockers block the transportation of dopamine**.** Mirtazapine, nefazodone and trazodone are the serotonin 5-hydroxy triptamine (5-$HT_{2a}$) receptor blockers.[7-32]

# PHARMACOKINETICS

All Selective serotonin reuptake inhibitors are well absorbed after oral administration. Peeks levels are seen in 5 hours approximately. There is a little effect of food on its absorption. Only sertraline undergoes important first- pass metabolism. The plasma half lives of Selective serotonin reuptake inhibitors ranges from 15 to 72 hours. The antidepressants are usually inactivated by metabolism by cytochrome P 450 enzymes found in liver. Most important among them are CYP 2D6, CYP 3A4 and, 2C9. Researches prove that fluvoxamine strongly inhibit the CYP 1A2 and CYP 2C group, and nefazodone to CYP 3A4. Metabolism by P450 dependent enzymes and glucuronide take place extensively. Fluoxetine is differ from other group members by having half life of 72 hours and is available as continued release preparation allowing once weekly dosing. Fluoxetine and paroxetine are powerful inhibitors of hepatic cytochrome P450 isoenzyme (CYP2D6) cause the elimination of tricyclics, neuroleptic drugs and some antiarrhythmia and β adrenergic antagonist drugs. Excretion of them is mainly through kidney except paroxetine and sertraline which undergo fecal excretion.

The half life of venlafaxine and duloxetine is 11 and 12 hours respectively. Duloxetine chiefly metabolizes in the liver in many metabolites that are excreted in the urine. So it is not suggested to the patients with end-stage renal disease. Foods delay the absorption of drug. It strongly binds to plasma protein.

Most of tricyclics are absorbed incompletely. They show significant first- pass metabolism. The strongly bind to the tissue protein and highly soluble in lipids that's why volume of distribution is very large. They are usually metabolized through two different chief routes; first one is the transformation of the tricyclic nucleus and other is transformation of aliphatic chain. The half lives of TCAs are generally in the range of 15 Hrs to 100 Hrs.

Monoamine oxidase inhibitors are readily absorbed in gastrointestinal tract. The hydrazide inhibitor phenelzine acetylates in liver and manifests distinction in elimination, depending upon acetylation phenotype of individual. Drug outcome carry on for 7 days (tranylcypromine) to 2 or 3 weeks (phenelzine, selegiline) after discontinuance of drug.

Metabolism of some antidepressants produce products that are active and prolong their action e.g. fluoxetine which is metabolized to norflouxetine having half life 200 h. Certain TCAs metabolized into another antidepressants e.g. nortriptyline form from amitriptyline, desipramine from lofepramine and imipramine from clomipramine . The half lives of TCAs are generally in the range of 15 h to 100 h.[33-45]

# DRUG INTERACTIONS

**Pharmacodynamic Interactions**

These depend upon the class of antidepressants. Those with sedative effects may be additive with other sedatives, especially alcohol. Alcoholism leads to the impairment of driving system for the patients taking tricyclics or mirtazapine. As monoamine oxidase inhibitors

increase the storage of catecholamine, so it causes to sensitize the patient to indirectly acting sympathomimetics such as tyramine that is found in some fermented food and beverages. And it also found in sympathomimetics drugs such as diethylprorion, phenylpropanoamine, or botanicals containing ephedrine. These type of sensitization Induce severe and fatal and hypertensive reactions. Pharmacodynamic interaction may occur when we take Selective serotonin reuptake inhibitors and monoamine oxidase inhibitors simultaneously. Storage of 5-HT plus inhibition of serotonin reuptake after release, increase the serotonin level in the synapse, cause serotonin syndrome. Sometimes this fatal syndrome includes hyperthermia, muscle rigidity, myoclonus and rapid change in mental status.

