

Therapeutic Class Overview

Serotonin and Norepinephrine Reuptake Inhibitors

Therapeutic Class

- Overview/Summary:** The serotonin and norepinephrine reuptake inhibitors (SNRIs) include desvenlafaxine (Pristiq[®]), duloxetine (Cymbalta[®]) and venlafaxine (Effexor[®], Effexor XR[®], venlafaxine extended release). These agents are believed to exert their effects through potentiating the serotonergic and noradrenergic activity in the central nervous system.¹⁻⁴ As a result, the SNRIs are used in the management of a variety of psychiatric disorders and all SNRIs are Food and Drug Administration (FDA)-approved for the treatment of major depressive disorder.¹⁻⁴ The venlafaxine extended-release capsules are also indicated for the treatment of generalized anxiety disorder, panic disorder and social anxiety disorder. In addition to major depressive disorder and generalized anxiety disorder, duloxetine is approved for the management of various pain syndromes including chronic musculoskeletal pain, fibromyalgia and neuropathic pain associated with diabetic peripheral neuropathy.¹⁻³ Desvenlafaxine is the primary active metabolite of venlafaxine and is approved for once-daily dosing. Unlike venlafaxine, desvenlafaxine does not undergo metabolism through cytochrome P450 2D6, and is therefore safe to use with inhibitors of this isoenzyme.⁴ The adverse event profiles appear to be similar between the two agents. Currently, venlafaxine is available generically in both immediate- and extended-release formulations, while desvenlafaxine and duloxetine are only available as branded products.^{5,6}

Treatment for psychiatric disorders includes psychotherapy, pharmacotherapy or the combination of the two. The decision to implement psychotherapy is dependent upon patient willingness and severity of illness. For all antidepressants, the FDA requires manufacturers to include a Black Box Warning notifying prescribers of the potential for antidepressants to increase suicidal thoughts in children and young adults.¹⁻⁴

Table 1. Current Medications Available in Therapeutic Class¹⁻⁴

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Desvenlafaxine succinate (Pristiq [®])	Treatment of major depressive disorder	Extended-release tablet: 50 mg 100 mg	-
Duloxetine (Cymbalta [®])	Management of chronic musculoskeletal pain, management of fibromyalgia, management of neuropathic pain associated with diabetic peripheral neuropathy, treatment of generalized anxiety disorder and treatment of major depressive disorder	Delayed-release capsule: 20 mg 30 mg 60 mg	-
Venlafaxine (Effexor [®] , Effexor XR [®] and venlafaxine ER)	Treatment of generalized anxiety disorder (Effexor XR [®]), treatment of major depressive disorder, treatment of panic disorder, with or without agoraphobia (Effexor XR [®]), treatment of social anxiety disorder (Effexor XR [®])	Extended-release capsule (Effexor XR [®]): 37.5 mg 75 mg 150 mg Extended-release tablet: 37.5 mg 75 mg 150 mg 225 mg Tablet: 25 mg	✓

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		37.5 mg 50 mg 75 mg 100 mg	

ER, XR=extended-release

Evidence-based Medicine

- Desvenlafaxine, duloxetine and venlafaxine have been shown to be efficacious for the management of major depressive disorder (MDD), as measured by improvements in Hamilton Rating Scale for Depression-17 and Montgomery-Asberg Depression Rating Scale scores, when compared to placebo.⁷⁻²⁷ Moreover, duloxetine and venlafaxine have also been shown to be comparable to other antidepressants for the treatment of MDD.^{17,23-25,28}
- A limited number of head-to-head trials comparing duloxetine and venlafaxine have yet to demonstrate that one of these agents is more efficacious than the other for the treatment of MDD.²⁹
- Several placebo-controlled trials support the efficacy and safety of both duloxetine and venlafaxine (extended-release) in decreasing Hamilton Rating Scale for Anxiety total scores in adults with generalized anxiety disorder.³⁰⁻³⁴ The results of a large meta-analysis supports the efficacy of venlafaxine compared to placebo in the management of generalized anxiety disorder.³⁵
- Results from several clinical trials demonstrate the efficacy duloxetine in reducing pain severity in adults with fibromyalgia when compared to placebo.³⁶⁻³⁸ In addition, several placebo-controlled trials support the efficacy of duloxetine in reducing pain severity in adult patients with chronic low back pain and osteoarthritis.³⁹⁻⁴⁵
- Duloxetine is consistently more effective compared to placebo in alleviating pain, improving functional outcomes and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory, Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey and Euro Quality of Life assessment scores. Commonly reported adverse events in patients receiving duloxetine include nausea, somnolence anorexia and dysuria.⁴⁶⁻⁴⁸
- In a 52-week, open-label study comparing duloxetine to routine care (gabapentin, amitriptyline or venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant treatment-group differences observed in Euro Quality of Life assessment scores; however, results differed with regard to Short Form-36 Health Survey subscale scores. In one study, there were no significant treatment-group differences in Short Form-36 Health Survey subscale scores, and in the other subscale scores for physical functioning, bodily pain, mental health, and vitality favored duloxetine.⁴⁹⁻⁵⁰ A second head-to-head study demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had experienced an inadequate pain response to gabapentin.⁵¹

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Despite the variety of pharmacologic options available, all antidepressants appear to be equally efficacious for mood disorders. Therefore, initial treatment should depend on the individual's overall medical condition and current medication profile. Pharmacology, tolerability and safety profiles differ among these classes and among individual agents.^{52,53}
 - Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder, while SSRIs and SNRIs are recommended for generalized anxiety disorder.⁵⁴⁻⁵⁶
 - Antidepressants (TCAs and SNRIs) and some anticonvulsants (gabapentin, sodium valproate and pregabalin) should be considered as initial therapy for the treatment of painful diabetic neuropathy or painful polyneuropathies.^{57,58}
 - Acetaminophen and nonsteroidal anti-inflammatory drugs are considered first-line therapy for most patients with chronic low back pain or osteoarthritis.^{59,60}

- Other Key Facts:
 - Venlafaxine immediate- and extended-release formulations are available generically.⁶

References

1. Effexor XR[®] [prescribing information]. Philadelphia (PA): Wyeth Pharmaceuticals, Inc.; 2012 Aug.
2. Effexor[®] [prescribing information]. Philadelphia (PA): Wyeth Pharmaceuticals, Inc.; 2011 Nov.
3. Cymbalta[®] [prescribing information]. Indianapolis (IN): Lilly USA, LLC.; 2012 Sept.
4. Pristiq[®] [prescribing information]. Philadelphia (PA): Wyeth Pharmaceuticals, Inc.; 2011 Oct.
5. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2012 [cited 2012 Oct]. Available from: <http://online.factsandcomparisons.com>.
6. DRUGS@FDA.com [database on the internet]. Rockville (MD): U.S. Food and Drug Administration [cited 2012 Oct]. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.
7. Hewett K, Chrzanowski W, Schmitz M, Savelle A, Milanova V, Gee M, et al. Eight-week, placebo-controlled, double-blind comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. *J Psychopharmacol*. 2009;23:531-8.
8. Dunlop BW, Reddy S, Yang L, Lubaczewski S, Focht K, Guico-Pabia CJ. Symptomatic and functional improvement in employed depressed patients. A double-blind clinical trial desvenlafaxine vs placebo. *J Clin Psychopharmacol*. 2011;31:569-76.
9. Liebowitz MR, Yeung PP, Entsuah R. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. *J Clin Psychiatry*. 2007;68:1663-72.
10. Boyer P, Montgomery S, Lepola U, Germain JM, Brisard C, Ganguly R, et al. Efficacy, safety, and tolerability of fixed-dose desvenlafaxine 50 and 100 mg/day for major depressive disorder in a placebo-controlled trial. *Int Clin Psychopharmacol*. 2008;23:243-53.
11. Liebowitz MR, Manley AL, Padmanabhan SK, Ganguly R, Tummala R, Tourian KA. Efficacy, safety and tolerability of desvenlafaxine 50 mg/day and 100 mg/day in outpatients with major depressive disorder (abstract). *Curr Med Res Opin*. 2008 Jul;24(7):1877-90.
12. Kornstein SG, Jiang Q, Reddy S, Musngung JJ, Guico-Pabia CJ. Short-term efficacy and safety of desvenlafaxine in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder. *J Clin Psychiatry*. 2010;71(8):1088-96.
13. Feiger AD, Tourian KA, Rosas GR, Padmanabhan SK. A placebo-controlled study evaluating the efficacy and safety of flexible-dose desvenlafaxine treatment in outpatients with major depressive disorder. *CNS Spectr*. 2009;14(1):41-50.
14. Septien-Velez L, Pitrosky B, Padmanabhan SK, Germain JM, Tourian KA. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. *Int Clin Psychopharmacol*. 2007;22:338-47.
15. Rickels K, Montgomery SA, Tourian KA, Guelfi JD, Pitrosky B, Padmanabhan SK, et al. Desvenlafaxine for the prevention of relapse in major depressive disorder. Results of a randomized trial. *J Clin Psychopharmacol*. 2010;30:18-24.
16. Clayton AH, Kornstein SG, Rosas G, Guico-Pabia C, Tourian KA. An integrated analysis of the safety and tolerability of desvenlafaxine compared to placebo in the treatment of major depressive disorder (abstract). *CNS Spectr*. 2009 Apr;14(4):183-95.
17. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial (abstract). *J Clin Psychiatry*. 2002 Mar;63(3):225-31.
18. Gaynor PJ, Gopal M, Zheng W, Martinez JM, Robinson MJ, Hann D, et al. Duloxetine vs placebo in the treatment of major depressive disorder and associated painful physical symptoms: a replication study. *Curr Med Res Opin*. 2011;27:1859-67.
19. Gaynor PJ, Gopal M, Zheng W, Martinez JM, Robinson MJ, Marangell LB. A randomized placebo-controlled trial of duloxetine in patients with major depressive disorder and associated painful physical symptoms. *Curr Med Res Opin*. 2011;27:1849-58.
20. Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacol*. 2004;14:457-70.
21. Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA. Duloxetine in the treatment of depression a double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol*. 2004;24:389-99.
22. Perahia DG, Wang F, Mallinckrodt CH, Walker DJ, Detke MJ. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Psychiatry*. 2006;21(6):367-78.
23. Nemeroff CB, Michael E. A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. *J Psychiatr Res*. 2007;41:351-9.
24. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affective Disorders*. 1999;56:171-81.
25. Richard IH, McDermott MP, Kurlan R, Lyness JM, Como PG, Pearson N, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. *Neurology*. 2012;78:1229-36.
26. Thase ME, Kornstein SG, Germain JM, Jiang Q, Guico-Pabia C, Ninan PT. An integrated analysis of the efficacy of desvenlafaxine compared to placebo in patients with major depressive disorder. *CNS Spectr*. 2009;14:144-54.
27. Vis PM, van Baardewijk M, Einarson TR. Duloxetine and venlafaxine-XR in the treatment of major depressive disorder: a meta-analysis of randomized clinical trials. *Ann Pharmacother*. 2005;39(11):1798-807.
28. Rosso G, Rigardetto S, Bogetto F, Maina G. A randomized, single-blind, comparison of duloxetine with bupropion in the treatment of SSRI-resistant major depression. *J Affect Disord*. 2012;136:172-6.
29. Perahia DG, Pritchett YL, Kajdasz DK, Bauer M, Jain R, Russell JM, et al. A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. *J Psychiatr Res*. 2008;42:22-34.
30. Rynn M, Russell J, Erickson J, Detke MJ, Ball S, Dinkel J, et al. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depression and Anxiety*. 2008;25:182-9.

31. Koponen H, Allgulander G, Erickson J, Dunayevich E, Pritchett Y, Detke MJ, et al. Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. *Prim Care Companion J Clin Psychiatry*. 2007;9:100-7.
32. Davidson JRT, Wittchen HU, Llorca PM, Erickson J, Detke M, Ball SG, et al. Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol*. 2008;18:673-81.
33. Hartford J, Kornstein S, Liebowitz M, Pigott T, Russell J, Detke M, et al. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol*. 2007;22:167-74.
34. Nicolini H, Bakish D, Duenas H, Spann M, Erickson J, Hallberg C, et al. Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial. *Psychol Med*. 2009;39:267-76.
35. Schmitt R, Gazalle FK, Lima MS, Cunha A, Souza J, Kapczinski F. The efficacy of antidepressants for generalized anxiety disorder: a systematic review and meta-analysis. *Rev Bras Psiquiatr*. 2005 Mar;27(1):18-24.
36. Mease PJ, Russell IJ, Kajdasz DK, Wiltse CG, Detke MJ, Wohlreich MM, et al. Long-term safety, tolerability, and efficacy of duloxetine in the treatment of fibromyalgia. *Semin Arthritis Rheum*. 2010;39:454-64.
37. Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a six-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain*. 2008;136:432-44.
38. Arnold LM, Hudson JI, Wang F, Wohlreich MM, Prakash A, Kajdasz DK, et al. Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with vs without major depressive disorder. *Clin J Pain*. 2009;25:461-8.
39. Skljarevski V, Zhang S, Chappell AS, Walker DJ, Murray I, Backonja M. Maintenance of effect of duloxetine in patients with chronic low back pain: a 41-week uncontrolled, dose-blinded study. *Pain Med*. 2010;11:648-57.
40. Skljarevski V, Desai D, Liu-Seifert H, Zhang Q, Chappell AS, Detke MJ, et al. Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine*. 2010;35:E578-85.
41. Chappell AS, Ossanna MJ, Liu-Seifert H, Iyengar S, Skljarevski V, Li LC, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain*. 2009;146:253-60.
42. Chappell AS, Desai D, Liu-Seifert H, Zhang Q, Skljarevski V, Belenkov Y, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. *Pain Pract*. 2010;11:33-41.
43. Skljarevski V, Zhang S, Desai D, Alaka KJ, Palacios S, Miazgowski T, et al. Duloxetine vs placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. *J Pain*. 2010;11:1282-90.
44. Skljarevski V, Ossanna M, Liu-Seifert H, Zhang Q, Chappell A, Iyengar S, et al. A double-blind, randomized trial of duloxetine vs placebo in the management of chronic low back pain. *Eur J Neurol*. 2009;16:1041-8.
45. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. *Curr Med Res Opin*. 2011;27:2361-72.
46. Yan G, Guang N, Wei-ping J, Zhi-guang Z, Zhang-rong X, Zhi-min L, et al. Duloxetine vs placebo in the treatment of patients with diabetic neuropathic pain in China. *Chin Med J*. 2010;123(22):3184-92.
47. Armstrong DG, Chappell AS, Le TK, Kajdasz DK, Backonja M, D'Souza DN, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evaluation of functional outcomes. *Pain Med*. 2007 Jul-Aug;8(5):410-8.
48. Kajdasz DK, Iyengar S, Desai D, Backonja MM, Farrar JT, Fishbain DA, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evidence-based findings from post hoc analysis of three multicenter, randomized, double-blind, placebo-controlled, parallel-group studies. *Clin Ther*. 2007;29:2536-46.
49. Wernicke JF, Wang F, Pritchett YL, Smith TR, Raskin J, D'Souza DN, et al. An open-label 52-week clinical extension comparing duloxetine with routine care in patients with diabetic peripheral neuropathic pain. *Pain Medicine*. 2007;8(6):503-13.
50. Raskin J, Smith TR, Wong K, Pritchett YL, D'Souza DN, Iyengar S, et al. Duloxetine vs routine care in the long-term management of diabetic peripheral neuropathic pain. *J Palliative Med*. 2006;9(1):29-40.
51. Tanenberg RJ, Irving GA, Risser RC, Ahl J, Robinson MJ, Skljarevski V, et al. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. *Mayo Clin Proc*. 2011;86(7):615-24.
52. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct [cited 2012 Oct]. 152 p. Available at: http://psychiatryonline.org/data/Books/prac/PG_Depression3rdEd.pdf.
53. National Institute for Clinical Excellence. Depression: the treatment and management of depression in adults (update). National Institute for Clinical Excellence; 2009 Oct [cited 2012 Oct]. Available at: <http://guidance.nice.org.uk/CG90>.
54. National Institute for Clinical Excellence. Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults. National Institute for Clinical Excellence; 2011 Jan [cited 2012 Oct]. Available at: <http://www.nice.org.uk/nicemedia/live/13314/52599/52599.pdf>.
55. Stein M, Goin M, Pollack M, Roy-Byrne P, Sareen J, Simon NM, et al. Practice guideline for the treatment of patients with panic disorder, second edition. American Psychiatric Association; 2009 [cited 2012 Oct]. Available at: http://psychiatryonline.org/data/Books/prac/PanicDisorder_2e_PracticeGuideline.pdf.
56. Connolly S, Bernstein G; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. American Academy of Child and Adolescent Psychiatry. *J Am Acad Child Adolesc Psychiatry*. 2007;46(2):267-83.
57. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010 Sep;17(9):1113-e88.
58. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011 May 17;76(20):1758-65.

59. Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, et al. Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007;147:478-91.
60. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012 Apr;64(4):455-74.

Therapeutic Class Review **Serotonin and Norepinephrine Reuptake Inhibitors**

Overview/Summary

The serotonin and norepinephrine reuptake inhibitors (SNRIs) include desvenlafaxine (Pristiq[®]), duloxetine (Cymbalta[®]) and venlafaxine (Effexor[®], Effexor XR[®], venlafaxine extended release). These agents are believed to exert their effects through potentiating the serotonergic and noradrenergic activity in the central nervous system.¹⁻⁴ As a result, the SNRIs are used in the management of a variety of psychiatric disorders and all SNRIs are Food and Drug Administration (FDA)-approved for the treatment of major depressive disorder.¹⁻⁴ The venlafaxine extended-release capsules are also indicated for the treatment of generalized anxiety disorder and panic disorder. Both extended-release formulations are also indicated for social anxiety disorder. In addition to major depressive disorder and generalized anxiety disorder, duloxetine is approved for the management of various pain syndromes including chronic musculoskeletal pain, fibromyalgia and neuropathic pain associated with diabetic peripheral neuropathy.¹⁻³ Desvenlafaxine is the primary active metabolite of venlafaxine and is approved for once-daily dosing. Unlike venlafaxine, desvenlafaxine does not undergo metabolism through cytochrome P450 2D6, and is therefore safe to use with inhibitors of this isoenzyme.⁴ The adverse event profiles appear to be similar between the two agents. Currently, venlafaxine is available generically in both immediate- and extended-release formulations, while desvenlafaxine and duloxetine are only available as branded products.^{5,6}

Treatment of psychiatric disorders includes psychotherapy, pharmacotherapy or the combination of the two. The decision to implement psychotherapy is dependent upon patient willingness and severity of illness. Despite the variety of pharmacologic options available, all antidepressants appear to be equally efficacious for mood disorders. Therefore, initial treatment should depend on the individual's overall medical condition and current medication profile. Pharmacology, tolerability and safety profiles differ among these classes and among individual agents.^{7,8} For all antidepressants, the FDA requires manufacturers to include a Black Box Warning notifying prescribers of the potential for antidepressants to increase suicidal thoughts in children and young adults.¹⁻⁴ Selective serotonin reuptake inhibitors (SSRIs), SNRIs, tricyclic antidepressants, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder, while SSRIs and SNRIs are recommended for generalized anxiety disorder.⁹⁻¹¹ The SNRIs are considered an initial treatment option for the management of neuropathic pain, while duloxetine is recommended for use in patients with fibromyalgia.^{12,13}

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Desvenlafaxine succinate (Pristiq [®])	Selective Serotonin- and Norepinephrine-reuptake Inhibitors	-
Duloxetine (Cymbalta [®])	Selective Serotonin- and Norepinephrine-reuptake Inhibitors	-
Venlafaxine (Effexor [®] , Effexor XR [®] , venlafaxine ER)	Selective Serotonin- and Norepinephrine-reuptake Inhibitors	✓

ER, XR=extended-release

Indications

Table 2. Food and Drug Administration Approved Indications¹⁻⁴

Indication(s)	Desvenlafaxine	Duloxetine	Venlafaxine
Management of chronic musculoskeletal pain		✓	
Management of fibromyalgia		✓	
Management of neuropathic pain associated		✓	

Indication(s)	Desvenlafaxine	Duloxetine	Venlafaxine
with diabetic peripheral neuropathy			
Treatment of generalized anxiety disorder		✓	✓ (Effexor XR [®])
Treatment of major depressive disorder	✓	✓	✓
Treatment of panic disorder, with or without agoraphobia			✓ (Effexor XR [®])
Treatment of social anxiety disorder			✓ (Effexor XR [®] , venlafaxine extended-release tablets)

Pharmacokinetics

Table 3. Pharmacokinetics¹⁻⁵

Generic Name	Bioavailability (%)	Metabolism	Active metabolites	Elimination (%)	Half-Life (hours)
Desvenlafaxine	80	Hepatic	O-desmethylvenlafaxine	Renal (45)	10 to 11
Duloxetine	Not Reported	Hepatic	4-hydroxy duloxetine glucuronide, 5-hydroxy, 6-methoxy duloxetine sulfate	Feces (20); renal (70)	8 to 17
Venlafaxine	12.6 (IR) ~45.0 (ER)	Hepatic	O-desmethylvenlafaxine	Renal (87)	5 (IR)

IR=immediate-release, ER=extended-release

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the serotonin and norepinephrine reuptake inhibitors (SNRIs) are outlined in Table 4.¹⁴⁻⁷⁴

Desvenlafaxine, duloxetine and venlafaxine have been shown to be efficacious for the management of major depressive disorder (MDD), as measured by improvements in Hamilton Rating Scale for Depression-17 and Montgomery-Åsberg Depression Rating Scale scores, when compared to placebo.^{14,17-24,26-29,31-36,44,46} Duloxetine and venlafaxine have also been shown to be comparable to other antidepressants for the treatment of MDD.^{27,34-36,40} A limited number of head-to-head trials comparing duloxetine and venlafaxine have yet to demonstrate that one of these agents is more efficacious than the other for the treatment of MDD.⁴¹ Trials comparing desvenlafaxine to an active comparator have not been conducted.

A large meta-analysis evaluating the incidence of suicide-related events with duloxetine in patients with MDD found no evidence of an increased risk of suicidal behaviors or ideation during treatment with duloxetine compared to treatment with placebo; Hamilton Rating Scale for Depression-3 suicidality scores were improved and there was less worsening of suicidal ideation with duloxetine.⁴⁵

Both duloxetine and venlafaxine (extended-release) are approved for the treatment of generalized anxiety disorder (GAD). Several placebo-controlled trials support the efficacy and safety of both agents in decreasing Hamilton Rating Scale for Anxiety total scores in adults with GAD.⁵²⁻⁵⁶ Duloxetine has also demonstrated a benefit over placebo in increasing the time to relapse and decreasing the proportion of patients experiencing relapse compared to placebo.⁵⁴ The results of a large meta-analysis supports the efficacy of venlafaxine compared to placebo in the management of GAD.⁵⁷

Results from several clinical trials demonstrate the efficacy of duloxetine in reducing pain severity in adults with fibromyalgia when compared to placebo.⁴⁹⁻⁵¹ In addition, several placebo-controlled trials

support the efficacy of duloxetine in reducing pain severity in adult patients with chronic low back pain and osteoarthritis.⁵⁹⁻⁶⁵

Duloxetine is consistently more effective compared to placebo in alleviating pain, improving functional outcomes and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory, Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey and Euro Quality of Life assessment scores. Commonly reported adverse events in patients receiving duloxetine include nausea, somnolence anorexia and dysuria.⁶⁶⁻⁶⁸

In a 52-week, open-label study comparing duloxetine to routine care (gabapentin, amitriptyline or venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant treatment-group differences observed in Euro Quality of Life assessment scores; however, results differed with regard to Short Form-36 Health Survey subscale scores. In one study, there were no significant treatment-group differences in Short Form-36 Health Survey subscale scores, and in the other subscale scores for physical functioning, bodily pain, mental health, and vitality favored duloxetine.^{69,70} A second head-to-head study demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had experienced an inadequate pain response to gabapentin.⁷¹

Table 4. Clinical Trials

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Depression/Major Depressive Disorder				
<p>Hewett et al¹⁴</p> <p>Bupropion ER 150 mg/day for 4 weeks, followed by 300 mg/day</p> <p>vs</p> <p>venlafaxine ER 75 mg/day for 4 weeks, followed by 150 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 64 years of age with MDD</p>	<p>N=576</p> <p>8 weeks</p>	<p>Primary: Mean change from baseline at week eight in the MADRS total score (LOCF)</p> <p>Secondary: MADRS total score (observed cases), MADRS subscore, percentage of MADRS responders and remitters at week eight; CGI-I score at week eight; CGI-S score and HAMA total score at weeks one, two, four, six and eight</p>	<p>Primary: The mean changes from baseline at week eight (LOCF) in MADRS total score were greater for patients receiving bupropion ER and venlafaxine ER compared to patients receiving placebo: -16.0 for bupropion ER ($P=0.006$ vs placebo), -17.1 for venlafaxine ER ($P<0.001$ vs placebo) and -13.5 for placebo. There was no significant difference between the bupropion ER group and the venlafaxine ER group (95% CI, -0.7 to 2.9).</p> <p>Secondary: The mean changes from baseline to week eight (observed cases) in MADRS total scores were significantly greater for bupropion ER and venlafaxine ER patients compared to the placebo group: -18.2 for bupropion ER ($P=0.003$), -18.5 for venlafaxine ER ($P<0.001$) and -15.8 for placebo.</p> <p>Significant improvements from baseline in MADRS sadness and concentration difficulties scores were observed for bupropion ER (-2.2; $P<0.001$ and -1.8; $P=0.004$, respectively) and venlafaxine ER (-2.3; $P<0.001$ and -1.9; $P<0.001$, respectively) compared to placebo at week eight (-1.7 and -1.4, respectively).</p> <p>Significant improvements in MADRS lassitude score were found for venlafaxine ER compared to placebo (-1.8 vs -1.5; $P=0.009$), but not for bupropion ER (-1.7 vs -1.5; $P=0.140$).</p> <p>A larger proportion of patients in the bupropion ER and venlafaxine ER groups were classified as MADRS responders ($\geq 50\%$ reduction in MADRS total score) and remitters (MADRS total score ≤ 11) at week eight compared to the placebo group. Response rates were 57% for bupropion ER ($P=0.033$), 65% for venlafaxine ER ($P<0.001$), and 46% for placebo. Remission rates were 47% for bupropion ER ($P=0.004$), 51% for venlafaxine ER ($P<0.001$), and 32% for placebo.</p> <p>CGI-I response rates for both active treatment groups were significantly better</p>

