ISSN 2581-6217

World Journal of Pharmaceutical Science & Technology

Journal homepage: www.wjpst.com

Review Article

CRITICAL REVIEW ON ANTIDEPRESSANT DRUGS

Dr. Sunildatta T. Gore[1], Prof. Dr. S.H. Bhosale[2], Mrs. Aditi S. Gore[3], Dr. Abhijeet A Jondhale[4], Prof. Rani J. Gaikwad[5], Dr. Vijay A. Kadnor[6]

1. Professor,at- Usha Dwarkadas Patharikar Institute of Pharmacy, Dogergaon Kawad, Pimpalgaon, Aurangabad.
2. Department of Pharmaceutical Chemistry, Poona College of Pharmacy, Erandwane, Pune-38.
3. Department of Pharmaceutical Chemistry, Poona College of Pharmacy, Erandwane, Pune-38.
4. Assistant Professor, Dr.Kolpe Institute of Pharmacy,Kolpewadi Address-A/P - Nimgaonjali Tahasil- Sangamner Dist-Ahmednagar Maharashtra.
5. Assistant Professor, Arts,Science & Commerce College, Kolhar, Tal-Rahata,Dist.-Ahmednagar.
6. Assistant Professor, Arts,Commerce & Science College, Satral, Tahsil-Rahuri, Dist-Ahmednagar.

Address for correspondence:

Dr. Sunildatta T. Gore, Professor,at- Usha Dwarkadas Patharikar Institute of Pharmacy, Dogergaon Kawad, Pimpalgaon, Aurangabad.
E-mail- sunilgore4u@gmail.com

Received: 15-10-2022, Revised: 29-10-2022, Accepted: 3-11-2022

ABSTRACT

Depression is a persistent, chronic condition that may require lifelong therapy using a variety of approaches. Multiple lines of evidence point to depression's significant role to medical morbidity. Comparing depressed patients to controls, premature death is more likely in depressed patients. Antidepressants are useful for treating a variety of disorders. Treatment for unipolar major depressive disorders is frequently referred to as antidepressant therapy, which is based on three groups of pharmacological agents: monoamine oxidase inhibitors, monoamine reuptake inhibitors, auto receptor desensitizers, and antagonists. Despite the fact that

they cannot treat the condition, they can relieve its symptoms. Therefore, the likelihood of responsiveness to the treatment option, vulnerability to adverse events, and potential advantages and hazards should all be taken into account when selecting ADs. The findings of this review shall help to carefully review the appropriateness of Antidepressants on an individual basis.

KEYWORDS: Depression, Anti- depressants, safety.

INTRODUCTION:

Depression is a major cause of disability worldwide, but we know little about the underlying fundamental biology. Depression can be understood as the interaction of genetic susceptibility and environmental factors; however, current classifications are purely descriptive. The complexity of this field is best approached by rigorous explorations of known candidate systems in conjunction with the use of genomic tools to discover new targets for antidepressants and to predict therapeutic outcomes.[i] The prevalence of depression is consistently high worldwide, and is associated with considerable morbidity and mortality.

Depression is a chronic and recurring illness that may require lifelong treatment with different modalities. Compelling evidence indicates that a significant proportion of patients with MDD remain inadequately treated, especially in primary care settings.[ii,iii] The immune system is a key mediator of brain–body interactions.[iv,v] Immune mediators such as cytokines influence various key CNS functions that are dysregulated in major depression — sleep, food intake, cognition, temperature and neuroendocrine regulation.[vi,vii]. The biology of specific brain cytokines has been the topic of recent reviews.[viii,ix] Two significant issues regarding the clinical aspects of depressive disorder continue to raise interesting conceptual questions and stimulate research: (a) endogenous versus nonendogenous depression and stress, and (b) stress in the prediction of first versus later onsets of depression.[x] Two approaches predominated in earlier research on possible stress-reactive types of depression: (a) those studies that defined groups differing on presence or absence of stressors prior to a depressive episode, and examined their endogenous versus nonendogenous symptom patterns, and (b) studies that identified groups differing on endogenous/nonendogenous symptom patterns and determined whether they experienced a precipitating stressor.[xi]

In one study, it appeared that 5-HTTLPR genotype influenced stress reactivity rather than directly "causing" depression.[xii] Adverse effects associated with the use of antidepressant drugs (ADs) are some of the most common factors responsible for nonadherence and the discontinuation of treatment.[xiii,xiv] Studies have shown that up to 43% of patients with MDD may discontinue antidepressants due to treatment-emergent adverse effects.[xv]

