1. Introduction

Major depressive disorder (MDD) is the leading cause of disability worldwide, and according to the STAR*D trial, only 33% of patients with MDD responded to initial drug therapy. Augmentation of the leading class of antidepressant treatment, selective serotonin reuptake inhibitors (SSRIs), with the 5-HT1A receptor agonist buspirone has been shown to be effective in treating patients that do not respond to initial SSRI therapy. This suggests that newer treatments may improve the clinical picture of MDD. The US Food and Drug Administration (FDA) approved the antidepressant drug vilazodone (EMD 68843), a novel SSR1 and 5-HT1A receptor partial agonist. Vilazodone has a half-life between 20–24 hours, reaches peak plasma concentrations at 3.7–5.3 hours, and is primarily metabolized by the hepatic CYP450 3A4 enzyme system.

Areas covered: The authors review the preclinical and clinical profile of vilazodone. The roles of serotonin, the 5-HT1A receptor, and current pharmacotherapy approaches for MDD are briefly reviewed. Next, the preclinical pharmacological, behavioral, and physiological effects of vilazodone are presented, followed by the pharmacokinetic properties and metabolism of vilazodone in humans. Last, a brief summary of the main efficacy, safety, and tolerability outcomes of clinical trials of vilazodone is provided.

Expert opinion: Vilazodone has shown efficacy versus placebo in improving depression symptoms in several double-blind, placebo-controlled trials. The long-term safety and tolerability of vilazodone treatment has also been established. Further studies are needed that directly compare patients treated with an SSRI (both with and without an adjunctive 5-HT1A partial agonist) versus patients treated with vilazodone.

1.1 Role of the serotonergic system in MDD

The serotonergic system has been implicated in having a major role in the pathophysiology of MDD. In 1987, fluoxetine became the first selective serotonin reuptake inhibitor (SSRI) to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDD.[9] The serotonergic pathway originates mainly from the raphe nuclei, and it plays a major role in a wide range of brain functions, including mood regulation, fear responses, sleep, appetite, and sexual behavior.[10] It is important to a wide range of functions because of its direct and indirect influence on other neurotransmitter systems, such as dopamine, norepinephrine, glutamate, acetylcholine, histamine, and GABA, and autoregulation of its own serotonergic pathways.[11,12] Not surprisingly, dysregulation of the serotonergic system is implicated in several mental disorders including MDD.

Several lines of evidence have implicated depletion of monoaminergic neurotransmitters, namely serotonin (5-HT), norepinephrine, epinephrine, and dopamine, in the pathophysiology of depression, which has led to the monoamine depletion hypothesis of depression.[13] Long-term longitudinal studies have linked reductions of cerebrospinal fluid levels of...
5-hydroxyindoleacetic acid (5-HIAA) and postmortem whole brain 5-HT concentrations in depressed patients and suicide victims.[14] Also, 5-HT depletion through dietary tryptophan restriction [15] or pharmacologically (i.e. reserpine or p-chlorophenylalanine) [16] induces relapse in depressed patients who have responded to antidepressant treatment. [17]

Furthermore, drugs that effectively improve symptoms of depression elevate levels of one or more monoamines. [13]

The monoamine hypothesis of depression has evolved over the years, and it is now assumed that adaptive changes in receptors play an increased role in antidepressant treatment response; this may partially explain why a gradual clinical response is typically observed with antidepressants, while the increase in the levels of extracellular monoamines is rapid. [18]

### 1.2 Serotonin receptors

There are 14 types of 5-HT receptors in the brain, and each has roles in a wide range of functions throughout the body, including mood, body temperature, anxiety, sleep, memory, and nausea. [19] The most widespread 5-HT receptor is 5-HT1A, which is located mostly in the raphe nuclei (presynaptic), hippocampus, frontal cortex, dorsal horn of the spinal cord, the lateral septum, and amygdala (postsynaptic). [20] The density of 5-HT1A receptors in the amygdala and hippocampus has been found to be lower in patients with MDD than in healthy patients. [21]