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				<p>than placebo with 68% of bupropion ER patients ($P<0.001$) and 65% of venlafaxine ER patients ($P=0.009$) rated 'much improved' or 'very much improved' at week eight compared to 53% of placebo patients.</p> <p>Significantly greater mean decreases from baseline in SDS total scores were observed for bupropion ER (-8.4; $P=0.003$) and venlafaxine ER (-9.0; $P<0.001$) compared to placebo (-6.2).</p> <p>The mean change from baseline in patient satisfaction with study medication was significantly greater for bupropion ER (4.9; $P=0.005$) and venlafaxine ER (5.2; $P<0.001$) than placebo (4.4).</p>
<p>Ferguson et al¹⁵</p> <p>Desvenlafaxine 100 or 200 mg/day</p>	<p>MC, OL</p> <p>Outpatients ≥ 65 years of age with MDD</p>	<p>N=52 (safety analysis)</p> <p>≤ 6 months</p>	<p>Primary: Safety</p> <p>Secondary: HAM-D-17 total scores</p>	<p>Primary:</p> <p>The most frequently reported adverse events were mild or moderate nausea (40%), dizziness (25%), and headache (21%). Primary and secondary adverse events led to discontinuation of treatment for 18 (35%) patients. The most common event cited as reasons for discontinuation were hypertension (10%) and nausea (10%). Two patients experienced three serious adverse events.</p> <p>Secondary:</p> <p>After three months of treatment, mean total HAM-D-17 score decreased 9.20 points (LOCF) from a baseline score of 21.68 ± 3.20. This improvement was maintained for the duration of the trial; the mean change from baseline at final evaluation at month six was -9.28 points, resulting in a mean HAM-D-17 total score of 12.40 ± 7.19. These improvements were maintained without dose escalation.</p> <p>HAM-D-17 based response rates were 42% (LOCF) at month three. The clinical responses were maintained by 65% of patients at month six. HAM-D-17 based remission rates were 28% at month two, which were maintained by 30% of patients at month six.</p>
<p>Sores et al¹⁶</p> <p>Desvenlafaxine 100 to 200 mg/day</p>	<p>MC, OL</p> <p>Post-menopausal women 40 to 70</p>	<p>N=123</p> <p>6 months</p>	<p>Primary: HAM-D-17 total score</p>	<p>Primary:</p> <p>At final evaluation, mean reductions from acute-phase baseline HAM-D-17 total scores were -11.33 and -11.41 with desvenlafaxine/desvenlafaxine and escitalopram/desvenlafaxine. Mean reductions from week eight of acute phase</p>

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	years of age with MDD who did not achieve clinical response to acute, DB treatment with desvenlafaxine or escitalopram		Secondary: CGI-I, HAMA, QIDS-SR, VAS-PI, MADRS, CSFQ, EQ-5D, Health State Today, MRS, SDS, treatment response (HAM-D-17 and MADRS based), safety	<p>at the final evaluation of the OL extension phase were -6.13 and -6.59, respectively. Consistent improvements in mean HAM-D-17 total scores were observed among patients in both treatment groups from baselines of both the DB acute phase and the OL extension phase.</p> <p>Secondary: Improvements were demonstrated for additional efficacy and health outcome measures for patients in both groups during the OL extension phase. Throughout the course of the overall study, desvenlafaxine/desvenlafaxine patients achieved mean improvements from baseline in CSFQ total scores after the acute phase and OL extension phase of 1.58 ± 6.84 and 1.84 ± 4.01, respectively; escitalopram/desvenlafaxine patients experienced improvements of 0.71 ± 6.08 and 2.60 ± 6.28 from respective baselines.</p> <p>HAM-D-17 response or remission rates after six months were achieved in 56 to 58 and 41 to 48% of desvenlafaxine/desvenlafaxine and escitalopram/desvenlafaxine patients. MADRS response rates were 72 and 64%, respectively. The median time to remission was 68 (95% CI, 41 to 84) and 70 days (95% CI, 44 to 125) with desvenlafaxine/desvenlafaxine and escitalopram/desvenlafaxine patients.</p> <p>Treatment-emergent adverse events were reported by 91% of patients, the most common being headache (17%), insomnia (17%), nausea (16%), dizziness (15%), infection (15%), abnormal dreams (12%), dry mouth (11%), pain (11%), and sweating (10%).</p>
Dunlop et al ¹⁷ Desvenlafaxine 50 mg/day vs placebo	DB, PC, RCT Gainfully employed (≥ 20 hours/week) outpatients with MDD	N=427 12 weeks	Primary: HAM-D-17 total score Secondary: SDS, safety	Primary: Desvenlafaxine demonstrated superiority over placebo beginning at week two, which continued through week 12. Adjusted mean endpoint scores with desvenlafaxine and placebo were 9.33 and 11.45, respectively. Mean change scores were -12.61 ± 0.45 and -10.50 ± 0.60 with desvenlafaxine and placebo, respectively. The adjusted mean difference in change from baseline between desvenlafaxine and placebo at week 12 was 2.12 (95% CI, 0.78 to 3.46; $P=0.002$).

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				<p>Secondary: The adjusted mean difference in change from baseline score on the SDS between the desvenlafaxine and placebo at week 12 was 1.33 (95% CI, -0.09 to 2.76), which narrowly missed significance ($P=0.067$).</p> <p>There were six serious adverse events (no deaths) that occurred in four and two desvenlafaxine- and placebo-treated patients. None of these events were considered non-treatment related. No new safety concerns about desvenlafaxine were identified from safety analyses.</p>
<p>Liebowitz et al¹⁸</p> <p>Desvenlafaxine 100 mg/day for days 1 to 14, increasing to 200 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥ 30 days prior to screening, HAM-D-17 total score ≥ 20, a HAM-D item 1 (depressed mood) score ≥ 2 and CGI-S score ≥ 4</p>	<p>N=247</p> <p>8 weeks</p>	<p>Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score</p> <p>Secondary: Change from baseline in CGI-I, MADRS, CGI-S, VAS-PI, vital signs, safety</p>	<p>Primary: There was no significant difference in the reduction of HAM-D-17 score from baseline between the desvenlafaxine and placebo group (14.1 vs 15.1 respectively; $P=0.277$).</p> <p>Secondary: There was no significant difference between CGI-I scores between the desvenlafaxine and the placebo group compared to baseline (2.5 vs 2.7 respectively; P value not reported).</p> <p>The CGI-S showed no difference from baseline between the desvenlafaxine and placebo groups (3.1 vs 3.3 respectively; P value not reported).</p> <p>Improvement was demonstrated at final evaluation between desvenlafaxine and placebo on the MADRS scale (16.8 vs 19.5 respectively; $P=0.047$), the VAS-PI overall pain scale (15.6 vs 11.6 respectively; $P=0.008$), the VAS-PI back pain scale (13.1 vs 20.5 respectively; $P=0.006$) and the VAS-PI arm, leg or joint pain scale (13.3 vs 21.6 respectively; $P<0.001$).</p> <p>There was a significant increase from baseline in supine systolic blood pressure (3.76 vs -1.59; $P<0.001$, respectively) and supine diastolic blood pressure (1.85 vs -0.91; $P=0.003$ respectively) in the desvenlafaxine group compared to the placebo group.</p> <p>There was a significant decrease in body weight seen in the desvenlafaxine</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				<p>group compared to the placebo group (-0.74 kg vs 0.36 kg; $P<0.001$).</p> <p>There was an increase in heart rate from baseline observed in the desvenlafaxine group (4.27 beats per minute; $P<0.01$) and a decrease from baseline in the placebo group (-2.27 beats per minute; $P<0.01$). A decrease in the QT interval was observed in the desvenlafaxine group from baseline (-4.27 ms; P value not significant) and an increase in QT interval from baseline was observed in the placebo group (4.90; $P<0.05$). The difference in these values was considered to be statistically significant ($P=0.01$).</p> <p>Anorexia ($P<0.001$), constipation ($P<0.05$), dry mouth ($P<0.01$), nausea ($P<0.001$), tremor ($P<0.01$) and yawning ($P<0.01$) were seen more commonly in the desvenlafaxine group compared to the placebo group.</p>
<p>Boyer et al¹⁹</p> <p>Desvenlafaxine 50 and 100 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Outpatients ≥ 18 years of age with MDD, depressive symptoms for ≥ 30 days before screening and baseline HAM-D-17 total score ≥ 20; HAM-D-17 item 1 (depressed mood) score ≥ 2; and CGI-S ≥ 4</p>	<p>N=438</p> <p>8 weeks (plus a 1 week taper phase)</p>	<p>Primary: HAM-D-17 total score</p> <p>Secondary: CGI-I, MADRS, CGI-S, VAS-PI, Covi Anxiety Scale total scores, remission rates, responder rates, safety</p>	<p>Primary: In a LOCF analysis, adjusted mean baseline changes in HAM-D-17 total scores were significantly greater with desvenlafaxine 50 (-13.2; $P=0.002$) and 100 mg/day (-13.7; $P<0.001$) compared to placebo (-10.7).</p> <p>Secondary: Significant differences on CGI-I scores were observed with desvenlafaxine 50 ($P=0.002$) and 100 mg/day ($P<0.001$) compared to placebo.</p> <p>For MADRS total score, the between-group difference vs placebo in adjusted mean was 3.1 (95% CI, 1.0 to 5.2) with desvenlafaxine 50 mg/day and 4.2 (95% CI, 2.1 to 6.3) with desvenlafaxine 100 mg/day. Adjusted mean changes from baseline were significantly greater with desvenlafaxine compared to placebo starting at week four ($P=0.036$ and $P=0.004$, respectively), and were sustained until the final evaluation ($P=0.004$ and $P<0.001$, respectively).</p> <p>For CGI-S score at final evaluation, adjusted mean changes from baseline were significantly greater than placebo for desvenlafaxine 50 ($P=0.003$) and 100 mg/day ($P<0.001$). Significant separation from placebo was observed beginning at week six and four for desvenlafaxine 50 ($P=0.002$) and 100 mg/day ($P=0.027$), and both groups remained significantly different through the final</p>

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				<p>evaluation.</p> <p>Results of the VAS-PI are not reported because of the heterogeneity of the format of the translated scale; it was impossible to properly analyze the corresponding data.</p> <p>For Covi Anxiety Scale total score at final evaluation, adjusted mean changes from baseline were significantly greater than placebo for desvenlafaxine 50 ($P=0.001$) and 100 mg/day ($P=0.004$).</p> <p>The adjusted OR for response relative to placebo was 1.943 (95% CI, 1.24 to 3.05) and 1.798 (95% CI, 1.14 to 2.83) with desvenlafaxine 50 and 100 mg/day ($P=0.004$ and $P=0.011$). For remission rates, the adjusted OR for remission relative to placebo was 1.488 (95% CI, 0.93 to 2.38) and 2.117 (95% CI, 1.32 to 3.39) with desvenlafaxine 50 and 100 mg/day ($P=0.099$ and $P=0.002$). Responder rates were significantly higher with desvenlafaxine 50 (65%) and 100 mg/day (63%) compared to placebo (50%; $P=0.005$ and $P=0.018$, respectively; NNT, 6.5 and 7.4). Significantly more patients receiving desvenlafaxine 100 mg/day achieved remission compared to patients receiving placebo (45 vs 29%, respectively; $P=0.003$; NNT, 6.1).</p> <p>Most of the treatment-emergent adverse events were mild or moderate in severity. The most common treatment-emergent adverse events were nausea, dizziness, insomnia, constipation, fatigue, anxiety, and decreased appetite.</p>
<p>Liebowitz et al²⁰ (abstract)</p> <p>Desvenlafaxine 50 or 100 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥ 30 days prior to</p>	<p>N=447</p> <p>8 weeks (plus a 1 week taper)</p>	<p>Primary: Change from baseline to final on-therapy evaluation on HAM-D-17score</p> <p>Secondary: Change from baseline in CGI-I, CGI-S, MADRS,</p>	<p>Primary: There was a significant decrease in the HAM-D-17 score from baseline in the desvenlafaxine 50 mg group (-11.5; $P=0.018$) but not for the desvenlafaxine 100 mg group (-11; $P=0.065$) compared to the placebo group (-9.53).</p> <p>Secondary: The decrease from baseline in the CGI-I score was not considered significant for the desvenlafaxine 50 mg group ($P=0.085$) and the 100 mg group ($P=0.076$) compared to the placebo group. The decrease from baseline in CGI-S scores were not significantly different than the desvenlafaxine 50 mg ($P=0.074$) and</p>

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	screening, HAM-D-17 total score ≥ 20 , and CGI-S score ≥ 4		VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease of $\geq 50\%$), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17 score decrease to $\leq 7\%$), SDS, WHO-5, safety	<p>100 mg groups ($P=0.208$) compared to the placebo group.</p> <p>There was a significant decrease from baseline in MADRS scores in the desvenlafaxine 50 mg group ($P=0.022$) but not the 100 mg group ($P=0.095$). VAS-PI overall pain score showed significant improvement compared to baseline in the 100 mg group ($P=0.041$) but not for the 50 mg group ($P=0.223$).</p> <p>There was no significant difference between the desvenlafaxine 50 and 100 mg groups compared to the placebo group in terms of HAM-D-17 rates of response ($P=0.133$, $P=0.246$, respectively) and remission ($P=0.075$, $P=0.194$, respectively).</p> <p>The desvenlafaxine 50 mg group showed significant improvements from baseline in SDS score (-8.96; $P=0.012$) and WHO-5 score (6.68; $P=0.020$) compared to the placebo group. There were no significant differences from baseline in the 100 mg group compared to the placebo group in SDS or WHO-5 score.</p> <p>The most common adverse events seen (incidence $\geq 10\%$ and at twice the rate in the placebo group) with desvenlafaxine treatment included: dry mouth, constipation, insomnia, decreased appetite, hyperhidrosis and dizziness (P values not reported).</p>
Kornstein et al ²¹ Desvenlafaxine 100 or 200 mg/day vs placebo	DB, MC, PC, RCT Perimenopausal and post-menopausal women 40 to 70 years of age with MDD, single or recurrent episode	N=387 8 weeks	Primary: HAM-D-17 total score Secondary: CGI-I, CGI-S, MADS, HAMA, QIDS-SR, MRS, EQ-5D, VAS-PI, safety	<p>Primary: Baseline reductions in HAM-D-17 total scores were significantly greater with desvenlafaxine (adjusted mean change, -12.64) compared to placebo (-8.33; $P<0.01$). Significant differences between treatments were observed at week one ($P=0.044$) and were sustained through week eight (week two; $P=0.013$, weeks three to eight; $P<0.001$).</p> <p>Both perimenopausal (adjusted mean change, -10.96; $P=0.003$) and postmenopausal (-11.09; $P<0.001$) subgroups achieved significant reductions in HAM-D-17 total scores with desvenlafaxine compared to placebo. The treatment effect (adjusted mean difference from placebo) in these two populations were -4.07 (95% CI, -6.77 to -1.37) and -2.37 (95% CI, -5.07 to $-$</p>

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				<p>1.47).</p> <p>HAM-D-17 based response (58.6%) and remission (38.2%) rates were significantly higher with desvenlafaxine compared to placebo (31.6 and 22.4%; $P<0.001$ and $P=0.008$, respectively).</p> <p>Secondary: Desvenlafaxine achieved significant improvement compared to placebo on all secondary outcomes. Desvenlafaxine-treated patients had significantly lower CGI-I scores at week eight compared to placebo-treated patients (2.00 vs 2.82; $P<0.001$); a significantly higher percentage of patients receiving desvenlafaxine had scored 1 (very much improved) or 2 (much improved) compared to patients receiving placebo (67.7 vs 41.2%; $P<0.001$).</p> <p>In total, 7.4 and 3.2% of desvenlafaxine- and placebo-treated patients discontinued study medication due to an adverse event. The event cited most commonly by patients discontinuing due to an adverse event was hypertension (five vs zero patients). Treatment-emergent adverse events were reported by 85.2 and 75.2% of desvenlafaxine- and placebo-treated patients. Most events were mild or moderate in severity. The most common treatment-emergent adverse events were dry mouth (24 vs 10%), somnolence (15 vs 7%), constipation (14 vs 6%), hypertension (7 vs 2%), sweating (7 vs 2%), dyspepsia (6 vs 2%), and anorexia (6 vs <1%). Serious adverse events were reported by three patients receiving desvenlafaxine (chest pain and hypertension, medication error and psychotic depression, and infection) and two patients receiving placebo (cerebrovascular disorder and skin carcinoma). No deaths were reported during the study or within 30 days after its conclusion.</p>
<p>Feiger et al²²</p> <p>Desvenlafaxine 200 to 400 mg/day</p> <p>vs</p>	<p>DB, MC, PC, PG, RCT</p> <p>Outpatients ≥18 years of age with MDD</p>	<p>N=235</p> <p>8 weeks (plus a 2 week tapering phase)</p>	<p>Primary: HAM-D-17</p> <p>Secondary: CGI-I, CGI-S, MADRS, HAM-D-6, safety</p>	<p>Primary: No significant difference was observed in the adjusted mean change from baseline in the HAM-D-17 total score between desvenlafaxine and placebo at the final evaluation (difference in adjusted means, 1.6; 95% CI, -0.2 to 3.4).</p> <p>No significant differences were observed between desvenlafaxine and placebo groups for HAM-D-17 clinical response rates at the final evaluation; the logistic</p>

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placebo				<p>regression analysis demonstrated adjusted ORs of 1.456 (95% CI, 0.85 to 2.50; $P=0.175$) for HAM-D-17 response. No significant difference in HAM-D-17 remission rates was observed between desvenlafaxine and placebo groups at final evaluation; the logistic regression analysis showed an adjusted OR of 1.158 (95% CI, 0.60 to 2.22; $P=0.66$).</p> <p>Secondary: At final evaluation, significant differences between desvenlafaxine and placebo were observed for the CGI-I (difference in adjusted means: 0.3; 95% CI, 0.0 to 0.6), CGI-S (0.3; 95% CI, 0.0 to 0.6), MADRS (2.9; 95% CI, 0.3 to 5.4), and HAM-D-6 (1.5; 95% CI, 0.5 to 2.6).</p> <p>A significant difference was observed between desvenlafaxine and placebo groups for MADRS clinical response rates; the logistic regression analysis demonstrated an adjusted OR of 1.754 (95% CI, 1.03 to 3.00; $P=0.04$).</p> <p>Treatment-emergent adverse events were reported by 112 patients (96%) and 101 patients (86%) receiving desvenlafaxine and placebo. Treatment-emergent adverse events reported by $\geq 5\%$ of patients receiving desvenlafaxine and at a frequency at least twice that of the placebo group included nausea, dry mouth, hyperhidrosis, insomnia, somnolence, decreased appetite, tremor, blurred vision, yawning, sedation, vomiting, mydriasis, middle insomnia, initial insomnia, erectile dysfunction, constipation, feeling jittery, and dyspepsia. Nausea, the most frequently reported adverse event in patients receiving desvenlafaxine (36%), was mild to moderate in the majority of cases (88%). Treatment-emergent adverse events resulted in reduction in dose of study medication for six (5%) and two (2%) patients receiving desvenlafaxine and placebo. Taper/post-study-emergent adverse events were consistent with what has been seen in previous trials of desvenlafaxine and with the SNRIs. Significantly more patients receiving desvenlafaxine (12%) discontinued the study because of treatment-emergent adverse events compared to patients receiving placebo (3%; $P=0.008$). No deaths or serious adverse events occurred during the study.</p>

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<p>Septein-Velez et al²³</p> <p>Desvenlafaxine 200 or 400 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Outpatients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥ 30 days prior to screening, HAM-D-17 total score ≥ 20, and CGI-S score ≥ 4</p>	<p>N=369</p> <p>8 weeks (plus a 2 week taper)</p>	<p>Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score</p> <p>Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease $\geq 50\%$), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17 score decrease to $\leq 7\%$), SDS, WHO-5</p>	<p>Primary: The decrease from baseline in HAM-D-17 score was significantly greater in the 200 mg group (-12.6; $P=0.002$) and the 400 mg group (-12.1; $P=0.008$) compared to the placebo group (-9.3).</p> <p>Secondary: A lower CGI-I score was observed in the 200 mg group ($P=0.004$) and the 400 mg group ($P=0.028$) compared to the placebo group. There was a significant difference in change in MADRS score from baseline favoring desvenlafaxine in the 200 mg ($P=0.001$) and 400 mg ($P=0.005$) groups compared to the placebo group.</p> <p>There was a significant difference in change in CGI-S score from baseline favoring patients treated with desvenlafaxine compared to patient treated with placebo ($P=0.001$ and $P=0.013$ for the desvenlafaxine 200 and 400 mg groups, respectively).</p> <p>There was a greater response on the HAM-D-17 rate of response assessment for the 200 mg (60%; $P<0.001$) and 400 mg (56%; $P=0.005$) groups compared to the placebo group (38%). A greater degree of remission was observed for the 200 mg group (37%; $P=0.017$) compared to the placebo group (23%). The degree of remission was not significant for the 400 mg group (P value not reported).</p> <p>The change in VAS-PI overall pain score from baseline favored the desvenlafaxine 200 mg group ($P=0.002$) compared to the placebo group. The difference between the 400 mg group and the placebo group was not considered significant ($P=0.053$).</p> <p>There was a significant improvement from baseline in SDS total score for the desvenlafaxine 200 mg ($P=0.004$) and 400 mg ($P=0.004$) groups compared to the placebo group. There was a significant improvement from baseline in WHO-5 score for the desvenlafaxine 200 mg ($P=0.001$) and 400 mg ($P=0.005$) groups compared to the placebo group.</p>

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<p>Rickels et al²⁴</p> <p>Desvenlafaxine 200 to 400 mg/day</p> <p>vs</p> <p>placebo</p> <p>After 12 weeks of OL treatment with desvenlafaxine, patients with HAM-D-17 total score ≤ 11 were randomized to continue desvenlafaxine or be switched to placebo.</p>	<p>DB, PC, RCT</p> <p>Patients 18 to 75 years of age with MDD, single or recurrent episode, without psychotic features</p>	<p>N=374 (DB phase) N=575 (OL phase)</p> <p>12 weeks of OL treatment, followed by a 6 month, DB phase</p>	<p>Primary: Time until relapse (HAM-D-17 total score ≥ 16 at any visit, CGI-I score ≥ 6 at any visit, or discontinuation due to unsatisfactory response)</p> <p>Secondary: HAM-D-17 total score, CGI-I, CGI-S, HAM-D-6, Covi Anxiety score, safety</p>	<p>Primary: Patients receiving desvenlafaxine experienced significantly longer times to relapse of MDD compared to patients receiving placebo during DB treatment ($P < 0.0001$). The proportions of patients relapsing were 42 and 24% of patients receiving placebo and desvenlafaxine, respectively ($P < 0.001$).</p> <p>Secondary: A significant difference in HAM-D-17 total scores in favor of desvenlafaxine was observed from DB week three onward ($P < 0.001$). At the final evaluation, adjusted mean changes were 0.85 and 5.03 for desvenlafaxine and placebo, respectively.</p> <p>Desvenlafaxine was also associated with significant differences compared to placebo on CGI-I, CGI-S, HAM-D-6, and Covi Anxiety scores.</p> <p>The most common primary reason cited for discontinuation of treatment during the OL phase was adverse events (19%), which consisted of nausea, dizziness, and insomnia. A total of 101 (55%) and 58 (31%) patients receiving placebo and desvenlafaxine discontinued treatment during the DB phase. The most frequent adverse event reported as the reason for discontinuation during the DB phase was depression (14 patients receiving placebo vs seven patients receiving desvenlafaxine).</p> <p>During the OL phase the most commonly reported adverse events with desvenlafaxine were nausea (42%), dry mouth (32%), headache (26%), dizziness (23%), hyperhidrosis (21%), insomnia (20%), constipation (15%), decreased appetite (12%), fatigue (12%), somnolence (11%), diarrhea (10%), tremor (10%), vomiting (8%), sedation (5%), and blurred vision (5%). During the DB phase, treatment-emergent adverse events were reported by 73 and 82% of patients receiving desvenlafaxine and placebo, respectively. The most commonly reported events with desvenlafaxine were headache (24%), dizziness (15%), nausea (14%), fatigue (13%), hyperhidrosis (13%), diarrhea (9%), abnormal dreams (9%), depression (8%), insomnia (8%), influenza (7%), irritability (7%), back pain (6%), upper respiratory tract infection (6%), abdominal pain (5%), anxiety (5%), muscle spasms (5%), nasopharyngitis (5%),</p>

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<p>Demartinis et al²⁵</p> <p>Desvenlafaxine 100, 200, or 400 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥ 30 days prior to screening, HAM-D-17 total score ≥ 20, a Ham-D item 1 (depressed mood) score ≥ 2 and CGI-S score ≥ 4</p>	<p>N=461</p> <p>8 weeks (plus a 2 week taper)</p>	<p>Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score</p> <p>Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease $\geq 50\%$), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17 score decrease to $\leq 7\%$), SDS, WHO-5, vital signs, safety</p>	<p>tremor (5%), delayed ejaculation (5% in men), erectile dysfunction (5% in men), vomiting (4%), vertigo (3%), myalgia (2%), paresthesia (2%), and altered mood (1%).</p> <p>Primary: Decrease in HAM-D-17 score from baseline was significantly greater at final on-therapy evaluation in the 100 mg (-10.60; $P=0.0038$) and 400 mg (-10.75; $P=0.0023$) groups compared to the placebo group (-7.65). However, the decrease in HAM-D-17 score from baseline in the 200 mg group was not significant (-9.63; $P=0.0764$) compared to the placebo group.</p> <p>Secondary: There were significant decreases in CGI-I score from baseline for the 100 mg (2.3; $P=0.008$), 200 mg (2.5; $P=0.0462$) and 400 mg (2.4; $P=0.0129$) groups compared to the placebo treated group (2.8).</p> <p>There were significant decreases in CGI-S scores from baseline in the 100 mg (-1.5; 95% CI, 0.2 to 0.8; $P=0.002$) and 400 mg (-1.5; 95% CI, 0.2 to 0.9; $P<0.001$) groups compared to the placebo group (-1.0). The CGI-S score difference observed in the 200 mg group was not significant (-1.13; 95% CI, 0.0 to 0.6; $P=0.056$).</p> <p>The decrease from baseline in MADRS score was significant for the 100 mg group (-13.6; 95% CI, 1.3 to 6.4; $P=0.004$), the 200 mg group (-13.5; 95% CI, 1.3 to 6.2; $P=0.005$), and the 400 mg group (-15.2; 95% CI, 3.1 to 8.3; $P<0.001$) compared to the placebo group (-9.9).</p> <p>Patients in the desvenlafaxine 100 mg group showed a significant improvement from baseline in overall pain score compared to the placebo group on the VAS-PI scale (-13.9 vs 5.9; $P=0.002$, respectively). There was no significant difference in either the 200 mg (-5.4; $P=0.357$) or the 400 mg (-10.1; $P=0.069$) groups.</p> <p>There was a significantly higher OR for response to the 100 mg group (2.15; 95% CI, 1.25 to 3.73; $P=0.006$) and 400 mg group (1.91; 95% CI, 1.11 to 3.32;</p>

