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Vilazodone for the Treatment of Major Depressive Disorder: Focusing on Its Clinical Studies and Mechanism of Action

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We tried to review and update clinical and preclinical studies evaluating vilazodone's role as an antidepressant for patients with major depressive disorder (MDD). In terms of its mechanism of actions, we sought to elaborate them mainly through preclinical animal studies. A data search was conducted in November 1, 2013, using the key terms "vilazodone" or "Viibryd," in PubMed and Medline databases. All published and unpublished studies are included and citations from publications were also reviewed for additional references. Five unpublished, phase-II and two pivotal published phase-III clinical trials with nearly identical design (8-week, double-blind, randomized, and placebo-controlled) investigated efficacy of vilazodone, were found for the treatment of patients with MDD. Two post-hoc studies and one long-term open study were also included. Data were thoroughly reviewed to incorporate the pharmacology, action mechanism, efficacy and safety for the vilazodone in the treatment of major depressive disorder. Vilazodone is an antidepressant with novel mechanism of action because its chemical structure is unrelated to conventional antidepressant, and it has a selective serotonin (5-HT) reuptake inhibitor and 5-HT1A receptor partial agonist profile. Vilazodone is an effective and safe treatment option with its novel action mechanisms for patients with depression. Its putative benefits compared with other antidepressants must be thoroughly studied in adequately-powered and well-designed future clinical trials.
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Key Words Vilazodone, Antidepressant, Novel mechanism, Efficacy, Safety.

INTRODUCTION

Major depressive disorder (MDD) is a chronic, recurrent and serious mental illness, and it is the third leading cause of moderate to severe disability and of disease burden worldwide.[1,2] Despite numerous antidepressants available, many patients with depression do not achieve adequate response rendering needs for novel antidepressants with different mechanism of actions.[3] Thus, diverse drugs with novel mechanism of action (not related to monoamine) were tested because studies raise limitations to the current monoamine theory.[4] However, the mechanism of actions of U.S. Food and Drug Administration (FDA) approved antidepressants still mainly resides in targeting monoamines.[5,6] Remission and response rates of depression may have been improved by a polypharmacy strategy including combination and augmentation.[7,8] However, augmentation and combination therapy also increased concerns about adverse events (AE) and healthcare cost burden.[9,10] Therapeutic lag between antidepressant administration and onset of clinical improvement is another big obstacle. Therefore, additional novel antidepressants may offer clinicians additional treatment options for enhancing symptom control, enhancing tolerability and safety, and hastening onset of action.

The vilazodone is a new antidepressant that was approved in 2011 for treatment of major depressive disorder (MDD).[11] Vilazodone is an antidepressant with novel mechanism of action because its chemical structure is unrelated to conventional antidepressant, and it has a selective serotonin (5-HT) reuptake inhibitor and 5-HT_{1A} receptor partial agonist profile.[12] Because of its unique action mechanism, indirect evidence enabled clinicians to speculate that vilazodone may potentially

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provide faster treatment onset along with enhanced remission and response rates with lower AE risks than preexisting antidepressants.[13-15] Preclinical studies and indirect evidences did suggest that vilazodone might result in faster treatment onset than conventional selective serotonin reuptake inhibitors (SSRIs),[16,17] but no direct comparative trials confirmed vilazodone's superiority over other antidepressants.

The purpose of this article is to review and update currently available clinical and preclinical studies evaluating vilazodone's role as an antidepressant including newly published papers, since former review article[18] gave some preliminarily informative data. The putative mechanism of actions incorporating mainly through preclinical animal studies, more detailed information on unpublished data, post-hoc analysis, long-term treatment data, practice points and future research directions are newly included and more elaborated in this review.

DATE SOURCE

A data search was conducted in November 1, 2013, using the key terms "vilazodone" or "Viibryd," in PubMed and Medline databases. The studies searched were verified for publication in English peer-reviewed journals, but date constraints were not utilized. Reference lists from identified articles and reviews were also used to find additional studies. Http://www.clinicaltrials.gov and drug-approval process were used to assess information regarding phase II trials, and packaging information was extracted online from http://www.fda.gov. Literature search and verification were handled first by one of the authors (SMW) and then independently reassessed by (CUP and SJL). This article aimed to provide review of vilazodone by focusing on its clinical implications and mechanisms of action for treatment of depression. Thus, all relevant studies meeting purpose of the present review were selected based on the consensus among all authors.

