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DRUG EVALUATION

Evaluation of vilazodone for the treatment of depressive and anxiety disorders

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ABSTRACT

Introduction: Major Depressive Disorder (MDD) and General Anxiety Disorder (GAD) significantly contribute to the global burden of disease. Vilazodone, a combined serotonin reuptake inhibitor and 5-HT1A partial agonist, is an approved therapy for the treatment of MDD and which has been further investigated for GAD.

Areas covered: This article covers the pharmacokinetics and pharmacodynamics of vilazodone and provides an evaluation of the clinical usefulness of vilazodone for the treatment of MDD and anxiety disorders. A literature search was performed using PubMed/MEDLINE, Web of Science and the Cochrane Library.

Expert opinion: Studies have shown that vilazodone is significantly superior to placebo. However, vilazodone cannot as yet be recommended as a first-line treatment option for MDD as it is unclear whether the drug's dual mechanism of action provides greater efficacy than prevailing treatment options. Moreover, more phase IV studies are needed to establish its efficacy and long-term safety in larger and more diverse populations. Although vilazodone may have an additional advantage for the treatment of anxiety symptoms in MDD, here also additional studies are required to confirm its efficacy over and above SSRI alternatives and other antidepressant treatments. Therefore, presently, vilazodone should be considered as a second- or third-line treatment option for MDD and GAD.

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5-HT1A receptor partial agonist; antidepressant; major depressive disorder; anxiety disorder; serotonin reuptake inhibitor; vilazodone

1. Introduction

Major depressive disorder (MDD) and generalized anxiety disorder (GAD) significantly contribute to the global burden of disease and affect people in all communities across the world [1]. MDD has a median 12-month prevalence rate of 6.9% [2] and a lifetime prevalence between 11.2% and 16.0% [3]. MDD is a debilitating disease that is characterized by abnormalities of affect, mood, neurovegetative functions (such as appetite and disturbed sleep), cognition (such as inappropriate guilt, and feelings of worthlessness), and psychomotor activity (such as agitation or retardation) [4]. MDD has a major impact on the person's family, work, and social lives, as well as health considerations.

This paper covers the pharmacokinetics and pharmacodynamics of vilazodone and provides an evaluation of the clinical usefulness of vilazodone (Box 1) for the treatment of MDD and anxiety disorders. We focused on its clinical implications by reviewing clinical trials. A PubMed/MEDLINE, Web of Science, and Cochrane Library search were performed using the search term 'Vilazodone'. The titles and abstracts of the retrieved references were examined for relevance (i.e. papers about the treatment of MDD, and papers concerning the efficacy and safety of vilazodone). In addition, we conducted hand-searches of reference lists of included studies and reviews. Studies that met the following inclusion criteria were used: (1) randomized controlled trials of vilazodone regarding the treatment of depressive or anxiety disorders; (2) and concerning patients with MDD or anxiety disorders. Exclusion criteria included: (1) study types: case reports, case series, retrospective studies, non-randomized studies, and cohort studies; (2) articles in languages other than English, (3) results published only in abstract form because insufficient information was available for quality assessment.

Initial searches were conducted in May 2018 with update searches in October 2018. Whereas the primary focus is on MDD, we also review trial data in patients with GAD and other patients with symptoms of anxiety, as these studies may add important information on adverse effects and the safety profile.

1.1. Overview of the market

Medications used to treat MDD include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), noradrenaline reuptake inhibitors (NaRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and other antidepressants such as mirtazapine [5]. An important aspect of the pharmacological treatment of MDD is the selection of an antidepressant by the clinician depending on various factors such as clinical features and comorbidities in the patient and adverse effects of the psychotropic such as weight gain. SSRIs are the most commonly prescribed first-line treatment options, although many patients do not adequately

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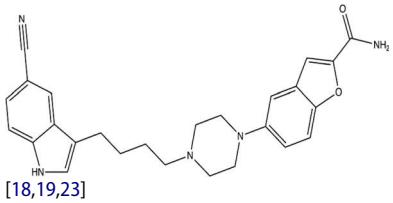
Box 1. Drug summary box.

Drug name	Vilazodone
Phase	Launched
Indication	Major depressive disorder
Pharmacology description	Serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	[18,19,23]

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respond to their initial SSRI [6]. The Sequences Treatment Alternatives to Relieve Depression (STAR*D) study showed that antidepressants exhibit rather similar efficacy, although there are differences in tolerability [7].

