ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are often recommended as first-line therapies in patients with major depressive disorder. It has been postulated, that the acute and long-term effects of these drugs may be limited due to autoregulatory feedback mechanisms involving the 5-HT1 class of serotonergic receptors. One approach to this drawback has been the investigation of augmentation therapies, such as the addition of 5-HT1A or 5-HT1B agonists to SSRIs in patients with MDD. Another approach has been the development of medications with additional mechanisms of action, such as Vilazodone, an SSRI and partial 5-HT1A receptor agonist that is currently approved for the treatment of Depression. Vilazodone a novel Serotonin Reuptake Inhibitor and 5-HT1A,Partial Agonist that is recently developed for the treatment of Major Depressive Disorder.

Keywords: Vilazodone, Safety, Efficacy, Major Depressive Disorder, Antidepressant
INTRODUCTION

Major Depressive Disorder is a disorder of mood in which the individual experiences one or more major depressive episodes without a history of manic, mixed, or hypomanic episodes. Depression is a serious chronic and recurrent psychiatric illness and is most common ailment among all psychiatric disorder. Depression was considered as the third major cause of disability and premature death across the world. According to WHO depressive disorder will be the second most important cause of Disability across the world by the year 2020. The prevalence of depression in India is 15.1% and is higher in female than male.

The underlying reason of depressive disorder was not yet fully understood; although psychiatric, social and biological factors play an important role. The catecholamine and serotonin deficiency hypothesis postulate that deficiency of monoamine (norepinephrine and serotonin) within the synaptic cleft play a major role in depression. There are multiple variations of depression that a person can suffer from, with the most general distinction being the depression in people who have or do not have a history of manic episodes.

The depressive episode involves symptoms such as depressed mood, loss of interest and enjoyment, and increased fatigability. Depending on the number and severity of symptoms, a depressive episode can be categorized as mild, moderate, or severe. An individual with a mild depressive episode will have some difficulty in continuing with ordinary work and social activities, but will probably not cease to function completely. During a severe depressive episode, it is very unlikely that the sufferer will be able to continue with social, work, or domestic activities, except to a very limited extent. The bipolar affective disorder typically consists of both manic and depressive episodes separated by periods of normal mood. Manic episodes involve elevated mood and increased energy, resulting in over-activity, the pressure of speech and decreased need for sleep.

The treatment of depressive disorders consists of a complex multimodal therapy that is determined by the current state of the illness. The treatment of depression includes pharmacotherapy, psychotherapy, and sociotherapy, whereas pharmacotherapy is not always mandatory for less severe forms of depression, severe depression usually requires pharmacotherapy or electroconvulsive therapy. In addition, a variety of other biologic intervention, such as sleep deprivation and bright light therapy, may be of use in certain patient subgroups.
In the 1950s, the discovery of the therapeutic effects of medications now classified as tricyclic antidepressants (TCAs) (Imipramine, Amitriptyline, Desipramine, Nortriptyline) and monoamine oxidase inhibitors (MAOIs) (Moclobemide, Clorgyline) led to more widespread treatment of depression. Although the antidepressant actions of the TCAs and MAOIs are likely to be initiated by different mechanisms, they ultimately have a similar effect of increasing neurotransmitter availability in the synaptic cleft. The TCAs inhibit reuptake of certain neurotransmitters, particularly norepinephrine and, for some TCAs, serotonin. The MAOIs, inhibit the metabolism of serotonin, dopamine, and norepinephrine. One major limiting factor in the use of these 2 drug classes is their side effect profiles. TCAs can produce adverse cholinergic and adrenergic effects, and, in excessive doses or overdoses, can cause seizures and potentially lethal arrhythmias. The MAOIs can produce orthostatic hypotension and edema. Moreover, because levels of the A form of the enzyme MAO are high in the gut and liver, inhibition of MAO requires dietary restrictions to reduce the risk of a serious and potentially fatal adverse event, hypertensive crisis. There was thus a clear motivation to develop newer, more selective antidepressant medications, and, by the late 1980s, research led to the introduction of a new class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs) (Fluoxetine, Sertraline, Citalopram, Escitalopram). As compared with the first-generation antidepressants, SSRIs were found to be generally similar in efficacy for the treatment of depressed outpatients, with a better tolerability profile. Moreover, the SSRIs were profoundly safer in overdose than the TCAs. As a result of these differences, the SSRIs rapidly supplanted the TCAs and MAOIs as the the first choice of antidepressant class for both psychiatrists and primary care providers. Indeed, by the end of the first decade of the "SSRI first" era, primary care physicians were prescribing more antidepressants than psychiatrists.

Shortly after the introduction of the SSRIs, another class of antidepressants known as the serotonin-norepinephrine reuptake inhibitors (SNRIs) (Duloxetine, Venlafaxine) was introduced. These medications inhibit the reuptake of norepinephrine in addition to serotonin and, as such, directly affect both serotonergic and noradrenergic neurotransmission. However, it should be noted that most of these compounds show much greater inhibition of serotonin reuptake than norepinephrine reuptake, such that at normal therapeutic doses, most of their activity very likely results from their serotonergic effects. Although not as widely prescribed as the SSRIs, several SNRIs are also now considered to be first-line treatment
options for MDD. It was proposed that the property of dual reuptake inhibition might convey an efficacy advantage for the SNRIs over SSRIs\textsuperscript{16}

Although newer antidepressant was better tolerated and caused fewer side effect, their specific side-effect profile has to be taken into account during the treatment of depression. In addition, the latency of several weeks until the onset of sufficient therapeutic effects remains a serious and clinically relevant problem. This principle holds true for each antidepressant and each class of antidepressant mechanisms. A further general problem in the pharmacotherapy of depression is the possible nonresponse to the first antidepressant treatment. Approximately 30\% of depressed patients do not show sufficient improvement after the first course of an adequate antidepressant treatment and a further 20\% discontinued due to tolerability problems. Adequacy of treatment include the use of a treatment with proven efficacy during a time interval of at least 4-6 weeks in a sufficient therapeutic dose range including reliable patient adherence to therapy. Half of patients who do not respond adequately to a first course also fail to respond to a second antidepressant treatment trial. Hence there is a need for alternative antidepressant with more rapid onset of action, better response, remission, and better tolerability.