### 1.3 Role of 5-HT1A receptors in antidepressant action

Presynaptic 5-HT1A receptors are autoreceptors that provide an autoregulatory mechanism that inhibits 5-HT neurons. Once activated, the receptor opens potassium channels, causing cell membrane hyperpolarization and a reduction in the 5-HT cell firing rate. [22, 23] The majority of antidepressant medications acts by increasing the concentration of 5-HT in the extracellular space through the inhibition of serotonin reuptake transporters (SERTs). This increase in extracellular 5-HT preferentially takes place in the raphe nuclei over the frontal cortex. In the raphe nuclei, increased extracellular 5-HT leads to greater negative feedback activation through the 5-HT1A autoreceptors, which results in attenuation of 5-HT cell firing and terminal release of 5-HT. [24–26] Because of this attenuation, the activation of postsynaptic 5-HT receptors that is thought to be responsible for the therapeutic effect of SERT blockade is lower than expected. [27, 28] However, the efficacy of 5-HT1A negative feedback becomes less marked following long-term treatment with SSRIs, which is thought to be mediated by desensitization of the presynaptic 5-HT1A autoreceptors. Desensitization eventually leads to a recovery of 5-HT neuron firing in the dorsal raphe nucleus, and consequently, to an increase in extracellular 5-HT release that is greater than that following a single or acute administration of SSRIs. [29, 30]

### 1.4 Role of 5-HT1A receptors in anxiolytic action

5-HT1A receptors, notably presynaptic 5-HT1A autoreceptors, play a central role in the pathophysiology and treatment of anxiety disorders. Microinjection of buspirone, a 5-HT1A receptor agonist, directly into limbic regions triggers a significant anxiolytic action. [31] Gene-targeting technology in mice resulting in 5-HT1A receptor overexpression has been shown to reduce anxiety-like behavior in transgenic mice. [32] Moreover, complete elimination of the 5-HT1A receptor in mice models leads to an increase in anxiety-like behavior due to the impaired neuronal autoinhibitory response. [33] Studies with human subjects have also demonstrated the importance of 5-HT1A receptors in anxiety disorders. Single positron emission tomography scan using the 5-HT1A tracer has shown a reduced presynaptic and postsynaptic 5-HT1A receptor binding in untreated patients with panic disorder in comparison with control subjects. [34]

### 1.5 Current pharmacotherapies for MDD

Patients who achieve acute response or remission from a first episode of MDD with pharmacotherapy typically receive 4–9 months of continuation treatment to prevent relapse; patients with recurrent MDD may receive long-term maintenance therapy. [35] Current antidepressant drugs can be divided into five major categories: SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and...
multimodal antidepressants (e.g. bupropion, mirtazapine, and vortioxetine).[36] Agomelatine, a new antidepressant agent, acts through a combination of antagonist activity at 5-HT2C receptors and agonist activity at melatonergic MT1/MT2 receptors. It is unique in that it does not possess a monoaminergic component and has no ability to interfere with the neuronal reuptake of 5-HT, norepinephrine, or dopamine.[37]

No drug class has proven to be effective in all patients; for instance, SSRIs and SNRIs typically achieve 25–35% and 25–45% remission rates, respectively.[38–40] Furthermore, many patients may experience a lag phase until efficacy is observed. The lag phase is thought to be due to the action of a 5-HT1A presynaptic receptor-mediated negative feedback system, and clinical effect may require up to 6 weeks of continuous treatment until receptor desensitization leads to a recovery of 5-HT neuron firing.[41–43] This approximate 6-week lag phase that is associated with SSRIs is believed to represent the time required for desensitization of the 5-HT1A receptor.[41] SSRIs also increase synaptic levels of 5-HT in forebrain regions, including the cortex, hippocampus, and striatum, which in turn stimulates presynaptic 5-HT1A receptors to decrease 5-HT levels.[44–47] In addition, coadministration of pindolol, a mixed 5-HT1A/β-adrenergic receptor partial agonist, with SSRIs enhanced the levels of extracellular 5-HT.[46–50]