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				<p>$P=0.020$). The OR for response to the 200 mg group was not significant (1.60; 95% CI, 0.93 to 2.76; $P=0.089$) compared to the placebo group.</p> <p>There was a significantly higher OR for remission in the 400 mg group compared to the placebo group (2.20; 95% CI, 1.17 to 4.14; $P=0.014$). The OR of the 100 mg group (1.86; 95% CI, 0.99 to 3.52; $P=0.053$) and 200 mg group (1.73; 95% CI, 0.92 to 3.26; $P=0.088$) were not significant compared to the placebo group.</p> <p>There was a statistically significant increase in supine pulse rate in the desvenlafaxine 400 mg group compared to baseline (4.19; $P<0.001$). The increase was considered statistically significant when compared to the placebo group (0.15; $P<0.05$). The change in supine pulse rate from baseline in the desvenlafaxine 100 mg (-0.03) and 200 mg (1.06) groups were not considered significant compared to the placebo group (P value not significant).</p> <p>The mean increase in supine systolic blood pressure was considered significant in all groups compared to baseline compared to the placebo group ($P<0.05$). The increase in diastolic blood pressure was considered significant in all treatment groups compared to baseline ($P<0.001$ for the 200 and 400 mg groups and $P<0.01$ for 100 mg group). There was a significant increase in diastolic blood pressure from baseline in both the desvenlafaxine 200 and 400 mg groups compared to the placebo group ($P<0.05$). The increase in diastolic blood pressure from baseline in the 100 mg group was not considered significant compared to the placebo group (P value not significant). There was a significant decrease in body weight in all desvenlafaxine treatment groups compared to baseline ($P<0.001$) and to the placebo group ($P<0.05$).</p> <p>Adverse events that occurred at twice the rate of placebo in at least 5% of desvenlafaxine-treated subjects included: nausea, somnolence, insomnia, dry mouth, sweating, dizziness, nervousness, anorexia, constipation, abnormal ejaculation/orgasm, asthenia and tremor (P values not reported).</p>

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<p>Clayton et al²⁶ (abstract)</p> <p>Desvenlafaxine 50 to 400 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCTs (integrated analysis of short-term 9 trials)</p> <p>Adult outpatients with MDD</p>	<p>N=2,950</p> <p>8 weeks</p>	<p>Primary: Treatment-emergent adverse events, laboratory values, vital signs, discontinuation symptoms</p> <p>Secondary: Not reported</p>	<p>Primary: The most common treatment-emergent adverse event was transient nausea that was generally mild to moderate. The most common sexual dysfunction associated with desvenlafaxine treatment was erectile dysfunction in men (7 vs 1%) and anorgasmia in women (1 vs 0%). One patient receiving desvenlafaxine died of a completed suicide; there were four suicide attempts (three vs one patient[s]) and eight cases of suicidal ideation (five vs three patients) during the on-therapy period.</p> <p>Desvenlafaxine was associated with small but significant mean changes in laboratory assessments, particularly lipid and liver enzyme elevations, and ECGs; few cases of these changes were clinically relevant.</p> <p>Small but significant changes in mean blood pressure occurred with all desvenlafaxine doses; clinically meaningful changes were observed in 1 and 2% of placebo- and desvenlafaxine-treated patients.</p> <p>In the overall population, adverse events resulted in discontinuations in 3 and 12% of placebo- and desvenlafaxine-treated patients; in the subset of fixed-dose trials, the rates were 4 and 4 to 18% with placebo and desvenlafaxine.</p> <p>Secondary: Not reported</p>
<p>Goldstein et al²⁷ (abstract)</p> <p>Duloxetine, titrated from 20 to 60 mg BID</p> <p>vs</p> <p>placebo</p> <p>vs</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 75 years of age with MDD</p>	<p>N=173</p> <p>8 weeks</p>	<p>Primary: HAM-D-17 total score</p> <p>Secondary: MADRS, CGI-S, CGI-I, PGI-I, safety</p>	<p>Primary: Duloxetine was superior to placebo in change in HAM-D-17 total score ($P=0.009$). Estimated probabilities of response and remission were 64 and 56%, respectively, with duloxetine compared to 52 and 30% with fluoxetine, and 48 and 32% with placebo.</p> <p>Duloxetine was numerically superior to fluoxetine on the primary outcome.</p> <p>Secondary: Duloxetine was numerically superior to fluoxetine on most secondary outcomes.</p>

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fluoxetine 20 mg/day				Duloxetine was well tolerated; 76% of patients achieved the maximum dose, and insomnia and asthenia were the only adverse events reported significantly more frequently compared to placebo ($P<0.05$).
Gaynor et al ²⁸ Duloxetine 60 mg/day vs placebo	DB, MC, PC, RCT Patients ≥ 18 years of age with a current episode of MDD and at least moderate pain	N=527 8 weeks	Primary: Mean change in MADRS total score and BPI average pain rating Secondary: Remission, PGI-I, SDS global functional impairment score	<p>Primary: Treatment with duloxetine resulted in a significantly greater improvement in MADRS total score compared to treatment with placebo (-14.96 vs -10.77, respectively; 48.3 vs 34.8% improvement from baseline, respectively; $P<0.001$).</p> <p>There was a significantly greater reduction in average pain rating from baseline to week eight with duloxetine compared to placebo (-1.66 vs -1.17, respectively; 27.7 vs 18.9% reduction in pain, respectively; $P<0.001$). Patients also had greater improvement in their average pain rating at weeks two, four, and eight with duloxetine compared to placebo (all $P<0.01$).</p> <p>Secondary: A significantly higher percentage of patients receiving duloxetine (37.3%) met the criteria for remission compared to patients receiving placebo (23.0%; $P<0.001$).</p> <p>Greater improvements were observed for the other pain severity ratings (worst pain; $P<0.001$, least pain; $P=0.003$, pain right now; $P<0.001$), as well as ratings of interference of pain with functioning (all $P<0.05$) with duloxetine vs placebo.</p> <p>The least squares mean PGI-I score demonstrated significantly greater improvements with duloxetine compared to placebo ($P\leq 0.01$). Scores of 1 ('very much better') or 2 ('much better') were reported by a significantly greater percentage of patients in the duloxetine group compared to the placebo group (53.3 vs 26.8%, respectively; $P<0.001$).</p> <p>Patients receiving duloxetine demonstrated significantly greater improvements in the SDS global functional impairment score compared to placebo (46.4 vs 31.8%, respectively; $P<0.001$).</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Gaynor et al ²⁹ Duloxetine 60 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a current episode of MDD and at least moderate pain	N=528 8 weeks	Primary: Mean change in MADRS total score and BPI average pain rating Secondary: Remission, PGI-I, SDS global functional impairment score, safety	Primary: Treatment with duloxetine resulted in a significantly greater improvement in MADRS total score compared to treatment with placebo (-16.77 vs -12.73, respectively; 57.9 vs 44.3% improvement from baseline, respectively; $P<0.001$). Duloxetine was more effective than placebo beginning at week two and at all remaining visits ($P\leq0.001$). There was a significantly greater reduction in average pain rating from baseline to week eight with duloxetine compared to placebo (-1.93 vs -1.31, respectively; 35.1 vs 22.9% reduction in pain, respectively; $P\leq0.001$). Patients also had a greater improvement in their average pain rating at weeks one, two, four, and eight with duloxetine compared to placebo (all $P\leq0.005$). Secondary: A significantly greater proportion of patients receiving duloxetine met the criteria for remission than patients receiving placebo ($P\leq0.01$). Overall scores for 'worst pain' and 'least pain' in the last 24 hours and for 'pain right now' were also reduced with duloxetine vs placebo (all $P\leq0.001$). The least squares mean PGI-I score demonstrated significantly greater improvements with duloxetine compared to placebo ($P\leq0.021$). Scores of 1 ('very much better') or 2 ('much better') were reported by a significantly greater percentage of patients in the duloxetine group (50.8%) compared to the placebo group (35.2%; $P\leq0.001$). Patients receiving duloxetine demonstrated significantly greater improvements in the SDS global functional impairment score compared to patients receiving placebo (48.2 vs 37.7%, respectively; $P=0.019$). Improvements in the individual items addressing social life/leisure activities and family life/home responsibilities were greater with duloxetine compared to placebo ($P\leq0.05$). The improvement in the item addressing school/work life was not significantly different between duloxetine and placebo ($P=0.112$). Treatment emergent adverse events with duloxetine were nausea, somnolence,

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				constipation, decreased appetite, and hyperhidrosis. Rates of discontinuation due to adverse events were greater for duloxetine than placebo (8.0 vs 3.4%, respectively; $P=0.024$).
Nierenberg et al ³⁰ Duloxetine 60 mg/day vs escitalopram 10 mg/day vs placebo	AC, DB, PC, RCT Patients ≥ 18 years of age with MDD	N=547 8 weeks	Primary: Percentage of patients achieving onset criteria at week two (defined as 20% decrease from baseline in HAM-D) Secondary: Not reported	Primary: No significant difference was observed in the probability of patients meeting onset criteria at week two between the duloxetine group and the escitalopram group ($P=0.097$). Duloxetine and escitalopram both showed significant improvement compared to placebo on primary efficacy analysis at week one and week eight ($P\leq 0.05$). Secondary: Not reported
Detke et al ³¹ Duloxetine 40 or 60 mg BID vs paroxetine 20 mg/day vs placebo After acute treatment, patients who had a $\geq 30\%$ reduction in baseline HAM-D-17 total score were allowed to continue on the same (blinded)	DB, PC, RCT Outpatients ≥ 18 years of age with MDD	N=367 (acute phase) N=273 (continuation phase) 8 weeks of acute treatment plus a 6 month continuation phase	Primary: HAM-D-17 total scores Secondary: HAM-D-17 subscales, MADRS, HAMA, VAS for pain, CGI-S, PGI-I, SSI, SDS, safety	Primary: In the acute phase, patients treated with duloxetine had significantly greater improvement in HAM-D-17 total scores at week eight ($P=0.001$ and $P<0.001$) compared to patients treated with placebo. Paroxetine also demonstrated significant superiority over placebo at week eight ($P<0.001$). In the acute phase, estimated probabilities of response at week eight for patients receiving duloxetine 80 (70%) and 120 mg/day (77%) were significantly superior to that of placebo (47%; $P=0.005$ and $P<0.001$). The estimated probability of response for paroxetine-treated patients was also significantly greater compared to placebo-treated patients ($P<0.001$). In the acute phase, estimated probabilities of remission for patients receiving duloxetine 80 and 120 mg/day, and paroxetine 20 mg/day were significantly superior to patients receiving placebo at week eight. In the continuation phase, patients within each active treatment group demonstrated significant within-group improvement in HAM-D-17 total score. In the continuation phase, a log-rank test demonstrated that duloxetine 80

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treatment for a 6 month continuation phase.				<p>mg/day, duloxetine 120 mg/day, and paroxetine each had a significantly longer time to loss of response compared to placebo ($P=0.002$, $P=0.018$, and $P=0.002$, respectively).</p> <p>Secondary: In the acute phase, duloxetine 80 mg/day, duloxetine 120 mg/day, and paroxetine showed significantly greater improvement on the HAM-D-17 anxiety/somatization, core factor, maier, and retardation subscales compared to placebo. Paroxetine-treated patients showed a significant improvement on the sleep subscale compared to patients receiving placebo.</p> <p>In the acute phase, patients receiving duloxetine 80 mg/day, duloxetine 120 mg/day, or paroxetine 20 mg/day has significantly greater improvements in MADRS ($P\leq 0.001$ vs placebo for all, $P\leq 0.05$ for duloxetine 120 vs 80 mg/day), HAMA ($P\leq 0.01$ for duloxetine 80 mg/day vs placebo, $P\leq 0.001$ for duloxetine 120 mg/day and paroxetine vs placebo), CGI-S ($P\leq 0.001$ for all comparisons), and PGI-I ($P\leq 0.01$ for duloxetine 80 mg/day vs placebo, $P\leq 0.001$ for duloxetine 120 mg/day and paroxetine vs placebo, $P\leq 0.05$ for duloxetine 80 mg/day vs paroxetine) scales compared to patients receiving placebo.</p> <p>In the acute phase, patients receiving duloxetine or paroxetine showed significantly greater improvement on both SSI 26- and 28-Item Averages compared to placebo-treated patients.</p> <p>Using mean change analysis, in the acute phase patients treated with duloxetine and paroxetine showed significantly greater improvement on the SDS work item, social life item, family life item, and total score compared to patients receiving placebo.</p> <p>In the continuation phase, patients within each active treatment group demonstrated significant within-group improvement in MADRS, HAMA, CGI-S, and PGI-I. Patients receiving placebo exhibited significant within-group improvement in HAMA and PGI-I.</p> <p>In the continuation phase, patients receiving duloxetine 120 mg/day showed</p>

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				<p>marginally significant improvement from baseline on the SSI 28-Item Average ($P=0.054$), while improvement was significant for the Pain Item Average ($P=0.034$).</p> <p>There were no deaths during the acute treatment phase. One serious adverse event occurred in a patient receiving paroxetine, but was considered to be non-treatment related. The proportion of patients who discontinued the study due to adverse events did not differ significantly across treatment groups (4.2, 3.2, 3.5, and 3.2%; $P=1.00$). The only adverse event leading to discontinuation in more than one patient within any treatment group was headache (two patients receiving duloxetine 120 mg/day). Treatment-emergent adverse events experienced by $\geq 5\%$ of patients receiving duloxetine 120 mg/day are constipation, dry mouth, increased sweating, somnolence, nausea, headache, and insomnia.</p> <p>Three patients died during the six-month continuation phase (one patient receiving duloxetine 120 mg/day and placebo died as a result of suicide, while one patient receiving duloxetine 80 mg/day died as a result of pulmonary edema). All three deaths were considered to be non-treatment related. Serious adverse events were reported by one placebo-treated patient, one duloxetine 80 mg/day-treated patient, and four duloxetine 120 mg/day-treated patients. The proportions of patients discontinuing treatment due to an adverse event were similar across groups.</p>
<p>Goldstein et al³²</p> <p>Duloxetine 20 to 40 mg BID</p> <p>vs</p> <p>paroxetine 20 mg/day</p> <p>vs</p>	<p>DB, PC, RCT</p> <p>Outpatients with depression</p>	<p>N=353</p> <p>8 weeks</p>	<p>Primary: HAM-D</p> <p>Secondary: Adverse effects</p>	<p>Primary: Duloxetine 80 mg/day was more effective than placebo on mean HAM-D-17 total change by 3.62 points (95% CI, 1.38 to 5.86; $P=0.002$).</p> <p>Duloxetine 40 mg/day was also significantly more efficacious than placebo by 2.43 points (95% CI, 0.19 to 4.66; $P=0.034$), while paroxetine was not (1.51 points; 95% CI, -0.55 to 3.56; $P=0.150$).</p> <p>Duloxetine 80 mg/day was more efficacious than placebo for most other measures, including overall pain severity, and was more efficacious than paroxetine on the HAM-D-17 improvement (by 2.39 points; 95% CI, 0.14 to</p>

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placebo				<p>4.65; $P=0.037$) and estimated probability of remission (57% for duloxetine 80 mg/day, 34% for paroxetine; $P=0.022$).</p> <p>Secondary: The only adverse event reported significantly more frequently for duloxetine 80 mg/day than for paroxetine was insomnia (19.8% for duloxetine 80 mg/day, 8.0% for paroxetine; $P=0.031$).</p>
<p>Perahia et al³³</p> <p>Duloxetine 40 mg BID; dose titrated as follows: 3 days at 20 mg BID, followed by 40 mg BID</p> <p>vs</p> <p>duloxetine 60 mg BID; dose titrated as follows: 3 days at 20 mg BID, followed by 3 days at 40 mg BID, followed by 60 mg BID</p> <p>vs</p> <p>paroxetine 20 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥ 18 years of age with MDD</p>	<p>N=392</p> <p>8 months</p>	<p>Primary: Mean change from baseline in HAM-D-17</p> <p>Secondary: Discontinuation of study drug due to adverse drug events</p>	<p>Primary: Patients treated with duloxetine 80 and 120 mg/day had significantly greater improvement in HAM-D-17 total scores at week eight compared to placebo-treated patients ($P=0.045$ and $P=0.014$, respectively).</p> <p>Paroxetine was not significantly different from placebo ($P=0.089$) on mean change on the HAM-D-17.</p> <p>Secondary: The proportion of patients who discontinued the study due to adverse events did not differ significantly ($P=0.836$) across treatment groups; placebo (2.0%), duloxetine 80 mg/day (4.3%), duloxetine 120 mg/day (3.9%), and paroxetine 20 mg (4.1%).</p>
<p>Nemeroff et al³⁴</p> <p>Venlafaxine 75 to 225 mg/day</p>	<p>DB, MC, PC, RCT</p> <p>Outpatients ≥ 18</p>	<p>N=308</p> <p>6 weeks</p>	<p>Primary: HAM-D</p> <p>Secondary:</p>	<p>Primary: On the HAM-D, overall differences among treatment groups at week six did not reach significance ($P=0.051$), though the difference between the venlafaxine and placebo groups was significant ($P=0.016$). The differences between</p>

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vs fluoxetine 20 to 60 mg/day vs placebo	years of age with MDD		Not reported	fluoxetine and placebo ($P=0.358$) and between venlafaxine and fluoxetine ($P=0.130$) were not significant. The difference on the HAM-D depressed mood item was significant among treatment groups at week six ($P<0.001$); both active treatments were significantly more effective than placebo (venlafaxine; $P<0.001$, fluoxetine; $P=0.024$). The difference between the active treatments was not statistically significant ($P=0.117$). Secondary: Not reported
Rudolph et al ³⁵ Venlafaxine ER 75 to 225 mg/day vs fluoxetine 20 to 60 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients ≥ 18 years of age with MDD	N=301 8 weeks	Primary: HAM-D, MADRS, CGI Secondary: Not reported	Primary: The percentages of patients who achieved full remission of their depression (HAM-D total score ≤ 7) at the end of treatment were 37, 22, and 18% for the venlafaxine ER, fluoxetine and placebo groups, respectively. The differences in remission rates between venlafaxine XR and the other groups were significant ($P<0.05$). Venlafaxine ER produced a significant lower mean total score on the MADRS analysis than did fluoxetine ($P=0.048$). The P value for the statistical test of center by center interaction was not significant, indicating that treatment outcomes did not differ significantly between individual investigational sites. Secondary: Not reported
Richard et al ³⁶ Venlafaxine ER, up to a maximum of 225 mg/day vs paroxetine, up to a	DB, PC, RCT Patients ≥ 30 years of age with idiopathic PD, without dementia, and depressive disorder or operationally	N=115 12 weeks	Primary: HAM-D-17 total score Secondary: MADRS, BDI-II, GDS, UPDRS, safety	Primary: Treatment effects relative to placebo, expressed as mean 12 week reduction in HAM-D-17 total score, were 6.2 points (97.5% CI, 2.2 to 10.3; $P=0.0007$) with paroxetine and 4.2 points (97.5% CI, 0.1 to 8.4; $P=0.02$) with venlafaxine ER. There was no difference noted between paroxetine and venlafaxine ER ($P=0.28$). Secondary: Significant beneficial effects of paroxetine and venlafaxine ER relative to

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
maximum of 40 mg/day vs placebo	defined subsyndromal depression			<p>placebo were apparent for the secondary outcomes (MADRS, BDI-II, and GDS; $P \leq 0.01$ for all comparisons).</p> <p>UPDRS total and motor scores improved in all three treatment groups, but there were no significant group differences in mean response. There was no evidence of treatment-associated worsening of motor function.</p> <p>One hundred patients reported at least one adverse event during the trial: 86, 85, and 90% with paroxetine, venlafaxine ER, and placebo. Insomnia was reported significantly less frequently with paroxetine compared to venlafaxine ER and placebo. There were three serious adverse events.</p>
Rush et al ³⁷ CO-MED Escitalopram 10 to 20 mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to 20 mg/day vs venlafaxine ER 150 to 300 mg/day plus mirtazapine 15 to 45 mg/day	MC, PC, RCT, SB Patients 18 to 75 years of age with MDD	N=665 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, quality of life, adverse events Secondary: Not reported	Primary: At 12 weeks, the remission rates were 38.8% for escitalopram plus placebo, 38.9% for bupropion SR plus escitalopram, and 37.7% for venlafaxine ER plus mirtazapine. The response rates were 51.6 to 52.4%. The treatment groups did not differ in the percentage of change in QIDS-SR score or in effects on quality of life. At seven months, the treatment groups were not different in terms of remission rate (range, 41.8 to 46.6%), response rate (range, 57.4 to 59.4%), or attrition rate. There was no difference in the percentage of change in QIDS-SR, quality of life, or work and social adjustment. The venlafaxine ER plus mirtazapine group had greater side effect frequency and intensity at 12 weeks and greater side effect frequency, intensity, and burden at seven months as compared to escitalopram plus placebo. Secondary: Not reported
Morris et al ³⁸ CO-MED Escitalopram 10 to 20	Subgroup analysis of CO-MED	N=665 (49.5% reported having no	Primary: Symptom remission (QIDS-SR), attrition, anxiety	Primary: No differences in outcomes between antidepressant monotherapy and either of the antidepressant combination therapies, regardless of the number of general medical conditions a patient had. Specifically, within each group having a given

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to 20 mg/day vs venlafaxine ER 150 to 300 mg/day plus mirtazapine 15 to 45 mg/day	Patients 18 to 75 years of age with MDD, with and without general medical conditions	treated general medical conditions, 23.8% reported having 1, 14.8% reported having 2, and 11.9% reported having ≥3) 7 months	(IDS-C), functioning, quality of life, adverse events Secondary: Not reported	number of conditions, the three treatments did not differ significantly with respect to any of the measures of efficacy or tolerability assessed, either at week 12 or 28. Secondary: Not reported
Kerber et al ³⁹ CO-MED Escitalopram 10 to 20 mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to 20 mg/day vs venlafaxine ER 150 to 300 mg/day plus mirtazapine 15 to 45 mg/day	Subgroup analysis of CO-MED Patients 18 to 75 years of age with MDD, with and without heart disease	N=665 (6% [n=40] reported having and being treated for heart disease) 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, quality of life, adverse events Secondary: Not reported	Primary: In general, patients with heart disease had fewer problems with treatment side effects at week 12 compared to patients without heart disease. At week 12, there were no significant differences between those with and without heart disease in terms of remission, response, quality of life, or functional measures. This pattern was also seen with regard to measures at trial end (week 28). There were no significant differential treatment effects among those with and without heart disease in side effect burden and symptom severity at weeks 12 and 28. Secondary: Not reported

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Rosso et al ⁴⁰ Duloxetine 120 mg/day vs bupropion ER 300 mg/day	RCT, SB Patients ≥18 years of age with MDD who failed to respond to 2 consecutive antidepressant trials with SSRIs	N=49 6 weeks	Primary: Change in HAM-D-17 Secondary: CGI-S, GAF	Primary: There was no significant difference in HAM-D-17 total score among the treatment groups ($P=0.793$). Secondary: There was no significant difference in CGI-S ($P=0.653$) or GAF ($P=0.565$) scores among the treatment groups. Compared to baseline, there was a significant improvement in HAM-D-17 and CGI-S total scores with duloxetine and bupropion ER compared to baseline (all $P<0.001$). The 6-item-HAM-D mean score decreased significantly by week two with duloxetine (from 11.84 to 6.04; $P<0.001$) and bupropion ER (from 12.05 to 5.52; $P<0.001$). There was no difference in the success rates (HAM-D response, HAM-D remission) between the treatment groups. Additional information obtained by the CGI-S success rate confirmed this finding.
Perahia et al ⁴¹ Duloxetine 60 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day	DB, MC, RCT (pooled analysis of 2 trials) Patients >18 years of age with MDD	N=667 12 weeks	Primary: GBR (remission at endpoint using HAM-D-17 ≤7) Secondary: Efficacy	Primary: There were no significant differences in GBR with duloxetine and venlafaxine ER at the end of six weeks of therapy (-1.418 vs -1.079; $P=0.217$) or 12 weeks (-0.349 vs -0.121; $P=0.440$). Secondary: Mean changes from baseline to endpoint in the HAM-D-17 total scores were not different between the duloxetine and venlafaxine ER treatment groups. Comparisons of mean change from baseline to endpoint on secondary efficacy measures (HAM-D-17 item 1, HAM-D-17 subscales [core, Maier, anxiety/somatization, retardation and sleep], HAMA total score, CGI-S, and PGI-I) were not significantly different between the treatment groups. Response and remission rates were not significantly different between

