Therapeutic Class Overview
Serotonin and Norepinephrine Reuptake Inhibitors

Therapeutic Class

- **Overview/Summary:** The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa) and premenstrual dysphoric disorder.[1-2] Anxiety disorders include agoraphobia, anxiety disorder due to another medical condition, generalized anxiety disorder, other specified anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder or social phobia, specific phobia, substance/medication induced anxiety disorder and unspecified anxiety disorder.[3-4] Some of the antidepressants are also approved to treat nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, moderate to severe vasomotor symptoms associated with menopause, nocturnal enuresis and tobacco abuse.[1-2]

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

  The SNRIs include desvenlafaxine, duloxetine, levomilnacipran, milnacipran and venlafaxine. These agents are believed to exert their effects through potentiating the serotonergic and noradrenergic activity in the central nervous system.[1-2,5-13] 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.[1-2,5-13] 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.[1-2,11-13] 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.[1-2,5-7] The adverse event profiles appear to be similar between the two agents.

  Levomilnacipran is a new SNRI approved by the FDA for the treatment of major depressive disorder. Of note, levomilnacipran has shown to be twice as selective for norepinephrine as serotonin. In addition, levomilnacipran has demonstrated 10-fold higher selectivity for norepinephrine vs serotonin reuptake inhibition when compared to duloxetine, venlafaxine and desvenlafaxine.[14-16] It is important to understand that despite the higher selectivity for norepinephrine reuptake inhibition, levomilnacipran has comparable binding potency at the norepinephrine reuptake pump to duloxetine, and a lower binding potency at the serotonin reuptake pump than duloxetine.[17]

  Levomilnacipran is the more active enantiomer of milnacipran (Savella®), a medication FDA-approved for the treatment of fibromyalgia, a functionally impairing disease state. Levomilnacipran is approximately twice as potent for reuptake inhibition of norepinephrine compared to milnacipran, its racemic mixture.[3,10]

  Currently, venlafaxine is available generically in both immediate- and extended-release formulations, while desvenlafaxine and duloxetine are only available as branded products.[5,6]

Table 1. Current Medications Available in the Therapeutic Class[1-2,5-13]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Desvenlafaxine succinate (desvenlafaxine ER, Pristiq®, Khedezla®)	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; treatment of major depressive disorder	Delayed-release capsule: 20 mg 30 mg 60 mg	-
Levomilnacipran (Fetzima®)	Treatment of major depressive disorder	Extended-release capsules: 20 mg 40 mg 80 mg 120 mg	-
Levomilnacipran (Fetzima®)	Management of fibromyalgia	Tablet: 12.5 mg 25 mg 50 mg 100 mg	-
Venlafaxine (Effexor®, Effexor XR®, venlafaxine ER)	Treatment of generalized anxiety disorder (extended-release capsule); treatment of major depressive disorder (extended-release capsule, extended-release tablet, tablet); treatment of panic disorder, with or without agoraphobia (extended-release capsule); treatment of social anxiety disorder (extended-release capsule)	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 37.5 mg 50 mg 75 mg 100 mg	✔

ER, XR=extended-release
*This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.

Evidence-based Medicine

- Clinical trials demonstrating the safety and efficacy of the serotonin and norepinephrine reuptake - inhibitors are outlined in Table 4.[14-111]
- Desvenlafaxine, duloxetine and venlafaxine have been shown to be efficacious for the management of major depressive disorder, as measured by improvements in Hamilton Rating Scale for Depression-17 and Montgomery-Åsberg Depression Rating Scale scores, when compared to

placebo.[14-33,38] Duloxetine and venlafaxine have also been shown to be comparable to other antidepressants for the treatment of major depressive disorder.[41-72] 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 major depressive disorder.[42-43] Trials comparing desvenlafaxine to an active comparator have not been conducted.

- Results from several clinical trials demonstrate the efficacy of duloxetine in reducing pain severity in adults with fibromyalgia when compared to placebo.[73-77] In addition, results from several clinical trials demonstrate the efficacy of duloxetine in reducing pain severity in adults with fibromyalgia when compared to placebo.[78-80]
- 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.[97-103]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - 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.[112-115]
  - 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.[112-115]
  - Antidepressants are recommended as first-line treatment for GAD, with the following agents considered treatment options: SSRIs, SNRIs, and nonsedating tricyclic antidepressants (TCAs).[116-118]
  - For the treatment of neuropathic pain, the SNRIs are recommended as initial therapy along with TCAs and anticonvulsants.[124-128]
- Other Key Facts:
  - 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.[1-12]

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Therapeutic Class Review
Serotonin and Norepinephrine Reuptake Inhibitors

Overview/Summary

The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa) and premenstrual dysphoric disorder.[1-2] Anxiety disorders include agoraphobia, anxiety disorder due to another medical condition, generalized anxiety disorder, other specified anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder or social phobia, specific phobia, substance/medication induced anxiety disorder and unspecified anxiety disorder.[3-4] Some of the antidepressants are also approved to treat nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, moderate to severe vasomotor symptoms associated with menopause, nocturnal enuresis and tobacco abuse.[1-2]

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

The SNRIs include desvenlafaxine, duloxetine, levomilnacipran, milnacipran and venlafaxine. These agents are believed to exert their effects through potentiating the serotonergic and noradrenergic activity in the central nervous system.[1-2,5-13] 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.[1-2,5-13] 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.[1-2,11-13] 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.[1-2,5-7] The adverse event profiles appear to be similar between the two agents.

Levomilnacipran is a new SNRI approved by the FDA for the treatment of major depressive disorder. Of note, levomilnacipran has shown to be twice as selective for norepinephrine as serotonin. In addition, levomilnacipran has demonstrated 10-fold higher selectivity for norepinephrine vs serotonin reuptake inhibition when compared to duloxetine, venlafaxine and desvenlafaxine.[14-16] It is important to understand that despite the higher selectivity for norepinephrine reuptake inhibition, levomilnacipran has comparable binding potency at the norepinephrine reuptake pump to duloxetine, and a lower binding potency at the serotonin reuptake pump than duloxetine.[17]

Levomilnacipran is the more active enantiomer of milnacipran (Savella®), a medication FDA-approved for the treatment of fibromyalgia, a functionally impairing disease state. Levomilnacipran is approximately twice as potent for reuptake inhibition of norepinephrine compared to milnacipran, its racemic mixture.[3,10]

Currently, venlafaxine is available generically in both immediate- and extended-release formulations, while desvenlafaxine and duloxetine are only available as branded products.[5,6]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Desvenlafaxine succinate (desvenlafaxine ER, Pristiq®, Khedezla®)	Selective Serotonin- and Norepinephrine-reuptake Inhibitors	-
Duloxetine (Cymbalta®)	Selective Serotonin- and Norepinephrine-reuptake Inhibitors	-
Levomilnacipran (Fetzima®)	Selective Serotonin- and Norepinephrine-reuptake Inhibitors	-
Milnacipran (Savella®)	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 Indications[1-2,5-13]

Indication(s)	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
Management of chronic musculoskeletal pain		✔ *			
Management of fibromyalgia		✔		✔	
Management of neuropathic pain associated 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)

*This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.

Pharmacokinetics

Table 3. Pharmacokinetics[1-2,5-13]

Generic Name	Bioavailability (%)	Metabolism	Active metabolites	Elimination (%)	Half-Life (hours)
Desvenlafaxine	80	Hepatic	O-desmethylvenlafaxine	Renal (45)	10 to 11
Duloxetine	30 to 80	Hepatic	4-hydroxy duloxetine glucoronide, 5-hydroy, 6-methoxy duloxetine sulfate	Feces (20); renal (70)	8 to 17

Generic Name	Bioavailability (%)	Metabolism	Active metabolites	Elimination (%)	Half-Life (hours)
Levomilnacipran	92	Hepatic	None	Renal (58)	12
Milnacipran	85 to 90	Hepatic	None	Renal (55)	6 to 8
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 are outlined in Table 4.[14-111]

Desvenlafaxine, duloxetine and venlafaxine have been shown to be efficacious for the management of major depressive disorder, as measured by improvements in Hamilton Rating Scale for Depression-17 and Montgomery-Åsberg Depression Rating Scale scores, when compared to placebo.[14-33,38] Duloxetine and venlafaxine have also been shown to be comparable to other antidepressants for the treatment of major depressive disorder.[41-72] 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 major depressive disorder.[42-43] Trials comparing desvenlafaxine to an active comparator have not been conducted.

Results from several clinical trials demonstrate the efficacy of duloxetine in reducing pain severity in adults with fibromyalgia when compared to placebo.[73-77] In addition, results from several clinical trials demonstrate the efficacy of duloxetine in reducing pain severity in adults with fibromyalgia when compared to placebo.[78-80]

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.[97-103]

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				
Ferguson et al.[14] (2010) Desvenlafaxine 100 or 200 mg/day	MC, OL Outpatients ≥65 years of age with MDD	N=52 (safety analysis) ≤6 months	Primary: Safety Secondary: HAM-D-17 total scores	Primary: 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. Secondary: 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. 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.
Soares et al.[15] (2011) Desvenlafaxine 100 to 200 mg/day	MC, OL Post-menopausal women 40 to 70 years of age with MDD who did not achieve clinical response to acute, DB treatment with desvenlafaxine or escitalopram	N=123 6 months	Primary: HAM-D-17 total score 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),	Primary: 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 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. 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
			safety	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. 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. 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%).
Dunlop et al.[16] (2011) 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). 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). 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.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Liebowitz et al.[17] (2007) Desvenlafaxine 100 mg/day for days 1 to 14, increasing to 200 mg/day vs placebo	DB, MC, PC, PG, RCT 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	N=247 8 weeks	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score Secondary: Change from baseline in CGI-I, MADRS, CGI-S, VAS-PI, vital signs, safety	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). 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). The CGI-S showed no difference from baseline between the desvenlafaxine and placebo groups (3.1 vs 3.3 respectively; P value not reported). 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). There was a significant increase from baseline in supine SBP (3.76 vs -1.59; P<0.001, respectively) and supine DBP (1.85 vs -0.91; P=0.003 respectively) in the desvenlafaxine group compared to the placebo group. There was a significant decrease in body weight seen in the desvenlafaxine group compared to the placebo group (-0.74 vs 0.36 kg; P<0.001). 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). Anorexia (P<0.001), constipation (P<0.05), dry mouth (P<0.01), nausea

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				(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.
Boyer et al.[18] (2008) Desvenlafaxine 50 and 100 mg/day vs placebo	DB, MC, PC, PG, RCT 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	N=438 8 weeks (plus a 1 week taper phase)	Primary: HAM-D-17 total score Secondary: CGI-I, MADRS, CGI-S, VAS-PI, Covi Anxiety Scale total scores, remission rates, responder rates, safety	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). 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. 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). 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 evaluation. 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. 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). The adjusted OR for response relative to placebo was 1.943 (95% CI, 1.24 to

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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). 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.
Liebowitz et al.[19] (abstract) (2008) Desvenlafaxine 50 or 100 mg/day vs placebo	DB, MC, PC, PG, RCT 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, and CGI-S score ≥4	N=447 8 weeks (plus a 1 week taper)	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17score 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 of ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17score	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). 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 100 mg groups (P=0.208) compared to the placebo group. 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). 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,

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			decrease to ≤7%), SDS, WHO-5, safety	respectively). 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. The most common adverse events seen (incidence ≥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).
Kornstein et al.[20] (2010) 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, MADRS, HAMA, QIDS-SR, MRS, EQ-5D, VAS-PI, safety	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 though week eight (week two; P=0.013, weeks three to eight; P<0.001). 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 -1.47). 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). 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;

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				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). 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.
Feiger et al.[21] (2009) Desvenlafaxine 200 to 400 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with MDD	N=235 8 weeks (plus a 2 week tapering phase)	Primary: HAM-D-17 Secondary: CGI-I, CGI-S, MADRS, HAM-D-6, safety	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). No significant differences were observed between desvenlafaxine and placebo groups for HAM-D-17 clinical response rates at the final evaluation; the logistic 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). 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

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				HAM-D-6 (1.5; 95% CI, 0.5 to 2.6). 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). Treatment-emergent adverse events were reported by 112 patients (96%) and 101 patients (86%) receiving desvenlafaxine and placebo. Treatment-emergent adverse events reported by ≥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 pervious 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.
Septein-Velez et al.[22] (2007) Desvenlafaxine 200 or 400 mg/day vs placebo	DB, MC, PC, PG, RCT 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	N=369 8 weeks (plus a 2 week taper)	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17	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). 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.

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	≥20, and CGI-S score ≥4		rate of response (percentage of patients with a HAM-D-17 score decrease ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17 score decrease to ≤7%), SDS, WHO-5	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). 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). 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). 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.
Rickels et al.[23] (2010) Desvenlafaxine 200 to 400 mg/day vs placebo After 12 weeks of OL treatment with	DB, PC, RCT Patients 18 to 75 years of age with MDD, single or recurrent episode, without psychotic features	N=374 (DB phase) N=575 (OL phase) 12 weeks of OL treatment, followed by a 6 month, DB phase	Primary: Time until relapse (HAMD-D-17 total score ≥16 at any visit, CGI-I score ≥6 at any visit, or discontinuation due to unsatisfactory response) Secondary: HAM-D-17 total	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). 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.

