Review Article

Neuropharmacological Classification of Antidepressant Agents Based on their Mechanisms of Action

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Abstract

The currently available clinical antidepressants can be classified into 13 different classes based on their mechanisms of action. These basic pharmacological concepts thoroughly elucidate and unravel the therapeutic actions and side effects of the wide range of antidepressants currently available. The two classical mechanisms are exhibited by tricyclic antidepressants (TCAs) and by monoamine oxidase inhibitors (MAOIs). Regarding the 11 relatively nonclassical antidepressants, the most widely prescribed agents are the selective serotonin reuptake inhibitors (SSRIs). The mechanisms of action for the other classes of antidepressants that exhibit additional actions on serotonergic neurotransmission are dual serotonin-norepinephrine reuptake inhibition (SNRI), serotonin receptors antagonism with serotonin reuptake inhibition (SARI), serotonin 5-HT_{1A} autoreceptor partial agonism with serotonin reuptake inhibition (SPARI), serotonin-norepinephrine reuptake inhibition and serotonin receptors antagonism antidepressant with potent antipsychotic D2 receptor blockade/antagonism (SNRISA with potent antipsychotic D2 receptor blockade/antagonism), norepinephrine reuptake inhibition with serotonin receptors antagonism (NRISA), noradrenergic α_2-receptor antagonism with specific serotonergic receptors-2 and-3 antagonism (NASSA), and atypical antipsychotics that exhibit weak D_2 receptor antagonism with potently strong 5-HT_{2A} receptor blockade. Furthermore, the two classes that exhibit selective norepinephrine reuptake inhibition (NRI) and dual norepinephrine-dopamine reuptake inhibition (NDRI) define separate novel classes of antidepressants that have a direct action on the noradrenergic neurotransmission system but have no direct action on the serotonergic neurotransmission system, while the last remaining one class of N-methyl-D-aspartate-glutamatergic ionoceptor antagonist/inverse agonist/partial agonist also represents a separate novel class of antidepressants with a direct action on the excitatory glutamatergic neurotransmission system but no direct action on the serotonergic, noradrenergic, or dopaminergic neurotransmission systems. Lastly, this review remarkably advocates for the incorporation of the atypical antipsychotics and NMDA-glutamatergic ionoceptor antagonist/inverse agonist/partial agonist as new member classes of the antidepressant agents because of their clinically significant roles in the management of depression disorders.

Keywords: Antidepressant agents, classification, mechanisms of action

Introduction

Major depressive disorder (MDD), also known as unipolar depression, is a mental disorder characterized by at least 2 weeks of low mood that is present across most situations. It is often accompanied by low self-esteem, loss of interest in normally pleasurable activities (anhedonia), low energy, feeling of worthlessness, sense of rejection, sense of guilt, loss of appetite, insomnia, unnecessary and excessive worry, suicidal thoughts, and pain without a clear cause. People may also occasionally have unshakable beliefs that may not necessarily be false but lack substantial evidence to support them (delusion) and see or hear things that others cannot perceive (hallucination).[1-3]

Regarding the evolution of antidepressant classification, from the time past, there have been several attempts to classify them based on different criteria which include classification based on their chemical structures, classification based on their pharmacological mechanisms of action, and among others. Out of these classification criteria, the classification based on their pharmacological mechanisms of action was most elaborate and useful as this provides completely thorough information about the drug(s) in each class using the dynamically evolving neuroscience base nomenclature of monoaminergic reuptake transporter pumps inhibition,

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monoamine oxidase inhibition and receptors' pharmacoactivity phenomenon. The classification based on chemical structure has not been so much useful pharmacologically, except in the area of prediction and analysis of structural activity relationship for the drugs; hence, this approach is of limited pharmacological importance when compared to the mechanisms of action-based classification.[1-3,5,6] Considering chemical structure-based classification, antidepressants can be classified as unicyclic (bupropion); tricyclic (imipramine, desipramine, and amitriptyline); tetracyclic (mirtazapine, mianserin, maprotiline, and amoxapine); and multi-ring structure (vilazodone). However, in this review, focus will be on the classification that is based on the pharmacological mechanisms of action.[1-3] The currently available clinical antidepressants work by 13 different mechanisms. These mechanisms of action include two that are classical and eleven that are relatively nonclassical. The classical mechanisms of action are those exhibited by tricyclic antidepressants (TCAs) and by monoamine oxidase inhibitors (MAOIs). The relatively nonclassical categories include selective serotonin reuptake inhibitors (SSRIs), dual serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin receptors antagonist with serotonin reuptake inhibition (SARI), serotonin 5-HT_{1A} autoreceptor partial agonist with serotonin reuptake inhibition (SPARI), serotonin-norepinephrine reuptake inhibitor and serotonin receptors antagonism antidepressant with potent antipsychotic D2 receptor blockade/antagonism (SNRISA with potent antipsychotic D2 receptor blockade/antagonism), norepinephrine reuptake inhibitor with serotonin receptors antagonism (NRISA), noradrenergic α_2-receptor antagonist with specific serotonergic receptors-2 and-3 antagonism (NASSA), selective norepinephrine reuptake inhibitors (NRIs), dual norepinephrine-dopamine reuptake inhibitor (NDRI), atypical antipsychotics that exhibit weak D_2 receptor antagonism with potently strong 5-HT_{2A} receptor blockade, and N-methyl-D-aspartate (NMDA)-glutamatergic ionoceptor antagonist/inverse agonist/partial agonist that exhibit a direct action on the excitatory glutamatergic neurotransmission system. There are many other therapies for depression which include forms of psychotherapy, electroconvulsive therapy (ECT), and other various augmenting methods such as daily left prefrontal repetitive transcranial magnetic stimulation therapy (rTMS). However, only the pharmacotherapeutic agents will be considered here.[1-6]

The Monoaminergic Theory of Depression

The monoaminergic theory of depression states that depression is related to a deficiency in the amount or function of cortical and limbic biogenic monoamines, namely serotonin (5-HT), norepinephrine (NE), and/or dopamine (DA). As of this present moment, eleven (11) out of these thirteen (13) classes of antidepressants accomplish their pharmacological actions by blocking one or more of the reuptake transporter pumps and/or receptors for these three monoaminergic neurotransmitters. The twelfth class inhibits the enzyme monoamine oxidase, while the thirteenth class works by blocking the NMDA-glutamatergic ionoceptor. Increasing neurotransmission seems to be the result of desensitization (or downregulation) of certain key neurotransmitter receptors. Interestingly, this desensitization has a delayed onset, just like the therapeutic actions of antidepressants. The development of tolerance to side effects of antidepressants also occurs with delayed onset. Thus, the monoaminergic receptors' desensitization hypothesis has also evolved from the monoaminergic theory and proposes that the increase in monoaminergic neurotransmission which occurs with most of the antidepressants are translated result of receptor desensitization to produce an antidepressant and anti-anxiety response clinically as well as to allow tolerance to develop to acute side effects. The most convincing line of evidence supporting the monoaminergic theory is the fact that (at the time of this writing) most of the available clinical antidepressants appear to have significant effects on the monoaminergic systems. These classes of antidepressants appear to enhance the synaptic availability of 5-HT, norepinephrine, and/or dopamine.[2,3,7,8]

The Emerging Glutamatergic Hypothesis of Depression

Attempts to develop antidepressants that work on other neurotransmitter systems are currently ongoing. One of such neurotransmitter system is the excitatory glutamatergic neurotransmitter pathway that appears to be important in the pathophysiology of depression. Clinical research has used both indirect and direct measures to evaluate the glutamatergic system in patients suffering from MDD, and have found evidence of glutamatergic dysfunction in MDD. For example, clinical studies that have used indirect measures for analysis, such as plasma, cerebrospinal fluid, and serum concentrations, have found differences in glutamate and glutamine in patients diagnosed with MDD as compared to healthy controls. Specifically, several studies have found increased concentrations of glutamate in plasma and increased concentration of glutamine in the cerebrospinal fluid of MDD patients. Furthermore, chronic antidepressant drug treatment has been found to reduce the serum and plasma glutamate concentrations, as well as cerebrospinal fluid glutamine concentrations. Also, antidepressants are known to impact glutamatergic neurotransmission in a variety of ways; for example, chronic antidepressant use is associated with reduction of glutamatergic neurotransmission processes, including a reduction in the presynaptic release of glutamate in the hippocampus and cortical areas. Similarly, the chronic administration of antidepressants significantly reduces depolarization-evoked release of glutamate in experimental animal models. Stress is known to enhance the release of glutamate in experimental animal models, and antidepressants inhibit stress-induced presynaptic release of glutamate in these models.[3,4,8] These findings suggest that these monoaminergic systems-selective antidepressant drugs are neuromodulating the functions of the glutamatergic neurotransmission system. In addition,