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				<p>duloxetine and venlafaxine ER at six weeks (response rate for duloxetine, 51.6%; venlafaxine, 54.5%; remission rate for duloxetine, 31.4%; venlafaxine, 35.2%) or 12 weeks (response rate for duloxetine, 62.6%; venlafaxine, 69.1%; remission rate for duloxetine, 48.1%; venlafaxine, 50.3%).</p> <p>Estimates of remission rates at two, four, eight and 12 weeks were 11.1, 36.6, 53.0, and 71.0% for the duloxetine-treated group and 10.4, 32.1, 51.7, and 67.4% for the venlafaxine-treated group, respectively ($P=0.309$).</p>
<p>Guelfi et al⁴²</p> <p>Venlafaxine 75 to 375 mg/day</p> <p>vs</p> <p>mirtazapine 15 to 60 mg/day</p>	<p>DB, MC, RCT</p> <p>Hospitalized patients with severe depressive episode with melancholic features</p>	<p>N=157</p> <p>8 weeks</p>	<p>Primary: HAM-D, MADRS</p> <p>Secondary: Adverse effects</p>	<p>Primary: A significant difference favoring mirtazapine was found on the HAM-D Sleep Disturbance factor at all assessment points ($P\leq 0.03$).</p> <p>Secondary: A significantly higher percentage of patients treated with venlafaxine (15.3%) than mirtazapine (5.1%) dropped out because of adverse events ($P=0.037$).</p>
<p>Cipriani et al⁴³</p> <p>New-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine‡, sertraline, venlafaxine)</p>	<p>MA (117 trials)</p> <p>Patients with MMD receiving acute treatment</p>	<p>N=25,928</p> <p>6 to 12 weeks</p>	<p>Primary: Response (defined as the proportion of patients who had a reduction $\geq 50\%$ from the baseline score on the HDRS or MADRS, or who scored much improved or very much improved on the CGI at eight weeks) and dropout rates</p> <p>Secondary: Not reported</p>	<p>Primary: <i>Direct Comparisons</i> Efficacy favored escitalopram over citalopram; citalopram over reboxetine and paroxetine; mirtazapine over fluoxetine and venlafaxine; sertraline over fluoxetine; and venlafaxine over fluoxetine and fluvoxamine.</p> <p>For dropouts, fluoxetine was better tolerated than reboxetine and citalopram than sertraline.</p> <p><i>Multiple-treatments MA</i> Escitalopram, mirtazapine, sertraline, and venlafaxine were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. Reboxetine was significantly less efficacious than all the other 11 antidepressants.</p> <p>Duloxetine and paroxetine were less well tolerated than escitalopram and sertraline; fluvoxamine was less well tolerated than citalopram, escitalopram,</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				<p>and sertraline; venlafaxine was less well tolerated than escitalopram; reboxetine was less well tolerated than many other antidepressants, such as bupropion, citalopram, escitalopram, fluoxetine, and sertraline; and escitalopram and sertraline were better tolerated than duloxetine, fluvoxamine, paroxetine, and reboxetine.</p> <p>Mirtazapine, escitalopram, venlafaxine, and sertraline were more efficacious than fluoxetine, and fluoxetine was more efficacious than reboxetine. Fluoxetine was better tolerated than reboxetine.</p> <p>Mirtazapine, escitalopram, venlafaxine, and sertraline were among the most efficacious treatments, and escitalopram, sertraline, bupropion, and citalopram were better tolerated than the other remaining antidepressants.</p> <p>The cumulative probabilities of being among the four most efficacious treatments were: mirtazapine (24.4%), escitalopram (23.7%), venlafaxine (22.3%), sertraline (20.3%), citalopram (3.4%), milnacipran (2.7%), bupropion (2.0%), duloxetine (0.9%), fluvoxamine (0.7%), paroxetine (0.1%), fluoxetine (0.0%), and reboxetine (0.0%).</p> <p>The cumulative probabilities of being among the four best treatments in terms of acceptability were escitalopram (27.6%), sertraline (21.3%), bupropion (19.3%), citalopram (18.7%), milnacipran (7.1%), mirtazapine (4.4%), fluoxetine (3.4%), venlafaxine (0.9%), duloxetine (0.7%), fluvoxamine (0.4%), paroxetine (0.2%), and reboxetine (0.1%).</p> <p>Secondary: Not reported</p>
<p>Thase et al⁴⁴</p> <p>Desvenlafaxine 50, 100, 200, or 400 mg/day</p>	<p>MA (9 trials)</p> <p>Outpatients ≥18 years of age with MDD</p>	<p>N=3,023</p> <p>8 weeks</p>	<p>Primary: HAM-D-17 total score</p> <p>Secondary: MADRS, HAM-D-6,</p>	<p>Primary: Significantly greater improvement with desvenlafaxine vs placebo on HAM-D-17 total scores was observed for the full data set (difference in adjusted means, -1.9; $P<0.001$). Significance was observed in all fixed-dose ($P<0.001$ for all) and flexible-dose trials ($P=0.24$).</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			CGI-I, CGI-S, remission and response rates, safety	<p>Secondary: For the overall desvenlafaxine group significant improvement from baseline was observed on all secondary outcome measures at the final evaluation. Overall, desvenlafaxine had a significantly greater change from baseline compared to placebo on the CGI-I, CGI-S, and MADRS total scores from week two onward and in the core symptoms of depression (HAM-D-6 total score) from week one onward.</p> <p>Overall rates of HAM-D-17 response (53 vs 41%) and remission (32 vs 23%) were significantly greater with desvenlafaxine vs placebo ($P<0.001$ for all).</p> <p>Discontinuation rates due to adverse events increased with desvenlafaxine dose (4 to 18 vs 3%). The most common treatment-emergent adverse events in the overall data set were nausea, dry mouth, hyperhidrosis, dizziness, and constipation.</p>
Archarya et al ⁴⁵ Duloxetine 40 to 120 mg/day vs placebo	MA (12 trials) Patients taking duloxetine for MDD	N=2,996 Duration varied	<p>Primary: Incidence of suicide-related events with duloxetine (MHID, MHRD, HAM-D Item-3)</p> <p>Secondary: Not reported</p>	<p>Primary: There were no significant differences in the incidence of suicide-related events with duloxetine vs placebo.</p> <p>The MHID for suicide-related behaviors was -0.03% (95% CI, -0.48 to 0.42) and MHRD -0.002 (95% CI, -0.02 to 0.02).</p> <p>Changes in HAM-D Item-3 suicidality scores showed a greater improvement with duloxetine ($P<0.001$) and less worsening of suicidal ideation with duloxetine ($P<0.001$).</p> <p>Secondary: Not reported</p>
Vis et al ⁴⁶ Duloxetine 40 to 120 mg/day vs	MA (8 trials) Outpatients >18 years of age with MDD	N=1,754 (efficacy) N=1,791 (safety)	<p>Primary: Remission and response (HAM-D, MADRS)</p> <p>Secondary:</p>	<p>Primary: Both treatment groups demonstrated a significant difference compared to placebo for both remission and response ($P<0.001$ for all).</p> <p>Secondary: More patients receiving placebo dropped out due to lack of efficacy compared</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
venlafaxine ER 75 to 225 mg/day vs placebo		8 weeks	Dropout rates and rates of adverse events	to patients in the treatment arms ($P < 0.001$ for both drugs). Dropout rates due to adverse reactions were also significant when active drugs were compared to placebo (P value not reported). More patients in the treatment groups than in the placebo groups dropped out due to adverse reactions (venlafaxine ER; $P < 0.001$ and duloxetine; $P = 0.008$).
Cipriani et al ⁴⁷ Fluoxetine 20 to 80 mg/day vs sertraline 50 to 200 mg mg/day vs nortriptyline 50 to 175 mg/day vs amitriptyline 75 to 300 mg/day vs venlafaxine 75 to 200 mg/day vs	MA (132 trials) Patients with depression	N=9,311 Duration varied	Primary: Number of patients who responded to treatment (HAM-D, MADRS) Secondary: Tolerability	Primary: On a dichotomous outcome fluoxetine was less effective than sertraline (PetoOR, 1.40; 95% CI, 1.11 to 1.76), mirtazapine (PetoOR, 1.64; 95% CI, 1.01 to 2.65) and venlafaxine (PetoOR, 1.40; 95% CI, 1.15 to 1.70; P values not reported). On a continuous outcome, fluoxetine was less effective than venlafaxine (standard mean difference random effect, 0.11; 95% CI, 0.00 to 0.23; P value not reported). Secondary: Fluoxetine was better tolerated than TCAs considered as a group (PetoOR, 0.78; 95% CI, 0.68 to 0.89), and was better tolerated in comparison with individual antidepressants, in particular than amitriptyline (PetoOR, 0.64; 95% CI, 0.47 to 0.85) and imipramine (PetoOR, 0.79; 95% CI, 0.63 to 0.99), and among newer antidepressants than pramipexole (PetoOR, 0.20; 95% CI, 0.08 to 0.47; P values not reported).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
imipramine 75 to 300 mg/day vs nefazodone 200 to 500 mg/day vs citalopram 20 to 40 mg/day vs desipramine 125 to 250 mg/day vs paroxetine 20 to 60 mg/day vs placebo vs pramipexole‡ 5 mg/day vs fluvoxamine 100 to 150 mg/day				

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs trazodone 50 to 400 mg/day vs bupropion 225 to 450 mg/day vs clomipramine 50 to 200 mg/day vs duloxetine 20 to 120 mg/day vs mirtazapine 30 to 60 mg/day vs doxepin 100 to 225 mg/day				
Van Baardewijk et al ⁴⁸ Duloxetine 40 to 120 mg/day for ≥8 weeks	MA Adults with moderate to	N=not specified 6 months	Primary: Remission (an improvement in the HAM-D scale to a	Primary: Patients receiving duloxetine and venlafaxine ER experienced similar success rates after six months of treatment, 53 and 57%, respectively (<i>P</i> value not reported).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs venlafaxine ER 75 to 225 mg/day for ≥8 weeks	severe MDD and a score ≥15 on the HAM-D or ≥18 on the MADRS scale		score <7, or a score ≤10 on the MADRS scale), symptom-free days Secondary: Not reported	Patients receiving duloxetine and venlafaxine ER experienced similar number of symptom-free days after six months of treatment, 52.72 and 57.03%, respectively (<i>P</i> value not reported). Duloxetine therapy was associated with a greater hospitalization rate compared to venlafaxine ER therapy, 47 and 43%, respectively (<i>P</i> value not reported). Secondary: Not reported
Fibromyalgia				
Mease et al ⁴⁹ Duloxetine 60 to 120 mg/day	ES Patients ≥18 years of age with fibromyalgia	N=278 6 months	Primary: Safety, efficacy Secondary: Not reported	Primary: Overall study drug compliance during the six-month ES was 81% in Study 1 and 79% in Study 2. The most common adverse events leading to discontinuation were fatigue and insomnia in Study 1, and diarrhea and nausea in Study 2. The most common treatment-emergent adverse events in Study 1 were nausea, dry mouth, and insomnia. The most common treatment-emergent adverse events in Study 2 were dry mouth, nausea, headache, hyperhidrosis, and muscle spasm. The majority of the treatment groups showed small mean change improvements in the BPI average pain severity score over the final six-month period. The placebo/duloxetine groups in both studies showed significant improvement in the PGI-I, as well as improvement in nearly all other efficacy and health outcome measures, including significant improvement in several SF-36 measures. The maintenance of efficacy analysis in Study 2 did not demonstrate statistical significance (90% CI, -0.39 to 0.77; <i>P</i> =0.580). The mean change in the BPI average pain severity score increased by 0.19 point during the extension phase. Secondary: Not reported

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
<p>Russell et al⁵⁰</p> <p>Duloxetine 20, 60, or 120 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥18 years of age with fibromyalgia</p>	<p>N=502</p> <p>6 months</p>	<p>Primary: Pain severity (BPI), PGI-I</p> <p>Secondary: FIQ, CGI-S, tender-point pain assessments, MFI, HAM-D-17, SDS, SF-36, EQ-5D</p>	<p>Primary:</p> <p>After three months of therapy, patients treated with duloxetine 60 and 120 mg/day experienced significantly greater improvements in average pain severity score compared to patients treated with placebo (-1.99, -2.31, -1.39, respectively; $P \leq 0.05$ and $P \leq 0.001$ vs placebo, respectively). There was no significant difference in pain severity with duloxetine 20 mg/day. At the six-month endpoint, patients treated with duloxetine experienced greater improvements in average pain severity score compared to patients treated with placebo (duloxetine 20/60 mg/day, -2.22 [$P \leq 0.05$]; duloxetine 60 mg/day, -1.98 [$P \leq 0.05$]; duloxetine 120 mg/day, -2.26 [$P \leq 0.01$]).</p> <p>After three months of therapy, the mean endpoint PGI-I score was significantly lower in patients treated with duloxetine 20 and 120 mg/day compared to patients treated with placebo (2.79, 2.93, 3.37, respectively; $P \leq 0.01$ and $P \leq 0.05$ vs placebo, respectively). There was no significant difference in PGI-I scores with duloxetine 60 mg/day compared to placebo. After six months of therapy, the mean endpoint PGI-I score was significantly lower in the duloxetine 20/60 mg/day (2.79; $P \leq 0.01$) and duloxetine 120 mg/day groups (2.93; $P \leq 0.05$), but not the duloxetine 60 mg/day group (3.08; P value not significant) compared to the placebo group (3.37).</p> <p>Secondary:</p> <p>After three months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (60 and 120 mg; $P \leq 0.01$ and $P \leq 0.001$, respectively), SF-36 mental component score (120 mg; $P \leq 0.05$), and some of the MFI domains (20 mg, 60 mg, 120 mg; $P \leq 0.05$, $P \leq 0.01$, and $P \leq 0.001$) compared to placebo-treated patients. There were no differences between duloxetine and placebo on other secondary efficacy and health outcome measures.</p> <p>After six months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (20/60 mg/day; $P \leq 0.05$, 60 mg/day; $P \leq 0.01$, 120 mg/day; $P \leq 0.001$) and MFI mental fatigue domain (20/60 mg/day; $P \leq 0.05$, 60 mg/day; $P \leq 0.05$, 120 mg/day; $P \leq 0.01$). The other efficacy and health outcome measures that achieved significance in the duloxetine treatment</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				<p>groups compared to the placebo group included the MFI physical fatigue domain and EQ-5D (duloxetine 20/60 mg/day) and the MFI physical fatigue, reduced motivation, and reduced activity domains, as well as SF-36 mental component score (duloxetine 120 mg/day).</p> <p>Response rates (defined as a $\geq 50\%$ improvement from baseline to the three-month endpoint in the average pain severity score) were significantly greater for duloxetine 120 mg/day (40.1%; $P=0.003$), but not for duloxetine 60 mg/day (34.0%; $P=0.067$) or for duloxetine 20 mg/day (32.5%; $P=0.200$) compared to placebo (23.7%). Response rates from baseline to the six-month endpoint were significantly greater for duloxetine 20/60 mg/day (36.4%; $P=0.025$), duloxetine 60 mg/day (32.6%; $P=0.045$), and duloxetine 120 mg/day (35.9%; $P=0.009$) compared to placebo (21.6%).</p> <p>In patients diagnosed with MDD at study entry, least squares mean changes in HAM-D-17 total score at six months were -4.8 for placebo, -5.2 for duloxetine 20/ 60 mg/day, -6.9 for duloxetine 60 mg/day, and -7.2 for 120 mg/day. Treatment group differences were not statistically significant when compared to placebo.</p>
<p>Arnold et al⁵¹</p> <p>Duloxetine 60 to 120 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT (pooled analysis of 4 trials)</p> <p>Outpatients ≥ 18 years of age with fibromyalgia and a score ≥ 4 on the average pain severity item of the BPI</p>	<p>N=1,332</p> <p>12 to 15 weeks</p>	<p>Primary: Pain severity (BPI)</p> <p>Secondary: BPI pain interference items, FIQ, CGI-S, PGI-I, HAM-D, SF-36, SDS, MFI</p>	<p>Primary: In both depressed and nondepressed patients, significantly more duloxetine-treated patients achieved $\geq 30\%$ reduction in BPI average pain score from baseline compared to placebo-treated patients ($P<0.001$). The treatment-by-MDD status interaction was not significant ($P=0.34$). In both depressed and nondepressed patients, significantly more duloxetine-treated patients achieved $\geq 50\%$ reduction in BPI average pain score from baseline compared to placebo-treated patients ($P<0.001$). The treatment-by-MDD status interaction was not significant ($P=0.39$).</p> <p>Secondary: For both depressed and nondepressed patients, mean changes from baseline to endpoint on the FIQ, SDS, and CGI-S were significantly greater for duloxetine-treated patients compared to placebo-treated patients ($P<0.05$). All treatment-by-MDD status interactions were not significant for these</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				<p>assessments (<i>P</i> value not significant).</p> <p>In patients with MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated patients were observed for the following SF-36 domains: mental component score, mental health score, bodily pain, physical role functioning, social functioning score, and vitality score. In patients without MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated patients were observed for the following SF-36 domains: mental component score, mental health score, general health score, bodily pain, physical functioning, emotional role functioning score, and vitality score. With the exception of the mental health subscale, for all SF-36 domains and composite scales, the treatment-by-MDD status interactions were not significant.</p> <p>In patients with MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated mental fatigue and reduced motivation; whereas in patients without MDD, the only significant difference between the duloxetine-treated and placebo-treated groups was observed for the mental fatigue score. For all MFI domains, the treatment-by-MDD status interactions were not significant.</p> <p>In the MDD subgroup, the mean improvement on the clinician-rated HAM-D-17 total score from baseline to endpoint was significantly greater for duloxetine-treated patients compared to placebo-treated patients. In patients without MDD, the mean improvement on the HAM-D-17 total score from baseline to endpoint was not significantly different between the treatment groups. The treatment by-MDD status interaction was not significant (<i>P</i>=0.14).</p> <p>For both depressed and nondepressed patients, significantly more duloxetine-treated patients rated themselves as “much improved” or “very much improved” compared to placebo-treated patients (<i>P</i><0.001). The treatment-by-MDD status interaction was not significant (<i>P</i>=0.45).</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Generalized Anxiety Disorder				
Rynn et al ⁵² Duloxetine 60 or 120 mg/day vs placebo	DB, PC, RCT Adult patients with GAD	N=327 10 weeks	Primary: HAMA total score Secondary: Response rate (HAMA total score reduction ≥50% from baseline), CGI-I, SDS, safety	Primary: Duloxetine resulted in significantly greater improvement in HAMA total scores compared to placebo ($P=0.023$); mean decrease for duloxetine was 8.12 (36% improvement from baseline) compared to a mean decrease of 5.89 (25% improvement from baseline). Significant differences between the two treatments were observed at week two of treatment and remained significant at each subsequent visit ($P\leq 0.001$). Secondary: Response and sustained improvement rates were significantly greater for duloxetine-treated patients compared to placebo-treated patients ($P<0.05$). With duloxetine, the response rate was 40% and sustained improvement was 43.7% compared to 32 and 33.1% with placebo. There was no difference in the proportion of patients meeting the criteria for remission (28 vs 23%; $P=0.27$). Duloxetine resulted in a significantly greater functional improvement based on CGI-I scores compared to placebo (2.68 vs 2.97; $P=0.04$). Duloxetine-treated patients were significantly more improved compared to placebo-treated patients on SDS global functioning ($P<0.01$), and work, social, and family/home improvement scores ($P<0.05$). The rate of discontinuation due to an adverse event was significantly higher with duloxetine compared to placebo ($P=0.002$). The most commonly reported adverse events with duloxetine treatment were nausea, dizziness, and somnolence.
Koponen et al ⁵³ Duloxetine 60 or 120 mg/day vs	DB, MC, PC, PG, RCT Patients ≥18 years of age with GAD of at least moderate	N=513 9 weeks	Primary: HAMA total score Secondary: SDS; HAMA psychic and somatic anxiety	Primary: Both doses of duloxetine demonstrated significantly greater improvements in HAMA total scores compared to placebo ($P\leq 0.001$ for both). Both doses of duloxetine resulted in mean decreases in HAMA total score that were more than four points greater than the decreases achieved with placebo; the mean change represents a 49% decrease from baseline with duloxetine. Significant differences between duloxetine and placebo were observed as early as two

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placebo	severity		factor scores; HAMA response, remission, and sustained improvement rates, safety	<p>weeks after treatment initiation, and remained significant at each subsequent visit.</p> <p>Secondary: Both doses of duloxetine demonstrated significantly greater functional improvements in SDS global and specific domain scores compared to placebo ($P \leq 0.001$). Both doses of duloxetine achieved a mean decrease of more than three points greater than the decreases achieved with placebo; the mean change represents a 47% improvement from baseline with duloxetine.</p> <p>Both doses of duloxetine demonstrated significantly greater improvements in HAMA psychic and somatic anxiety factor scores compared to placebo ($P \leq 0.001$ for all comparisons).</p> <p>Both doses of duloxetine resulted in significantly greater HAMA response (58, 56, and 31% with duloxetine 60 mg/day, duloxetine 120 mg/day, and placebo; $P \leq 0.001$ for both), remission (31, 38, and 19%; $P \leq 0.01$ for duloxetine 60 mg/day vs placebo and $P \leq 0.001$ for duloxetine 120 mg/day vs placebo), and sustained improvement rates (64, 67, and 43%; $P \leq 0.001$ for both) compared to placebo.</p> <p>There were no significant differences between the two doses of duloxetine on any of the efficacy outcome measures.</p> <p>Approximately 20% of patients receiving duloxetine had their dose decreased during the first two weeks of acute treatment. The rate of study discontinuation due to an adverse event was 11.3, 15.3, and 2.3% with duloxetine 60 mg/day, duloxetine 120 mg/day, and placebo ($P \leq 0.001$). Overall, nausea was the most frequent adverse event, which resulted in study discontinuation for 6.0 and 2.4% of duloxetine 60- and 120 mg/day-treated patients.</p>
Davidson et al ⁵⁴ Duloxetine	DB, PC, RCT Patients ≥ 18 years of age with	N=533 (N=887 OL phase)	Primary: Time to relapse (increase in CGI-S rating ≥ 2 points)	Primary: Significantly more placebo-treated patients (41.8%) met relapse criteria compared to duloxetine-treated patients (13.7%; $P \leq 0.001$).

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<p>vs placebo</p> <p>All patients received OL duloxetine for 26 weeks.</p> <p>Treatment responders ($\geq 50\%$ reduction in HAMA total score to ≤ 11 and "much"/"very much improved" ratings for the last 2 visits of the OL phase.</p>	<p>moderate to severe GAD</p>	<p>26 weeks</p>	<p>from randomization to a score ≥ 4 while meeting criteria for GAD or by discontinuation due to lack of efficacy)</p> <p>Secondary: HAMA total score, HAMA psychic factor score, HAMA somatic factor scores, HADS-A, CGI-I, PGI-I, SDS, EQ-5D VAS, safety</p>	<p>Among patients who did relapse, duloxetine-treated patients had a longer time to relapse compared to patients who were switched to placebo ($P \leq 0.001$).</p> <p>Secondary: Patients who continued duloxetine maintained the improvements that were demonstrated during the OL phase. Patients who were switched to placebo significantly worsened on each of the secondary outcomes, including HAMA total score, HAMA psychic factor score, HAMA somatic factor scores, and HADS-A ($P \leq 0.001$ for all comparisons). The remission rate for duloxetine-treated patients at endpoint was 68.1 and 39.3% for placebo-treated patients ($P \leq 0.001$).</p> <p>Patients receiving placebo were rated as overall less improved by the CGI-I and PGI-I mean endpoint scores compared to patients receiving duloxetine ($P \leq 0.001$ for both).</p> <p>Patients treated with placebo also had worsening of their role functioning in all SDS domains of work/school, social life, and family/home management compared to patients who continued with duloxetine ($P \leq 0.001$). By endpoint, mean SDS global functioning impairment score with placebo had significantly increased into the range indicating mild to moderate impairment ($P \leq 0.001$).</p> <p>The switch to placebo was also associated with decreased life satisfaction and poorer perceived health, as measured by changes in EQ-5D VAS scores ($P \leq 0.001$ for all comparisons) compared to patients who continued duloxetine.</p> <p>During the OL phase, 15 treatment-emergent adverse events occurred at a frequency of $\geq 5\%$: nausea (28.3%), headache (18.7%), dry mouth (14.3%), diarrhea (14.2%), dizziness (13.4%), constipation (12.5%), fatigue (11.5%), hyperhidrosis (10.0%), insomnia (9.8%), somnolence (8.2%), decreased appetite (6.1%), upper respiratory tract infection (5.5%), decreased libido (5.4%), vomiting (5.4%), and nasopharyngitis (5.0%). Most adverse events were mild to moderate in severity.</p> <p>During the DB, continuation phase patients experienced discontinuation-</p>

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				<p>emergent adverse events as the study medication was being withdrawn. Compared to patients receiving duloxetine, dizziness was the only adverse event to occur significantly more often with patients receiving placebo (9.9 vs 3.7%; $P \leq 0.05$). No significant increases in pulse rate, diastolic blood pressure, or systolic blood pressure were observed in duloxetine-treated patients compared to placebo-treated patients. Most events were mild to moderate in severity. Discontinuation from study due to adverse events occurred in four and two patients receiving duloxetine and placebo.</p>
<p>Hartford et al⁵⁵</p> <p>Duloxetine 60 to 120 mg/day</p> <p>vs</p> <p>venlafaxine ER 75 to 225 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Outpatients ≥ 18 years of age with GAD</p>	<p>N=487</p> <p>10 weeks</p>	<p>Primary: HAMA total score</p> <p>Secondary: HAMA psychic anxiety factor score, somatic anxiety factor score, mood item, and tension item; HADS anxiety and depression subscales scores; CGI-I, PGI-I; SDS</p>	<p>Primary: Patients receiving duloxetine or venlafaxine ER experienced greater improvements in anxiety symptom severity (as measured by HAMA) compared to patients receiving placebo (duloxetine; $P=0.007$ and venlafaxine ER; $P<0.001$). The mean decrease in the HAMA total scores was 11.8 for duloxetine and 12.4 for venlafaxine ER compared to 9.2 for placebo.</p> <p>Secondary: Patients treated with duloxetine and venlafaxine ER demonstrated greater improvements in HAMA psychic anxiety factor score, HAMA anxious mood, HAMA tension, and HADS anxiety and depression subscales compared to patients treated with placebo ($P<0.01$ for all comparisons).</p> <p>Patients treated with both duloxetine and venlafaxine ER had greater improvement ratings at endpoint on the CGI-I and PGI-I compared to patients treated with placebo ($P<0.01$ for all comparisons).</p> <p>Treatment response was seen in 47% of patients receiving duloxetine, 54% of patients receiving venlafaxine ER, and 37% of patients receiving placebo ($P<0.001$ for venlafaxine ER vs placebo).</p> <p>Using the CGI-I endpoint score, the percentage of responders was greater for duloxetine (55.7%; $P=0.007$) and venlafaxine ER (60.4%; $P<0.001$) compared to placebo (41.8%).</p> <p>More venlafaxine ER-treated patients met remission criteria (30%) than</p>

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				<p>placebo-treated patients (19%; $P<0.05$). The difference was not significant for duloxetine compared to placebo (23%; P value not significant).</p> <p>Sustained improvement rates were greater with duloxetine (55%) and venlafaxine ER (54%) compared to placebo (39%; $P<0.01$).</p> <p>Duloxetine and venlafaxine ER-treated patients experienced greater improvements in their functioning (SDS global improvement score) from baseline to endpoint compared to placebo (duloxetine, -8.03; venlafaxine ER, -7.97; placebo, -5.42; $P<0.01$).</p>
<p>Nicolini et al⁵⁶</p> <p>Duloxetine 20 mg/day</p> <p>vs</p> <p>duloxetine 60 to 120 mg/day</p> <p>vs</p> <p>venlafaxine ER 75 to 225 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Outpatients ≥ 18 years of age with GAD</p>	<p>N=581</p> <p>10 weeks</p>	<p>Primary: HAMA total score</p> <p>Secondary: HAMA psychic and somatic factor scores, SDS, HAMA, CGI-I, PGI-I</p>	<p>Primary: For the HAMA total score, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day, -14.7 [$P\leq 0.01$]; duloxetine 60 to 120 mg/day, -15.3 [$P\leq 0.001$]; venlafaxine ER, -15.5 [$P\leq 0.001$]; placebo -11.6).</p> <p>Secondary: For the HAMA psychic factor scores, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day, -8.1 [$P\leq 0.01$]; duloxetine 60 to 120 mg/day, -8.7 [$P\leq 0.001$]; venlafaxine ER, -8.6 [$P\leq 0.001$]; placebo -6.0).</p> <p>For the HAMA somatic factor score, all three treatments led to improvements from baseline compared to placebo (duloxetine 20 mg/day, -6.6 [$P=0.07$]; duloxetine 60 to 120 mg/day, -6.6 [$P\leq 0.05$]; venlafaxine ER, -7.0 [$P\leq 0.01$]; placebo -5.5).</p> <p>Response rates were 60% for duloxetine 20 mg/day ($P<0.01$), 65% for duloxetine 60 to 120 mg/day ($P<0.001$), 61% for venlafaxine ER ($P<0.001$), and 42% for placebo.</p> <p>Remission rates were 42% for duloxetine 20 mg/day, 44% for duloxetine 60 to 120 mg/day, 44% for venlafaxine ER, and 20% for placebo ($P<0.001$ for each comparisons vs placebo).</p>