According to the National Institute of Mental Health’s STAR*D trial, only 33% of patients with MDD responded to initial drug therapy, and each subsequent treatment was likely be less successful than the previous one.[21,51] Additionally, 33% of patients continued to have significant symptoms after 1 year of successive treatments with a new antidepressant drug.[21,51] On the basis of the STAR*D trial, augmentation of SSRIs with buspirone has been shown to be effective in treating patients who do not respond to initial SSRI therapy, suggesting that addition of 5-HT1A partial agonism to 5-HT reuptake inhibition may improve the clinical picture in MDD. The antidepressant drug vilazodone (EMD 68843), which shows SSRI and 5-HT1A partial agonist activity (Table 1), was approved by the FDA on 21 January 2011 for the treatment of MDD in adults.[19,52]

2. Pharmacological profile of vilazodone

2.1 Mechanism of action

Vilazodone is an indolalkylamine that acts as both a potent SSRI (IC50 = 0.2 nM, Ki = 0.1 nM) and a 5-HT1A receptor partial agonist (IC50 = 0.5 nM). While vilazodone exhibits high affinity toward the 5-HT1A reuptake site, it does not bind to the norepinephrine (Ki = 56 nM) or dopamine (Ki = 37 nM) reuptake sites as avidly.[19] It has also been suggested that the 5-HT1A partial agonist activity of vilazodone may eliminate the efficacy lag phase observed with SSRIs, thereby effectively reducing patient response time.[19]

Vilazodone is 60 times more selective for the 5-HT1A receptor than buspirone, the only 5-HT1A receptor partial agonist that is approved for clinical use as an antidepressant.[53] Overstimulation of presynaptic 5-HT1A receptors is interpreted by the neuron as toxic activity, and it leads to 5-HT1A autoreceptor downregulation; this process reduces the negative feedback mechanism and prevents increased extracellular 5-HT release.[21] Accordingly, vilazodone has been shown to reduce the sensitivity of 5-HT1A autoreceptors in the dorsal raphe nuclei more rapidly than the SSRIs fluoxetine and paroxetine.[54] Unlike vilazodone, administration of 5-HT1A receptor agonists or partial agonists such as buspirone, 8-hydroxy-2-(dipropylamino)tetralin hydrobromide (8-OH-DPAT), and MKC-242 caused an increase in extracellular dopamine and norepinephrine in the rat brain.[55–58] Molecular experiments using ligand-facilitated binding of [35S]GTP[S to G1 proteins together with the 5-HT1A receptor expressed in SF9 cells showed that compared to vehicle, vilazodone (partial agonist) increased binding by fourfold, whereas the full agonist 8-OH-DPAT increased binding by eightfold.[59]

Vilazodone has high affinity for SERT and achieved 100% occupancy at 10 mg/kg and 50% occupancy at 1–3 mg/kg in rat cortex and hippocampus ex vivo.[59] This differs from in vivo occupancy, which is difficult to assume, because intrinsic activity depends on the receptor reserve available and concentration of endogenous agonist (i.e. 5-HT); notably, vilazodone (1 and 10 mg/kg) caused no change in extracellular levels of norepinephrine or dopamine.[59] Moreover, the SSRI activity of vilazodone is 30 times more potent than fluoxetine, which likely contributes to a faster proposed onset of action.[60] Page et al. (2002) compared brain 5-HT levels in response to systemic injection with fluoxetine or vilazodone in rats. In that study, 5-HT levels measured 3 h after injection revealed that acute administration of vilazodone produced larger maximal increases of extracellular 5-HT than the SSRI fluoxetine in both the ventral hippocampus (558 vs. 274%) and the frontal cortex (527 vs. 165%).[61] Despite these encouraging results, there is currently no clinical data that compares the onset of action of vilazodone to other antidepressants.

