Vilazodone: A landmark antidepressant approval or another "me-too" drug?

Abimbola Farinde, Pharm.D., MS[1]

[1]Clinical Staff Pharmacist, Clear Lake Regional Medical Center
Webster Texas Adjunct Faculty, Columbia Southern University, Orange Beach, AL

ABSTRACT

Vilazodone is a novel antidepressant which is indicated for the treatment of major depressive disorder (MDD) in adult patients. This article reviews the pharmacodynamics and pharmacokinetics of vilazodone, and discusses published and ongoing research on the medication.

KEYWORDS

vilazodone, antidepressant, major depressive disorder (MDD)

Major depressive disorder (MDD) is defined as a debilitating and chronic psychiatric disorder that is generally characterized by mood symptoms (e.g., depressed or sad mood), cognitive symptoms (e.g., inability to concentrate or difficulty with decision-making), and physical symptoms (e.g., lethargy, fatigue, insomnia) that has the potential to significantly impact quality of life, the performance of activities of daily living, and day to day functioning.[1] If left untreated, MDD may lead to detrimental outcomes.[2,3] The cost of this disabling condition is considerable, both on an individual (e.g., reduced quality of life), and on a societal level (e.g., lost productivity).[4,5] While the current pharmaceutical market is saturated with many antidepressants, most people do not achieve an adequate treatment response with initial antidepressant therapy. This was demonstrated in the four-phase Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which examined the use of the selective serotonin reuptake inhibitor citalopram for 12 weeks.[6] The initial remission rates on step one of the STAR*D study with citalopram alone were 36.8% which decreased after each round of either augmentation or switching medications. The participants of the study that did not achieve remission were asked to participate in the second phase of the trial of augmentation or replacement therapy. In step 2, an additional 30.6% of patients remitted. At step 3, 13.7% remitted, and after step 4, 13% went into remission. After four different regimens, the cumulative remission rate was 67%. The group that did not remit until after four treatments experienced the highest relapse rates. Only 4% remained well during the follow-up. Relapse rates were lowest among those who went into remission during the earlier phases of the study.[6] The STAR*D study indicated that combination therapy or multiple antidepressant trials might be needed to achieve remission in many patients.[7,8] The selective serotonin reuptake inhibitors (SSRIs) are considered first line treatment in MDD due to their efficacy, tolerable side effect profile and low risk of fatality with overdose.[8] SSRIs generally take 3-4 weeks or more to achieve therapeutic effect. According to Celeda and colleagues, the ongoing proposal has been for the availability of an antidepressant that is able to overcome the adaptive mechanisms that can delay the therapeutic onset of antidepressant activity to yield a quicker onset of action.[7,8] This proposal lead to the Food and Drug Administration approval of vilazodone (Viibryd) in January 2011.[6,7,8]

PHARMACODYNAMICS AND PHARMACOKINETICS

Vilazodone is a novel antidepressant that is placed under the pharmacologic category of an SSRI and Serotonin 1A (5HT-1A) receptor partial agonist which is indicated for the treatment of MDD in adults.[9] Vilazodone has little to no effect on norepinephrine or dopamine.[10,11,12]

The absorption of vilazodone is significantly dependent on food, as taking the drug under fasting conditions can reduce its plasma level by 50% compared to the postprandial condition.[12,13] It undergoes extensive hepatic metabolism primarily via cytochrome P450 (CYP) 3A4, with a minor pathway via CYP 2D6, as well as non-CYP-mediated metabolism (possibly by carboxylase).[13,14] The elimination of vilazodone is primarily via hepatic metabolism with a mean elimination half-life of about 25 hours. The pharmacokinetic properties of vilazodone have not been extensively evaluated in patients with severe renal or hepatic impairment. Dosage adjustment is not required in patients with renal impairment, and a specific dosage adjustment has not been recommended for those with severe hepatic impairments based on the lack of available studies in this population.[14,15] The recommended starting dose of vilazodone is 10mg once daily to be taken with food for seven days, then 20mg

daily for seven days, then 40mg once daily thereafter.[11,14,15] Higher doses of vilazodone have not been assessed for safety and efficacy.[15,17]

