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REVIEW ARTICLE

A review of current evidence for vilazodone in major depressive disorder

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Abstract

Objectives. This review is to inform clinicians of currently available data on vilazodone for treating patients with major depressive disorder (MDD), focusing on its differential action mechanism and extended clinical utility. *Methods.* A data search was conducted in June 2012 using the PubMed/MEDLINE/relevant clinical trial databases with the key terms "vilazodone" or "Viibryd." *Results.* The efficacy, safety, and tolerability of vilazodone have been demonstrated in two pivotal 8-week, randomized, double-blinded, placebo-controlled studies. Certain pharmacological characteristics of vilazodone were observed, including early onset of action, fewer sexual side effects, the absence of known cardiac toxicity, and minimal effect on weight gain, that may provide potential clinical advantages compared with currently available antidepressants. However, such possibilities should be replicated and confirmed in more well-designed and adequately powered clinical trials. Vilazodone requires dose titration up to 2 weeks to reach a target dose of 40 mg/d due to high rate of gastrointestinal side effects. No direct comparative studies with other antidepressants are currently available to confirm the aforementioned potential clinical utility. *Conclusion.* Vilazodone is a newer antidepressant possessing different action mechanisms compared to currently available antidepressants but whether it has superiority to other class of antidepressants in terms of efficacy and safety should still warrant further evaluation through more well-controlled and direct comparison clinical trials.

Key words: Vilazodone, action mechanism, antidepressant, major depressive disorder

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Introduction

Major depressive disorder (MDD) is a serious illness resulting in functional disability, decrease in quality of life, and increase in healthcare costs (Egede 2007; Jo et al. 2011). Although a large array of antidepressants with differential mechanisms of action are currently available, many patients are not adequately treated and do not achieve proper treatment outcomes such as functional recovery (Kocsis et al. 2009). Delayed onset of action, intolerable side effects, and low remission rates are some of the important limitations of currently marketed antidepressants (Trivedi et al. 2006; Bech et al. 2000). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial indicated that only 47% of patients receiving the selective serotonin reuptake inhibitor (SSRI) citalopram showed a clinical response (Trivedi et al. 2006). Although remission and response rates, including treatment-resistant depression (TRD), may be improved by a polypharmacy strategy (Trivedi et al. 2006; Barowsky and Schwartz 2006; Blier et al. 2010; Rush et al. 2006), antidepressant-related prevailing adverse events (AEs) such as sexual dysfunction and weight gain are still challenging in clinical practice. Atypical antipsychotics such as aripiprazole, quetiapine, and olanzapine have been recently FDA-approved for the treatment of MDD, enabling clinicians to diversify treatment options to enhance treatment outcomes (Berman et al. 2007; Marcus et al. 2008; Bauer et al. 2009; Thase et al. 2007). However, augmentation with atypical antipsychotics also increases concerns about AEs and healthcare cost burden (Nelson and Papakostas 2009; Taneja et al. 2012). Hence, additional novel antidepressants may offer clinicians additional treatment options for enhancing symptom control, hastening onset of action, and enhancing tolerability and safety.

The indolalkylamine vilazodone is a new antidepressant that was approved in 2011 for treating MDD. It is a novel antidepressant with a distinctive mechanism of action, as it combines the properties of an SSRI with those of a 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) partial agonist (Bartoszyk et al. 1997; Hughes et al. 2005). Indirect evidence suggests that vilazodone may potentially provide faster treatment onset, enhanced remission and response rates, and lower AE profiles (particularly lower sexual dysfunction and weight gain) when compared with those of preexisting antidepressants due to its unique dual mechanism of action (Trivedi et al. 2006; Othmer and Othmer 1987; Artigas et al. 1994; Bouwer and Stein 1997). Animal studies support a potential advantage of vilazodone for faster treatment onset compared with that of SSRIs (Duxon et al. 2000; Hogg and Dalvi 2004).

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However, no direct comparative clinical trials showing superiority of vilazodone over other antidepressants have been conducted. Therefore, an exact comparison between vilazodone and other antidepressants regarding efficacy and tolerability is not available at this point.

This article summarizes the currently available evidence for the differential effects, mechanisms of action, drug–drug interactions, AE profiles, and possibility of extended utility of vilazodone as a newer antidepressant.

Data search

A data search was conducted in June 2012 using the PubMed and MEDLINE databases with the key terms "vilazodone" and "Viibryd." The studies searched were verified for publication in peer-reviewed journals, and neither date nor language constraints were utilized. Information regarding phase II trials was assessed from http://www.clinicaltrials.gov, and drug-approval process and packaging information were extracted online from http://www.fda.gov. The package label (Forest Pharmaceuticals I 2012) was also included in this review. One of the authors (SMW) conducted the first data search and verification, which was independently reassessed by the other authors (CUP and SJL).

This article is a narrative review focusing on the clinical implications and mechanisms of action of vilazodone for treating MDD. All relevant studies meeting the scope of the present review based on consensus among all authors were selected.