GENERAL INFORMATION

The summary of general information of vilazodone, refers to data in human, is provided in Table 1. Activity of vilazodone is primarily to its parent drug, and its pharmacokinetics is dose proportional from 5 to 80 mg.[11] Since primary clearance route of vilazodone is hepatic (CYP3A4), vilazodone dosage should be reduced to 20 mg/d when used in combination with a strong CYP3A4 inhibitor (ketoconazole). Vilazodone's recommended daily dosage is 40 mg/d, but gradual dosage increment from 10 mg/d is needed in order to reduce risk of developing gastrointestinal discomfort. No dose adjustment is required for age, gender, and mild to moderate renal or hepatic dysfunction, but its use in severe renal or hepatic dysfunction has not been studied.[11,19]

MECHANISM OF ACTIONS

Vilazodone has unique mechanism of action because it not only potently and selectively inhibits serotonin (5-HT) reuptake (IC_{50}=1.6 nM) but also selectively binds to 5-HT1A receptors with high affinity (IC_{50}=2.1 nM). Vilazodone's affinity is much higher for the 5-HT reuptake site (Ki=0.1 nM) than for the norepinephrine (Ki=56 nM) or for the dopamine (Ki=37 nM).[20] Therefore, vilazodone is considered as a selective serotonin reuptake inhibitor plus a 5-HT_{1A} partial agonist.[21,22] Before elaborating mechanism of action of vilazodone, it is first important to understand complicated role of 5-HT_{1A} receptors in depression.

Cumulative evidence suggests that pre- and postsynaptic $5HT_{1A}$ receptors have opposite role in depression.[23] Pre-synaptic $5HT_{1A}$ receptors located on raphe nuclei are autoreceptors, so activating these pre-synaptic $5HT_{1A}$ receptors could decreases the firing and secretion of 5-HT.[24,25] In contrast, postsynaptic receptors located on the hippocampus may activate firing and secretion of 5-HT.[26] When an antidepressant (i.e., SSRI) is administered acutely, it results in increase of extraneuronal 5-HT level. However, this increase of 5-HT is immediately counteracted by neuronal negative feedback mechanisms mediated by 5-HT_{1A} autoreceptors (Figure 1).[27] Chronic stimulation of $5HT_{1A}$ receptors (via continuous antidepres-

Table 1. General information of vilazodone

Pharmacokinetics	
C_{max} (ng/mL)	156
T_{max} (h)	4–5
t½ (h)	25
Absolute Bioavailability with food (%)	72
Protein binding (%)	96–99
Time to steady state concentration (days)	3
Major metabolism	Hepatic (CYP 3A4)
Dosing and administration	
Recommended daily dose	40 mg/day taken with food
Recommended titration schedule	
1st week	10 mg/day
2nd week	20 mg/day
3rd week	40 mg/day
Category	C
Use in child	Not established

C_{max}: maximum plasma vilazodone concentration, t½: terminal elimination half-life, T_{max}: time to C_{max}

sant) may result in desensitization of pre-synaptic autoreceptor but not the postsynaptic receptors.[28,29] Efficacy of the autoreceptor-mediated negative feedback will be reduced, enabling a normalization of 5-HT release and a greater activation of postsynaptic 5-HT receptors result in improvement of depression symptoms.[23] Thus, negative feedback mechanism described above is speculated to play major role in the delayed action of antidepressants because it takes time to overcome the autoreceptor-mediated serotonin inhibition and 5-HT_{1A} autoreceptor down-regulation with SSRI.[30] Desensitization of the autoreceptors before increasing extracellular serotonin concentration is thought to be important in determining the fast onset of antidepressants.[31,32]

In this regard, vilazodone may cause faster and larger desensitization of 5-HT_{1A} autoreceptors without causing excess activation of 5-HT_{1A} autoreceptor-mediated serotonin inhibition by acting only as a partial agonist at these receptors.[33,34] Synergistic with its SSRI property, vilazodone would yield even more serotonin release by lowering negative feedback mechanisms mediated by 5-HT_{1A} autoreceptors and increasing stimulation of 5-HT_{1A} postsynaptic receptors (Figure 2).[35,36]