CLINICAL TRIALS WITH VILAZODONE

The approval of vilazodone was based on its efficacy being shown in two 8-week randomized, double-blind, placebo-controlled studies in adults with MDD. In these two studies combined, study participants were randomized to vilazodone (titrated up to 40mg daily over 2 weeks; n=435) or placebo (n=433).[18] Both studies evidenced efficacy for vilazodone as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS). The number needed to treat for response vs. placebo was 8 (95% CI 6-16) and for remission was 14 (95% CI 8-55). The primary end-point of a significant change from baseline at 8 weeks in the MADRS total score was compared to placebo (P=0.001).[18] The least squares mean difference from placebo were -3.2 (95% confidence interval [CI],-5.2 to -1.3) for Study 1 and -2.5 (95% CI -4.4 to 0.6) for Study 2 with a statistically significant difference being observed at week 1. In addition, in both studies, vilazodone produced a clinically significant improvement in MADRS total scores in patients with a first episode MDD ((Least Squares Mean treatment difference vs. placebo, -2.1; p = not significant [n = 277]).]). The most commonly identified side effects were nausea and diarrhea which were generally mild to moderate, with occurrence most common in the first week and duration of 4-5 days.[19] Overall, the studies indicate that 7.1% of patients discontinued participation in the clinical trials on vilazodone compared to 3.2% of placebo patients.[9] The most commonly encountered adverse effects (incidence ≥ 5% and at least twice the rate of placebo) were diarrhea, nausea, vomiting and insomnia, with number needed to harm (NNH) values vs. placebo of 6 (95% CI 5-8), 6 (95% CI 5-8), 30 (95% CI 18-82) and 26 (95% CI 16-78), respectively. NNH vs. placebo for any sexual adverse effect was 12 (95% CI 9-18), but systematically collected data using rating scales of sexual function did not reveal treatment associated effects.[20]

To date, vilazodone is only indicated for the treatment of MDD in adults.[20] In addition, vilazodone 40mg once daily demonstrated an improvement in depressive symptoms in a long-term, 52 week, non-comparative, phase III study. Based on a double blind randomized, placebo-controlled crossover study in 10 healthy male subjects, an assessment was performed on the effect of 20 mg vilazodone on sleep electroencephalography.[21] Reduction in rapid eye movement as well as changes in slow wave sleep and wakefulness through central activation were observed.[21]

As it currently stands, the primary indication for vilazodone is treatment of MDD in adults; due to its unique mechanism of action, this may also show promise in patients who cannot tolerate or do not respond to previous trials of antidepressants. There are currently no comparative efficacy studies available, and therefore, this is a theoretical proposal. In the future, the use of vilazodone may extend to the treatment of other mental health disorders that are similar to those that are treated by selective serotonin reuptake inhibitors.[22] Other agents with serotonin reuptake inhibition and 5HT-1A agonism also carry approved indications for generalized anxiety disorder (GAD), obsessive compulsive disorder, social anxiety disorder, posttraumatic stress disorder (PTSD), eating disorders, and premenstrual disorders. It is conceptually feasible that vilazodone's pharmacodynamic mechanism may also prove to be useful in alleviating the symptoms that can be associated with these disorders.[22, 23, 24]

ONGOING RESEARCH

Presently, there are clinical trials that are undergoing recruitment for participants to evaluate the safety, efficacy, and tolerability of vilazodone for GAD in comparison to placebo, a double-blind placebo-controlled randomized trial of vilazodone for PTSD, a double-blind study of vilazodone for the treatment of social anxiety disorder, and the efficacy of vilazodone for reducing marijuana use in marijuana-dependent adults. Any one of these studies has the potential to produce an additional indication for the use of vilazodone based on the study's outcome, thus promoting the increased use of this newer antidepressant.[25] Table 1 describes the detailed information related to each ongoing vilazodone trial.

There are currently no available studies in which vilazodone has been studied in these other conditions and therefore there is the chance that it may not be effective in these conditions. Another observable advantage to vilazodone is the cost, which is the same for all strengths (10mg, 20mg, and 40mg) at $5.52 per dose or approximately $165.86 per month.[25,26,27] The number needed to treat for vilazodone is 8 and with its cost of $5.52/day to treat, it would cost $44.16/day (over $16,000/year) to have an additional responder vs. placebo.