Mechanism of action

Vilazodone is the first in a new class of chemical entities exhibiting a dual-action mechanism for treating MDD. Vilazodone not only potently and selectively inhibits serotonin 5-HT reuptake ($IC_{50} = 1.6$ nM), but also selectively binds to 5-HT_{1A} receptors with high affinity ($IC_{50} = 2.1$ nM) (Administration 2012). The affinity of vilazodone is much higher for the 5-HT reuptake site with a K_i of 0.1 nM compared with that of norepinephrine ($K_i = 56$ nM) or dopamine reuptake sites ($K_i = 37$ nM). Therefore, vilazodone is an SRI plus a 5-HT_{1A} partial agonist (Bartoszyk et al. 1997; Sorbera et al. 2001). Some authors have used the term serotonin partial agonist reuptake inhibitor (SPARI) to define this class of antidepressants representing a unique mechanism of action (Stahl 2011).

Vilazodone acts in a similar way to SSRIs by selectively inhibiting serotonin reuptake, which can increase local serotonin concentrations in the synapse, resulting in improvement in MDD symptoms (Roberts et al. 2005). Additionally, the 5-HT_{1A} receptor partial agonist effect reduces the negative feedback of endogenous serotonin, which may result in intensification of the antidepressant effect of vilazodone (Celada et al. 2004; Dawson and Watson 2009). The net results of the 5-HT_{1A} receptor partial agonism on serotonergic neurotransmission and its role in antidepressant effect have not been clearly elucidated. However, studies suggest that presynaptic 5-HT_{1A} receptors and postsynaptic 5-HT_{1A} receptors have opposing effects on the secretion of 5-HT (Lanfumey and Hamon 2000). Presynaptic receptors are autoreceptors located on raphe nuclei, and their activation decreases the firing and secretion of 5-HT, whereas postsynaptic receptors located on the hippocampus may activate firing and secretion of 5-HT. Chronic stimulation of 5-HT_{1A} receptors by 5-HT may result in functional desensitization of the autoreceptors but not the postsynaptic receptors. Therefore, a general increase in serotonin levels could result in desensitization of the 5-HT_{1A} autoreceptors and activate 5-HT_{1A} postsynaptic receptors, which together improve MDD symptoms (Blier and Abbott 2001). It has been hypothesized that 5-HT_{1A} autoreceptor-mediated inhibition of serotonin release is one of the most important causes for the therapeutic lag commonly observed in antidepressants such as SSRIs, because it takes time to overcome the autoreceptor-mediated serotonin inhibition and 5-HT_{1A} autoreceptor downregulation with chronic SSRI treatment (Hjorth et al. 2000). Therefore, desensitization of the autoreceptor before increasing extracellular serotonin concentration may be an important factor determining the effectiveness of antidepressants (Hjorth et al. 2000; Briley and Moret 1993). 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 inhibition of serotonin release by providing only a partial agonist action at 5-HT_{1A} receptors (both presynatpic and postsynaptic) (Starr et al. 2007; Hughes et al. 2007). This eventually lowers the negative feedback mechanism of 5-HT neurons via the autoreceptor, and stimulation of the postsynaptic 5-HT_{1A} receptors would yield even more serotonin release synergistic with its SSRI properties (Dawson and Watson 2009; Hjorth et al. 2000; Briley and Moret 1993).

In line with this speculation, animal studies have suggested that vilazodone may have a more rapid treatment onset than SSRIs due to more robust serotonergic action (Duxon et al. 2000; Hogg and Dalvi 2004; Dawson and Watson 2009). Theoretically, partial agonist action at the postsynaptic 5-HT_{1A} receptor may also potentially lower the risk of sexual dysfunction (Le Poul et al. 1995; Li et al. 1997). For example, sexual function was normalized in eight of ten patients with generalized anxiety disorder (GAD) after 4 weeks of treatment with buspirone (Othmer and Othmer 1987). However, no clinical trials have been conducted to confirm the faster treatment onset, more robust antidepressant effects, and lower sexual dysfunction with vilazodone compared with currently popular antidepressants such as SSRIs and SNRIs.

Pharmacokinetics

Currently available data regarding vilazodone pharmacokinetics are quite limited, as no full phase I or phase II pharmacokinetic studies of vilazodone have been reported. It is recognized that the activity of vilazodone is due primarily to the parent drug and that the pharmacokinetics of vilazodone are dose proportional from 5 to 80 mg (Administration 2012; Forest Pharmaceuticals I 2012). The median time to peak plasma concentration (T_{max}) is about 4–5 h, and terminal half-life is approximately 25 h. Steady state is achieved in approximately 72 h (Administration 2012). The mean area under the plasma vilazodone concentration–time curve to 24 h (AUC_{24}) is 1,645 ng·h/mL, and the mean maximum plasma vilazodone concentration (C_{max}) is 156

ng/mL (Forest Pharmaceuticals I 2012). Administration of vilazodone with food, particularly a high-fat or light meal, increases oral bioavailability (147–160% increase of C_{max} and 64–85% increase of AUC). For this reason, vilazodone is recommended to be taken with food. The absolute oral bioavailability of vilazodone with food is 72%, and 96–99% is protein-bound (Administration 2012; Forest Pharmaceuticals I 2012) (Table I). Both cytochrome (CYP) P_{450} and non-CYP pathways (possibly by carboxylesterases) have major roles in vilazodone metabolism. Only 1% of vilazodone is recovered unchanged in the urine, and 2% in feces. According to *in vitro* studies, vilazodone is metabolized primarily by CYP3A4 and secondarily by CYP2C19 and CYP2D6. Elimination of vilazodone depends primarily on hepatic metabolism.