Animal studies have supported this speculation suggesting that vilazodone may have a more rapid treatment onset than SSRIs due to more robust serotonergic actions.[16,17,37] More importantly, recent electrophysiological study showed that vilazodone has more rapid 5-HT_{1A} autoreceptor inhibition action than other SSRIs.[38] The study compared effect of vilazodone with two SSRIs (fluoxetine and paroxetine) on the sensitivity of 5-HT_{1A} autoreceptors in the dorsal raphe nucleus (DRN) of rats. The 5-HT_{1A} receptor agonist (±) 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT) was used as a pharmacologic probe to assess changes in 5-HT_{1A} autoreceptor sensitivity. A decrease in 5-HT_{1A} autoreceptor sensitivity was measured as a significant increase in the inhibition of firing (ID_{50}) of 8-OH-DPAT in drug-treated (compared with vehicle-treated) animals. The results showed that both acute and subchronic vilazodone, but not fluoxetine and paroxetine, administration significantly increased the ID_{50} value of 8-OH-DPAT.[38] The study further suggested that this effect could be due to desensitization of 5-HT_{1A} autoreceptors rather than ascribed to vilazodone's 5-HT reuptake inhibiting properties. However, no head-to-head clinical trials have been conducted to confirm that vilazodone has faster treatment onset than other antidepressants such as SSRIs and SNRIs.[38]

CLINICAL EVIDENCE

Efficacy from clinical trials

Unpublished phase II studies

Five unpublished, phase II trials with nearly identical designs (8-week, double-blind, randomized, and placebo-controlled) investigated efficacy of vilazodone 5−100 mg/d in patients meeting Diagnostic and Statistical Manual of Mental Disorder IV criteria for MDD (Table 2).[20,39] Among them, three studies included both placebo and active comparator (trials

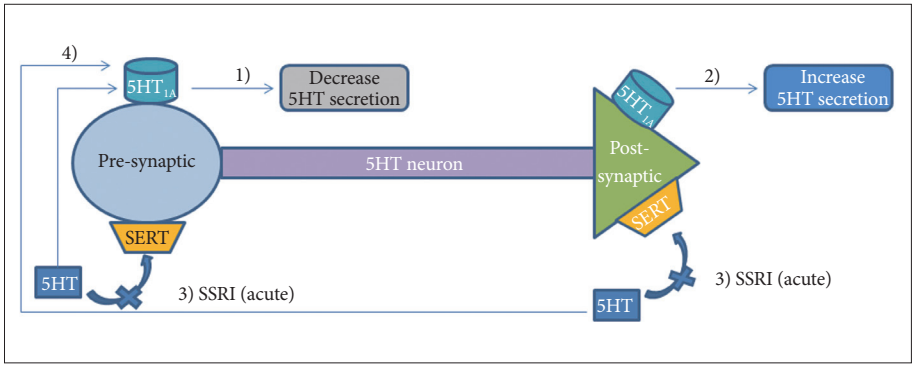

Fig 1. Opposite role of pre- and postsynaptic $5HT_{1A}$ receptors in depression. 1) Activation of pre-synaptic $5HT_{1A}$ receptors, autoreceptors, decrease the firing and secretion of 5-HT, where as 2) activation of post-synaptic $5HT_{1A}$ receptors increase firing and secretion of 5HT, 3) Acute SSRI administration results in net increase of extracellular 5HT, 4) which is immediately counteracted by neuronal negative feedback mechanisms mediated by 5-HT_{1A} autoreceptors causing therapeutic lag of SSRI. 5HT: serotonin, SERT: serotonin transporter.