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desvenlafaxine, patients with HAM-D-17 total score ≤11 were randomized to continue desvenlafaxine or be switched to placebo.			score, CGI-I, CGI-S, HAM-D-6, Covi Anxiety score, safety	Desvenlafaxine was also associated with significant differences compared to placebo on CGI-I, CGI-S, HAM-D-6, and Covi Anxiety scores. 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). 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%), tremor (5%), delayed ejaculation (5% in men), erectile dysfunction (5% in men), vomiting (4%), vertigo (3%), myalgia (2%), paresthesia (2%), and altered mood (1%).
Demartinis et al.[24] (2007) Desvenlafaxine 100, 200, or 400 mg/day vs	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a primary diagnosis of MDD, depressive	N=461 8 weeks (plus a 2 week taper)	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score Secondary:	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. Secondary:

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placebo	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		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 ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17 score decrease to ≤7%), SDS, WHO-5, vital signs, safety	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). 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). 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). 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. 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=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. 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. 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

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				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). The mean increase in supine SBP was considered significant in all groups compared to baseline compared to the placebo group (P<0.05). The increase in DBP 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 DBP from baseline in both the desvenlafaxine 200 and 400 mg groups compared to the placebo group (P<0.05). The increase in DBP 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). 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).
Clayton et al.[25] (abstract) (2009) Desvenlafaxine 50 to 400 mg/day vs placebo	DB, PC, RCTs (integrated analysis of short-term 9 trials) Adult outpatients with MDD	N=2,950 8 weeks	Primary: Treatment-emergent adverse events, laboratory values, vital signs, discontinuation symptoms Secondary: Not reported	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. 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. Small but significant changes in mean blood pressure occurred with all desvenlafaxine doses; clinically meaningful changes were observed in 1 and

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				2% of placebo- and desvenlafaxine-treated patients. 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. Secondary: Not reported
Thase et al.[26] (2009) Desvenlafaxine 50 to 400 mg/day vs placebo	MA (9 trials) Outpatients ≥18 years of age with MDD	N=3,023 8 weeks	Primary: HAM-D-17 total score Secondary: MADRS, HAM-D-6, CGI-I, CGI-S, remission and response rates, safety	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). 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. 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). 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.
Tourian et al.[27] (2013) Desvenlafaxine 25 mg/day from days 1 to	MC, OL Japanese patients with MDD who had	N=304 10 weeks	Primary: Safety, HAM-D17 Secondary: Not reported	Primary: Treatment-emergent adverse events were reported by 240 patients (78.9%) during the on-therapy period; the most common adverse events were nasopharyngitis (37.2%), somnolence (11.5%), headache (10.5%), and nausea (10.2%).

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14, with subsequent upward titration, to a maximum of 100 mg/day, determined by clinical response	completed an 8-week, DB, PC study in which patients received 25 or 50 mg/day desvenlafaxine or placebo			For the ITT-LOCF population, the mean change from baseline in the HAM-D17 total score was -4.76 (95% CI, -5.47 to -4.05). Continued numerical improvements in the HAM-D17 total scores and other depression outcome measures were observed irrespective of treatment in the previous study. Secondary: Not reported
Rosenthal et al.[28] (2013) Desvenlafaxine 50 mg/day vs placebo	DB, MC, PC, RCT Adult outpatients age >18 years of age with MDD (DSM-IV criteria) and a HDRS17 total score >20 at screening and baseline	N=874 11 months	Primary: Time to relapse (HDRS17 total score >16, discontinuation for unsatisfactory response, hospitalization for depression, suicide attempt, or suicide) Secondary: Safety and tolerability	Primary: Time to relapse was significantly shorter for placebo vs desvenlafaxine (P<0.001). At the end of the six-month DB treatment, the estimated probability of relapse was 30.2% for placebo vs 14.3% for desvenlafaxine 50 mg/day. Secondary: Safety and tolerability results were generally consistent with those in short-term studies of desvenlafaxine 50 mg/day.
Clayton et al.[29] (2013) Desvenlafaxine 50 mg/day vs placebo	DB Adult outpatients with MDD	N=422 12 weeks	Primary: Mean change from baseline Arizona Sexual Experiences Scale scores Secondary: Not reported	Primary: Among women (desvenlafaxine, n=184; placebo, n=92), baseline scores were 20.0 (5.2) and 20.5 (5.3) for desvenlafaxine and placebo, respectively; mean changes at week 12 were -1.93 (0.37) and -1.03 (0.54), respectively (mean difference: 0.90 [-0.38, 2.18]; P=0.169). Among men (desvenlafaxine, n=97; placebo, n=49), baseline scores were 16.4 (4.9) and 15.9 (4.8) for desvenlafaxine and placebo, respectively; mean changes at week 12 were -1.13 (0.47) and -1.06 (0.70), respectively (mean difference: 0.07 [-1.59, 1.74]; P=0.932). Significantly greater orgasmic dysfunction at week 12 was observed in the

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				subgroup of men without baseline sexual dysfunction treated with desvenlafaxine relative to placebo. Conversely, women without baseline sexual dysfunction experienced poorer overall sexual functioning and orgasm satisfaction at week 12 with placebo relative to desvenlafaxine treatment. Subgroup analyses of treatment responders and nonresponders found no difference in the proportion of men or women that developed or had resolution of sexual dysfunction in the desvenlafaxine and placebo groups.
Gaynor et al.[30] (2011) Duloxetine 60 mg QD 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	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). 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). 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). 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. The least squares mean PGI-I score demonstrated significantly greater improvements with duloxetine compared to placebo (P≤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). Patients receiving duloxetine demonstrated significantly greater improvements

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				in the SDS global functional impairment score compared to placebo (46.4 vs 31.8%, respectively; P<0.001).
Gaynor et al.[31] (2011) Duloxetine 60 mg QD 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≤0.001). 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≤0.001). 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≤0.005). Secondary: A significantly greater proportion of patients receiving duloxetine met the criteria for remission than patients receiving placebo (P≤0.01). 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≤0.001). The least squares mean PGI-I score demonstrated significantly greater improvements with duloxetine compared to placebo (P≤0.021). 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≤0.001). 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≤0.05). The improvement in the item addressing school/work life was not significantly different between

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				duloxetine and placebo (P=0.112). Treatment emergent adverse events with duloxetine were nausea, somnolence, 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).
Acharya et al.[32] (2006) Duloxetine 40 to 120 mg daily vs placebo	MA (12 trials) Patients taking duloxetine for MDD	N=2,996 Duration varied	Primary: Incidence of suicide-related events with duloxetine (MHID, MHRD, HAM-D Item-3) Secondary: Not reported	Primary: There were no significant differences in the incidence of suicide-related events with duloxetine vs placebo. 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). 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). Secondary: Not reported
Mancini et al.[33] (2012) Duloxetine vs placebo	MA (6DB, PC, PG, RCT) Patients with MDD	N=2,496 Short-term (7 to 13 weeks) and the long-term (>24 weeks) endpoint	Primary: SDS total score Secondary: Functional remission (SDS total< 6) rates, VAS	Primary: The between-treatment difference of -2.52 between duloxetine and placebo in the SDS total score at the short-term endpoint was statistically significant in favor of duloxetine vs placebo (95% CI, -3.17, -1.87; P<0.001). Secondary: The endpoint functional remission rates were 39.5% with duloxetine and 28.7% with placebo. Time since first depression episode, antidepressant pretreatment (yes/no), baseline VAS pain (<30/>30 mm), and sex were significant prognostic factors. The effect of duloxetine was maintained at the long-term endpoint.
Asnis et al.[34] (2013) Levomilnacipran 40 mg QD	DB, MC, PC, RCT Patents 18 to 65 years of age, met	N=708 N=506 completed study	Primary: Mean reduction of MADRS score from baseline at week eight (reported as	Primary: The LSMD from placebo of MADRS scores for levomilnacipran 40, 80 and 120 mg at week eight were -3.23; P=0.0186, -3.99; P=0.0038 and -4.86; P=0.0005, respectively.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
or levomilnacipran 80 mg QD or levomilnacipran 120 mg QD vs placebo	the diagnostic criteria of MDD per the DSM-IV-TR, current ongoing depressive episode ≥8 weeks in duration, MADRS score ≥30 at baseline, MADRS-SR ≥26 at baseline	8 weeks	LSMD from placebo) Secondary: Mean reduction of SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight, mean change from baseline of CGI-S total score at week eight and mean reduction from baseline of CGI-I total score at week eight (all reported as LSMD from placebo)	Secondary: The LSMD from placebo on the SDS total score for levomilnacipran 40, 80 and 120 mg was -1.4; P>0.05, -2.51; P<0.05, -2.57; P<0.05, respectively. The LSMD from placebo on the $HDRS_{17}$ for levomilnacipran 40, 80 and 120 mg was -1.2; P>0.05; -2.09; P<0.05 and -2.34; P<0.05, respectively. The LSMD from placebo on the CGI-S for levomilnacipran 40, 80 and 120 mg was -.04; P>0.05, -0.43; P<0.01 and -0.35; P<0.05, respectively. The LSMD from placebo on the CGI-I score for levomilnacipran 40, 80 and 120 mg was -0.1; P>0.05, -0.34; P<0.05 and -0.32; P<0.05, respectively.
Bakish et al.[35] (2013) Levomilnacipran 40 mg QD or levomilnacipran 80 mg QD vs	DB, MC, PC, RCT Patients 18 to 75 years of age, met diagnostic criteria per the DSM-IV-TR for recurrent MDD, current ongoing depressive episode 6 weeks to 12 months in	N=557 N=441 completed study 8 weeks	Primary: Mean reduction of MADRS score from baseline at week eight (reported as LSMD from placebo) Secondary: Mean reduction of SDS score from baseline at week eight, mean	Primary: The LSMD from placebo week eight for levomilnacipran 40 and 80 mg was -3.3; P=0.003 and -3.1; P=0.004, respectively. Secondary: The LSMD from placebo at week eight for levomilnacipran 40 and 80 mg was -1.8; P=0.046 and - 2.7; P=0.003, respectively. The LSMD from placebo on $HDRS_{17}$ scores for levomilnacipran 40 and 80 mg were -2.2; P=0.007 and -1.6; P=0.043. The LSMD from placebo on CGI-S scores for levomilnacipran 40 and 80 mg was -0.3 for both arms with P=0.020 and P=0.015, respectively.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
placebo	duration, 5 or fewer major depressive episodes within the previous 5 years, MADRS score ≥26 at baseline, CGI-S score ≥4 at baseline		reduction on $HDRS_{17}$ from baseline at week eight and mean reduction from baseline of CGI-S total score at week eight (all reported as LSMD from placebo)	
Sambunaris et al.[36] (2013) Levomilnacipran 40 to 120 mg vs placebo	DB, FD, MC, PC, RCT Patients 18 to 80 years of age, met the diagnostic criteria for MDD per the DSM-IV-TR, ongoing major depressive episode of at least 4 weeks in duration, MADRS score ≥30 at baseline and MADRS-SR ≥26 at baseline	N=429 N=335 completed study 8 weeks	Primary: Mean reduction of MADRS score from baseline at week eight (reported as LSMD from placebo Secondary: Mean reduction of SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight, mean change from baseline of CGI-I total score at week eight, mean reduction from baseline of CGI-S total score at week eight and mean	Primary: The LSMD from placebo on the MADRS score at week eight was -3.095; P=0.0051 for levomilnacipran 40 to 120 mg. Secondary: The LSMD from placebo on the SDS at week eight was -2.632; P=0.0010 for levomilnacipran 40 to 120 mg. The LSMD from placebo on the $HDRS_{17}$ score for levomilnacipran 40 to 120 mg was -2.146; P=0.0038. Levomilnacipran 40 to 120 mg did not show statistically significant results for the LSMD from placebo on the CGI-I total score at week eight (-0.207; P=0.0881). Levomilnacipran 40 to 120 mg showed a LSMD from placebo on the CGI-S at week eight of -0.352; P=0.0083. The LSMD from placebo on the MEI-SF for levomilnacipran 40 to 120 mg at week eight was 5.048; P=0.0382.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
			change from baseline on MEI-SF total score at week eight (all reported as LSMD from placebo)	
Montgomery et al.[37] (2013) Levomilnacipran 75 or 100 mg QD Levomilnacipran dose was increased to 100 mg/day over 12 days. vs placebo	DB, FD, MC, PC, RCT Outpatients 18 to 70 years of age who met DSM-IV criteria for MDD (duration > 1 month) with a HDRS17 score > 22 and SDS score > 10	N=553 10 weeks	Primary: MADRS score change from baseline to week 10 Secondary: HDRS17, SDS, CGI-I, MADRS response (>50% decrease from baseline) and remission (score <10), safety	Primary: Levomilnacipran was significantly "superior" to placebo on MADRS total score change from baseline to week 10 (LSMD, -4.2; 95% CI, -5.7 to -2.6; P<.0001). Secondary: Statistical significance in favor of levomilnacipran was demonstrated on change from baseline to week 10 in HDRS17 total score (LSMD, -3.4; 95% CI, -4.7 to -2.2; P<0.0001) and SDS total score (LSMD, -3.4; 95% CI, -4.6 to -2.2; P<0.0001) and subscales. Significantly more levomilnacipran patients vs placebo patients achieved MADRS response (59.1 vs 42.2%; P<0.0001) and remission (46.4 vs 26.0%; P<0.0001). Levomilnacipran was generally safe and well tolerated; more levomilnacipran patients (9.4%) vs placebo patients (6.5%) discontinued due to adverse events, but more placebo patients vs levomilnacipran patients discontinued overall (24.9 vs 20.2%).
Vis et al.[38] (2005) Duloxetine 40 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day vs	MA (8 trials) Outpatients >18 years of age with MDD	N=1,754 (efficacy) N=1,791 (safety) 8 weeks	Primary: Remission and response (HAM-D, MADRS) Secondary: Dropout rates and rates of adverse events	Primary: Both treatment groups demonstrated a significant difference compared to placebo for both remission and response (P<0.001 for all). Secondary: More patients receiving placebo dropped out due to lack of efficacy compared 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).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
placebo				
Perahia et al.[39] (2008) 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 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%). 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).
Van Baardewijk et al.[40] (2005) Duloxetine 40 to 120 mg daily for at least 8 weeks vs venlafaxine ER	MA Adults with moderate to severe MDD and a score ≥15 on the HAM-D or ≥18 on the MADRS scale	N=not specified 6 months	Primary: Remission (an improvement in the HAM-D scale to a score <7, or a score ≤10 on the MADRS scale), symptom-free days Secondary:	Primary: Patients receiving duloxetine and venlafaxine ER experienced similar success rates after six months of treatment, 53 and 57%, respectively (P value 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 (P value not reported). Duloxetine therapy was associated with a greater hospitalization rate compared