Drug–drug interactions

Effect of other drugs on vilazodone

Co-administration of vilazodone with ethanol or a proton pump inhibitor (pantoprozole) does not affect the rate or extent of vilazodone absorption (Forest Pharmaceuticals I 2012). Studies on several drugs indicate a significant pharmacokinetic interaction only when vilazodone is combined with strong 3A4 inhibitors (Administration 2012). When vilazodone is administered with ketoconazole (a strong 3A4 inhibitor), the C_{max} and AUC of vilazodone increase by 50%. Therefore, vilazodone dose should be reduced to 20 mg when used in combination with a strong CYP3A4 inhibitor. No dose adjustment is recommended for mild CYP3A4 inhibitors (e.g., cimetidine) (Forest Pharmaceuticals I 2012). The interaction between vilazodone and CYP3A4 inducers has not been studied, but such inducers are expected to decrease vilazodone concentration, which could possibly diminish the effectiveness of the drug. Other CYP isoenzyme inhibitors and inducers have only minimal effects on vilazodone.

Effect of vilazodone on other drugs

A study in healthy volunteers showed that when 20 mg/day vilazodone was administered for 8–10 days with caffeine, flurbiprofen, nifedipine, or debrisoquine, which are probes for CYP1A2, CYP2C9, CYP3A4, and CYP2D6, respectively, no significant effects on their pharmacokinetic profiles were observed (Administration 2012). *In vitro* studies suggest that vilazodone may inhibit biotransformation of CYP2C8 substrates, but this has not been tested *in vivo*. Coadministration with other drugs that are also highly protein bound may increase the free plasma concentration of the other drugs. However, the interaction between vilazodone and other highly protein-bound drugs has not been evaluated. According to the package insert, coadministration of vilazodone with any drug that may affect serotonergic neurotransmitter systems should be carefully applied, and it requires a clinical monitoring due to the potential for serotonin syndrome.

Table I. Pharmacokinetic parameters of vilazodone.

Pharmacokinetic parameters	Pharmacokinetic dose proportional for doses 5–80 mg
T_{max} (h)	4–5
$t_{½}$ (h)	25
AUC_{24} (ng·h/mL)	1645
C_{max} (ng/mL)	156
Absolute bioavailability with food (%)	72
Protein binding (%)	96~99
Time to steady-state concentration (days)	3

Mean value after daily dosing with vilazodone 40 mg under fed condition. AUC_{24} = area under the plasma vilazodone concentration–time curve from time zero to 24 h; C_{max} = maximum plasma vilazodone concentration; $t_{½}$ = terminal elimination half-life; and T_{max} = time to C_{max}.

Efficacy from clinical trials

Phase II studies

Five phase II trials have been conducted with 5–100 mg/day vilazodone (Administration 2012). All trials were double-blinded, randomized, placebo-controlled, 8-week, parallel group trials, and the subjects included were outpatients meeting Diagnostic and Statistical Manual of Mental Disorder IV criteria for MDD. Two of the trials used fixed-dose designs (trials 246 and 248), and the other three used flexible-titration designs with active comparators for sensitivity assessment (trials 244, 245, and 247). The total score change on the 17-item Hamilton Depression Rating Scale (HAM-D-17) from baseline to the end point was the primary end point in all five trials. However, all five trials failed to demonstrate a significant treatment effect for vilazodone over placebo at its primary end point. Additionally, none of the three active comparators showed a significant superiority over placebo for improving depressive symptoms, indicating that these three trials lacked assay sensitivity. Therefore, the three trials with comparators could be considered "failed" trials, whereas the two other trials could be considered "negative" trials. Although these trials were unsuccessful for their primary outcome measures, the two fixed-dose trials (trials 246 and 248) showed a possible treatment effect of vilazodone (20 mg/day) over placebo on the Montgomery–Asberg Depression Rating Scale (MADRS) as the secondary end point. Table II summarizes important data regarding these phase II trials.

Phase III studies

Two similarly designed controlled clinical trials formed the basis of the efficacy evaluation of vilazodone for treating MDD (Rickels et al. 2009; Khan et al. 2011). Both studies were randomized, double-blinded, parallel-group, placebo-controlled, 8-week, multicenter trials conducted in the United States. In the first study conducted by Rickels et al. (2009), the efficacy and tolerability of vilazodone in patients with MDD were investigated in 410 patients (intent-to-treat analysis [ITT], vilazodone $n = 198$ and placebo $n = 199$) with MDD. Patients were required to have an HAM-D-17 score of ≥ 22, a HAM-D-17 item depressed mood score of ≥ 1, and a current MDD episode with a duration of at least 4 weeks but no longer than 2 years. Patients randomized to the vilazodone-treated group underwent a weekly titration (week 1, 10 mg/day; week 2, 20 mg/day; and 40 mg/day from week 3 for the last 6 weeks). Patients who did not tolerate 40

Table II. Summary of phase II clinical trials of vilazodone in patients with major depression.

