**VILAZODONE: A UNIQUE SPARI WITH STELLAR HYBRID ACTION**

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**ABSTRACT**

**Introduction:** Vilazodone is a SERT inhibitor and partial agonist of 5HT1A receptor introduced as a new antidepressant. The dual mechanism of action attributes to faster onset of antidepressant action and more rapid improvement of symptoms. **Methodology:** The systemic review of available literatures including pubmed, google scholar, science direct, cochrane database has been reviewed with the available search engines. **Results:** The molecular structure, pharmacodynamics, pharmacokinetice, mechanism of action, adverse reactions has been described. The outcome measures has been compared in between disease related and patient related evidences. The commonest adverse effects are nausea, diarrhoea and headache which decrease with time. Because of less drug interaction, suitable for geriatric patients with comorbidities. **Conclusion:** The therapeutic
evidences have been summarized in a chart. The therapeutic efficacy is established and the molecule is generally well accepted and can be effective first line antidepressant, even in severely depressed patients.

**KEYWORDS:** vilazodone, SERT & SPARI, antidepressant, review.

**INTRODUCTION**

Vilazodone is a member of the prolific family of Indolealkylamines, sharing origin with naturally occurring psychoactive substances such as Bufotenin. Its structural similarity with Serotonin (5 – HydroxyTryptamine, 5HT) is a predictor of its affinity for the serotonergic receptors. It exerts its action at both pre and post synaptic 5HT1A receptors. In function assays the potency of reuptake inhibition of Vilazadone is 30 times higher than Fluoxetine. It acts by SERT inhibition as well as 5HT1A partial agonism. Thus, it has dual mechanism of action as Selective Serotonin Reuptake Inhibitor (SSRI) and as SPARI (Serotonin partial agonist reuptake inhibitor). Inhibition of SERT causes immediate release of serotonin in somatodendritic region and which in turn desensitize and downregulate 5HT1A autoreceptors. There is no inhibition of impulse which results in increased release of serotonin in the axonal terminal. Finally, there is desensitization of postsynaptic 5HT receptors which also may lead to downstream enhancement of dopamine release and this can mitigate the sexual dysfunction normally observed with SSRI. The dual mechanism of action attributes to faster onset of antidepressant action and more rapid improvement of mood symptoms.

It has been developed by MERCK in India in 1997 and licensed to GSK for drug trial. Unfortunately during initial period, Vilazodone had not so encouraging results with 2 RCTs showed Vilazodone was not superior to placebo and later in 3 RCTs it didn’t perform better than placebo (failed trials). A drug for its approval must have to show 2 statistically significant results hence application for approval was abandoned. Later Genaissance, a subsidiary of Clinical It has been developed by MERCK in India in 1997 and licensed to GSK for drug trial. Unfortunately during initial period, Vilazodone had not so encouraging results with 2 RCTs showed Vilazodone was not superior to placebo in treatment of major depression in adults and later in 3 RCTs it didn’t perform better than placebo (failed trials) although these trials also showed that it performed equally well as other positive controls i.e. other proven antidepressants. A drug for its approval must have to show 2 statistically significant results hence application for approval was abandoned. Later Genaissance, a
subsidiary of Clinical Data Inc. specialized in pharmacogenomics acquired the molecule in 2005, conducted trial by Forest Labs at last found significant statistical results to prove that Vilazodone is superior to placebo. An application had been submitted to FDA for its approval in 2009 and finally Vilazodone has been approved by FDA in January 2011 for treatment of depression and a remark was added regarding it being equal unless proved otherwise in terms of anti-depressant activity to other SSRI. It is available in 10, 20 and 40 mg tablets packaging formats.

Fig 1: Chemical structure of Vilazodone.

**MODE OF ACTION**

Vilazodone acts by SERT inhibition as well as 5HT1A partial agonism. When administered, 50% SERT and 50% 5HT1A receptors are immediately equally occupied. Vilazodone very selectively inhibits 5HT reuptake which is 400 times more than its Dopamine reuptake and 300 times more than NE reuptake. Therefore it’s a highly selective on its activity. PET scan has shown at a dose of 40 mg/day it has significant occupancy to 5HT1A receptor.\(^1\) It has been hypothesized that SERT inhibition and SPARI agonism with negative feedback circuitry will enhance the neuroadaptation and hasten therapeutic efficacy. The in vitro preclinical study has established the fact both in clonal and native systems. But in vivo study has shown that in contrast to 8-OH-DPAT and paroxetine, vilazodone selectively enhances serotonergic output in the prefrontal cortex of rats. Thus it has proven efficacy in putative depression model (forced swim test) and anxiety model (ultrasonic vocalization model) in rats.\(^2\)
Table 1: Pharmacodynamics of Vilazodone.