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				<p>Overall improvement ratings at endpoint were greater for duloxetine-treated patients (20 or 60 to 120 mg/day) and venlafaxine ER-treated patients compared to placebo-treated patients by the CGI-I scores ($P < 0.001$ for all comparisons).</p> <p>All three treatments demonstrated significant improvement on the mean HADS anxiety subscale scores compared to placebo (duloxetine 20 mg/day, -7.0 points; duloxetine 60 to 120 mg/day, -7.7 points; venlafaxine ER, -6.9 points; placebo, -4.9 points; $P < 0.001$ for all comparisons).</p> <p>All three treatments demonstrated significant improvement on the mean HADS depression subscale score compared to placebo (duloxetine 20 mg/day, -3.3 points; duloxetine 60 to 120 mg/day, -3.5 points; venlafaxine ER, -3.6 points; placebo, -1.9 points; $P < 0.001$ for all comparisons).</p> <p>For the SDS global functioning improvement score, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day group, -8.5 [$P < 0.05$]; duloxetine 60 to 120 mg/day, -8.9 [$P < 0.01$]; venlafaxine ER, -9.1 [$P < 0.001$]; placebo, -6.2).</p>
<p>Schmitt et al⁵⁷</p> <p>Venlafaxine 37.5, 75, 150, or 225 mg/day</p> <p>vs</p> <p>placebo</p> <p>vs</p> <p>paroxetine 20 mg/day</p> <p>vs</p>	<p>MA</p> <p>RCTs evaluating antidepressants in GAD</p>	<p>N=2,238</p> <p>8 to 28 weeks</p>	<p>Primary:</p> <p>Absence of treatment response (defined as absence of sufficient symptoms to meet diagnostic criteria for GAD)</p> <p>Secondary:</p> <p>Acceptability of the treatment as measured by the number of people</p>	<p>Primary:</p> <p>Antidepressants (imipramine, venlafaxine, and paroxetine) were found to be more effective when compared to placebo in treating GAD. The calculated NNT for antidepressants as a group in GAD was 5.15.</p> <p>Considering all trials, the pooled RR for nontreatment response was 0.70 (95% CI, 0.62 to 0.79), favoring antidepressant treatment. The calculated NNT was 5.5 (95% CI, 4.1 to 8.4).</p> <p>For imipramine the calculated RR was 0.67 (95% CI, 0.50 to 0.91) and the NNT was 4.0 (95% CI, 2.4 to 13.7).</p> <p>For venlafaxine the calculated RR for nontreatment response was 0.68 (95% CI, 0.46 to 0.99), and the calculated NNT was 5.00 (95% CI, 3.58 to 8.62).</p>

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imipramine 143 mg/day vs trazodone 225 mg/day vs diazepam 26 mg/day vs imipramine 50 to 100 mg/day vs sertraline			dropping out during the trial	For paroxetine the calculated RR was 0.72 (95% CI, 0.56 to 0.92), and the calculated NNT was 6.72 (95% CI, 3.90 to 24.70). For paroxetine vs imipramine the calculated RR was 1.73 (95% CI, 0.31 to 9.57). Secondary: No significant differences were found between antidepressants and placebo with regard to drop out rate. The RR for dropout for any antidepressant was 0.95 (95% CI, 0.84 to 1.09). Similarly, when individual antidepressants were considered, no differences were found between individual treatments and the placebo group: imipramine: RR, 0.71 (95% CI, 0.41 to 1.24); venlafaxine: RR, 0.86 (95% CI, 0.72 to 1.02); sertraline: RR, 0.45 (95% CI, 0.03 to 5.84); paroxetine: RR, 1.15 (95% CI, 0.74 to 1.78); and paroxetine vs imipramine: RR, 1.62 (95% CI, 0.58 to 4.48).
Multiple Disease				
Wernicke et al ⁵⁸ Duloxetine vs placebo	MA (42 RCTs) Patients diagnosed with either an MDD, diabetic peripheral neuropathy, fibromyalgia, GAD, or lower urinary tract infection	N=8,504 4 to 12 weeks	Primary: Vital signs, ECG findings, cardiovascular side effects of the study drug Secondary: Not reported	Primary: Patients receiving duloxetine were noted to have statistically significant changes from baseline in ECG findings (PR, RR, QRS, QT intervals) compared to patients receiving placebo ($P<0.001$). However, the differences in ECG findings of patients taking duloxetine were not judged to be of clinical significance. Demographic subgroup analysis suggests that there is no difference in risk of ECG abnormality or vital sign changes between patients ≥ 65 years of age and a younger population (P value not reported). Although patients receiving duloxetine experienced statistically significant pulse and blood pressure elevations compared to patients receiving placebo ($P<0.001$), those changes were transient returning to baseline values with sustained therapy.

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				<p>There was no statistically significant difference between placebo and duloxetine groups in sustained blood pressure ($P=0.631$), systolic blood pressure ($P=0.740$), or diastolic blood pressure ($P=1.00$) measured during three consecutive visits.</p> <p>Patients randomized to duloxetine therapy experienced higher incidences of palpitations ($P=0.004$), tachycardia ($P=0.007$), orthostatic hypotension ($P=0.004$), increased blood pressure ($P<0.001$), blood total cholesterol ($P=0.031$), and peripheral coldness ($P=0.044$) compared to patients randomized to placebo.</p> <p>Secondary: Not reported</p>
Musculoskeletal Pain				
<p>Skljarevski et al⁵⁹</p> <p>Duloxetine 60 to 120 mg/day</p>	<p>ES</p> <p>Patients ≥ 18 years of age with chronic low back pain</p>	<p>N=181</p> <p>41 weeks</p>	<p>Primary: Reduction of pain severity (BPI 24-hour average pain rating)</p> <p>Secondary: Response rates, PGI-I, RMDQ-24, BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36)</p>	<p>Primary: For patients who received duloxetine during the initial 13-week trial, pain reduction continued during the extension phase. The mean change in BPI average pain in the extension phase was -0.97 ($P<0.001$).</p> <p>Secondary: The 30%, 50%, and sustained response rates were $\sim 10\%$ higher for patients who received duloxetine during the initial 13-week trial compared to those who received placebo. A total of 94.8% of placebo-controlled phase duloxetine responders still met response criteria at the end of the 41-week extension phase.</p> <p>The BPI average pain, worst pain, least pain, pain right now, and average interference all showed significant within-group improvement for both treatment groups.</p> <p>Both treatment groups showed significant improvement on the RMDQ-24 measures, CGI-S measures, and most of the health outcome assessments.</p>

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				<p>No significant change was observed in the BDI total score and HADS depression score.</p> <p>Duloxetine was well tolerated with no new safety findings reported.</p>
<p>Skljarevski et al⁶⁰</p> <p>Duloxetine 60 to 120 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥18 years of age with chronic low back pain</p>	<p>N=236</p> <p>13 weeks</p>	<p>Primary: Reduction of pain severity (BPI 24-hour average pain rating)</p> <p>Secondary: PGI-I, RMDQ-24, BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36), WPAI</p>	<p>Primary: There was a significantly greater reduction in the BPI 24-hour average pain in patients treated with duloxetine compared to patients treated with placebo at all time points (-1.42 vs -0.78, respectively; <i>P</i>=0.016 at week four; -2.06 vs -1.17, respectively; <i>P</i>=0.001 at week seven; and -2.32 vs -1.50, respectively; <i>P</i>=0.004 at week 13).</p> <p>Secondary: Duloxetine-treated patients reported significantly greater improvements in PGI-I scores compared to placebo-treated patients at all time points (3.12 vs 3.51, respectively; <i>P</i>=0.007 at week four; 2.82 vs 3.32, respectively; <i>P</i>=0.001 at week seven; 2.59 vs 3.16, respectively; <i>P</i>=0.001 at week 13).</p> <p>There was a significant difference in RMDQ-24 scores at endpoint with duloxetine compared to placebo (-3.60 vs -1.93, respectively; <i>P</i>=0.009).</p> <p>The mean changes in pain scores, including BPI-S (worst pain, least pain, and pain right now) items; BPI-I average pain; and weekly mean of the 24-hour average pain, night pain, and worst pain scores from patient diaries were significantly improved with duloxetine compared to placebo.</p> <p>There was no significant difference in the CGI-S and Athens Insomnia Scale scores among the treatment groups.</p> <p>There was no significant difference in response rates with duloxetine compared to placebo (30% response: 53.2 vs 40.0%, respectively; <i>P</i>=0.060 and 50% response: 38.5 vs 27.0%, respectively; <i>P</i>=0.087).</p> <p>The depression and anxiety scores were not significantly changed from baseline to endpoint. The improvement in BPI average pain was because of the</p>

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				<p>direct analgesic effect (80.4%; $P=0.012$) of duloxetine treatment and not dependent on the improvement in mood (BDI-II total score, 19.2%) or anxiety (HADS-A, 0.3%) symptoms.</p> <p>The United Kingdom and United States indexes of EQ-5D did not change significantly in patients treated with duloxetine compared to patients treated with placebo. Among the eight subscales of SF-36 only bodily pain ($P=0.038$), general health ($P=0.041$), and vitality ($P=0.040$) were significantly improved with duloxetine compared to placebo.</p> <p>In the WPAI, work activity impairment was the only item that significantly ($P=0.002$) improved with duloxetine compared to placebo.</p> <p>Significantly more patients in the duloxetine group (13.9%) compared to the placebo group (5.8%) discontinued because of adverse events ($P=0.047$). The most common treatment-emergent adverse events in the duloxetine group included nausea, dry mouth, fatigue, diarrhea, hyperhidrosis, dizziness, and constipation.</p>
<p>Chappell et al⁶¹</p> <p>Duloxetine 60 to 120 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥ 40 years of age with osteoarthritis of the knee and pain for ≥ 14 days/month</p>	<p>N=231</p> <p>13 weeks</p>	<p>Primary: Mean changes in the weekly mean 24-hour average pain score</p> <p>Secondary: Patients' perceived improvement as measured by PGI-I and on the change in patients' functioning as measured by the WOMAC physical functioning</p>	<p>Primary: Duloxetine was more effective than placebo on the primary efficacy measure (weekly mean 24-hour pain scores) beginning at week one and continuing through the treatment period ($P<0.05$). There was a significant reduction in the average pain score in the duloxetine group compared to the placebo group at each week. The mean change from baseline to endpoint in the 24-hour average pain score also showed a significant benefit for duloxetine over placebo ($P=0.006$).</p> <p>Analysis of the weekly 24-hour average pain score response rates (30% reduction in score from baseline to endpoint) showed a significant difference between duloxetine (59.3%) and placebo (44.5%; $P=0.033$). The 50% response rates revealed a similar pattern (duloxetine, 47.2%; placebo, 29.4%; $P=0.006$).</p> <p>Secondary: There was a significant improvement with duloxetine in most secondary</p>

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			<p>subscale, weekly mean of the 24-hour worst pain score, CGI-S, WOMAC pain and stiffness subscales, BPI-S and BPI-I, response to treatments, health outcomes, safety</p>	<p>endpoints compared to placebo. Mean changes in BDI-II and HADS-A did not differ significantly between treatment groups.</p> <p>For patients randomly re-assigned to duloxetine at week seven, there was a significant improvement in mean change in the weekly 24-hour average pain score in the duloxetine 120 mg/day group compared to the duloxetine 60 mg/day group ($P=0.039$). No significant differences were observed between the two duloxetine groups in the Mixed Model Repeated Measures analysis of the weekly 24-hour average pain score or the 30% and 50% response rates at endpoint.</p> <p>Adverse event rates did not differ significantly between treatment groups (49.5% for duloxetine and 40.8% for placebo). A total of 45.0% of patients reported ≥ 1 treatment-emergent adverse events.</p>
<p>Chappell et al⁶²</p> <p>Duloxetine 60 to 120 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥ 40 years of age with osteoarthritis of the knee and pain for ≥ 14 days/month</p>	<p>N=256</p> <p>13 weeks</p>	<p>Primary: BPI 24-hour average pain rating</p> <p>Secondary: Weekly mean 24-hour average pain and worst pain rating, patients' perceived improvement as measured by PGI-I and on the change in patients' functioning as measured by the WOMAC physical functioning subscale, CGI-S,</p>	<p>Primary: There was a significant reduction in the BPI average pain rating with duloxetine compared to placebo at all time points ($P \leq 0.001$).</p> <p>The BPI average pain response rates ($\geq 30\%$ pain reduction from baseline to endpoint) were significantly higher with duloxetine (65.3%) compared to placebo (44.1%; $P \leq 0.001$). The 50% response rates of BPI average pain did not significantly differ between the treatment groups (duloxetine, 43.8%; placebo, 32.3%; $P=0.068$).</p> <p>Secondary: The least squares mean changes in the weekly mean 24-hour average pain rating was significantly reduced with duloxetine compared to placebo as early as at week two and remained significant at all time points.</p> <p>The weekly mean 24-hour worst pain ratings were significantly improved with duloxetine compared to placebo.</p> <p>Patients receiving duloxetine experienced greater improvements in many secondary endpoints compared to placebo, including CGI-S, BPI-S items, and</p>

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			<p>WOMAC pain and stiffness subscales, BPI-S and BPI-I, response to treatments, health outcomes, safety</p>	<p>BPI-I items (general activity and normal work). The other BPI-I items (mood, walking ability, relations with other people, sleep, enjoyment of life, and average interference) were not significantly different between the two treatment groups. No significant improvement in PGI-I was observed in the duloxetine group compared to the placebo group ($P=0.164$).</p> <p>The mean changes from baseline to endpoint were improved significantly for WOMAC total score ($P=0.004$) and physical functioning subscale ($P=0.016$) in patients treated with duloxetine compared to placebo. The other two WOMAC subscales (pain and stiffness) did not show significant improvement with duloxetine treatment.</p> <p>Both the United Kingdom and the United States indexes of EQ-5D did not change significantly with either treatment. Physical component summary and three of the subscales of SF-36 were significantly improved with duloxetine compared to placebo. The other SF-36 items (mental component summary, general health, mental health, role-emotional, social functioning, and vitality) were not significantly improved with duloxetine compared to placebo.</p> <p>The frequency of nausea, constipation, and hyperhidrosis were significantly higher in the duloxetine group ($P\leq 0.05$). Significantly more duloxetine-treated patients discontinued therapy because of adverse events ($P=0.002$).</p>
<p>Skljarevski et al⁶³</p> <p>Duloxetine 60 mg mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients ≥ 18 years of age with chronic low back pain</p>	<p>N=401</p> <p>12 weeks</p>	<p>Primary: Reduction of pain severity (BPI 24-hour average pain rating)</p> <p>Secondary: PGI-I, RMDQ-24, CGI-S, BPI-S, BPI-I, response rates, health outcomes (EQ-5D and SF-36)</p>	<p>Primary: There was a significantly greater reduction in the BPI 24-hour average pain in patients treated with duloxetine compared to patients treated with placebo ($P\leq 0.001$).</p> <p>Secondary: Duloxetine-treated patients reported significantly greater improvements in PGI-I scores compared to placebo-treated patients (2.88 vs 3.19, respectively; $P=0.011$).</p> <p>There was no significant difference in RMDQ-24 scores with duloxetine compared to placebo (-2.69 vs -2.22, respectively; $P=0.255$).</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				<p>There was no significant difference in CGI-S among the treatment groups.</p> <p>There was a significant reduction in all four domains of BPI-S (average pain, worst pain, least pain, and pain right now) pain scores reported with duloxetine compared to placebo. All seven domains of the BPI-I (general activity, mood, walking ability, normal work, relations with others, sleep, enjoyment of life) were significantly better with duloxetine compared to placebo.</p> <p>A greater percentage of patients receiving duloxetine reported $\geq 50\%$ pain reduction compared to patients receiving placebo ($P=0.006$). There was no significant difference in the 30% pain response rates among the treatment groups.</p> <p>There were significant differences in changes on four of six mood states on the POMS-Brief Form, along with the total mood disturbance score, between the two treatment groups: tension-anxiety ($P\leq 0.001$), anger-hostility ($P\leq 0.001$), vigor-activity ($P=0.003$), confusion-bewilderment ($P=0.006$), and total mood disturbance ($P\leq 0.001$). Changes in depression-dejection and fatigue-inertia states were not significant.</p> <p>The change in EQ-5D was significantly different between duloxetine and placebo with the United Kingdom index ($P\leq 0.001$) and United States index ($P=0.002$). In the SF-36 domains, the differences between duloxetine and placebo treatments were significant with regard to mental component summary ($P=0.010$), bodily pain ($P=0.016$), mental health transformed ($P\leq 0.001$), social functioning ($P=0.030$), and vitality transformed ($P=0.022$). There was no significant difference among the treatment groups in other domains.</p> <p>The WPAI questionnaire demonstrated a significant difference between the treatment groups with regard to activity impairment ($P=0.007$). There was no significant difference among the treatment groups in other domains.</p> <p>Significantly more patients in the duloxetine group (15.2%) than patients in the placebo group (5.4%) discontinued because of adverse events ($P=0.002$).</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
<p>Skljarevski et al⁶⁴</p> <p>Duloxetine 20, 60, or 120 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Adult patients with non-radicular chronic low back pain</p>	<p>N=404</p> <p>13 weeks</p>	<p>Primary: Weekly mean 24 hour average pain (duloxetine 60 mg/day vs placebo)</p> <p>Secondary: RMDQ-24, PGI-I, BPI, safety</p>	<p>Nausea and dry mouth were the most common treatment-emergent adverse events with rates significantly higher in duloxetine-treated patients.</p> <p>Primary: Improvement in average weekly pain was significantly greater for duloxetine 60 and 120 mg/day doses beginning at week three, but the significance was lost at weeks 12 and 13, respectively. The mean change from baseline to endpoint in average weekly pain did not differ significantly from placebo for 60 mg/day ($P=0.104$) or any other duloxetine doses.</p> <p>Analysis of average weekly pain response rates (30% reduction from baseline to end-point) showed a significantly greater percentage of responders with duloxetine 120 mg/day (57.8%) compared to placebo (43.4%; $P=0.033$), but neither 20 (41.1%) or 60 mg/day (53.6%) differed significantly from placebo (P values not reported). There were no significant differences between any doses in 50% response rates.</p> <p>Secondary: Patients overall improvement (PGI-I) was greater for patients receiving duloxetine 60 mg/day, and improvement in physical functioning (RMDQ-24) was greater for patients receiving duloxetine 60 and/or 120 mg/day compared to patients receiving placebo. Patients receiving duloxetine 60 mg/day also demonstrated significant improvement over patients receiving placebo on several measures of pain severity, interference of pain with activities, and sleep.</p> <p>Eight (1.98%) patients experienced at least one serious adverse event (three placebo-treated patients and one duloxetine 20- and 60 mg/day-treated patients, and three duloxetine 120 mg/day-treated patients). Duloxetine 120 mg/day was associated with a significantly higher proportion of treatment-emergent adverse events compare to placebo ($P=0.038$).</p>
<p>Frakes et al⁶⁵</p> <p>Duloxetine 60 to 120 mg/day</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥ 40 years of age with</p>	<p>N=524</p> <p>10 weeks</p>	<p>Primary: Weekly mean of the daily average pain rating at week eight</p>	<p>Primary: Patients receiving duloxetine experienced significantly greater pain reduction at week eight than those receiving placebo. The estimated mean change was -2.46 for duloxetine compared to -1.55 for placebo ($P<0.001$). Duloxetine demonstrated greater improvement as early as week one ($P<0.01$), and at each</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Patients were also required to take a NSAID and a proton pump inhibitor.	osteoarthritis of the knee and pain for ≥ 14 days/month and who were using NSAIDs on most days of the week		Secondary: Endpoint PGI-I, change in WOMAC physical function	subsequent week ($P < 0.001$). Secondary: There was no significant difference in the use of acetaminophen as rescue medication for knee pain due to osteoarthritis ($P = 0.08$). The mean PGI-I and the change in the WOMAC physical function scale were significantly different between the duloxetine and placebo groups ($P < 0.001$ for each). Estimated mean improvement in diary-based night pain and worst pain ratings were significantly greater for duloxetine compared to placebo ($P < 0.001$ for each). Duloxetine-treated patients showed greater reductions for each item on the pain and interference ratings on the BPI compared to placebo-treated patients ($P < 0.001$ for each). Mean reductions for the total score and remaining subscale scores (pain and stiffness) of the WOMAC were significantly different ($P < 0.001$ for each). Treatment with duloxetine was associated with significantly more nausea, dry mouth, constipation, fatigue and decreased appetite than treatment with placebo ($P < 0.05$). Discontinuation due to adverse events occurred more commonly in the duloxetine group than the placebo group ($P = 0.03$).
Neuropathic Pain				
Yan et al ⁶⁶ Duloxetine 60 to 120 mg daily vs placebo	DB, PC, RCT Adult Chinese patients with diabetic peripheral neuropathic pain and Brief Pain	N=215 12 weeks	Primary: Change from baseline to endpoint in Brief Pain Inventory average pain score	Primary: Mean change from baseline to endpoint in Brief Pain Inventory average pain score was not significantly different between treatments (-2.31 ± 0.18 vs -2.69 ± 0.19 ; $P = 0.124$). Duloxetine-treated patients showed significantly greater pain reduction compared to placebo-treated patients at weeks one, two, and four ($P = 0.004$, $P = 0.009$, and $P = 0.006$), but not at week eight ($P = 0.125$) and 12 ($P = 0.107$).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	Inventory 24-hour average pain severity rating ≥ 4		Secondary: Brief Pain Inventory-severity and -interference, PGII, CGIS, EQ-5D, Athens Insomnia Scale, safety	<p>Secondary: Duloxetine-treated patients experienced significant improvement in PGII (2.32 ± 0.11 vs 2.64 ± 0.10; $P=0.028$), CGIS (-1.24 ± 0.11 vs -0.99 ± 0.11; $P=0.036$), AUC for pain relief, Brief Pain Inventory-severity pain right now (-2.72 ± 0.26 vs -1.99 ± 0.25; $P=0.012$), and Brief Pain Inventory-interference walking ability (-2.45 ± 0.24 vs -1.82 ± 0.23; $P=0.016$).</p> <p>Patients receiving duloxetine had numerically higher 30 and 50% response rates on Brief Pain Inventory average pain compared to placebo-treated patients. A higher proportion of patients receiving duloxetine (62.5%) met the criteria for sustained response compared to patients receiving placebo (50.5%).</p> <p>All other secondary efficacy measures, including health outcomes measures, were numerically but not significantly improved in patients receiving duloxetine compared to patients receiving placebo.</p> <p>Duloxetine-treated patients reported nausea, somnolence, anorexia, and dysuria significantly more compared to placebo.</p>
Armstrong et al ⁶⁷ Duloxetine 20 or 60 mg QD, or 60 mg BID vs placebo	3 DB, MC, PC, RCT Patients with diabetic peripheral neuropathic pain	N=1,139 12 weeks	Primary: Patient-reported functional outcomes (SF-36, Brief Pain Inventory, EQ-5D) Secondary: Not reported	<p>Primary: Diabetic peripheral neuropathic pain patients treated with duloxetine 60 mg QD or BID had greater improvement, compared to placebo, in all SF-36 domains of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Within treatment group changes among the domain scores ranged from 0.9 to 23.5 points. Duloxetine 60 mg BID showed some advantage over duloxetine 60 mg QD on general health ($P=0.02$) and mental health ($P=0.04$) status. Consistent results were seen in the ITT population with the exception that the above indicated advantages of duloxetine 60 mg BID over 60 mg QD in the domains of general and mental health were not significant.</p> <p>Duloxetine 60 mg QD and 60 mg BID were significantly superior to placebo at reducing scores in all Brief Pain Inventory interference items thereby indicating improvements in all seven items, with similar results demonstrated for the ITT population.</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				<p>In the analysis of the EQ-5D, patients on duloxetine 60 mg QD ($P=0.004$) and 60 mg BID ($P<0.001$) were both significantly better compared to placebo for the trial completers. Results for the ITT analysis were consistent, thus demonstrating the superiority of duloxetine 60 mg QD and BID compared to placebo with regard to changes in all included function and quality of life measures.</p> <p>Secondary: Not reported</p>
<p>Kajdasz et al⁶⁸</p> <p>Duloxetine 20 or 60 mg QD, or 60 mg BID</p> <p>vs</p> <p>placebo</p>	<p>Post-hoc analysis of 3 DB, MC, PC, RCT</p> <p>Patients with diabetic peripheral neuropathic pain</p>	<p>N=1,139</p> <p>12 weeks</p>	<p>Primary: Response rate (defined as ≥ 30 and $\geq 50\%$ reductions from baseline in weekly mean of the 24-hour average pain severity scores)</p> <p>Secondary: NNH (based on rates of discontinuation due to adverse events)</p>	<p>Primary: NNTs based on 50% reduction for patients receiving duloxetine 60 mg QD and 60 mg BID were 5.2 (95% CI, 3.8 to 8.3) and 4.9 (95% CI, 3.6 to 7.6), respectively, based on last observation carried forward. Similarly, NNTs of 5.3 (95% CI, 3.8 to 8.3) for 60 mg QD and 5.7 (95% CI, 4.1 to 9.7) for 60 mg BID observed based on baseline observation carried forward.</p> <p>Secondary: The NNHs based on discontinuation due to adverse events were 17.5 (95% CI, 10.2 to 58.8) with duloxetine 60 mg QD and 8.8 (95% CI, 6.3 to 14.7) with duloxetine 60 mg BID.</p>
<p>Wernicke et al⁶⁹</p> <p>Duloxetine 60 mg BID</p> <p>vs</p> <p>routine care (gabapentin, amitriptyline, and</p>	<p>ES, OL, RCT</p> <p>Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1</p>	<p>N=293</p> <p>52 weeks</p>	<p>Primary: Not reported</p> <p>Secondary: Health outcomes, safety</p>	<p>Primary: Not reported</p> <p>Secondary: There were significant treatment-group differences observed in favor of duloxetine in the SF-36 physical component summary score, and subscale scores of physical functioning, bodily pain, mental health, and vitality. A significant treatment-by-investigator interaction was seen for general health perceptions ($P=0.073$), mental health ($P=0.092$), and social functions ($P=0.003$)</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
venlafaxine)	or 2 diabetes			<p>subscales. There were no significant treatment-group differences observed on the EQ-5D questionnaire.</p> <p>During the trial, four deaths occurred. Deaths were considered to be unrelated to the study drug or protocol procedures. During the trial, 22 (11.2%) duloxetine vs 16 (16.7%) routine care-treated patients experienced at least one serious adverse event. The most frequently reported serious adverse events for both treatments together were cerebrovascular accident and diabetes, and these events were not considered drug-related. Fourteen (4.8%) patients discontinued due to any adverse event; which included 11 and three duloxetine- and routine care-treated patients ($P=0.560$). A total of 157 (53.6%) patients reported at least one treatment-emergent adverse event, and there were no treatment-group differences in the overall incidence of these events.</p> <p>There was a significant increase in mean uric acid levels in routine care-treated patients compared to duloxetine-treated patients with regard to chemistry/urinalysis.</p> <p>Both treatments experienced a slight increase in HbA_{1c}, with duloxetine-treated patients experiencing a larger increase in the mean change from baseline to endpoint ($P<0.001$). No significant treatment-group differences were observed in low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels.</p> <p>There were no significant treatment-group differences observed in the mean change in the Michigan Neuropathy Screening Instrument score from baseline to endpoint.</p> <p>There were no significant treatment-group differences observed in either subset of patients in the ulnar F-wave, ulnar distal sensory latency, and peroneal compound muscle action potential from baseline to endpoint for all patients. There was a significant increase observed in the peroneal F-wave measure for routine care-treated patients ($P=0.05$).</p> <p>There were no significant treatment-group differences observed for any of the</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				<p>ophthalmologic exam measures.</p> <p>There was a significant treatment-group difference observed in the mean change in microalbumin/creatinine ratio from baseline to endpoint ($P=0.031$), with duloxetine-treated patients experiencing a bigger mean decrease compared to routine care-treated patients.</p> <p>There was no significant treatment-group difference observed in the mean change from baseline to endpoint vital signs and weight.</p> <p>One duloxetine-treated patient and one routine care-treated patient met the definition for sustained elevation in systolic blood pressure, and there were no significant differences between treatments.</p> <p>There were no ECG parameters that were significantly different between treatments. Significantly more routine-care patients had potentially clinically significant Fridericia-corrected QT interval increases ($P=0.034$).</p>
<p>Raskin et al⁷⁰</p> <p>Duloxetine 60 mg BID</p> <p>vs</p> <p>routine care (gabapentin, amitriptyline, and venlafaxine)</p>	<p>ES, OL, RCT</p> <p>Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes</p>	<p>N=237</p> <p>52 weeks</p>	<p>Primary: Not reported</p> <p>Secondary: SF-36 and EQ-5D, safety</p>	<p>Primary: Not reported</p> <p>Secondary: No significant treatment-group differences were observed in the SF-36 subscales or in the EQ-5D questionnaire.</p> <p>A higher proportion of routine care-treated patients experienced one or more serious adverse events. No significant treatment-group difference was observed in the overall incidence of treatment-emergent adverse events. The treatment-emergent adverse events reported by at least 10% of patients receiving duloxetine 60 mg BID were nausea, and by the patients receiving routine care were peripheral edema, pain in the extremity, somnolence, and dizziness. Duloxetine did not appear to adversely affect glycemic control, lipid profiles, nerve function, or the course of diabetic peripheral neuropathic pain.</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
<p>Tanenberg et al⁷¹</p> <p>Duloxetine vs pregabalin vs duloxetine plus pregabalin</p>	<p>MC, NI, OL, RCT</p> <p>Adult patients with type 1 or 2 with HbA_{1c} ≤12%, and diabetic peripheral neuropathic pain who had been treated with gabapentin (900 mg/day) and had an inadequate response</p>	<p>N=407</p> <p>12 weeks</p>	<p>Primary: Reduction from baseline in the weekly mean of the daily 24-hour pain diary ratings at week 12</p> <p>Secondary: Worst pain and night pain ratings, Clinician Global Impression of Severity, Brief Pain Inventory severity and interference, Beck Depression Inventory II, Patient Global Impression of Improvement, Sheehan Disability Scale, response rate, safety</p>	<p>Primary: The estimated mean change in the daily pain severity score at 12 weeks was -2.6 for duloxetine and -2.1 for pregabalin, representing an observed 0.49 advantage of duloxetine; therefore, NI was established.</p> <p>Significant superiority vs pregabalin in the mean daily pain diary ratings was observed at weeks, two, three, and five through 11 with duloxetine and with duloxetine plus gabapentin at weeks two and eight, but between-treatment differences at the 12 week endpoint met NI criteria, not statistical superiority.</p> <p>The NI comparison between duloxetine and combination therapy on the differences between endpoint mean changes in daily pain diary ratings in the ITT patient population was also met.</p> <p>Secondary: Reduction from baseline in Brief Pain Inventory average pain and Brief Pain Inventory worst pain severity ratings was significantly greater with duloxetine vs pregabalin, but differences between treatments were not significant for the other Brief Pain Inventory pain measures, Clinical Global Impression of Severity, depressive symptoms, or the Sheehan Disability Scale global measure. Also, no significant between-treatment differences were found among the various response outcomes.</p> <p>Significantly more discontinuations occurred as a result of adverse events with duloxetine (19.6%; <i>P</i>=0.04) compared to pregabalin (10.4%), but no vs combination therapy (13.3%; <i>P</i>=0.19). Peripheral edema associated with pregabalin (3.7%) was the only adverse event reported as a reason for discontinuation with significantly greater frequency compared to other treatments (duloxetine, 0%; <i>P</i>=0.3; combination therapy, 0%; <i>P</i>=0.03). Rates of discontinuation for other reasons did not differ among the treatments. The treatment-related adverse events of nausea, insomnia, hyperhidrosis, and decreased appetite occurred significantly more frequently with duloxetine compared to pregabalin. The frequency of insomnia was also significantly greater with duloxetine compared to combination therapy. The occurrence of peripheral edema was significantly greater with pregabalin compared to the</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
<p>Wernicke J et al⁷²</p> <p>Duloxetine vs placebo</p>	<p>MA (42 RCTs)</p> <p>Patients diagnosed with either an MDD, diabetic peripheral neuropathy, fibromyalgia, generalized anxiety disorder, or lower urinary tract infection</p>	<p>N=8,504</p> <p>4 to 12 weeks</p>	<p>Primary: Vital signs, ECG findings, cardiovascular side effects of the study drug</p> <p>Secondary: Not reported</p>	<p>other two treatments. Combination treatment was associated with significantly greater occurrences of nausea, hyperhidrosis, decreased appetite, and vomiting compared to pregabalin monotherapy.</p> <p>Primary: Patients receiving duloxetine were noted to have statistically significant changes from baseline in ECG findings (PR, RR, QRS, QT intervals) compared to placebo ($P<0.001$). However, the differences in ECG findings of patients taking duloxetine were not judged to be of clinical significance.</p> <p>Demographic subgroup analysis suggests that there is no difference in risk of ECG abnormality or vital sign changes between patients ≥ 65 years of age and a younger population (P value not reported).</p> <p>Although patients receiving duloxetine experienced statistically significant pulse and blood pressure elevations compared to placebo ($P<0.001$), those changes were transient returning to baseline values with sustained therapy.</p> <p>There was no statistically significant difference between placebo and duloxetine groups in sustained blood pressure ($P=0.631$), SBP ($P=0.740$), or DBP ($P=1.00$) measured during three consecutive visits.</p> <p>Patients randomized to duloxetine therapy experienced higher incidences of palpitations ($P=0.004$), tachycardia ($P=0.007$), orthostatic hypotension ($P=0.004$), increased blood pressure ($P<0.001$), blood total cholesterol ($P=0.031$), and peripheral coldness ($P=0.044$) compared to patients randomized to placebo.</p> <p>Secondary: Not reported</p>
<p>Lunn et al⁷³</p> <p>Duloxetine vs</p>	<p>SR (6 RCTs)</p> <p>Patients with painful peripheral neuropathy or</p>	<p>N=2,200</p> <p>≥ 8 weeks</p>	<p>Primary: Short term (≤ 12 weeks) improvement in pain</p>	<p>Primary: Three trials in painful diabetic neuropathy reported data on the primary outcome measure of 50% improvement of pain compared to baseline at <12 weeks. Patients were treated with duloxetine 20, 60, or 120 mg/day. Combining data from all doses from the three trials together, the RR of 50% improvement with</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo or control</p> <p>Only outcomes for painful peripheral neuropathy are reported.</p>	<p>chronic pain conditions</p>		<p>Secondary: Long term (>12 weeks) improvement in pain, improvement in short and long term pain ≥30%, improvement in any validated quality of life score ≥30%</p>	<p>any dose was 1.63 (95% CI, 1.35 to 1.97) greater than placebo. The RR of improvement was significantly greater compared to placebo for the 60 and 120 mg/day doses, but not 20 mg/day, for which it was 1.43 (95% CI, 0.98 to 2.09). The RR of improvement with 120 mg/day (1.66; 95% CI, 1.35 to 2.04) was not significantly greater compared to 60 mg/day (1.65; 95% CI, 1.34 to 2.03). The mean improvement in pain at <12 weeks on an 11-point Likert scale was significantly greater compared to placebo with 60 (-1.04; 95% CI, -1.37 to -0.71) and 120 mg/day (-1.16; 95% CI, -1.49 to -0.83) of duloxetine.</p> <p>Secondary: None of the included trials of painful diabetic neuropathy included outcomes >12 weeks.</p> <p>Two trials included data on >30% improvement of pain at ≤12 weeks. The results were similar to those for ≥50% improvement. Relative rates of improvement were significantly greater compared to placebo with duloxetine for the 60 mg/day (1.53; 95% CI, 1.27 to 1.83), 120 mg/day (1.55; 95% CI, 1.30 to 1.86), and for both doses combined (1.54; 95% CI, 1.30 to 1.82).</p> <p>Trials that included quality of life information used the SF-36. In painful diabetic neuropathy, the effect of duloxetine 20 mg was not significant on any of the selected SF-36 subscores at up to 12 weeks (relevant physical, mental, and bodily pain subsections). The WMD of improvement on the physical summary component was significantly greater with 60 mg/day (2.51; 95% CI, 1.00 to 4.01) and 120 mg/day (2.80; 95% CI, 1.04 to 4.55). The weighted mean difference on the mental summary component was significantly greater only with 120 mg/day (2.23; 95% CI, 0.69 to 3.77). The weighted mean difference on the bodily pain subscale showed significantly more improvement compared to placebo with 60 mg/day (5.58; 95% CI, 1.74 to 9.42) and with 120 mg/day (8.19; 95% CI, 4.33 to 12.05). Three trials reported the Patient Global Impression of Change and pain at rest, and two reported the bodily pain index. The weighted mean difference for each outcome was significant and similar in magnitude for 60 and 120 mg/day. However, a clinically meaningful differences in the Patient Global Impression of Change is suggested as one point and hence the change associated with 60 mg/day (-0.59; 95% CI, -0.78 to -0.41)</p>