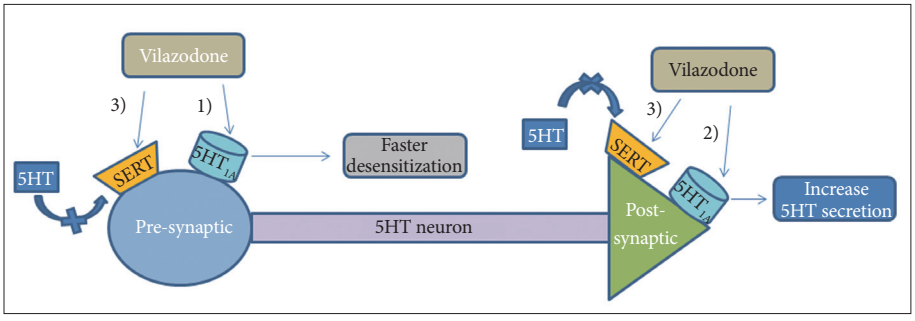

Fig 2. Vilazodone's mechanism of action. By acting only as a partial agonist at 5-HT_{1A} autoreceptors, vilazodone may more rapidly desensitize 5-HT_{1A} autoreceptors without causing excess activation of 5-HT_{1A} autoreceptor-mediated serotonin inhibition. In 5-HT_{1A} postsynaptic receptors, vilazodone will enhance 5-HT. Synergistic with its SSRI properties, vilazodone would yield even more serotonin release. 5HT: serotonin, SERT: serotonin transporter, SSRI: selective serotonin reuptake inhibitor.

Table 2. Summary of unpublished clinical (Phase II) trials of vilazodone in patients with depression

Study	Duration	Design	Daily dose (mg/d)	N	Primary outcome			Efficacy results
					Measure	Baseline mean (SD)	Change* (SD)	
244	8 weeks	RCT	VLD (20−100)	86	HDS-17	23.4 (2.9)	-8.9 (0.8)	No significant difference
			FOX (20)	89		24.4 (3.2)	-9.5 (0.8)	
			PBO	95		24.0 (3.1)	-9.6 (0.8)	
245	8 weeks	RCT	VLD (10−20)	104	HDS-17	23.8 (3.0)	-9.7 (0.7)	No significant difference
			VLD (40−60)	97		23.9 (3.1)	-10.5 (0.8)	
			VLD (80−100)	93		23.5 (3.0)	-8.6 (0.8)	
			FOX (20)	92		23.5 (2.3)	-11.1 (0.8)	
			PBO	99		23.4 (2.8)	-10.2 (0.8)	
246	8 weeks	RCT	VLD (10)	120	HDS-17	23.8 (3.1)	-10.8 (0.7)	No significant difference
			VLD (20)	123		23.7 (3.1)	-11.1 (0.7)	
			CTAM (20)	117		23.1 (2.6)	-10.9 (0.7)	
			PBO	129		23.3 (2.8)	-10.2 (0.7)	
247	8 weeks	RCT	VLD (5−20)	109	HDS-17	23.3 (2.7)	-10.7 (0.7)	No significant difference
			PBO	111		23.5 (2.5)	-9.7 (0.7)	
248	8 weeks	RCT	VLD (5)	140	HDS-17	24.0 (3.0)	-11.0 (0.6)	No significant difference
			VLD (10)	133		24.5 (3.3)	-12.8 (0.6)	
			VLD (20)	132		24.3 (3.0)	-11.7 (0.6)	
			PBO	128		23.7 (2.9)	-11.5 (0.7)	

*least-square mean change from baseline to end-point (week 8). CTAM: citalopram, FOX: fluoxetine, HDS-17: 17 item-hamilton depression rating scale, RCT: randomized, double-blind, placebo controlled, PBO: placebo, VLD: vilazodone

244−246), where as other two (trials 247 and 248) included placebo only. Moreover, 2 (trials 246 and 248) trials used fixed-dose design, and the other three (trials 244, 245, and 247) used flexible-titration design. All five trials used mean score change on the 17-item Hamilton Depression Rating Scale (HDS-17) from baseline to the endpoint as their primary endpoint measures. All five trials failed to demonstrate superior outcome over placebo at its primary endpoint. Since none of the active comparators showed superior efficacy compared with placebo, the three trials containing active comparator (trials 244−246) could be recognized as "failed" studies. Those two studies not containing active comparator could be recognized as "negative" studies. However, the two fixed-dose trials (trials 246 and 248) showed a possible treatment effect of vilazodone (20 mg/day) over placebo on its secondary outcome measure, Montgomery Asberg Depression Rating Scale (MADRS). More importantly, depression symptoms tended to decrease as daily dose of vilazodone increased to 20 mg in these two phase 2 trials (trial 246, p=0.12 and 0.06 for vilazodone 10 mg and 20 mg respectively; trial 248, p=0.73, 0.12, and 0.06 for vilazodone 5 mg, 10 mg, and 20 mg respectively).