2.2 Behavioral and physiological effects of vilazodone in rodents

Several experiments in rats have been conducted to further establish the mechanism of action of vilazodone. Vilazodone administration inhibited ultrasonic vocalization, which is a behavioral model for anxiolytic activity that is mediated by presynaptic 5-HT1A receptor activation.[61] The reduction in ultrasonic vocalization was blocked by coadministration with the potent 5-HT1A receptor antagonist WAY 100,635.[62] In contrast, administration of fluoxetine had no effect on ultrasonic vocalization.[62] Vilazodone also demonstrated dose-dependent anxiolytic efficacy in both the predator-induced stress paradigm (20–40 mg/kg) and the shock probe test (10–40 mg/kg); the latter measures defensive burying behavior in response to a shock from a stationary electrified probe. [62] Vilazodone blocked the predator-induced stress response both 90 min before and 10 min after exposure to the predator. However, no significant anxiolytic effects were observed on the elevated plus maze (EPM); in the EPM test, the animal is paced in the center of an elevated four-arm maze that has two open and well-lit arms and two closed and dimly lit arms. This outcome may not be surprising because the EPM test is
known to result in highly variable responses with other serotonergic drugs.[63]

Antidepressant efficacy of vilazodone in rats was assessed using the forced swim test (FST). Prior to the FST, rats were injected intraperitoneally with three doses of vilazodone (1, 3, or 10 mg/kg). All three treatment groups showed reduced immobility and increased swimming behavior, which indicated antidepressant-like response, although only the 1-mg/kg dosing group exhibited significant changes.[64] Core body temperature change, which is mediated by postsynaptic 5-HT\textsubscript{1A} receptor activity, was not observed after vilazodone administration in rats.[65] However, intraperitoneal vilazodone (1–10 mg/kg) exhibited a significant dose-dependent hypothermic response in mice and also attenuated stress-induced hyperthermia in mice. These effects of vilazodone were reversed by WAY 100635, a potent 5-HT\textsubscript{1A} receptor antagonist [66], suggesting that vilazodone may have thermoregulatory effects that can be attributed to its partial 5-HT\textsubscript{1A} receptor agonism. Symptoms of 5-HT syndrome were not observed in rats with the highest doses of vilazodone, in contrast to high doses of the full 5-HT\textsubscript{1A} receptor agonist 8-0H-DPAT, which did cause 5-HT syndrome symptoms. These differences were likely mediated by full (8-0H-DPAT) versus partial (vilazodone) 5-HT\textsubscript{1A} receptor agonist activity.[61]

### 2.3 Pharmacokinetics of vilazodone in humans

Vilazodone is available in 10-, 20-, and 40-mg tablets for daily treatment to be taken preferably in the morning with food. Initial dosage is recommended at 10 mg once daily for the first 7 days, 20 mg once daily for 7 days (to minimize the potential for adverse gastrointestinal side effects), and finally 20 or 40 mg once daily to achieve the recommended maintenance dose.[41,67]

The pharmacokinetics of vilazodone was investigated in healthy volunteers with doses ranging from 2.5 to 80 mg. Serum concentrations were found to be dose dependent, with mean maximum concentrations of 1.5 ng/ml for 2.5-mg dose and 156 ng/ml for 80-mg dose.[68] Peak plasma concentrations were observed at 3.7–5.3 h, and the half-life was between 20 and 24 h (Table 1). Vilazodone must be ingested with food in order to increase its bioavailability from 22 to 72% and to protect the gastrointestinal system.[21,36] Vomiting after 7 h decreased absorption by 25%; however, no replacement dosage was required.[69] Once absorbed, it was widely distributed throughout the body, with 96–99% of vilazodone being protein bound. This high level of protein binding may temporarily disrupt digoxin or Coumadin binding, as it displaces these drugs into a nonprotein-bound, free plasma state that increases their availability and activity.[21] For this reason, caution is needed when vilazodone is taken with other highly protein-bound drugs, including phenytoin and warfarin.[70]

