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Review Article

Current Status of Vilazodone

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Abstract

Vilazodone is a serotonin transporter (SERT) and a partial agonist of $HT_{1A.}$ It has been approved by food and drug administration of United States (US FDA) for the treatment of major depressive disorder (MDD) in adults. This agent is considered as a new class of drug "serotonin partial agonist and reuptake inhibitor (SPARI)" by the World Health Organization (WHO). The authors planned to review the drug by using the key word of "vilazodone" on different data base and synthesize a working theory regarding the mechanism of selective serotonin reuptake inhibitor (SSRI) mediated serotonergic neurotransmision. The review also focuses on 5-HT_{1A} autoreceptors. Due to its novel mechanism of action, initially it gave hope to the clinicians and researchers as majority of depressive patients are partial responders or treatment resistant to previously available antidepressants. But later research works suggested that the vilazodone is not much different than the drug available in market. Its side effects were found to be lower than other antidepressant but higher than placebo. It can be concluded that more comparative research between vilazodone and other antidepressant is required in making better opinion about this drug.

Keywords: Vilazodone, 5-$HT_{1A,}$ SPARI, SSRI, MDD.

INTRODUCTION

According to WHO, MDD is a leading cause of disability [1]. It is also the second leading cause of years lived with disability [2]. Introduction of drugs like monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) resulted in landscape change in the management of depression [3]. But the limitation of these drug classes were their adverse effect profiles. Limitations of TCAs are their anticholinergic effects, which also can lead to precipitation of seizures and arrhythmias in overdoses [3, 4] while MAOIs can produce edema and orthostatic hypotension [5, 6].

Shortcomings of previous antidepressants led to the need for a newer, more selective antidepressant having lesser adverse effects. By the decade of 1980, extensive researches lead to the introduction of a more selective class of antidepressants, the SSRIs. These medicines are as efficacious as MAO and TCA with better tolerability.

STAR*D trial has shown that only one third of patients remit with monotherapy in MDD. Four subsequent antidepressant trials demonstrated remission of only two third patients [7]. This indicates that there was a requirement of a novel antidepressant with a different mechanism of action [8]. US FDA approved Vilazodone (a newer SSRI) on January 2011 which have given hope to fulfill this need by its unique mechanism of action.

METHODOLOGY

We have searched articles related to vilazodone on PubMed and Cochrane data base and internet by using the key word "vilazodone". The search provided 176 medical literatures out of which 115 were human studies while 44 were related to animal models. Among them 26 were clinical trials, 53 review articles. All the studies thoroughly read by first two authors. We included all research article, review articles, case report which are informative.

Chemical structure

Vilazodone is chemically 2-benzofurancarboxamide, 5-[4- [4 (5 cyano-1H-indol-3-yl) butyl]-1-piperazinyl]-, hydrochloride (1:1). Its molecular weight is 477.99 with chemical formula $C_{26}H_{27}N_2O_2$ [9, 10].

Mechanism of action

Vilazodone binds to SERT and inhibits it in a dose dependent manner leading to an increase in serotonin levels. Serotonin levels in hippocampus and cortex of rats were found to be increased in "in vivo microdialysis" by this agent [11, 12]. It is also a partial agonist to 5- HT_{1A} receptor, which has additional antidepressant activity [13]. In MDD patients there is an alteration in expression and activity of 5-HT_{1A} receptor in hippocampus raphe nuclei and other cortical regions [14-17]. Serotonergic agent binding to full receptor along with partial receptor (5-HT_{1A}) results in inhibition of serotonin release by neurons [18]. But prolonged 5-HT_{1A} receptor stimulation results in down regulation of the same receptor which is responsible for inhibition of serotonin release [19]. This explains why serotonergic antidepressant takes several weeks for maximum symptomatic improvement [20-22]. Vilazodone desensitizes partial receptor (5-HT_{1A}) more rapidly than conventional SSRI in animal models [23].

Pharmacokinetics

Vilazodone has a half life of approximately 25 hours. Bioavailability of the drug is 72% when it is taken with meal. At steady state, vilazodone 40 mg per day with meal causes mean area under the curve ($AUC_{0\text{-}24\ hr}$) around 1,645 nghours/mL and mean maximum plasma concentration (Cmax) 156 ng/ml. When vilazodone administered with high fat containing diet, Cmax raised by 147% to 160% and AUC concentration by 64% to 85%. Vilazodone has a substantially large volume of distribution. It is highly protein bound, approximately 96% to 99% [9, 10]. It is metabolized by cytochrome P450 (CYP) 3A4, CYP2C19 and CYP2D6. In non CYP450 metabolism, carboxyl esterase plays an important role. Only a fraction of drug is excreted in feces (2%) and urine (1%) as an unchanged form. Clearance of drug is not affected in mild to moderate impairment of kidney and liver [9, 10].