<table>
<thead>
<tr>
<th>SSRI like activity</th>
<th>SPARI activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inhibits serotonin reuptake with minimal inhibition of noradrenaline and dopamine uptake in vitro.</td>
<td>1. High affinity for 5HT1A receptors in vitro with negligible affinity for other 5HT receptors</td>
</tr>
<tr>
<td>3. In frontal cortex and ventral hippocampus increases extracellular serotonin levels.</td>
<td>3. Desensitizes 5HT1A autoreceptors in dorsal raphe nucleus and inhibits shock-elicited ultrasonic vocalization.</td>
</tr>
<tr>
<td>4. In vitro, found to inhibit serotonin reuptake in dorsal raphe nucleus.</td>
<td>4. Exhibited 5HT1A receptor agonism-like activity in a drug discrimination procedure.</td>
</tr>
</tbody>
</table>

Pharmacokinetics and Drug interactions.

**Pharmacokinetics**

In contrast to active metabolites of other SSRI the parent drug itself is the active one and has this unique class difference. It’s a high protin bound drug (96-99% bound to plasma protein) with terminal half-life approximately 25 hrs and steady state thus achieved in 4 days (four half-lives) with consistent dosing. Vilazodone is absorbed well orally and should be taken with food as food increases the bioavailability of the drug. Tmax of Vilazodone is approximately 4 hours, max Cmax = 156.3 ng/ml. Volume of distribution (Vd= 60.52).[^2]

There are no active metabolites. Approximately 68% excreted in faeces, 20% in urine and 3% excreted unchanged in urine. No difference in PK has been found in mild to moderate liver or renal disease hence dose adjustment is not required.

It is extensively metabolized via Cyt P450 3A4 enzyme system. With concomitant use of potent inhibitor of Cyp 450 3A4 like erythromycin, Amiodarone, protease inhibitors, or ketoconazole, the dose should be reduced to 20 mg/day.

CYP 3A4 inducers like carbamazepine, phenytoin and phenobarbitone reduce the efficacy of Vilazodone and increase in dose of the Vilazodone is required. Serotonergic syndrome has also been noted with opioid agonist drugs like Tramadol hydrochloride. Risk of bleeding with administration of Vilazodone increases with NSAIDs, Aspirin and Warfarin.^[3]

**Adverse effect profile**

In 24 human trials involving 2898 human subjects the FDA reviewed the drug in terms of clinical efficacy, adverse effects and safety concerns.^[4] The data extracted showed the efficacy of Vilazodone in treating MDD at doses of 40mg/day but also showed the need for
gradual escalation of dose to reach this target in order to minimize gastrointestinal side effects. To begin with, 10mg/day in first week followed by 20 mg/day in second week with final titration to a daily dose of 40 mg/day has been targeted.[5] The general profile of side effects was similar to that of other SSRI.[4] In an open label one year study, mean weight gain has been found 1.7 kg among observed cases in a follow up for one year. Some of the adverse effects may be explained by nocebo effect.(Table 2).

Table 2: Relative frequency and Number Needed for Harm (NNH) for common side effects of Viladozone.[6]

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>NNH value vs placebo</th>
<th>99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diarrhoea</td>
<td>6</td>
<td>5-8</td>
</tr>
<tr>
<td>2. Nausea</td>
<td>6</td>
<td>5-8</td>
</tr>
<tr>
<td>3. Vomiting</td>
<td>30</td>
<td>18-82</td>
</tr>
<tr>
<td>4. Insomnia</td>
<td>26</td>
<td>16-78</td>
</tr>
<tr>
<td>5. Sexual adverse effects</td>
<td>12</td>
<td>16-78</td>
</tr>
</tbody>
</table>

NNT for response has been found 8 (95% CI 6-16) and for remission14 (95% CI 8-55) vs placebo.