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
75 to 225 mg daily for at least 8 weeks			Not reported	to venlafaxine ER therapy, 47 and 43%, respectively (P value not reported). Secondary: Not reported
Soares et al.[41] (2010) Desvenlafaxine 100 to 200 mg/day vs escitalopram 10 to 20 mg/day	AC, DB, MC, RCT Postmenopausal women 40 to 70 years of age with MDD	N=607 Acute phase: 8 weeks Continuation phase: 6 months	Primary: HAM-D_{17} total score, response and remission rates, anxiety scores, QOL, menopause-related symptoms, safety and tolerability Secondary: Not reported	Primary: <u>Acute phase</u> There was no significant difference in HAM-D_{17} total score with desvenlafaxine and escitalopram (-13.63 vs -14.30, respectively; P=0.243). There were no significant differences in secondary efficacy and health outcomes data related to depression between treatment groups. On assessments of menopause-related symptoms, there were no significant between-group differences, and improvements from baseline were comparable for both groups. Significantly higher rates were found for escitalopram compared to desvenlafaxine for HAM-D_{17} remission (48 vs 38%, respectively; P<0.01) and response (73 vs 64%, respectively; P<0.05). No significant differences between the escitalopram and desvenlafaxine groups were observed in rates of response on the MADRS (70 and 67%, respectively) and CGI-I (75 and 70%, respectively). <u>Continuation phase</u> The proportion of women who maintained or improved their HAM-D_{17} response to treatment was similar between the treatment groups (desvenlafaxine, 82%; escitalopram, 80%; P=0.702). There were no significant differences between treatment groups in the proportion of women who achieved HAM-D_{17} remission during the continuation phase or at endpoint (desvenlafaxine, 68%; escitalopram, 61%; P=0.234). There were no significant differences between the desvenlafaxine and

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				escitalopram groups in rates of response on the MADRS (92 and 88%, respectively) and CGI-I (90 and 86%, respectively). No significant differences between groups were found at endpoint in the analyses of secondary efficacy data or core health outcome measures, including assessments of menopause-related symptoms. In both phases, desvenlafaxine and escitalopram were generally safe and well tolerated. Secondary: Not reported
Nierenberg et al.[42] (2007) Duloxetine 60 mg daily vs escitalopram 10 mg daily 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≤0.05). Secondary: Not reported
Pigott et al.[43] (2007) <u>Acute Phase</u> Duloxetine 60 mg/day vs escitalopram 10 mg/day	DB, MC, PC, RCT Patients >18 years of age with MDD	N=684 <u>Acute Phase</u> 8 weeks <u>Extension Phase</u> 24 weeks	Primary: HAM-D_{17}, CGI-S, PGI-I, HAMA, remission rates Secondary: Not reported	Primary: After eight months of treatment, there were no significant differences in efficacy between duloxetine and escitalopram as assessed by mean changes from baseline in the HAM-D_{17} total score and the HAM-D_{17} Maier, anxiety/somatization, and retardation/ somatization subscales. The only HAM-D_{17} subscale with a significant drug difference was the HAM-D_{17} sleep subscale, which demonstrated that escitalopram was associated with a significantly greater improvement in insomnia than duloxetine at the eight-

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Extension Phase Duloxetine 60 to 120 mg/day vs escitalopram 10 to 20 mg/day				month study endpoint. There were no significant differences in efficacy among the treatment groups as assessed by the CGI-S and the PGI-I. After eight months of treatment, there were no significant differences between the treatment groups with regards to anxiety symptoms as measured by the HAMA total score and the HAMA subscales (psychic and somatic). There was no significant difference in remission at eight weeks (duloxetine 40%, escitalopram 33%; P=0.25) or at eight months (duloxetine 70%, escitalopram 75%; P=0.44). Secondary: Not reported
Wade et al.[44] (2007) Escitalopram 20 mg/day vs duloxetine 60 mg/day	DB, RCT Patients 18 to 65 years of age with MDD	N=294 24 weeks	Primary: Mean change in MADRS total score from baseline to week 24 Secondary: MADRS total score, HAM-D_{17}, CGI-I, CGI-S, HAMA scores	Primary: The mean change from baseline in MADRS total scores was –23.4 for escitalopram-treated patients and –21.7 for duloxetine treated patients (P=0.055). Secondary: At week eight, the mean change from baseline in MADRS total scores was –19.5 for escitalopram-treated patients and –17.4 for duloxetine-treated patients (P<0.05). There was no significant difference in the mean change from baseline in HAM-D_{17} (7.13 vs 8.47; P=0.096), HAMA (7.73 vs 8.62; P=0.267), CGI-I (1.76 vs 1.99; P=0.077), CGI-S (2.11 vs 2.28; P=0.214) at 24 weeks between escitalopram-treated patients and duloxetine-treated patients.
Khan et al.[45] (2007) Escitalopram 10 to 20 mg daily	DB, MC, PG, RCT Patients with MDD	N=278 8 weeks	Primary: Change from base-line to week eight in MADRS scores using the LOCF	Primary: At week eight, a significantly greater decrease in MADRS scores (LOCF) was observed in the escitalopram group compared to the duloxetine group (P<0.05). No significant differences in MADRS scores were observed between groups in

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs duloxetine 60 mg daily			Secondary: Not reported	the observed case analysis (P=0.79). Secondary: Not reported
Goldstein et al.[46] (abstract) (2002) Duloxetine, titrated from 20 to 60 mg BID vs placebo vs fluoxetine 20 mg/day	DB, MC, PC, RCT Patients 18 to 75 years of age with MDD	N=173 8 weeks	Primary: HAM-D-17 total score Secondary: MADRS, CGI-S, CGI-I, PGI-I, safety	Primary: Duloxetine was more efficacious 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. Duloxetine was numerically more efficacious to fluoxetine on the primary outcome. Secondary: Duloxetine was numerically more efficacious to fluoxetine on most secondary outcomes. 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).
Detke et al.[47] (2004) Duloxetine 40 or 60 mg BID vs paroxetine 20 mg/day vs placebo	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 more efficacious 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
After acute treatment, patients who had a ≥30% reduction in baseline HAM-D-17 total score were allowed to continue on the same (blinded) treatment for a 6 month continuation phase.				more efficacious 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 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). 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. 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≤0.001 vs placebo for all, P≤0.05 for duloxetine 120 vs 80 mg/day), HAMA (P≤0.01 for duloxetine 80 mg/day vs placebo, P≤0.001 for duloxetine 120 mg/day and paroxetine vs placebo), CGI-S (P≤0.001 for all comparisons), and PGI-I (P≤0.01 for duloxetine 80 mg/day vs placebo, P≤0.001 for duloxetine 120 mg/day and paroxetine vs placebo, P≤0.05 for duloxetine 80 mg/day vs paroxetine) scales compared to patients receiving placebo. 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. 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.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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. In the continuation phase, patients receiving duloxetine 120 mg/day showed 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). 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 ≥5% of patients receiving duloxetine 120 mg/day are constipation, dry mouth, increased sweating, somnolence, nausea, headache, and insomnia. 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.
Goldstein et al.[48] (2004) Duloxetine 20 to 40 mg BID	DB, PC, RCT Outpatients with depression	N=353 8 weeks	Primary: HAM-D Secondary: Adverse effects	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). Duloxetine 40 mg/day was also significantly more efficacious than placebo by

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs paroxetine 20 mg daily vs placebo				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). 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 4.65; P=0.037) and estimated probability of remission (57% for duloxetine 80 mg/day, 34% for paroxetine; P=0.022). 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).
Perahia et al.[49] (2006) Duloxetine 40 mg BID vs duloxetine 60 mg BID vs paroxetine 20 mg daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with MDD	N=392 8 months	Primary: Mean change from baseline in HAM-D-17 Secondary: Discontinuation of study drug due to adverse drug events	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). Paroxetine was not significantly different from placebo (P=0.089) on mean change on the HAM-D-17. 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%).
Rosso et al.[50] (2012) Duloxetine 120 mg/day	RCT, SB Patients ≥18 years of age with MDD who failed	N=49 6 weeks	Primary: Change in HAM-D-17 Secondary:	Primary: There was no significant difference in HAM-D-17 total score among the treatment groups (P=0.793). Secondary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs bupropion ER 300 mg/day	to respond to 2 consecutive antidepressant trials with SSRIs		CGI-S, GAF	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.
Katona C, et al.[51] (2012) Vortioxetine 5 mg QD or duloxetine 60 mg QD vs placebo QD	AC, DB, MC, PC, PG, RCT Patients ≥65 years of age, with a primary diagnosis of MDD per DSM-IV-TR criteria and a MADRS score ≥26	N=453 (N=392 completed the study) 8 weeks	Primary: Change from baseline in HAMD-24 total score at weeks one, two, four, six, and eight. Secondary: Change in baseline from CGI-I, MADRS total score, HAMA and CGI-S at week eight. Cognitive changes from baseline assessed via the RAVLT and DSST at week eight	Primary: The vortioxetine treatment group did not meet the primary endpoint until week six of the study, and it was not reported when the duloxetine treatment group began to separate from placebo for the primary endpoint. The vortioxetine treatment group began to separate on the HAMD-24 scale from placebo at week six (P=0.024). At week eight, vortioxetine 5 mg had a mean change from baseline in HAMD-24 score of -13.7 (P<0.01), and duloxetine 60 mg had a mean change from baseline on the HAMD-24 of -15.8 (P<0.0001). Secondary: Vortioxetine 5 mg and duloxetine 60 mg both met all secondary endpoints at week eight. A change in CGI-I of -0.56 (P<0.001) was reported for the vortioxetine group, along with a decrease in MADRS total change of -4.29 (P<0.001), a decrease in HAMA scores of -2.35 (P<0.01) and a decrease of CGI-S of -0.60 (P<0.001). Duloxetine showed similar results for these secondary endpoints with a P<0.001 for all of these measures. The cognitive measures also showed positive results for both treatment groups. Vortioxetine 5 mg showed a difference from placebo on the DSST change of 2.79 (P>0.05), and vortioxetine showed a difference from placebo in RAVLT for

