1. INTRODUCTION

The World Health Organization recently categorized depression as one of the world’s most disabling diseases, affecting nearly 340 million people worldwide and 18 million people in the United States at any given time. Few lay people realize that major depression and related mood disorders are potentially deadly afflictions; unrecognized major depressive disorder (MDD) is associated with a suicidal risk of approximately 15%. Beyond the risk of suicide, depressed patients also show a higher risk of mortality from all causes. However, mortality studies alone cannot fully characterize the hidden costs and true global impact of mental illness. The Global Burden of Disease Study was initiated in order to objectively evaluate the burden of over 100 common medical conditions by utilizing the metric of disability-adjusted life years (DALYs). The report stated that psychiatric conditions, though responsible for little over 1% of deaths, accounted for almost 11% of the disease burden worldwide. Furthermore, MDD was found to be the fourth largest source of DALYs in 1990, and has been projected to rise to second place by 2020. In addition, independent studies have ranked MDD as the third most costly and disabling illness in the United States. Earlier Indian studies have reported prevalence rates of depression that vary from 21–83% in primary care practices. Given the scope of the public health need, significant improvement in the therapies available to treat major depression has potentially far-reaching beneficial consequences. The research efforts involved in developing the current generation of antidepressant agents have helped to increase awareness of the diagnosis and treatment of major depression. However, the antidepressant medications currently employed to treat MDD possess a number of limitations, including tolerability drawbacks (approximately 50% of patients stop treatment within 3 months due to side effects or lack of efficacy and rather low probabilities of remission typically in the range of 35% to 45%).[1]

Depression is characterized by the presence of two core symptoms, depressed mood and anhedonia (decreased pleasure or interest). However, it is also accompanied by a plethora of other signs and symptoms, such as changes in appetite, sleeping, fatigue, loss of energy, psychomotor agitation or retardation, feelings of worthlessness or inappropriate guilt, diminished ability to think or concentrate, and recurrent thoughts of death or suicide.[2] In the brain, a relationship exists between the monoamine neurotransmitters like
norepinephrine (NE) and serotonin (5- hydroxytryptamine, 5-HT) and the symptoms of major depressive disorder (Figure 1). Specific symptoms are thought to be associated with the increase or decrease of specific monoamines, implying the involvement of specific neurochemical mechanisms. [3]

Virtually all antidepressants increase the synaptic concentrations of 5-HT and/or NE by blocking the reuptake of one or both of these neurotransmitters. The archetypal tricyclic antidepressants (TCAs) block NE and 5-HT transporters to a varying extent depending on the particular compound. [4] Although ranked among the most effective antidepressants available, the poor tolerance and toxicity of TCAs in overdose due to the involvement of other neurotransmitter systems make them difficult to be used at effective doses. [5] The principal side effects of the TCAs are attributed to their relatively high affinity for α1-adrenergic receptors, H1-histamine receptors, and muscarinic cholinergic receptors. [6] The selective serotonin reuptake inhibitors (SSRIs), which inhibit selectively 5-HT, are regarded as effective antidepressants. Although they have no affinity for α1-adrenergic receptors, H1-histamine receptors, and muscarinic cholinergic receptors, and are better tolerated than TCAs, [6] they have their intrinsic limitations, such as aggravation of sexual dysfunction, interaction with co-administered drugs and, a discontinuation syndrome for many. [7] In addition, some of them appear to be less effective than TCAs, with the number of TCAs employed therapeutically being four compared to six for SSRIs in primary care. [8] The difference is most pronounced in more severely depressed patients. [9]

1.1 THE MONOAMINE DEFICIENCY HYPOTHESIS OF DEPRESSION

Although the monoamine deficiency hypothesis, posited over 30 years ago, has proven to be an overly simplistic model for the complex pathophysiology of depression, [10, 11] it persists as a central heuristic guiding the development of antidepressants. The long held monoamine hypothesis states that decreased activity of monoaminergic pathways leads to depression. This is supported by the finding that compounds that increase monoaminergic activity through different mechanisms such as reuptake inhibition or monoamine oxidase inhibition have antidepressant activity.
In contrast, compounds that decrease monoaminergic function such as reserpine, which depletes monoamine stores, are depressogenic.\(^\text{[12]}\) Furthermore, clinical research has established that monoamine availability is required for the antidepressant activity of reuptake inhibitors. Depletion of the serotonin precursor tryptophan is more likely to lead to relapse of depressive symptoms in patients treated with the selective serotonin reuptake inhibitor (SSRI) fluoxetine than those treated with the NE reuptake inhibitor desipramine.\(^\text{[13]}\) Similarly, catecholamine-depletion via inhibition of tyrosine hydroxylase by α-methyl-\(p\)-tyrosine is more likely to induce transient relapse of depressive symptoms in desipramine-treated patients than fluoxetine-treated patients. Thus, 5-HT and NE neuronal systems are independently involved in antidepressant therapy.\(^\text{[14-16]}\)