Published clinical studies

The pivotal phase III trials used for the approval of vilazodone in treatment of MDD comprised of two 8-week, randomized, double-blind, placebo-controlled studies.[15,40] Key inclusion criteria in both studies were patients having current MDD episode of ≥4 weeks and <2 years. They were required to have a HDS-17 score ≥22 and a HDS-17 item depressed mood score ≥1. Vilazodone was initiated with 10 mg/d, and dosage was doubled every week, which was titrated to 40 mg/d from week 3 until end of the trial. Patients not tolerating 40 mg/d were allowed to reduce the dosage to 20 mg/d. MADRS, HDS-17, Hamilton Anxiety Rating Scale (HAM-A), and Clinical Global Impression-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales were used to measure efficacy. Among them, mean change in MADRS score from baseline to the end of treatment (week 8) was defined as the primary efficacy endpoint.

The first study investigated the efficacy and tolerability of vilazodone in 410 patients [intent-to-treat (ITT) analysis, vilazodone n=198 and placebo n=199], aged 18 to 65, with MDD.[40] The results showed that vilazodone group showed significant superior efficacy over placebo group in mean changes on the MADRS, HDS-17, CGI-I, CGI-S, and HAM-A total scores from baseline to the end of treatment. Notably significant improvements on the MADRS and HAM-D-17 were recorded from week 1. The second study comprised of 481 patients with MDD (ITT, vilazodone n=231 and placebo n=232) aged 18 to 70. Consistent with the results from the first study, vilazodone showed superior outcome in depressive symptoms evidenced by mean changes in the MADRS, HDS-17, CGI-I, CGI-S, and HAM-A total scores.[15]

To assess the efficacy of vilazodone across a range of symp-

Table 3. Summary of published clinical trials of investigating efficacy of vilazodone in patients with depression

Study	Duration	Design	Daily dose (mg/d)	N†	Primary outcome			Other efficacy results
					Measure	Baseline mean (SD)	Change‡ (SD)	
Phase III (pivotal) trials								
Rickels et al.[40]	8 weeks	RCT	VLD (40)	198	MADRS	30.8 (3.9)	-12.9 (0.8)**	VLD>PBO in HDS-17*, CGI-I**, CGI-S**, and HAM-A*
			PBO	199		30.7 (3.9)	-9.6 (0.8)	(Improvements on MADRS & HDS-17 noted from week 1)
Khan et al.[15]	8 weeks	RCT	VLD (40)	231	MADRS	31.9 (3.5)	-13.3 (0.9)**	VLD>PBO in HDS-17*, CGI-I**, CGI-S**, and HAM-A*
			PBO	232		32.0 (3.6)	-10.8 (0.9)	
Post hoc or pooled analyses of two pivotal trials								
Khan et al.[14]	8 weeks	Pooled	VLD (40)	431	MADRS	31.4 (3.7)	-13.0 (0.6)***	VLD>PBO in HDS-17**, CGI-I***, CGI-S***, HAM-A**
		analysis¶	PBO	432		31.3 (3.8)	-10.3 (0.6)	
Jain et al.[13]	8 weeks	Post hoc¶	VLD (40)	431	MADRS	N	N	VLD>PBO in response rate***,††, sustained response**,‡‡ rate**,‡‡, and sustained response+MADRS <12**
			PBO	432	response§			
Open label studies								
Robinson et al.[41]	1 year	Open label	VLD (40)	599‖	MADRS	29.9 (4.5)	-21.7 (N)	Statistical significance not provided

