Therapeutic Class Overview
Serotonin modulators

Therapeutic Class

- **Overview/Summary:** The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa) and premenstrual dysphoric disorder.[1-5] Anxiety disorders include agoraphobia, anxiety disorder due to another medical condition, generalized anxiety disorder, other specified anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder or social phobia, specific phobia, substance/medication induced anxiety disorder and unspecified anxiety disorder.[6-7] Some of the antidepressants are also approved to treat nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, moderate to severe vasomotor symptoms associated with menopause, nocturnal enuresis and tobacco abuse.[1-2]

  The antidepressants are categorized into six different American Hospital Formulary Service (AHFS) subclasses, including monoamine oxidase inhibitors (MAOIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs) and miscellaneous agents. The agents which make up these subclasses differ with respect to their FDA-approved indications, mechanism of action, pharmacokinetics, adverse events and drug interactions.

  The exact mechanism of action of the serotonin modulators is unknown. Nefazodone inhibits neuronal uptake of serotonin and norepinephrine, and is a direct antagonist of serotonin (5-HT2) receptors. It also blocks alpha1-adrenergic receptors, which may be associated with postural hypotension.[1-2] Trazodone is thought to selectively inhibit serotonin uptake at the presynaptic neuronal membrane.[1-3] Vilazodone is a selective serotonin reuptake inhibitor and partial serotonin 5-HT1A receptor agonist.[1-2,4] Vortioxetine is the newest serotonin modulator. The mechanism of action for vortioxetine is not fully understood; however, it is thought to exert its multi-modal pharmacological effects through selective re-uptake inhibition of 5-HT, and antagonistic effects at 5-HT3, 5-HT7 and 5-HT1D receptors. Vortioxetine has also exhibited agonistic effects at 5-HT1A receptors, partial agonistic effects at 5-HT1B receptors and inhibition of the 5-HT transporter.[1-2,5]

Table 1. Current Medications Available in the Therapeutic Class[1-20]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Nefazodone*	Depression	Tablet: 50 mg 100 mg 150 mg 200 mg 250 mg	✔
Trazodone* (Oleptro®)	Major depressive disorder	Tablet (extended release): 150 mg 300 mg Tablet (immediate release): 50 mg 100 mg 150 mg 300 mg	✔
Vilazodone (Viibryd®)	Major depressive disorder	Tablet: 10 mg 20 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		40 mg	
Vortioxetine (Brintellix®)	Major depressive disorder	Tablet: 5 mg 10 mg 15 mg 20 mg	-

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- The serotonin modulator trazodone has been shown to be efficacious in improving Hamilton Rating Scale for Depression-17 (HAMD-17) and Montgomery-Åsberg Depression Rating Scale (MADRS) scores when compared to placebo in patients with major depressive disorder (MDD).[9]
- Vortioxetine has been shown to be more effective than placebo in clinical trials, with effects seen as early as one week.[10-13]
- Vortioxetine has been compared to placebo and although studies have shown a significant improvement vs placebo these results were not consistent across trials and outcomes.[14-18]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Guidelines do not give preference to one agent over another. Rather, the selection of an antidepressant should be based on adverse events, tolerability and patient preference.[19-22]
- Other Key Facts:
  - Numerous clinical trials have been conducted with the antidepressants and comparative studies have demonstrated similar efficacy in patients with major depressive disorder.
  - Vilazodone has been shown to be more effective than placebo in clinical trials, with effects seen as early as one week. The SSRIs have also been shown to be effective after one week of use.[10-13]
  - There were no studies found in the medical literature directly comparing vilazodone to other antidepressants.
  - Vortioxetine use is associated with a high incidence of nausea at therapeutic doses.[1-2,5]

References

1. Drug Facts and Comparisons [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Dec]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2014 [cited 2014 Jan 25]. Available from: http://www.thomsonhc.com.
3. Oleptro® [package insert]. Princeton, NJ: Angelini Labopharm, LLC; December 2010.
4. Viibryd® [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; December 2012.
5. Brintellix® [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; September 2013.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders.5th ed. (DSM-V) [monograph on the internet]. Arlington, VA: American Psychiatric Association; 2013 [cited 2014 Jan 22]. Available from: http://dsm.psychiatryonline.org/content.aspx?bookid=556&sectionid=41101761.
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association;2000:356.
8. Feighner J, Targum S, Bennet M, et al. A double-blind, placebo-controlled trial of nefazodone in the treatment of patients hospitalized for major depression. J Clin Psychiatry. 1998;59(5):246-53.
9. Sheehan DV, Croft HA, Gossen ER, et al. Extended-release trazodone in major depressive disorder: a randomized, double-blind, placebo-controlled study. Psychiatry (Edgmont). 2009;6:20-33.
10. Rickels K, Athanasiou M, Robinson DS, et al. 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;70:326-33.
11. Khan A, Cutler AJ, Kajdasz DK, et al. A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. J Clin Psychiatry. 2011;72:441-7.
12. Robinson DS, Kajdasz DK, Gallipoli S, et al. A one-year, open-label study assessing the safety and tolerability of vilazodone in patients with major depressive disorder. J Clin Psychopharmacol. 2011;31:643-6.
13. Reed CR, Kajdasz DK, Whalen H, Athanasiou MC, Gallipoli S, Thase ME. The efficacy profile of vilazodone, a novel antidepressant for the treatment of major depressive disorder. Curr Med Res Opin. 2012 Jan;28(1):27-39.

14. Henigsberg N, Mahableshwarkar AR, Jacobsen P, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled eight-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder [abstract]. 2012 Jul 1;73(7):953-59.
15. Baldwin DS, Hansen T, Florea I. Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. Current Medical Research & Opinion. 2012 Oct. 28(10):1717-24.
16. Jain R, Mahableshwarkar AR, Jacobsen PL, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. International Journal of Neuropsychopharmacology. 2013 Mar. 16(2):313-21.
17. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. 2012 July 1;27(4):215-23.
18. Mahableshwarkar AR, Jacobsen PL, Chen Y. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) vs placebo for 8 weeks in adults with major depressive disorder. Current Medical Research & Opinion. 2013 March 29(3):217-26.S
19. American Psychiatric Association (APA). Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition [guideline on the internet]. Arlington, Virginia: American Psychiatric Association; 2010 [cited 2014 Jan 25]. Available from: http://psychiatryonline.org/content.aspx?bookid=28&sectionid=1667485.
20. National Institute for Health and Care Excellence (NICE). Depression in adults: The treatment and management of depression in adults [guideline on the internet]. London, England, UK: National Institute for Health and Care Excellence; 2009 [cited 2014 Jan 25]. Available from: http://publications.nice.org.uk/depression-in-adults-cg90.
21. Qaseem A, Snow V, Denberg T, Forciea MA, Owens DK, Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008;18;149:725-33.
22. Birmaher B, Brent D, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. American Academy of Child and Adolescent Psychiatry (AACAP). J Am Acad Child Adolesc Psychiatry. 2007;46:1503-26.

Therapeutic Class Review
Serotonin modulators

Overview/Summary

The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa) and premenstrual dysphoric disorder.[1-5] Anxiety disorders include agoraphobia, anxiety disorder due to another medical condition, generalized anxiety disorder, other specified anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder or social phobia, specific phobia, substance/medication induced anxiety disorder and unspecified anxiety disorder.[6-7] Some of the antidepressants are also approved to treat nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, moderate to severe vasomotor symptoms associated with menopause, nocturnal enuresis and tobacco abuse.[1-2]

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The exact mechanism of action of the serotonin modulators is unknown. Nefazodone inhibits neuronal uptake of serotonin and norepinephrine, and is a direct antagonist of serotonin ($5\text{-}HT_2$) receptors. It also blocks $alpha_1$-adrenergic receptors, which may be associated with postural hypotension.[1-2] Trazodone is thought to selectively inhibit serotonin uptake at the presynaptic neuronal membrane.[1-3] Vilazodone is a selective serotonin reuptake inhibitor and partial serotonin $5\text{-}HT_{1A}$ receptor agonist.[1-2,4] Vortioxetine is the newest serotonin modulator. The mechanism of action for vortioxetine is not fully understood; however, it is thought to exert its multi-modal pharmacological effects through selective re-uptake inhibition of 5-HT, and antagonistic effects at $5\text{-}HT_3$, $5\text{-}HT_7$ and $5\text{-}HT_{1D}$ receptors. Vortioxetine has also exhibited agonistic effects at $5\text{-}HT_{1A}$ receptors, partial agonistic effects at $5\text{-}HT_{1B}$ receptors and inhibition of the 5-HT transporter.[1-2,5]