Evidence of therapeutic effects
In a trial among 410 randomly assigned patients receiving Vilazodone (n=198) vs placebo (n=199) were included for ITT (Intent to treat analysis) sample. It has been found that, Vilazodone is effective for treatment of MDD in adults and symptom relief starts from week 1 and is reasonably well tolerated in the dose of 40 mg/day.[7]

In a RDBPCT, for 8 weeks duration with an adult sample (n=481) it has been found that Vilazadone 40 mg/day was well tolerated and effective in adult patients with MDD with less weight gain.[8,9] In a one year study, Vilazodone (n=253) 40 mg/day was compared with placebo (252) compared in outpatients and there is statistically significant improvement in MADRS and CGIs scale has been documented with and the molecule has been found to be better tolerated. Approximately 83% patients have completed the study.[10] In the multicentric, 8 weeks DBPCT, Vilazodone 40 mg/day has been found to achieve remission of depressive and anxiety symptoms (as measured by HAMA and MADRS scale) with odds ratio 2.0 times higher than the comparator placebo.[11] In a study with two positive phase 3 trials as obtained by pooled data analysis the categorical improvement in depressive symptoms has been noted.[12] The open label multicentric study for one year at a dose of 40 mg/day of Vilazodone shows most frequent AEs were diarrhoeas (35.7%), nausea (31.6%) and
headache (20.0%). Most of these AEs (90%) were mild or moderate. The safety population comprised of 599 patients of which 254 patients completed 1 year of treatment. Mean weight gain was 1.7 kg in observed cases. Improved throughout the treatment in both sexes.\cite{13} It has been reported that Vilazodone may be effective in patients with Major depressive disorder who exhibit somatic and psychic subscales of HAMA 17 scale and MADRS inner tension item.\cite{14}

Though the efficacy of Vilazodone has not been established in Phase 2 trials for primary outcomes of the 17 item Hamilton Rating Scale for Depression (HAM-D 17) but has shown significant improvement in secondary outcome measures e.g CGIs and MADRS.\cite{15}

**Vilazodone in Anxiety disorders**

In a trial in GAD for 8 weeks using Sheehan Disability Scale total score for vilazodone versus placebo, there was no statistically significant difference has been found. Adverse events were reported in 60% of placebo-treated and 83% of vilazodone-treated patients. This was a positive clinical trial of 20-40 mg/day vilazodone versus placebo in the treatment of GAD.\cite{16} In a trial involving 10 healthy subjects at a single dose of Vilazodone it reduces REM sleep, increases slow wave sleep and increases wakefulness and increase time spent on REM sleep.\cite{17}

**Sexual effects of Vilazodone**

The onset of clinical effects starts within one week and there is no statistically significant sexual adverse effects noted when measured by Arizona Sexual Experience scale (ASEX). The unique feature of this study is the development of biomarker which will predict treatment response and adverse effects. The decrease in libido has been found in 3.7% population in comparison to 0.2% in placebo group. Similarly, ejaculatory delay has been seen in only 2% in Vilazodone group whereas none has been found in placebo group. The Changes in Sexual Functioning Questionnaire (CSFQ) has 36 items and measures 5 aspects of sexual functioning. In a study, the CFSQ mean score was 46.5 and 46.6 in men and 39.4 and 40.2 in women in vilazodone and placebo group respectively. After 8 weeks, mean CFSQ total score changes from baseline with improvement in vilazodone group 0.6±7.9 and in placebo group 1.8±6.4 points. The most common sexual adverse effect was loss of libido, seen in 4.7% patients on vilazodone with none in placebo group.\cite{18} Like other SSRIs, during initial few months and during change of doses, patients should be monitored for emergence of suicidal thoughts. Vilazodone should be discontinued if there is development of serotonin syndrome.
or neuroleptic malignant syndrome (NMS) during the course of it. Vilazodone is contraindicated with comcomitant administration with MAOI (monoamine oxidase inhibitor) or two weeks wash out period is required before initiation of Vilazodone after MAOI therapy because of potential drug interaction and development of cheese reaction. In a long term follow up non comparator phase III study for 52 weeks, vilazodone has significantly improved depressive symptoms from baseline. In a review with 47 PubMed articles for thirteen years, it has been established that by inhibiting SERT and by virtue of the SPARI activity in 5HT1 receptors as partial agonist Vilazodone has faster onset of action. No important changes have been found on vital signs, laboratory parameters and in EEG either. None of the trials compared with other antidepressants in two RDBPCT and one open label study of one year duration.

Table 3: Summary of outcome measures of Vilazodone.