Several lines of evidence indicate an important contribution of depression to medical morbidity. Depressed patients have an increased risk of premature death when compared with control subjects.[xvi,xvii] Depression seems to increase the risk of death by cardiovascular disease, especially in men, but depression does not seem to increase the risk of death by cancer. Variability in methods prevents a more rigorous meta-analysis of risk.[xviii] The rate of suicide is even more alarming when it is examined as a function of age. Suicide is the sixth leading cause of death in the 5–14 age group, the third leading cause of death in the 15–24 age group, and the fourth leading cause of death in the 25–44 age group.[xix]

There are now dozens of approved drugs, which belong to four different classes — tricyclic drugs, selective serotonin reuptake inhibitors, MAO inhibitors and miscellaneous antidepressants. Each drug has a success rate of about 60%. When patients do not respond to one drug, they are switched to a different one, usually of a different class, until various classes of antidepressant are tried. (Wong M. L.)

By addressing chemical imbalances of neurotransmitters in the brain, antidepressants are a class of medications used to treat the signs and symptoms of depressive disorders. Alterations in mood and behaviour may also be attributed to chemical imbalances. Although antidepressants come in many different forms, all of them function by affecting the brain's bound neurotransmitters, such as serotonin and norepinephrine.

Numerous illnesses can benefit from the usage of antidepressants. In some cases, dysmenorrhea, snoring, migraines, attention-deficit hyperactivity disorder (ADHD), substance abuse, and sleep disorders are also included. They include depression, dysthymia, anxiety, anxiety disorders, obsessive compulsive disorder, eating disorders, chronic pain, and neuropathic pain. They can be used either on their own or in combination with other alternative drugs. The therapy of people with moderate or severe depression sometimes includes antidepressants. Antidepressants will lessen the symptoms even if they may not be able to treat depression. During the initial phase of treatment, the main antidepressant medication tries to work well. However, it has negative effects on the person if it does not relieve the symptoms.[xx] Therefore, the first step is to identify the proper antidepressant based on the patient's medical history and depressive symptoms.

Antidepressant therapy often refers to treatment for unipolar major depressive disorders and is based on three classes of pharmacological substances, including monoamine oxidase inhibitors, monoamine reuptake inhibitors, auto receptor desensitizers, and antagonists. There are medications that help improve depression patients' mood. Most antidepressants have some effect on monoaminergic transmission in the brain, and many of them also have additional side effects. A congruent classification is challenging because, especially in the last two decades, a great number of antidepressants have become available with a variety of effects on the reuptake/metabolism of biogenic amines and on pro/post-junctional aminergic/cholinergic receptors.

The market is flooded with antidepressant medications. The crucial factor is the amount of time that may be needed for a specific drug effect on the individual, or the response time of a medicine, which can be determined over time.

Treatment for MDD underwent a radical change in the 1950s with the development of monoamine oxidase inhibitors and tricyclic antidepressants (TCAs). Since then, efforts have been made to find ADs that are more selective and perhaps better tolerated. Selective serotonin reuptake inhibitors were created as a result of this rational drug development movement (SSRIs). In the years that followed, SSRIs underwent a transformation into first-line treatments for MDD among other indications.[xxi] Serotonin and noradrenaline reuptake inhibitors (such as venlafaxine, desvenlafaxine, and duloxetine), bupropion (a noradrenaline and dopamine reuptake inhibitor), mirtazapine (a noradrenaline and selective serotonin antagonist), and trazodone are just a few of the newer generation antidepressants that have been approved as treatments for MDD in the wake of SS (serotonin antagonist and reuptake inhibitor). All other drugs largely affect monoaminergic neurotransmission, with the exception of agomelatine (a melatonin receptor agonist with 5-HT2C receptor antagonist characteristics).[xxii,xxiii] They are referred to as younger generation antidepressants, along with SSRIs. Vilazodone, levomilnacipran, and vortioxetine are three more antidepressants that the US Food and Drug Administration (FDA) has licenced for the treatment of MDD.[xxiv] Additionally, there were no clinically significant differences between the efficacy of SSRIs and TCAs in a meta-analysis that comprised 102 studies.

1. **Monoamine Oxidase Inhibitors (MAOls)[xxv]:**

Although TCA and other antidepressants with superior clinical efficacies and typically fewer adverse effects largely repressed the MAOI class of medications, they were among the first to be clinically introduced as antidepressants. These medications do not differentiate between the two main isoenzymes, monoamine oxidase-A (MAO-A) and monoamine oxidase-8, and cause an irreversible suppression of the enzyme (MAO-8). Recently, interest in this class of medication has been reignited by the discovery of reversible inhibitors that preferentially display isoenzymes.

Without significantly changing the vesicular stores that make up the pool that is releasable by nerve stimulation, the principal action of MAOI is to enhance the cytoplasmic concentration of monoamines in nerve terminals. The enlarged cytoplasmic pool causes a rise in the rate of spontaneous monoamine leakage as well as an increase in the release of sympathomimetic amines with indirect action, including amphetamine and tyramine.