postmortem studies have revealed significant increase in the frontal and dorsolateral prefrontal cortex of depressed patients. Likewise, structural neuroimaging studies have consistently found volumetric changes in the brain areas of depressed patients in which glutamatergic neurons and their connections are most abundant, including the amygdala and hippocampus. Currently, the NMDA-glutamatergic receptor (NMDAR) is a heteromeric complex that has three (3) different subunits with a total of fourteen (14) isoform variants for all of these subunits. The NMDA receptor heteromeric complex interacts with multiple intracellular proteins by these three different subunits namely: NR1, NR2 and NR3. The NR1 subunits have eight different isoform variants generated by alternative splicing from a single gene GRIN1. These different isoform variants of NR1 subunits are NR1-1a (the most abundantly expressed isoform variant), NR1-1b, NR1-2a, NR1-2b, NR1-3a, NR1-3b, NR1-4a and NR1-4b. In vertebrates, there are expressions of four different isoform variants of NR2 subunits which are NR2A, NR2B, NR2C and NR2D that are encoded by the GRIN2A, GRIN2B, GRIN2C and GRIN2D genes respectively. Glutamate binding site and the control of the Mg2+ block are formed by the NR2B subunit isoform variant. Furthermore, NR2B is predominant in the early postnatal brain, but the number of NR2A subunits grows, and eventually NR2A subunits outnumber NR2B. This is called the NR2B-to-NR2A developmental switch, and is notable because of the different kinetics each NR2 subunit isoform variant lends to the NMDA receptor. For instance, greater ratios of the NR2B subunit leads to NMDA receptors which remain open longer compared to those with more NR2A. Unlike NR1 subunits, the NR2 subunits are expressed differentially across various cell types and control the electrophysiological properties of the NMDA receptor. The NR2B subunit isoform variant is mainly present in immature neurons and in extrasynaptic locations. The basic structure and functions associated with the NMDA receptor can be predominantly attributed to the NR2B subunit. The NR2B subunit has been involved in modulating activity such as learning, memory, processing and feeding behaviors, as well as being implicated in number of human pathological derangements such as MDD. Late in the 20th century, the NR3 subunits were discovered with two isoform variants NR3A and NR3B that are encoded by the GRIN3A and GRIN3B genes respectively. Furthermore, the family of NR3 subunits (i.e, NR3A and NR3B isoform variants) also possesses a glycine binding site each that exhibit an inhibitory (antagonistic/negative modulatory) effect on NMDA receptor activity/function in contrast to the stimulatory (agonistic/positive modulatory) effect exhibited by the NR1 subunits when they are bound to the co-agonist glycine. This depicts that the co-agonist glycine binds to any of the NR3 subunit isoform variants to inhibit and antagonize (negative modulation) the activation of NMDA receptor activity/function. All the NMDAR subunits share a common membrane topology that is dominated by a large extracellular N-terminus, a membrane region comprising three transmembrane segments, a re-entrant pore loop, an extracellular loop between the transmembrane segments that are structurally not well known, and an intracellular C-terminus, which are different in size depending on the subunit and provide multiple sites of interaction with many intracellular proteins. Multiple receptor isoform variants with distinct brain distributions and functional properties arise by selective splicing of the NR1 transcripts and differential expression of the NR2 subunits. A functional NMDA-glutamatergic receptor must comprise of a minimum heterotetramer complex with at least two obligatory NR1 subunits and two regionally localized variable NR2 subunits. The NR1/NR2B transmembrane segments are considered to be the part of the receptor that forms the binding pockets for uncompetitive NMDA receptor antagonists. The high affinity sites for glycine antagonist/inverse agonist/partial agonist are also exclusively displayed by the NR1/NR2B subunits of NMDA receptor. It is claimed that the presence of three (3) binding sites within the receptor namely, A644 on the NR2B subunit with A645 and N616 on the NR1 subunit, are important for binding of ketamine, memantine and other uncompetitive NMDA receptor antagonists. Unlike other ligand-gated ion channels, NMDA receptors require two distinct mechanisms in order to be activated. First, NMDA-glutamatergic receptor channels require co-agonist binding at the glycine (or D-serine) binding site on the NR1 subunit and at the glutamate (or D-aspartate) binding site on the NR2 subunit. Thus, if one of these co-agonists (glycine/D-serine or glutamate/D-aspartate) is not bound to their respective binding site, the ion channel will not open. Second, the NMDA receptor channels are blocked by magnesium ions [Mg2+] during the resting state. Depolarization of the neuron is required to dispel the magnesium ions [Mg2+] from NMDA receptor channels, which is usually achieved by the activation of the postsynaptic AMPA receptors. The NMDA receptor ion channel is non-selective and will allow both sodium ions [Na+] and calcium ions [Ca2+] to enter. The influx of calcium ions [Ca2+] is associated with the induction of various signaling cascades. Several postmortem studies have also found changes in the expression of NMDA-glutamatergic receptor subunits in MDD patients, which are likely compensatory effects to the changes in glutamatergic substrate concentrations, and appear to be brain region specific. For example, the NR2B and NR2C subunits have been shown to have increased expression in the locus coeruleus in postmortem tissue of MDD patients. Additionally, the expression of NR2A subunits has been found to be elevated in the lateral amygdala. Furthermore, MDD patients have shown an increase in glutamate binding in the hippocampus and a greater sensitivity to glutamate as measured by intracellular calcium influx. On the other hand, the NR2A and NR2B subunits transcription have been shown to be reduced in the perirhinal and prefrontal cortices in postmortem tissue from MDD patients. Moreover, postmortem studies have found decreased levels of the NR1subunit in the superior temporal cortex and prefrontal cortex. The NR1 and NR2 subunits are required for functional NMDA-glutamatergic receptor heteromeric complexes, and thus, increase/decrease in the levels of these NR1/NR2 subunits can be interpreted as

changes in total number of functional NMDA-glutamatergic receptors. Based on these previous experimental results, it was hypothesized that depression is associated with the hyperfunction of NMDA receptors in subcortical regions (i.e. hippocampus, locus coeruleus, and amygdala); whereas at the same time, depression is associated with the hypofunction of NMDA receptors in cortical regions (i.e. prefrontal, perirhinal and temporal cortices). And this findings has led to a conclusion that postulates the new "Glutamatergic hypothesis of depression" which is now moving our understanding of the pathophysiology of MDD a step further from the several decades old "Monoaminergic theory of depression".[3-10] Collectively, clinical data suggest the involvement of the glutamatergic system in the pathophysiology of MDD, which includes disruptions in glutamatergic substrate concentrations and NMDA receptor alterations. Although the role of glutamatergic systems is yet to be fully elucidated, but a "proof of concept" clinical study reported that the non-competitive NMDA-glutamatergic receptor antagonist ketamine produced rapid and prolonged antidepressant effects in patients suffering from MDD. Still, this has generated tremendous interest in developing new drugs that will target the glutamatergic neurotransmission mechanisms for the treatment of MDD. These potential drug targets are the NMDA-glutamatergic receptor as antagonist or inverse agonist or partial agonist; metabotropic glutamatergic receptors as positive or negative modulator; excitatory amino acid transporter-2 (EAAT-2) as a reuptake enhancer; and as a terminal presynaptic glutamate release inhibitor .[1-3,4,6,8]

Classes of Clinically Available Antidepressants

Interestingly, no subsequent antidepressants have surpassed the classical antidepressant agents in overall efficacy in clinical trials. However, the nonclassical agents are far safer and better tolerated.[1-3,5,6,9-11,13-15] These different classes of antidepressants are as follows:

1. TCAs such as amitriptyline, imipramine, desipramine, nortriptyline, clomipramine, trimipramine, protriptyline, and doxepin
2. MAOIs such as phenelzine, nialamide, isocarboxazid, hydracarbazine, tranylcypromine, moclobemide, bifemelane, pirlindole, toloxatone, selegiline, rasagiline, and safinamide
3. SSRIs such as fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine
4. SNRIs such as venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran
5. Norepinephrine-dopamine reuptake inhibitor (NDRI) such as bupropion
6. Selective NRIs such as reboxetine and atomoxetine
7. Serotonin receptors antagonist with serotonin reuptake inhibition (SARI) such as trazodone, nefazodone, and vortioxetine
8. Serotonin 5-HT_{1A} autoreceptor partial agonist with serotonin reuptake inhibition (SPARI) such as vilazodone
9. Noradrenergic α_2-receptor antagonist with specific serotonergic receptors-2 and-3 antagonism (NASSA) such as mirtazapine and mianserin
10. Norepinephrine reuptake inhibitor with serotonin receptors antagonism (NRISA) such as maprotiline
11. Serotonin-norepinephrine reuptake inhibitor and serotonin receptors antagonism antidepressant with potent antipsychotic D2 receptor blockade/antagonism (SNRISA with potent antipsychotic D2 receptor blockade/antagonism) such as amoxapine.
12. Atypical antipsychotics that exhibit weak D_2 receptor antagonism with potently strong 5-HT_{2A} receptor blockade such as olanzapine, quetiapine, risperidone, lurasidone, and aripiprazole
13. NMDA-glutamatergic ionoceptor antagonist/inverse agonist/partial agonist that exhibit a direct action on the excitatory glutamatergic neurotransmission system such as ketamine.