After daily doses of vilazodone 40 mg with food, the mean maximum plasma concentration (C\textsubscript{max}) at steady state was 156 ng/ml, and the mean area-under-the-curve (AUC\textsubscript{0–24h}) concentration was 1645 ng-h/ml; AUC\textsubscript{0–24h} increased from 147 to 160% and 64 to 85% when patients had either a high-fat or light meal, respectively. Neither the C\textsubscript{max} nor AUC of vilazodone was affected by ethanol intake.[69] Vilazodone metabolism occurs in the liver, with only 1 and 2% unchanged vilazodone recovered in urine and feces, respectively. A study by Boinpally et al. (2013) compared the pharmacokinetics of vilazodone 20 mg in 32 subjects with mild to moderate kidney impairment with that in healthy controls; total drug clearance, mean drug recovery in urine, AUC, C\textsubscript{max}, and half-life parameters were found to be not significantly different. Also, no vilazodone dosage change was needed in patients with renal or hepatic impairment.[71] A gradual withdrawal from vilazodone is suggested to prevent 5-HT discontinuation syndrome.[21]

### 2.4 Metabolism of vilazodone

Vilazodone is metabolized primarily by the hepatic CYP450 3A4 enzyme system and secondarily by CYP2C19, CYP2D6, and other non-CYP pathways that are mediated by carboxylesterases.[72,73] For this reason, the vilazodone dose should not exceed 20 mg if coadministered with moderate CYP3A4 enzyme inhibitors (e.g. erythromycin or ketoconazole) in patients who experienced intolerable adverse events due to a 50% increase in observed plasma concentration.[70] Because of this drug interaction, vilazodone in combination with strong CYP3A4 inhibitors such as ketoconazole may warrant up to a 50% decrease of vilazodone dosage. Equally, the maximum of 80 mg/day dosage of vilazodone should be considered when given in combination with strong CYP3A4 inducers such as carbamazepine.[74] However, no vilazodone dose adjustment is necessary when it is coadministered with mild inhibitors of CYP3A4 (e.g. cimetidine). Conversely, inducers of CYP3A4 have the potential to reduce systemic vilazodone exposure, although this has not been systematically evaluated. And finally, coadministration with CYP2C8 substrates has been shown to disrupt the metabolism of vilazodone in vitro [70]; this has not been evaluated in vivo. M17 and M10 are two major inactive metabolites of vilazodone that are formed as a by-product of hepatic metabolism. M17 is under postapproval surveillance for human embryofetal toxicity. The projected exposures to M10 and M17 represented more than 10% of total circulating vilazodone-related species at steady state after a single 20-mg dose to healthy male subjects.[75]

Because of the action of 5-HT in platelet function, the use of SSRIs may increase the risk of upper gastrointestinal bleeding; coadministration of nonsteroidal anti-inflammatory drugs or aspirin may potentiate the risk of bleeding. Increased bleeding has occurred when SSRIs and SNRIs were coadministered with warfarin. No significant adverse effects of vilazodone 20 mg were found in healthy volunteers on biotransformation of substrates for CYP1A2 (caffeine), CYP2C9 (flurbiprofen), CYP2D6 (debrisoquine), and CYP3A4 (nifedipine).[36]

### 2.5 Drug interactions

Because of the mechanism of action of vilazodone and its effect on increased extracellular 5-HT release, many drugs should not to be taken with vilazodone. These include MAOIs, SSRIs, SNRIs, buspirone (Buspar, Bristol-Myers Squibb), tramadol (Ultram, Janssen/PriCara), triptans, and tryptophan, a 5-HT precursor. The combination of vilazodone with 5-HT-
stabilizing drugs is contraindicated. When use of an MAOI and vilazodone is necessary, administration should occur at least 14 days apart. The use of SSRIs and antipsychotic drugs or SNRIs may cause fatal neuroleptic malignant syndrome (NMS)-like reactions or 5-HT syndrome.[69]