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				acquisition change of 1.14 (P<0.05) and delayed recall change of 0.47 (P<0.05). The duloxetine group did not show statistical significance for DSST change with a value of 0.77 (no P value reported). The duloxetine group did show statistical significance on the RAVLT for acquisition of change of 1.41 (P<0.01) and delayed recall change of 0.64 (P<0.01)
Mahableshwarkar, et. al.[52] (2013) Vortioxetine 2.5 mg QD or vortioxetine 5 mg QD vs duloxetine 60 mg QD vs placebo QD	DB, PC Adult patients with MDD	N=611 8 weeks	Primary: Change from baseline in the HAM-D24 Secondary: Responder rate, CGI-I), and remission rate; adverse events, ASEX	Primary: Both doses of vortioxetine were associated with declines in HAM-D24 total scores compared to placebo but were not statistically significant. At eight weeks, changes from baseline were [mean]: -10.50 (0.76) placebo, -12.04 (0.74) 2.5 mg vortioxetine, and -11.08 (0.74) 5 mg vortioxetine. Secondary: CGI-I and remission rate were not significantly different from placebo. Duloxetine treatment was associated with declines in HAM-D24 total score [-13.47(0.75); P=0.005] as well as significant improvements in secondary outcome measures vs placebo (P<0.05). The most common adverse events for vortioxetine were nausea, dry mouth, and headache. Rates of sexual dysfunction (ASEX) were 51.0, 37.5, 46.9, and 33.3% in the vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine, and placebo groups, respectively.
Lenox-Smith et al.[53] (2008) Venlafaxine ER 75 to 300 mg/day vs citalopram 20 to 60 mg/day	DB, MC, RCT Patients 18 to 65 years of age with MDD who had not experienced a treatment response to 8 weeks of monotherapy with an adequate regimen of an	N=406 12 weeks	Primary: HAM-D_{21} total score Secondary: MADRS, CGI-S, CGI-I	Primary: There was no significant difference between venlafaxine ER and citalopram on the HAM-D_{21} total score (-17.0 vs -16.5, respectively; P=0.4778). Secondary: There were no significant differences between venlafaxine ER and citalopram on the MADRS total scores (P=0.5002) or CGI-S (P=0.3014), or in the analyses of response (P=0.953). Significant differences between treatment groups were observed for one subscale analysis: more venlafaxine ER patients had a CGI-I score of 1 at week 12 (P=0.024).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	SSRI			
Montgomery et al.[54] (2004) Escitalopram 10 to 20 mg daily vs venlafaxine ER 75 to 150 mg daily	DB, RCT Patients with MDD	N=293 8 weeks	Primary: Change from baseline in MADRS scores Secondary: Not reported	Primary: No significant difference between groups was observed at week eight in MADRS scores. Escitalopram-treated patients achieved remission significantly faster compared to venlafaxine patients in a post-hoc analysis. Secondary: Not reported
Bielski et al.[55] (2004) Venlafaxine ER 225 mg/day vs escitalopram 20 mg/day	DB, RCT Patients with MDD	N=195 8 weeks	Primary: MADRS Secondary: Adverse effects	Primary: There were no significant differences in efficacy, remission rates, or response rates between venlafaxine ER and escitalopram. Mean changes from baseline to endpoint in MADRS total score for escitalopram and venlafaxine ER were –15.9 and –13.6, respectively. Remission (MADRS score of ≤10) rates at endpoint were 41.2% for escitalopram and 36.7% for venlafaxine ER. Response (≥50% reduction from baseline MADRS score) rates for the escitalopram and venlafaxine ER groups were 58.8 and 48.0%, respectively. Secondary: More patients in venlafaxine ER group had treatment-emergent adverse effects compared to escitalopram (85.0 vs 68.4%) but this was not statistically significant and may have been due to rapid titration of the venlafaxine dose. Venlafaxine ER had a higher incidence of discontinuation due to adverse events (16.0 vs 4.1%; P<0.01).
Nemeroff et al.[56] (2007) Venlafaxine 75 to 225 mg/day	DB, MC, PC, RCT Outpatients ≥18 years of age with	N=308 6 weeks	Primary: HAM-D Secondary: Not reported	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 fluoxetine and placebo (P=0.358) and between venlafaxine and fluoxetine

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs fluoxetine 20 to 60 mg/day vs placebo	MDD			(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.[57] (1999) 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 ER 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
Mazeh et al.[58] (2007) Venlafaxine 75 to 300 mg/day vs paroxetine 10 to 60 mg/day	RCT, SB Inpatients ≥65 years of age with MDD who did not respond to two adequate pharmacological treatments for depression	N=30 6 weeks	Primary: CGI, HAM-D, GDS Secondary: Not reported	Primary: Nine patients treated with venlafaxine (60%) and five patients treated with paroxetine (33%) remitted after eight weeks of treatment. Three patients from each group responded without achieving remission after eight weeks of treatment (20%). Four patients treated with venlafaxine (26.7%) and eight patients treated with paroxetine (53.3%) failed to respond.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	during the current depressive episode			Mean score changes from baseline to endpoint for paroxetine were: HAM-D=-12.5, CGI=-2.3, and GDS=-3.2. Mean score changes from baseline to endpoint for venlafaxine were: HAM-D=-19.1, CGI=-2.3, and GDS=-6.0 in the venlafaxine group. Venlafaxine was more effective than paroxetine on CGI and HAM-D measures (P<0.0003). Secondary: Not reported
Richard et al.[59] (2012) Venlafaxine ER, up to a maximum of 225 mg/day vs paroxetine, up to a maximum of 40 mg/day vs placebo	DB, PC, RCT Patients ≥30 years of age with idiopathic PD, without dementia, and depressive disorder or operationally defined subsyndromal depression	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 placebo were apparent for the secondary outcomes (MADRS, BDI-II, and GDS; P≤0.01 for all comparisons). 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. 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.
Hewett et al.[60] (2009) Bupropion ER	DB, MC, PC, RCT Patients 18 to 64	N=576 8 weeks	Primary: Mean change from baseline at week eight in the MADRS	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), -

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
150 mg/day for 4 weeks, then 300 mg/day vs venlafaxine ER 75 mg/day for 4 weeks, then 150 mg/day vs placebo	years of age with MDD		total score (LOCF) 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	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). 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. 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). 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). A larger proportion of patients in the bupropion ER and venlafaxine ER groups were classified as MADRS responders (≥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. CGI-I response rates for both active treatment groups were significantly better 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. 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).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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).
Benkert et al.[61] (1996) Venlafaxine 150 to 375 mg/day vs imipramine 200 mg/day	DB, PG, RCT Hospitalized patients with major depression and melancholia	N=167 6 weeks	Primary: HAM-D, MADRS Secondary: Not reported	Primary: No differences in the response rates on the HAM-D or MADRS were observed between treatments. Among patients who demonstrated a response on the HAM-D, there was a significantly faster onset of response (P=0.036) and sustained response (P=0.018) in the venlafaxine group. The median time to response on the HAM-D among responders was 14 days with venlafaxine and 21 days with imipramine. However, no differences between treatments were observed among responders on the MADRS. Secondary: Not reported
Guelfi et al.[62] (2001) Mirtazapine 15 to 60 mg/day vs venlafaxine 75 to 375 mg/day	DB, MC, RCT Hospitalized patients with severe depressive episode with melancholic features	N=157 8 weeks	Primary: HAM-D, MADRS Secondary: Adverse effects	Primary: A significant difference favoring mirtazapine was found on the HAM-D Sleep Disturbance factor at all assessment points (P≤0.03). 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).
Kok et al.[63] (2007) Venlafaxine ER 75 to 375 mg/day	DB, RCT Inpatients ≥60 years of age with MDD	N=81 12 weeks	Primary: Remission (MADRS ≤10) Secondary: Remission on	Primary: There was no significant difference in remission between the treatment groups as measured by a reduction in MADRS (venlafaxine, 27.5% vs nortriptyline, 36.6%; P=0.381). Secondary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs nortriptyline 25 to 200 mg/day			HAM-D and GDS, response rates	There was no significant difference in remission rates between the treatment groups as measured by HAM-D and GDS (P=NS). There was no significant difference in response rates between the treatment groups as measured by MADRS, HAM-D, GDS, and CGI-I (P=NS).
Rush et al.[64] CO-MED (2011) Escitalopram 10 to 20 mg/day and placebo vs bupropion SR 300 to 400 mg/day and escitalopram 10 to 20 mg/day vs venlafaxine XR 150 to 300 mg/day and 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, QOL, 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 QOL. 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, QOL, 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.[65] CO-MED (2012) Escitalopram 10 to 20 mg/day plus placebo vs	Subgroup analysis of CO-MED Patients 18 to 75 years of age with MDD, with and without general medical	N=665 (49.5% reported having no treated general medical conditions, 23.8%	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, QOL, adverse events Secondary:	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 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:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
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	conditions	reported having 1, 14.8% reported having 2, and 11.9% reported having ≥3) 7 months	Not reported	Not reported
Kerber et al.[66] CO-MED (2012) 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, QOL, 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, QOL, 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
Martinez et al.[67] (2012)	AC, MC, RCT Adult outpatients	N=750 12 weeks	Primary: Remission at week 12 as measured by	Primary: Remission rates derived from the QIDS-SR at week 12 did not significantly differ between the duloxetine and SSRI treatment groups (36 vs 32%,

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Duloxetine 30 to 120 mg QD vs generic SSRIs (citalopram 20 to 40 mg/day, fluoxetine 20 to 80 mg/day, paroxetine 20 to 50 mg/day, or sertraline 50 to 200 mg/day at the investigator's discretion)	with severe MDD		QIDS-SR Secondary: Response as measured by QIDS-SR, probability of response and remission as measured by HAM-D_{17}, BPI, SDS	respectively). The groups did not differ significantly with respect to changes in QIDS-SR scores across 12 weeks of therapy. Secondary: The QIDS-SR estimated probability of response did not differ significantly between duloxetine-treated and SSRI-treated patients (71 vs 64%; P=0.085). On the HAM-D_{17}, patients treated with duloxetine had significantly greater probabilities of response compared to patients treated with SSRIs (73 vs 61%; P=0.001) and remission (53 vs 44%; P=0.034). The NNT for one additional case of remission was 25 for the QIDS-SR, and was 12 for the HAM-D_{17}. The NNT for one additional case of response was 15 for the QIDS-SR, and was 9 for the HAM-D_{17}. Patients treated with duloxetine demonstrated significantly greater mean changes on the HAM-D_{17} total score and HAM-D subscales (anxiety/ somatization, Bech, Maier, and retardation). Improvement in associated painful symptoms was significantly greater with duloxetine compared to SSRIs as measured by the mean change in the BPI 24-hour average pain score in both the pain-enriched cohort of patients (P=0.034) and in the entire study population (P=0.030). Patients receiving duloxetine demonstrated significantly greater improvements on the SDS global functional score (P=0.002), and on each of the individual items that measure work/school (P=0.013), family functioning (P=0.015), and social functioning (P=0.005) compared to SSRIs. Dry mouth and constipation occurred at a significantly greater rate in patients treated with duloxetine vs patients treated with SSRIs (P=0.023 and 0.003, respectively). There was no significant difference between duloxetine and the SSRI group in the occurrence of any of the other most commonly reported treatment emergent adverse events.
Cipriani et al.[68] (2005)	MA (132 trials)	N=9,311	Primary: Number of patients	Primary: On a dichotomous outcome fluoxetine was less effective than sertraline

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Fluoxetine, sertraline, nortriptyline, amitriptyline, venlafaxine, imipramine, nefazodone, citalopram, desipramine, paroxetine, pramipexole, fluvoxamine, trazodone, bupropion, clomipramine, duloxetine, mirtazapine, doxepin	Patients with depression	Duration varied	who responded to treatment (HAM-D, MADRS) Secondary: Tolerability	(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 (SMD 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).
DeSilva et al.[69] (2012) Venlafaxine vs an SSRI	MA Published, randomized, DB, head-to-head trials, which compared venlafaxine and an SSRI in the treatment of MDD in adults	N=26 trials Duration varied	Primary: Remission, response, discontinuation Secondary: Not reported	Primary: MA using a random effect model showed that venlafaxine was more efficacious compared to SSRIs in achieving remission (OR, =1.13; 95% CI, 1.0 to 1.28; P=0.05) and response (OR, 1.17; 95% CI, 1.03 to 1.34; P=0.02). Subgroup analysis found that venlafaxine had a significantly better response rate than fluoxetine (OR, 1.28; 95% CI, 1.05 to 1.55; P=0.01). There were no significant differences in response or remission between venlafaxine and other individual SSRIs. There was no significant difference in all cause discontinuation between venlafaxine and SSRIs (OR, 1.10; 95% CI, 0.97 to 1.25; P=0.15). Venlafaxine had significantly higher discontinuation due to adverse events compared to SSRIs (OR, 1.41; 95% CI, 1.10 to 1.79; P=0.006). Secondary: Not reported

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Walsh et al.[70] (2002) Antidepressants vs placebo	MA Adult outpatients with MDD	N=not specified (75 trials) Variable duration	Primary: HAM-D, CGI Secondary: Not reported	Primary: The mean proportion of patients in the placebo group who responded was 29.7% (range, 12.5 to 51.8). Response was determined by a reduction of at least 50% in their score on the HAM-D and/or CGI rating of markedly or moderately improved. Both the proportion of patients responding to placebo and the proportion responding to medication were significantly positively correlated with the year of publication (for placebo P<0.001; for medication P=0.02). The association between year of publication and response rate was more statistically robust for placebo than medication. Secondary; Not reported
Geddes et al.[71] (2003) Antidepressants vs placebo	MA Studies evaluating relapse prevention of depression	N=4,410 (31 trials) 6 to 36 months	Primary: Proportion of patients relapsing; withdrawal from the trial Secondary: Not reported	Primary: Continuing treatment with antidepressants reduced the odds of relapse by 70% (95% CI, 62 to 78; P<0.00001) compared to treatment discontinuation. The average rate of relapse on placebo was 41% compared to 18% on active treatment. The treatment effect seemed to persist for up to 36 months, although most trials were of 12 months duration, and so the evidence on longer-term treatment requires confirmation. Significantly more participants allocated antidepressants withdrew from the trials than did those allocated to placebo (18 vs 15%, respectively; OR, 1.30; 95% CI, 1.07 to 1.59). Secondary: Not reported
Cipriani et al.[72] (2009) New-generation antidepressants	MA (117 trials) Patients with MMD receiving acute treatment	N=25,928 6 to 12 weeks	Primary: Response (defined as the proportion of patients who had a reduction ≥50%	Primary: *Direct Comparisons* Efficacy favored escitalopram over citalopram; citalopram over reboxetine and paroxetine; mirtazapine over fluoxetine and venlafaxine; sertraline over fluoxetine; and venlafaxine over fluoxetine and fluvoxamine.