Medications

Table 1. Medications Included Within Class Review

Generic Name(s) (Trade name)	Medication Class	Generic Availability
Nefazodone*	Serotonin modulators	✔
Trazodone* (Oleptro®)	Serotonin modulators	✔
Vilazodone (Viibryd®)	Serotonin modulators	-
Vortioxetine (Brintellix®)	Serotonin modulators	-

*Available generically in one dosage for or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-5]

Generic Name(s)	Depression	Major Depressive Disorder
Nefazodone	✔	
Trazodone		✔
Vilazodone		✔
Vortioxetine		✔

Pharmacokinetics

Table 3. Pharmacokinetics[1-5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Nefazodone	20	>99	Liver	Renal (55) Feces (20 to 30)	2 to 4
Trazodone	65	89 to 95	Liver	Renal (70 to 75) Feces (21)	10
Vilazodone	72	96 to 99	Liver	Renal (1) Feces (2)	25
Vortioxetine	75	98	Liver	Renal (59) Feces (26)	66

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the serotonin modulators are described in Table 4.[8-18]

The serotonin modulator trazodone has been shown to be efficacious in improving Hamilton Rating Scale for Depression-17 (HAMD-17) and Montgomery-Åsberg Depression Rating Scale (MADRS) scores when compared to placebo in patients with major depressive disorder (MDD).[9] Vortioxetine has been shown to be more effective than placebo in clinical trials, with effects seen as early as one week.[10-13] Vortioxetine has been compared to placebo and although studies have shown a significant improvement vs placebo these results were not consistent across trials and outcomes.[14-18]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Depression				
Feighner et al.[8] (1998) Nefazodone 200 mg twice daily vs placebo	DB, PC, PG Patients that were hospitalized due to depression	N=120 6 weeks	Primary: HAM-D_{17}, CGI-I, MADRS Secondary: Not reported	Primary: Nefazodone treatment resulted in a significant reduction (*P*<0.01) of the HAM-D_{17} total score compared to placebo from the end of the first treatment week through the end of the study (–12.2 nefazodone vs –7.7 placebo). At the end of the trial, significantly more nefazodone-treated patients (50%) than placebo-treated patients (29%) had responded, as indicated by their CGI-I score (P=0.021) or by a ≥50% reduction in their HAM-D_{17} scores (*P*=0.017). Significantly more patients treated with nefazodone (36%) than placebo-treated patients (14%) had a HAM-D_{17} score ≤10 at the end of treatment (*P*=0.004). Significant treatment differences (*P*<0.01) in favor of nefazodone were also seen in the MADRS; the HAM-D retardation, anxiety, and sleep disturbance factors; and HAM-D item 1 (depressed mood). Patients with dysthymia in addition to major depression also showed significant improvement (*P*<0.05) when treated with nefazodone, with significant differences in response rates seen as early as week two and through the end of the trial. Secondary: Not reported
Sheehan et al.[9] (2009) Trazodone ER 150 to 375 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with MDD, current episode of MDD for a minimum of 1 month, dysphoria for most days over the previous 4 weeks, and a MADRS total	N=412 8 weeks	Primary: Change from baseline in HAM-D-17 total score Secondary: HAM-D-17 responders, HAM-D-17 remitters, change in HAM-D-17 depressed mood item from baseline, change	Primary: The change in the HAM-D-17 total score from baseline decreased by an average of 11.4±8.2 and 9.3±7.9 in the trazodone and placebo groups, which statistically favored treatment with trazodone (*P*=0.012). Results demonstrated a significantly greater improvement in the mean HAM-D-17 total score in the trazodone group compared to the placebo group by the first week of treatment (day seven of titration: 5.6±5.2 vs 3.9±4.8, respectively; *P*=0.005). The significantly greater differences were maintained throughout the study. Secondary: The number of HAM-D-17 responders (decrease ≥50% from baseline HAM-D-17 total score) in the trazodone group was significantly greater compared to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	score ≥26 at screening and baseline		in MADRS total score from baseline, CGI-I responders, PGI-I responders, change in CGI-S from baseline, CGI-I at last study visit, PGI-I at last study visit, discontinuations due to lack of efficacy, and overall quality of sleep	placebo group (54.0 vs 41.2%; *P*=0.003). No difference in the proportion of HAM-D-17 remitters (HAM-D-17 total score ≤7) was observed between treatment groups (35.6 vs 31.9%; *P*=0.22). The change in the HAM-D-17 depressed mood item from baseline decreased by average of 1.6±1.3 and 1.3±1.2 in the trazodone and placebo groups, which statistically favored treatment with trazodone (*P*=0.030). The change in MADRS total score from baseline also statistically favored treatment with trazodone (-16.6±11.3 vs -14.1±11.9; *P*=0.036). No difference in the proportion of CGI-I responders ("much improved" or "very much improved" at last study visit) was observed between treatment groups (53.3 vs 48.6%; *P*=0.22). No difference in the proportion of PGI-I responders ("much improved" or "very much improved" at last study visit) was observed between treatment groups (51.1 vs 43.7%; *P*=0.15). The change in the CGI-S from baseline decreased by 1.7±1.4 and 1.4±1.4 in the trazodone and placebo groups, which statistically favored treatment with trazodone (*P*=0.036). The CGI-I scores at the last study visit were comparable in both treatment groups (*P*=0.22). The PGI-I scores at the last study visit were comparable in both treatment groups (*P*=0.084). Four percent of patients in the trazodone group discontinued treatment due to lack of efficacy compared to 4.4% of patients in the placebo group (*P*>0.99). At the end of the study, patients treated with trazodone had statistically significant improvements compared to placebo in all quality of sleep parameters.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rickels et al.[10] (2009) Vilazodone 40 mg once daily vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with MDD (single episode or recurrent)	N=410 8 weeks	Primary: Change in MADRS total score, HAM-D_{17} total score, and HAM-A total score, CGI-S and CGI-I scores Secondary: Response (≥50% decrease in total score on MADRS, and HAM-D_{17} total scores, or a score of 1 or 2 on the CGI-I)	Primary: The mean change on the MADRS total score was significantly greater with vilazodone compared to placebo (-12.9 vs -9.6, respectively; *P*=0.001). The difference was evident by week one (*P*<0.001) and on each subsequent visit (*P*<0.05). The mean change on the HAM-D_{17} total score was significantly greater with vilazodone compared to placebo (-10.4 vs -8.6, respectively; *P*=0.022). The difference was evident by week one and on each subsequent visit (*P*<0.05). The mean score change on the CGI-S was significantly greater with vilazodone compared to placebo (-1.4 vs -1.0, respectively; *P*=0.001). The mean score change on the CGI-I was significantly improved with vilazodone compared to placebo (2.6 vs 3.0, respectively; *P*=0.001). The mean change on the HAM-A total score was significantly greater with vilazodone compared to placebo (-6.6 vs -5.1, respectively; *P*=0.045). Secondary: Response rates were significantly better with vilazodone than with placebo on the MADRS (*P*=0.007), HAM-D_{17} (*P*=0.011), and CGI-I (*P*=0.001). Treatment-emergent adverse events with vilazodone included diarrhea, nausea and somnolence. Most of the adverse events were mild-to-moderate in severity.
Khan et al.[11] (2011) Vilazodone 40 mg once daily vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age with MDD (single episode or recurrent)	N=481 8 weeks	Primary: Change in MADRS total score Secondary: MADRS and HDRS-17 response, HDRS-21, HARS, CGI-S, CGI-I scores, CSFQ	Primary: Patients receiving vilazodone showed significantly greater improvements in mean MADRS scores compared to placebo (LSM treatment difference, -2.5; *P*=0.009). Secondary: Treatment with vilazodone resulted in significant improvements for the HDRS-17 (*P*=0.026), HDRS-21 (*P*=0.029), HARS (*P*=0.037) and CGI-S (*P*=0.004) scores. CGI-I scores at week eight showed significantly greater global improvement with vilazodone compared to placebo (*P*=0.004). The MADRS response rate was significantly greater among patients receiving