The cost of vilazodone is somewhat comparable to the brand versions of two prominent antidepressants on the market, compared to Prozac (fluoxetine) which is priced

at $8.22 per dose (10mg), $8.44 per dose (50mg), and $16.88 per dose (40mg), and Paxil (paroxetine) which is priced at $4.88 per dose (10mg), $5.09 per dose (20mg), $5.24 per dose (30mg), and $5.55 per dose (40mg). A current disadvantage with vilazodone is the lack of a generic equivalent on the market which may offer cost savings that are already available with generic versions of other antidepressants.[26,27] The generic versions of the SSRIs are usually much cheaper and are often included on discount drug lists that are offered by many chain pharmacies.

Vilazodone serves as an alternative antidepressant for those who may not respond to other antidepressant treatments. While the combined 5-HT reuptake inhibition and 5-HT1A receptor partial activity of vilazodone is presumed to yield more rapid and specific desensitization of the somatodendric 5HT-1A autoreceptor, leading to a

Table 1: Ongoing vilazodone randomized clinical trials

Title	Objective	Estimated Enrollment and Eligibility	Primary and Secondary Outcomes
A Double-Blind, Placebo-Controlled, Flexible-Dose Study of Vilazodone in Patients With Generalized Anxiety Disorder.	The purpose of this study is to evaluate the efficacy, safety and tolerability of vilazodone relative to placebo in the treatment of generalized anxiety disorder (GAD)	**Estimated Enrollment: 400** Ages Eligible for Study: 18-70 Genders Eligible for Study: Both Accepts Healthy Volunteers: No **Inclusion Criteria:** Male or female outpatient, 18-70 years of age Currently meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for Generalized Anxiety Disorder Minimum score of 20 on Hamilton Rating Scale for Anxiety	**Primary Outcomes** Hamilton Rating Scale for Anxiety (HAM-A) total score [Time Frame: 8 weeks] **Secondary Outcomes** Sheehan Disability Scale (SDS) total score [Time Frame: 8 weeks]
Double-blind, Placebo-controlled Randomized Trial of Vilazodone in the Treatment of Posttraumatic Stress Disorder	The purpose of this study is to determine whether vilazodone is effective in the treatment of Posttraumatic Stress Disorder (PTSD) and co-morbid mild or more depression.	**Estimated Enrollment: 64** Ages Eligible for Study: 18-75 Genders Eligible for Study: Both Accepts Healthy Volunteers: No **Inclusion Criteria:** Participants must satisfy DSM-IV diagnostic criteria for chronic PTSD Evidence of PTSD disease base upon one or more of the following: Mild or greater depression on the Beck Depression Inventory -II (BDI-II, score> 12). May have other symptom co-morbid with PTSD (e.g., anxiety or somatic pain) Ability to comprehend and satisfactorily comply with protocol required and signed written informed consent prior to entering study procedure May be in psychotherapy if initiated at least three months prior to the screening visit. Subject must not discontinue or otherwise alter therapy during the study. Subject may not have taken any psychopharmacological medications within 7 days prior to Baseline visit. Negative urine pregnancy test at screening visit and for the duration of the study for women of childbearing potential.	**Primary Outcomes** PTSD symptoms [Time Frame: 4 months] PTSD Diagnosis [Time Frame: 4 months] **Secondary Outcomes** Depression [Time Frame: 4 months] Sleep [Time Frame: 4 months] Anxiety [Time Frame: 4 months]