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(bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine)			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 Secondary: Not reported	For dropouts, fluoxetine was better tolerated than reboxetine and citalopram than sertraline. *Multiple-treatments MA* 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. Duloxetine and paroxetine were less well tolerated than escitalopram and sertraline; fluvoxamine was less well tolerated than citalopram, escitalopram, 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. Mirtazapine, escitalopram, venlafaxine, and sertraline were more efficacious than fluoxetine, and fluoxetine was more efficacious than reboxetine. Fluoxetine was better tolerated than reboxetine. 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. 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%). 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%),

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				venlafaxine (0.9%), duloxetine (0.7%), fluvoxamine (0.4%), paroxetine (0.2%), and reboxetine (0.1%). Secondary: Not reported
Fibromyalgia				
Mease et al.[73] (2010) 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; P=0.580). The mean change in the BPI average pain severity score increased by 0.19 point during the extension phase. Secondary: Not reported
Russell et al.[74] (2008) Duloxetine 20 mg/day	DB, MC, PC, RCT Patients ≥18	N=502 6 months	Primary: Pain severity (BPI), PGI-I	Primary: 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,

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs duloxetine 60 mg/day vs duloxetine 120 mg/day vs placebo	years of age with fibromyalgia		Secondary: FIQ, CGI-S, tender-point pain assessments, MFI, HAM-D-17, SDS, SF-36, EQ-5D	respectively; P≤0.05 and P≤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≤0.05]; duloxetine 60 mg/day, -1.98 [P≤0.05]; duloxetine 120 mg/day, -2.26 [P≤0.01]). 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≤0.01 and P≤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≤0.01) and duloxetine 120 mg/day groups (2.93; P≤0.05), but not the duloxetine 60 mg/day group (3.08; P value not significant) compared to the placebo group (3.37). Secondary: After three months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (60 and 120 mg; P≤0.01 and P≤0.001, respectively), SF-36 mental component score (120 mg; P≤0.05), and some of the MFI domains (20, 60, 120 mg; P≤0.05, P≤0.01, and P≤0.001) compared to placebo-treated patients. There were no differences between duloxetine and placebo on other secondary efficacy and health outcome measures. After six months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (20/60 mg/day; P≤0.05, 60 mg/day; P≤0.01, 120 mg/day; P≤0.001) and MFI mental fatigue domain (20/60 mg/day; P≤0.05, 60 mg/day; P≤0.05, 120 mg/day; P≤0.01). The other efficacy and health outcome measures that achieved significance in the duloxetine treatment 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).

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				Response rates (defined as a ≥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%). 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.
Arnold et al.[75] (2009) Duloxetine 60 to 120 mg/day vs placebo	DB, MC, PC, RCT (pooled analysis of 4 trials) Outpatients ≥18 years of age with fibromyalgia and a score ≥4 on the average pain severity item of the BPI	N=1,332 12 to 15 weeks	Primary: Pain severity (BPI) Secondary: BPI pain interference items, FIQ, CGI-S, PGI-I, HAM-D, SF-36, SDS, MFI	Primary: In both depressed and nondepressed patients, significantly more duloxetine-treated patients achieved ≥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 ≥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). 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 assessments (P value not significant). 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

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				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. 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. 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 (P=0.14). 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 (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.45).
Arnold et al.[76] (2012) Duloxetine 30 mg/day	DB, PC, RCT Patients meeting the criteria for primary fibromyalgia as defined by the	N=308 12 weeks	Primary: Average pain severity item from the BPI-Modified Short Form, Secondary: PGI-I,	Primary: Duloxetine-treated patients did not have a statistically significant BPI-Modified Short Form average pain severity reduction vs placebo-treated patients (-2.04 vs -1.70; P=0.202). Secondary: There was a significant difference between duloxetine-treated and placebo-

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	American College of Rheumatology		FIQ total score and those measuring pain, depression, anxiety, health outcomes, and safety	treated patients (P<0.05) for the PGI-I endpoint score (2.97 vs 3.35) and the changes in FIQ total score (-14.62 vs -9.75) and the SF-36 mental component score. Discontinuations due to adverse events did not differ significantly between treatment groups; nausea and dry mouth were the only adverse events with a significantly higher incidence with duloxetine vs placebo.
Hauser et al.[77] (2013) Duloxetine or milnacipran vs placebo	MA, SR (10 RCTs) Adult patients >18 years of age with clinical diagnosis of fibromyalgia syndrome by any published, recognized and standardized criteria	N=6,038 Study duration had to be >4 weeks	Primary: Reduction in pain (50%), fatigue, sleep problems, disease-related QOL as measured by total score of FIQ, safety Secondary: 30% reduction in pain, depression, anxiety, disability, sexual function, PGI-C or CGI, cognitive disturbances, tenderness	Primary: Duloxetine and milnacipran had a small effect over placebo in reducing pain (SMD, -0.23; 95% CI, -0.29 to -0.18; 6.1% relative improvement; P<0.001). One-hundred and ninety-two participants per 1,000 on placebo reported an at least 50% pain reduction compared to 286 per 1,000 on duloxetine or milnacipran (RR, 1.49; 95% CI, 1.35 to 1.64; NNT, 11; 95% CI, 9 to 15; P<0.0001). Duloxetine and milnacipran did not reduce fatigue substantially (SMD, -0.14; 95% CI, -0.19 to -0.08; 2.5% relative improvement; NNT, 17; 95% CI, 12 to 29; P<0.001), and did not improve QOL substantially (SMD, -0.20; 95% CI, -0.25 to -0.14; 4.6% relative improvement; NNT, 12; 95% CI, 9 to 17; P<0.001) compared to placebo. There were no statistically significant differences between either duloxetine or milnacipran and placebo in reducing sleep problems (SMD, -0.07; 95% CI, -0.16 to 0.03; 2.5% relative improvement; P=0.15). Secondary: Duloxetine and milnacipran had a significant effect over placebo in 30% pain reduction (RR, 1.36; 95% CI, 1.26 to 1.46; P<0.0001). Duloxetine and milnacipran did not reduce depression substantially (SMD, -0.15; 95% CI, -0.21 to -0.10; P<0.001), and did not improve disability substantially (SMD, -0.22; 95% CI, -0.28 to -0.16; P<0.001) compared to placebo. There were no statistically significant differences between either duloxetine or milnacipran and placebo in reducing anxiety (P=0.54).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Out of two studies that reported on sexual function, one study lacked data for reporting and the other study found no difference in reducing sexual problems between milnacipran and placebo. Duloxetine and milnacipran did not improve PGI-C substantially (SMD, -0.27; 95% CI, -0.33 to -0.21; P<0.001), did not have a substantial effect on cognitive disturbances (SMD, -0.15; 95% CI, -0.21 to -0.10; P<0.001), and did not substantially raise the tender point pain threshold (SMD, -0.23; 95% CI, -0.35 to -0.12; P<0.001), compared to placebo. Dropout rates due to adverse events were significantly higher in duloxetine or milnacipran groups at 20.6% compared to 10.9% in the placebo groups (RR, 1.83; 95% CI, 1.53 to 2.18; NNH, 11; 95% CI, 9 to 13; P<0.001). There was no statistically significant difference in serious adverse events between either duloxetine or milnacipran and placebo (RR, 0.78; 95% CI, 0.55 to 1.12; P=0.15). The most frequently reported symptoms leading to stopping medication were nausea, dry mouth, constipation, headache, somnolence/dizziness and insomnia.
Clauw et al.[78] (2008) Milnacipran 100 mg daily, administered twice daily in divided doses vs milnacipran 200 mg daily, administered BID in divided doses vs	DB, MC, PC, RCT Patients 18 to 70 years of age with fibromyalgia	N=1,196 15 weeks	Primary: Efficacy as determined by rates of fibromyalgia composite responders (defined as ≥30% improvement from baseline in the morning-recall VAS pain score, a PGIC rating of much improved or very much improved, and a ≥6-point	Primary: At week 15, a significantly greater proportion of patients treated with either milnacipran 100 or 200 mg were fibromyalgia composite responders compared to those who received placebo (P=0.01 and P=0.02, respectively). Significantly greater proportion of patients receiving either the 100 or 200 mg milnacipran dose were fibromyalgia pain composite responders compared to placebo (P=0.03 and P=0.004, respectively). Secondary: Both milnacipran doses were associated with significant improvement in the time-weighted averages of the weekly mean morning-recall pain scores (P<0.001) and PGIC scores (P<0.001) compared to placebo. Time-weighted averages of SF-36 PCS scores indicated significant improvement with milnacipran 100 mg/day (P<0.001).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
placebo, administered BID in divided doses			improvement in the SF-36 PCS score by week-15); fibromyalgia pain composite responders (defined as ≥30% improvement from baseline in the morning-recall VAS pain score and a PGIC rating of much improved or very much improved) Secondary: Time-weighted averages of the weekly mean morning-recall pain scores and PGIC scores, time-weighted averages of SF-36 PCS scores, SF-36 PCS and pain response rates, weekly averages of pain scores, change from baseline in FIQ total score, and side effects	Compared to placebo, both milnacipran 100 and 200 mg were associated with a significantly greater mean change in pain scores from baseline (P=0.03 and P=0.002, respectively) and pain response (≥30% improvement from baseline) (P=0.009 and P<0.001, respectively). A significant reduction in pain was observed one week after therapy initiation in both milnacipran treatment groups (P<0.05). Maximum pain relief occurred within nine weeks of study onset. The PGIC response rate favored milnacipran, with OR of 1.94 (95% CI, 1.37 to 2.74) for milnacipran 100 mg and 2.19 (95% CI, 1.55 to 3.11) for milnacipran 200 mg. At week 15, significantly more patients who received milnacipran 100 mg were SF-36 PCS responders (≥6-point improvement from baseline) compared to placebo (32.3 vs 25.4%; P=0.03). The difference between milnacipran 200 mg and placebo did not reach statistical significance. Milnacipran 100 mg was associated with a significant improvement from baseline in SF-36 PCS mean scores (P=0.004) whereas milnacipran 200 mg was not. Milnacipran was associated with significant improvements compared to placebo in the change from baseline in FIQ total score (milnacipran 100 mg; P<0.001; milnacipran 200 mg; P=0.008). Treatment-related adverse effects occurred in 89.7% of patients receiving milnacipran 100 mg, 87.4% of the milnacipran 200 mg group, and 79.1% of the placebo group (P value not reported). The most common adverse effects included nausea, constipation, hot flush, dizziness, palpitations, hyperhidrosis, hypertension, vomiting and migraine.
Mease et al.[79]	DB, MC, PC,	N=888	Primary:	Primary:

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2009 Milnacipran 100 mg daily, administered BID in divided doses vs milnacipran 200 mg daily, administered BID in divided doses vs placebo, administered BID in divided doses	RCT Patients 18 to 70 years of age with fibromyalgia	6 months	Composite responder rate and composite responder rate for pain Secondary: Pain severity assessed by weekly average or 24 hour morning recall pain scores, weekly average of real-time pain scores, and weekly recall, PGIC, SF-36 PCS, SF-36 FIQ, MFI, score, Sleep Problem Indices, adverse effects	At 15 weeks, a significantly greater percentage of patients receiving milnacipran 100 and 200 mg daily were fibromyalgia composite responders compared to those receiving placebo (P=0.028, P=0.017, respectively). At 27 weeks, the difference between the milnacipran and placebo groups was not statistically significant (P>0.05). At 15 and 27 weeks, a significantly higher percentage of patients receiving milnacipran 200 mg daily were fibromyalgia composite responders for pain compared to those receiving placebo (P=0.032, P=0.034, respectively). Secondary: At 15 weeks, patients treated with milnacipran 200 mg daily experienced significant improvements from baseline compared to the placebo group in the weekly average or 24 hour morning recall pain scores, weekly average of real-time pain scores, and weekly recall pain scores (P<0.05). Improvement in pain was generally similar between the 200 and the 100 mg milnacipran groups. Maximum pain relief was observed after nine9 weeks of therapy in both milnacipran groups and continued throughout the study. A significantly greater percentage of patients receiving milnacipran 100 and 200 mg therapy experienced ≥30% improvement in pain relief compared to the placebo group (P=0.028, P=0.001, respectively). A significantly greater percentage of patients receiving milnacipran 200 mg therapy experienced ≥50% improvement in pain relief compared to the placebo group (P=0.021). There was a significantly greater improvement in PGIC scores from baseline at week-15 among patients receiving milnacipran 100 and 200 mg daily compared to placebo (P=0.009, P<0.001, respectively). At 15-weeks of follow-up, significant improvements in the SF-36 domains of physical functioning, bodily pain, and mental health were observed with milnacipran 200 mg daily compared to placebo (P<0.05).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				At 15 and 27-weeks, patients receiving milnacipran 200 mg daily experienced significant improvements in fatigue, measured by the MFI score, and cognition, measured by the change from baseline, compared to placebo (P<0.05). Patients receiving milnacipran 100 mg daily experienced a significant reduction in fatigue at 15 weeks, compared to placebo (P=0.042). There was no difference between the milnacipran and placebo groups in the quality of sleep, measured by the Sleep Problem Indices. Treatment-related adverse effects occurred in 83.9% of patients receiving milnacipran 100 mg, 90.7% of the milnacipran 200 mg group, and 85.2% of the placebo group (P value not reported). Nausea was the most commonly reported adverse effect. Other common adverse effects included constipation, hyperhidrosis, hot flush, vomiting, increased heart rate, dry mouth, palpitations, and hypertension.
Vitton et al.[80] (2004) Milnacipran QD or BID up to 200 mg daily vs placebo QD or BID	DB, MC, PC, RCT Patients 18 to 70 years of age with fibromyalgia	N=125 12 weeks	Primary: Magnitude of improvement in patient reported pain score (VAS and an anchored logarithmic scale) Secondary: Change in patient global impression of change, FIQ, and Jenkins sleep scale scores, and adverse effects	Primary: According to weekly scores, 37.0% of BID milnacipran-treated patients reported at least 50.0% reduction in pain intensity, compared to 14.0% of placebo-treated patients (P<0.05). According to the responder analysis, BID milnacipran was significantly more effective as an analgesic compared to the QD regimen. Secondary: Over 70.0% of patients randomized to milnacipran, either QD or BID exhibited improvement in the global impression of change, as opposed to 38.0% of patients in the placebo group (P<0.05). Therapy with milnacipran did not result in statistically significant differences in the total FIQ scores. Milnacipran therapy was associated with statistically significant improvements in