New treatment options are needed. The serotonin transporter and serotonin receptors are useful targets in the management of MDD and anxiety disorders. There are seven families of serotonin receptors, one of which is the 5-hydroxytryptamine-1 (5-HT_1) subfamily of receptors (consisting of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}). The 5-HT_{1A} receptor is the most widespread of all 5-HT receptors. The 5-HT_{1A} receptors are metabotropic receptors, as these are not linked directly to ion channels, but act on ion channels through second messengers. The 5-HT_{1A} receptors are coupled to intermediate molecules called G-proteins that affect second messengers through adenylyl cyclase and other pathways. The 5-HT_{1A} receptors are located in the brain both as presynaptic autoreceptors and as heteroreceptors. The autoreceptors on the neurons in the raphe nuclei (located in the brain stem) inhibit the firing of these neurons. These autoreceptors thus dampen the increase of serotonin release initially when starting SSRI treatment. The 5-HT_{1A} autoreceptor desensitization may take weeks. Postsynaptic heteroreceptors are found in the limbic system, hypothalamus, and frontal cortex (among others), affecting mood, cognition, and memory [8].

Adding 5-HT_{1A} partial agonism to SSRIs causes more immediate and robust elevations of brain 5HT levels than SSRIs do alone in animal models [9]. The search for a drug with combined activity at the serotonin transporter (SERT) and 5-HT_{1A} auto- and heteroreceptors at the right balance turned out to be challenging, because there must be an optimal potency ratio between the targets and an optimal functional activity at the 5-HT_{1A} receptor. Vilazodone is as yet the only antidepressant with this target combination of effects that has made it to the market.

2. Introduction of the compound

Vilazodone has been developed by Clinical Data Inc. and was approved in 2011 by the U.S. Food and Drug Administration for the treatment of MDD. Vilazodone is available in 10, 20, and 40 mg tablets. The recommended target dose is 40 mg per day. The initial dose is 10 mg once daily for 7 days, followed by a dose of 20 mg once daily for 7 days, and then this should be titrated toward the target dose of 40 mg once daily. Vilazodone should be taken together with food, as administration without food can have an lowering effect on the drug concentrations and may diminish effectiveness [10]. The absolute bioavailability is 72% when vilazodone is taken with food. The administration of vilazodone with a high-fat or light meal increases the maximum plasma concentration by approximately 147–160%. If vomiting occurs within 7 h of ingestion, absorption is decreased by approximately 25%. In that case, no replacement dose is needed. When treatment is discontinued, gradual dosage reduction is recommended to avoid adverse reactions due to the serotonin discontinuation syndrome [11].

3. Chemistry

2-benzofurancarboxamide is the chemical formula for vilazodone, 5-[4-[4-(5-cyano-1H-indol-3-yl) butyl]-1-piperazinyl]-, hydrochloride. $C_{26}H_{27}N_5O_2$ is the molecular formula and the molecular weight is 478.0. Vilazodone is a combined serotonin reuptake inhibitor (5-HT, IC50 = 0.2 nM) and 5-HT_{1A} partial agonist (IC50 = 0.5 nM) [12], both of presynaptic autoreceptors and postsynaptic heteroreceptors. The term 'serotonin partial agonist and reuptake inhibitor' (SPARI) has been coined to define this class of antidepressants [13]. Buspirone is another 5HT1A receptor partial agonist. Vilazodone shows negligible activity against the other 5-HT receptors (5-HT_{1D}, 5-HT_{2A}, and 5-HT_{2C}) [11].

4. Pharmacodynamics

Vilazodone is a potent inhibitor of serotonin (5-hydroxytryptamine, 5-HT) reuptake. It does not bind to the norepinephrine (Ki = 56 nM) or dopamine (Ki = 37 nM) reuptake sites. It is hypothesized that the 5-HT_{1A} partial agonism may contribute to an earlier onset of therapeutic effect [14]. Preclinical research suggests that the rapid onset of antidepressant action, may be due to 5-HT auto-augmenting properties [15,16]. No direct comparative study as yet has confirmed a faster onset of effect of vilazodone treatment compared with conventional SSRIs.