**Pharmacokinetic Interactions**

TCAs and Selective serotonin reuptake inhibitors metabolize majorly by cytochrome P 450 enzymes. Actually the drugs taken in combination and metabolise by the same enzyme produce potential for competitive inhibition. So in this way they increase the unexpected plasma level. For example fluoxetine and paroxetine (CYP 2D6), fluoxetine and nefazodone (CYP 3A4) cause the adverse effects and reduce the metabolic breakdown of co-prescribed drug. Antidepressants are usually prescribed in combination with antipsychosis drugs e.g. paroxetine + thioridazine (CYP 2D6), fluvoxamine + sertindole (CYP 3A4) and fluoxetine + olanzapine (CYP 1A2). There is inhibition of zuclopenthixol metabolism (CYP 2D6) due to fluoxetine or paroxetine and enhacement of this effect by the antipsychotic (CYP 2D6) cause to induce the over sedation and respiratory depression. Co-prescription of β adrenocptors with enzyme inhibiting antidepressants can cause to induce the antihypertensive effects. The inhibition of P 450 enzyme by Selective serotonin reuptake inhibitors increase the effects of alcohol, tramadol, methadone, terfenadine (risk of cardiac arryrhmia), and theophylline. [46-67]

## THERAPEUTIC EFFECTS OF ANTIDEPRESSANTS

The major use of antidepressants is to treat the depression, but there are some other uses that are proved on the basis of clinical trails.

**Depression**

These drugs are mainly useful in the treatment of depression. The diagnosis of major depression may be uncertain in some cases, so that on balance this condition is under diagnose and under treated. Standard antidepressants are added to lithium or another antimanic agent; Selective serotonin reuptake inhibitors are less likely to induce mania. Recently controlled studies support the additional labeling of the anticonvulsant lamotrigine for maintenance and prophylaxis of the depressed phase of bipolar illness.

**Anxiety Disorders**

Imipramine was the first antidepressant which showed the positive effects on acute episode of anxiety that is now called as panic attacks. Selective serotonin reuptake inhibitors, velnafaxine, and duloxetine are useful in panic, generalized anxiety disorder (GAD), and also for social phobia, but they require 6 to 8 weeks for treatment. In some instances, they are well tolerated and their clinical effects become evident promptly. However benzodiazepienes are preferable drugs for anxiety disorder.

**Obsessive Compulsive Disorders**

Potent Selective serotonin reuptake inhibitors are very effective for these disorders. Except them clomipramine, fluvoxamine, the most potent mixed serotonin and norepinephrine transporter inhibitor are also used for treatment.

**Enuresis**
It is an established indication for tricyclis. Proof of efficacy for this indication is considerable, but drug therapy is not an appreciable approach, especially given the risks of cardiovascular effects and dangers from over doses.

**Chronic Pain**
Tricyclics are useful for a variety of chronically painful states. Tricyclics and other norepinephrine transporter inhibitors work directly on pain pathways. Venlafaxine is also effective for this disorder. However, selective serotonin reuptake inhibitors have no effect on it.

**Other Indications**
Many antidepressants are effective for eating disorder bulimia nervosa particularly fluoxetine. That is also effective for premenstrual dysphonic disorder. Imipramine and desipramine are useful for attention deficit hyperkinetic disorder. Atomoxetine is recently introduced for attention deficit hyperkinetic disorder. [68-82]

## PHARMACOTHERAPY FOR DEPRESSION

Usually, antidepressants are given in combination with some supportive psychotherapy. For mild depression, psychotherapy is enough to treat. However evidences proved that antidepressants in combination with psychotherapy are better for more severe conditions than using alone. [83-84]

## CHOICE OF DRUG

Experiments show that different antidepressants have roughly same efficacy. But it may possible that a single patient give different response towards different antidepressants. The history of patient's drug experience is important to consider.
Greater tolerability, free of sedative effects, safe in over dose and due to having mild adverse effects make Selective serotonin reuptake inhibitors, the more preferable drugs. Despite of their higher cost, they are prescribed more than any other drug and accepted by patients. Recently introduced drugs such as bupropion, venlafaxine, and duloxetine are also free from such effects just like Selective serotonin reuptake inhibitors, whereas nefazodone and mirtazapine have strong sedating effect. Amoxapine, maprotiline and tricyclics are very dangerous in over dose. In 2004, Because of apparent increase in suicidal thoughts in children due to Selective serotonin reuptake inhibitors, the FDA issued a general warning about increased risk of suicide with newly introduced drugs. But after this more researches prove it wrong. However there is an increase risk of suicide with older antidepressants.
Clinical reports, prescription database and few trials prove that it is better to use the Selective serotonin reuptake inhibitors with some tricyclics such as desipramine and bupropion for those patients who do not give response to a single agent. [85-93]