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				pain (P=0.042), fatigue (P=0.017) and morning stiffness (P=0.003) compared to the placebo group. Milnacipran therapy was associated with improvements in the total sleep scores, but these improvements did not achieve statistical significance (P value not reported). Milnacipran therapy was associated with improvements in each of the components of the Jenkins inventory compared to placebo (P value not reported). Therapy discontinuation due to adverse effects occurred in 14.4% of patients. Side effects such as nausea, abdominal pain, headache, dizziness, hot flushes and palpitation were more frequent among patients taking milnacipran 200 mg once daily compared to those receiving the twice daily regimen.
Hauser et al.[81] (abstract) (2010) Duloxetine, milnacipran or pregabalin vs placebo	MA (17 RCTs) Patients with fibromyalgia syndrome	N=7,739 Not noted (efficacy noted up to 6 months)	Primary: Symptom reduction (pain, fatigue, sleep disturbance, depressed mood, reduced HRQoL) and adverse events Secondary: Not reported	Primary: Duloxetine, milnacipran and pregabalin were superior to placebo for the outcomes noted except for the following: duloxetine for fatigue, milnacipran for sleep disturbance, and pregabalin for depressed mood were not more efficacious to placebo. There were no significant differences between duloxetine, milnacipran, or pregabalin for 30% pain relief per adjusted indirect comparisons. Differences in average symptom reduction were noted as follows: duloxetine and pregabalin were more efficacious to milnacipran in reduction of pain and sleep disturbances; duloxetine was more efficacious to milnacipran and pregabalin in reducing depressed mood; and milnacipran and pregabalin were more efficacious to duloxetine in reducing fatigue. Secondary: Not reported
Generalized Anxiety Disorder				
Rynn et al.[82]	DB, PC, RCT	N=327	Primary:	Primary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
(2008) Duloxetine 60 or 120 mg/day vs placebo	Adult patients with GAD	10 weeks	HAMA total score Secondary: Response rate (HAMA total score reduction ≥50% from baseline), CGI-I, SDS, safety	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≤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 32.0 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.[83] (2007) Duloxetine 60 or 120 mg/day vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with GAD of at least moderate severity	N=513 9 weeks	Primary: HAMA total score Secondary: SDS; HAMA psychic and somatic anxiety factor scores; HAMA response,	Primary: Both doses of duloxetine demonstrated significantly greater improvements in HAMA total scores compared to placebo (P≤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 weeks after treatment initiation, and remained significant at each subsequent visit.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
			remission, and sustained improvement rates, safety	Secondary: Both doses of duloxetine demonstrated significantly greater functional improvements in SDS global and specific domain scores compared to placebo (P≤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. Both doses of duloxetine demonstrated significantly greater improvements in HAMA psychic and somatic anxiety factor scores compared to placebo (P≤0.001 for all comparisons). 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≤0.001 for both), remission (31, 38, and 19%; P≤0.01 for duloxetine 60 mg/day vs placebo and P≤0.001 for duloxetine 120 mg/day vs placebo), and sustained improvement rates (64, 67, and 43%; P≤0.001 for both) compared to placebo. There were no significant differences between the two doses of duloxetine on any of the efficacy outcome measures. 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≤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.
Davidson et al.[84] (2008) Duloxetine vs	DB, PC, RCT Patients ≥18 years of age with moderate to severe GAD	N=533 (N=887 OL phase) 26 weeks	Primary: Time to relapse (increase in CGI-S rating ≥2 points from randomization to a score ≥4 while	Primary: Significantly more placebo-treated patients (41.8%) met relapse criteria compared to duloxetine-treated patients (13.7%; P≤0.001). Among patients who did relapse, duloxetine-treated patients had a longer time to relapse compared to patients who were switched to placebo (P≤0.001).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
placebo All patients received OL duloxetine for 26 weeks. Treatment responders (≥50% reduction in HAMA total score to ≤11 and “much”/”very much improved” ratings for the last 2 visits of the OL phase.			meeting criteria for GAD or by discontinuation due to lack of efficacy) Secondary: HAMA total score, HAMA psychic factor score, HAMA somatic factor scores, HADS-A, CGI-I, PGI-I, SDS, EQ-5D VAS, safety	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≤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≤0.001). 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≤0.001 for both). 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≤0.001). By endpoint, mean SDS global functioning impairment score with placebo had significantly increased into the range indicating mild to moderate impairment (P≤0.001). 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≤0.001 for all comparisons) compared to patients who continued duloxetine. During the OL phase, 15 treatment-emergent adverse events occurred at a frequency of ≥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. During the DB, continuation phase patients experienced discontinuation-emergent adverse events as the study medication was being withdrawn. Compared to patients receiving duloxetine, dizziness was the only adverse

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				event to occur significantly more often with patients receiving placebo (9.9 vs 3.7%; P≤0.05). No significant increases in pulse rate, DBP, or SBP 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.
Hartford et al.[85] (2007) Duloxetine 60 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	DB, MC, PC, RCT Outpatients ≥18 years of age with GAD	N=487 10 weeks	Primary: HAMA total score 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	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. 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). 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). 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). 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%). More venlafaxine ER-treated patients met remission criteria (30%) than placebo-treated patients (19%; P<0.05). The difference was not significant for duloxetine compared to placebo (23%; P value not significant).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Sustained improvement rates were greater with duloxetine (55%) and venlafaxine ER (54%) compared to placebo (39%; P<0.01). 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).
Nicolini et al.[86] (2009) Duloxetine 20 mg/day vs duloxetine 60 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	DB, MC, PC, RCT Outpatients ≥18 years of age with GAD	N=581 10 weeks	Primary: HAMA total score Secondary: HAMA psychic and somatic factor scores, SDS, HAMA, CGI-I, PGI-I	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≤0.01]; duloxetine 60 to 120 mg/day, -15.3 [P≤0.001]; venlafaxine ER, -15.5 [P≤0.001]; placebo -11.6). 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≤0.01]; duloxetine 60 to 120 mg/day, -8.7 [P≤0.001]; venlafaxine ER, -8.6 [P≤0.001]; placebo -6.0). 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≤0.05]; venlafaxine ER, -7.0 [P≤0.01]; placebo -5.5). 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. 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). Overall improvement ratings at endpoint were greater for duloxetine-treated

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				patients (20 or 60 to120 mg/day) and venlafaxine ER-treated patients compared to placebo-treated patients by the CGI-I scores (P<0.001 for all comparisons). 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). 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). 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).
Bose et al.[87] (2008) Escitalopram 10 to 20 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	DB, PC, RCT Outpatients 18 to 65 years of age with GAD	N=404 8 weeks	Primary: Change from baseline to week eight in the HAMA total score Secondary: HAMA psychic anxiety subscale, CGI-I, CGI-S, VAS, HADS QOL, SDS	Primary: The mean change in HAMA total score (LOCF) for escitalopram and venlafaxine ER vs placebo was -1.52 (P=0.09) and -2.27 (P=0.01), respectively at week eight. The mean change in HAMA total score for escitalopram and venlafaxine ER vs placebo was -1.92 (P=0.033) and -3.02 (P=0.001), respectively at week eight. Secondary: Neither escitalopram nor venlafaxine produced greater HAMA response or remission than placebo (response: 52.8 and 52.0% for escitalopram and venlafaxine, respectively vs 42.2% for placebo; remission: 31.2% for both escitalopram and venlafaxine vs 23.7% for placebo; P>0.05 vs placebo, LOCF). Both escitalopram and venlafaxine had significantly higher CGI-I response rates than the placebo (escitalopram 60.0%, venlafaxine 65.6%, placebo 45.9%, P<0.05, LOCF). Both groups had higher CGI-S and HADS response rates compared to placebo.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				There was no significant difference in VAS, QOL or SDS for escitalopram compared to placebo (LOCF). There was no significant difference in VAS or QOL for venlafaxine compared to placebo (LOCF).
Schmitt et al.[88] (2005) Venlafaxine, paroxetine, imipramine, trazodone, diazepam, sertraline	MA RCTs evaluating antidepressants in GAD	N=2,238 8 to 28 weeks	Primary: Absence of treatment response (defined as absence of sufficient symptoms to meet diagnostic criteria for GAD) Secondary: Acceptability of the treatment as measured by the number of people dropping out during the trial	Primary: 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. 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). 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). 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). 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);

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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.[89] (2007) 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 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. 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. 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. Secondary: Not reported
Musculoskeletal Pain				
Skljarevski et al.[90] (2010)	ES Patients ≥18	N=181 41 weeks	Primary: Reduction of pain severity (BPI 24-	Primary: For patients who received duloxetine during the initial 13-week trial, pain reduction continued during the extension phase. The mean change in BPI

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Duloxetine 60 to 120 mg QD	years of age with chronic low back pain		hour average pain rating) 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)	average pain in the extension phase was -0.97 (P<0.001). Secondary: The 30%, 50%, and sustained response rates were ~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 PC phase duloxetine responders still met response criteria at the end of the 41-week extension phase. The BPI average pain, worst pain, least pain, pain right now, and average interference all showed significant within-group improvement for both treatment groups. Both treatment groups showed significant improvement on the RMDQ-24 measures, CGI-S measures, and most of the health outcome assessments. No significant change was observed in the BDI total score and HADS depression score. Duloxetine was well tolerated with no new safety findings reported.
Skljarevski et al.[91] (2010) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with chronic low back pain	N=236 13 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating) Secondary: PGI-I, RMDQ-24, BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36), WPAI	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; P=0.016 at week four; -2.06 vs -1.17, respectively; P=0.001 at week seven; and -2.32 vs -1.50, respectively; P=0.004 at week 13). 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; P=0.007 at week four; 2.82 vs 3.32, respectively; P=0.001 at week seven; 2.59 vs 3.16, respectively; P=0.001 at week 13). There was a significant difference in RMDQ-24 scores at endpoint with duloxetine compared to placebo (-3.60 vs -1.93, respectively; P=0.009).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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. There was no significant difference in the CGI-S and Athens Insomnia Scale scores among the treatment groups. There was no significant difference in response rates with duloxetine compared to placebo (30% response: 53.2 vs 40.0%, respectively; P=0.060 and 50% response: 38.5 vs 27.0%, respectively; P=0.087). The depression and anxiety scores were not significantly changed from baseline to endpoint. The improvement in BPI average pain was because of the 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. The United Kingdome 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. In the WPAI, work activity impairment was the only item that significantly (P=0.002) improved with duloxetine compared to placebo. 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.
Chappell et al.[92] (2009)	DB, MC, PC,	N=231	Primary:	Primary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Duloxetine 60 to 120 mg QD vs placebo	RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month	13 weeks	Mean changes in the weekly mean 24-hour average pain score Secondary: Patients' perceived improvement as measured by PGI-I and on the change in patients' functioning as measured by the WOMAC physical functioning 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	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). 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). Secondary: There was a significant improvement with duloxetine in most secondary endpoints compared to placebo. Mean changes in BDI-II and HADS-A did not differ significantly between treatment groups. 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. 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.
Chappell et al.[93] (2010) Duloxetine 60 to 120 mg QD	DB, MC, PC, RCT Patients ≥40 years of age with	N=256 13 weeks	Primary: BPI 24-hour average pain rating	Primary: There was a significant reduction in the BPI average pain rating with duloxetine compared to placebo at all time points (P≤0.001). The BPI average pain response rates (≥30% pain reduction from baseline to

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	osteoarthritis of the knee and pain for ≥14 days/month		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, WOMAC pain and stiffness subscales, BPI-S and BPI-I, response to treatments, health outcomes, safety	endpoint) were significantly higher with duloxetine (65.3%) compared to placebo (44.1%; P≤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). 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. The weekly mean 24-hour worst pain ratings were significantly improved with duloxetine compared to placebo. Patients receiving duloxetine experienced greater improvements in many secondary endpoints compared to placebo, including CGI-S, BPI-S items, and 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). 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. Both the United Kingdome 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. The frequency of nausea, constipation, and hyperhidrosis were significantly