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Level of evidence</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT RELATED EVIDENCE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction of depressive symptoms</td>
<td>Clear</td>
<td>Vilazodone is more effective than placebo and as effective as Citalopram.</td>
</tr>
<tr>
<td>Improvement of anxiety symptoms</td>
<td>Suggestive</td>
<td>Significant improvement of comorbid anxiety symptoms in depressive patients.</td>
</tr>
<tr>
<td>DISEASE ORIENTED EVIDENCE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom relief in terms of MADRS score</td>
<td>Clear</td>
<td>More effective than placebo.</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>Clear</td>
<td>More effective than placebo.</td>
</tr>
<tr>
<td>Remission after treatment</td>
<td>Clear</td>
<td>More effective than placebo.</td>
</tr>
</tbody>
</table>

**Overdose**

Overdose among 5 adults has been reviewed on a range of intake of 200 to 280 mg and serotonergic syndrome has been seen. In a 19 month girl intake of Vilazodone has been reported at a dose 37 mg/kg. A 23 month old girl (weight 11 kg) has taken the medicine at a dose of 5 mg/kg (3 Vilazodone 20 mg tablets) which is 8 times the therapeutic dose of an adult and experienced 3 episodes of GTCS with hyperreflexia and lethargy.

In 24 human trials involving 2898 human subjects the FDA reviewed the drug in terms of clinical efficacy, adverse effects and safety concerns. The precaution mentioned with packaging includes serotonin syndrome, suicidality, seizure, mania, history of bleeding,
hyponatremia and abrupt discontinuation of the medicine with contraindication of using with MAOI. The special consideration while using it should be taken with meal (otherwise it loses 50% of bioavailability if taken on empty stomach), gradual dose titration is required. No reduction of doses is required in hepatic or renal impairment. It is extensively metabolized via Cyt p450 3A4 enzyme system. With concomitant use of potent inhibitor of Cyp 450 3A4 like erythromycin, amiodarone, protease inhibitors, or ketoconazole, the dose should be reduced to 20 mg/day. In contrast to active metabolites the parent drug itself is the active one and has this unique class difference. It’s a high protin bound drug (96-99% bound to plasma protein) with terminal half-life approximately 25 hrs and steady state thus achieved in 4 days (four half-lives) with consistent dosing. Carbamazepine, Blonanserin and Vilazodone absorbed well and should be taken with food as food increases the bioavailability of the drug. Tmax of Vilazodone is approximately 4 hours, max Cmax = 156.3 ng/ml. Volume of distribution (Vd= 60.52).\[26,27\] In STAR* D trial it has been established that anxious depressed population has worse outcome and this unmet need may be addressed by vilazodone. In anxiety disorders like panic disorders, generalized anxiety disorders, social phobia the trial of monotherapy with vilazodone will be worth interesting so as in obsessive compulsive disorders.\[27\]