*p<0.05, **p<0.01, ***p<0.001, †number of total intent-to-treat patients, ‡least-square mean change from baseline to end-point (week 8), §>50% reduction in baseline score at week 8 ‖safety population, ¶studies included Khan et al.[15] and Rickels et al.,[40] ††rate of >50% reduction in baseline MADRS total score at week 8, ‡‡rate of >50% reduction in baseline MADRS total score at last two study visits. CGI-I: Clinical Global Impressions-Improvement Scale, CGI-S: Clinical Global Impressions-Severity of Illness Scale, HAM-A: Hamilton Rating Scale for Anxiety, HDS-17: 17-item Hamilton Rating Scale for Depression, MADRS: Montgomery-Asberg Depression Rating Scale, N: not applicable, RCT: randomized, double-blind, placebo controlled, PBO: placebo, SD: standard deviation, SE: standard error, VLD: vilazodone

toms and severities of depression, data from these two pivotal phase III trials were pooled for analysis.[14] A total of 891 patients were randomized to receive either vilazodone or placebo (ITT, vilazodone n=431 and placebo n=432). Evaluation of change from baseline to week-8 in MADRS total score as well as change in HDS-17, HAM-A, CGI-S, and CGI-I scores were used to assess vilazodone's efficacy. The results showed that least squares mean improvement from baseline to week-8 in MADRS was significantly greater for vilazodone group compared with placebo group (p<0.0001). Moreover, the statistically significant differences were observed from week 1 throughout double-blind treatment (p<0.01, all weeks). Similar trends were also observed for HDS-17, CGI-S, and CGI-I scores, but significant improvement for HAM-A was observed from week.[6]

More recently, a post hoc analyses on pooled data from the two pivotal phase III trials were conducted to retrospectively examine the timing of depressive symptom improvement in patients treated with vilazodone.[13] Main efficacy measures included response rate (rate of >50% reduction in baseline MADRS total score at week 8), sustained response rate (rate of >50% reduction in baseline MADRS total score at last two study visits), and rate of sustained response+MADRS score <12 (>50% reduction in baseline MADRS score and MADRS score <12 at the last two study visits). The results showed that vilazodone was superior to placebo in response rate, sustained response rate, and rate of sustained response+MADRS <12. In addition, cumulative response rate was significantly greater for vilazodone than for placebo from week 1 (p<0.05), and the time to cumulative response was significantly faster for vilazodone compared with placebo (p<0.0001). Thus, study suggested that vilazodone treatment might be associated with early and persistent symptomatic improvement and response rate.

A 1-year, open-label, multicenter trial conducted at 39 US centers investigated the long-term efficacy of vilazodone in patients with MDD.[41] The study consisted of 599 patients (safety population) with a HDS-17 score ≥18, and 254 (41.2%) patients completed the entire study. Vilazodone was titrated to 40 mg/day over 2 weeks, and its effectiveness was measured primarily using MADRS. The mean MADRS total scores improved continuously from 29.9 at baseline to 11.4 at week 8 and 7.1 at week 52, but statistical significance was not provided.

The outcome summary of these clinical studies is presented in Table 3.

SAFETY

The 1-year, open-label, multicenter trial showed that the most frequent AE were diarrhea (35.7%), nausea (31.6%), and headache (20.0%).[41] More importantly, 95% of these AE were

mild to moderate. AE leading to discontinuation occurred in 124 patients (20.7%), and the most frequent causes were nausea (n=8, 1.3%) and diarrhea (n=7, 1.2%).[33] Serious adverse events (SAEs) were reported in 23 patients, but most of them were judged to be not related with vilazodone. Pooled analysis of phase II studies suggest that the most common adverse events (AE) of vilazodone, which occurred in ≥5% of patients with at least twice the frequency of placebo, include nausea (22.3% vs. 7.2%), dizziness (16.5% vs. 3.3%), diarrhea (15.5% vs. 6.1%), insomnia (11.1% vs. 5.4%), fatigue (8.7% vs. 3.0%), vomiting (6.8% vs. 1.1%), and lethargy (6.8% vs. 0.5%).[42] The most common AEs of vilazodone in a pooled analysis of the two pivotal phase III trials (vilazodone n=436 and placebo n=433) were diarrhea (28.0% vs. 9.2% in placebo), nausea (23.4% vs. 5.1% in placebo), headache (13.4% vs. 12.0% in placebo), dizziness (8.5% vs. 4.6% in placebo), dry mouth (8.0% vs. 5.1% in placebo), and insomnia (6.0% vs. 2.1% in placebo).[11,39] Moreover, discontinuation rates due to AEs for vilazodone and placebo were 7.1% and 3.2%, respectively.