5. Pharmacokinetics and metabolism

The accumulation of vilazodone does not vary with dose and steady-state is achieved in approximately 3 or 4 days. Vilazodone concentrations peak at a median of 4–5 h after administration and decline with a terminal half-life of approximately 25 h (17–36 h). Vilazodone is widely distributed throughout the systemic circulation and approximately 96–99% protein-bound. The volume of distribution (Vd) of vilazodone is 7–17 L/kg [17].

Vilazodone is extensively metabolized through hepatic P450 CYP and non-CYP pathways (possibly by carboxylesterase), with only 1% of the dose recovered in the urine and 2% of the dose recovered in the feces as unchanged vilazodone. CYP3A4 is

primarily responsible for its metabolism among CYP pathways, with minor contributions from CYP2C19 and CYP2D6. Moderate and strong inhibitors of CYP3A4 (e.g. grapefruit and commonly used drugs such as clarithromycin, erythromycin, diltiazem, ketoconazole, and verapamil) can reduce the metabolism of vilazodone *in vivo* and increase exposure. Conversely, inducers of CYP3A4 can decrease vilazodone exposure.

Vilazodone is eliminated primarily by hepatic metabolism with a terminal half-life of approximately 25 h [10,11].

6. Clinical efficacy in major depressive disorder

The efficacy of vilazodone in MDD was established in 12 previous studies (Table 1) [18–29]. Trials included between 42 and 1133 adult and adolescent patients with MDD, with one study in elderly patients [27]. Most trials compared one or more doses of vilazodone among each other or to placebo. Four trials also included a group with an active SSRI compound (i.e. citalopram, 40 mg per day, paroxetine 10–30 mg per day and escitalopram 10–20 mg per day), at which two trials directly compare vilazodone with an SSRI [27,28]. The duration of the intervention was between 6 and 12 weeks, while one randomized trial assessed relapse prevention in a 28-week double-blind period [29] and one non-randomized trial treated patients for 52 weeks, assessing long-term safety [23].

Five unpublished phase II studies failed to show superior efficacy of vilazodone compared with placebo. These 8-week, double-blind, randomized, and placebo-controlled trials were not able to prove significant treatment effects on the Hamilton Rating Scale for Depression (HAM-D) [30,31].

Rickels et al. [18], Kahn et al. [19] and Croft et al. [20] conducted three controlled trials to test the efficacy of vilazodone during 8 weeks versus placebo. These trials showed statistically and clinically significant improvements in the Montgomery-Asberg Depression Rating Scale (MADRS) and the HAM-D, two depression severity rating scales.

Mathews et al. [21] conducted a controlled trial that included 1133 patients who were randomized to vilazodone 40 mg/day or 20 mg/day, citalopram 40 mg/day, or placebo during 10 weeks of treatment. The primary efficacy endpoint was the change in the MADRS at week 10 from baseline. Patients in the vilazodone 40 mg and the citalopram arms experienced similar reductions of disease severity scores after 10 weeks, but this comparison was not directly tested. Response rates were similar between the two treatment groups, but the study did not report remission rates. There was no direct comparison between vilazodone and citalopram, because it was not powered to detect differences in efficacy and tolerability between active treatment groups [21]. Another study that included an SSRI, is the study of Grant et al. [26] Forty-two patients who remained symptomatic after 6 weeks treatment of citalopram (20mg/day) were assigned to a higher dose of citalopram (40 mg/day) or to vilazodone (40 mg/day). In both groups there was a decrease in outcome measures, but the study showed no significant differences between groups [26].

Rele et al. [22] conducted a controlled trial that included 70 patients with MDD. Patients who had received fluoxetine, escitalopram, citalopram, sertraline, paroxetine, or venlafaxine were randomized to three groups of varying doses of vilazodone. The existing antidepressants were stopped abruptly, and vilazodone was started without a washout period. All three arms of the study reported significant reductions in mean MADRS, Clinical Global Impressions-Severity (CGI-S), Clinical Global Impressions-Improvement (CGI-I) and HAM-D scores [22].

Ramaswamy et al. [25] included patients with a posttraumatic stress disorder (PTSD) in combination with a comorbid depression. No significant differences were observed between the vilazodone-treated patients and the placebo-treated patients, in other words, treatment with vilazodone did not improve symptoms of PTSD and comorbid depression [25].