Considering chemical structure, bupropion is a unicyclic compound, while mirtazapine, mianserin, maprotiline, and amoxapine are tetracyclic compounds.

Tricyclic Antidepressants (TCAs)

The TCAs used in the clinical practice are amitriptyline, imipramine, desipramine, nortriptyline, clomipramine, trimipramine, protriptyline, and doxepin. The TCAs were the dominant class of antidepressants until the introduction of SSRIs in the 1980s and 1990s. They work mainly by blocking the reuptake pumps of norepinephrine (NET) and serotonin (SERT), with little or no action on dopamine reuptake pumps (DAT). They have an iminodibenzyl (tricyclic) core. The chemical differences between the TCAs are relatively subtle. For example, the prototype TCA imipramine and its metabolite desipramine differ by only a methyl group in the propylamine side chain. However, this minor difference results in a substantial change in their pharmacological profiles. Imipramine is highly anticholinergic and is a relatively strong SRI as well as NRI. In contrast, desipramine is much less anticholinergic and is a more potent and somewhat more selective NRI than is imipramine. TCAs are actually five or more drugs in one: (1) a serotonin reuptake inhibitor (SRI), (2) a norepinephrine reuptake inhibitor (NRI), (3) some have weak dopamine reuptake inhibitor (DRI) activity, (4) an anticholinergic-antimuscarinic drug (unselective muscarinic acetylcholine M receptors blockade activity), (5) an α_1-adrenergic antagonist, and (6) an antihistamine (H_1). They also inhibit sodium channels at overdose levels, causing potentially lethal cardiac arrhythmias and seizures. The main therapeutic actions of TCAs are due to serotonin reuptake inhibition (SRI) as well as norepinephrine reuptake inhibition (NRI). The degree and selectivity of inhibition of the SERT versus NET differ across the family of TCAs, with clomipramine being a preferential inhibitor of the SERT reuptake pumps, while desipramine is a preferential inhibitor of the NET reuptake pumps. Side effects of the TCA can be

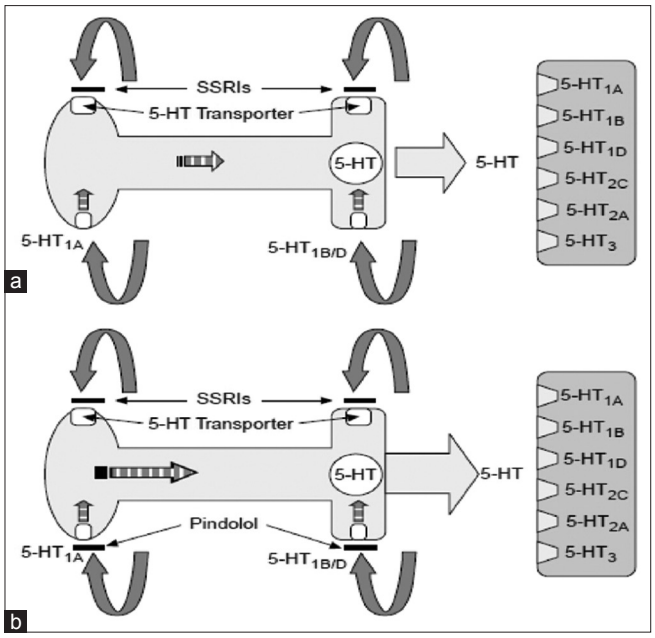

Figure 1: (a) Increase serotonin at the somatodendritic and terminal presynaptic region, which as a result of SSRI or SNRI or NASSA pharmacodynamics effect activates the 5-HT_{1A} and 5-HT_{1B} autoreceptors, thereby leading to a decrease in serotonin release in the terminal presynaptic region and firing rate in the somatodendritic region and thus reduced antidepressant and anti-anxiety clinical responses. (b) The addition of a drug such as a selective 5-HT_{1A} autoreceptor partial agonist (buspirone) or 5-HT_{1A} and 5-HT_{1B} autoreceptors antagonist (pindolol) can hasten antidepressant and anti-anxiety clinical responses to SSRI or SNRI or NASSA

explained by their (unwanted) blockade of neurotransmitter receptors. H_1 (antihistamine) blockade of histamine receptors causes weight gain and drowsiness; unselective blockade of muscarinic acetylcholine M receptors (anticholinergic-antimuscarinic activity) causes constipation, blurred vision, dry mouth, and drowsiness; α_1 blockade causes the side effects of dizziness, decreased blood pressure, and drowsiness. At the present time, the TCAs are reserved primarily for depression that is unresponsive to more commonly prescribed antidepressants such as the SSRIs or SNRIs or NASSA. Their loss of popularity stems in large part from relatively poorer tolerability compared to the relatively newer nonclassical agents, to difficulty of use, and to lethality in overdose. Other uses for TCAs include the treatment of neuropathic and chronic pain conditions, enuresis, and insomnia.[1-3,5,6,9-11,13-15]

Monoamine Oxidase Inhibitors (Maois)

MAOIs are a class of drugs that inhibit the activity of one or both monoamine oxidase enzymes namely monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B). They have a long history of use as medications prescribed for the treatment of depression. MAOIs act by inhibiting the activity of monoamine oxidase enzyme(s), thus preventing the breakdown of monoaminergic neurotransmitters and thereby increasing their synaptic availability. There are two isoforms of monoamine oxidase, MAO-A and MAO-B. MAO-A preferentially deaminates serotonin, melatonin, epinephrine, and norepinephrine. MAO-B preferentially deaminates phenethylamine and certain other trace amines; in contrast, MAO-A preferentially deaminates other trace amines, such as tyramine, whereas dopamine is equally deaminated by both types. The action of an MAOI is to increase the availability of the monoamine neurotransmitters NE, DA, and 5-HT by blocking their metabolism. They are particularly effective in treating atypical depression, Parkinson's disease and several other disorders. The classical MAOIs include both hydrazine and nonhydrazine derivatives. The hydrazine derivatives are phenelzine, nialamide, isocarboxazid, and hydracarbazine while the nonhydrazine derivative is tranylcypromine. These classical MAOIs exhibit unselective and irreversible inhibition, but the newer MAOIs are selective for either MAO-A or MAO-B isoenzyme as well as reversible for MAO-A. Reversible inhibitors of monoamine oxidase A (RIMAs) are a subclass of MAOIs that selectively and reversibly inhibit the activity of MAO-A enzyme. RIMAs are used clinically in the treatment of depression and dysthymia although they have not gained widespread clinical prescription worldwide. Because of their reversibility and selectivity, RIMAs are safer than the older MAOIs such as phenelzine and tranylcypromine. Several selective reversible inhibitors of MAO-A are used outside USA; but only moclobemide is currently approved for use within and outside the United States by the FDA. These selective reversible inhibitors of MAO-A used outside USA are bifemelane (not yet approved by FDA but is available in Japan), pirlindole (not yet approved by FDA but is available in Russia), and toloxatone (not yet approved by FDA but is available in France). Furthermore, available selective inhibitors of MAO-B which have been approved by FDA and are currently available for use within and outside USA are selegiline, rasagiline, and safinamide. The selective MAO-B inhibitor drugs have been approved by the FDA without any dietary restrictions, except in high-dosage treatment, wherein they lose their selectivity. Because of potentially lethal dietary and drug interactions, MAOIs have historically been reserved as a last line of treatment, used only when other classes of antidepressant drugs (for example, SSRIs and TCAs) have failed. However, some practitioners may have a poor understanding of these potentially lethal dietary and drug interactions with MAOIs; as they can be very serious and life-threatening, concomitant medication use or certain dietary intake (tyramine-containing meal or drinks) must be stringently avoided, monitored, or well overseen as they can cause dangerous or fatal serotonin syndrome or hypertensive crisis.[1-3,6,9-11,13-15]

