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Vilazodone for major depressive disorder

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Vilazodone improved scores on multiple depression rating scales compared with placebo and was well tolerated

In January 2011, the FDA approved vilazodone for the treatment of major depressive disorder (MDD) (***Table 1***).

Vilazodone was discovered by Merck KGaA in Germany.[1] In February 2001, Merck KGaA licensed vilazodone to GlaxoSmithKline. In April 2003, GlaxoSmithKline returned all rights to Merck KGaA because phase IIb clinical data did not support progression to phase III clinical trials. In September 2004, Genaissance Pharmaceuticals Inc. acquired an exclusive worldwide license from Merck KGaA to develop and commercialize vilazodone for depression treatment.[2] Subsequently, Clinical Data Inc. acquired Genaissance Pharmaceuticals Inc., including vilazodone, and proceeded with 2 phase III trials and a large safety trial resulting in FDA approval. In February 2011, Forest Laboratories Inc. acquired Clinical Data Inc. and will launch vilazodone in second quarter of 2011.

How it works

Similar to all antidepressants, vilazodone's mechanism of action is not fully understood, but is thought to be related to its inhibition of serotonin (ie, 5-HT) reuptake and partial agonism of 5-HT1A receptors.[3] Vilazodone technically is not a selective serotonin reuptake inhibitor (SSRI) because it has greater affinity for the 5-HT1A receptor (0.2nM) than it does for the 5-HT reuptake pump (0.5nM).[4]

Vilazodone was developed based on the theory that inhibition of 5-HT1A autoreceptor inhibition was responsible for SSRIs' delayed (approximately 2 weeks) onset of antidepressant efficacy. Briefly, this theory is as follows: In humans, 5-HT1A receptors are primarily presynaptic in the raphe nuclei and postsynaptic 5-HT1A receptors predominate in the neocortex and limbic regions of the brain.[5] Presynaptically, 5-HT1A are autoreceptors, ie, serotonin stimulation of these receptors results in inhibition of firing of 5-HT neurons, while postsynaptically they may be involved in downstream serotonergic effects such as sexual function.[5] SSRIs are thought to work as antidepressants by increasing 5-HT concentration in the synapse but their initial effect is to turn off 5-HT neuronal firing as a result of increased concentration of 5-HT at the presynaptic 5-HT1A autoreceptor. Subsequently, these 5-HT1A autoreceptors subsensitize such that 5-HT neuronal firing rate returns to normal. The time course for this subsensitization parallels the onset of SSRI antidepressant efficacy. For several years, efforts have been made to antagonize the 5-HT1A presynaptic autoreceptors as a means of potentially shortening SSRIs' onset of efficacy.[6-8]

Pharmacokinetics

Vilazodone is absorbed in the gastrointestinal tract and reaches peak concentration at a median of 4 to 5 hours. Its bioavailability increases when taken with food such that Cmax (maximum concentration) is increased by 147% to 160%, and area under the curve is increased by 64% to 85%. Its absolute bioavailability in the presence of food is 72%.[4] In systemic circulation, the drug is 96% to 99%

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protein-bound.[3] Vilazodone is eliminated primarily through cytochrome P450 (CYP) 3A4 metabolism in the liver.[3]

Terminal half-life of vilazodone is 25 hours. In general, steady state is achieved in 4 to 5 times the half-life at a stable dose. However, dosing guidelines for vilazodone recommend titration over 2 weeks to achieve a target of 40 mg/d. Thus, steady state will not be achieved until the patient has been on the stable target dose for approximately 2.5 weeks.[3]

Efficacy

Vilazodone' efficacy for MDD treatment was established in 2 pivotal 8-week, randomized, double-blind, placebo-controlled, but not active-controlled, trials (***Table 2, page 86***).[9-11] Study participants were outpatients age 18 to 65 who met DSM-IV-TR criteria for MDD. Patients were required to have a 17-item Hamilton Rating Scale for Depression (HAM-D-17) score >22 and a HAM-D-17 item 1 (depressed mood) score >2.