The clinical trial of Durgam et al. [24] included adolescent patients, ages 12–17 years, with MDD. In this double-blind randomized clinical trial of adolescents, no statistically significant benefit was observed between vilazodone 15 mg/day or 30 mg/day versus placebo in the Children's Depression Rating Scale-Revised (CDS-R) or CGI-S scores, indicating a lack of clear efficacy in adolescents. The results of a post hoc analysis of randomized trials in MDD suggest a greater efficacy in patients 60 years of age or older as compared to patients younger than 60 years of age [32].

Vilazodone has been directly compared with another antidepressant in two known studies. In the study conducted by Eyre et al. [27], vilazodone and paroxetine showed a significant decrease in HDRS-scores, however no significant differences were observed between the two groups. In the study of Bathla et al. [28] there was also no significant effect of vilazodone compared with escitalopram.

Efficacy outcomes of vilazodone were also reported in the 1-year open-label study of Robinson et al. [23] Two hundred and fifty-four patients completed 1 year of treatment. Patients received vilazodone according to a fixed-titration schedule to reach a dose of 40 mg/day. Mean MADRS total scores improved from 29.9 at baseline to 11.4 at week 8 and 7.1 at week 52. This study shows progressive improvement during long-term treatment and provided data on long-term safety [23]. Durgam et al. [29] showed no significant difference between either vilazodone group (20 mg or 40 mg per day) and placebo group for time to first relapse.

A meta-analysis of four studies of vilazodone [33] examined the efficacy of vilazodone (20 and 40 mg/day) in the treatment of MDD. They found that both dosages of vilazodone showed superior efficacy compared to placebo; the MADRS response rate was significantly higher for vilazodone than for placebo with risk ratio (RR) values of 1.42 for 40 mg/day and 1.27 for 20 mg/day. The risk of discontinuing treatment due to adverse events was also higher with vilazodone compared to placebo, with RR values of 2.09 for 40 mg/day and 2.79 for 20 mg/day [33]. In post hoc analyses [34,35], it has been suggested that vilazodone may be of benefit to depressed patients with comorbid symptoms of anxiety. An overview of the main characteristics of the clinical trials discussed above can be found in Table 1.

7. Clinical efficacy in anxiety disorders

The additional partial agonist activity at the $5HT_{1A}$ receptor may be anxiolytic, as is buspirone with its $5HT_{1A}$ activity [36].

Table 1. Data from randomized, controlled trials and observational studies of the effects of vilazodone on depressive and anxiety disorders.

Source	Registration number	Total N	N, Comparison	Duration (wk)	Mean age (range)	Primary endpoint	Target population	Baseline severity	Main side effect (safety)	Design issues	Conclusions
Depressive disorders:											
Rickels et al. 2009 [18]	NCT00285376	397	198: VILA (40 mg), 199: PLAC	8	39.9 (18–65)	MADRS	MDD patients	MADRS: 30.8 and 30.7	Diarrhea (23.9%), nausea (18.5%), headache (13.2%); similar rates of serious adverse events:2.4%	Lack of active comparison compound.	Significant reduced MADRS total score for VILA.
Kahn et al. 2011 [19]	NCT00683592	463	231: VILA (40 mg), 232: PLAC	8	41.7 (18–70)	MADRS	MDD outpatients	MADRS: 31.9 and 32.0	Diarrhea (30.6%), nausea (26.0%), headache (12.8%); serious adverse events: 6.4% VILA and 5.6% PLAC	Lack of active comparison compound.	Significant reduced MADRS total score for VILA.
Croft et al. 2014 [20]	NCT01473394	505	253: VILA (40 mg); 252: PLAC	8	40.2 (18–70)	MADRS	MDD outpatients	MADRS: 30.6 and 30.9	Diarrhea (32.5%), nausea (24.7%), headache (9.4%); serious adverse events: 0.8% VILA and 0.4% PLAC	Lack of active comparison compound.	Response rate van 27% for VILA and 17% for PLAC ($P < 0.01$).
Mathews et al. 2015 [21]	NCT01473381	1133	288: VILA (20 mg), 284: VILA (40 mg), 280: CITA (40 mg), 281: PLAC	10	41.8 (18–70)	MADRS	MDD outpatients	MADRS: 31.0, 30.8, 31.1 and 31.3	Similar discontinuation rates due to adverse events; VILA: 8,7%; CITA 6.4%.	Remission rates were not reported. No direct comparison between VILA and CITA.	Significant reduced MADRS total score for VILA. Similar reductions of MADRS scores and response rates among active treatment groups.
Rele at al. 2015 [22]	NCT02015546 and NCT01473381	70	22: VILA (10 mg), 22: VILA (20 mg), 26 VILA (40 mg)	8	45 (18–65)	MADRS	MDD	MADRS: 32.6, 28.4 and 31.1	Dry mouth: 92%; nausea: 17%; diarrhea: 8%; no serious adverse events.	Lack of placebo group.	Significant reduction in mean MADRS score from baseline to week 8 in entire sample, no significant differences between the 3 VILA dose-initiation groups
Grant et al. 2017 [26]	NCT01742832	42	19: VILA (40 mg), 23: CITA (40mg)	6	34.9 (18–60)	MADRS	MDD outpatients	NA	Diarrhea: 5.3%; dry mouth: 5.3%; sexual side effects; 5.3% Further information NA	Study was small and underpowered. Only CITA 20mg nonresponders or partial responders. No direct comparison between VILA and CITA	Decreases in outcome measures in both groups, no significant differences between groups