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				vilazodone compared to placebo (43.7 vs 30.3%, respectively; *P*=0.002), as was the HDRS-17 response rate (44.2 vs 32.9%; *P*=0.013). Remission rates for vilazodone were not significantly different than placebo based on MADRS (27.3 vs 20.3%, respectively; *P*=0.066) or HDRS-17 (24.2 vs 17.7%, respectively; *P*=0.088). More patients receiving vilazodone (82.1%) experienced a treatment-related adverse event compared to placebo (64.4%). The most frequently reported adverse events with vilazodone compared to placebo were diarrhea (30.6 vs 10.7%), nausea (26.0 vs 5.6%) and headache (12.8 vs 10.3%). Most adverse events were considered mild-to-moderate in nature. Treatment-related effects on sexual function as measured by CSFQ were small and similar among the treatment groups. Effects on weight were similar to placebo.
Robinson et al.[12] (2011) Vilazodone 40 mg once daily	MC, OL Patients 18 to 70 years of age with MDD	N=616 52 weeks	Primary: Safety, sexual function (CSFQ), effectiveness (MADRS, CGI-S and CGI-I scales) Secondary: Not reported	Primary: A total of 93.8% of patients had ≥1 treatment-emergent adverse events. The most frequent treatment-emergent adverse events were diarrhea (35.7%), nausea (31.6%), and headache (20.0%). The incidence of severe adverse events was 14.9%. The incidence of severe gastrointestinal adverse events was 3.5% and the incidence of severe headache was 1.2%. Mean weight increase was 1.7 kg at week 52. At six months, mean weight change for patients with normal baseline weight was 1.3 kg; for overweight and obese patients, mean weight increases were 1.6 and 1.0 kg, respectively. The mean CSFQ scores at baseline were 46.9 for men and 38.7 for women; both scores indicative of sexual dysfunction. The CSFQ mean scores improved and exceeded threshold values for sexual dysfunction at week four for men and week eight for women. Adverse events pertaining to impaired sexual desire or function were decreased libido (4.2%) and anorgasmia including abnormal orgasm (2.3%). Those pertaining to males only were erectile dysfunction (4.2%) and delayed ejaculation (3.1%). There were a total of eight patients who had adverse events of either suicidal ideation or behavior.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The mean MADRS scores improved from 29.9 at baseline to 11.4 at week eight (change, -18.5), 8.2 at week 24 (change, -21.7), and 7.1 at one year (change, -22.8). The mean CGI-S improved from 4.3 at baseline to 2.5 at week eight (change, -1.9) and 1.7 at one year (change, -2.6). The CGI-I mean score decreased from 3.5 at week one to 1.9 at week eight and 1.4 at one year. Secondary: Not reported
Reed et al.[13] (2012) Vilazodone 40 mg once daily	2 DP, PC, RCT Patients with MDD	N=410 (RCT-1), 481 (RCT-2) 8 weeks	Primary: Change from baseline to end of treatment MADRS total score; mixed-effects repeated-measures analyses were conducted in the PC trials; effectiveness analyses in the long-term study included mean MADRS score change over time Secondary; Not reported	Primary: Vilazodone-treated patients in both short-term studies showed greater improvement from baseline to end of treatment in mean MADRS scores than placebo-treated patients (LSM treatment difference, -3.2; *P*=0.00 RCT-1 and -2.5; *P*=0.009 RCT-2). CGI-I mean scores at end of treatment reflected greater improvement with vilazodone compared to placebo in both studies (LSM treatment difference, -0.4; *P*=0.001 RCT-1 and -0.3; *P*=0.004 RCT-2). MADRS response rates were significantly greater among patients receiving vilazodone vs those receiving placebo (RCT-1, 40.4 vs 28.1%, respectively; *P*=0.007 and RCT-2, 43.7 vs 30.3%, respectively; *P*=0.002). The greater efficacy of vilazodone vs placebo was consistent for the majority of demographic and MDD characteristic subgroups. In the long-term study, the mean MADRS score improved from 29.9 (baseline) to 11.4 (week eight), 8.2 (week 24), and 7.1 (week 52). Secondary; Not reported
Heisenberg N, et. al.[14] (2012) Vortioxetine 1 mg once daily	DB, MC, PC, PG, RCT Patients 18 to 75 years of age, had a current MDE	N=556 (N=505 completed study)	Primary: Change from baseline in HAMD-24 after eight weeks of treatment	Primary: At eight weeks, all treatment groups had a significantly greater decrease from baseline in HAMD-24 compared to placebo. Vortioxetine 1 mg had a decrease from baseline on the HAMD-24 of -14.82 (*P*<0.001). Vortioxetine 5 mg had a decrease from baseline of -15.42 (*P*<0.001), and vortioxetine 10 mg had a decrease from baseline on the HAMD-24 of -16.23 (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or vortioxetine 5 mg once daily or vortioxetine 10 mg once daily vs placebo once daily	per DSM-IV-TR criteria, ambulatory and a baseline MADRS total score ≥26	8 weeks	Secondary: Decrease from baseline on SDS, CGI-I score and decrease from baseline on MADRS	Secondary: None of the vortioxetine treatment groups had statistically significant decrease from baseline on the SDS as compared to placebo for (*P* values not reported). Vortioxetine 1, 5 and 10 mg all met the secondary endpoint of CGI-I compared to placebo; 2.37, 2.37 and 2.29 respectively (*P*<0.001 for all comparators). Vortioxetine 1, 5, and 10 mg all met statistical significance for the endpoint of decrease from baseline on the MADRS total score; -14.89, -15.09 and -15.65, respectively (*P*<0.001 for all).
Baldwin et al.[15] (2012) Vortioxetine 2.5 mg once daily or vortioxetine 5 mg once daily or vortioxetine 10 mg once daily	OL Patients with MDD	N=535 52 weeks	Primary: Safety and tolerability, MADRS Secondary: Not reported	Primary: Adverse events reported by >10% of patients were nausea, headache, and nasopharyngitis. Six patients had eight adverse events related to sexual dysfunction. There were no clinically significant safety findings with respect to mean changes of vital signs, weight, ECG parameters, or clinical laboratory values. Patients entered the extension study with a mean MADRS total score of 13.5+8.7. The mean MADRS total score decreased (improved) by approximately 8 points to 5.5+6.0 at week 52. By the end of the study, the proportion of responders had increased from 63 to 94%, as had the proportion in remission (MADRS <10), increasing from 42 to 83%. Patients in remission (n=226) at the start of this study had a relapse rate (MADRS >22) of 9.7%. Secondary: Not reported
Jain et al.[16] (2013) Vortioxetine 5 mg once daily vs	DB, PC Patients 18 to 75 years of age with MDD and a baseline MADRS total score >30	N=600 8 weeks	Primary: Change from baseline in HAMD-24 total score at week six compared to placebo	Primary: There were no significant differences in efficacy measures between subjects in the 5 mg vortioxetine and placebo groups at week six. Secondary: HAMD-24 total score in subjects with baseline HAMA >19 in the 5 mg vortioxetine group was improved at weeks three to six compared to the placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo once daily			Secondary: Response and remission rates, CGI-I, HAMA, MADRS-S total score, adverse events	group (*P*<0.05). The most common adverse events for the vortioxetine and placebo groups were nausea (19.1 and 9.4%), headache (17.1 and 15.1%) and diarrhoea (11.4 and 7.0%), respectively.
Katona C, et. al.[17] (2012) Vortioxetine 5 mg once daily or duloxetine 60 mg once daily vs placebo once daily	AC, DB, MC, PC, PG, RCT Patients ≥65 years of age, with a primary diagnosis of MDD per DSM-IV-TR criteria and a MADRS score ≥26	N=453 (N=392 completed the study) 8 weeks	Primary: Change from baseline in HAMD-24 total score at weeks one, two, four, six, and eight. Secondary: Change in baseline from CGI-I, MADRS total score, HAMA and CGI-S at week eight. Cognitive changes from baseline assessed via the RAVLT and DSST at week eight	Primary: The vortioxetine treatment group did not meet the primary endpoint until week six of the study, and it was not reported when the duloxetine treatment group began to separate from placebo for the primary endpoint. The vortioxetine treatment group began to separate on the HAMD-24 scale from placebo at week six (*P*=0.024). At week eight, vortioxetine 5 mg had a mean change from baseline in HAMD-24 score of -13.7 (*P*<0.01), and duloxetine 60 mg had a mean change from baseline on the HAMD-24 of -15.8 (*P*<0.0001). Secondary: Vortioxetine 5 mg and duloxetine 60 mg both met all secondary endpoints at week eight. A change in CGI-I of -0.56 (*P*<0.001) was reported for the vortioxetine group, along with a decrease in MADRS total change of -4.29 (*P*<0.001), a decrease in HAMA scores of -2.35 (*P*<0.01) and a decrease of CGI-S of -0.60 (*P*<0.001). Duloxetine showed similar results for these secondary endpoints with a *P*<0.001 for all of these measures. The cognitive measures also showed positive results for both treatment groups. Vortioxetine 5 mg showed a difference from placebo on the DSST change of 2.79 (*P*>0.05), and vortioxetine showed a difference from placebo in RAVLT for acquisition change of 1.14 (*P*<0.05) and delayed recall change of 0.47 (*P*<0.05). The duloxetine group did not show statistical significance for DSST change with a value of 0.77 (no *P* value reported). The duloxetine group did show statistical significance on the RAVLT for acquisition of change of 1.41 (*P*<0.01) and delayed recall change of 0.64 (*P*<0.01)
Mahableshwarkar, et. al.[18] (2013)	DB, PC Adult patients	N=611 8 weeks	Primary: Change from baseline in the	Primary: Both doses of vortioxetine were associated with declines in HAM-D24 total scores compared to placebo but were not statistically significant. At eight weeks,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Vortioxetine 2.5 mg once daily or vortioxetine 5 mg once daily vs duloxetine 60 mg once daily vs placebo once daily	with MDD		HAM-D24 Secondary: Responder rate, CGI-I), and remission rate; adverse events, ASEX	changes from baseline were [mean]: -10.50 (0.76) placebo, -12.04 (0.74) 2.5 mg vortioxetine, and -11.08 (0.74) 5 mg vortioxetine. Secondary: CGI-I and remission rate were not significantly different from placebo. Duloxetine treatment was associated with declines in HAM-D24 total score [-13.47(0.75); *P*=0.005] as well as significant improvements in secondary outcome measures vs placebo (*P*<0.05). The most common adverse events for vortioxetine were nausea, dry mouth, and headache. Rates of sexual dysfunction (ASEX) were 51.0, 37.5, 46.9, and 33.3% in the vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine, and placebo groups, respectively.