In the first clinical trial, 410 patients were randomly assigned to vilazodone or placebo. In the vilazodone group, patients were started on 10 mg/d for 1 week, titrated to 20 mg/d for a second week, and then 40 mg/d for the remainder of the study. At week 8, the mean change from baseline on the Montgomery-Åsberg Depression Rating Scale (MADRS), HAM-D-17, Clinical Global Impression-Improvement scale (CGI-I), Clinical Global Impression-Severity scale (CGI-S), and Hamilton Anxiety scale (HAM-A) was statistically greater with vilazodone than placebo ($P < .05$).[9] Compared with placebo, vilazodone-treated patients showed a statistically significant ($P < .05$) improvement in MADRS and HAM-D-17 scores at week 1. Approximately 12% more vilazodone-treated patients achieved response (defined as ≥50% decrease in total score at end of treatment) on the primary efficacy measure, which was MADRS (40.4% vs 28.1%, $P = .007$), and the 2 secondary efficacy measures, which were HAM-D-17 (44.4% vs 32.7%, $P = .011$) and CGI-I (48.0 vs 32.7, $P = .001$). Remission rates (MADRS <10) were not reported in this study, but the authors stated that there was no statistical difference in remission rates between the vilazodone and placebo groups.[9]

Table 1

Vilazodone: Fast facts

Brand name: Viibryd
Class: Serotonin reuptake inhibitor and 5-HT1A receptor partial agonist
Indication: Major depressive disorder
Approval date: January 24, 2011
Availability date: Second quarter of 2011
Manufacturer: Forest Laboratories Inc.
Dosage forms: 10 mg, 20 mg, and 40 mg tablets
Starting dose: 10 mg/d
Target dose: 40 mg/d

In a second trial, which featured design and titration schedule identical to that of the first study, 481 patients were randomized to vilazodone or placebo.[10] At week 8, the vilazodone-treated patients had significantly greater improvement in MADRS, HAM-D-17, HAM-A, CGI-S, and CGI-I score compared with the placebo group ($P < .05$). Approximately 14% more patients in the vilazodone group were MADRS responders compared with placebo (44% vs 30%, $P = .002$). Remission rates were not statistically different between patients taking vilazodone vs placebo (27% vs 20% respectively).[10] Demonstrating a statistically significant difference between a 27% vs 20% remission rate would require a much larger number of patients than were included in this study.

Tolerability

Vilazodone's safety was evaluated in 2,177 patients (age 18 to 70) diagnosed with MDD who participated in clinical studies, including the two 8-week, randomized, double-blind, placebo-controlled studies (N = 891) and a 52-week, open-label study of 599 patients.[12] Overall, 7.1% of patients who received vilazodone discontinued treatment because of an adverse reaction, compared with 3.2% of placebo-treated patients in the double-blind studies.[3] Diarrhea, nausea, and headache were the most commonly reported adverse events; the incidence of headache

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The number needed to treat to demonstrate benefit with vilazodone was 7 to 8

Table 2

Efficacy of vilazodone in phase III clinical trials

Trial	Drug response rate	Placebo response rate	Drug-specific response rate*	NNT†	Average reduction in MADRS change (drug minus placebo) (mean)	Average reduction in HAM-D change (drug minus placebo) (mean)
Rickels et al[9]	40%	28%	12%	100/12 = 8	12.9 to 9.6 (3.3)	10.4 to 8.6 (1.8)
Khan et al[10]	44%	30%	14%	100/14 = 7	13.3 to 10.8 (2.5)	10.7 to 9.1 (1.6)

HAM-D: Hamilton Rating Scale for Depression; MADRS: Montgomery-Åsburg Depression Rating Scale; NNT: number needed to treat

*Difference in response rate between the drug and placebo groups. This rate is what the drug added to the treatment effects seen as a result of time and clinical management provided in the trial

†The number of patients who need to be treated to benefit (ie, achieve response) one additional patient compared with placebo

Source: Reference 11. Table reproduced with permission from Sheldon H. Preskorn, MD

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Overall sexual function for men and women was similar for vilazodone and placebo groups

was similar to that in the placebo group (13.2% vs 14.2%).[10] These adverse events are consistent with serotonin agonism, mild to moderate intensity, and occurred mainly during the first week of treatment.[3]