**Table 4: Therapeutic promises of Vilazodone.**

<table>
<thead>
<tr>
<th>Challenges in management of Depression.</th>
<th>Vilazodone is the first and only SSRI with 5HT1A receptor partial agonist activity. Unique action reveals the power of SPARI.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics.</td>
<td>Bioavailability: 72% with food. AUC may be decreased by approximately 50% in a fasting state. Metabolism: Extensively hepatic via CYP3A4 (major pathway) and 2C19 and 2D6 (minor pathways). Excretion: 1% unchanged drug in urine and 2% unchanged drug in feces. Half-life elimination: Terminal-25 hrs. Time to peak serum concentration: 4-5 hrs. Protein binding: Approximately 96-99%.</td>
</tr>
<tr>
<td>Efficacy.</td>
<td>Effective first line antidepressant, even in severely depressed patients. Fastest onset of action, superior to placebo from first week onwards and sustained throughout. Higher and sustained response and remission than placebo. Long term treatment shows continued</td>
</tr>
<tr>
<td>Selection of patients.</td>
<td>Likely to respond in those who don’t respond or tolerate SSRI/SNRI. Useful in patients who develops sexual dysfunction, weight gain or increase in blood pressure on SSRI/SNRI. Can be tried in patients who can’t tolerate or risk intervention with an atypical second generation antipsychotic due to weight gain, sedation, extrapyramidal symptoms or dyslipidemia. Therapeutic promises to be effective in MDD, GAD, OCD, Social anxiety disorder (SAD), panic disorder, PTSD (Post traumatic stress disorder), Eating disorders, Premenstrual disorders etc. [^{28,29}]</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Safety &amp; Tolerability</td>
<td>Due to lack of affinity for receptors/binding sites, unlike other psychotropic medicines, adverse effects are less. The most observed adverse effects are nausea, diarrhoea and headache which decrease with time. Fewer discontinuation rates, weight neutral and long term adverse effects are not greater than acute adverse effects. No impairment of cognition or psychomotor function, Less drug interaction, suitable for geriatric patients with comorbidities. Concurrent use of NSAID may increase the risk of bleeding. Prolonged bleeding has been seen with warfarin. MAOI should be avoided. Concomitant use of CYP 3A4 inhibitor may increase plasma concentration of Vilazodone by 50%. It’s a highly plasma protein bound and increases free concentrations of other highly protein bound drugs.</td>
</tr>
<tr>
<td>Dose.</td>
<td>Dosage forms: 10, 20 and 40 mg oral tablets. Oral: Starting dose 10 mg OD for 7 days, followed by 20 mg OD for 7 days and then the dose increased to 40 mg OD. It should be taken with food otherwise if taken without food in empty stomach, the drug concentration may decrease by 50%. If combined with CYP3A4 inhibitors, the dose of Vilazodone should be 20 mg/day.</td>
</tr>
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</table>
Table 5: Cost comparison of Vilazodone vs Citalopram in New York City.\textsuperscript{[30]}

<table>
<thead>
<tr>
<th></th>
<th>Vilazodone</th>
<th>Citalopram</th>
</tr>
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<tbody>
<tr>
<td>Packaging</td>
<td>Packaging=30 tabs</td>
<td>Packaging=30 tabs</td>
</tr>
<tr>
<td>Strength</td>
<td>Strength=20 mg</td>
<td>Strength=20 mg</td>
</tr>
<tr>
<td>Dose</td>
<td>Dose= suboptimal (optimal dose is 40 mg).</td>
<td>Dose= Optimal dose.</td>
</tr>
<tr>
<td>Cost</td>
<td>Cost= US $ 177</td>
<td>Cost= US $ 14</td>
</tr>
</tbody>
</table>

Clinical pearls

In a 22 year individual who remained seizure free over 8 years, seizure has been reported on initiation of therapy with Vilazodone at a dose 40 mg/day.\textsuperscript{[30]} In 157 healthy male and females examined, who were put on Vilazodone and there is no effect in ECG on PR, RR and QTc intervals has been seen. Vilazodone has been found to be excreted in milk.\textsuperscript{[31]} Antidepressant is in ‘dry-pipeline’ in recent years with a search of newer molecule with novel mechanism.\textsuperscript{[32]} Most of the SSRIs and some SNRIs now available in generics and they are less expensive than Vilazodone.

CONCLUSION

Despite the theoretical superiority and the claim of Vilazodone having novel dual mechanism of action, faster onset of action, more appropriate pharmacologically complete action and fewer side effects, in clinical trials and practice this has not been established as yet. Another claim of working better in depression with high anxiety or anxious depression group is also not very convincing. Vilazodone could be efficacious in non-responders of SSRI and SNRI monotherapies. The dose has to be uptitrated gradually especially to minimize gastrointestinal side effects. To begin with, 10mg/day in first week followed by 20 mg/day in second week with final titration to a daily dose of 40 mg/day has been targeted. Vilazodone is the first dual acting SSRI with SPARI activity indicated for treatment of Major depressive disorder. The molecule has been approved by US FDA and DCGI and its activity on 5HT1A receptor is believed to be responsible for lesser sexual side effects. The unique hybrid mechanism of action addresses many unmet needs. It causes less somnolence and it’s a weight neutral drug and generally very well tolerated. The most common adverse effects are diarrhoea and nausea, but it’s a class effect of SSRI and are mild to moderate and subsides after few days.

No dose adjustment is required based upon age, hepatic impairment (mild to moderate) and renal impairment. The safety of Vilazodone has not been tried in severe hepatic impairment.

Source of funding: Nil.

Conflicts of interest: None.
ACKNOWLEDGEMENT
The author is indebted to Prof Chittaranjan Andrade, Professor, NIMHANS, Bangaluru for his valuable discussion and highlighting important areas on the clinical trials of Vilazodone.

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