Selective Serotonin Reuptake Inhibitors (Ssris)

SSRI agents currently available in the clinical practice are fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine. Escitalopram is the (S)-enantiomer of citalopram. Their primary mechanism of action is via inhibition of the serotonin reuptake transporter (SERT). Their development emerged out of search for chemicals that had high affinity for monoaminergic reuptake transporter pumps and/or

receptors but lacked the affinity for histamine, acetylcholine, and α_1 adrenoceptors that is seen with the TCAs. As with all antidepressants, SSRIs are highly lipophilic. The popularity of SSRIs stems largely from their ease of use, safety in overdose, relative tolerability, cost (all are available as generic products), and broad spectrum of uses. Another advantage of the SSRIs is the breadth of their therapeutic profile, extending far beyond antidepressant actions. Thus, SSRIs have proven efficacy in panic disorder, generalized anxiety disorders, obsessive–compulsive disorder (OCD), and bulimia, with encouraging findings in social phobia, post-traumatic stress disorder, premenstrual dysphoric disorder, migraine, dysthymia, and many other conditions.[4,5,14,15,17,18]

Mechanism of action for selective serotonin reuptake inhibitors

The primary mechanism of action of SSRIs is usually explained simply by their selective inhibition of the serotonin transporter (SERT). However, a more precise mechanism of SSRI therapeutic action is "delayed disinhibition of serotonergic neurotransmission in at least four key pathways that occur following desensitization of 5-HT_{1A} and 5-HT_{1B} autoreceptors." When an SSRI is administered, it indeed blocks the serotonin reuptake pump, and this happens immediately. However, this action causes a sudden increase in serotonin predominately in the somatodendritic region and not at the terminal presynaptic region where serotonin is presumably needed to exert therapeutic actions. Perhaps this explains why SSRIs do not have rapid onset of therapeutic actions. If SSRIs are administered chronically, the sustained increase of serotonin in the somatodendritic region of the serotonergic neurons causes the somatodendritic 5-HT_{1A} autoreceptors to desensitize. Once the somatodendritic 5-HT_{1A} autoreceptors desensitize, neuronal impulse flow is no longer readily inhibited by serotonin. Thus, neuronal impulse flow is turned on. Another way to say this is that serotonergic neurotransmission is disinhibited, and more serotonin is released from the terminal presynaptic membrane region. However, this increase is delayed compared with the increase of serotonin in the somatodendritic region of the serotonergic neurons. This delay is the result of the time it takes for somatodendritic serotonin to desensitize the 5-HT_{1A} autoreceptors and turn on (i.e., disinhibition process) neuronal impulse flow in the serotonergic neurons. As mentioned earlier, this delay may account for why SSRIs do not relieve depression and anxiety immediately. Furthermore, once an SSRI has blocked the serotonin reuptake pumps, increased somatodendritic serotonin concentration desensitized the somatodendritic 5-HT_{1A} autoreceptors, disinhibited neuronal impulse flow, and increased release of serotonin from terminal presynaptic membrane region; the final step is the desensitization of both the terminal presynaptic 5-HT_{1B} autoreceptors and the postsynaptic serotonin receptors. Desensitization of these receptors may contribute to the therapeutic actions of SSRIs, and/or it could account for the development of tolerance to acute side effects of SSRIs. In summary, the pharmacologic profile of an SSRI is to cause powerful if delayed disinhibition of neurotransmission process in every serotonergic fiber in the central nervous system (CNS). Since different serotonergic pathways are known to mediate different CNS functions, the various therapeutic effects of SSRIs may be mediated by disinhibition in different pathways. Thus, disinhibition of serotonergic neurotransmission pathway from midbrain raphe to prefrontal cortex could hypothetically help mediate the antidepressant effects of SSRIs. Similarly, disinhibition of the pathway from midbrain raphe to basal ganglia could hypothetically mediate therapeutic actions of SSRIs in OCD; while disinhibition of the pathway to mesolimbic cortex and hippocampus could mediate therapeutic actions in panic disorders; and disinhibition of the pathway to hypothalamus could mediate therapeutic actions in bulimia and binge-eating disorder. In each case, SSRI induced disinhibition of serotonergic neurotransmission with delivering of neurotransmitter where it is needed, hypothetically in different places for different psychiatric disorders. Clinical observations support the notion that different pathways mediate the different therapeutic actions of SSRIs, since SSRIs' action on different cortical areas depends on which psychiatric disorder is being targeted.[3,5,6] Furthermore, Figure 1 illustrates the detail mechanisms operating in the serotonergic neurotransmission system. The 5-HT_{1B} and 5-HT_{1A} autoreceptors play important roles in regulating the terminal presynaptic release of serotonin neurotransmitter and the somatodendritic-onset depolarizing activity of serotonergic neurons, respectively. It is also worth mentioning here that the addition of a selective 5-HT_{1A} autoreceptor partial agonist such as buspirone or 5-HT_{1A} and 5-HT_{1B} autoreceptors antagonist such as pindolol to SSRI or SNRI or NASSA treatment decouples the negative feedback inhibition mechanism of serotonergic neurotransmission, thereby accelerating and enhancing their antidepressant and anti-anxiety response clinically. This effect is achieved as a fast disinhibition process coupled with increased outflow of generated serotonergic neurotransmission action potential from the somatodendritic region toward the terminal presynaptic membrane region which leads to increase serotonin release.[6,7,14,15,17,18]

Side effects associated with selective serotonin reuptake inhibitors administration

The SSRIs can also have side effects that are bothersome, such as anxiety, sleep disturbances, sexual dysfunction, and gastrointestinal disturbances. To understand the mechanism of these side effects, it is helpful to know the functions of 5-HT_2 and 5-HT_3 receptors. As already mentioned, stimulation and then subsequent desensitization or downregulation of some 5-HT_2 receptors by serotonin when serotonergic neurons are disinhibited may play an important role in some of the therapeutic effects of SSRIs. Stimulation of other 5-HT_2 receptors hypothetically mediates several of the side effects of the SSRIs, including anxiety, sleep disturbances, sexual dysfunction, SSRI-induced insomnia, nocturnal myoclonus and akathisia. Stimulation of the 5-HT_3 receptor appears to be responsible for various gastrointestinal side effects of the

SSRIs. These effects are mediated not only in CNS pathways such as the brain stem chemoreceptors trigger zone and the pathway to hypothalamus but also outside the brain in the gut itself, which also has 5-HT_3 receptors within the enteric plexus. Thus, SSRIs can cause nausea, gastrointestinal cramps, and diarrhea. Disinhibition of the serotonergic pathway from brainstem to hypothalamus, which mediates aspects of appetite and eating behaviors, is responsible for the reduced appetite, nausea, and even weight loss associated with SSRIs administration.[7,8,14,15,17,18]

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

The SNRIs include venlafaxine, its metabolite desvenlafaxine, duloxetine, and levomilnacipran. Levomilnacipran is the active enantiomer of a racemic SNRI, milnacipran. Milnacipran has been approved for the treatment of fibromyalgia in the USA and has been used in the treatment of depression in Europe for many years. In addition to their use in major depression, SNRIs have applications in the treatment of pain disorders including neuropathies and fibromyalgia. SNRIs are also used in the treatment of generalized anxiety disorder, stress urinary incontinence, and vasomotor symptoms of menopause. The pharmacological properties of SNRIs are dose dependent, namely, at low doses, they behave essentially like an SSRI; while at medium doses, additional NE reuptake inhibition occurs; and at high-to-very high doses, they weakly inhibit the reuptake of dopamine with recent evidence, showing that the norepinephrine transporter also transports some dopamine as well, since dopamine is inactivated by norepinephrine reuptake pumps in the prefrontal cortex. The prefrontal cortex significantly lack dopamine reuptake transporters (DAT); therefore, SNRIs can substantially increase dopaminergic neurotransmission in this part of the brain. Thus, at low doses, the actions of SNRIs are similar to those explained for the SSRIs, and as the dose increases, the bupropion-like actions progressively kick-in. SNRIs are chemically unrelated to each other. All the SNRIs bind to inhibit the serotonin reuptake (SERT) and norepinephrine reuptake (NET) transporters, as do the TCAs. However, unlike the TCAs, the SNRIs do not have much affinity for other receptors.[1-3,6,9-11,14-16] Recently, levomilnacipran, the levorotatory enantiomer of milnacipran, has been found to act as an inhibitor of beta-site amyloid precursor protein cleaving enzyme-1 (BACE-1), which is responsible for β-amyloid plaque formation, and hence may be a potentially useful drug in the treatment of Alzheimer's disease in the near future.[8,16]