Study abbreviations: AC=active-controlled, DB=double-blind, ER=extended release, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviations: ASEX=Arizona Sexual Experience Scale, CGI-I=Clinical Global Impression of Improvement, CGI-S=Clinical Global Impression of Severity, CSFQ=Changes in Sexual Functioning Questionnaire, DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders IV (Text Revision), DSST=Digit Symbol Substitution Test, HAMA=Hamilton Rating Scale for Anxiety, HAMD-24=Hamilton Depression Rating Scale (24 item), HARS=Hamilton Anxiety Rating Scale, HDRS-17=17-item Hamilton Depression Rating Scale, MADRS= Montgomery-Åsberg Depression Rating Scale, MDD=Major Depressive Disorder, MDE=Major Depressive Episode, PGI=Patient Global Impression, RAVLT=Rey Auditory Verbal Learning Test, SDS=Sheehan Disability Scale

Special Populations

Table 5. Special Populations[1-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Nefazodone	No dose adjustment is necessary in the elderly. Safety and efficacy in children have not been established.	There is no dose adjustment necessary with any degree of renal dysfunction.	Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. Discontinue nefazodone if clinical signs or symptoms suggest liver failure.	C	Yes; use is not recommended.
Trazodone	No overall differences in safety/efficacy observed between patients over the age of 65 and younger patients (Oleptro®). Not reported (trazodone). Safety and efficacy in children have not been established.	Not studied in renal dysfunction; use with caution (Oleptro®). No dosage adjustment required (trazodone).	Not studied in hepatic dysfunction; use with caution (Oleptro®). No dosage adjustment required (trazodone).	C	Yes; use with caution.
Vilazodone	No dose adjustment is necessary in the elderly. Safety and efficacy in children have not been established.	There is no dose adjustment necessary with any degree of renal dysfunction.	There is no dose adjustment necessary with any degree of renal dysfunction.	C	Unknown; use with caution.
Vortioxetine	No dose adjustment is necessary in the elderly. Safety and efficacy in children have not	There is no dose adjustment necessary with any degree of renal dysfunction.	No dosage adjustment is necessary in mild to moderate hepatic dysfunction; however,	C	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	been established.		vortioxetine has not been studied in the setting of severe hepatic dysfunction, so its use is recommended against in severe hepatic dysfunction.		

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-5]

Adverse Events	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Cardiovascular				
Atrioventricular block	<1	-	-	-
Bradycardia	1 to 10	<1	-	-
Edema	-	1 to 10	-	-
Hypertension	-	1 to 10	-	-
Hypotension	1 to 10	1 to 10	-	-
Palpitation	-	-	2	-
Peripheral edema	1 to 10	-	-	-
Postural hypotension	1 to 10	-	-	-
Syncope	-	1 to 10	-	-
Tachycardia	-	<1	-	-
Vasodilation	1 to 10	-	-	-
Ventricular extrasystoles	-	-	<1	-
Central Nervous System				
Abnormal dreams	1 to 10	-	4	<1 to 3
Agitation	>10	<1	-	-
Anxiety	-	<1	-	-
Ataxia	1 to 10	-	-	-
Chills	1 to 10	-	-	-
Concentration decreased	1 to 10	1 to 10	-	-
Confusion	1 to 10	1 to 10	-	-
Dizziness	>10	>10	9	6 to 9
Drowsiness	>10	-	-	-
Fatigue	-	1 to 10	4	-
Fever	1 to 10	-	-	-
Hallucinations	<1	-	-	-
Headache	>10	>10	1 to 10	-
Incoordination	1 to 10	1 to 10	-	-
Insomnia	>10	-	6	-
Lightheadedness	1 to 10	-	-	-
Mania	-	-	<1	-
Memory impairment	1 to 10	-	-	-
Panic attacks	-	-	<1	-
Paresthesia	1 to 10	-	3	-

Adverse Events	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Psychomotor retardation	1 to 10	-	-	-
Restlessness	-	-	3	-
Sedation	-	>10	1 to 10	-
Seizure	<1	<1	-	-
Speech impairment	-	<1	-	-
Dermatological				
Alopecia	-	<1	-	-
Hyperhidrosis	-	-	1 to 10	-
Photosensitivity	<1	-	-	-
Pruritus	1 to 10	-	-	1 to 3
Rash	1 to 10	<1	-	-
Stevens-Johnson syndrome	<1	-	-	-
Endocrine and Metabolic				
Galactorrhea	<1	-	-	-
Gynecomastia	<1	-	-	-
Hepatic failure	<1	-	-	-
Hepatic necrosis	<1	-	-	-
Hepatitis	<1	-	-	-
Hyponatremia	<1	-	-	-
Liver function tests abnormal	<1	-	-	-
Prolactin increased	<1	-	-	-
Weight gain	-	1 to 10	-	-
Weight loss	-	1 to 10	-	-
Gastrointestinal				
Abnormal taste	1 to 10	-	-	-
Appetite decreased	-	-	1 to 10	-
Appetite increased	1 to 10	-	2	-
Constipation	>10	1 to 10	-	3 to 6
Diarrhea	1 to 10	1 to 10	28	7 to 10
Dry mouth	-	-	-	6 to 8
Dyspepsia	1 to 10	-	3	-
Flatulence	-	-	3	1 to 3
Gastroenteritis	1 to 10	-	3	-
Nausea	>10	>10	23	21 to 32
Vomiting	1 to 10	-	5	3 to 6
Xerostomia	>10	>10	8	-
Genitourinary				
Ejaculation delayed	-	-	2	-
Erectile dysfunction	-	-	2	-
Impotence	1 to 10	-	-	-
Libido decreased	1 to 10	-	3 to 5	-
Orgasm abnormal	-	-	2 to 4	-
Priapism	<1	<1	-	-
Sexual dysfunction	-	-	<2	-
Urinary frequency	1 to 10	-	-	-
Urinary retention	1 to 10	<1	-	-
Hematologic				
Hematocrit decreased	1 to 10	-	-	-
Leukopenia	<1	-	-	-
Thrombocytopenia	<1	-	-	-
Musculoskeletal				
Arthralgia	1 to 10	-	3	-

Adverse Events	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Extrapyramidal symptoms	-	<1	-	-
Hypertonia	1 to 10	-	-	-
Jittery	-	-	2	-
Myalgia	-	1 to 10	-	-
Neck rigidity	1 to 10	-	-	-
Rhabdomyolysis	<1	-	-	-
Tremor	1 to 10	1 to 10	2	-
Weakness	>10	-	-	-
Respiratory				
Bronchitis	1 to 10	-	-	-
Cough	1 to 10	-	-	-
Dyspnea	1 to 10	-	-	-
Nasal congestion	-	1 to 10	-	-
Pharyngitis	1 to 10	-	-	-
Other				
Abnormal feeling	-	-	<1	-
Abnormal taste	-	-	<1	-
Allergic reaction	<1	<1	-	-
Angioedema	<1	-	-	-
Blurred/abnormal vision	7 to 9	>10	1 to 10	-
Breast pain	1 to 10	-	-	-
Cataracts	-	-	<1	-
Eye pain	1 to 10	-	-	-
Flu syndrome	1 to 10	-	-	-
Infection	1 to 10	-	-	-
Night sweats	-	-	1 to 10	-
Serotonin syndrome	<1	-	-	-
Thirst	1 to 10	-	-	-
Tinnitus	1 to 10	-	-	-
Visual field defect	1 to 10	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications

Table 7. Contraindications[1-5]

Contraindication	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Coadministration of terfenadine, astemizole, cisapride, pimozide, triazolam, or carbamazepine with nefazodone	✔	-	-	-
Do not use monoamine oxidase inhibitors intended to treat psychiatric disorders during or within 14 days of stopping treatment; do not use within 14 days of stopping an monoamine oxidase inhibitor intended to treat psychiatric disorders	-	-	✔	✔
Do not initiate in a patient who is being treated with linezolid or intravenous methylene blue	-	-	✔	-
Hypersensitivity	✔	✔	-	✔

Contraindication	Nefazodone	Trazodone	Vilazodone	Vortioxetine
		(immediate release)		
Use in patients withdrawn from nefazodone because of evidence of liver injury	✔	-	-	-

Black Box Warning for nefazodone[1]

WARNING

Suicidality and antidepressants:
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of nefazodone or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults older than 24 years; there was a reduction in risk with antidepressants compared to placebo in adults 65 years and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Monitor patients of all ages who are started on antidepressant therapy appropriately and observe them closely for clinical worsening, suicidality, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with the health care provider. Nefazodone is not approved for use in pediatric patients.

Hepatotoxicity:
Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. The reported rate in the United States is approximately one case of liver failure resulting in death or transplant per 250,000 to 300,000 patient-years of nefazodone treatment. The total patient-years is a summation of each patient's duration of exposure expressed in years. For example, one patient-year is equal to two patients each treated for six months, three patients each treated for four months, etc.

Ordinarily, treatment with nefazodone should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. There is no evidence that preexisting liver disease increases the likelihood of developing liver failure; however, baseline abnormalities can complicate patient monitoring.

Advise patients to be alert for signs and symptoms of liver dysfunction (e.g., jaundice, anorexia, gastrointestinal complaints, malaise) and to report them to their health care provider immediately if they occur.

Discontinue nefazodone if clinical signs or symptoms suggest liver failure. If nefazodone-treated patients develop evidence of hepatocellular injury, such as increased serum aspartate aminotransferase or serum Alanine transaminase levels at least three times the upper limit of normal, withdraw the drug. Presume these patients to be at increased risk for liver injury if nefazodone is reintroduced. Accordingly, do not consider such patients for retreatment.

Black Box Warning for trazodone[1]

WARNING

Suicidality and antidepressants:
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Oleptro or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults

WARNING
beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Oleptro® is not approved for use in pediatric patients.

Black Box Warning for vilazodone[1]

WARNING
Suicidality and antidepressants: Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for clinical worsening and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. Viibryd® is not approved for use in pediatric patients.

Black Box Warning for vortioxetine[1]

WARNING
Suicidality and antidepressants: Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend toward reduced risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. Brintellix® has not been evaluated for use in pediatric patients.

Warnings/Precautions

Table 8. Warnings and Precautions[1-5]

Warnings(s)/Precaution(s)	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Abnormal bleeding; use may increase the risk of bleeding events	-	✔ (extended release)	✔	✔
Activation of mania/hypomania can occur with treatment; screen patients for bipolar disorder	-	-	✔	✔
Clinical worsening and suicide risk; patients with major depressive disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behavior or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs	✔	✔	✔	-
Discontinuation of treatment; abrupt	-	✔	✔	-

Warnings(s)/Precaution(s)	Nefazodone	Trazodone	Vilazodone	Vortioxetine
discontinuation or dose reduction has been associated with the appearance of new symptoms		✔ (extended release)		
General anesthetics; little is known about the interaction between therapy and general anesthetics; therefore, prior to elective surgery, therapy should be discontinued for as long as clinically feasible	-	✔ (immediate release)	-	-
Hepatotoxicity	✔	-	-	-
Hyponatremia may occur as a result of therapy and appears to result from the syndrome of inappropriate antidiuretic hormone secretion	-	✔ (extended release)	✔	✔
Orthostatic hypotension and syncope have been reported	✔	✔	-	-
Potential for cognitive and motor impairment; therapy may cause somnolence or sedation and may impair the mental and/or physical ability	-	✔ (extended release)	-	-
Priapism; rare cases have been reported	✔	✔ (extended release)	-	-
QT prolongation and risk of sudden death; therapy is known to prolong the QT/QTc interval	-	✔ (extended release)	-	-
Screening patients for bipolar disorder; a major depressive episode may be the initial presentation of bipolar disorder; therefore, prior to initiating antidepressant therapy patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder	✔	✔	-	-
Seizures can occur with treatment; use with caution in patients with a seizure disorder	✔	-	-	-
Serotonin syndrome or Neuroleptic Malignant Syndrome-like reactions; the development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome-like reaction have been reported, with monotherapy or when used concomitantly with serotonergic drugs	-	✔ (extended release)	✔	✔
Use in patients with heart disease; therapy is not recommended for use during the initial recovery phase of myocardial infarction and therapy should be used with caution in patients with cardiac disease	-	✔ (extended release)	-	-

Drug Interactions

Table 9. Drug Interactions[1]

Generic Name	Interacting Medication or Disease	Potential Result
Nefazodone	Aldosterone blockers	Nefazodone may increase plasma concentrations and pharmacologic or toxic effects of aldosterone blockers.
Nefazodone	Benzodiazepines	Nefazodone may increase the pharmacologic effects of certain benzodiazepines. Impaired psychomotor performance and increased sedation may result from elevated benzodiazepine plasma concentrations. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of certain benzodiazepines.
Nefazodone	Epothilones	The pharmacologic effects of epothilones may be increased by nefazodone due to a decrease in the metabolic elimination of epothilones through the inhibition of CYP3A4 by nefazodone.
Nefazodone	H-1 antagonists	Coadministration of nefazodone and H-1 antagonists may cause severe cardiac abnormalities.
Nefazodone	Histone deacetylase inhibitors	Plasma concentrations and pharmacologic effects of histone deacetylase inhibitors may be increased by nefazodone. The potential for histone deacetylase inhibitors-related adverse effects, including QT prolongation, should be considered.
Nefazodone	Human immunodeficiency virus protease inhibitors	Human immunodeficiency virus protease inhibitors may increase the plasma concentration of nefazodone, which may be due to the inhibition of CYP3A4 by human immunodeficiency virus protease inhibitors, which may decrease the metabolic elimination of nefazodone.
Nefazodone	Muscarinic receptor antagonists	Plasma concentrations and pharmacologic effects of muscarinic receptor antagonists may be increased by nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of muscarinic receptor antagonists.
Nefazodone	Narcotic analgesics	Plasma concentrations and pharmacologic effects of narcotic analgesics may be increased by these serotonin modulators. Inhibition of CYP3A4 metabolism by these serotonin modulators may decrease the metabolic elimination of narcotic analgesics.
Nefazodone	Statins	The risk of rhabdomyolysis and myositis may be increased with certain statins. Nefazodone inhibits the metabolism of statins.
Nefazodone	Sympathomimetics	The pharmacologic effects of sympathomimetics may be increased by nefazodone. Elevated sympathomimetic plasma concentrations with cardiovascular toxicity may occur. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of the sympathomimetic dose
Nefazodone	Triptans	Plasma concentrations and pharmacologic effects of triptans may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Tyrosine kinase receptor inhibitors	Plasma concentrations and pharmacologic effects of tyrosine kinase receptor inhibitors may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Vasopressin receptor agonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be increased by nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of vasopressin receptor antagonists.
Nefazodone	Axitinib	Plasma concentrations and pharmacologic effects of axitinib may be increased by nefazodone.