Vilazodone- a new antidepressant is selective and potent serotonin reuptake inhibitor and serotonin 1A receptor partial agonist approved by FDA in January 2011 for treatment of MDD.\textsuperscript{17} The combination of serotonin reuptake inhibition with 5-HT1A partial agonistic action leads to more rapid onset of mood elevation and enhanced therapeutic efficacy. Partial Agonist action at presynaptic somalodentric 5 HT level hence contribute to antidepressant action and partial agonist action at postsynaptic 5HT1A receptor lead to less sexual Dysfunction.\textsuperscript{18} Mechanism of action include SERT inhibition with a serotonin (5HT) 1A partial agonism, hence called Serotonin Partial Agonist Reuptake Inhibitor (SPARI).
When the SPARI is administered, about half of SERTs and half of serotonin 5-HT1A receptors are occupied immediately.

Blockade of the serotonin transporter (SERT) causes serotonin to increase initially in the somatodendritic area of the serotonin neuron.
The consequence of serotonin increasing in the somatodendritic area of the serotonin neuron is that the somatodendritic 5-HT1A autoreceptors desensitize or down-regulate.

Once the somatodendritic receptors down-regulate, there is no longer inhibition of impulse flow in the serotonin neuron. Thus, neuronal impulse flow is turned on. The consequence of this is release of serotonin in the axon terminal.
Finally, once the SPARIs have blocked the SERT, increased somatodendritic serotonin, desensitized somatodendritic 5-HT autoreceptors, turned on neuronal impulse flow and increased release of 5-HT from axon terminals, finally desensitization of postsynaptic 5HT receptors In addition, the predominance of 5-HT actions may lead to downstream enhancement of dopamine release, which may mitigate sexual dysfunction.\(^{19,20}\)

The recommended dosage is 40 mg once daily. Vilazodone should be titrated, starting with an initial dosage of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then an increase to 40 mg once daily. Vilazodone should be taken with food. If vilazodone is taken without food, inadequate drug concentrations may result and the drug's effectiveness may be diminished.\(^{19}\)

Common ADR include diarrhea, nausea, insomnia and vomiting. Other adverse effects included dizziness, dry mouth, fatigue, abnormal dreams, decreased, libido, arthralgia, and palpitations.\(^{19}\)

Patients should be monitored for clinical worsening, suicidality, and unusual changes in behavior while they are taking vilazodone. Clinicians should discontinue vilazodone and begin supportive treatment if serotonin syndrome or neuroleptic malignant syndrome occurs during vilazodone therapy. Like other antidepressants, vilazodone should be used with caution in patients with a history of a seizure disorder. Treatment with vilazodone may also increase the risk of bleeding if the drug is taken with NSAIDs, aspirin, and other agents that
affect coagulation. Vilazodone should not be stopped abruptly; the dose should be reduced gradually. Although no cases of hyponatremia were associated with vilazodone therapy in clinical studies, hyponatremia has occurred as a result of treatment with other SSRIs and SNRIs. Activation of mania or hypomania can occur with vilazodone therapy. Therefore, patients should be screened for bipolar disorder.  

THE ROLE OF VILAZODONE IN CLINICAL PRACTICE

The pharmacologic profile of vilazodone may address several unmet needs inherent in the pharmacotherapy of depression. First, the proposed mechanism of action is consistent with a rapid onset of clinical efficacy. Perhaps equally important, vilazodone may fill the void for a serotonergic antidepressant that has a low incidence of sexual side effects hence patients who develop significant sexual side effects on other SSRIs can be readily switched to vilazodone, with preservation of response and restoration of sexual function. Another unmet need for antidepressant therapy is better remediation of comorbid anxiety symptoms. Indeed, the negative impact of anxiety on treatment outcome for a range of first-line and second-line therapies was one of the strongest findings in MDD. It is important to note, however, that the completed clinical trials were not specifically designed to assess onset of efficacy, side effects, or efficacy in patients, so future studies will be needed to confirm these proposed mechanism-based benefits.

BENEFITS OF VILAZODONE THERAPY

Combined SSRI and 5-HT1A receptor partial agonist action more rapid onset of mood elevation and enhanced therapeutic efficacy.

Highly selective 5-HT reuptake inhibition consistent antidepressant response.

Partial agonist action at presynaptic somatodendritic 5-HT1A autoreceptors greater increase in endogenous 5-HT levels, contribute to antidepressant actions.

Partial agonist actions at postsynaptic 5-HT1A receptors less dysfunction.

CONCLUSION

A very exciting concept for the treatment of depression is the novel antidepressant Vilazodone, a compound that exhibit a selective and potent serotonin reuptake inhibition and
serotonin receptor partial agonistic action. Vilazodone treatment is most efficacious in patient 
with severe symptoms and thereby prove the therapeutic benefit of drug across a spectrum of 
depressive severities. Treatment related side effect is also less and hence conclude that 
Vilazodone may become a unique treatment option for depression with a rapid onset, minimal 
side effect and enhanced therapeutic efficacy.

REFERENCES