3. Clinical profile of vilazodone

3.1 MDD

FDA approval of vilazodone came after two, 8-week placebo-controlled phase III trials with adult patients with MDD and a current depressive episode between 4 weeks and 2 years in duration.[76,77] In both of these studies, the mean change from baseline to week 8 on the Montgomery-Åsberg Depression Rating Scale (MADRS), the primary efficacy parameter, showed significant improvements with vilazodone treatment compared to placebo. Response rates in the two studies (≥50% MADRS score decrease) were determined to be 40 and 28% (p = .007), for vilazodone and placebo, respectively [76], and 44 and 30% (p = .002), for vilazodone and placebo, respectively.[77] These results were similar to other antidepressant drugs trials, including TCAs (39 vs. 28% placebo) and the SSRI escitalopram (52 vs. 37% placebo).[78] The efficacy of vilazodone 40 mg/day was further supported in two double-blind, randomized phase IV trials. One of these trials had a vilazodone 20-mg/day treatment arm, with positive results supporting the efficacy of vilazodone at lower doses. In both trials, all vilazodone-treated groups showed significant improvement relative to placebo in MADRS score starting at week 2 and persisting to the end of double-blind treatment.[79,80] A 52-week open-label study to assess the safety and tolerability of vilazodone 40 mg/day in 616 adult patients with MDD reported the mean change in MADRS score to be −18.5 at week 8, −21.7 at week 24, and −22.8 at week 52, which suggested that long-term efficacy was maintained with vilazodone.[81] There are currently no head-to-head studies comparing efficacy against other antidepressant agents published.

3.2 Generalized anxiety disorder

Positive results have been reported for vilazodone in three of three, double-blind, randomized, placebo-controlled, 8-week trials in adult patients with generalized anxiety disorder (GAD). One study evaluated fixed-dose vilazodone 20 or 40 mg/day [82], and two studies evaluated flexibly dosed vilazodone 20–40 mg/day.[83,84] The primary outcome measure in each study was change from baseline to week 8 in Hamilton Anxiety Rating Scale (HAMA) total score. In the fixed-dose study, vilazodone 40 mg/day was significantly superior to placebo on the primary efficacy measure; the difference in mean reduction in HAMA score between vilazodone 20 mg/day and placebo did not reach statistical significance. In both flexible-dose studies, statistically significant improvement in HAMA total score was seen for vilazodone 20–40 mg/day relative to placebo. Given the high comorbidity between MDD and GAD, proven efficacy in GAD may make vilazodone a favorable treatment option for patients with depression and prominent symptoms of anxiety. There are currently no head-to-head studies comparing efficacy against other anxiolytic agents published.

4. Tolerability and safety of vilazodone

4.1 Tolerability

Studies have shown that vilazodone is generally well tolerated under doses of 40 mg per day; according to the FDA, doses of vilazodone higher than 40 mg may be poorly tolerated.[85] In a phase III clinical study, 23.9% of patients taking vilazodone reported diarrhea and 18.5% reported nausea compared to 7.3 and 4.4%, respectively, in the placebo group. The majority of these adverse events was labeled as mild or moderate in intensity and were self-limiting, with a median duration of 4 or 5 days. Only 18 vilazodone-treated patients (8.8%) and 11 placebo-treated patients (5.4%) complained of severe symptoms.[76] Although no cases of hyponatremia were associated with vilazodone therapy in clinical studies, hyponatremia is known to occur as a result of treatment with SSRIs and SNRIs. Activation of mania or hypomania can occur with vilazodone therapy; therefore, patients should be screened for bipolar disorder.[69]

In a 52-week open-label study designed to assess the safety and tolerability of vilazodone 40 mg/day in 616 adult patients with MDD, 51% completed at least 6 months of the study and 41% completed 1 year.[65] Overall, 20.7% patients discontinued the trial because of adverse effects, which were mostly gastrointestinal (diarrhea, 35.7%; nausea, 31.6%) and headache (20.0%). Similar to the adverse effects observed in the short-term trials, the majority of side effects was considered mild or moderate in intensity, with 14.9% of patients reporting severe adverse events (gastrointestinal = 21 patients; headache = 7 patients). No abnormal changes were recorded in liver enzyme elevations, blood pressure, heart rate, or electrocardiograms. The mean weight increase over the 52 weeks was only 1.7 kg, which may have been due to vilazodone’s lack of effects on histamine blockade and 5-HT2 receptor antagonism.[86] The 52-week study showed that vilazodone 40 mg/day was safe and well tolerated; however, the lack of a placebo group limits conclusions about the long-term effectiveness of vilazodone.[81] There are no reported head-to-head studies comparing tolerability of vilazodone against other antidepressant agents.