Drug interaction

Precaution should be taken if vilazodone is prescribed concomitantly with other serotonergic drugs, like MAO inhibitors, serotonin norepinephrine reuptake inhibitors (SNRIs), SSRIs, buspirone, triptans, tramadol, and tryptophan containing products. If vilazodone is administered within 2 weeks of discontinuation of MAOIs, it may cause serotonin syndrome [9]. Patients who are on strong CYP3A4 inhibitors, like ketoconazole, vilazodone should not be prescribed above 20 mg/day. These inhibitors can raise vilazodone plasma concentration by 50%. There is no dose modification is required in co-administration with cimetidine, another CYP3A4, inhibitor [9].

No data is available on vilazodone plasma levels in subjects concomitantly taking CYP3A4 inducers. But these inducers have the potential to decrease the level of vilazodone. Therefore, patients who are on warfarin should be monitored closely if they have started vilazodone [9].

Contraindication and precaution

Patients who are prescribed vilazodone should be monitored for abnormal behavior worsening of the symptoms and suicidal ideation. The appearance of signs symptoms suggestive of serotonin syndrome (SS) or neuroleptic malignant syndrome (NMS) warrant discontinuation of vilazodone immediately and begin supportive treatment. One should be very cautious in patients with seizure disorder who are taking vilazodone. Co-administration with NSAID like aspirin can increase bleeding time. To avoid withdrawl symptoms it should be tapered slowly. Depressive patients may switch to mania or hypomania with vilazodone therapy. Therefore, every patient should be screened for bipolarity [9].

Dosage and administration

Vilazodone is available in three strengths 10, 20 and 40 mg. To avoid gastrointestinal side effect it should be started with 10 mg/day for a week, escalate 20 mg/day for next week before achieving 40 mg/day [9].

Adverse effect

Initially, 40 mg or lower dose of vilazodone was supposed neutral on libido. But it is reported that even 20 mg/day can affect sexual desire. So it is too early to say it safe in this regard. Till now there is no head to head trial has been conducted to compare reduction in libido.

Research finding demonstrated that about one in 14 patients taking vilazodone for eight weeks discontinued medication because of unwanted side effects, which is about twice as common as in patients taking placebo [24-26]. The most commonly reported adverse effect demonstrated in clinical trials of patients treated with vilazodone versus placebo were diarrhea (28.0%vs9.2%), nausea (23.4%vs5.1%), dizziness (8.5%vs4.6%), abnormal dreams (4.1% vs 1.2%) and insomnia (6.0%vs2.1%), vomiting (4.6%vs1.2%).[24,27] Dose titration is recommended to minimize gastrointestinal and other adverse effects.

Sexual functioning questionnaire [25] and arizona sexual experiences questionnaire [26] were applied on patients to evaluate sexual function in two different studies. Patients who had taken 8 week treatment of vilazodone, showed minimal sexual dysfunction, similar to placebo [28].

Researchers hypothesized that drug induced sexual dysfunction is minimum due to its partial agonistic activity on 5-HT_{1A} receptors. This hypothesis is supported by studies in which less SSRI induced sexual dysfunction was found, who were also taking 5-HT_{1A} receptor partial agonists (for example, buspirone

or pindolol) [29-32]. More clinical trials are needed which include head to head comparison to test this hypothesis [33].

Trials

Unpublished phase ii studies:

Five, phase II, randomized, double blind, placebo controlled (RCT) study conducted for 8 weeks, compared the efficacy of vilazodone dose ranging from 5–100 mg/day in patients of MDD fulfilling the Diagnostic criteria according to Diagnostic and Statistical Manual-IV (DSM- IV) [31, 34].

Three of those five RCTs included placebo as well as an active comparator (two used fluoxetine, 20 mg, and one citalopram, 20 mg) where as rest two did not have an active comparator. Two trials used fixed dose design, whereas the other three used flexible titration design. The primary endpoint measure in all five trials was the mean score change on the 17-item Hamilton Depression Rating Scale (HDRS -17) from baseline to the end point. None of the trials demonstrated superior outcome over placebo at its primary endpoint. Since none of the active comparators demonstrated superior efficacy over placebo, so these trials could be considered as "failed" studies. While the two studies containing only placebo are recognised as "negative" studies. However, the two fixed dose trials showed a possible treatment effect of vilazodone (20 mg/day) over placebo on its secondary outcome measure i.e. Montgomery Asberg Depression Rating Scale (MADRS). It was also observed, depression symptoms decreased vilazodone increased to 20 mg in two phase 2 trials but the observation was not found to be statistically significant.

Published studies

The clinical efficacy of vilazodone over placebo was observed in two 8 weeks, phase III, double-blind, randomized, placebo controlled trials [25, 26] in patients diagnosed with MDD according to DSM-IV-TR criteria [32]. After 8 weeks, there was a significant reduction in scores of MADRS [33] and Hamilton Depression Rating Scale (HDRS-17) [35].