(*Continued*)

Table 1. (Continued).

Source	Registration number	Total N	N, Comparison	Duration (wk)	Mean age (range)	Primary endpoint	Target population	Baseline severity	Main side effect (safety)	Design issues	Conclusions
Ramaswamy et al. 2017 [25]	NCT01715519	59	29: VILA (40 mg), 30: PLAC	12	32.7 (18–55)	CAPS, PSS-SR	Outpatients with PTSD plus MDD	CAPS: 75.3 and 75.6; PSS-SR: 30.0 and 32.1 (visit 2)	Percentages not available. 2 serious adverse events in 1 patient in VILA group	Relative small sample size, mixed state of depression and PTSD	No significant effect of VILA versus PLAC
Eyre and al. 2017 [27]	NCT01608295	56	26: VILA (10–40mg), 30: PAROX (10–30mg)	12	71.5	HDRS	MDD outpatients	HDRS: 17.2 and 16.6	No adverse events. In both groups 2 patients with side effects. Further information NA	Small sample size. Limited information about safety	No significant effect of VILA versus PAROX, greater decrease in leukocyte proinflammatory gene expression for VILA compared to PAROX
Bathla et al. 2018 [28]	NA	60	30: VILA (variable dose), 30: ESCITA (variable dose)	12	NA	HDRS	Depressive episode outpatients	HDRS:18.8 and 18.8	Percentages not available	Small sample size, no information about safety	No significant effect of VILA versus ESCITA, less weight gain and sexual dysfunction VILA versus ESCITA
Durgam et al. 2018 [29]	NCT01573598	564	185: VILA (20 mg), 187 VILA (40 mg), 192 PLAC	28	44.4	MADRS	MDD	MADRS: 4.8, 5.0 and 4.6	VILA 20mg: nasopharyngitis (8.6%), headache (8.1%), diarrhea (7.0%), VILA 40mg: headache (9.7%), diarrhea (8.1%), nasopharyngitis (8.1%), serious adverse events: 2.7% VILA (20mg), 0.5% VILA (40mg) and 2.1% PLAC	Lack of active comparison	No conclusions on relapse prevention of VILA. Long-term treatment VILA well tolerated

(*Continued*)

Table 1. (Continued).