			Efficacy results					
			HAM-D-17[a]				MADRS[b]	
Trials	Treatment (mg/d)	N	Baseline (SD)	Change[c] (SE)	DFP	P-value	DFP	P-value
244 (EMD 68 843–009)	Vilazodone (20–100)	86	23.4 (2.9)	−8.9 (0.8)	0.76	0.4938	NR	NR
	Fluoxetine (20)	89	24.4 (3.2)	−9.5 (0.8)	0.15	0.8924	NR	NR
	PBO	95	24.0 (3.1)	−9.6 (0.8)				
245 (EMD 68 843–010)	Vilazodone (10–20)	104	23.8 (3.0)	−9.7 (0.7)	0.5	0.6479	NR	NR
	Vilazodone (40–60)	97	23.9 (3.1)	−10.5 (0.8)	−0.3	0.7527	NR	NR
	Vilazodone (80–100)	93	23.5 (3.0)	−8.6 (0.8)	1.6	0.1310	NR	NR
	Fluoxetine (20)	92	23.5 (2.3)	−11.1 (0.8)	−0.9	0.3866	NR	NR
	PBO	99	23.4 (2.8)	−10.2 (0.8)				
246 (SB 659746–003)	Vilazodone (10)	120	23.8 (3.1)	−10.8 (0.7)	−0.5	0.5852	−2.3	0.123
	Vilazodone (20)	123	23.7 (3.1)	−11.1 (0.7)	−0.8	0.4069	−2.8	0.059
	Citalopram (20)	117	23.1 (2.6)	−10.9 (0.7)	−0.7	0.5111	NR	NR
	PBO	129	23.3 (2.8)	−10.2 (0.7)				
247 (SB 659746–014)	Vilazodone (5–20)	109	23.3 (2.7)	−10.7 (0.7)	−1.0	0.2723	NR	NR
	PBO	111	23.5 (2.5)	−9.7 (0.7)				
248 (SB 659746–002)	Vilazodone (5)	140	24.0 (3.0)	−11.0 (0.6)	0.5	0.5654	−0.4	0.725
	Vilazodone (10)	133	24.5 (3.3)	−12.8 (0.6)	−1.2	0.1770	−1.9	0.158
	Vilazodone (20)	132	24.3 (3.0)	−11.7 (0.6)	−0.2	0.8019	−2.5	0.062
	PBO	128	23.7 (2.9)	−11.5 (0.7)				

HAM-D-17, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery–Asberg Depression Rating Scale; NR, not reported; SD, standard deviation; SE, standard error; DFP, difference from placebo (PBO).
[a]primary outcome measure.
[b]secondary outcome measure.
[c] least-square mean change from baseline to end point (week 8).

mg/day were reduced to 20 mg/day for the remainder of the study; however, 91.4% of the patients tolerated 40 mg/day for the last 6-week period. Treatment response was assessed by the MADRS, HAM-D-17, Hamilton Anxiety Rating Scale (HAM-A), and Clinical Global Impression-Severity of Illness (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scales at weeks 1, 2, 4, 6, and 8. Among the measures, mean change in MADRS score from baseline to the end of treatment (week 8) was defined as the primary efficacy end point. The superiority of vilazodone over placebo was evidenced by mean changes on the MADRS, HAM-D-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. However, such rapid onset of vilazodone may be challenged and cautiously interpreted since the study did not use active comparator, and such effect was not replicated in the subsequent trial, the effect size was not large enough to be translated into clinical practice, and other antidepressant trials also showed such effects indicating that such rapid onset is not unique in vilazodone trial. The response rates were also significantly better with vilazodone than with placebo on the MADRS, HAM-D-17, and CG-I.

Khan et al. (2011) conducted a very similar randomized, double-blinded study of 481 patients with MDD (ITT, vilazodone $n = 231$ and placebo $n = 232$). Except for the age range of the patients, study entry, exclusion criteria, and treatment end points were nearly identical to those of the previous study (Rickels et al. 2009). Overall, vilazodone was associated with significantly greater improvement in depressive symptoms than placebo in both the primary and secondary efficacy end points, which was consistent with the results from the previous study (Rickels et al. 2009).

When pooling the two pivotal 8-week studies, the remission and response rates of vilazodone were 25.4% and 42.2%, respectively, whereas the response and remission rates of placebo were 18.1% and 29.2%, respectively (Citrome 2012). These findings are comparable with those from newer antidepressants such as duloxetine and venlafaxine-XR for treating MDD, in which the remission and response rates were 17.8% and 24.4% for venlafaxine-XR and 14.2% and 18.6% for duloxetine (Vis et al. 2005). The outcome summary of these two pivotal studies is presented in Table III.

Open-label long-term study

A 1-year, open-label, multicenter study assessed the long-term efficacy of vilazodone in patients with MDD (Robinson et al. 2011). A total of 616 patients with a HAM-D-17 score of ≥ 18 were enrolled. Of these, 599 patients comprised the safety population, and 254 (41.2%) completed the entire study. Vilazodone was administered with a fixed-titration schedule over 2 weeks to reach the recommended therapeutic dose of 40 mg/day. The MADRS, CGI-S, and CGI-I scales were used to assess vilazodone effectiveness. The mean MADRS total scores were 29.9 at baseline, which improved progressively to 11.4 at week 8 and 7.1 at week 52. A similar trend was also noted for changes in total CGI-S scores. The mean total CGI-S score at baseline was 4.3, which improved to 2.5 at week 8 and 1.7 at week 52. The mean total CGI-I score also improved from 3.5 at baseline to 1.4 at week 52.