As noted above, insomnia is one of the important adverse effects caused by vilazodone. Its effect on sleep was specifically investigated via analyzing and electroencephalogram (EEG) patterns in a randomized crossover study with 10 healthy young men.[43] Subjects received either a single dose of 20 mg/day vilazodone or placebo. The results showed that total sleep time and wakefulness after sleep onset was significantly lower in vilazodone group than in control group (for both $p<0.01$). Rapid eye movement almost totally disappeared in patients receiving vilazodone. Moreover, increases in slow-wave sleep and EEG delta power were noted in the first and third trimesters of the night resembling 5-HT_{1A} agonist actions,[44,45] and more wakefulness was recorded in the second and third trimesters of the night resembling SSRI actions.[46] This study suggest that vilazodone might result in sleep disturbances even at lower than therapeutic dosages.

The cardiac safety of vilazodone has been shown in a recent phase I, randomized, double-blind, placebo- and active-controlled, 3-arm, parallel study.[47] 157 healthy subjects were randomized to receive placebo (n=45), moxifloxacin 400 mg (n=46), or vilazodone 20−80 mg (n=66). Electrocardiogram (ECG) assessments were conducted, and the results showed that vilazodone had no significant effect on cardiac repolarization, heart rate, PR or QRS interval duration, and ECG morphology.

Studies suggest that vilazodone might have lower likelihood of causing weight gain. Patients treated with vilazodone in the two pivotal trials did not show statistically significant weight gain,[15,40] and the mean weight increase in patients treated with vilazodone was 1.7 kg in the long-term study.[41]

Since postsynaptic 5-HT_{1A} receptor actions may diminish sexual dysfunction,[48,49] vilazodone was speculated to not only have lower risk of causing sexual side effect but also improve depression related sexual dysfunctions.[36,50] A recent study by Clayton et al.[51] sought to summarize effects of vilazodone on sexual function in patients with MDD by obtaining data from two pivotal clinical trials and one open label long-term study.[15,40,41] Sexual function was assessed by analyzing changes from baseline to end of treatment using Arizona Sexual Experience Scale (ASEX) or Changes in Sexual Functioning Questionnaire (CSFQ). The result, which combined data from three studies, showed that sexual dysfunction was highly prevalent at baseline (50% in men, 68% in women; data not shown), but it declined in both vilazodone and placebo groups during the treatment period. Two groups did not statistically differ in change from baseline to end of treatment in sexual function score (both ASEX and CSFQ). However, the percentage of patients reporting at least one sexual-function-related treatment emergent adverse events was statistically higher in the vilazodone (8.0%) group than in the placebo (0.9%) group ($p<0.001$) in the two pivotal trials. Since a meta-analysis revealed that treatment-emergent sexual dysfunction in the active SSRIs ranged from 25.8% (fluvoxamine) to 80.3% (sertraline),[52] Clayton et al.[51] argued that rates of treatment-emergent sexual dysfunction observed in patients with vilazodone are relatively low and closer to that of placebo.

These evidences suggest that vilazodone is generally safe and well tolerated. However, more severe toxicity of vilazodone from accidental overdose was recently noted via case report.[53] A previously healthy 23-month-old child weighing 11 kg started to show tonic-clonic type seizure approximately 2 hours after unwitnessed ingestion of up to three 20-mg vilazodone tablets. The patient fully recovered 24 hours after the initial ingestion, but she was under intensive medical care including intubation.