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
<p>Quilici et al⁷⁴</p> <p>Duloxetine vs pregabalin and gabapentin</p> <p>Placebo was used a common comparator.</p>	<p>MA (11 RCTs; duloxetine, 3 trials; pregabalin, 6 trials; gabapentin, 2 trials)</p> <p>Patients with diabetic peripheral neuropathic pain</p>	<p>N=not specified</p> <p>≥5 to 13 weeks</p>	<p>Primary: Reduction in 24-hour pain severity, response rate (≥50% pain reduction), overall health improvement (PGII and PGIC)</p> <p>Secondary: Safety</p>	<p>may not be clinically significant. The RR for the bodily pain index is significantly reduced by -0.97 (95% CI, -1.38 to -0.57) but again this borders on a change considered clinically significant.</p> <p>Primary: <i>Direct comparisons</i> All three agents were superior to placebo for all efficacy parameters. For 24-hour pain severity effect values were -1.13 (95% CI, -1.36 to -0.89), -0.90 (95% CI, -1.23 to -0.57), and -1.44 (95% CI, -2.21 to -0.66) with duloxetine, pregabalin, and gabapentin. Corresponding effect values for response rates were 0.86 (95% CI, 0.63 to 1.09; NNT, 5; 95% CI, 3 to 7) and 0.84 (95% CI, 0.52 to 1.16; NNT, 5; 95% CI, 4 to 8) with duloxetine and pregabalin, and for Patient Global Impression of Improvement/Patient Global Impression of Change were -0.76 (95% CI, -1.00 to -0.51) and -1.29 (95% CI, -1.72 to -0.86) with duloxetine and pregabalin.</p> <p><i>Indirect comparisons</i> For the primary efficacy outcome of 24-hour reduction in pain severity, a difference of -0.248 (95% CI, -0.677 to 0.162) was observed in favor of duloxetine over pregabalin. Duloxetine was not inferior to pregabalin on this outcome. For response rates, the difference between duloxetine and pregabalin was close to zero and not significant. For PPGII/PGIC outcomes, pregabalin showed an improvement of 0.542 points over duloxetine, a difference that reached significant (95% CI, 0.016 to 1.060).</p> <p>Secondary: Duloxetine produced a significantly lower incidence of dizziness compared to pregabalin. No differences between these two treatments were observed in the rates of premature discontinuation, diarrhea, headache, and somnolence.</p>

‡Agent not available in the United States.

Drug regimen abbreviations: BID=Twice-Daily, ER=Extended-Release, QD=Once-Daily, SR=Sustained-Release

Study abbreviations: AC=Active-Controlled, CI=Confidence Interval, CrCl=Creatinine Clearance, DB=Double-blind, DD=Double-dummy, ES=Extension Study, ITT=Intent to Treat, LOCF=Last Observation Carried Forward, MA=Meta-Analysis, MC=Multicenter, NI=Noninferiority, NNH=Number Needed to Harm, NNT=Number Needed to Treat, OL=Open-label, OR=Odds Ratio, PC=Placebo-controlled, PG=Parallel-group, PRO=Prospective, RCT=Randomized Controlled Trial, RETRO=Retrospective, RR=Relative Risk, SB=Single-Blind

Miscellaneous abbreviations: AUC=Area Under the Curve, BDI-II=Beck Depression Inventory-II, BPI=Brief Pain Inventory, BPI-I=Brief Pain Inventory-Interference, BPI-S=Brief Pain Inventory-Severity, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Impression-Severity, CSFQ=Changes in Sexual Functioning Questionnaire, DBP=Diastolic Blood Pressure, ECG=Electrocardiogram, EQ-5D=EuroQoL Questionnaire-5 Dimensions, FIQ=Fibromyalgia Impact Questionnaire, GAD=Generalized Anxiety Disorder, GAF=Global Assessment of Functioning,

GBR=Global Benefit-risk, GDS=Geriatric Depression Scale, HbA_{1c}=Glycosylated Hemoglobin, HADS=Hospital Anxiety Depression Scale, HADS-A=Hospital Anxiety Depression Scale Anxiety Subscale, HAMA=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, HDRS=Hamilton Depression Rating Scale, IDS-C=30-item Inventory of Depressive Symptomatology-Clinician-Rated, MADRS=Montgomery-Åsberg Depression Rating Scale, MDD=Major Depressive Disorder, MFI=Multidimensional Fatigue Inventory, MHID=Mantel-Haenszel Incidence Difference, MHRD=Mantel-Haenszel Exposure Time-adjusted Rate Difference, MRS=Menopause Rating Scale, NSAID=Nonsteroidal Anti-inflammatory drug, PD=Parkinson's Disease, PGI-I=Patient Global Impression-Improvement, PGI-C=Patient Global Impression of Change, POMS=Profile of Mood State, QIDS-SR=Quick Inventory of Depressive Symptomatology Self-Report, RMDQ-24=Roland Morris Disability Questionnaire, SBP=Systolic Blood Pressure, SDS=Sheehan Disability Scale, SF-36=Short-Form Health Survey, SNRI=Serotonin Norepinephrine Reuptake inhibitor, SSI=28-item Somatic Symptom Inventory, SSRIs=Selective Serotonin-reuptake Inhibitors, TCA=tricyclic antidepressants, UPDRS=Unified Parkinson's Disease Rating Scale, VAS=visual analog scale, VAS-PI=Visual Analog Scale-Pain Intensity, WHO-5=World Health Organization 5-item Well Being Index, WMD=Weighted Mean Difference, WOMAC=Western Ontario McMaster Osteoarthritis Index, WPAI=work productivity and activity impairment instrument

Special Populations**Table 5. Special Populations¹⁻⁵**

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Desvenlafaxine	<p>No overall differences in safety/efficacy observed between patients over the age of 65 and younger patients.</p> <p>Has been associated with cases of clinically significant hyponatremia in elderly patients.</p> <p>Safety and efficacy in children have not been established.</p>	<p>Recommended dose in patients with moderate renal impairment (24-hour creatinine clearance 30 to 50 mL/minute) is 50 mg daily.</p> <p>Recommended dose in patients with severe renal impairment (creatinine clearance <30 mL/minute) or end-stage renal disease is 50 mg every other day.</p>	<p>Starting dosage adjustment is not necessary.</p> <p>Maximum recommended dose in this patient population is 100 mg daily.</p>	C	Yes; % not specified.
Duloxetine	<p>No dose adjustment is recommended for elderly patients based on age.</p> <p>Safety and efficacy in children have not been established.</p>	<p>Not recommended in patients with end-stage renal disease or severe renal function impairment (creatinine clearance <30 mL/minute).</p>	<p>Should not be administered to patients with any hepatic function impairment.</p>	C; D if taken in second half of pregnancy	Yes; ~0.14% of maternal dose.
Venlafaxine	<p>No dose adjustment is recommended for elderly patients based on age.</p> <p>Safety and efficacy in children have not been established.</p>	<p>Total daily dose should be reduced by 25% in patients with mild to moderate renal function impairment.</p>	<p>Total daily dose should be reduced by 50% in patients with mild to moderate hepatic function impairment.</p>	C	Yes; % not specified.

Adverse Drug Events**Table 6. Adverse Drug Events¹⁻⁵**

Adverse Event	Desvenlafaxine	Duloxetine	Venlafaxine
Cardiovascular			
Chest pain	-	-	2
Edema	-	-	✓
Hypertension, dose related	<1	-	3 to 13
Myocardial infarction	<2	<1	<1
Orthostatic hypotension	<2	<1	-
Palpitation	≤3	1 to 2	3
Postural hypotension	-	-	1
Syncope	<2	<1	<1
Tachycardia	-	<1	2
Vasodilation	-	-	3 to 4
Central Nervous System			
Abnormal dreams	2 to 3	2 to 3	3 to 7
Abnormal thinking	-	-	2
Agitation	-	5 to 6	2 to 4
Amnesia	-	-	✓
Anxiety	3 to 5	3	5 to 6
Blurred vision	-	4	4 to 6
Chills	-	-	3
Confusion	-	-	2
Depersonalization	<2	-	1
Depression	-	-	1 to 3
Dizziness	10 to 13	6 to 17	11 to 20
Extrapyramidal symptoms	<2	-	-
Fatigue	7	2 to 15	-
Fever	-	1 to 3	✓
Headache	-	13	25 to 38
Hypoesthesia	-	1	✓
Hypomania	<2	-	-
Insomnia	9 to 12	8 to 16	15 to 23
Irritability	2	1	-
Lethargy	-	1	-
Migraine	-	-	✓
Nervousness	-	1	6 to 21
Nightmares	-	1	-
Paresthesia	≤2	1	2 to 3
Restlessness	-	1	-
Sleep disorder	-	1	-
Somnolence	≤9	13 to 20	12 to 23
Trismus	-	-	✓
Vertigo	-	1	✓
Yawning	-	1	3 to 5
Dermatological			
Bruising	-	-	✓
Hyperhidrosis	-	6 to 8	-
Pruritus	-	3	1
Rash	1	4	3
Endocrine and Metabolic			
Cholesterol increased	3 to 4	<1	-

Adverse Event	Desvenlafaxine	Duloxetine	Venlafaxine
Hot flushes	-	2 to 3	-
Hypercholesterolemia	-	<1	<15
Hypoglycemia	-	1	<1
Liver enzymes increased	≤2	<1	<1
Low density lipoprotein cholesterol increased	≤1	-	-
Transaminase elevation	-	1	-
Triglycerides increased	-	-	✓
Weight gain	-	<1	✓
Weight loss	≤2	1 to 2	1 to 4
Gastrointestinal			
Abdominal pain	-	<1	6
Abnormal taste	-	-	2
Anorexia	5 to 8	3 to 5	8 to 20
Appetite decreased	-	3 to 11	-
Appetite increased	-	-	✓
Constipation	9 to 11	5 to 15	8 to 15
Diarrhea	9 to 11	7 to 13	6 to 8
Dyspepsia	-	4 to 5	7
Flatulence	-	-	3 to 4
Gastritis	-	1	-
Loose stools	-	2 to 3	-
Nausea	22 to 26	14 to 30	21 to 58
Vomiting	≤4	1 to 6	3 to 6
Xerostomia	11 to 17	5 to 18	12 to 22
Genitourinary			
Dysuria	-	1	-
Ejaculation abnormality	≤1	1 to 4	2 to 19
Erectile dysfunction	3 to 6	1 to 5	-
Impotence	-	-	4 to 10
Libido decreased	4 to 5	2 to 4	3 to 9
Pollakiuria	-	1 to 5	-
Prostatic disorder	-	-	✓
Proteinuria	6 to 8	-	-
Urinary frequency	-	-	3
Urinary retention	-	<1	1
Urinary symptoms	≤1	1	-
Urination impaired	-	-	2
Musculoskeletal			
Arthralgia	-	-	✓
Hypertonia	-	-	3
Muscle cramp	-	4 to 5	-
Muscle pain	-	1 to 5	-
Muscle tightness	-	1	1 to 2
Muscle twitching	-	4	<1
Myalgia	-	1 to 3	-
Neck pain/rigidity	-	-	✓
Rigors	-	1	-
Tremor	≤3	3 to 4	4 to 10
Weakness	≤2	2 to 8	8 to 19
Respiratory			
Cough	-	3 to 6	✓
Dyspnea	-	-	✓

Adverse Event	Desvenlafaxine	Duloxetine	Venlafaxine
Epistaxis	<2	-	-
Nasopharyngitis	-	7 to 9	-
Pharyngitis	-	-	7
Pharyngolaryngeal pain	-	1 to 6	-
Sinusitis	-	-	2
Upper respiratory infection	-	7	-
Other			
Blurred/abnormal vision	-	1 to 3	4 to 6
Diaphoresis increased	10 to 14	6	10 to 14
Flu-like syndrome	-	<1	6
Hypersensitivity reaction	<2	-	-
Infection	-	-	6
Mydriasis	2	-	2
Night sweats	-	1	-
Suicidal ideation/attempt	-	<1	<1 to 2
Tinnitus	2	-	2
Trauma	-	-	2

✓ Percent not specified.

- Event not reported.

Contraindications

Table 7. Contraindications¹⁻⁵

Contraindication	Desvenlafaxine	Duloxetine	Venlafaxine
Hypersensitivity	✓	-	✓
Monoamine oxidase inhibitors; do not use concomitantly in patients taking monoamine oxidase inhibitors or in patients who have taken such agents within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions	✓	✓	✓
Uncontrolled narrow-angle glaucoma	-	✓	-

Black Box Warning for desvenlafaxine⁴

WARNING
Suicidality and antidepressant drugs: 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 and other psychiatric disorders. Anyone considering the use of desvenlafaxine 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 of age; there was a reduction in risk with antidepressants compared to placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are associated with increases in the risk of suicide. Monitor patients of all ages who are started on antidepressant therapy appropriately and observe closely for clinical worsening, suicidality, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with the prescriber. Desvenlafaxine is not approved for use in children.

Black Box Warning for duloxetine³

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term

WARNING

studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of duloxetine 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 of age; there was a reduction in risk with antidepressants compared to placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Appropriately monitor patients of all ages who are started on antidepressant therapy and closely observe patients for clinical worsening, suicidality, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with the prescribing health care provider. Duloxetine is not approved for use in children.

Black Box Warning for venlafaxine, venlafaxine extended-release^{1,2}

WARNING

Suicidality and antidepressant drugs: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) compared to placebo in short-term studies in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders. Anyone considering the use of venlafaxine 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 of age; there was a reduction in risk with antidepressants compared to placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Closely observe and appropriately monitor patients of all ages who are started on antidepressant therapy 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. Venlafaxine is not approved for use in children.

Warnings/Precautions

Table 8. Warnings and Precautions¹⁻⁵

Warning/Precaution	Desvenlafaxine	Duloxetine	Venlafaxine
Abnormal bleeding; use may increase the risk of bleeding events	✓	✓	✓
Activation of mania/hypomania has been reported in clinical trials	✓	✓	✓
Cardiovascular/cerebrovascular disease; caution is advised in administering therapy to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders	✓	-	-
Changes in appetite; treatment-emergent anorexia and decreases in appetite have been observed in clinical trials	-	-	✓
Changes in height; increases in height have been observed in clinical trials	-	-	✓
Changes in weight; weight loss has been observed in clinical trials	-	-	✓
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	✓	✓	✓

Warning/Precaution	Desvenlafaxine	Duloxetine	Venlafaxine
Coadministration of drugs containing desvenlafaxine and venlafaxine; do not coadminister such drugs	✓	-	-
Discontinuation of treatment; abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms	✓	✓	✓
Elevated blood pressure; increases in blood pressure were observed in clinical trials	✓	✓	✓
Hepatotoxicity; there have been reports of hepatic failure, sometimes fatal, in patients receiving therapy	-	✓	-
Hyponatremia; may occur as a result of therapy and appears to result from the syndrome of inappropriate antidiuretic hormone secretion	✓	✓	✓
Insomnia and nervousness; treatment-emergent insomnia and nervousness were more common in clinical trials with therapy compared to placebo	-	-	✓
Interstitial lung disease and eosinophilic pneumonia have been rarely reported and the possibility of such events should be considered in patients receiving therapy who present with progressive dyspnea, cough, or chest discomfort	✓	-	✓
Narrow-angle glaucoma; mydriasis has been reported in association with treatment	✓	-	✓
Orthostatic hypotension and syncope have been reported with therapeutic doses	-	✓	-
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	✓	✓	✓
Seizure; cases have been reported and therapy has not been systematically evaluated in patients with seizure disorder and therapy should be used with caution in patients with a history of seizures	✓	✓	✓
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	✓	✓	✓
Serum cholesterol and triglyceride elevation; elevations in fasting serum lipid parameters were observed in controlled trials	✓	-	✓
Severe skin reactions can occur with therapy	-	✓	-
Sustained hypertension; therapy is associated with sustained hypertension	-	-	✓
Urinary hesitation and retention; agent is in a class of drugs known to affect urethral resistance	-	✓	-
Use in patients with concomitant illness; clinical experience is limited	-	✓	✓

Drug Interactions**Table 9. Drug Interactions¹⁻⁵**

Generic Name	Interacting Medication or Disease	Potential Result
Duloxetine, venlafaxine	Monoamine oxidase inhibitors	Serotonin syndrome may occur.
Duloxetine, venlafaxine	Selective 5-HT ₁ receptor agonists	Serotonin syndrome may occur.
Duloxetine, venlafaxine	Sympathomimetics	Increased sensitivity to sympathomimetic effects and increased risk of serotonin syndrome.
Duloxetine, venlafaxine	Linezolid	Serotonin syndrome may occur.
Duloxetine, venlafaxine	Tramadol	Serotonin syndrome may occur.
Duloxetine	β blockers	Excessive β blockade (bradycardia) may occur.
Duloxetine	Nonsteroidal anti-inflammatory drugs	The risk of upper gastrointestinal bleeding may be increased.
Duloxetine	Fluvoxamine	Duloxetine plasma concentrations may be elevated, increasing the pharmacologic effects and adverse reactions.
Duloxetine	Propafenone	Propafenone plasma levels may be elevated, increasing the pharmacologic and adverse reactions.
Duloxetine	Thioridazine	Thioridazine plasma concentrations may be elevated, increasing the risk of life-threatening ventricular arrhythmias and sudden death.
Venlafaxine	Azole antifungals	Venlafaxine plasma levels may be elevated, increasing the adverse effects.
Venlafaxine	Bupropion	Venlafaxine plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Venlafaxine	Cyproheptadine	Decreased pharmacologic effects of venlafaxine.
Venlafaxine	Lithium	Elevated lithium levels and neurotoxicity may occur. Serotonin syndrome may occur.
Venlafaxine	Metoclopramide	Serotonin syndrome may occur. Metoclopramide plasma levels may be elevated, increasing the risk of adverse reactions.
Venlafaxine	Sibutramine	Serotonin syndrome may occur.
Venlafaxine	Terbinafine	Venlafaxine plasma concentrations may be elevated, increasing the pharmacologic effects and adverse reactions.
Venlafaxine	Trazodone	Plasma trazodone levels may be elevated, increasing the pharmacologic and toxic effects. Serotonin syndrome may occur.