Norepinephrine-Dopamine Reuptake Inhibitor (NDRI)

The NDRI antidepressant drug bupropion ignores the serotonergic system and acts selectively to inhibit the noradrenergic (NET) and dopaminergic (DAT) reuptake transporter pump systems. This property renders the actions of bupropion to be unique not only from the SSRIs but from the other classes of antidepressants, which cause serotonergic interactions of one type or another. Not surprisingly, the therapeutic profile, side effects, and clinical applications of bupropion are different from and indeed often complementary to those of the widely used SSRIs and SNRIs. The pharmacology of bupropion suggests clinical actions in areas where boosting norepinephrine and dopamine would be especially desired. Both preclinical studies and empiric clinical observations suggest that symptoms of dopamine deficiency could include psychomotor retardation, anhedonia, hypersomnia, cognitive slowing, inattention, pseudodementia, and craving. Not surprisingly, such symptoms may be preferably targeted by bupropion. In addition, when patients do not respond to or do not tolerate SSRIs or SNRIs, bupropion can be substituted because of its "mirror-image like effects" pharmacology or added as an augmenting agent either to amplify therapeutic response or to eliminate side effects, particularly SSRI-induced sexual dysfunction. Other novel applications of the noradrenergic and dopaminergic pharmacology of bupropion include use in attention-deficit hyperactive disorder (ADHD); in the treatment of substance of abuse dependence disorders such as opioid withdrawal, alcohol withdrawal, smoking cessation, and psychostimulants addiction where craving during opioid, alcohol, nicotine, or psychostimulants withdrawal may be mitigated by boosting CNS dopamine level in order to stimulate the dopaminergic neurotransmission pathways in the rewarding and pleasure centre of nucleus accumbens. A significant number of patients treated with bupropion compare with placebo have reduced urge to smoke, drink alcohol or get addicted to opioids. In addition, patients taking bupropion experience fewer craving symptoms, mood symptoms, and possibly less weight gain while withdrawing from nicotine, alcohol, or opioid dependence. Bupropion appears to be about as effective as nicotine patches in smoking cessation. The mechanism by which bupropion is helpful in this application is unknown, but the drug may mimic nicotine's effects on dopaminergic and noradrenergic neurotransmission pathways in the rewarding and pleasure centre; and may also function as a non-competitive antagonist of the α3β2, α3β4, α4β2, and, very weakly α7 neuronal nicotinic acetylcholine receptors, and these actions appear to be importantly involved in its beneficial effects not only in smoking cessation, alcohol withdrawal, opioid withdrawal, or psychostimulants detoxification, but in depression as well. Nicotine is also known to have antidepressant effects in some people, and bupropion may substitute for this effect. In conjunction with substance abuse psychotherapy (counselling); bupropion can be used for the purpose of reducing methamphetamine abuse in dependent individuals with high likelihood of success. In addition to the treatment of major depression; bupropion is used off-label for the treatment of attention deficit hyperactive disorder (ADHD), panic disorder, bulimia nervosa, narcolepsy, therapy-resistant paediatric nocturnal enuresis, obesity, and the reversal of sexual dysfunction (weak erection adverse effects) associated with

SSRI use. In ADHD treatment, bupropion may be used alone or in combination with CNS stimulants such as methylphenidate, methamphetamine, lisdexamfetamine, or amphetamine depending on the individual patient's clinical response. On the other hand, the pro-adrenergic pharmacology of bupropion can also go too far, with overstimulation, agitation, insomnia, or nausea as possible adverse effects. However, seizure disorder, which with the original, immediate release formulation of bupropion is increased about four-fold over the other antidepressant classes, but is less likely to occur with the new, controlled-release formulation of bupropion.[1-3,9-11,13-15,20-23]

Selective Norepinephrine Reuptake Inhibitors (NRIs)

Reboxetine and atomoxetine belong to the selective NRIs class of antidepressants used for the treatment of major depression, although they have also been used off-label for panic disorder, ADHD, bulimia nervosa, narcolepsy, and treating therapy-resistant pediatric nocturnal enuresis. They are approved for the use in many countries worldwide including the United Kingdom but have not been approved for depression treatment in the United States. Although their effectiveness as an antidepressant has been challenged in multiple published reports, still their popularity has continued to increase.[1-3,6,9]

Serotonin Receptors Antagonist With Serotonin Reuptake Inhibition (SARI)

The SARI class of antidepressant agents includes nefazodone, trazodone, and vortioxetine. They exhibit the pharmacological property of a moderate-to-strong serotonin receptor(s) antagonism with a weak serotonin reuptake transporter (SERT) inhibition, so their primary pharmacodynamics effects and mechanisms of action are not due to SERT inhibition. Trazodone's structure includes a triazolo-moiety that is thought to impart its antidepressant effects. Its primary metabolite, m-chlorphenylpiperazine (m-cpp), is a potent 5-HT_2 antagonist. Trazodone was among the most commonly prescribed antidepressants until it was supplanted by the SSRIs in the late 1980s. The most common use of trazodone in the current clinical practice is as an unlabelled sedative-hypnotic and anxiolytic agent since it is highly sedating and neither associated with tolerance nor dependence. Nefazodone is chemically related to trazodone. Its primary metabolites hydroxynefazodone and m-cpp are both inhibitors of the 5-HT_2 receptors. Nefazodone received an FDA black box warning in 2001 implicating it in hepatotoxicity, including lethal cases of hepatic failure. Although still available generically, nefazodone is no longer commonly prescribed. The primary indications for both nefazodone and trazodone are major depression although both have also been used in the treatment of anxiety disorders. The pharmacology of nefazodone and trazodone can be thought of as a weak SSRI (i.e., a weak SERT inhibition) explained earlier above with one additional and important pharmacological property involving strong 5-HT_2 receptors antagonism; whereas 5-HT_2 receptors are stimulated by the SSRIs via serotonin. This leads to a difference in the therapeutic and side effect profiles between nefazodone/trazodone and the SSRIs. Perhaps, the biggest differences are that powerful serotonin-2 (5-HT_2) receptors blockade reduces anxiety and insomnia due to nocturnal awakenings and myoclonus, whereas SSRIs may cause short-term increase in anxiety and insomnia due to nocturnal awakenings and myoclonus. Furthermore, serotonin-2 (5-HT_2) receptors blockade will likely decrease the incidence of akathisia and sexual dysfunction as opposed serotonin-2 (5-HT_2) receptor stimulation by SSRIs that may lead to SSRI-induced akathisia and sexual dysfunction.[1-3,6,8,9]

Vortioxetine is a newer member agent of the SARI class. Some reference literature refers to vortioxetine as a "serotonin modulator and stimulator" because of its various and diverse pharmacodynamic actions at different serotonergic receptors. It has been shown to possess the following pharmacological activities namely an antagonist of the 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors, a partial agonist of the 5-HT_{1B} receptor, an agonist of the 5HT_{1A} receptor, and a weak inhibitor of the serotonin reuptake transporter (SERT), but its actions are not primarily due to the weak SERT inhibition and it is therefore not classified as an SSRI. It has no active metabolites (i.e., it is not a prodrug) and has demonstrated efficacy on major depression in a number of controlled clinical studies. In addition, there is some preliminary evidence that the drug also may improve some aspects of neurocognitive functions in depressed patients possibly due to its somatodendritic 5-HT_7 autoreceptors blockade activity.[1-3,5,6,7-10]

Serotonin 5-HT_{1A} Autoreceptor Partial Agonist With Serotonin Reuptake Inhibition (SPARI)

Vilazodone was approved in 2011 by the FDA for use in the United States to treat MDD. It has a multi-ring structure that allows it to exhibit its pharmacological activities. In some ways, its activity can be conceptualized as a combination of an SSRI and buspirone, i.e., vilazodone acts as a SRI with partial agonist activity at the serotonergic somatodendritic 5-HT_{1A} autoreceptors. According to two 8-week, randomized, double-blind, placebo-controlled trials in adults, vilazodone elicits an antidepressant response after 1 week of treatment. After 8 weeks, subjects assigned to vilazodone 40 mg daily dose (titrated over 2 weeks) experienced a higher response rate than the group given placebo (44% vs. 30%, $P = 0.002$), but the remission rates for vilazodone were not significantly different compare to placebo.[1-3,6,9,10]

Noradrenergic α Receptor-2 Antagonist With Specific Serotonergic Receptors-2 And-3 Antagonism (NASSA)

The antidepressants class of NASSA has mirtazapine and mianserin as members. Mirtazapine and mianserin are

atypical antidepressants which are used primarily in the treatment of MDD and other mood disorders such as bipolar affective disorders and schizoaffective disorders. In addition to their strong antidepressant properties, mirtazapine or mianserin has anxiolytic, sedative and hypnotic, antiemetic, and appetite stimulant effects and is sometimes used in the treatment of anxiety disorders, substance of abuse dependence, insomnia, nausea and vomiting, itching, SSRI-induced erectile dysfunction, and headache syndromes such as migraine and to produce weight gain when desirable.