Doses up to 80 mg/d have not been associated with clinically significant changes in ECG parameters or laboratory parameters in serum chemistry hematology and urine analysis.[9,10] The drug had no effect on weight as measured by mean change from baseline.[9,10]

In one 8-week trial, there were no substantial differences between vilazodone and placebo in Arizona Sexual Experience Scale (ASEX) scores at treatment end for either sex.[9] ASEX is a 5-item scale used to assess sexual dysfunction; a score >18 indicates clinically significant sexual dysfunction. At baseline, mean ASEX scores among men were 15.8 in the placebo group and 16.5 in the vilazodone group. Among women, the mean ASEX score was 21.2 in both groups.[9] Overall sexual function for men and women was similar for vilazodone and placebo, as measured by the Changes in Sexual Function Questionnaire.[10] The most commonly reported sexual adverse effect was decreased libido.[10]

Contraindications

Vilazodone is contraindicated for concomitant use with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping or starting an MAOI. Vilazodone is contraindicated in patients taking strong CYP3A4 inhibitors (eg, ketoconazole) because of increased vilazodone concentrations and resulting concentration-dependent adverse effects.[3] Concomitant administration of strong CYP3A4 inducers (eg, rifampin) might result in a reduction in vilazodone levels leading to lack or loss of efficacy.[13]

As with other antidepressants, vilazodone carries a black-box warning about increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders.[3] Vilazodone showed evidence of developmental toxicity in rats, but was not teratogenic in rats or rabbits. There are no adequate, well-controlled studies of vilazodone in pregnant women and no human data regarding vilazodone concentrations in breast milk.[3] Women taking vilazodone are advised to breast-feed only if the potential benefits outweigh the risks. Vilazodone is not recommended for use in pediatric patients.[3]

Similar to other antidepressants, vilazodone labeling carries warnings about serotonin syndrome, seizures, abnormal bleeding, activation of mania/hypomania, and hyponatremia.[4]

Dosing

Vilazodone is available as 10 mg, 20 mg, and 40 mg tablets. The recommended target dose for vilazodone is 40 mg/d, with a starting

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Related Resource

- Khan A. Vilazodone, a novel dual-acting serotonergic antidepressant for managing major depression. Expert Opin Investig Drugs. 2009;18(11):1753-1764.

Drug Brand Names

Ketoconazole • Nizoral
Rifampin • Rifadin
Verapamil • Isoptin
Vilazodone • Viibryd

Disclosures

Drs. Kalia and Mittal report no financial relationship with any company whose products are mentioned in this article, or with manufacturers of competing products.

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Dose should be reduced to 20 mg/d when vilazodone is coadministered with strong CYP3A4 inhibitors

dose of 10 mg/d for 7 days, followed by 20 mg/d for 7 days, then 40 mg/d.[3] The drug should be taken with food, but unlike other psychotropics, the manufacturer does not recommended a specific calorie amount.[3] Dose tapering is recommended when the drug is discontinued.[3]

Dose should be reduced to 20 mg/d when vilazodone is coadministered with strong CYP3A4 inhibitors, such as azole antifungals, macrolides, protease inhibitors, and verapamil.[13] No dosage adjustment is recommended based on age, mild or moderate liver impairment, or renal impairment of any severity.[3] Vilazodone has not been studied in patients with severe hepatic impairment.[3]

How does vilazodone compare?

Ideally, it would be good to know how vilazodone compares with other marketed antidepressants. Unfortunately, there are no published head-to-head comparison data to address this matter. The number needed to treat with vilazodone is between 7 and 8 based on the data from the 2 phase III trials (***Table 2, page 86***).[9-11] This is comparable to other antidepressants. One phase III study showed a statistically greater reduction in depressive symptomatology in vilazodone-treated patients after 1 week,[9] but that was not replicated in the second trial.[10]

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Bottom Line

Vilazodone, a serotonin reuptake inhibitor and partial agonist of serotonergic receptors, shows clinically significant improvement on depression rating scale scores compared with placebo. In clinical trials, vilazodone was well tolerated; diarrhea, nausea, and headache were the most commonly reported adverse events.