Dosing and administration

Vilazodone is available in 10-, 20-, and 40-mg strengths (Forest Pharmaceuticals I 2012). The recommended daily dosage of vilazodone is 40 mg/day, and it should be taken with food, because a fasted state can decrease bioavailability.

Table III. Summary of two pivotal randomized, double-blinded, placebo-controlled, 8-week, phase III clinical trials of vilazodone in patients with MDD.

Study	Treatment (mg/d)	Patients[a]	MADRS		HAM-D-17		CGI-I		CGI-S		HAM-A	
			Baseline (SD)	Change[b] (SE)	Baseline (SD)	Change[b] (SE)	Baseline	Change[b] (SE)	Baseline (SD)	Change[b] (SE)	Baseline (SD)	Change[b] (SE)
Rickels et al. (2009)	Vilazodone (40)	198	30.8 (3.9)	−12.9 (0.8)**	24.8 (2.4)	−10.4 (0.6)*	N	2.6 (0.1)**	4.5 (0.5)	−1.4 (0.1)**	18.3 (5.1)	−6.6 (0.6)*
	Placebo	199	30.7 (3.9)	−9.6 (0.8)	24.9 (2.4)	−8.6 (0.6)	N	3.0 (0.1)	4.4 (0.5)	−1.1 (0.1)	18.5 (5.3)	−5.1 (0.5)
Khan et al. (2011)	Vilazodone (40)	231	31.9 (3.5)	−13.3 (0.9)**	25.0 (2.4)	−10.7 (0.7)*	N	2.5 (0.1)**	4.4 (0.5)	−1.4 (0.1)**	18.0 (5.3)	−7.0 (0.6)*
	Placebo	232	32.0 (3.6)	−10.8 (0.9)	25.3 (2.6)	-9.2 (0.7)	N	2.8 (0.1)	4.4 (0.5)	−1.1 (0.1)	18.1 (5.8)	−5.7 (0.6)

CGI-I, Clinical Global Impressions-Improvement scale; CGI-S, Clinical Global Impressions-Severity of Illness scale; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D-17, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery–Asberg Depression Rating Scale; N, not applicable; SD, standard deviation; SE, standard error. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

[a]number of total intent-to-treat patients.

[b]least-square mean change from baseline to end point (week 8).

Titration starting at 10 mg/day for the first week, 20 mg/day for the second weeks, and an increase to 40 mg/day thereafter is recommended because of the possible gastrointestinal discomfort AE. Since vilazodone may require 2-week titration period to minimize the gastrointestinal AEs, 20 mg/d of vilazodone should provide lower margin of efficacy, and the AEs tended to increase with dose increment in phase II trials, proper dosing issue may call clinicians' attention in clinical practice. No dose adjustment is required for age, gender, or mild to moderate renal or hepatic dysfunction (Administration 2012). Patients with severe renal or hepatic dysfunction have not been studied. No controlled studies regarding the use of vilazodone in pregnant women are available. When pregnant rats and rabbits were treated with vilazodone, no fetal abnormalities were observed (Forest Pharmaceuticals I 2012). Therefore, it has been labeled as pregnancy category C. Although the effect of vilazodone on lactation and nursing in humans is unknown, administration of vilazodone in breast feeding women should be very careful monitored, as vilazodone is excreted in the milk of lactating rats. The efficacy and safety of vilazodone for children are not yet established, and its use in children is not yet approved.

Safety and tolerability

Common AEs

According to a pooled analysis of phase II studies (Khan 2009), the most common AEs which occurred in ≥5% of patients with at least twice the frequency of placebo are 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%). The median daily dose was 54.5 mg/day, and the AE incidence increased proportionally by a dose increase and was highest when the dose exceeded the median dosage.

When the two pivotal 8-week random controlled trials were pooled together (vilazodone $n = 436$ and placebo $n = 433$) (Rickels et al. 2009; Khan et al. 2011), discontinuation rates due to AEs were 7.1% and 3.2%, respectively. In the vilazodone-treated group, the most common AEs 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).

In a 1-year open-label study (Robinson et al. 2011), 20.7% of patients discontinued vilazodone due to AEs; the most frequent AEs leading to discontinuation were nausea (1.3%), diarrhea (1.2%), and anxiety (1%). The common AEs were largely similar between these two pivotal studies, and most of the AEs were mild to moderate in severity (Table IV).

Benefit–risk decisions are the most valuable point in evidence-based pharmacological treatment. Regarding this viewpoint, the number needed to treat (NNT) and number needed to harm (NNH) can quantify differences between two medications in terms of benefits and risks for the treatment of MDD. The most commonly encountered AEs, diarrhea, nausea, vomiting and insomnia, can also be presented with NNH values versus placebo of 6 (95% confidence interval (CI), 5–8), 6 (95% CI, 5–8), 30 (95% CI, 18–82) and 26

Table IV. Summary of treatment-emergent AEs of two pivotal phase III 8-week randomized controlled studies and one open-label study.