Dosage and Administration**Table 10. Dosing and Administration¹⁻⁴**

Generic Name	Adult Dose	Pediatric Dose	Availability
Desvenlafaxine	Treatment of major depressive disorder:	Safety and efficacy in children have not	Extended-release tablet:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Extended-release tablet: 50 mg once-daily	been established.	50 mg 100 mg
Duloxetine	<p><u>Management of chronic musculoskeletal pain:</u> Delayed-release capsule: initial, 30 mg/day; maintenance, 60 mg once-daily; maximum, 60 mg/day</p> <p><u>Management of fibromyalgia:</u> Delayed-release capsule: initial, 30 mg/day; maintenance, 60 mg once-daily; maximum, 60 mg/day</p> <p><u>Management of neuropathic pain associated with diabetic peripheral neuropathy:</u> Delayed-release capsule: 60 mg once-daily</p> <p><u>Treatment of generalized anxiety disorder:</u> Delayed-release capsule: initial, 60 mg/day; maintenance, 60 mg once-daily; maximum, 120 mg/day</p> <p><u>Treatment of major depressive disorder:</u> Delayed-release capsule: initial, 40 to 60 mg/day; maintenance (acute treatment), 40 (20 mg twice-daily) to 60 mg/day (once-daily or 30 mg twice-daily); maintenance, 60 mg/day; maximum, 120 mg/day</p>	Safety and efficacy in children have not been established.	Delayed-release capsule: 20 mg 30 mg 60 mg
Venlafaxine	<p><u>Treatment of generalized anxiety disorder:</u> Extended-release capsule: initial, 75 mg once-daily; maximum, 225 mg/day</p> <p><u>Treatment of major depressive disorder:</u> Extended-release capsule: initial, 75 mg once-daily; maximum, 225 mg/day</p> <p>Extended-release tablet: 37.5 to 75 mg/day; maximum, 225 mg/day</p> <p>Tablet: initial, 75 mg/day administered in two or three divided doses; maintenance, 150 to 225 mg/day; maximum, 375 mg/day</p> <p><u>Treatment of panic disorder, with or without agoraphobia:</u> Extended-release capsule: initial, 37.5</p>	Safety and efficacy in children have not been established.	<p>Extended-release capsule (Effexor XR[®]): 37.5 mg 75 mg 150 mg</p> <p>Extended-release tablet: 37.5 mg 75 mg 150 mg 225 mg</p> <p>Tablet: 25 mg 37.5 mg 50 mg 75 mg 100 mg</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
	mg once-daily for one week; maximum, 225 mg/day <u>Treatment of social anxiety disorder:</u> Extended-release capsule, extended-release tablet: 75 mg once-daily		

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American Psychiatric Association: Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition (2010) ⁷	<p><u>Choice of an initial treatment modality</u></p> <ul style="list-style-type: none"> 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 unless electroconvulsive therapy is planned. Because 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 for the individual patient, pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, and patient preference. For most patients, a selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), mirtazapine, or bupropion is optimal. In general, the use of nonselective monoamine oxidase inhibitors (e.g., phenelzine, tranylcypromine, isocarboxazid) should be restricted to patients who do not respond to other treatments. In patients who prefer complementary and alternative therapies, S-adenosyl methionine or St. John's wort might be considered, although evidence for their efficacy is modest at best, and careful attention to drug-drug interactions is needed with St. John's wort.
National Institute for Health and Clinical Excellence: Treatment and Management of Depression in Adults (Update) (2009) ⁸	<p><u>Persistent subthreshold depressive symptoms or mild to moderate depression</u></p> <ul style="list-style-type: none"> Do not use antidepressants routinely to treat persistent subthreshold depressive symptoms or mild depression. Consider antidepressants for the following people: <ul style="list-style-type: none"> A history of moderate or severe depression. Initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least two years). Subthreshold depressive symptoms or mild depression that persist(s) after other interventions. <p><u>Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression</u></p> <ul style="list-style-type: none"> For those 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 and provide: <ul style="list-style-type: none"> An antidepressant (normally a SSRI). OR

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> ○ A high-intensity psychological intervention. ○ For those with moderate or severe depression, provide a combination of antidepressant medication and a high-intensity psychological intervention. ● When an antidepressant is to be prescribed, it should normally be an SSRI in a generic form because SSRIs are equally effective as other antidepressants and have a favorable risk-benefit ratio. ● When prescribing antidepressants, the following should be taken into account: <ul style="list-style-type: none"> ○ SSRIs are associated with an increased risk of bleeding, especially in older people or in people taking other drugs that have the potential to damage the gastrointestinal mucosa or interfere with clotting. ○ Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs. ○ Paroxetine is associated with a higher incidence of discontinuation symptoms than other SSRIs. ○ There is an increased likelihood of stopping treatment because of side effects with venlafaxine, duloxetine and tricyclic antidepressants (TCAs). ○ Higher doses of venlafaxine have the potential to exacerbate cardiac arrhythmias. ○ There is an increased risk of possible exacerbation of hypertension with venlafaxine and duloxetine. ○ There is an increased risk for postural hypotension and arrhythmias with TCAs. ○ Non-reversible monoamine oxidase inhibitors should normally be prescribed only by specialist mental health professionals. ● Take into account toxicity in overdose when choosing an antidepressant for people at significant risk of suicide. <ul style="list-style-type: none"> ○ Compared to other equally effective antidepressants recommended for routine use in primary care, venlafaxine is associated with a greater risk of death from overdose. ○ TCAs are associated with the greatest risk in overdose. ● The evidence for the relative advantage of switching within or between classes is weak. When switching therapy, consider switching to: <ul style="list-style-type: none"> ○ Initially, a different SSRI or a better-tolerated newer-generation antidepressant. ○ An antidepressant from a different pharmacological class that may be less well-tolerated (venlafaxine, TCA, monoamine oxidase inhibitor). <p><u>Complex and severe depression</u></p> <ul style="list-style-type: none"> ● Referral to specialist mental health services should normally be for people with depression who are at significant risk of self-harm, have psychotic symptoms, require complex multidisciplinary care, or where an expert opinion on treatment and management is needed.
<p>American College of Physicians: Clinical Practice Guideline: Using Second-Generation Antidepressants to Treat Depressive</p>	<p><u>Treatment of MDD</u></p> <ul style="list-style-type: none"> ● 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 SNRIs, or other second-generation antidepressants. ● Mirtazapine had a significantly faster onset of action; however, after four

Clinical Guideline	Recommendations
<p>Disorders (2008)⁷⁵</p>	<p>weeks, most response rates were similar.</p> <ul style="list-style-type: none"> • Second-generation antidepressants did not differ in the rate of achieving remission. • First-generation antidepressants (TCA and monoamine oxidase inhibitors) are less commonly used than second-generation antidepressants, which have similar efficacy to and lower toxicity in overdose than first-generation antidepressants. <p><u>Treatment of depression in patients with accompanying symptom clusters</u></p> <ul style="list-style-type: none"> • 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. <p><u>Treatment of depression in selected patient populations</u></p> <ul style="list-style-type: none"> • Second-generation antidepressants did not differ in efficacy among subgroups and special populations categorized according to age, sex, race or ethnicity, or comorbid conditions. <p><u>Risk for harms and adverse events</u></p> <ul style="list-style-type: none"> • 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. <p><u>Recommendations</u></p> <ul style="list-style-type: none"> • Clinicians should select second-generation antidepressants based on 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 MDD. • Clinicians should continue treatment for four to nine months after a satisfactory response in patients with a first episode of MDD. For patients who have had two or more episodes of depression, an even longer duration of therapy may be beneficial.
<p>American Academy of Child and Adolescent Psychiatry: Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders</p>	<p><u>All types of childhood/adolescent depression</u></p> <ul style="list-style-type: none"> • All patients with depression should receive therapy in the acute (six to 12 weeks) and continuation phases (six to 12 months); 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.

Clinical Guideline	Recommendations
(2007) ⁶	<p><u>Uncomplicated depression/brief depression/mild psychosocial impairment</u></p> <ul style="list-style-type: none"> Initial management: education, support, and case management. Reevaluate if no response after four to six weeks. <p><u>Moderate to severe depression</u></p> <ul style="list-style-type: none"> 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 (FDA)-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 deficit-hyperactivity disorder (ADHD). TCA's should not be used as first line therapy for child/adolescent depression due to poor efficacy (not statistically different from placebo) and unfavorable side-effect profile. <p><u>Psychotic depression</u></p> <ul style="list-style-type: none"> SSRIs combined with atypical antipsychotics are the treatment of choice. <p><u>Seasonal affective disorder</u></p> <ul style="list-style-type: none"> Bright light therapy is recommended as treatment of seasonal affective disorder in youths. <p><u>Bipolar disorder</u></p> <ul style="list-style-type: none"> A mood stabilizer such as lithium, valproate, or lamotrigine may be used.
National Institute for Clinical Excellence: Generalized Anxiety Disorder and Panic Disorder (With or Without Agoraphobia) in Adults (2011) ⁹	<p><u>Stepped care for people with generalized anxiety disorder (GAD)</u></p> <ul style="list-style-type: none"> If a person with GAD chooses drug treatment, offer an SSRI, specifically sertraline. If sertraline is ineffective, offer an alternative SSRI or a SNRI, taking into account the following factors: <ul style="list-style-type: none"> Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine). The side-effect profile and the potential for drug interactions. The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine). The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference). If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin. Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Do not offer an antipsychotic for the treatment of GAD in primary care.

Clinical Guideline	Recommendations
	<p><u>Panic disorder general considerations</u></p> <ul style="list-style-type: none"> • Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder. • Sedating antihistamines or antipsychotics should not be prescribed for panic disorder. • Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account: <ul style="list-style-type: none"> ○ Psychological therapy (i.e., cognitive behavioral therapy, structured problem solving, psychoeducation). ○ Pharmacological therapy (antidepressant therapy). ○ Self-help interventions (i.e., bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface). • Antidepressants should be the only pharmacologic intervention used in the longer term. • Two types of medication are considered in the guideline for the treatment of panic disorder; TCAs and SSRIs. • Unless otherwise indicated, an SSRI (e.g., paroxetine, fluvoxamine, citalopram) licensed for panic disorder should be offered. If an SSRI is not suitable or there is no improvement after a 12-week course and if further medication is appropriate, imipramine or clomipramine may be considered. • If the patient is showing improvement, the medication should be continued for at least six months after optimal dose is reached, after which the dose may be tapered slowly over an extended period to minimize the risk of discontinuation/withdrawal symptoms.
<p>American Psychiatric Association: Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)¹⁰</p>	<ul style="list-style-type: none"> • SSRIs, SNRIs, TCAs, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder. • Because SSRIs, SNRIs, TCAs, and benzodiazepines appear roughly comparable in their efficacy for panic disorder, selecting a medication involves considerations of side effects, pharmacological properties, potential drug interactions, prior treatment history, and comorbid medical and psychiatric conditions. • The relatively favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • There is no evidence of differential efficacy between the SSRIs, although differences in the side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), half-life, propensity for drug interactions, and availability of generic formulations may be clinically relevant. They are safer than TCAs and monoamine oxidase inhibitors. They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine extended release has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. No systematic data are currently available supporting the use of duloxetine, in panic disorder, although its mechanism of action suggests it might be an effective agent. • Although TCAs are effective, the side effects and greater toxicity in overdose limit their acceptability to patients and clinical utility. Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than

Clinical Guideline	Recommendations
	<p>agents that are more serotonergic.</p> <ul style="list-style-type: none"> • SSRIs, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. Benzodiazepines may be especially useful adjunctively with antidepressants to treat residual anxiety symptoms. • Benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects and physiological dependence that may lead to difficulty discontinuing the medication. • Monoamine oxidase inhibitors appear effective for panic disorder but, because of their safety profile, they are generally reserved for patients who have failed to respond to several first-line treatments. • Neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder. There is minimal support for the use of trazodone in panic disorder and it appears less effective than imipramine and alprazolam. There are a few small, uncontrolled studies showing benefits of nefazodone in some patients with panic disorder; however, its use has been limited by concerns about liver toxicity. • Bupropion was effective in one small trial and ineffective in another. It cannot be recommended as a first line treatment for panic disorder. • Other medications with less empirical data may be considered as monotherapies or adjunctive treatments for panic disorder when patients have failed to respond to several standard treatments or based on other individual circumstances.
<p>American Academy of Child and Adolescent Psychiatry: Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders (2007)¹¹</p>	<ul style="list-style-type: none"> • A multimodal treatment approach for children and adolescents with anxiety disorders should consider education of the parents and the child about the anxiety disorder, consultation with school personnel and primary care physicians, cognitive-behavioral interventions, psychodynamic psychotherapy, family therapy, and pharmacotherapy. • Treatment of childhood anxiety disorders of mild severity should begin with psychotherapy. • Valid reasons for combining medication and treatment with psychotherapy include the following: <ul style="list-style-type: none"> ○ Need for acute symptom reduction in a moderately to severely anxious child. ○ A comorbid disorder that requires concurrent treatment. ○ Partial response to psychotherapy and potential for improved outcome with combined treatment. • SSRIs have emerged as the medication of choice in the treatment of childhood anxiety disorders. • When anxiety disorder symptoms are moderate or severe or impairment makes participation in psychotherapy difficult, or psychotherapy results in a partial response, treatment with medication is recommended. • No controlled studies are available for medication treatment of childhood-onset panic disorder. The use of a SSRI in adolescents with panic disorder has shown significant improvement in panic symptoms. • Controlled trials have established the safety and efficacy of short-term treatment with SSRIs for childhood anxiety disorders; however, the benefits and risks of long-term use of SSRIs have not been studied. It is recommended that clinicians consider a medication-free trial for children who have a significant reduction in anxiety or depressive symptoms on an SSRI and maintain stability in these symptoms for one year.

Clinical Guideline	Recommendations																																																															
	<ul style="list-style-type: none"> • There is no empirical evidence that a particular SSRI is more effective than another for treatment of childhood anxiety disorders. The choice is often based on side effects, duration of action, or positive response to a particular SSRI in a first-degree relative with anxiety. • The risk-benefit ratio for a medication trial needs to be carefully assessed because cognitive-behavioral therapy has been shown to be effective and long-term side effects of medications have not been studied in youths. • The safety and efficacy of medications other than SSRIs for the treatment of childhood anxiety disorders have not been established. • Noradrenergic antidepressants (venlafaxine and TCAs), buspirone, and benzodiazepines have been suggested as alternatives to be used alone or in combination with the SSRIs. • Data are limited in childhood anxiety disorders to guide treatment with combinations of medications when a single medication is not effective in managing anxiety symptoms. Comorbid diagnoses are strongly considered in selection of medication. • Preliminary findings from controlled trials of extended-release venlafaxine in the treatment of youths with GAD and social phobia suggest it may be well tolerated and effective relative to placebo. • Controlled trials with TCAs for pediatric anxiety disorders have shown conflicting results and have not established efficacy for this use. • Buspirone may be an alternative to SSRIs for GAD in youths, but there are no published controlled trials. • Benzodiazepines have not shown efficacy in controlled trials in childhood anxiety disorders despite established benefit in adult trials. They are used as an adjunct short-term treatment with SSRIs to achieve rapid reduction in severe anxiety symptoms that may permit initiation of the exposure phase of cognitive-behavioral therapy. Clinicians should use benzodiazepines cautiously because of the possibility of developing dependency. 																																																															
<p>A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society: Diagnosis and Treatment of Low Back Pain (2007)⁷⁷</p>	<ul style="list-style-type: none"> • Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work) and duration of symptoms. • The potential interventions for low back pain are outlined below: <table border="1" data-bbox="511 1249 1382 1837"> <thead> <tr> <th colspan="4" data-bbox="511 1249 1382 1276">Interventions for the Management of Low Back Pain</th> </tr> <tr> <th colspan="2" data-bbox="511 1276 1015 1346">Intervention Type</th> <th data-bbox="1015 1276 1161 1346">Acute pain (duration <4 weeks)</th> <th data-bbox="1161 1276 1382 1346">Subacute or chronic pain (duration >4 weeks)</th> </tr> </thead> <tbody> <tr> <td data-bbox="511 1346 690 1430" rowspan="3">Self-care</td> <td data-bbox="690 1346 1015 1373">Advice to remain active</td> <td data-bbox="1015 1346 1161 1373">Yes</td> <td data-bbox="1161 1346 1382 1373">Yes</td> </tr> <tr> <td data-bbox="690 1373 1015 1400">Application of superficial heat</td> <td data-bbox="1015 1373 1161 1400">Yes</td> <td data-bbox="1161 1373 1382 1400">No</td> </tr> <tr> <td data-bbox="690 1400 1015 1430">Book, handouts</td> <td data-bbox="1015 1400 1161 1430">Yes</td> <td data-bbox="1161 1400 1382 1430">Yes</td> </tr> <tr> <td data-bbox="511 1430 690 1608" rowspan="6">Pharmacologic Therapy</td> <td data-bbox="690 1430 1015 1457">Acetaminophen</td> <td data-bbox="1015 1430 1161 1457">Yes</td> <td data-bbox="1161 1430 1382 1457">Yes</td> </tr> <tr> <td data-bbox="690 1457 1015 1484">TCA</td> <td data-bbox="1015 1457 1161 1484">No</td> <td data-bbox="1161 1457 1382 1484">Yes</td> </tr> <tr> <td data-bbox="690 1484 1015 1512">Benzodiazepines</td> <td data-bbox="1015 1484 1161 1512">Yes</td> <td data-bbox="1161 1484 1382 1512">Yes</td> </tr> <tr> <td data-bbox="690 1512 1015 1539">Non steroidal anti-inflammatory drugs (NSAIDs)</td> <td data-bbox="1015 1512 1161 1539">Yes</td> <td data-bbox="1161 1512 1382 1539">Yes</td> </tr> <tr> <td data-bbox="690 1539 1015 1566">Skeletal muscle relaxants</td> <td data-bbox="1015 1539 1161 1566">Yes</td> <td data-bbox="1161 1539 1382 1566">No</td> </tr> <tr> <td data-bbox="690 1566 1015 1608">Tramadol, opioids</td> <td data-bbox="1015 1566 1161 1608">Yes</td> <td data-bbox="1161 1566 1382 1608">Yes</td> </tr> <tr> <td data-bbox="511 1608 690 1837" rowspan="7">Non-pharmacologic Therapy</td> <td data-bbox="690 1608 1015 1635">Acupuncture</td> <td data-bbox="1015 1608 1161 1635">No</td> <td data-bbox="1161 1608 1382 1635">Yes</td> </tr> <tr> <td data-bbox="690 1635 1015 1663">Cognitive behavior therapy</td> <td data-bbox="1015 1635 1161 1663">No</td> <td data-bbox="1161 1635 1382 1663">Yes</td> </tr> <tr> <td data-bbox="690 1663 1015 1690">Exercise therapy</td> <td data-bbox="1015 1663 1161 1690">No</td> <td data-bbox="1161 1663 1382 1690">Yes</td> </tr> <tr> <td data-bbox="690 1690 1015 1717">Massage</td> <td data-bbox="1015 1690 1161 1717">No</td> <td data-bbox="1161 1690 1382 1717">Yes</td> </tr> <tr> <td data-bbox="690 1717 1015 1745">Progressive relaxation</td> <td data-bbox="1015 1717 1161 1745">No</td> <td data-bbox="1161 1717 1382 1745">Yes</td> </tr> <tr> <td data-bbox="690 1745 1015 1772">Spinal manipulation</td> <td data-bbox="1015 1745 1161 1772">Yes</td> <td data-bbox="1161 1745 1382 1772">Yes</td> </tr> <tr> <td data-bbox="690 1772 1015 1837">Yoga</td> <td data-bbox="1015 1772 1161 1837">No</td> <td data-bbox="1161 1772 1382 1837">Yes</td> </tr> <tr> <td data-bbox="511 1837 690 1850"></td> <td data-bbox="690 1837 1015 1850">Intensive interdisciplinary rehabilitation</td> <td data-bbox="1015 1837 1161 1850">No</td> <td data-bbox="1161 1837 1382 1850">Yes</td> </tr> </tbody> </table> <p data-bbox="560 1837 1382 1860">Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a</p>	Interventions for the Management of Low Back Pain				Intervention Type		Acute pain (duration <4 weeks)	Subacute or chronic pain (duration >4 weeks)	Self-care	Advice to remain active	Yes	Yes	Application of superficial heat	Yes	No	Book, handouts	Yes	Yes	Pharmacologic Therapy	Acetaminophen	Yes	Yes	TCA	No	Yes	Benzodiazepines	Yes	Yes	Non steroidal anti-inflammatory drugs (NSAIDs)	Yes	Yes	Skeletal muscle relaxants	Yes	No	Tramadol, opioids	Yes	Yes	Non-pharmacologic Therapy	Acupuncture	No	Yes	Cognitive behavior therapy	No	Yes	Exercise therapy	No	Yes	Massage	No	Yes	Progressive relaxation	No	Yes	Spinal manipulation	Yes	Yes	Yoga	No	Yes		Intensive interdisciplinary rehabilitation	No	Yes
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Clinical Guideline	Recommendations
	<p>joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-8]. Ann Intern Med. 2007;147(7):482.</p> <ul style="list-style-type: none"> • Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors. • In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, acetaminophen or NSAIDs are the first line options. • Acetaminophen is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Nonselective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen. • Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation). These agents should be used with caution. • Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance. • Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with acetaminophen or NSAIDs. Evidence is insufficient to recommend one opioid over another. • Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long-term use. These agents should be used with caution.
<p>American College of Rheumatology: American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (2012)⁷⁸</p>	<p><u>Nonpharmacologic recommendations for the management of hand osteoarthritis</u></p> <ul style="list-style-type: none"> • It is recommended that health professionals should: <ul style="list-style-type: none"> ○ Evaluate the ability to perform activities of daily living. ○ Instruct in joint protection techniques. ○ Provide assistive devices, as needed, to help patients perform activities of daily living. ○ Instruct in use of thermal modalities. ○ Provide splints for patients with trapeziometacarpal joint osteoarthritis. <p><u>Pharmacologic recommendations for the initial management of hand osteoarthritis</u></p> <ul style="list-style-type: none"> • It is recommended that health professionals should use one or more of the following: <ul style="list-style-type: none"> ○ Topical capsaicin. ○ Topical NSAIDs, including trolamine salicylate. ○ Oral NSAIDs, including cyclooxygenase-2 selective inhibitors. ○ Tramadol. • It is conditionally recommend that health professionals should not use the following: <ul style="list-style-type: none"> ○ Intraarticular therapies. ○ Opioid analgesics. • It is conditionally recommend that:

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> ○ In persons ≥ 75 years of age should use topical rather than oral NSAIDs. ○ In persons < 75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. <p><u>Nonpharmacologic recommendations for the management of knee osteoarthritis</u></p> <ul style="list-style-type: none"> ● It is strongly recommend that patients with knee osteoarthritis do the following: <ul style="list-style-type: none"> ○ Participate in cardiovascular (aerobic) and/or resistance land-based exercise. ○ Participate in aquatic exercise. ○ Lose weight (for persons who are overweight). ● It is conditionally recommend that patients with knee osteoarthritis do the following: <ul style="list-style-type: none"> ○ Participate in self-management programs. ○ Receive manual therapy in combination with supervised exercise. ○ Receive psychosocial interventions. ○ Use medially directed patellar taping. ○ Wear medially wedged insoles if they have lateral compartment osteoarthritis. ○ Wear laterally wedged subtalar strapped insoles if they have medial compartment osteoarthritis. ○ Be instructed in the use of thermal agents. ○ Receive walking aids, as needed. ○ Participate in tai chi programs. ○ Be treated with traditional Chinese acupuncture (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). ○ Be instructed in the use of transcutaneous electrical stimulation (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). ● No recommendation is made regarding the following: <ul style="list-style-type: none"> ○ Participation in balance exercises, either alone or in combination with strengthening exercises. ○ Wearing laterally wedged insoles. ○ Receiving manual therapy alone. ○ Wearing knee braces. ○ Using laterally directed patellar taping. <p><u>Pharmacologic recommendations for the initial management of knee osteoarthritis</u></p> <ul style="list-style-type: none"> ● It is conditionally recommend that patients with knee osteoarthritis use one of the following:

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> ○ Acetaminophen. ○ Oral NSAIDs. ○ Topical NSAIDs. ○ Tramadol. ○ Intraarticular corticosteroid injections. ● It is conditionally recommend that patients with knee osteoarthritis not use the following: <ul style="list-style-type: none"> ○ Chondroitin sulfate. ○ Glucosamine. ○ Topical capsaicin. ● No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. <p><u>Nonpharmacologic recommendations for the management of hip osteoarthritis</u></p> <ul style="list-style-type: none"> ● It is strongly recommend that patients with hip osteoarthritis do the following: <ul style="list-style-type: none"> ○ Participate in cardiovascular and/or resistance land based exercise. ○ Participate in aquatic exercise. ○ Lose weight (for persons who are overweight). ● It is conditionally recommend that patients with hip osteoarthritis do the following: <ul style="list-style-type: none"> ○ Participate in self-management programs. ○ Receive manual therapy in combination with supervised exercise. ○ Receive psychosocial interventions. ○ Be instructed in the use of thermal agents. ○ Receive walking aids, as needed. ● No recommendation is made regarding the following: <ul style="list-style-type: none"> ○ Participation in balance exercises, either alone or in combination with strengthening exercises. ○ Participation in tai chi. ○ Receiving manual therapy alone. <p><u>Pharmacologic recommendations for the initial management of hip osteoarthritis</u></p> <ul style="list-style-type: none"> ● It is conditionally recommend that patients with hip osteoarthritis use one of the following: <ul style="list-style-type: none"> ○ Acetaminophen. ○ Oral NSAIDs. ○ Tramadol. ○ Intraarticular corticosteroid injections. ● It is conditionally recommend that patients with hip osteoarthritis not use the following: <ul style="list-style-type: none"> ○ Chondroitin sulfate. ○ Glucosamine. ● No recommendation is made regarding the use of the following: <ul style="list-style-type: none"> ○ Topical NSAIDs. ○ Intraarticular hyaluronate injections. ○ Duloxetine. ● Opioid analgesics.
<p>American Academy of Orthopedic Surgeons:</p>	<p><u>Nonpharmacological/surgical therapy</u></p> <ul style="list-style-type: none"> ● Patients with symptomatic osteoarthritis of the knee should be