2. **Tricyclic Antidepressant Drugs (TCAs)[xxvi,xxvii]:**

An important class of antidepressants used in therapeutic settings are tricyclic antidepressants. However, they are far from ideal. In reality, the development of newer SSRI medications and other antidepressants was driven by the demand for medications that function more swiftly, consistently, and with fewer side effects.

- Mechanism of action:

TCA competes for the binding site of the transport proteins, which has the primary consequence of preventing amine uptake by nerve terminals. A few TCAs appear to increase transmitter release by inhibiting presynaptic a-adrenoceptors, but amine synthesis, storage in synaptic vesicles, and release are not directly impacted. Most TCA have significantly less of an impact on dopamine uptake than they do on the uptake of noradrenaline and 5-HT into brain synaptosomes. According to some theories, treatment of emotional symptoms is mostly due to an improvement in 5-HT-mediated transmission, whereas relief of biological symptoms is thought to be the result of facilitating noradrenergic transmission. The fact that the primary metabolites of TCA have significant pharmacological activity and frequently differ from the parent medication in terms of their noradrenaline/5-HT selectivity makes interpretation challenging.

3. Selective Serotonin Reuptake Inhibitors (SSRIs)[xxviii]:

Since the 1980s, a significant number of brand-new antidepressants have been produced to address the drawbacks of TCA. In terms of overall efficacy and tolerability, newer medications have subdued previous TCAs. They are now first-line medications for depression due to their relative safety and improved tolerability.

- Mechanism of action:

Similar to tricyclic antidepressants, which prevent norepinephrine reuptake, serotonin reuptake inhibitors prevent serotonin from being transported into neurons promptly and, it appears, permanently, resulting in complex secondary reactions. In the formation of endogenous depression, the serotonergic system in general and the 5-HT receptors in particular appear to be key factors. The majority of antidepressants appear to work in similar ways to boost 5-HT neurotransmitter and 5-HT receptor activation.[xxix] Numerous post synaptic 5-HT receptor types are stimulated by increased serotonin synaptic availability. The frequent side effects of this family of medications, such as gastrointestinal and sexual side effects, are thought to be caused by stimulation of the 5-HT% receptors (delayed or impaired orgasm). The 5-HT subtype autoreceptors in the serotonin system repress serotonin neurons in the raphe nuclei of the brainstem, inhibiting tryptophan hydroxylase and serotonin release from the neurons. Over the course of many weeks, repeated therapy causes the autoreceptor mechanisms to gradually shut down and desensitize, with

presynaptic activity, serotonin production, and release returning to normal or increasing. Complex late adaptation to repeated therapy with selective serotonin reuptake inhibitors develops, similar to responses to norepinephrine transport inhibitors. These include a net increase in the synthesis of cyclic AMP and different protein kinase activity in particular cells.

4. Serotonin and norepinephrine re-uptake inhibitors (SNRIs):

SNRIs presumably block both 5-HTT and the norepinephrine transporter (NET). Blocking these transporters prevents the neuron from vacuuming up excess neurotransmitters, permitting a lot of to stay within the synapse and stimulate postsynaptic receptors. SSRIs have important effect on NE as well, and the SNRIs behave much more like SSRIs.

5. Lithium Salts[xxx]:

Lithium is used for manic depression. Manic-depressive patients' expertise severe mood changes, starting from associate degree excited or frenzied state to depression or unhappiness.

6. Serotonin receptor modulators (SRMs)[xxxi]:

Serotonin receptor modulators utilized in the treatment of irritable intestine syndrome. Serotonin plays a major role within the initiation of peristaltic and humour reflexes, and in modulation of visceral sensations.

CONCLUSION:

It seems crucial that each patient receives tailored care. When administered to another depressed patient, a medication that appears to have an antidepressant effect in one patient might not have the same effect. The same medicine may have varied effects on a patient depending on the situation. The idea, occurrence, and variety of depression, as well as its many forms, may be somewhat connected to the disparity in patient responses. Additional study is required, both in connection to the type of depression as well as the particular medications listed. In conclusion, clinical testing will establish the degree to which many of the techniques discussed in this study offer unique advantages over currently available medicines and, ultimately, indicate the genuine innovation connected with these novel processes.

REFERENCES:

[i] Wong ML, Licinio J. Research and treatment approaches to depression. Nature Reviews Neuroscience. 2001 May;2(5):343-51.

[ii] Castro-Rodríguez JI, Olariu E, GarnierLacueva C, Martín-López LM, Pérez-Solà V, Alonso J, Forero CG; INSAyD Investigators: Diagnostic accuracy and adequacy of treatment of depressive and anxiety disorders: a comparison of primary care and specialized care patients. J Affect Disord 2015; 172:462-471.