The clinical impact of monoamine-based antidepressant medications support the view that alterations in both 5-HT and NE functions contribute to depression,\(^\text{[17-20]}\) and a number of neurochemical studies show that depression is associated with alterations in both 5-HT and NE neurotransmitters,\(^\text{[21-24]}\) 5-HT receptors and transporters,\(^\text{[25-28]}\) and NE receptors.\(^\text{[29]}\) However, depressed patients do not consistently demonstrate alterations in these neurochemical measures.\(^\text{[29]}\)

Several findings support the view that combined 5-HT and NE enhancement has greater therapeutic efficacy compared with the enhancement of either neurotransmitter alone. For example, although the selective reuptake inhibition of either 5-HT with SSRIs or NE with the selective norepinephrine reuptake inhibitor (NRI) reboxetine or TCAs (imipramine, desipramine, maprotiline), are equipotent in the treatment of depression,\(^\text{[30, 31]}\) a retrospective, open 4-week study revealed that the combination of the SSRI fluoxetine and desipramine, a relatively selective NE reuptake inhibitor, exhibited a more rapid and robust therapeutic effect than desipramine alone.\(^\text{[32]}\) Moreover, fluoxetine was found to raise the blood levels of desipramine.\(^\text{[32]}\) In another study, 30 depressed outpatients with 90% meeting criteria for major depression had fluoxetine (20–60 mg) added to their ongoing and ineffective therapy which included a TCA-like drug (56%) alone or in a combination of drugs (44%) including lithium, benzodiazepines or carbamazepine.\(^\text{[33]}\) Positive response was reported for the combination in 26 out of the 30 patients. Combination of nor-triptolene and...
either fluoxetine or sertraline to treat eight patients with resistant and recurrent depression produced significant improvement despite the fact that these patients had failed on multiple drug regimens and electroconvulsive therapy.\(^{[34]}\)

### 1.2 POTENTIAL NEUROBIOLOGICAL SUBSTRATES OF DUAL REUPTAKE INHIBITORS

Although the pharmacological activity of monoamine oxidase inhibitors and reuptake inhibitors take place in several hours, several weeks are required to achieve complete antidepressant activity. This suggests that downstream mechanisms are involved in the pharmacotherapeutic activity of antidepressant agents (Figure 1). The delayed onset of activity has been attributed to a cascade of latent neuroadaptive processes including the down-regulation of monoamine receptors and/or autoreceptors \(^{[35-38]}\), the augmentation of monoamine receptor coupled second messengers including cAMP and inositol phosphate and protein kinases, the activation of neurotrophic factors (e.g., BDNF), 100 and/or alterations in gene expression. \(^{[39, 40]}\) Moreover, such processes may additionally increase neurogenesis in critical brain regions,\(^{[41]}\) including the prefrontal cortex and hippocampus, adversely affected by stress and/or depression. Hence, enhancing multiple monoamine neurotransmitter systems and multiple downstream intracellular pathways by dual reuptake inhibitors may induce additive and/or synergistic effects on both disparate as well as common neuroplastic processes. The induction of such molecular cascades in dysfunctional brain regions such as the prefrontal cortex, may in turn accelerate the course of onset of antidepressant activity or manifest a higher antidepressant efficacy compared to the agents acting on one monoamine pathway.\(^{[42]}\)
**Figure: 01** There are a number of potential sites of interaction of 5-HT and NE neuronal systems that may have additive or synergistic effects on signal transduction.

**Site 1** is the somatodendritic inhibitory autoreceptor (5-HT$_{1A}$ or 2-adrenergic receptors). The dual reuptake inhibitors do not have affinity for the autoreceptors, but activate them indirectly via increased monoamine levels due to reuptake blockade at the cell bodies.

**Site 2** is potential cross talk between respective raphe 5-HT cell bodies and locus coeruleus NE cell bodies. Evidence suggests that NE increases 5-HT cell body firing and this is a potential site of synergy.