Generic Name	Interacting Medication or Disease	Potential Result
Nefazodone	Cisapride	Cisapride and nefazodone may, in theory, cause torsades de pointes and other types of ventricular arrhythmias.
Nefazodone	Brentuximab	Plasma concentrations and pharmacologic effects of brentuximab may be increased by nefazodone. The inhibition of CYP3A4 by nefazodone may increase the plasma concentrations of monomethyl auristatin E (MMAE), the microtubule disrupting agent in brentuximab.
Nefazodone	Budesonide	Plasma concentrations and pharmacologic effects of oral or inhaled budesonide may be increased by nefazodone. Corticosteroid toxicity and/or adrenal suppression may occur.
Nefazodone	Buspirone	Plasma concentrations and pharmacologic effects of buspirone may be increased by nefazodone. The risk of buspirone-induced adverse reactions may be increased. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of buspirone.
Nefazodone	Cabazitaxel	Plasma concentrations and pharmacologic effects cabazitaxel may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Cilostazol	Plasma concentration and pharmacologic effects of cilostazol may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Colchicine	Plasma concentrations of colchicine may be increased by nefazodone and life-threatening and fatal colchicine toxicity may occur. Inhibition of CYP3A4 or P-glycoprotein transporter protein by nefazodone may increase the absorption and decrease the elimination of colchicine.
Nefazodone	Crizotinib	Plasma concentrations and toxic effects of crizotinib may be increased by nefazodone4.
Nefazodone	Cyclosporine	Cyclosporine concentration may be increased as nefazodone may inhibit the metabolism (CYP3A4) of cyclosporine.
Nefazodone	Docetaxel	Plasma concentrations and pharmacologic effects of docetaxel may be increased by nefazodone. Use of nefazodone with docetaxel may increase the risk and/or severity of docetaxel-related toxicity.
Nefazodone	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of dronedarone.
Nefazodone	Erlotinib	Plasma concentrations of erlotinib may be increased by coadministration of nefazodone. The potential for increased adverse effects due to erlotinib exists. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of erlotinib.
Nefazodone	Eszopiclone	Plasma concentrations and the pharmacologic effects of eszopiclone may be increased by nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of eszopiclone.
Nefazodone	Iloperidone	Plasma concentrations and pharmacologic effects of iloperidone may be increased by nefazodone.
Nefazodone	Ivacaftor	Plasma concentrations and pharmacologic effects of ivacaftor may be increased by nefazodone.
Nefazodone	Lurasidone	Plasma concentrations and pharmacologic effects of lurasidone

Generic Name	Interacting Medication or Disease	Potential Result
		may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Maraviroc	The pharmacologic effects of maraviroc may be increased by nefazodone. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of maraviroc.
Nefazodone	Mifepristone	Plasma concentrations and pharmacologic effects of mifepristone may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Nilotinib	Plasma concentrations and pharmacologic effects of nilotinib may be increased by nefazodone. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of nilotinib.
Nefazodone	Oxycodone	Plasma concentrations and pharmacologic effects of oxycodone may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Pimozide	The risk of life-threatening cardiac arrhythmias may be increased, as nefazodone may inhibit the metabolism (CYP3A4) of pimozide.
Nefazodone	Ranolazine	Plasma concentrations and pharmacologic effects of ranolazine may be increased when coadministered with nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of ranolazine.
Nefazodone	Ruxolitinib	Plasma concentrations and pharmacologic effects of ruxolitinib may be increased by nefazodone.
Nefazodone	Saxagliptin	Plasma concentrations and pharmacologic effects of saxagliptin may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Ticagrelor	Plasma concentrations and pharmacologic effects of ticagrelor may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Toremifene	Plasma concentrations and pharmacologic effects of toremifene may be increased by nefazodone. Toxicity, including QT prolongation may occur.
Trazodone	Protease inhibitors	Trazodone plasma concentrations may be elevated, increasing the pharmacologic and adverse effects.
Trazodone	Serotonin reuptake inhibitors	Plasma trazodone levels may be elevated, increasing pharmacologic and adverse effects.
Trazodone	Sodium oxybate	Concurrent use of sodium oxybate and trazodone may result in an increase in sleep duration and central nervous system depression, due to additive effects.
Trazodone	Warfarin	The hypoprothrombinemic effect of warfarin may be decreased. Suboptimal anticoagulation with possible exacerbation of the disease being treated may occur.
Vilazodone	Fenfluramine & derivatives	Use of fenfluramine and derivatives with vilazodone may increase the risk of adverse effects, including serotonin syndrome due to both of the agents' ability to increase the activity of serotonin.
Vilazodone	Narcotic analgesics	Plasma concentrations and pharmacologic effects of narcotic analgesics may be increased by these serotonin modulators. Inhibition of CYP3A4 metabolism by these serotonin modulators may decrease the metabolic elimination of narcotic analgesics.

Generic Name	Interacting Medication or Disease	Potential Result
Vilazodone	Nonsteroidal anti-inflammatory drugs	Toxic effects may be increased with concurrent administration of nonsteroidal anti-inflammatory drugs and vilazodone. The risk of upper gastrointestinal bleeding may be increased. The mechanism of this interaction is unknown.
Vilazodone	Salicylates	The risk of upper gastrointestinal bleeding may be increased with concurrent administration of salicylates and vilazodone. The mechanism of this interaction is unknown.
Vilazodone	Serotonin- and norepinephrine-reuptake inhibitors	The potential exists for the occurrence of additive serotonergic activity. Inhibition of cytochrome P450 2D6 isoenzymes by vilazodone may decrease the metabolic elimination of serotonin- and norepinephrine-reuptake inhibitors. The development of serotonin syndrome is possible when the combination of serotonin- and norepinephrine-reuptake inhibitors and vilazodone are coadministered. In addition, plasma concentrations of serotonin- and norepinephrine-reuptake inhibitors may be increased by vilazodone.
Vilazodone	Cyproheptadine	Pharmacologic effects of may be decreased or reversed by cyproheptadine. Symptoms of depression may recur, because cyproheptadine may directly antagonize the serotonin receptor activity of vilazodone.
Vilazodone	Ketorolac (nasal)	Toxic effects may be increased with concurrent administration of nasal ketorolac and vilazodone. The risk of upper gastrointestinal bleeding may be increased. The mechanism of this interaction is unknown.
Vilazodone	Linezolid	Coadministration of vilazodone and linezolid may cause central nervous system toxicity characterized by symptoms of serotonin syndrome.
Vilazodone	Lithium	Coadministration of lithium and vilazodone may cause central nervous system toxicity, including serotonin syndrome. Serum lithium concentrations may be increased lithium and vilazodone may increase serotonergic neurotransmission.
Vilazodone	L-tryptophan	Both agents acutely increase central nervous system serotonin activity. Coadministration of these two agents could result in serotonin syndrome.
Vilazodone	Methylene blue	Coadministration of vilazodone and methylene blue may increase the risk of central nervous system toxicity, including serotonin syndrome. This may be the result in increased serotonin concentrations in the central nervous system and produce serotonin-related toxicity.
Vilazodone	Selegiline	The combination of vilazodone and selegiline may produce unexpected toxicity, characterized by manic-like behavior, shivering, diaphoresis, hypertension and ataxia. The mechanism of this interaction is unknown.
Vilazodone	Sibutramine	Use of sibutramine with vilazodone has been reported by the manufacturer of sibutramine to increase the potential risk for serotonin syndrome. The mechanism of this interaction is unknown.
Vilazodone	St. john’s wort	Unexpected toxicity may occur when St. john's wort and vilazodone are coadministered. The mechanism of this is unknown.
Vilazodone	Strong CYP3A4 inhibitors	Strong CYP3A4 inhibitors may decrease the metabolic elimination of vilazodone, increasing the plasma concentrations

Generic Name	Interacting Medication or Disease	Potential Result
		and pharmacological effects of vilazodone.
Vilazodone	Tramadol	Increased risk of seizures is listed in the manufacturer's package labeling as a possibility when tramadol and vilazodone are coadministered. Serotonin syndrome is also a potential risk with this combination. The mechanism of this interaction is unknown.
Vortioxetine	Anticoagulants, nonsteroidal antiinflammatory drugs, and aspirin	Use of psychotropic medications that interfere with serotonin reuptake have been reported to increase risk of upper gastrointestinal bleeding in epidemiological studies of case-control and cohort design. The concurrent use of nonsteroidal antiinflammatory drugs or Aspirin may potentiate this risk. Altered anticoagulant effects, including increased bleeding, have been reported with selective serotonin reuptake inhibitors and serotonin- and norepinephrine-reuptake inhibitors when coadministered with warfarin.
Vortioxetine	Monoamine oxidase inhibitors	Concomitant or over-lapping administration may result in increased risk for serotonin syndrome.
Vortioxetine	Potent CYP2D6 inhibitors (e.g., bupropion, paroxetine, fluoxetine)	For concomitant use of vortioxetine and a potent CYP2D6 inhibitor, it is recommended that the vortioxetine dose be reduced by half.
Vortioxetine	Potent CYP inducers (e.g., rifampin, phenytoin, carbamazepine)	For concomitant use of vortioxetine and a potent CYP inhibitor, it is recommended that the vortioxetine dose be increased, but not to exceed three times the original dose.
Vortioxetine	Serotonergic Agents	Concomitant or over-lapping administration may result in increased risk for serotonin syndrome.