Source	Registration number	Total N	N, Comparison	Duration (wk)	Mean age (range)	Primary endpoint	Target population	Baseline severity	Main side effect (safety)	Design issues	Conclusions
Durgam et al. 2018 [24]	NCT01878292	524	174: VILA (15 mg), 180: VILA (30 mg), 170: PLAC	8	15 (12–17)	CDS-R, CGI-S	Adolescent MDD patients	CDS-R: 57.8, 56.8 and 57.5; CGI-S: 4.6, 4.6 and 4.5	VILA 15mg: nausea (29.1%), headache (12.6%), diarrhea (8.6%), VILA 30mg: nausea (27.2%), headache (16.1%), upper abdominal pain (15.6%), serious adverse events: 1.1% VILA (15mg),1.7% VILA (30mg) and 0.6% PLAC	Lack of active comparison compound, strict inclusion and exclusion criteria	No significant effect of VILA versus PLAC.
Robinson et al. 2011 [23]	NCT00644358	599	VILA (40 mg)	52	(18–70)	Side effects	MDD outpatients	MADRS: 29.9	Diarrhea: 36%; nausea: 32%; headache: 20%; mean weight gain + 1.7 kg. Serious adverse events: 15%.	Lack of placebo group	254 patients completed 1 year of treatment; VILA for 1 year was safe and well tolerated.
Anxiety disorders:											
Gommoll et al. 2015a [37]	NCT01629966	667	223: VILA (20 mg), 223 VILA (40 mg), 221 PLAC	8	40.2 (18–70)	HAMA	GAD outpatients	HAMA: 24.7, 24.4 and 24.4	VILA 20 mg: diarrhea (25.1%), nausea (24.2%), headache (14.1%); VILA 40mg: nausea (25.8%), diarrhea (21.3%), headache (11.1%), serious adverse events: 0.4% VILA (20mg), 0% VILA (40mg) and 0.5% PLAC	Lack of active comparison compound	Significant reduced HAMA total score for VILA 40 mg, no significant effect for VILA 20 mg
Gommoll et al. 2015b [38]	NCT01766401	395	198: VILA (20–40 mg); 197: PLAC	8	40.1 (18 –70)	HAMA	GAD outpatients	HAMA: 25.9 and 24.9	VILA: nausea (31.5%), diarrhea (31.0%), dizziness (7.5%), headache (7.5%); no serious adverse events	Lack of active comparison compound	Significant reduced HAMA total score for VILA 20–40mg (flexible dose)

(*Continued*)

Table 1. (Continued).

Source	Registration number	Total N	N, Comparison	Duration (wk)	Mean age (range)	Primary endpoint	Target population	Baseline severity	Main side effect (safety)	Design issues	Conclusions
Careri et al. 2015 [41]	NCT01712321	39	20: VILA (20–40mg); 19: PLAC	12	(18–75)	LSAS	Generalized social anxiety disorder	LSAS: 88.0 and 96.0	nausea (25%), drowsiness (25%), diarrhea (20%), serious adverse events: 5% VILA and 0% PLAC	Small sample size, lack of active comparison compound	Significant reduced LSAS score for VILA 20–40mg (flexible dose)
Durgam et al. 2016 [39]	NCT01844115	415	208: VILA (20 – 40 mg); 207: PLAC	8	39.9 (18–70)	HAMA	GAD outpatients	HAMA: 24.5 and 25.0	nausea (29.7%), diarrhea (27.7%), dizziness (10.9%), headache (10.9%); serious adverse events: 1.5% VILA and 0% PLAC	Lack of active comparison compound	Significant reduced HAMA total score for VILA 20–40mg (flexible dose)
Schneier et al. 2017 [40]	NCT01999920	24	13: VILA (15 mg), 11: PLAC	12	35.2 (18–60)	CGI-C	Separation anxiety disorder outpatients	Results CGI-C NA	Headache 46.2%, decreased libido in men 40%, sexual dysfunction in men, discontinuation rate due to adverse events; 7,7%;	Study was small and underpowered.	No significant effect of VILA versus PLAC, but response rates were VILA 5/6 [83.3%] vs. PLAC 4/9 [44.4%].

Abbreviations: CAPS, Clinically Administered PTSD Scale; CDRS-R, Children's Depression Rating Scale-Revised; CGI-S, Clinical Global Impressions-Severity scale; CITA, citalopram; ESCITA, escitalopram; FLUO, fluoxetine; GAD, Generalized Anxiety Disorder; HAMA, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; LSAS, Liebowitz Social Anxiety Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, Major Depressive Disorder; NA, not available; PAROX, paroxetine; PLAC, placebo; PTSD, posttraumatic stress disorder, PSS-SR, PTSD Symptom Scale – Self Report; VILA, vilazodone.

Vilazodone has been found to be efficacious compared with placebo in several studies of anxiety disorders [37–41]. The trials were conducted in outpatients with GAD, separation anxiety disorder and generalized social anxiety disorder. All trials compared one or more doses of vilazodone among each other or to placebo, none of the trials compared vilazodone with another active compound. The duration of the trials was 8 weeks or 12 weeks. Two trials were underpowered with a small sample size, these studies had less than 40 patients in total.