[iii] Duhoux A, Fournier L, Gauvin L, Roberge P: What is the association between quality of treatment for depression and patient outcomes? A cohort study of adults consulting in primary care. J Affect Disord 2013 151: 265–274.
[iv] Solomon, G. F. Psychoneuroimmunology: interactions between central nervous system and immune system. J. Neurosci. Res. 18, 1–9 (1987).
[v] Sternberg, E. M. Emotions and disease: from balance of humors to balance of molecules. Nature Med. 1997. 3, 264–267.
[vi] Licinio, J., Wong, M. L. & Gold, P. W. Localization of interleukin-1 receptor antagonist mRNA in rat brain. Endocrinology 129, 562–564 (1991).
[vii] Rothwell, N. J. & Hopkins, S. J. Cytokines and the nervous system II: Actions and mechanisms of action. Trends Neurosci. 18, 130–136 (1995).
[viii] Van Wagoner, N. J. & Benveniste, E. N. Interleukin-6 expression and regulation in astrocytes. J. Neuroimmunol. 100, 124–139 (1999).
[ix] Rothwell, N. J. & Luheshi, G. N. Interleukin 1 in the brain: biology, pathology and therapeutic target. Trends Neurosci. 23, 618–625 (2000).
[x] Hammen C. Stress and depression. Annual Review of Clinical Psychology (2005). 2005 Apr 27;1(1):293-319.
[xi] Hammen C. 1995. Stress and depression: research findings on the validity of an endogenous subtype of depression. Dir. Psychiatry 15:1–8.
[xii] Levinson DF. The genetics of depression: a review. Biological psychiatry. 2006 Jul 15;60(2):84-92.
[xiii] Hung CI: Factors predicting adherence to antidepressant treatment. Curr Opin Psychiatry 2014; 27: 344–349.
[xiv] Fortney JC, Pyne JM, Edlund MJ, Stecker T, Mittal D, Robinson DE, Henderson KL: Reasons for antidepressant nonadherence among veterans treated in primary care clinics. J Clin Psychiatry 2011; 72: 827–834.
[xv] Bull SA, Hunkeler EM, Lee JY, Rowland CR, Williamson TE, Schwab JR, Hurt SW: Discontinuing or switching selective serotoninreuptake inhibitors. Ann Pharmacother 2002; 36:578–584.
[xvi] Kerr, T. A., Schapira, K. & Roth, M. The relationship between premature death and affective disorders. Br. J. Psychiatry, 115, 1277–1282 (1969).
[xvii] Harris, E. C. & Barraclough, B. Excess mortality of mental disorder. Br. J. Psychiatry 173, 11–53 (1998).
[xviii] Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. Psychosomatic medicine. 1999 Jan 1;61(1):6-17.
[xix] Murphy, S. L. Deaths: Final data for 1998. National Vital Statistics Reports (CDC) 48, 1–106 (2000).
[xx] http://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20046273
[xxi] Anderson IM: Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord 2000; 58: 19–36.
[xxii] Machado-Vieira R, Henter ID, Zarate CA: New targets for rapid antidepressant action. Prog Neurobiol 2015, Epub ahead of print.
[xxiii] Rosenblat JD, McIntyre RS, Alves GS, Fountoulakis KN, Carvalho AF: Beyond monoamines-novel targets for treatment-resistant depression: a comprehensive review. Curr Neuropharmacol 2015; 13: 636–655.
[xxiv] Elmaadawi A, Singh N, Reddy J: Prescriber's guide to using 3 new antidepressants. Curr Psychiatry 2016; 14: 32–36.
[xxv] Rang H P, Dale M M, Ritter J M, Moore P K, Pharmacology, 5" edi., Churchill Livingstone, 2005; 535- 548.
[xxvi] Gilman G A, The Pharmacological Basis of Therapeutics, 10th ed, McGraw-Hill medical publishing division, 2001; 447-483.
[xxvii] Racagni G, Tinelli D, Binachi E, cAMP-dependent binding proteins and endogenous phosphorylation after antidepressant, IN 5- hydroxytryptamine in psychiatry: A spectrum ideas, 1991; 116-123.
[xxviii] Tripathi K D, Essentials of Medical pharmacology, 5" ed., Jaypee Brothers, New Delhi, 2003; 405-414.
[xxix] Porsolt RD, Anton G, Blavet N, Jalfre M,Behavioral despair in rats: A new model sensitive to antidepressant, Eu. J. Pharmaco/, 1978; 47:379-391.
[xxx] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2503665/
[xxxi] http://www.patient.co.uk/health/tricyclic-antidepressants