Mirtazapine has α_2-blockade, antiserotonergic, and antihistaminergic activity; it is specifically a potent antagonist or inverse agonist of the α_{2A}-, α_{2B}-, and α_{2C} adrenergic receptors, the serotonin 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors, and the histamine H_1 receptor. Unlike many other antidepressants, it does neither inhibit the reuptake of serotonin, norepinephrine, dopamine nor inhibit monoamine oxidase. Similarly, mirtazapine has very weak activity as an anticholinergic-antimuscarinic, but there is neither activity blockade of sodium nor calcium channels, in contrast to most TCAs. As mirtazapine is an extremely potent H_1 receptor antagonist; antagonism of the H_1 receptor is by far the strongest activity of mirtazapine, with the drug acting as a selective H_1 receptor antagonist at very low concentrations. Blockade of the H_1 receptor may improve preexisting allergies, pruritus, nausea and vomiting, and insomnia in afflicted individuals and may also contribute to weight gain. Although it could be classified as an α_2 antagonist, this designation alone does not do justice to its other important pharmacologic properties. The name used in some reference literature for mirtazapine is NASSA or noradrenergic α_2 antagonist with specific serotonergic receptors-2 and-3 antagonism antidepressant. By this, it implied that mirtazapine has:

- Pro-adrenergic activity (i.e., α_2 autoreceptors antagonism effect leads to the disinhibition of neurotransmission impulse outflow from the somatodendritic region toward the terminal presynaptic membrane and also to enhance more norepinephrine release from the presynaptic membrane of noradrenergic nerve terminals into their synaptic space)
- Pro-serotonergic activity (i.e., α_2 heteroreceptors antagonism effect leads to the disinhibition of neurotransmission impulse outflow from the somatodendritic region towards the terminal presynaptic membrane and also to enhance more serotonin release from the presynaptic membrane of serotonergic nerve terminals into their synaptic space)
- Pro-dopaminergic activity (i.e., α_2 heteroreceptors antagonism effect leads to the disinhibition of neurotransmission impulse outflow from the somatodendritic region towards the terminal presynaptic membrane and also to enhance more dopamine release from the presynaptic membrane of dopaminergic nerve terminals into their synaptic space)
- Pro-cholinergic activity (i.e., α_2 heteroreceptors antagonism effect leads to the disinhibition of neurotransmission impulse outflow from the somatodendritic region towards the terminal presynaptic membrane and also to enhance more acetylcholine release from the presynaptic membrane of cholinergic nerve terminals into their synaptic space)
- Its serotonergic actions are being selectively antagonized at (or shifted away from) the postsynaptic 5-HT_2 and 5-HT_3 receptors toward the terminal presynaptic 5-HT_{1B} autoreceptors, somatodendritic 5-HT_{1A} autoreceptors, and other postsynaptic serotonergic receptors such as 5-HT_6 and 5-HT_7
- Its noradrenergic actions are being directed toward the postsynaptic α_1 and β_1 adrenoceptors
- Its dopaminergic actions are being directed toward the terminal presynaptic D_2 autoreceptor, postsynaptic D_2 receptor, and the other D_1, D_3, D_4, and D_5 dopaminergic receptors
- Finally, its cholinergic actions are being selectively antagonized at (or shifted away from) the postsynaptic M_3 receptors toward the terminal presynaptic M_2 autoreceptors and other postsynaptic cholinergic receptors such as M_1, M_4, M_5, N_N, and N_M.

The pro-adrenergic, pro-serotonergic, pro-dopaminergic, and pro-cholinergic actions of mirtazapine are due to its α_2 receptor antagonistic properties at both the somatodendritic membrane region and terminal presynaptic membrane region of noradrenergic, serotonergic, dopaminergic, and cholinergic neurons. This α_2 antagonistic activity of mirtazapine results in disinhibition of norepinephrine-, serotonin-, dopamine-, and acetylcholine-mediated neurotransmission impulse outflow from the somatodendritic membrane region of noradrenergic, serotonergic, dopaminergic, and cholinergic neurons, respectively, and also due to the attenuation of negative feedback mechanism orchestrated by norepinephrine on noradrenergic, serotonergic, dopaminergic, and cholinergic terminal presynaptic membrane. These main actions of mirtazapine result from the blockade of the α_2-adrenoceptors, which would enhance the release of more norepinephrine, serotonin, dopamine, and acetylcholine in the CNS and periphery since these α_2-adrenoceptors control the firing rate (in cell body region) and the release (in the terminal presynaptic region) of norepinephrine, serotonin, dopamine, and acetylcholine. In addition, since mirtazapine has serotonin-2 (5-HT_2) antagonist properties, its profile changes from that of an SSRI to that of other serotonin-2 (5-HT_2) antagonists as discussed above for nefazodone and trazodone. Since mirtazapine is also a serotonin-3 (5-HT_3) antagonist, it does not share the actions of SSRIs that lead to 5-HT_3 stimulation. Thus, mirtazapine is not associated with the gastrointestinal disturbances exhibited by the SSRIs. Furthermore, mirtazapine has strong antihistamine activity (at the H_1 receptor), which explains its side effects of weight gain and sedation.

Mianserin first patent was issued in the Netherlands in 1967. It was launched in France in 1979 and soon thereafter in the

UK. Investigators conducting clinical trials in the US submitted fraudulent data, and it was never approved in the US. Mianserin is an antagonist/inverse agonist (at most or all sites) of the α_1-and α_2-adrenergic receptors; serotonin 5-HT_{1D}, 5-HT_{1F}, 5-HT_2, 5-HT_3, 5-HT_6, and 5-HT_7 receptors; and histamine H_1 receptor with moderate inhibition of the reuptake transporter pumps of norepinephrine (NET, reuptake 1) as well. As an H_1 receptor inverse agonist with high affinity, mianserin has strong antihistamine effects such as sedation and weight gain. Blockade of H_1 receptor produces sedative effects, while antagonism of the 5-HT_{2A} and α_1-adrenergic receptors inhibits activation of intracellular phospholipase C, which seems to be a common target for several different classes of antidepressants. By antagonizing the somatodendritic and terminal presynaptic α_2-adrenergic receptors which function predominantly as inhibitory autoreceptors and heteroreceptors, mianserin disinhibits the release of norepinephrine, dopamine, serotonin, and acetylcholine in various areas of the central nervous system and periphery.[1-3,6,9-13]

Norepinephrine Reuptake Inhibitor With Serotonin Receptors Antagonism (NRISA)

Maprotiline has been shown to possess the following pharmacological actions which are a strong inhibitor of norepinephrine reuptake transporter pump (NET); a moderate antagonist of the 5-HT_2, 5-HT_7, and α_1-adrenergic receptors; and a strong antagonist of the histaminergic H_1 receptor. The recent identification of maprotiline as a potent antagonist of the 5-HT_7 receptor has revealed that this action potentially plays an important contributory role in its antidepressant effectiveness. Maprotiline is a strong antihistamine, but unlike most TCAs, it has minimal anticholinergic-antimuscarinic effects. The pharmacological profile of maprotiline explains its antidepressant, sedative, anxiolytic, and sympathomimetic activities. Furthermore, its sympathomimetic actions are selectively being antagonized and diverted away from the α_1-adrenergic receptor. In accordance with its pharmacological characteristics, maprotiline is used in the treatment of major depressive disorders, such as depression associated with agitation, anxiety, or unresponsive to other antidepressant agents. In addition, it shows strong antagonism against reserpine-induced effects in animal studies, as do the other "classical" antidepressants.[1-3,6,9-15]