Gommoll et al. [37] conducted a controlled trial of 8 weeks of vilazodone versus placebo. Although there was a significant reduction in HAMA (Hamilton Anxiety Rating Scale) scores in the vilazodone 40 mg/day arm compared with placebo, there was no significant difference between vilazodone 20 mg/day and placebo. The flexible-dose study (20–40 mg/day) of Gommoll et al. [38] showed a significant improvement on the HAMA total score in the patient group treated with vilazodone compared to placebo. The randomized, placebo-controlled flexible-dose study (20–40 mg/day) of Durgam et al. [39] found a significantly reduced HAMA total score for vilazodone compared with placebo [39]. The difference between the vilazodone-treated patients and the placebo-treated patients was statistically significant beginning at week 4, and it remained significant throughout week 8.

Careri et al. [41] examined vilazodone in generalized social anxiety disorder. The vilazodone group had improved significantly more than the placebo group. The pilot study of Schneier et al. [40] included patients with adult separation anxiety disorder (ASAD). This study showed no significant difference in response rates between the vilazodone and placebo groups among completers at week 12.

In a recent meta-analysis [42], the number needed to treat (NNT) was 10 for the induction of response, whereas the number needed to harm (NNH) for the induction of any adverse effect (mainly due to nausea and diarrhea) was to be 7. An overview of the main characteristics of the clinical trials discussed above can be found in Table 1.

8. Safety and tolerability

The safety and tolerability profile for vilazodone has been studied in several trials (Table 1) [18–26,37–41]. Dry mouth, diarrhea, nausea, headache, and dizziness were the most commonly reported side effects. In almost all studies there were similar rates of serious adverse events between the vilazodone-treated patients and placebo-treated patients with a slighty increased percentage in the vilazodone group. In the randomized trials, the percentages for discontinuation ranged from 4.4% to 20.7% of participants in vilazodone groups versus only 1.7–5.1% in the placebo groups (Table 1). In the three large trials in GAD patients [37–39,42], there were serious adverse reactions in four patients out of 854 patients, though these were not related to vilazodone treatment. In the meta-analysis of these three GAD trials [42], adverse events were significantly more frequent with vilazodone, furthermore, vilazodone was significantly more likely than placebo to be discontinued due to adverse events.

In a 1-year open-label treatment study [23], vilazodone 40 mg/day was found to be safe and about 21% (124 patients out of 599 patients) discontinued treatment because of side effects, which severity was considered to be mostly mild to moderate in severity. Again, gastrointestinal side effects were most common, and weight gain was relatively limited (mean 1.7 kg after 52 weeks). In the trial that included vilazodone (40 mg/day) and citalopram (40 mg/day) [21], significantly more patients on vilazodone experienced diarrhea (26.5% vs. 10.6%) and vomiting (6.6% vs. 1.8%) . But, the overall risks of adverse events during 10 weeks of treatment were rather similar (8.7% vs. 6.4%). Another study found that a higher dose of 40 mg/day might be associated with more diarrhea than lower doses of 10 and 20 mg/day [22]. There was a similar risk for suicidal ideation between patients on vilazodone and citalopram as assessed on the Columbia-Suicide Severity Rating Scale (18.1% vs. 16.3%). There was one patient out of 1133 patients in the vilazodone 20 mg/day group who attempted suicide [21].

The main reason for a focus on sexual dysfunction is the fact that the additional partial agonist activity on the 5-HT_{1A} receptor of vilazodone might theoretically limit the risk of sexual dysfunction compared with SSRIs and also improve depression related sexual dysfunctions [13,43]. Although rather low rates of sexual dysfunction were reported [11], treatment-emergent sexual dysfunction was more frequent with vilazodone than with placebo in trials in GAD patients [37–39]. Also in placebo-controlled trials in adult MDD patients, 8.0% of vilazodone-treated patients and 0.9% of placebo-treated patients reported one or more treatment-emergent sexual dysfunction ($P < 0.001$) [44].

There are no adequate well-controlled studies of vilazodone during pregnancy. The FDA has designated vilazodone as a pregnancy category C drug; the use of vilazodone should be recommended in pregnancy only if the potential benefits outweigh the potential risks. Vilazodone caused some developmental toxicity in rats, but there were no teratogenic effects in rats or rabbits [10,43].