Title	Objective	Estimated Enrollment and Eligibility	Primary and Secondary Outcomes
Vilazodone in the Treatment of Social Anxiety Disorder: A Double Blind Study	The purpose of this study is to determine whether vilazodone is effective in the treatment of symptoms of Social Anxiety Disorder among adults.	**Estimated Enrollment: 30** Ages Eligible for Study: 18-75 Genders Eligible for Study: Both Accepts Healthy Volunteers: No **Inclusion Criteria:** Diagnosis of Social Anxiety Disorder, generalized subtype Liebowitz Social Anxiety Scale (LSAS) total score of 70 at visits 1 and 2	**Primary Outcomes** Change in Liebowitz Social Anxiety Scale (LSAS) - total score **Secondary Outcomes** Responder rate, as defined by Clinical Global Impression of Improvement score of 1 or 2 [Time Frame: Study Endpoint: minimum 6 weeks - maximum 12 weeks] Change in the Clinical Global Impression of Severity of Illness score [Time Frame: Change from Baseline to Study Endpoint: minimum 6 weeks - maximum 12 weeks] Change on the LSAS anxiety and avoidance subscales [Time Frame: Change from Baseline to Study Endpoint: minimum 6 weeks - maximum 12 weeks] Change in Hamilton Depression scale total [Time Frame: Change from Baseline to Study Endpoint: minimum 6 weeks - maximum 12 weeks] Change in Hamilton Anxiety scale total [Time Frame: Change from Baseline to Study Endpoint: minimum 6 weeks - maximum 12 weeks] Subject-assessed responder rate [Time Frame: Study Endpoint: minimum 6 weeks - maximum 12 weeks]
Vilazodone Treatment for Marijuana Dependence	This study will evaluate the efficacy of vilazodone for reducing marijuana use in marijuana-dependent adults	**Estimated Enrollment: 76** Ages Eligible for Study: 18 to 65 Genders Eligible for Study: Both Accepts Healthy Volunteers: No **Inclusion Criteria:** Must meet DSM-IV criteria for marijuana dependence Must be between the ages of 18 and 65 years old If female and of childbearing potential, must agree to use acceptable method of birth control for duration of the trial. Cannabis-positive urine drug screen at screening Must consent to random assignment Must be able to read and provide informed consent	**Primary Outcomes** Percent marijuana-positive urine drug screens [Time Frame: 8 weeks] **Secondary Outcomes** Time to first negative urine drug screen [Time Frame: 8 weeks] Secondary efficacy endpoint is time to first negative (passed) urine screen. Percent of marijuana-positive self-reported days [Time Frame: 8 weeks] Secondary efficacy endpoint is percentage of marijuana-positive self-reported days Study retention [Time Frame: 8 weeks] Secondary efficacy endpoint is retention in the study. Marijuana craving and withdrawal [Time Frame: 8 weeks] Secondary endpoint of marijuana craving and withdrawal