4.2 Cardiovascular adverse events

Effects on cardiac health were investigated in a phase I study enrolling 45 placebo-treated and 66 vilazodone-treated patients who received daily doses of vilazodone that increased every 3 days (10, 20, 40, 60, and finally 80 mg) for 15 days total vilazodone treatment; there was no significant change in QTc interval from baseline (range, −1.3 to 2.7 ms).[87]

4.3 Pregnancy and pediatrics

Vilazodone may be taken during pregnancy if the benefits outweigh the potential risks, despite its observed adverse effect on animal fetuses and lack of information in human trials.[67,88] Higher need for intensive care treatment and...
risks of pulmonary hypertension and neonatal behavioral syndrome have been reported in some infants born to mothers taking SSRIs.[89] The black box warning label emphasizes that vilazodone is not indicated for pediatric use.[69]

4.4 Sexual dysfunction

Sexual dysfunction is a common symptom of MDD, with untreated male and female patients reporting decreased libido (42 and 50%, respectively), inability to sustain an erection in men (46%), and difficulty in obtaining vaginal lubrication in women (40%).[90,91] Antidepressant drugs can also negatively affect sexual functioning in patients with MDD due to changes in 5-HT, dopamine, and norepinephrine synaptic release and signaling.[92–94] Activation of 5-HT1A receptors has been shown to reverse inhibited sexual function by increasing libido and facilitating ejaculation.[92,95]

The effects of vilazodone and prototypical SSRIs (citalopram and paroxetine) on copulatory and ejaculatory behaviors in male rats were recently investigated.[96] After 7 and 14 days of treatment with citalopram (10 and 30 mg/kg) or paroxetine (10 mg/kg), impaired sexual behaviors were observed, including reduced ejaculatory frequency and copulatory efficiency. In contrast, vilazodone (1–10 mg/kg) did not exhibit significant changes in sexual behaviors as compared to vehicle controls. Audioradiographic assays performed after 14 days of treatment showed that chronic administration of vilazodone resulted in smaller reductions in 5-HT transporter (5-HTT) levels in the forebrain as compared to citalopram and paroxetine.[96] Chronic vilazodone treatment also decreased 5-HT1A receptor density in cortical and hippocampal regions, whereas both SSRIs increased 5-HT1A receptors in the same regions. These differential effects on 5-HTT and 5-HT1A levels may be related to the ability of vilazodone to limit SSRI-induced sexual side effects.

A post hoc pooled investigation by Clayton et al. (2013) on the effects of vilazodone on sexual function was conducted in 869 patients from placebo-controlled studies and 599 from the open-label vilazodone study.[97] In the placebo-controlled studies, 91.2% of male and 92.9% of female vilazodone-treated patients displayed either improved or stable sexual function, which was similar to the rates observed in placebo-treated male (90.8%) and female (95.6%) patients. In the open-label vilazodone study, 87.9% of men and 91.8% of women showed either improved or stable sexual function from baseline, which was also similar to the rates in placebo-treated patients.[97] In a placebo- and active-controlled phase IV study, baseline sexual function was improved in men and women, MDD responders, and patients with baseline sexual dysfunction following 10 weeks of treatment with vilazodone.[98]

In the GAD studies, the Changes in Sexual Functioning Questionnaire (CSFQ) [99], a prospective measure of sexual functioning, was used in each trial. Small and similar mean changes in CSFQ total score were seen for men and women in the vilazodone (range, −0.3 to +1.9) and placebo (range, +0.5 to +1.8) groups in all three studies, suggesting that the effect of treatment on sexual functioning was similar for vilazodone and placebo.