	Randomized controlled studies[a]		Open label study (Robinson et al. 2011)
Preferred Term	Vilazodone (N = 436)	Placebo (N = 433)	Vilazodone (n = 599)
Diarrhea	122 (28.0)	40 (9.2)	214 (35.7)
Nausea	102 (23.4)	22 (5.1)	189 (31.6)
Headache	58 (13.3)	52 (12.0)	120 (20.0)
Dizziness	37 (8.5)	20 (4.6)	64 (10.7)
Dry mouth	35 (8.0)	22 (5.1)	66 (11.0)
Insomnia	26 (6.0)	9 (2.1)	78 (13.0)
Nasopharyngitis	23 (5.3)	20 (4.6)	45 (7.5)
Vomiting	20 (4.6)	5 (1.2)	44 (7.3)
Abnormal dreams	18 (4.1)	5 (1.2)	62 (10.4)
Fatigue	16 (3.7)	12 (2.8)	46 (7.7)
Decreased libido	8 (1.8)	1 (0.2)	25 (4.2)
Abnormal orgasm (Includes anorgasmia)	6 (1.4)	0 (0)	14 (2.3)
Delayed Ejaculation[b]	2 (1.8)	0 (0)	19 (3.1)
Erectile Dysfunction[b]	2 (1.8)	1 (0.1)	25 (4.2)

Data represent numbers (%).
[a]Data adopted from reference (Citrome 2012).
[b]Male patients only (vilazodone n = 170, placebo n = 182).

(95% CI, 16–78), respectively (Citrome 2012). Regarding gastrointestinal disturbance including nausea and vomiting, although there was no single AE leading to discontinuation in > 1% of patients, the most common type of AEs leading to discontinuation were gastrointestinal complaints (2.3% vs 0.2% in placebo) in two pivotal 8-week trials (Rickels et al. 2009; Khan et al. 2011). The metric of likelihood to be helped or harmed (LHH = NNH/NNT) can also be helpful in quantifying the benefit–risk ratio in clinical practice (Citrome 2012). For instance, relevant example of LHH is for the outcome of achieving response (8) or remission (14) and encountering nausea, LHH of 6/8 = 0.75 and of 6/14 = 0.43, respectively. This means that the likelihood of achieving a response or remission is actually less than the likelihood of encountering nausea (Citrome 2012). In other words, nausea is 1.3 or 2.3 times more likely to be encountered than a therapeutic response or remission in vilazodone trial for MDD patients (Citrome 2012). The same trend is also applicable for diarrhea. The NNH for vomiting is 30; thus, the LHH for response or remission versus encountering vomiting should be presented as 30/8 = 3.75 or 30/14 = 2.14, respectively, indicating that the likelihood of achieving a response or remission is actually more than the likelihood of encountering vomiting. As seen in LHH calculation and absolute data from clinical trials, clinicians are strongly recommended to carefully watch these problematic short-term gastrointestinal AEs. Although, the 2-week titration to target dose of vilazodone is recommended to reduce such gastrointestinal AEs, the utility of such strategy should be more investigated in future researches.

A minimal weight gain seen in the pivotal trials and open-label long-term study is noteworthy (Administration 2012; Ferguson 2001) because weight gain is one of major leading causes of noncompliance during antidepressant treatment (Trivedi et al. 2007). In two such pivotal studies, patients treated with vilazodone did not experience statistically significant weight changes (Rickels et al. 2009; Khan et al. 2011). The mean weight increase in patients treated with vilazodone was 1.7 kg in a 1-year long-term study (Robinson et al. 2011).

Sexual dysfunction

Antidepressant-associated sexual dysfunction is a challenging AE occurring in 30–40% of patients treated with SSRIs or SNRIs (Clayton et al. 2002; Clayton and Montejo 2006). The sexual dysfunction rates of vilazodone were much lower in all phases of studies to date (Table IV). None of the vilazodone-treated patients discontinued treatment due to sexual dysfunction. Pooled data from all phase II studies reported that erectile dysfunction occurred in less than 2% and abnormal orgasm occurred in less than 1% of male patients (Khan 2009). In the two pivotal studies, decreased libido, abnormal orgasm, delayed ejaculation, and erectile dysfunction were seen in 1.8%, 1.4%, 1.8%, and 1.8% for vilazodone, respectively (compared with 0.2%, 0.0%, 0.0%, and 0.1% for placebo, respectively) (Rickels et al. 2009; Khan et al. 2011). In the first phase III study, the Arizona Sexual Experience Scale (ASEX) was used to evaluate the changes in sexual function (Rickels et al. 2009). No clinically significant differences in ASEX total scores were observed between placebo and vilazodone, regardless of gender. Additionally, the changes in ASEX total score from baseline to end point decreased. In the second phase III study, sexual dysfunction was assessed by changes on the Sexual Functioning Questionnaire (SFQ), and sexual dysfunction rates were comparable with those with placebo (Khan et al. 2011). In the long-term study, mean SFQ scores even improved throughout treatment in both males and females (Robinson et al. 2011). However, favorable pharmacodynamic profile of vilazodone regarding sexual dysfunction compared to other antidepressants may not be confirmative yet since currently available clinical trials of vilazodone did not use SSRIs or SNRIs as active comparators and the individual items of sexual dysfunction scales did not show consistent pattern compared those from placebo treatment in pivotal trials. Thus, we have to wait for data from

direct comparative clinical trials between vilazodone and other antidepressants to reach firm clinical remarks about differential effects on sexual dysfunction.