Serotonin-Norepinephrine Reuptake Inhibitor And Serotonin Receptors Antagonism Antidepressant With Potent Antipsychotic D2 Receptor Blockade/Antagonism (SNRISA With Potent Antipsychotic D2 Receptor Blockade/Antagonism)

Amoxapine is the N-methylated metabolite of loxapine, an older antipsychotic drug. Amoxapine received the first marketing approval in United States in 1992. From pharmacological point of view, amoxapine possesses a wide array of pharmacodynamics effects which are a moderate reuptake inhibition of serotonin transporter pump (SERT) and a strong reuptake inhibition of norepinephrine transporter pump (NET) and also binds to block 5-HT_2, 5-HT_3, 5-HT_6, 5-HT_7, D_2, α_1-adrenergic, D_3, D_4, and H_1 receptors with varying but significant affinity, where it acts as an antagonist (or inverse agonist) depending on the receptor in question at all sites. Amoxapine is metabolized into two main active metabolites: 7-hydroxy amoxapine and 8-hydroxy amoxapine. In addition, 7-hydroxy amoxapine is a major active metabolite of amoxapine with a more potent dopamine D_2 receptor antagonist activity and contributes to its neuroleptic efficacy; whereas 8-hydroxy amoxapine is a stronger SRI but a moderate NRI and helps to balance amoxapine's ratio of serotonin to norepinephrine reuptake transporter blockade. Like maprotiline, amoxapine shares structural similarities and side effects comparable to the TCAs. As a result, it is not commonly being prescribed in current clinical practice and its primary indication is for MDDs that have been unresponsive to other antidepressant agents. Compared to other antidepressants, amoxapine is believed to have a faster onset of action, with therapeutic effects seen within 4–7 days of treatment. In excess of 80% of patients who do respond to amoxapine are reported to respond within a fortnight of beginning treatment. It also has properties similar to those of the atypical antipsychotics and may behave as one and may be used in the treatment of schizophrenia and schizoaffective disorders off-label. Despite its apparent lack of extrapyramidal side effects in patients with schizophrenia, it has been found to exacerbate motor symptoms in patients with Parkinson's disease psychosis.[1-3,6,9,15,19]

Atypical Antipsychotics

Atypical antipsychotics exhibit weak D_2 receptor antagonism with potently strong 5-HT_{2A} receptor blockade (or inverse agonism). In most cases, they also act as partial agonists at the 5-HT_{1A} receptor, which produces synergistic effects with 5-HT_{2A} receptor antagonism. Most atypical antipsychotics are either 5-HT_6 or 5-HT_7 receptor antagonists. Atypical antipsychotics such as olanzapine, quetiapine, risperidone, lurasidone, and aripiprazole are now being used by clinical psychiatrists as an adjunct pharmacotherapeutic agent in the management of MDD that has been unresponsive or showed inadequate remission after 4–8 weeks of active treatment with other classes of antidepressants such as the SSRIs, SNRIs, or TCAs. A fixed-dose combination of SSRI plus atypical antipsychotic such as fluoxetine plus olanzapine has received FDA approval for the pharmacotherapy of MDD, acute bipolar depression, and schizoaffective disorders. The atypical antipsychotics appear to be more consistently effective in the treatment of bipolar depression and also do not increase the risk of inducing mania or increasing the frequency of bipolar cycling.[24-32]

N-Methyl-D-Aspartate-Glutamatergic Ionoceptor Antagonist/Inverse Agonist/Partial Agonist

Ketamine is a non-competitive and unselective antagonist for the NR2 subunits of NMDA-glutamatergic receptor (aka channel blocker) that binds to the phencyclidine binding site inside the ion channel of the NMDA receptor, blocking the channel in a way that is similar to how Mg2+ ion blocks NMDA receptors, and is unselective for the NR2A-D subunits of the NMDA receptor channel. Non-competitive NMDA-glutamatergic ionoceptor antagonists that exhibit a direct action on the excitatory glutamatergic neurotransmission system such as ketamine are now being promoted for off-label use in the treatment of MDD, bipolar depression and schizoaffective depression. Sub-anaesthetic low dose ketamine has been found to possess rapid onset antidepressant action with a minimal dissociative anaesthetic effect clinically. Because of this property clinical psychiatrists are now using this drug as an adjunct pharmacotherapeutic agent in the management of MDD or bipolar depression or schizoaffective depression so as to facilitate and enhance fast remission. The indication of ketamine for this purpose in MDD or bipolar depression or schizoaffective depression has not been officially approved by the FDA. Ketamine is a potent, high-affinity, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that has long been used in anaesthesia and is a common drug of abuse in some parts of the world. A number of preclinical and clinical studies have demonstrated rapid antidepressant effects of ketamine. Multiple studies have suggested that a single dose of intravenous ketamine at sub-anaesthetic doses produces rapid relief of depression, even in treatment-resistant patients, that may persist for 1 week or longer. Unfortunately, ketamine is associated with neurocognitive dysfunction, dissociative, and psychotomimetic properties that make it unsuitable as a long-term treatment for depression. Still, a number of other NMDA-glutamatergic receptor antagonist or inverse agonist or partial agonist; metabotropic glutamatergic receptors positive or negative modulator; excitatory amino acid transporter-2 (EAAT-2) reuptake pump enhancer; and terminal presynaptic glutamate release inhibitor are under investigation as potential antidepressants for clinical use.[1,6,15,19]

In the Berman *et al*. (2000) study, the non-competitive NMDA receptor antagonist ketamine was first used in a "proof of concept" randomized, double- blind study to assess the effects of ketamine on MDD in seven patients who received both vehicle (placebo) and ketamine treatment (counter-balanced). A single, sub-anaesthetic dose of ketamine (0.5 mg/kg) was intravenously (i.v.) infused over 40 minutes, and the antidepressant effects of ketamine were assessed using the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventor (BDI). In comparison, an anaesthetic dose for ketamine in humans ranges from 1.0 mg/kg to 4.5 mg/kg intravenous and from 6.5 mg/kg to 13.0 mg/kg intramuscular. In this study, ketamine produced rapid, within four hours, and prolonged antidepressant effects that lasted up to 72 hours as compared to placebo control. This rapid antidepressant effect of ketamine is far superior to the 4-12 week delay with current antidepressant drugs. The hallucinogenic (or psychotomimetic) effects (e.g. out of body experience, hallucinations, etc.) of ketamine subsided (within two hours) prior to the onset of the antidepressant effects as measured by the Visual Analog Scales for intoxication "high" (VAS-high) and Brief Psychiatric Rating Scale (BPRS). This was the first clinical study to demonstrate that glutamatergic drugs may be effective for the treatment of MDD.

In another clinical study conducted by Zarate and colleagues to assess the antidepressant effects of ketamine in patients with treatment-resistant MDD and to determine a better understanding of the duration of the antidepressant effects; following a single low-dose 0.5 mg/kg infusion of ketamine, treatment-resistant patients showed a significant reduction in depression scores at 110 min that lasted up to seven days as measured by HDRS. Specifically, 71% of the patients achieved response criteria one day after the infusion, while 29% achieved full remission. Additionally, 35% maintained response criteria on day seven. Again, the hallucinogenic (or psychotomimetic) effects diminished before the onset of the antidepressant effects of ketamine (within two hours). This study confirmed the finding in the Berman *et al*. (2000) study that ketamine produces rapid and prolonged antidepressant effects in the treatment of depression and extended ketamine's efficacy to treatment-resistant MDD.

Another study conducted by Ghasemi *et al*. (2014) to compared the effects of ketamine and electroconvulsive therapy (ECT) in patients suffering from MDD. This study found out that both ketamine and ECT produced antidepressant effects; however, ketamine produced superior antidepressant effects in terms of fast response onset. For example, ketamine produced rapid antidepressant effects starting at 24 hours; whereas, the antidepressant effects of ECT were not expressed until after 48 hours. The antidepressant effects of both ketamine and ECT lasted until the completion of the study, which was seven days. These results suggest that ketamine is as efficacious, if not more efficacious, as ECT for treating MDD.

In addition to these previously mentioned studies, several other clinical studies have found that i.v. infusions of low-dose ketamine produce rapid and sustained antidepressant effects in patients with MDD; a rapid reduction in suicidal ideation but produced some neurocognitive dysfunction in patients with treatment-resistant MDD.