PRACTICE POINTS

Vilazodone, a novel antidepressant having simultaneous action on 5-HT reuptake inhibition and 5-HT_{1A} partial agonist, has extended treatment options for patients suffering from MDD. Its clinical efficacy in patients with depression was investigated in 7 RCTs. Five phase II trials failed to distinguish vilazodone from placebo in treatment of MDD.[20,39] Only two-pivotal phase III randomized, double-blind, placebo-controlled studies showed its benefit and these two studies formed the basis of approval for vilazodone in treatment of MDD.[15,40] Post-hoc and pooled analyses of these pivotal studies further showed its efficacy, and its longer term efficacy and safety were demonstrated by an open label trial.[13,14,41] Number needed to treat (NNT) and number needed to harm (NNH) are impor-

tant concepts enabling comparison of two medications in terms of benefits and risks for the treatment of MDD. Based on the two pivotal clinical trials,[15,40] NNT values vs. placebo for response and remission were 8 (95% CI 6−16) and 14 (95% CI 8−55) respectively.[50] The most commonly encountered AEs, diarrhea, nausea, vomiting and insomnia, when presented using NNH values vs. placebo are 6 (95%, CI 5−8), 6 (95% CI 5−8), 30 (95% CI 18−82) and 26 (95% CI 16−78), respectively.[50]

No studies conducted so far have directly shown superiority of vilazodone over other antidepressants. However, its potential advantage over other antidepressants could be speculated from its distinctive mechanism of action and clinical and preclinical studies. Vilazodone's partial agonist actions in both presynaptic and postsynaptic 5-HT_{1A} receptors may overcome the chronological lag observed in other antidepressants.[23,30] This putative benefit was demonstrated in a recent electrophysiological animal study.[38] In line with preclinical findings, the two pivotal trials, a pooled analysis, and a post-hoc study also showed that significant improvements in depressive symptoms were noted within 1 week after vilazodone administration.[13,14,40] However, more rapid onset of vilazodone should be interpreted with caution because the study did not have an active comparator. Moreover, such rapid effect of vilazodone was not replicated in the subsequent trial, and the effect size was also not large enough to be translated into clinical practice. Because of its postsynaptic 5-HT_{1A} receptor actions, vilazodone may have lower risk of causing sexual side effect than other conventional antidepressants.[51] The lower likelihood of vilazodone causing weight gain and cardiac toxicity compared to other antidepressants may be another potential benefit. In contrast, certain AEs, such as diarrhea, nausea, headache, dizziness, dry mouth, and insomnia, may require clinical attention in clinical practice.[50] A decrease in REM and increases in wakefulness have been noted with vilazodone indicating that vilazodone could result in sleep disturbances even at lower than therapeutic dosages.[43] More severe toxicity of vilazodone, seizure, was noted in a child who presumably took 60mg of vilazodone.

FUTURE PERSPECTIVES AND CONCLUSION

First of all, although vilazodone's longer term effectiveness and safety have been demonstrated in one open label trial, more well-controlled trials are needed especially to confirm its longer term efficacy in preventing relapse. Its potential advantage in providing more rapid onset of action in MDD has been thoroughly discussed, but only 1 RCT along with a pooled analysis and a post-hoc study suggested this possibility. Thus, direct head-to-head studies should be conducted to investigate this putative benefit. A 5-HT_{1A} partial agonist, buspirone, has proven efficacy for treating anxiety disorders, especially generalized anxiety disorder (GAD).[54] SSRI and SNRIs also are effective in GAD.[55] Due to its dual mechanism of actions, both of which have been found useful in GAD, vilazodone may be effective in patients with GAD (with or without MDD). Thus, this speculation should also be verified via future studies. Augmenting non-antidepressants (i.e., atypical antipsychotics, mood stabilizers, anxiolytics, and others) is one of treatment options in patient showing partial or inadequate response to current antidepressant[56,57] and buspirone is an important option as an augmenting agent.[54] In this respect, vilazodone was considered to be more effective in these patients with treatment-refractory depression because it may provide enhanced effect without increasing the AE burden due to polypharmacy.[36] Accumulative evidences gathered from studies are necessary to support such a potential benefit.

In conclusion, vilazodone is an effective and safe treatment option with novel action mechanisms for patients with depression. Its putative benefits compared with other antidepressants must be thoroughly studied in adequately-powered and well-designed future clinical trials. Moreover, if its superior clinically efficacy, especially tolerability, over SSRI+buspirone is proved via well controlled studies, vilazodone will no doubt be one of the most important options for patients not only with MDD but also for anxiety disorders.

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