National Institutes of Health. Clinical trials

quicker onset of action, this has not been evaluated in comparative research with other antidepressants.[22,27] In a current market filled with various antidepressant classes, vilazodone appears to offer a different and alternative mechanism of action to assist with providing remission of depressive symptoms. Since up to 50% of patients may not respond to initial pharmacotherapy, they may achieve some benefit from another agent that does not belong to the same therapeutic class.[27,28] While some patients may have an enhanced response due to the unique mechanism of action of vilazodone, it has not been compared with existing therapies on the market which may have lower costs to patients.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition, text revision. Washington, DC: American Psychiatric Association; 2000:317-91.
2. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52(12):1048-60. DOI: 10.1001/archpsyc.1995.03950240066012.
3. Narasimhan M, Raynor JD, Jones AB. Depression in the medically ill: diagnostic and therapeutic implications. Curr Psychiatry Rep. 2008;10(3):272-9. PubMed PMID: 18652797.
4. .Mental Health: Depression [Internet]. Geneva (Switzerland): World Health Organization. c2013 [Updated 2013; cited 2013 Sept 30]. Available from: http://www.who.int/mental_health/management/depression/en/index.html
5. Edmunds MW, Mayhew MS. Pharmacology for the Primary Care Provider. 3rd ed. Mosey, Inc; 2009.
6. Choi E, Zmarlicka M, Ehret MJ. Vilazodone: a novel antidepressant. Am J Health Syst Pharm. 2012;69(18):1551-7. DOI: 10.2146/ajhp110374. PubMed PMID: 22935937.
7. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;163(1):28-40. DOI: 10.1176/appi.ajp.163.1.28. PubMed PMID: 16390886.
8. Celada P, Puig M, Amargós-Bosch M, Adell A, Artigas F. The therapeutic role of 5-HT1A and 5-HT2A receptors in depression. J Psychiatry Neurosci. 2004;29(4):252-65. PubMed PMID: 15309042.
9. Frampton JE. Vilazodone: in major depressive disorder. CNS Drugs. 2011;25(7):615-27. DOI: 10.2165/11207550-000000000-00000. PubMed PMID: 21699273.
10. Uppal A, Singh A, Gahtori P, Ghosh SK, Ahmad MZ. Antidepressants: current strategies and future opportunities. Curr Pharm Des. 2010;16(38):4243-53. PubMed PMID: 21208177.
11. Traynor K. Vilazodone approved for major depression. Am J Health Syst Pharm. 2011;68(5):366. DOI: 10.2146/news110009. PubMed PMID: 21330672.
12. Elliott WT, Chan J. Vilazodone Hydrochloride Tablets (Viibryd). Internal Medicine Alert. 2011;33(5)37-38.
13. Viibryd (vilazodone) [Package insert]. New Haven (CT): Trovis Pharmaceuticals, 2011.
14. Viibryd (vilazodone) [Package insert]. St. Louis (MO): Forest Pharmaceuticals Inc., 2011, Revised Dec 2012.
15. Dopheide JA. Vilazodone's comparative merits yet to be demonstrated. Am J Health Syst Pharm. 2012;69(18):1549.
16. Kehne JH, Bartoszyk GD, Greiner HE, et al. In vitro characterization of vilazodone as a dual-acting serotonin reuptake inhibitor and 5-HT1A receptor partial agonist [abstract]. Biol Psychiatry 2010;1(67)(9 Suppl. 1):237S.
17. Sorbera LA, Rabasseda X, Silvestre J, Castañer J. Vilazodone Hydrochloride. Drugs Fut. 2001;26(3):247-52. DOI: 10.1358/dof.2001.026.03.611242.
18. Khan A. Vilazodone, a novel dual-acting serotonergic antidepressant for managing major depression. Expert Opin Investig Drugs. 2009;18(11):1753-64. DOI: 10.1517/13543780903286396. PubMed PMID: 19764890.
19. Rickels K, Athanasiou M, Robinson DS, Gibertini M, Whalen H, Reed CR. Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70(3):326-33. PubMed PMID: 19284933.
20. Citrome L. Vilazodone for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract. 2012;66(4):356-68. DOI: 10.1111/j.1742-1241.2011.02885.x. PubMed PMID: 22284853.
21. Dawson LA, Watson JM. Vilazodone: a 5-HT $_{1A}$ receptor agonist/serotonin transporter inhibitor for the treatment of affective disorders. CNS Neurosci Ther. 2009;15(2):107-17. DOI: 10.1111/j.1755-5949.2008.00067.x.
22. Singh M, Schwartz TL. Clinical utility of vilazodone for the treatment of adults with major depressive disorder and theoretical implications for future clinical use. Neuropsychiatr Dis Treat. 2012;8:123-30. DOI: 10.2147/NDT.S20683. PubMed PMID: 22536068; PubMed Central PMCID: PMC3333788.
23. Stahl S. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge, UK: Cambridge University Press; 2008.
24. Hirschfeld RM, Montgomery SA, Aguglia E, Amore M, Delgado PL, Gastpar M, et al. Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. J Clin Psychiatry. 2002;63(9):826-37. PubMed PMID: 12363125.
25. Clinicaltrials.gov, Search results for "vilazodone" [Internet]. Bethesda (MD): National Institutes of Health. [Updated 2013, cited 2013 Sept 30]. Available from http://clinicaltrials.gov/ct2/results?term=vilazodone
26. Cruz MP. Vilazodone HCl (Viibryd): A Serotonin Partial Agonist and Reuptake Inhibitor For the Treatment of Major Depressive Disorder. P T. 2012;37(1):28-31. PubMed PMID: 22346333.
27. Viibryd (vilazodone). Lexi-Comp Online, Lexicomp. Hudson, Ohio: Lexi-Comp, Inc.; June 26, 2013.
28. Page ME, Cryan JF, Sullivan A, Dalvi A, Saucy B, Manning DR, et al. Behavioral and neurochemical effects of 5-(4-[4-(5-Cyano-3-indolyl)-butyl)-butyl]-1-piperazinyl)-benzofuran-2-carboxamide (EMD 68843): a combined selective inhibitor of serotonin reuptake and 5-hydroxytryptamine(1A) receptor partial agonist. J Pharmacol Exp Ther. 2002;302(3):1220-7. DOI: 10.1124/jpet.102.034280. PubMed PMID: 12183683.

How to cite this editor-reviewed article
Farinde A. Vilazodone: A landmark antidepressant approval or another "me-too" drug?. Ment Health Clin [Internet]. 2013;3(4):193-7. Available from: http://dx.doi.org/10.9740/mhc.n172355