During postmarketing experience there are reports of acute pancreatitis and sleep paralysis. Skin disorders including rash, urticaria, and drug eruption were also reported with vilazodone. Psychiatric symptoms reported during the postmarketing surveillance of vilazodone were hallucinations, suicide attempt, and suicidal ideation [10].

All in all, side effect profiles seem to be largely comparable to those of SSRIs, but studies directly comparing vilazodone and SSRIs are needed to enable a more comprehensive risk-benefit assessment.

9. Conclusions

Vilazodone was found to be an efficacious antidepressant compared with placebo, as shown by the reduction of the MADRS/HAM-D scores in adults with MDD, but not in adolescents with MDD [24]. It is also supported by higher MADRS and HAM-D response rates with vilazodone compared with placebo [18,19]. However, at this point in time, vilazodone has shown no substantial differences in efficacy as first-step treatments in MDD compared to SSRIs and other second-generation antidepressants [45].

Further investigation is needed to clarify its role in the treatment of MDD. The recommended therapeutic dose is 40 mg/d [10].

In clinical trials, vilazodone was generally well tolerated. Diarrhea, nausea, headache, and dizziness were the most common side effects and were assessed as mild or moderate in severity in most cases. Previous studies have shown similar rates of serious adverse events between the vilazodone-treated patients and placebo-treated patients through with a slightly increased percentage in the vilazodone group [19,20,24,39,41]. Sexual function-related adverse events were considered mild or moderate in severity [20,21,37,38]. Weight gain in the long-term MDD trial was limited (mean increase: 1.7 kg) [23].

In conclusion, vilazodone is safe and effective for the treatment of MDD, with a new mode of action as a 5-HT_{1A} receptor antagonist. Its current long-term efficacy and safety profile is largely based on one study with a 1-year duration. Therefore, more long-term studies are necessary. Furthermore, additional Phase III trials are needed to compare the efficacy with SSRIs. In addition, such trials could reveal whether the onset of action of vilazodone is faster than other antidepressants in patients with MDD and GAD.

Several trials are ongoing, which will hopefully provide answers to these questions. While most studies were done in middle-aged patients, more studies are currently underway in elderly patients as well as studies in anxiety disorders.

10. Expert opinion

Vilazodone is a relatively novel treatment option for MDD and GAD. When considering the current evidence from the actual available trials, vilazodone has shown efficacy compared to placebo, though further long-term placebo-controlled trials are required. It should be noted, that so far, only one long-term (28 weeks) placebo-controlled trial has been performed with vilazodone. In this relapse study there was no significant difference between vilazodone and placebo for time to first relapse [29].

Only a few studies directly compare vilazodone with SSRIs, but these studies were underpowered and showed no significant differences between vilazodone and SSRIs. It would be valuable to determine whether vilazodone shows faster and increased efficacy in a large-scale study with direct comparison with SSRIs.

In the flexible-dose trials, most patients had their doses titrated to 40 mg/day, suggesting lower efficacy with lower doses. New studies need to be conducted to compare fixed doses of vilazodone to detect a dose-response relationship.

In our opinion, vilazodone cannot be recommended as a first-line treatment option for MDD as it is unclear whether the drug's dual mechanism of action provides greater efficacy than prevailing treatment options. Present studies do not suggest the superiority of vilazodone compared with other antidepressants. The theoretical advantages of vilazodone, such as a rapid onset of action, a higher degree of tolerability and fewer side effects (such as sexual dysfunction) than other antidepressant agents, have as yet not been strongly supported in the actually available studies. The partial agonistic effect on the 5-HT_{1A} receptor was suggested to have some benefits, particularly for depressed patients with comorbid symptoms of anxiety. However, more postmarketing phase IV studies are needed to establish its efficacy and safety in larger and more diverse populations. For example, there is no data over whether vilazodone can be safely prescribed for pregnant or breastfeeding patients. Although there are indications that vilazodone may have some additional advantage for the treatment of anxiety symptoms in MDD [34,35], here also well-designed studies are required to confirm efficacy over and above SSRI treatment. Therefore, vilazodone should currently be considered as a second- or third-line treatment option for MDD and GAD.

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