**Site 3** is the transporter (reuptake) site and the dual reuptake inhibitors block both NE and 5-HT transporters and thereby enhance neurotransmission of each neuronal system which is a potential site of enhanced effectiveness.

**Site 4** is the presynaptic inhibitory autoreceptor (in some species 5-HT$_{1B/1D}$ and 2-adrenergic receptors) and activation of these receptors decrease neurotransmitter release. Dual reuptake inhibitors have no affinity for these receptors, but indirectly activate them by increasing monoamine levels in the synapse due to reuptake inhibition.

**Site 5** is the postsynaptic NE or 5-HT receptor which upon activation by the neurotransmitter initiates a cascade of secondary and tertiary messenger processes.

**Site 6** represents the induction of intracellular secondary messenger processes by both 5-HT and NE receptor stimulation leading to the activation of protein kinases (e.g., PKC, PKA), transcriptional factors, and neurotrophic factors. Neurotrophic factors may promote neurogenesis and/or protect neurons in dysfunctional regions of the depressed brain. The prefrontal cortex uniquely has interconnections to all major areas of the brain, receives input from the limbic system and the hypothalamic pathways, and has reciprocal connections with brain stem raphe nuclei (5-HT) and locus ceruleus (NE) cell bodies.
Figure: 02 The amin hypothesis of major depression. Depression appears to be associated with changes in serotonin and norepinephrine signaling in brain (or both) with significant downstream effects. Most antidepressants cause changes in amine signaling. AC, adenylyl cyclase; 5-HT, serotonin; CREB, cAMP response element binding (protein); DAG, diacyl glycerol; IP3, inositol trisphosphate; MAO (monoamine oxidase), NET (norepinephrine transporter), PKC: protein kinase C; PLC, phospholipase C; SERT, serotonin transporter.
Figure: 03 The serotonin synapse. Serotonin is synthesized from tryptophan by the enzyme tryptophan hydroxylase. Serotonin is then packaged into vesicles for release into the synaptic cleft, which occurs when there is sufficient stimulation of the neuron. Serotonin released from the serotonin neuron into the synaptic cleft has multiple actions. (1) Serotonin binds to its receptors on other neurons. Activation of postsynaptic receptors results in transduction of the signal that initially stimulated the serotonin neuron. (2) Serotonin also binds to presynaptic serotonin receptors on the neuron from which it was released, which provides feedback and regulates plasticity of the neuron. (3) Serotonin is taken up back into the presynaptic serotonin neuron by the serotonin transporter. Serotonin is then recycled for future release or broken down by monoamine oxidase and excreted in urine.
From many years, tricyclic antidepressants (TCAs) are used as the backbone of the treatment of MDD. All the effective antidepressant drugs block the reuptake of the 5-HT and/or NE neurotransmitters and increase their synaptic concentrations. This property of the antidepressants first discovered in TCAs. Apart from the inhibition of 5-HT and NE reuptake, TCAs also act through adrenergic, muscarinic and histaminergic receptor sites. Because of the non-specific binding of the TCAs leads to adverse events and interactions. Therefore TCAs show poor tolerability and toxicity due to various interactions at neurotransmitter receptors. Because of these reasons, the use of TCAs becomes limited today.\(^{[43]}\)

Another class of antidepressants is the serotonin selective reuptake inhibitors (SSRIs). It was developed with the target of more selectivity towards serotonin neurotransmitter as compare to TCAs. SSRIs selectively block the 5-HT reuptake. In addition, SSRIs are the more tolerable and effective drug than TCAs. Despite of presence of these antidepressants, the response rate was usually 60% to 70% and remission rate is around less than 50%. There was a still requirement of a more efficacious and tolerable antidepressant drug which can be used in the patients with severe depression and increase the patient compliance.\(^{[43]}\)

In general, antidepressants achieve a response (≥50% reduction in baseline depression score) in less than 70% of patients and remission (a complete absence of depressive symptoms) in less than 50%. Increasing evidence of the importance of NE in the etiology of depression\(^{[44]}\) and the idea that “two actions are better than one” have led to the development of a new class of compounds that block the reuptake of both 5-HT and NE without the nonspecific, side effect-inducing receptor interactions of TCAs. This class, the serotonin and norepinephrine reuptake inhibitors (SNRIs) comprising of duloxetine, venlafaxine, mirtazapine and milnacipran.\(^{[43]}\)