Dosage and Administration

Table 10. Dosing and Administration[1-5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Nefazodone	Depression: Tablet: 200 mg/day divided in two doses initially, with a range of 300m to 600 mg/day in two divided doses thereafter	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg 150 mg 200 mg 250 mg
Trazodone	Major depressive disorder: Extended-release tablet: initial, 150 mg once daily; maintenance, may increase by 75 mg/day every three days; maximum, 375 mg/day Tablet: initial, 150 mg/day in three divided doses; maintenance, dose may be increased by 50 mg/day every three to seven days; maximum, 400 (outpatients) and 600 (inpatients) mg/day	Safety and efficacy in children have not been established.	Tablet (extended release): 150 mg 300 mg Tablet (immediate release): 50 mg 100 mg 150 mg 300 mg
Vilazodone	Major depressive disorder:	Safety and efficacy in	Tablet:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Tablet: Initial, 10 mg once daily for seven days, then increase to 20 mg once daily for seven days, then to recommended dose of 40 mg daily	children have not been established.	10 mg 20 mg 40 mg
Vortioxetine	Major depressive disorder: Tablet: initial, 10 mg once daily; maintenance, increase to 20 mg once daily, as tolerated; maximum, 20 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 15 mg 20 mg

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Psychiatric Association: **Practice Guideline for the Treatment of Patients With Major Depressive Disorder (2010)**[19]	Acute phase • Pharmacotherapy: o An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder (MDD) and definitely should be provided for those with severe MDD. o Due to the fact that the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects; the safety or tolerability of these side effects; pharmacological properties of the medication and additional factors such as medication response in prior episodes, cost and patient preference. o For the majority of patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), bupropion or mirtazapine is optimal. o In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) should be restricted to patients who do not respond to other treatments. o During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy. o If side effects do occur, an initial strategy is to lower the dose of the antidepressants or to change to an antidepressant that is not associated with those side effects. • Assessing the adequacy of treatment response: o It is important to establish that treatment has been administered for a sufficient duration and at a sufficient frequency or, in the case of medication, dose. o Generally, four to eight weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention. • Strategies to address non-response: o For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely, as an incomplete response to

Clinical Guideline	Recommendation(s)
	treatment is often associated with poor functional outcomes. o If at least a moderate improvement in symptoms is not observed within four to eight weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed and the treatment plan adjusted. o It is important to assess the quality of the therapeutic alliance and treatment adherence. o If medications are prescribed, the psychiatrist should determine whether pharmacokinetic or pharmacodynamic factors suggest a need to adjust medication dose. o After an additional four to eight weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan. o There are a number of strategies available when a change in treatment seems necessary. ▪ For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached. ▪ In patients who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy or with other agents or with changing to another non-MAOI antidepressant. ▪ Patients may be changed to an antidepressant from the same pharmacological class or to one from a different class. ▪ Patients who have not responded to an SSRI, may respond to SNRI. ▪ Augmentation of antidepressant medications can utilize another non-MAOI antidepressant, generally from a different pharmacological class, or a non-antidepressant medication, such as lithium, thyroid hormone or a second generation antipsychotic. <u>Continuation phase</u> • During the continuation phase of treatment, the patient should be carefully monitored for signs of possible relapse. • Systematic assessment of symptoms, side effects, adherence and functional status is essential and may be facilitated through the use of clinician- and/or patient-administered rating scales. • To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase

Clinical Guideline	Recommendation(s)
	should continue treatment with these agents for four to nine months. • In general, the dose used in the acute phase should be used in the continuation phase. • To prevent a relapse of depression in the continuation phase, depression-focused psychotherapy is recommended, with the best evidence available for cognitive behavioral therapy (CBT). Maintenance phase • In order to reduce the risk of a recurrent depressive episode, patients who have had three or more prior MDD episodes or who have chronic MDD should proceed to the maintenance phase of treatment after completing the continuation phase. • Maintenance therapy should also be considered for patients with additional risk factors for recurrence. • Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes, the persistence of depressive symptoms after recovery and the presence of co-occurring disorders. Such factors also contribute to decisions about the duration of the maintenance phase. • For many patients, some form of maintenance treatment will be required indefinitely. • An antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose. • For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression-focused psychotherapy but who have shown a response to electroconvulsive therapy (ECT), maintenance ECT may be considered. • Due to the risk of recurrence, patients should be monitored systematically and at regular intervals during the maintenance phase. Discontinuation of treatment • When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks. • To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home. • A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome when discontinuing antidepressants or reducing antidepressant doses. • Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms. • After discontinuation of medications, patients should continue to

Clinical Guideline	Recommendation(s)
	be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur.
National Institute for Health and Clinical Excellence: **The Treatment and Management of Depression in Adults (2009)**[20]	<u>Persistent subthreshold depressive symptoms or mild to moderate depression</u> • Do not use antidepressants routinely to treat persistent subthreshold depressive symptoms or mild depression. • Consider antidepressants for the following people: o A past history of moderate or severe depression. o Initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least two years). o Subthreshold depressive symptoms or mild depression that persist(s) after other interventions. <u>Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression</u> • For patients with persistent subthreshold depressive symptoms or mild to moderate depression who have not benefited from a low-intensity psychosocial intervention, discuss the relative merits of different interventions with the person and provide: o An antidepressant (normally an SSRI) or a high intensity psychosocial intervention. • For people with moderate or severe depression, provide a combination of an antidepressant medication and a high intensity psychological intervention. • The choice of intervention should be influenced by the duration of the episodes of depression and the trajectory of symptoms, previous course of depression and response to treatment, likelihood of adherence to treatment and any potential adverse effects and the patient's treatment preference and priorities. <u>Antidepressant drugs</u> • Choice of antidepressant: o Discuss the choice of antidepressant with the patient, including any anticipated adverse events and potential drug interactions, and their perception of the efficacy and tolerability of any antidepressant they have previously taken. o When an antidepressant is used, it should normally be an SSRI in a generic form. The SSRIs are equally effective as other antidepressants and have a favorable risk-benefit ratio. Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs, and paroxetine is associated with a higher incidence of discontinuation symptoms than other SSRIs. o Take into account toxicity in overdose when choosing an antidepressant for people at significant risk for suicide. Be aware that compared to other equally effective antidepressants routinely used in primary care, venlafaxine is associated with a greater risk of death from overdose, and tri-cyclic antidepressants (TCAs),

Clinical Guideline	Recommendation(s)
	except lofepramine, are associated with the greatest risk in overdose. o When prescribing drugs other than SSRIs, take the following into account: the increased likelihood of the person stopping treatment because of side effects with duloxetine, venlafaxine and TCAs, the specific cautions, contraindications and monitoring requirements for some drugs, that non-reversible MAOIs should normally be prescribed only by specialists. • Starting and initial phase of treatment: o When prescribing antidepressants, explore any concerns the patient has. Explain the gradual development of the full antidepressant effect, the importance of taking the medication as prescribed, the need to continue treatment after remission, potential side effects, the potential for interactions with other medications, the risk and nature of discontinuation symptoms with all antidepressants and how these symptoms can be minimized and the fact that addiction does not occur with antidepressants. o If side effects develop early in antidepressant treatment, provide appropriate information and consider one of the following strategies: monitor symptoms closely where side effects are mild and acceptable to the patient, stop the antidepressant, change to a different antidepressant if the person prefers or consider short term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic (this should usually be for no longer than two weeks in order to prevent the development of dependence). o Patients who start on low dose TCAs and who have clear clinical response can be maintained on that dose with careful monitoring. o If the patient's depression shows no improvement after two to four weeks with the first antidepressant, check that the drug has been taken regularly and in the prescribed dose. o If response is absent or minimal after three to four weeks of treatment with a therapeutic dose of an antidepressant, increase the level of support and consider increasing the dose in line with the summary of product characteristics if there are no significant side effects or switching to another antidepressant. o If the patient's depression shows some improvement by four weeks, continue treatment for another two to four weeks. Consider switching to another antidepressant if response is still not adequate, there are side effects or the person prefers to change treatment.
American College of Physicians: **Clinical Practice Guideline: Using Second-Generation Antidepressants to Treat Depressive Disorders**[21]	Treatment of major depressive disorder • When treating acute-phase MDD, the second-generation antidepressants did not significantly differ in efficacy, effectiveness, or quality of life among the SSRIs, SNRIs, selective serotonin norepinephrine reuptake inhibitors (SSNRIs), or other second-generation antidepressants.