An anti-anhedonic effect of ketamine treatment in treatment-resistant bipolar depression was recently demonstrated by Lally *et al*. (2014). In a randomized, placeb-controlled, double-blind crossover design, 36 treatment-resistant bipolar depression patients were treated with a single, low intravenous dose of 0.5 mg/kg ketamine. They found that

ketamine rapidly reduced anhedonia in these patients within 40 minutes and that these effects preceded reductions in other depressive symptoms. Also, the decrease in anhedonic symptoms persisted up to 14 days. The authors concluded that these findings demonstrate the importance of glutamatergic mechanisms for the treatment of treatment-refractory bipolar depression and especially for the treatment of anhedonia symptoms.[1,6,15,19-22]

Emerging Adjunct And Augmenting Pharmacotherapeutic Agents Used For Treating Depression Disorders

Agomelatine

Agomelatine is a melatonergic MT1 and MT2 receptor agonist and a serotonin 5-HT2C receptor antagonist. Binding studies indicate that it has no effect on monoaminergic reuptake transporter pumps and no affinity for noradrenergic, histaminergic, cholinergic, dopaminergic, and benzodiazepine receptors, nor other serotonergic receptors. Agomelatine resynchronises circadian rhythms in experimental animal models of delayed sleep phase syndrome. By antagonizing 5-HT2C receptors, it disinhibits/increases norepinephrine and dopamine release specifically in the prefrontal cortex. Therefore, it is sometimes classified as a norepinephrine–dopamine disinhibitor (NDD). It has no influence on the extracellular levels of serotonin. Agomelatine has shown an antidepressant-like effect in experimental animal models of depression (learned helplessness test, despair test, chronic mild stress) as well as in models with circadian rhythm desynchronisation and in models related to stress and anxiety. In humans, agomelatine has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset. From the pharmacological point of view, agomelatine will be efficacious as an adjunct or augmenting pharmacotherapeutic agent for the treatment of patients having anxious depression disorders (either MDD or bipolar depression or schizoaffective depression) with anxiety disorders, insomnia, SSRI-induced sexual dysfunction and/or SSRI-induced nocturnal myclonus/akathisia. Agomelatine alone may not be effective as a monotherapy for the treatment of unipolar depression or bipolar depression or schizoaffective depression because of its unique mechanism of action as a melatonergic MT1 and MT2 receptor agonist and a serotonin 5-HT2C receptor antagonist. Because agomelatine lacks inhibitory pharmacoactivity at the monoaminergic reuptake transporter pumps (SERT, NET and DAT), does not inhibit the enzyme monoamine oxidase, and also lacks antagonistic activity at both the noradrenergic α receptor-2 and NMDA-glutamatergic ionoceptor; it is not actually regarded and acceptable as an antidepressant but rather it should be classified as an anxiolytic-sedative agent.

Agomelatine was discovered and developed by the European pharmaceutical company Servier Laboratories Limited. Servier developed the drug and conducted its phase III trials in the European Union. In March 2005, Servier submitted agomelatine to the European Medicines Agency (EMA) for licencing and marketing approval. On 27 July 2006, the Committee for Medical Products for Human Use (CHMP) of the EMA recommended a refusal of the marketing authorisation. The major concern was that efficacy had not been sufficiently shown, while there were no special concerns about side effects. Again, in September 2007, Servier submitted a new marketing application to the EMA. In March 2006, Servier announced it had sold the rights to market agomelatine in the United States to Novartis. It was undergoing several phase III clinical trials in the US, and until October 2011 Novartis listed the drug as scheduled for submission to the FDA no earlier than 2012. However, the development for the US market was discontinued and withdrawn in October 2011, when the results from the last of those trials became available. It received EMA approval for marketing in the European Union in February 2009 and TGA approval for marketing in Australia in August 2010.[33-36]

What this review adds to the body of knowledge ?

- This review enumerates the current update on the classification of antidepressant agents base on their different distinct and unique pharmacological mechanisms of action.
- This review remarkably advocates for the incorporation of the atypical antipsychotics and NMDA-glutamatergic ionoceptor antagonist/inverse agonist/partial agonist as new member classes of the antidepressant agents because of their clinically significant roles in the management of depression disorders.
- Vilazodone is currently the only clinically available member agent that belongs to the pharmacologically distinct and unique class SPARI.
- The newer member antidepressants are: Vilazodone (SPARI); Vortioxetine (SARI); ketamine (Non-competitive NMDA-glutamatergic ionoceptor antagonist); and atypical antipsychotics such as olanzapine, quetiapine, risperidone, lurasidone, and aripiprazole.
- Currently, ketamine is a better inexpensive, less strenuous and more effective substitute for Electroconvulsive therapy (ECT) in the management of treatment-resistant MDD or bipolar depression or schizoaffective depression. Both sub-anaesthetic low dose of ketamine and ECT produced antidepressant effects; however, ketamine produced superior antidepressant effects in terms of fast response onset. For example, ketamine produced rapid antidepressant effects starting at 24 hours; whereas, the antidepressant effects of ECT were not expressed until after 48 hours. The antidepressant effects of both ketamine and ECT lasted for at least seven days. This shows that ketamine is more efficacious than ECT for treating MDD or bipolar depression or schizoaffective depression.
- More proactive research should be done to synthesize rapid-onset novel antidepressant agents that will act selectively on the NMDA-glutamatergic ionoceptor as

an antagonist or inverse agonist or partial agonist without producing the neurocognitive dysfunction, dissociative, and psychotomimetic (hallucinogenic) effect associated with the blockade of this receptor.

- From the pharmacological point of view, agomelatine will be efficacious as an adjunct or augmenting pharmacotherapeutic agent for the treatment of patients having anxious depression disorders (either MDD or bipolar depression or schizoaffective depression) with anxiety disorders, insomnia, SSRI-induced sexual dysfunction and/or SSRI-induced nocturnal myclonus/akathisia.
- Agomelatine alone may not be effective as a monotherapy for the treatment of unipolar depression or bipolar depression or schizoaffective depression because of its unique mechanism of action as a melatonergic MT1 and MT2 receptor agonist and a serotonin 5-HT2C receptor antagonist.
- Because agomelatine lacks inhibitory pharmacoactivity at the monoaminergic reuptake transporter pumps (SERT, NET and DAT), does not inhibit the enzyme monoamine oxidase, and also lacks antagonistic activity at both the noradrenergic α receptor-2 and NMDA-glutamatergic ionoceptor; it is not actually regarded and acceptable as an antidepressant but rather it should be classified as an anxiolytic-sedative agent.
- These new evolving potential drug targets for depression treatment are the NMDA-glutamatergic receptor as antagonist or inverse agonist or partial agonist; metabotropic glutamatergic receptors as positive or negative modulator; excitatory amino acid transporter-2 (EAAT-2) as a reuptake transporter pump enhancer; and as a terminal presynaptic glutamate release inhibitor.

Conclusion

Majority of the currently available clinical antidepressant agents increase serotonergic, noradrenergic, and/or dopaminergic neurotransmission in the CNS. These currently available antidepressants exhibit this activity by thirteen (13) different mechanisms of action. As of this present moment, eleven (11) out of these thirteen (13) classes of antidepressants accomplish their pharmacological actions by blocking one or more of the reuptake transporter pumps and/or receptors for the three monoaminergic neurotransmitters. The twelfth class inhibits the enzyme monoamine oxidase, while the thirteenth class works by blocking the NMDA-glutamatergic ionoceptor. More proactive research should be done to synthesize rapid-onset novel antidepressant agents that will act selectively on the NMDA-glutamatergic ionoceptor as an antagonist or inverse agonist or partial agonist without producing the neurocognitive dysfunction, dissociative, and psychotomimetic (hallucinogenic) effects associated with the blockade of this receptor. It is not yet possible to determine which mechanism to match with individual depressed patient on the basis of objective laboratory tests or clinical criteria. However, these mechanisms satisfactorily elucidate and unravel their pharmacological effects in most instances. In addition, clinicians can use knowledge of these mechanisms of action to avoid undesirable side effects, enhance dose optimization, and increase the chances of successful and well-tolerated antidepressant treatment when one agent with a given mechanism fails by switching to another class with different mechanism or by making rational combinations of two or more antidepressant agents from different classes with diverse mechanisms of action and favorable pharmacodynamics profiles. Lastly, this review remarkably advocates for the incorporation of the atypical antipsychotics and NMDA-glutamatergic ionoceptor antagonist/inverse agonist/partial agonist as new member classes of the antidepressant agents because of their clinically significant roles in the management of depression disorders.

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Conflicts of interest

There are no conflicts of interest.

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