In a trial, at the end of one week, a significant reduction was observed in the scores of MADRS and HDRS-17 in patients who were prescribed vilazodone compared to placebo. This finding suggested that vilazodone has a rapid onset of action [26]. In another trial, at the end of six weeks, a significant reduction was observed in scores of MADRS, in patients who were taking vilazodone compared with placebo [25].

Efficacy of vilazodone was assessed by pooling the data from both phase III trials [36]. All the patients (891) were randomized, among them, 431 were prescribed vilazodone and rest were given a placebo. At the end of 8 weeks, there was significantly greater improvement in terms of MADRS score in vilazodone group patients compared to the placebo group (level of significance was $p<0.0001$). The significant difference was also seen at the end of the first week and subsequent weeks ($p<0.01$, all weeks).Similar results were also seen for HDRS-17, Clinical Global Impression Severity of Illness (CGI-S), and Clinical Global Impression-Improvement (CGI-I) scores [37].

Another pooled data analysis confirmed the superiority of vilazodone over placebo in terms of sustained response rate. The cumulative response rate of vilazodone was significantly greater than placebo after 1 week ($p<0.05$). The time to cumulative response of vilazodone was also significantly faster compared to placebo ($p<0.0001$). Both the observation indicates that treatment with vilazodone is associated with early and persistent symptomatic improvement and response rate [38].

To evaluate the efficacy of vilazodone in MDD patients, an open label, multicenteric trial was conducted in the USA at 39 centres for 1 year. The trial included 599 patients with HDRS-17 more than 18. Only 254 (41.2%) completed the study. Vilazodone was prescribed 40 mg/day over two weeks. Its effectiveness was measured by using MADRS. At baseline, mean MADRS score was 29.9. After 8 weeks the MADRS score reduced to 11.4 and at 52 week score was found 7.1 [39].

Effect of vilazodone on 24 patients diagnosed as adult onset separation anxiety disorder (ASAD) was seen in a 12 week pilot study. The result was evaluated by an independent researcher. Results demonstrated that vilazodone may have role in treatment of ASAD [40].

An open label randomized controlled study on 60 depressive patients conducted in india, which compared vilazodone and escitalopram. The finding of the study was demonstrated that both the drug have equally efficacious. However there is little weight gain and sexual dysfunction in patients taking vilazodone which was statistically significant [41].

Results of a phase three double blind randomized placebo controlled study demonstrated that there is no statistically significant difference among vilazodone 15 mg/day, 30mg/day and placebo in terms of children's depression rating scale revised version (CDRS-R) and CGI score. There was no significant difference in term of suicidal ideation and suicidal behavior. The most common treatment emergent adverse effect was nausea, vomiting and upper abdominal pain [42].

A meta-analysis compared 16 US FDA approved antidepressant in terms of effect size. Results demonstrated venlafaxine had highest effect size followed by paroxetine. However bupropion and vilazodone had lowest effect size [43].

Black box

Vilazodone has a black box warning regarding suicidality. According to some short term studies, antidepressants have a tendency to increase suicidal thoughts and behaviour in children and young adults when compared to placebo. Hence vilazodone is not approved in children [9].

Limitations of use

One major limitation of vilazodone is its high price comparision to other SSRIs. The cost of one month vilazodone 40 mg/day is around 1000 Indian Rupees. This amount is sufficient for the supply of amitryptyline 50 mg per day for 200 days and escitalopram 10 mg per day for 120 days. Other limitations of its use are inadequate studies, scarcity of data on long term follow up. There is lack of long term studies which compare vilazodone to other antidepressants in terms of adverse effects.

Limitations of review

Not all published trials were included in this review.

CONCLUSION

Vilazodone, a FDA approved antidepressant, was particularly intended to work by inhibiting SERT like an SSRI and as a partial agonist at $5HT_{1A}$ receptors, very similar to pindolol and buspirone. Its dual mechanism of action results in quicker onset of antidepressant activity, negligible sexual side effects, and enhanced anxiolytic properties. The efficacy of vilazodone in major depressive disorder has been demonstrated in 2 large, randomized, double blind, placebo controlled trials where is have failed to produce its efficacy. In both trials patients showed significant improvement after 8 weeks. In another study, significant improvement was observed as early as a week, although this rapid time course of efficacy remains to be validated. If clinical studies support the theoretical advantages accredited to its dual mechanism of action, vilazodone has the potential of becoming a novel treatment option in the treatment of MDD. Larger and long term clinical trials are needed to assess the efficacy and safety of vilazodone therapy, because patients with acute episodes of MDD may require several months or longer of sustained pharmacological treatment.

Conflict of interest: Nil

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