## PATIENTS SHOWING NO RESPONSE TO DRUGS

Usually one third or more patients do not response the drugs. And almost 2/3 fails to achieve to get full remission. If patient give limited response to the treatment then again ensure the diagnosis, drug, dose, duration of treatment, and different treatment.
If the patient does not give any appreciable response up to 2 -3weeks of adequate plasma concentration then reassessed the diagnosis. Lithium might be added if the patient is bipolar. And if psychotic then treat with antipsychotic agent. Desipramine, bupropion or mirtazapine

may be used in combination with Selective serotonin reuptake inhibitors. It is more effective and safe to use. Combination of venlafaxine and duloxetine with selective serotonin reuptake inhibitors is not good because they are full serotonin reuptake inhibitors. One should wait up to 6-8 weeks before giving up a drug or a combination of drugs.

If the patient is unresponsive then it is better to try the drugs belonging to different classes instead of different drugs belonging to same class. Dose and duration are valuable during the treatment. Many patients fail to rehabilitate due to inadequate dosage. More than 50% of the patients get full remission after the treatment of 8 weeks. Some patients require totally different treatment such as "Electroconvulsive therapy" (ECT). It is the final treatment. But for the psychotic depression patients, it may be a first choice. Time taken to show the desired therapeutic effects and inability to tolerate the adverse effects of antidepressants are two major causes for noncompliance.[94-96]

## ADVERSE EFFECTS

### Tricyclics

The most common unwanted adverse effects are Sleepiness, additive effects with other sedative drugs, tremor, insomnia, blurred vision and difficulty with accomodation, raised intraocular pressure, bladder neck obstruction(may lead to urinary retention in older males), constipation, urinary hesitancy, confusion, postural hypotension(due to inhibition of α adrenorecptors), conduction defects, arrhythmias, aggravation of psychosis, withdrawal syndrome, seizures, weight gain, antimuscuranic (dry mouth), and sexual disturbances. There is a risk factor of QTc interval prolongation, polymorphic ventricular tachycardia (PVT)/ torsade de points (TdP) and/or sudden cardiac death while taking antidepressants or the combination of them with antipsychotic drugs, especially in the patients that are 60 or more than 60 years old. Dothiepin and amitriptyline cause toxicity in overdose, and responsible for up to 300 deaths per year in UK. Warm, dry skin from vasodilation and inhibition of sweating, pupillary dilatation and urinary obstruction are the results of antimuscuranic effects.

### Selective Serotonin Reuptake Inhibitors

Anxiety, insomnia, nausea, anorexia, dizziness, akathisia, anorgasmia, gastrointestinal symptoms, decreased libido, and sexual dysfunction. Gestational contact with antidepressants, especially paroxetine and venlafaxine, may lead to spontaneous abortion. They do not produce sedative effects directly. It is their major advantage for those who drive the vehicles. They disturb the sleeping pattern by increasing the awakening. They cause the weight loss through anoretic effects. Overdoses are not harmful. The serotonin syndrome, cause the restlessness, shivering, tremor and myoclonus sometimes leading to convulsion, coma and death. Risk increases when taken in combination especially with Monoamine oxidase inhibitors.

### Monoamine Oxidase Inhibitors

Headache, drowsiness, dry mouth, weight gain, postural hypotension, sexual disturbances, dysuria, constipation, blurred vision, hypertension, nausea, tachycardia and other cardiac arrhythmias and stroke, dizziness, irritability, apathy, insomnia, ataxia, difficult micturition, sweating, peripheral oedema, restlessness, tremulousness, and hyperthermia.

Trazodone and nefazadone cause drowsiness, dizziness, insomnia, nausea, agitation, pianism. Mirtazapinn causes somnolence, increased appetite, weight gain, dizziness. Venlafaxine causes nausea, somnolence, sweating, dizziness, anxiety, sexual disturbances, hypertension. [97-100]

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