Clinical Guideline	Recommendation(s)
(2008)	• Mirtazapine had a significantly faster onset of action; however, after four weeks, most response rates were similar. • Second-generation antidepressants did not differ in the rate of achieving remission. • First-generation antidepressants (TCAs and MAOIs) are less commonly used than second-generation antidepressants, which have similar efficacy to and lower toxicity in overdose than first-generation antidepressants. Treatment of depression in patients with accompanying symptom clusters • When treating symptom clusters in patients with accompanying depression, second-generation antidepressants did not differ in efficacy in treating accompanying anxiety, pain, and somatization. • Limited evidence suggests that some agents may be more effective in treating insomnia. Treatment of depression in selected patient populations • Second-generation antidepressants did not differ in efficacy among subgroups and special populations categorized according to age, sex, race or ethnicity, or comorbid conditions. Risk for harms and adverse events • Most of the second-generation antidepressants had similar adverse effects. • The most commonly reported adverse events were constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence. Nausea and vomiting were the most common reasons for discontinuation in efficacy studies. • Paroxetine was associated with an increased risk for sexual dysfunction. • SSRIs resulted in an increased risk for nonfatal suicide attempts. Recommendations • Clinicians should select second-generation antidepressants on the basis of adverse effect profiles and patient preferences. • Clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within one to two weeks of initiation of therapy. • Clinicians should modify treatment if the patient does not have an adequate response to pharmacotherapy within six to eight weeks of the initiation of therapy for major depressive disorder. • Clinicians should continue treatment for four to nine months after a satisfactory response in patients with a first episode of major depressive disorder. For patients who have had two or more episodes of depression, an even longer duration of therapy may be beneficial.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the**	All Types of childhood/adolescent depression • All patients with depression should receive therapy in the acute (six to 12 weeks) and continuation phases (six to 12 months);

Clinical Guideline	Recommendation(s)
Assessment and Treatment of Children and Adolescents with Depressive Disorders[22] (2007)	some will require maintenance treatment (longer than 12 months). During each phase, treatment should be accompanied by psychotherapy, education, as well as family and school involvement. • Treatment should encompass the management of comorbid conditions. • Medication regimen may be optimized or augmented in partial responders; while switching to another regimen may be appropriate in non-responders. <u>Uncomplicated depression/brief depression/mild psychosocial impairment</u> • Initial management: education, support, and case management. Reevaluate if no response after four to six weeks. <u>Moderate-to-severe depression</u> • A trial of cognitive-behavioral therapy or interpersonal psychotherapy with and/or antidepressant therapy is indicated. • Antidepressant therapy may be initiated alone or with psychotherapy. Non-responders to monotherapy may benefit from combined psychotherapy and antidepressant therapy. • Fluoxetine is the only SSRI that is Food and Drug Administration-approved for the treatment of child/adolescent depression. Other SSRIs failed to demonstrate significant advantage over placebo. • In clinical trials, venlafaxine was not more effective in treating children and adolescents with depression than either mirtazapine or placebo. Secondary analysis suggests that venlafaxine may be more effective in treating adolescents than children. • Limited evidence suggests that bupropion may be used to treat child and adolescent depression with or without comorbid attention hyperactivity deficit disorder (ADHD). • TCAs should not be used as 1st line therapy for child/adolescent depression due to poor efficacy (not statistically different from placebo) and unfavorable side-effect profile. <u>Psychotic depression</u> • SSRIs combined with atypical antipsychotics are the treatment of choice. <u>Seasonal affective disorder (SAD)</u> • Bright light therapy is recommended as treatment of SAD in youths. <u>Bipolar disorder</u> • A mood stabilizer such as lithium, valproate, or lamotrigine may be used.

<u>Conclusions</u>

The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, eating disorders (bulimia nervosa), mood disorders and premenstrual dysphoric disorder.[1-5] Some of the

agents are also approved for the treatment of nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, nocturnal enuresis and tobacco abuse.[1-32] The antidepressants are categorized into six different American Hospital Formulary Service subclasses, including monoamine oxidase inhibitors (MAOIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs) and miscellaneous agents. The agents which make up these subclasses differ with respect to their Food and Drug Administration (FDA)-approved indications, mechanism of action, pharmacokinetics, adverse events and drug interactions. The majority of the products are available in a generic formulation, and there is at least one generic product available in each antidepressant subclass.

Numerous clinical trials have been conducted with the antidepressants and comparative studies have demonstrated similar efficacy in patients with major depressive disorder. Guidelines do not give preference to one agent over another. Rather, the selection of an antidepressant should be based on adverse events, tolerability and patient preference.[19-22]

In 2010, the FDA approved an extended-release formulation of trazodone for the treatment of depression.[1-3] This agent has been shown to be more effective than placebo.[9] Trazodone (immediate-release tablets) is available in a generic formulation.

Vilazodone is a selective serotonin reuptake inhibitor and partial serotonin 5-HT_{1A} receptor agonist, which was approved by the FDA in January 2011 for the treatment of depression.[1-2,4] It has been shown to be more effective than placebo in clinical trials, with effects seen as early as one week. The SSRIs have also been shown to be effective after one week of use.[10-13] There were no studies found in the medical literature directly comparing vilazodone to other antidepressants.

Vortioxetine is a novel antidepressant that could provide a therapeutic option for patients unable to tolerate or achieve therapeutic goals with more traditional antidepressants. The nature of the treatment of depression is very individualized, and vortioxetine could make a positive impact in the setting of major depressive disorder. Vortioxetine use is associated with a high incidence of nausea at therapeutic doses, and lack of an established position in consensus treatment guidelines.[1-2,5,19-22]

References

1. Drug Facts and Comparisons [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Dec]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2014 [cited 2014 Jan 25]. Available from: http://www.thomsonhc.com.
3. Oleptro® [package insert]. Princeton, NJ: Angelini Labopharm, LLC; December 2010.
4. Viibryd® [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; December 2012.
5. Brintellix® [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; September 2013.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders.5th ed. (DSM-V) [monograph on the internet]. Arlington, VA: American Psychiatric Association; 2013 [cited 2014 Jan 22]. Available from: http://dsm.psychiatryonline.org/content.aspx?bookid=556&sectionid=41101761.
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association;2000:356.
8. Feighner J, Targum S, Bennet M, et al. A double-blind, placebo-controlled trial of nefazodone in the treatment of patients hospitalized for major depression. J Clin Psychiatry. 1998;59(5):246-53.
9. Sheehan DV, Croft HA, Gossen ER, et al. Extended-release trazodone in major depressive disorder: a randomized, double-blind, placebo-controlled study. Psychiatry (Edgmont). 2009;6:20-33.
10. Rickels K, Athanasiou M, Robinson DS, et al. 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;70:326-33.
11. Khan A, Cutler AJ, Kajdasz DK, et al. A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. J Clin Psychiatry. 2011;72:441-7.
12. Robinson DS, Kajdasz DK, Gallipoli S, et al. A one-year, open-label study assessing the safety and tolerability of vilazodone in patients with major depressive disorder. J Clin Psychopharmacol. 2011;31:643-6.
13. Reed CR, Kajdasz DK, Whalen H, Athanasiou MC, Gallipoli S, Thase ME. The efficacy profile of vilazodone, a novel antidepressant for the treatment of major depressive disorder. Curr Med Res Opin. 2012 Jan;28(1):27-39.
14. Henigsberg N, Mahableshwarkar AR, Jacobsen P, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled eight-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder [abstract]. 2012 Jul 1;73(7):953-59.
15. Baldwin DS, Hansen T, Florea I. Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. Current Medical Research & Opinion. 2012 Oct. 28(10):1717-24.
16. Jain R, Mahableshwarkar AR, Jacobsen PL, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. International Journal of Neuropsychopharmacology. 2013 Mar. 16(2):313-21.
17. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. 2012 July 1;27(4):215-23.
18. Mahableshwarkar AR, Jacobsen PL, Chen Y. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) vs placebo for 8 weeks in adults with major depressive disorder. Current Medical Research & Opinion. 2013 March 29(3):217-26.S
19. American Psychiatric Association (APA). Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition [guideline on the internet]. Arlington, Virginia: American Psychiatric Association; 2010 [cited 2014 Jan 25]. Available from: http://psychiatryonline.org/content.aspx?bookid=28&sectionid=1667485.
20. National Institute for Health and Care Excellence (NICE). Depression in adults: The treatment and management of depression in adults [guideline on the internet]. London, England, UK: National Institute for Health and Care Excellence; 2009 [cited 2014 Jan 25]. Available from: http://publications.nice.org.uk/depression-in-adults-cg90.
21. Qaseem A, Snow V, Denberg T, Forciea MA, Owens DK, Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using second-generation antidepressants to treat depressive

disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008;18;149:725-33.
22. Birmaher B, Brent D, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. American Academy of Child and Adolescent Psychiatry (AACAP). J Am Acad Child Adolesc Psychiatry. 2007;46:1503-26.