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				higher in the duloxetine group (P≤0.05). Significantly more duloxetine-treated patients discontinued therapy because of adverse events (P=0.002).
Skljarevski et al.[94] (2010) Duloxetine 60 mg QD vs placebo	DB, PC, RCT Patients ≥18 years of age with chronic low back pain	N=401 12 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating) Secondary: PGI-I, RMDQ-24, CGI-S, BPI-S, BPI-I, response rates, health outcomes (EQ-5D and SF-36)	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≤0.001). 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). There was no significant difference in RMDQ-24 scores with duloxetine compared to placebo (-2.69 vs -2.22, respectively; P=0.255). There was no significant difference in CGI-S among the treatment groups. 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. A greater percentage of patients receiving duloxetine reported ≥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. 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≤0.001), anger-hostility (P≤0.001), vigor-activity (P=0.003), confusion-bewilderment (P=0.006), and total mood disturbance (P≤0.001). Changes in depression-dejection and fatigue-inertia states were not significant.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				The change in EQ-5D was significantly different between duloxetine and placebo with the United Kingdome index (P≤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≤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. 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. 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). Nausea and dry mouth were the most common treatment-emergent adverse events with rates significantly higher in duloxetine-treated patients.
Skljarevski et al. [95] (2009) Duloxetine 20, 60, or 120 mg/day vs placebo	DB, MC, PC, RCT Adult patients with non-radicular chronic low back pain	N=404 13 weeks	Primary: Weekly mean 24 hour average pain (duloxetine 60 mg/day vs placebo) Secondary: RMDQ-24, PGI-I, BPI, safety	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. 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. Secondary: Patients overall improvement (PGI-I) was greater for patients receiving duloxetine 60 mg/day, and improvement in physical functioning (RMDQ-24) was

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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. 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).
Frakes et al.[96] (2011) Duloxetine 60 to 120 mg QD vs placebo Patients were also required to take an NSAID and PPI.	DB, MC, PC, RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month and who were using NSAIDs on most days of the week	N=524 10 weeks	Primary: Weekly mean of the daily average pain rating at week eight Secondary: Endpoint PGI-I, change in WOMAC physical function	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 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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).
Mazza et al.[97] (2010) Escitalopram 20 mg QD vs duloxetine 60 mg QD	RCT Adult patients with non-radicular chronic low back pain	N=85 13 weeks	Primary: Weekly mean of the 24-hour average pain ratings Secondary: CGI-S and the 36-item SF-36	Primary: The mean change in average weekly pain did not differ significantly between the escitalopram group and duloxetine group (P=0.15). The average weekly pain response rates (30% reduction from baseline to end point) showed no significant difference between the two groups (P=0.12). There were no significant differences between groups in 50% response rates. Secondary: Both escitalopram and duloxetine demonstrated significant improvement on CGI-S and SF-36. No patient experienced serious adverse events and the incidence of side effects did not differ significantly between treatment groups.
Neuropathic Pain				
Yan et al.[98] (2010) Duloxetine 60 to 120 mg daily vs placebo	DB, PC, RCT Adult Chinese patients with diabetic peripheral neuropathic pain and BPI 24-hour average pain severity rating ≥4	N=215 12 weeks	Primary: Change from baseline to endpoint in BPI average pain score Secondary: BPI-S and BPI-I, PGI-I, CGI-S, EQ-5D, Athens Insomnia Scale	Primary: Mean change from baseline to endpoint in BPI 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). Secondary: Duloxetine-treated patients experienced significant improvement in PGI-I (2.32±0.11 vs 2.64±0.10; P=0.028), CGI-S (-1.24±0.11 vs -0.99±0.11; P=0.036), AUC for pain relief, BPI-S pain right now (-2.72±0.26 vs -1.99±0.25; P=0.012), and BPI-I walking ability (-2.45±0.24 vs -1.82±0.23; P=0.016).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Patients receiving duloxetine had numerically higher 30 and 50% response rates on BPI 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%). All other secondary efficacy measures, including health outcomes measures, were numerically but not significantly improved in patients receiving duloxetine compared to patients receiving placebo.
Armstrong et al.[99] (2007) 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, BPI, EQ-5D) Secondary: Not reported	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. Duloxetine 60 mg QD and 60 mg BID were significantly more efficacious to placebo at reducing scores in all BPI-I items thereby indicating improvements in all seven items, with similar results demonstrated for the ITT population. 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 QOL measures. Secondary: Not reported
Kajdasz et al.[100] (2007)	Post-hoc analysis of 3 DB, MC, PC,	N=1,139	Primary: Response rate	Primary: NNTs based on 50% reduction for patients receiving duloxetine 60 mg QD and

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Duloxetine 20 or 60 mg QD, or 60 mg BID vs placebo	RCT Patients with diabetic peripheral neuropathic pain	12 weeks	(defined as ≥30 and ≥50% reductions from baseline in weekly mean of the 24-hour average pain severity scores) Secondary: NNH (based on rates of dis-continuation due to adverse events)	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 LOCF. 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. 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.
Wernicke et al.[101] (2007) 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 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. 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. Patients randomized to duloxetine therapy experienced higher incidences of palpitations (P=0.004), tachycardia (P=0.007), orthostatic hypotension

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				(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. Secondary: Not reported
Lunn et al.[102] (2009) Duloxetine vs placebo or control Only outcomes for painful peripheral neuropathy are reported.	SR (6 RCTs) Patients with painful peripheral neuropathy or chronic pain conditions	N=2,200 ≥8 weeks	Primary: Short term (≤12 weeks) improvement in pain Secondary: Long term (>12 weeks) improvement in pain, improvement in short and long term pain ≥30%, improvement in any validated QOL score ≥30%	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 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. Secondary: None of the included trials of painful diabetic neuropathy included outcomes >12 weeks. 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). Trials that included QOL 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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 WMD on the mental summary component was significantly greater only with 120 mg/day (2.23; 95% CI, 0.69 to 3.77). The WMD 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 PGI-C and pain at rest, and two reported the bodily pain index. The WMD for each outcome was significant and similar in magnitude for 60 and 120 mg/day. However, a clinically meaningful differences in the PGI-C is suggested as one point and hence the change associated with 60 mg/day (-0.59; 95% CI, -0.78 to -0.41) 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.
Kaur et al.[103] (2011) Duloxetine 20 to 60 mg QD for 6 weeks vs amitriptyline 10 to 50 mg QD at bedtime for 6 weeks	AC, DB, RCT, XO Patients 18 to 75 years of age with type 2 diabetes who had painful diabetic neuropathy for ≥1 month	N=58 14 weeks	Primary: Reduction in the median pain score from baseline Secondary: Assessment of pain by McGill Pain Questionnaire, overall improvement score, 24-point HAM-D, change in sleep pattern, and patient self-evaluation of change in PGI-C scale	Primary: There was a significant improvement in pain at six weeks with both treatments compared to their baseline values (P<0.001 for both). For duloxetine, 59% of patients showed good improvement, 22% showed moderate improvement, and 9% showed mild improvement. For amitriptyline, 55% of patients showed good improvement, 24% showed moderate improvement, and 16% showed mild improvement. Overall pain relief of >30% was observed in 64% of patients receiving duloxetine and 62% of patients receiving amitriptyline. A >50% improvement was seen in 50% of patients receiving duloxetine and 55% of patients receiving placebo. Secondary: There was no significant difference in efficacy among the treatment groups as assessed by the McGill Pain Questionnaire and Likert scale. Significant improvement in sleep and overall well being was observed with both drugs (P<0.001 for both).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Overall, 48% of patients preferred duloxetine compared to 36% of patients who preferred amitriptyline (P=0.18). Based on pain relief and tolerability, 5, 14 and 30% of patients preferred duloxetine 20, 40, and 60 mg, respectively. A total of 5, 22, and 9% of patients preferred amitriptyline 10, 25, and 50 mg. The number of mild treatment-emergent adverse effects was higher with duloxetine compared to amitriptyline (P<0.02). The number of moderate to severe treatment emergent adverse event was higher with amitriptyline (P<0.01). Dry mouth was significantly more common with amitriptyline that duloxetine (55 vs 24%, respectively; P<0.01).
Wernicke et al.[104] (2007) Duloxetine 60 mg BID vs routine care (gabapentin, amitriptyline, and venlafaxine)	ES, OL, RCT Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes	N=293 52 weeks	Primary: Not reported Secondary: Health outcomes	Primary: Not reported 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) subscales. There were no significant treatment-group differences observed on the EQ-5D questionnaire. 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 to be 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				incidence of these events. 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. 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. There were no significant treatment-group differences observed in the mean change in the Michigan Neuropathy Screening Instrument score from baseline to endpoint. 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). There were no significant treatment-group differences observed for any of the ophthalmologic exam measures. 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. There was no significant treatment-group difference observed in the mean change from baseline to endpoint vital signs and weight. One duloxetine-treated patient and one routine care-treated patient met the definition for sustained elevation in SBP, and there were no significant

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				differences between treatments. 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).
Raskin et al.[105] (2006) Duloxetine 60 mg BID vs routine care (gabapentin, amitriptyline, and venlafaxine)	ES, OL, RCT Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes	N=237 52 weeks	Primary: Not reported Secondary: SF-36, EQ-5D	Primary: Not reported Secondary: No significant treatment-group differences were observed in the SF-36 subscales or in the EQ-5D questionnaire.
Boyle et al.[106] (abstract) (2012) Duloxetine 60 mg/day vs amitriptyline 50 mg/day vs pregabalin 300 mg/day	AC, DB, PG, RCT Patients ≥18 years of age with diabetes (type 1 or type 2) for ≥1 year and neuropathic pain of diabetic origin (≥1 of the following: dysesthesia, burning pain, cold or heat allodynia, shooting or lancinating pains and hyperalgesia	N=83 4 weeks	Primary: BPI Secondary: SF-36, sleep, mood and daytime sleepiness	Primary: All three treatments significantly reduced pain compared to placebo. No one treatment was “superior” to the others with regard to pain. Secondary: For sleep, pregabalin improved sleep continuity (P<0.001), whereas duloxetine increased wake and reduced TST (P<0.01 and P<0.001). Despite negative effects on sleep, duloxetine enhanced central nervous system arousal and performance on sensory motor tasks. There were no significant safety findings; however, there were a significantly higher number of adverse events in the pregabalin treatment group.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	affecting both lower extremities at any level below the mid-thighs) and LANSS score >12			
Tanenberg et al.[107] (2011) Duloxetine 60 mg/day vs pregabalin 300 mg/day vs duloxetine 60 mg/day and gabapentin ≥900 mg/day (existing therapy)	MC, NI, OL, RCT 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	N=407 12 weeks	Primary: Reduction from baseline in the weekly mean of the daily 24-hour pain diary ratings at week 12 Secondary: Worst pain and night pain ratings, Clinician Global Impression of Severity, BPI-S and BPI-I, BDI-II, PGI-I, SDS, response rate	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. 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 end point met NI criteria, not statistical superiority. The NI comparison between duloxetine and combination therapy on the differences between end point mean changes in daily pain diary ratings in the ITT patient population was also met. Secondary: Reduction from baseline in BPI average pain and BPI worst pain severity ratings was significantly greater with duloxetine vs pregabalin, but differences between treatments were not significant for the other BPI pain measures, CGI-S, depressive symptoms, or the SDS global measure. Also, no significant between-treatment differences were found among the various response outcomes.
Quilici et al.[108] (2009) Duloxetine vs	MA (11 RCTs; duloxetine, 3 trials; pregabalin, 6 trials; gabapentin, 2 trials)	N=not specified ≥5 to 13 weeks	Primary: Reduction in 24-hour pain severity, response rate (≥50% pain reduction), overall	Primary: Direct comparisons All three agents were more efficacious 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
pregabalin and gabapentin Placebo was used a common comparator.	Patients with diabetic peripheral neuropathic pain		health improvement (PGI-I and PGI-C) Secondary: Not reported	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 PGI-I/C were -0.76 (95% CI, -1.00 to -0.51) and -1.29 (95% CI, -1.72 to -0.86) with duloxetine and pregabalin. Indirect comparisons 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 PGI-I/C outcomes, pregabalin showed an improvement of 0.542 points over duloxetine, a difference that reached significant (95% CI, 0.016 to 1.060). Secondary: Not reported
Ney et al.[109] (2013) Duloxetine, Dextromethorphan-quinidine, lacosamide, pregabalin, oxcarbazepine, topiramate or zonisamide vs placebo	MA (17 RCTs) Patients with peripheral neuropathic pain	N=5,975 ≥12 weeks	Primary: Reduction in pain at ≥12 weeks or pain at ≥12 weeks Secondary: Sleep interference score, ≥50% reduction in pain and global improvement measure	Primary: The greatest reduction in pain at ≥12 weeks compared to placebo occurred with duloxetine 120 mg (-1.17; 95% CI, 0.77 to 1.58; P<0.001), pregabalin 600 mg (-1.11; 95% CI, 0.77 to 1.45; P<0.001) and duloxetine 60 mg (-1.08; 95% CI, 0.70 to 1.46; P<0.001). There was no statistically significant difference in pain between placebo and treatment with zonisamide 540 mg (P=0.13), pregabalin 150 mg (P=0.10), oxcarbazepine 1,200 mg (P=0.20), topiramate 100 mg (P=1.00), 200 mg (P=0.01), 400 mg (P=0.08) or lacosamide 200 mg (P=0.09). Secondary: The greatest change in sleep interference scores compared to placebo occurred with pregabalin 600 mg (1.1; 95% CI, 0.7 to 1.6; P<0.001) and lacosamide (1.0; 95% CI, 0.3 to 1.6; P=0.003). Duloxetine 60 mg and pregabalin 300 mg each improved scores by 0.9 points compared to placebo (P<0.001 for both).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				The NNT for a single 50% improvement in pain was 3.7 with zonisamide 540 mg and dextromethorphan-quinidine 90/60 mg (P<0.001 for both), 4.1 with pregabalin 600 mg (P<0.001), 4.9 with duloxetine 120 mg (P<0.001), 5.1 with duloxetine 60 mg (P<0.001), six with oxcarbazepine 1,800 mg (P<0.02) 6.9 with topiramate 400 mg (P<0.004) and nine for pregabalin 300 mg (P=0.017). Improvements with other strengths of these agents were not statistically significant. The number needed for a single greater than-minimal improvement was 4.5 and 4.6 with duloxetine 120 and 60 mg, respectively (P<0.001 for both), followed by 4.7 with lacosamide 600 mg (P=0.006), 5.1 with oxcarbazepine 1,800 mg (P=0.004) and pregabalin 600 mg (P<0.001). The NNT for improvement was 6.8 with lacosamide 400 mg (P=0.022) and 8.5 with topiramate 400 mg (P=0.022). Improvements with other evaluated doses were not statistically significant.
Obsessive-compulsive Disorder				
Denys et al.[110] (2003) Paroxetine 15 to 60 mg daily vs venlafaxine 75 to 300 mg daily	DB, PG, RCT Patients with OCD	N=150 12 weeks	Primary: Y-BOCS Secondary; Not reported	Primary: Both paroxetine and venlafaxine were efficacious with a mean decrease of 7.8 and 7.2 points, respectively, at the end of the study, as measured by the reduction in total Y-BOCS scores. Analyses of covariance, adjusted for the mean baseline Y-BOCS scores, revealed a highly significant treatment effect over the 12-week trial period for both treatment groups (P=0.001). A significant decrease in total Y-BOCS scores from baseline was found in the venlafaxine group at week three (P=0.008), whereas in the paroxetine group, a significant decrease in total Y-BOCS scores from baseline was evident as of the fifth week of treatment (P=0.018). Significant decreases in total Y-BOCS scores for both medications were observed until week 10, whereas from week 10 till week 12, no further decrease was detected. Secondary; Not reported