Clinical Guideline	Recommendations
<p>Clinical Practice Guideline on Osteoarthritis of the Knee (2008)⁷⁹</p>	<p>encouraged to participate in self-management educational programs, lose and maintain weight loss if overweight (body mass index >25), participate in low-impact aerobic fitness exercises and use range of motion/flexibility exercises and quadriceps strengthening.</p> <ul style="list-style-type: none"> • Patients with symptomatic osteoarthritis of the knee should use patellar taping for short term relief of pain and improvement in function. Lateral heel wedges should not be prescribed for patients with symptomatic medial compartmental osteoarthritis of the knee. • Needle lavage and arthroscopy with debridement or lavage should not be used for patients with primary symptomatic osteoarthritis of the knee. Arthroscopic partial meniscectomy or loose body removal is an option in patients with symptomatic osteoarthritis of the knee who also have primary signs and symptoms of a torn meniscus and/or a loose body. <p><u>Pharmacological therapy</u></p> <ul style="list-style-type: none"> • Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee. • Patients with symptomatic osteoarthritis of the knee should receive one of the following analgesics for pain unless there are contraindications to this treatment: <ul style="list-style-type: none"> ○ Acetaminophen (not to exceed 4 g per day). ○ NSAIDs. • Patients with symptomatic osteoarthritis of the knee and increased gastrointestinal risk (age ≥60 years, comorbid medical conditions, history of peptic ulcer disease, history of gastrointestinal bleeding, concurrent corticosteroids and/or concomitant use of anticoagulants) should receive one of the following analgesics for pain: <ul style="list-style-type: none"> ○ Acetaminophen (not to exceed 4 g per day). ○ Topical NSAIDs. ○ Nonselective oral NSAIDs plus gastro-protective agent. ○ Cyclooxygenase-2 inhibitors. • Intra-articular corticosteroids can be used for short-term pain relief for patients with symptomatic osteoarthritis of the knee.
<p>European League Against Rheumatism: Evidence-based Recommendations for the Management of Fibromyalgia Syndrome (2008)⁸⁰</p>	<ul style="list-style-type: none"> • Tramadol is recommended for the management of pain in fibromyalgia. • Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. • Corticosteroids and strong opioids are not recommended. • Amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole (not available in the United States), reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia. • Tropicisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia.
<p>European Federation of Neurological Societies: Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)¹²</p>	<p><u>Painful polyneuropathy</u></p> <ul style="list-style-type: none"> • Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus (HIV)-induced neuropathy. • Recommended first-line treatments include TCA, gabapentin, pregabalin, and serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine). • Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse. In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful. <p><u>Post herpetic neuropathy</u></p> <ul style="list-style-type: none"> Recommended first-line treatments include a TCA, gabapentin, or pregabalin. Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. Strong opioids and capsaicin cream are recommended as second-line therapies.
<p>American Academy of Neurology/American Association of Neuromuscular and Electrodiagnostic Medicine/American Academy of Physical Medicine and Rehabilitation: Treatment of Painful Diabetic Neuropathy (2011)¹³</p>	<p><u>Anticonvulsants</u></p> <ul style="list-style-type: none"> If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate should be considered for treatment. There is insufficient evidence to support or refute the use of topiramate for treatment. Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment. <p><u>Antidepressants</u></p> <ul style="list-style-type: none"> Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another. Venlafaxine may be added to gabapentin for a better response. There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy. <p><u>Opioids</u></p> <ul style="list-style-type: none"> Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other. <p><u>Other pharmacologic options</u></p> <ul style="list-style-type: none"> Capsaicin and isosorbide dinitrate spray should be considered for treatment. Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment. Lidocaine patch may be considered for treatment. There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment. <p><u>Nonpharmacologic options</u></p> <ul style="list-style-type: none"> Percutaneous electrical nerve stimulation should be considered for treatment. Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment. Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment.
<p>American Association</p>	<p><u>Neuropathy</u></p>

Clinical Guideline	Recommendations
<p>of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)⁸¹</p>	<ul style="list-style-type: none"> • All patients with type 2 diabetes should be assessed for neuropathy at the time of diagnosis, and all patients with type 1 diabetes should be assessed five years after diagnosis. Annual examinations should be performed thereafter in all patients. • Inspect the patient's feet at every visit to evaluate skin, nails, pulses, temperature, evidence of pressure, and hygiene. • Perform an annual comprehensive foot examination to assess sensory function by pinprick, temperature and vibration sensation using a tuning fork, or pressure using a monofilament. • Refer patient to a qualified podiatrist, orthopedist, or neurologist if there is lack of sensation or mechanical foot changes. • Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy. • When treating patients with cardiac autonomic neuropathy, strategies appropriate for protection against cardiovascular disease should be utilized. • TCA; topical capsaicin; and antiepileptic drugs such as carbamazepine, gabapentin, pregabalin, topiramate, and lamotrigine may provide symptomatic relief, but must be prescribed with knowledge of potential toxicities. • Further study is required before botanical preparations and dietary supplements can be advocated to treat neuropathic symptoms. • Maintain a referral network for podiatric and peripheral vascular studies and care.
<p>American Diabetes Association: Diabetic Neuropathies (2005)⁸²</p>	<p><u>Algorithm for the management of symptoms diabetic polyneuropathy</u></p> <ul style="list-style-type: none"> • Exclude nondiabetic etiologies, followed by, stabilize glycemic control (insulin not always required in type 2 diabetes), followed by, TCA (e.g., amitriptyline 25 to 250 mg before bed), followed by, anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day), followed by, opioid or opioid-like drugs (e.g., tramadol, oxycodone), followed by, consider pain clinical referral.
<p>American Academy of Neurology: Practice Parameter: Treatment of Postherpetic Neuralgia (2004)⁸³</p>	<ul style="list-style-type: none"> • TCAs (amitriptyline, nortriptyline, desipramine, maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of post herpetic neuropathy. • There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another. • Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine. • Aspirin cream is possibly effective in the relief of pain in patients with postherpetic neuralgia, but the magnitude of benefit is low, as seen with capsaicin. • In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of postherpetic neuralgia. • Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimeidine are not of benefit. • The effectiveness of carbamazepine, nifedipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of <i>Ganoderma lucidum</i>, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of postherpetic neuralgia. • There is insufficient evidence to make any recommendations on the long-term effects of these treatments.

Clinical Guideline	Recommendations
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents (2012)⁸⁴</p>	<p><u>Medication trials</u></p> <ul style="list-style-type: none"> • Prescribe FDA-approved treatments for ADHD in children, including psychostimulants and/or non-stimulants. • The decision to use medication should be made in conjunction with parents following a thorough discussion of expected benefits and potential risks. Factors such as the child's age, severity of symptoms and presence of comorbidity should also be considered and may involve decision-making regarding choice of medication. • Optimal medication management alone is superior to other modalities for the core symptoms of ADHD. • Response to one stimulant does not predict response to the others. If a child is a non-responder to one stimulant, it is advisable to attempt a second or third trial with other stimulants. • Atomoxetine is a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or physician. Atomoxetine is a non-controlled substance that may make it preferable in certain clinical situations. • Extended-release guanfacine and extended-release clonidine are the first ADHD medications to achieve FDA approval as adjunctive therapy with stimulant medications. • Extended-release guanfacine is the first ADHD medication to look for improvement of oppositional symptoms in addition to ADHD core symptoms. <p><u>Alternative medications</u></p> <ul style="list-style-type: none"> • When adequate stimulant and atomoxetine trials are unsuccessful (due to either poor response or side effects in spite of adjustment), or if associated comorbidity is present, alternative medication trials may be considered. • Second-line medications for ADHD therapy include TCAs (imipramine, desipramine), alpha adrenergic agonist (clonidine) a non-TCA (bupropion), or immediate-release guanfacine.
<p>American Academy of Sleep Medicine: Practice Parameters for the Treatment of Narcolepsy and Other Hypersomnias of Central Origin (2007)⁸⁵</p>	<ul style="list-style-type: none"> • Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other rapid eye movement sleep associated symptoms. Most antidepressants and anti-cataplectics have little effect on alertness. However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the targeted symptoms. Coadministration of two or more classes of compounds may be needed in some patients to adequately address their symptoms. • Modafinil is effective for treatment of daytime sleepiness due to narcolepsy. • Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. • Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy. • Selegiline may be an effective treatment for cataplexy and daytime sleepiness. • TCAs, SSRIs, and venlafaxine may be effective treatment for cataplexy. • Scheduled naps can be beneficial to combat sleepiness, but seldom suffice as primary therapy for narcolepsy.

Conclusions

The serotonin and norepinephrine reuptake inhibitors (SNRIs) are approved by the Food and Drug Administration (FDA) to treat a number of psychological conditions including depression and various subtypes of anxiety disorders. All agents within the class are approved for the treatment of major depressive disorder. Moreover, venlafaxine extended-release capsules (Effexor XR[®]) are approved for the management generalized anxiety disorder (GAD) and panic disorder. Both extended-release formulations are approved for the treatment of social anxiety disorder. Duloxetine (Cymbalta[®]) is the only agent within the class that carries indications for treating fibromyalgia, chronic musculoskeletal pain and painful diabetic neuropathy. All of the SNRI products have a Black Box Warning regarding the potential for antidepressants to increase suicidal thoughts in children and young adults.¹⁻⁴ Immediate- and extended-release formulations of venlafaxine are available generically; however, dexvenlafaxine (Pristiq[®]) and duloxetine remain branded products.

National and international treatment guidelines for the treatment of depression state that selecting an agent should be driven by anticipated side effects, tolerability, patient preference, and quantity and quality of available clinical data, and that the effectiveness of antidepressants is usually comparable within and between medication classes.^{7,8} Guidelines also state that medications that can be considered first-line therapy for most patients include selective serotonin reuptake inhibitors (SSRIs), SNRIs, mirtazapine, or bupropion, while monoamine oxidase inhibitors (MAOIs) should be reserved for patients who are unresponsive to other available medications. These guidelines do not recommend one SSRI, SNRI or MAOI over another.⁷ Antidepressants are recommended as first-line treatment for GAD, with the following agents considered treatment options: SSRIs, SNRIs, and nonsedating tricyclic antidepressants (TCAs). For the treatment of neuropathic pain, the SNRIs are recommended as initial therapy along with TCAs and anticonvulsants.¹²⁻¹³

The results of clinical trials have generally not demonstrated one antidepressant to be significantly more effective than another. The majority of clinical studies support the conclusion that antidepressants are of equivalent efficacy when administered in comparable doses. The choice of an antidepressant is influenced by the patient's diagnosis, current medical history, past history of response, the potential for drug-drug interactions and the adverse events profile. Treatment failure to one antidepressant class or to any specific antidepressant within a class does not predict treatment failure to another antidepressant agent, either within or outside of the same drug class. The SNRIs have been shown to be efficacious when compared to placebo for their FDA indications. Venlafaxine and duloxetine have also been shown to be comparable to other antidepressants and to each other. Currently no head-to-head trials directly compare desvenlafaxine to an active comparator.¹⁴⁻⁷⁴

References

1. Effexor XR[®] [prescribing information]. Philadelphia (PA): Wyeth Pharmaceuticals, Inc.; 2012 Aug.
2. Effexor[®] [prescribing information]. Philadelphia (PA): Wyeth Pharmaceuticals, Inc.; 2011 Nov.
3. Cymbalta[®] [prescribing information]. Indianapolis (IN): Lilly USA, LLC.; 2012 Sept.
4. Pristiq[®] [prescribing information]. Philadelphia (PA): Wyeth Pharmaceuticals, Inc.; 2011 Oct.
5. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2012 [cited 2012 Oct]. Available from: <http://online.factsandcomparisons.com>.
6. DRUGS@FDA.com [database on the internet]. Rockville (MD): U.S. Food and Drug Administration [cited 2012 Oct]. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.
7. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct [cited 2012 Oct]. 152 p. Available at: http://psychiatryonline.org/data/Books/prac/PG_Depression3rdEd.pdf.
8. National Institute for Clinical Excellence. Depression: the treatment and management of depression in adults (update). National Institute for Clinical Excellence; 2009 Oct [cited 2012 Oct]. Available at: <http://guidance.nice.org.uk/CG90>.
9. National Institute for Clinical Excellence. Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults. National Institute for Clinical Excellence; 2011 Jan [cited 2012 Oct]. Available at: <http://www.nice.org.uk/nicemedia/live/13314/52599/52599.pdf>.
10. Stein M, Goin M, Pollack M, Roy-Byrne P, Sareen J, Simon NM, et al. Practice guideline for the treatment of patients with panic disorder, second edition. American Psychiatric Association; 2009 [cited 2012 Oct]. Available at: http://psychiatryonline.org/data/Books/prac/PanicDisorder_2e_PracticeGuideline.pdf.
11. Connolly S, Bernstein G; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. American Academy of Child and Adolescent Psychiatry. *J Am Acad Child Adolesc Psychiatry*. 2007;46(2):267-83.
12. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010 Sep;17(9):1113-e88.
13. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011 May 17;76(20):1758-65.
14. Hewett K, Chrzanowski W, Schmitz M, Savelle A, Milanova V, Gee M, et al. Eight-week, placebo-controlled, double-blind comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. *J Psychopharmacol*. 2009;23:531-8.
15. Ferguson J, Tourian KA, Manley AL, Padmanadhan SK, Nichols A. An evaluation of the efficacy, safety, and tolerability of desvenlafaxine in the long-term treatment of elderly outpatients with major depressive disorder. *Prim Psychiatry*. 2010;17(1):66-73.
16. Soares CN, Thase ME, Clayton A, Guico-Pabia CJ, Focht K, Jiang Q, et al. Open-label treatment with desvenlafaxine in postmenopausal women with major depressive disorder not responding to acute treatment with desvenlafaxine or escitalopram. *CNS Drugs*. 2011;25(3):227-38.
17. Dunlop BW, Reddy S, Yang L, Lubaczewski S, Focht K, Guico-Pabia CJ. Symptomatic and functional improvement in employed depressed patients. A double-blind clinical trial desvenlafaxine vs placebo. *J Clin Psychopharmacol*. 2011;31:569-76.
18. Liebowitz MR, Yeung PP, Entsuah R. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. *J Clin Psychiatry*. 2007;68:1663-72.
19. Boyer P, Montgomery S, Lepola U, Germain JM, Brisard C, Ganguly R, et al. Efficacy, safety, and tolerability of fixed-dose desvenlafaxine 50 and 100 mg/day for major depressive disorder in a placebo-controlled trial. *Int Clin Psychopharmacol*. 2008;23:243-53.
20. Liebowitz MR, Manley AL, Padmanabhan SK, Ganguly R, Tummala R, Tourian KA. Efficacy, safety and tolerability of desvenlafaxine 50 mg/day and 100 mg/day in outpatients with major depressive disorder (abstract). *Curr Med Res Opin*. 2008 Jul;24(7):1877-90.

21. Kornstein SG, Jiang Q, Reddy S, Musgnung JJ, Guico-Pabia CJ. Short-term efficacy and safety of desvenlafaxine in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder. *J Clin Psychiatry*. 2010;71(8):1088-96.
22. Feiger AD, Tourian KA, Rosas GR, Padmanabhan SK. A placebo-controlled study evaluating the efficacy and safety of flexible-dose desvenlafaxine treatment in outpatients with major depressive disorder. *CNS Spectr*. 2009;14(1):41-50.
23. Septien-Velez L, Pitrosky B, Padmanabhan SK, Germain JM, Tourian KA. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. *Int Clin Psychopharmacology*. 2007;22:338-47.
24. Rickels K, Montgomery SA, Tourian KA, Guelfi JD, Pitrosky B, Padmanabhan SK, et al. Desvenlafaxine for the prevention of relapse in major depressive disorder. Results of a randomized trial. *J Clin Psychopharmacol*. 2010;30:18-24.
25. Demartinis NA, Yeung PP, Entsuh R, Manley AL. A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. *J Clin Psychiatry*. 2007;69:677-88.
26. Clayton AH, Kornstein SG, Rosas G, Guico-Pabia C, Tourian KA. An integrated analysis of the safety and tolerability of desvenlafaxine compared to placebo in the treatment of major depressive disorder (abstract). *CNS Spectr*. 2009 Apr;14(4):183-95.
27. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial (abstract). *J Clin Psychiatry*. 2002 Mar;63(3):225-31.
28. Gaynor PJ, Gopal M, Zheng W, Martinez JM, Robinson MJ, Hann D, et al. Duloxetine vs placebo in the treatment of major depressive disorder and associated painful physical symptoms: a replication study. *Curr Med Res Opin*. 2011;27:1859-67.
29. Gaynor PJ, Gopal M, Zheng W, Martinez JM, Robinson MJ, Marangell LB. A randomized placebo-controlled trial of duloxetine in patients with major depressive disorder and associated painful physical symptoms. *Curr Med Res Opin*. 2011;27:1849-58.
30. Nierenberg AA, Greist JH, Mallinckrodt CH, Prakash A, Sambunaris A, Tollefson GD, Wohlreich MM. Duloxetine vs escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. *Curr Med Res Opin*. 2007 Feb;23(2):401-16.
31. Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacol*. 2004;14:457-70.
32. Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA. Duloxetine in the treatment of depression a double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol*. 2004;24:389-99.
33. Perahia DG, Wang F, Mallinckrodt CH, Walker DJ, Detke MJ. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Psychiatry*. 2006;21(6):367-78.
34. Nemeroff CB, Michael E. A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. *J Psychiatr Res*. 2007;41:351-9.
35. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affective Disorders*. 1999;56:171-81.
36. Richard IH, McDermott MP, Kurlan R, Lyness JM, Como PG, Pearson N, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. *Neurology*. 2012;78:1229-36.
37. Rush AJ, Trivedi MH, Stewart JW, Nierenberg AA, Fava M, Kurian BT, et al. Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. *Am J Psychiatry*. 2011;168:689-701.
38. Morris DW, Budhwar N, Husain M, Wisniewski SR, Kurian BT, Luther JF, et al. Depression treatment in patients with general medical conditions: results from the CO-MED trial. *Ann Fam Med*. 2012;10:23-33.
39. Kerber KB, Wisniewski SR, Luther JF, Leuchter AF, D'Empaire I, Trivedi MH, et al. Effects of heart disease on depression treatment: results from the COMED study. *General Hospital Psychiatry*. 2012;34:24-34.

40. Rosso G, Rigardetto S, Bogetto F, Maina G. A randomized, single-blind, comparison of duloxetine with bupropion in the treatment of SSRI-resistant major depression. *J Affect Disord.* 2012;136:172-6.
41. Perahia DG, Pritchett YL, Kajdasz DK, Bauer M, Jain R, Russell JM, et al. A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. *J Psychiatr Res.* 2008;42:22-34.
42. Guelfi D, Ansseau M, Timmerman L, et al. Mirtazapine vs venlafaxine in hospitalized severely depressed patients with melancholic features. *J Clin Psychopharmacol.* 2001;21:425-31.
43. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet.* 2009;373:746-58.
44. Thase ME, Kornstein SG, Germain JM, Jiang Q, Guico-Pabia C, Ninan PT. An integrated analysis of the efficacy of desvenlafaxine compared to placebo in patients with major depressive disorder. *CNS Spectr.* 2009;14:144-54.
45. Acharya N, Rosen AS, Polzer JP, D'Souza DN, Perahia DG, Cavazzoni PA, Baldessarini RJ. Duloxetine: meta-analyses of suicidal behaviors and ideation in clinical trials for major depressive disorder. *J Clin Psychopharmacol.* 2006;26(6):587-94.
46. Vis PM, van Baardewijk M, Einarson TR. Duloxetine and venlafaxine-XR in the treatment of major depressive disorder: a meta-analysis of randomized clinical trials. *Ann Pharmacother.* 2005;39(11):1798-807.
47. Cipriani A, Brambilla P, Furukawa T, Geddes J, Gregis M, Hotopf M, et al. Fluoxetine vs other types of pharmacotherapy for depression. *Cochrane Database Syst Rev.* 2005 Oct 19;(4):CD004185.
48. Van Baardewijk M, Vis PMJ, Einarson TR. Cost effectiveness of duloxetine compared to venlafaxine-XR in the treatment of major depressive disorder. *Curr Med Res Opin.* 2005;21(8):1271-9.
49. Mease PJ, Russell IJ, Kajdasz DK, Wiltse CG, Detke MJ, Wohlreich MM, et al. Long-term safety, tolerability, and efficacy of duloxetine in the treatment of fibromyalgia. *Semin Arthritis Rheum.* 2010;39:454-64.
50. Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a six-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain.* 2008;136:432-44.
51. Arnold LM, Hudson JI, Wang F, Wohlreich MM, Prakash A, Kajdasz DK, et al. Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with vs without major depressive disorder. *Clin J Pain.* 2009;25:461-8.
52. Rynn M, Russell J, Erickson J, Detke MJ, Ball S, Dinkel J, et al. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depression and Anxiety.* 2008;25:182-9.
53. Koponen H, Allgulander G, Erickson J, Dunayevich E, Pritchett Y, Detke MJ, et al. Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. *Prim Care Companion J Clin Psychiatry.* 2007;9:100-7.
54. Davidson JRT, Wittchen HU, Llorca PM, Erickson J, Detke M, Ball SG, et al. Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol.* 2008;18:673-81.
55. Hartford J, Kornstein S, Liebowitz M, Pigott T, Russell J, Detke M, et al. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol.* 2007;22:167-74.
56. Nicolini H, Bakish D, Duenas H, Spann M, Erickson J, Hallberg C, et al. Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial. *Psychol Med.* 2009;39:267-76.
57. Schmitt R, Gazalle FK, Lima MS, Cunha A, Souza J, Kapczinski F. The efficacy of antidepressants for generalized anxiety disorder: a systematic review and meta-analysis. *Rev Bras Psiquiatr.* 2005 Mar;27(1):18-24.
58. Wernicke J, Lledo A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine. *Drug Safety.* 2007;30(5):437-55.

59. Skljarevski V, Zhang S, Chappell AS, Walker DJ, Murray I, Backonja M. Maintenance of effect of duloxetine in patients with chronic low back pain: a 41-week uncontrolled, dose-blinded study. *Pain Med.* 2010;11:648-57.
60. Skljarevski V, Desai D, Liu-Seifert H, Zhang Q, Chappell AS, Detke MJ, et al. Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine.* 2010;35:E578-85.
61. Chappell AS, Ossanna MJ, Liu-Seifert H, Iyengar S, Skljarevski V, Li LC, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain.* 2009;146:253-60.
62. Chappell AS, Desai D, Liu-Seifert H, Zhang S, Skljarevski V, Belenkov Y, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. *Pain Pract.* 2010;11:33-41.
63. Skljarevski V, Zhang S, Desai D, Alaka KJ, Palacios S, Miazgowski T, et al. Duloxetine vs placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. *J Pain.* 2010;11:1282-90.
64. Skljarevski V, Ossanna M, Liu-Seifert H, Zhang Q, Chappell A, Iyengar S, et al. A double-blind, randomized trial of duloxetine vs placebo in the management of chronic low back pain. *Eur J Neurol.* 2009;16:1041-8.
65. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. *Curr Med Res Opin.* 2011;27:2361-72.
66. Yan G, Guang N, Wei-ping J, Zhi-guang Z, Zhang-rong X, Zhi-min L, et al. Duloxetine vs placebo in the treatment of patients with diabetic neuropathic pain in China. *Chin Med J.* 2010;123(22):3184-92.
67. Armstrong DG, Chappell AS, Le TK, Kajdasz DK, Backonja M, D'Souza DN, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evaluation of functional outcomes. *Pain Med.* 2007 Jul-Aug;8(5):410-8.
68. Kajdasz DK, Iyengar S, Desai D, Backonja MM, Farrar JT, Fishbain DA, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evidence-based findings from post hoc analysis of three multicenter, randomized, double-blind, placebo-controlled, parallel-group studies. *Clin Ther.* 2007;29:2536-46.
69. Wernicke JF, Wang F, Pritchett YL, Smith TR, Raskin J, D'Souza DN, et al. An open-label 52-week clinical extension comparing duloxetine with routine care in patients with diabetic peripheral neuropathic pain. *Pain Medicine.* 2007;8(6):503-13.
70. Raskin J, Smith TR, Wong K, Pritchett YL, D'Souza DN, Iyengar S, et al. Duloxetine vs routine care in the long-term management of diabetic peripheral neuropathic pain. *J Palliative Med.* 2006;9(1):29-40.
71. Tanenberg RJ, Irving GA, Risser RC, Ahl J, Robinson MJ, Skljarevski V, et al. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. *Mayo Clin Proc.* 2011;86(7):615-24.
72. Wernicke J, Lledo A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine. *Drug Safety.* 2007;30(5):437-55.
73. Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.CD007115.
74. Quilici S, Chancellor J, Lothgren M, Simon D, Said G, Le TK, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. *BMC Neurology.* 2009;9:6-19.
75. Qaseem A, Snow V, Denberg T, Forcica 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;149:725-33.
76. 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. J Am Acad Child Adolesc Psychiatry.* 2007;46:1503-26.
77. Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, et al. Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med.* 2007;147:478-91.

78. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012 Apr;64(4):455-74.
79. American Academy of Orthopedic Surgeons: Clinical practice guideline on the treatment of osteoarthritis of the knee (non-arthroplasty). Rosemont (IL): 2008 [Guideline on the internet] [cited 2012 Oct] Available from: <http://www.aaos.org/research/guidelines/OAKguideline.pdf>.
80. Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis*. 2008;67:536-41.
81. Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract*. 2007 May-Jun;13(Suppl 1):S1-68.
82. Boulton AJ, Vinkik AL, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care*. 2005;28(4):956-62.
83. Dubinsky RM, Kabbani H, El-Chami, Boutwell C, Ali H; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004;63:959.
84. Institute for Clinical Systems Improvement. Health care guideline: diagnosis and management of attention deficit hyperactivity disorder in primary care for school-age children and adolescents [guideline on the Internet]. 9th ed. Bloomington (MN): Institute for Clinical Systems Improvement; 2012 Mar [cited 2012 Oct]. Available at: http://www.icsi.org/adhd/adhd_2300.html.
85. American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007;30:1705-11.