Cardiac safety

The cardiac safety of vilazodone has been verified in a phase I study, whose results were presented as a poster at an academic meeting (Morganroth et al. 2010). In this randomized, double-blinded, placebo and moxifloxacin controlled study with 157 healthy volunteers, 45 were given placebo, 46 were given 400 mg/day moxifloxacin, and 66 were given 20–80 mg/day vilazodone. Electrocardiogram (ECG) assessments were conducted, and no AEs were noted for heart rate, pulse rate, QT, QTc, or QRS intervals. The prescribing information also states that vilazodone has not been associated with any clinically significant changes on ECG or vital signs including systolic/diastolic blood pressure (Forest Pharmaceuticals I 2012).

Sleep

The effects of vilazodone on sleep and electroencephalogram (EEG) pattern were analyzed in a randomized crossover study with 10 healthy young men (Murck et al. 2001). Subjects received either a single dose of 20 mg/day vilazodone or placebo. Rapid eye movement (REM) almost totally disappeared in patients receiving vilazodone. Additionally, increases in slow-wave sleep and EEG delta power were noted in the first and third trimesters of the night. More wakefulness was also recorded in the second and third trimesters of the night. The 5-HT_{1A} agonist actions of vilazodone may have resulted in the increase in slow-wave sleep and the decrease in REM sleep (Quattrochi et al. 1993; Seifritz et al. 1997; Driver et al. 1995). Increased wakefulness in the second trimester of the night and REM suppression are similar to the effects shown with SSRIs (Sharpley et al. 1996). These findings suggest that vilazodone possibly leads to sleep disturbances even at dosages lower than therapeutic dosages. Hence, caution and proper counseling are necessary for patients experiencing insomnia before and during vilazodone therapy.

Expansion of clinical utility

Comorbid anxiety disorders

Some intriguing clinical wisdom can be drawn from the unique mechanisms of action of vilazodone. 5-HT_{1A} partial agonists (e.g., busprione) have proven efficacy for treating anxiety disorders, although the first-line treatment is usually either an SSRI or an SNRI based on clear efficacy and good tolerability in clinical practice. In view of the dual mechanism of actions, both of which have been found useful in GAD, it is likely on theoretical grounds that vilazodone will be effective in GAD. However, in the absence of direct studies for GAD, no recommendations can be made.

Early augmentation effects with the unique mechanism of action of vilazodone

Vilazodone initiates an immediate and simultaneous combination of 5-HT transporter inhibition and 5-HT_{1A} partial agonism at the onset of treatment, by which it may theoretically offer a hastening of the augmentation effects of a 5-HT_{1A} partial agonist that is commonly used in clinical practice without waiting to observe treatment outcomes of first-line antidepressants. However, this viewpoint is completely hypothetical and no clinical trials of vilazodone investigated this rapid onset in patients with MDD yet. Thus, we will need direct clinical trial data on this putative effect.

Others

5-HT_{1A} partial agonists have been used for various substance dependence and withdrawal conditions based on findings from a number of clinical trials and the pharmacological rationale. Extensive evidence from animal models indicates that activation of 5-HT_{1A} receptors substantially avoids extrapyramidal symptoms induced by D2 receptor blockade, leading to facilitation of dopaminergic neurotransmission in the frontal cortex, a positive influence on mood, and protection against N-methyl D-aspartate receptor antagonist-induced cognitive and social interaction deficits (Newman-Tancredi 2010). Hence, vilazodone may also offer potential utility in schizophrenia cases based on its mechanism of action. However, there has been no such clinical trial data supporting a possibility of vilazodone use for substance disorders or schizophrenia.

Conclusion and summary

Vilazodone may extend treatment options for patients suffering from MDD. Two pivotal, well-controlled trials demonstrated the short-term efficacy and safety of vilazodone (Rickels et al. 2009; Khan et al. 2011). One-year open label study also demonstrated the long-term safety and tolerability of vilazodone (Robinson et al. 2011). Vilazodone should be administered with a 2-week titration period starting at 10 mg/day to a target dose of 40 mg/day, as it can cause gastrointestinal side effects (Forest Pharmaceuticals I 2012). A fasting state can decrease the bioavailability of vilazodone by 50%, so it should be taken with food.

Studies comparing the efficacy and safety of vilazodone with those of other antidepressants have not yet been conducted. Table V represents clinical comparisons with other antidepressants (Table V).

First, its distinct pharmacodynamic characteristics, such as simultaneous action on 5-HT reuptake inhibition and the 5-HT_{1A} receptor, may provide further clinical benefits (Forest Pharmaceuticals I 2012). Partial agonist action at both presynatpic and postsynaptic 5-HT1A receptors may overcome the chronological lag commonly observed with conventional antidepressants (Hjorth et al. 2000). This putative benefit was demonstrated in one pivotal trial showing that significant improvements in depressive symptoms were noted within 1 week after commencing vilazodone (Rickels et al. 2009). Postsynaptic 5-HT1A receptor actions may also diminish sexual dysfunction (Le Poul et al. 1995; Li et al. 1997), and fewer sexual side effects observed in all phase trials support this speculation (Rickels et al. 2009; Khan et al. 2011; Robinson et al. 2011; Khan 2009). The STAR*D trial suggested that a combination of antidepressants or

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Table V. Comparative data of vilazodone and other available antidepressants.