5. Conclusions

Vilazodone is an SSRI and 5-HT1A partial agonist that is approved for the treatment of MDD in adults. Acute treatment (8–10 weeks) with vilazodone 20–40 mg/day versus placebo resulted in significantly greater improvements from baseline in MADRS total score ( predefined primary efficacy parameter) and significantly higher percentages of patients with MADRS response (≥50% total score improvement from baseline). [76,77,79,80] In a multicenter open-label study, MADRS total score decreased by approximately 20 points after 8 weeks of treatment; similar decreases were observed at subsequent study visits up to 52 weeks, suggesting that long-term efficacy was maintained in MDD patients treated with vilazodone 40 mg/day.[81]

Acute treatment with vilazodone 20–40 mg/day has also been shown to reduce anxiety symptoms in adults with GAD, as demonstrated by the significantly greater mean improvements from baseline with vilazodone versus placebo in HAMA total score in three randomized, double-blind, placebo-controlled trials.[82–84] The results from these GAD studies, along with the improvements in anxious depression that were found in a post hoc analysis of the MDD studies [100], suggest that vilazodone may be a suitable treatment option in patients with comorbid MDD and GAD, or in MDD patients with prominent anxiety symptoms.

The clinical trials with vilazodone, including the 52-week study in MDD patients [81], indicate that this medication is generally safe and tolerable at doses up to 40 mg/day. In both MDD and GAD patients, gastrointestinal disturbances (e.g., nausea, diarrhea, and vomiting), headache, and dizziness were the most common treatment-emergent adverse events. In contrast to prototypical SSRIs, vilazodone has not been associated with treatment-emergent sexual difficulties or dysfunction. No clinically significant changes in blood pressure, heart rate, electrocardiograms, or laboratory tests were observed. However, more studies are needed to further evaluate the long-term safety of vilazodone in both MDD and GAD patients.

6. Expert opinion

A number of pharmacological options are available for the treatment of MDD and GAD, with SSRIs and SNRIs often used as first-line therapies. However, as no single medication is effective in all patients, the ongoing discovery and development of medications for these disorders are merited. The approval of vilazodone for the treatment of MDD in adults was based on the efficacy and safety of this drug in four double-blind, placebo-controlled trials and one long-term, open-label study.[69] The results of these studies adequately demonstrate the clinical benefits of vilazodone in MDD patients, but the unique pharmacological profile of this drug also warrants some consideration.

In addition to being an SSRI, vilazodone is a potent 5-HT1A receptor partial agonist. As decreased 5-HT1A density has been found in patients with MDD, targeted activation of these receptors may help to restore their modulatory effects on 5-HT neurotransmission. In preclinical studies, partial 5-HT1A
receptor agonism has been shown to decrease the lag between SSRI administration and antidepressant effects, decrease anxiety-related behaviors, and mitigate SSRI-induced sexual problems. It is not completely known how these mechanisms translate into the clinical profile of vilazodone, but similar effects were found in adult MDD and GAD patients who received this drug during clinical trials.

Although partial 5-HT\textsubscript{1A} receptor agonism can be achieved with adjunctive buspirone, vilazodone has been shown to have a much greater selectivity for 5-HT\textsubscript{1A} receptors than buspirone with less effects on extracellular dopamine and norepinephrine levels. Whether these pharmacological differences have any clinically meaningful implications – not only in terms of efficacy, but also in terms of tolerability, safety, medication adherence, patient satisfaction, and quality of life – remains to be seen. Future studies are needed that directly compare such parameters in patients treated with an SSRI (both with and without an adjunctive 5-HT\textsubscript{1A} partial agonist) versus patients treated with vilazodone. The comparative effects of such therapies on long-term efficacy outcomes including remission and relapse, as well as long-term safety would be of particular clinical interest.

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**Review of neurobiological theories, pharmacotherapies and psychotherapy for depression.**


Rapid onset of action is correlated with greater antidepressant efficacy.


Assessment of remission rates in depressed patients after several treatment steps.


Neurochemical mechanism of action of vilazodone


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