Class	Drug name (Generic)	Indication[a]	Side effects	
			Common side effects	Remarks
SSRI	Escitalopram	MDD, GAD	GI side effects (nausea, diarrhea, heartburn), Headache, Insomnia/Somnolence, Sexual side effects (decreased libido, delayed orgasm)	Fluoxetine: Lowest rate of withdrawal symptoms. Paroxetine: Highest sexual dysfunction incidence compared to SSRIs as a class (16% vs 6%). Withdrawal symptoms also highest among SSRIs.
	Fluoxetine	MDD, OCD, PMDD; bulimia nervosa, PD		
	Fluvoxamine	OCD, SAD		
	Paroxetine	GAD, MDD, OCD, PD, PMDD, PTSD SAD		
	Sertraline	MDD, OCD, PD, PMDD, PTSD SAD		
SNRI	Venlafaxine	GAD, MDD, PD, SAD	Nausea, somnolence, dry mouth, dizziness	Venlafaxine: Nausea and vomiting higher than those of SSRIs as a class (33% vs 22%). Along with paroxetine, highest withdrawal symptoms. Concern of increased blood pressure in all three SNRIs.
	Duloxetine	GAD, MDD, neuropathic pain, fibromyalgia, chronic musculoskeletal pain	Nausea, somnolence, insomnia, dizziness	
	Milnacipran	Fibromyalgia, MDD (not approved in United States)	Nausea, headache, constipation, dizziness	
DNRI	Bupropion	MDD, seasonal affective disorder, smoking cessation	Headache, insomnia, dry mouth, tremor	Lower incidence of sexual dysfunction than comparator (escitalopram, fluoxetine, paroxetine, sertraline) drugs.
NaSSA	Mirtazapine	MDD	Dizziness, blurred vision, sedation/ somnolence, increased appetite	Greater weight gain than comparator (fluoxetine, paroxetine, trazodone, venlafaxine) drugs (0.8–3.0 kg after 6–8 weeks).
Other	Agomelatine[b]	MDD (not approved in United States)	Nausea, dizziness	
	Tianeptine[c]	MDD (not approved in United States)	Dry mouth, constipation, dizziness/syncope, drowsiness	Sexual dysfunction: rare.
	Buspirone[d]	GAD	Dizziness, drowsiness, nausea, headache	
SPARI	Vilazodone	MDD	Diarrhea, nausea, headache, dizziness	Potentially lower sexual dysfunction and weight gain. Not confirmed by direct comparison study.

DNRI, Dopamine and norepinephrine reuptake inhibitor; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive–compulsive disorder; PD, panic disorder; PMDD, premenstrual dysphoric disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; SNRI, serotonin and norepinephrine reuptake inhibitor; SPARI, serotonin (5-HT_{1A}) partial agonist reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor
References (Gartlehner et al. 2011; Anderson et al. 2008; Schatzberg et al. 2010; McEwen et al. 2010).

[a]Approved by US Food and Drug Administration and indications may vary among countries.

[b]Melatonin receptor (MT_1 and MT_2) agonist + serotonin $5HT_{2C}$ antagonist.

[c]Selective serotonin reuptake enhancer and/or glutamate receptor modulator.

[d]Serotonin ($5HT_{1A}$) partial agonist.

augmentation with other agents may be more effective for achieving remission than currently inadequate monotherapy (Rush et al. 2006; Rush 2007). Buspirone, a 5-HT1A receptor partial agonist, which is considered an important augmenting agent, should be included when treating TRD (Trivedi et al. 2006; Nierenberg 2009). Theoretically, vilazodone may be more effective for TRD without increasing the AE burden due to polypharmacy, although strong evidence to support this potential advantage is still lacking. The lower likelihood that vilazodone will cause sexual dysfunction, weight gain, and cardiac toxicity may be another putative benefit (Forest Pharmaceuticals I 2012). However, currently existing data potentially suggest that the safety profile of vilazodone may be comparable those those from other antidepressants, and we have no direct comparison clinical trials between vilazodone and other antidepressants to support such benefit yet. In addition, certain AEs, such as diarrhea, nausea, headache, dizziness, dry mouth, and insomnia, may require clinical attention in routine clinical practice (Citrome 2012). A decrease in REM and increases in slow-wave sleep and delta wave activity have been noted, indicating that vilazodone may potentially result in sleep disturbances (Murck et al. 2001).

In conclusion, vilazodone may be another effective and safe treatment option for patients with MDD. Its role in relapse prevention as well as long-term efficacy, should be further investigated in patients with MDD. Finally, its putative benefits compared with other antidepressants must be thoroughly studied in adequately powered and well-designed future clinical trials.

Key points

- Vilazodone is a new antidepressant having different action mechanisms and was approved in 2011 in the USA for treating MDD
- Vilazodone not only potently and selectively inhibits serotonin 5-HT reuptake but also selectively binds to 5-HT_{1A} receptors with high affinity
- Vilazodone has demonstrated comparable efficacy and slightly differential tolerability profiles in comparison with other antidepressants for patients suffering from MDD
- Relapse prevention effect and long-term efficacy of vilazodone should be established in adequately powered, large clinical trials in the near future.

Acknowledgment

Vilazodone is only approved for the treatment of MDD; the potential utility of vilzodone for other clinical conditions described in this review is the authors' speculation and thereby vilazodone should be off-label usage for such conditions.

Statement of interest

None of the authors reports conflicts of interest.

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