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Panic Disorder				
Pollack et al.[111] (2007) Venlafaxine ER 75 mg/day vs venlafaxine ER 225 mg/day vs paroxetine 40 mg/day vs placebo	DB, MC, PC, RCT Outpatients ≥18 years of age with panic disorder (with or without agoraphobia)	N=653 12 weeks	Primary: Percentage of patients free from full-symptom panic attacks at endpoint (LOCF) Secondary: Changes from baseline in the Panic Disorder Severity Scale total score and panic attack frequency	Primary: Each of the active treatment groups had a significantly higher proportion of patients who were free of full-symptom panic attacks than in the placebo group (venlafaxine ER 75 mg, 64.7% [P≤0.001 vs placebo]; venlafaxine ER 225 mg, 70.0% [P≤0.001 vs placebo; P≤0.05 vs paroxetine]; paroxetine, 58.3% [P≤0.05 vs placebo]; placebo, 47.8%). Secondary: All three treatment groups had significantly greater mean reductions in Panic Disorder Severity Scale total score compared to the placebo group at study endpoint. The venlafaxine ER 225 mg group had a significantly lower Panic Disorder Severity Scale total score (4.78 vs 6.26; P<0.05) at endpoint than the paroxetine group. Each of the active treatment groups had significantly more CGI-I responders than the placebo group (venlafaxine ER 75 mg, 81.4%; venlafaxine ER 225 mg, 85.0%; paroxetine, 83.3%; placebo, 59.9%; P<0.001 vs placebo for all comparisons). The percentage of patients who experienced remission was higher in the active treatment groups (venlafaxine ER 225 mg, 50.0%; venlafaxine ER 75 mg, 41.0%; paroxetine 40 mg, 39.3%) than in the placebo group (26.8%).

Drug abbreviations: BID=twice daily, CR=controlled release, ER=extended release, QD=once daily, SR=sustained release, XR=extended release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, ES=extension study, FD=fixed dose, ITT=intention to treat, LOCF=last observation carried forward, LSM=least square mean, LSMD=least square mean difference, MA=meta-analysis, MC=multicenter, NI=non inferiority, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind, SC=single center, SMD=standard mean difference, SR=systemic review, XO=cross over
Diagnostic Criteria: DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition
Miscellaneous abbreviations: ASEX=Arizona Sexual Experience Scale, BAI=Beck Anxiety Inventory, BDI-FS=Beck Depression Inventory Fast Screen, BDI-II=Beck Depression Inventory-II, BPI=brief pain inventory, CAPS-S=Clinician-Administered PTSD Scale, CES-D=Center for Epidemiological Studies-Depression Scale, CGI-I=Clinical Global Impression, Improvement, CGI-S=Clinical Global Impression, Severity, CSFQ=Changes in Sexual Functioning Questionnaire, DBP=diastolic blood pressure, DSST=digital symbol substitution test, ECG=electrocardiogram, EQ-5D=EuroQoL: 5 Dimensions Questionnaire, FIQ=Fibromyalgia Impact Questionnaire, GAD=Generalized Anxiety Disorder, GAF=Global Assessment of Functioning, GDS=Geriatric Depression Scale, GSP=Generalized Social Phobia, HADS-A=Hospital Anxiety and Depression Scale – Anxiety subscale, HAMA=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, HARS=Hamilton Anxiety Rating Scale, HDRS-17=17-item Hamilton Depression Rating Scale, HRQOL=health related quality of life, IDS=Inventory of Depressive Symptomatology-Clinician-Rated, IES=Impact of Event Scale, IU-GAM=Indiana University Generalized Anxiety Measurement Scale, LANSS=Leeds Assessment of Neuropathic Symptoms and Signs, LPS=Latency to Persistent Sleep, LSAS=Liebowitz Social Anxiety Scale, MADRS=Montgomery-Åsberg Depression Rating Scale, MAOIs=Monoamine Oxidase Inhibitors, 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, NIMH-OC=National Institute of Mental Health-Obsessive-Compulsive Scale, NSAID=nonsteroidal anti-inflammatory drug, OCD=obsessive compulsive disorder, PAS=Panic and Agoraphobia Scale, PGI-C=Patient Global Impression of Change, PGI-I=Patient Global Impressions of Improvement, PMDD=premenstrual dysphoric disorder, PPI=proton pump inhibitor, PTSD=Posttraumatic Stress Disorder, QOL=Quality of Life, Q-LES-Q=Quality of Life, Enjoyment, and Satisfaction Questionnaire, RAVLT=Rey Auditory Verbal Learning Test, REM=rapid eye movement, RMDQ-24=Roland Morris Disability Questionnaire, SBP=systolic blood pressure, SDS=Sheehan Disability Scale, SF-36=36-item Short-Form Health Status Survey, SNRI=serotonin norepinephrine reuptake inhibitor, SSI=28-item Somatic Symptom Inventory, SSRIs=Selective Serotonin-reuptake Inhibitors, TST=Total Sleep Time, UPDRS=Unified Parkinson's Disease Rating Scale, VAS=Visual Analog Scale, WASO=Wake Time After Sleep Onset, WHO-5=World Health Organization 5-item Well Being Index, WOMAC=Western Ontario and McMaster Universities, WTAS=Wake Time After Sleep, WTDS=Wake Time During Sleep, Y-BOCS=Yale-Brown Obsessive-Compulsive Scale

Special Populations

Table 5. Special Populations[1-2,5-13]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Desvenlafaxine	No overall differences in safety/efficacy observed between patients over the age of 65 and younger patients. Associated with cases of clinically significant hyponatremia in elderly patients. Safety and efficacy in children have not been established.	Recommended dose in patients with moderate renal impairment (24-hour creatinine clearance 30 to 50 mL/minute) is 50 mg daily. Recommended dose in patients with severe renal impairment (creatinine clearance <30 mL/minute) or end-stage renal disease is 50 mg every other day.	Starting dosage adjustment is not necessary. Maximum recommended dose in this patient population is 100 mg daily.	C	Yes; % not specified.
Duloxetine	No dose adjustment is recommended for elderly patients on the basis of age. Safety and efficacy in children have not been established.	Not recommended in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/minute).	Not recommended in patients with any hepatic insufficiency.	C	Yes (0.14%)
Levomilnacipran	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Dosage adjustment is not necessary for patients with creatinine clearance above 60 mL/minute. For patients with moderate renal impairment (creatinine clearance 30 to 59 mL/minute), the maximum recommended dose is 80	No dosage adjustment required.	C	Not known, use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		mg/day. For patients with severe renal impairment (creatinine clearance 15 to 29 mL/minute), the maximum recommended dose is 40 mg/day. Not recommended in end stage renal disease.			
Milnacipran	No dose adjustment is recommended for elderly patients based on age. Safety and efficacy in children have not been established.	Dosage adjustment required for severe renal impairment; dose should be decreased to 25 mg twice daily and based on response can be increased to 50 mg twice daily. Use with caution in patients with moderate renal impairment.	No dosage adjustment required.	C	Not known, use with caution.
Venlafaxine	No dose adjustment is recommended for elderly patients based on age. Safety and efficacy in children have not been established.	Total daily dose should be reduced by 25% in patients with mild to moderate renal function impairment.	Total daily dose should be reduced by 50% in patients with mild to moderate hepatic function impairment.	C	Yes; % not specified.

Adverse Drug Events

Table 6. Adverse Drug Events[1-2,5-13]

Adverse Events	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
Cardiovascular					
Aneurysm	-	-	-	-	<1
Angina pectoris	-	-	<2	-	<1
Arrhythmia	-	-	-	-	<1
Atrial fibrillation	-	<1	-	-	-
Atrioventricular block	-	-	-	-	<1
Bigeminy	-	-	-	-	<1
Blood pressure increase	-	-	3	3	-
Bradycardia	-	-	-	-	<1
Bundle branch block	-	<1	-	-	<1
Cardiovascular disorder	-	-	-	-	<1
Cerebral ischemia	-	-	-	-	<1
Chest pain	-	-	<2	2	2
Congestive heart failure	-	<1	-	-	<1
Coronary artery disease	-	-	-	-	<1
Edema	-	-	-	-	✔
Electrocardiogram abnormalities	-	-	-	-	<1
Extrasystoles	-	-	<2	-	<1
Flushing	-	-	-	3	-
Heart arrest	-	-	-	-	<1
Heart rate increase	-	-	6	6	-
Hemorrhage	-	-	-	-	<1
Hypertension, dose related and dose independent	<1	-	3	5	3 to 13
Hypertensive crisis	-	<1	-	-	-
Hypotension	-	-	3	-	<1
Myocardial infarct	<2	<1	-	-	<1
Myocardial ischemia	<1	-	-	-	-
Orthostatic hypotension	<2	<1	-	-	-
Palpitation	≤3	1 to 2	5	7	3
Peripheral edema	-	<1	-	-	-
Postural hypotension	-	-	-	-	1
Syncope	<2	<1	<2	-	<1
Tachycardia	-	<1	6	2	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	-	2 to 4
Aggression	-	<1	<2	✔	-
Amnesia	-	-	-	-	✔
Anger	-	-	<2	✔	-
Anxiety	3 to 5	3	-	4	5 to 6
Ataxia	-	<1	-	-	<1
Blurred vision	-	4	-	2	4 to 6
Bradykinesia	-	-	-	-	<1
Chills	-	-	-	-	3
Concentration decreased	≤1	-	-	-	-

Adverse Events	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
Confusion	-	-	-	-	2
Deafness	-	-	-	-	<1
Delusions	-	-	-	✔	<1
Dementia	-	-	-	-	<1
Depersonalization	<2	-	-	-	1
Depression	-	-	-	✔	1 to 3
Diplopia	-	<1	-	-	-
Disorientation	-	<1	-	-	-
Dizziness	10 to 13	6 to 17	-	10	11 to 20
Dystonia	-	-	-	-	<1
Extrapyramidal symptoms	<2	-	<2	-	-
Fatigue	7	2 to 15	-	✔	-
Fever	-	1 to 3	-	-	✔
Guillain-Barre syndrome	-	-	-	-	<1
Hallucination	-	-	-	✔	-
Hostility	-	-	-	-	<1
Hypoesthesia	-	1	-	-	-
Headache	-	13	-	18	25 to 38
Hypoesthesia	-	1	-	1	✔
Hypomania	<2	-	-	-	-
Insomnia	9 to 12	8- to 6	-	12	15 to 23
Irritability	2	1	-	-	-
Lethargy	-	1	-	-	-
Loss of consciousness	-	-	-	-	<1
Mania	-	<1	-	-	-
Migraine	-	-	<2	5	✔
Mood swings	-	<1	-	-	-
Nervousness	-	1	-	-	6 to 21
Neuropathy	-	-	-	-	<1
Neutropenia	-	-	-	-	<1
Nightmares	-	1	-	-	-
Panic attack	-	-	<2	-	-
Paresthesia	≤2	1	<2	2	2 to 3
Parkinsonism	<1	-	-	✔	-
Photopsia	-	<1	-	-	-
Photosensitivity	-	<1	-	-	-
Restlessness	-	1	-	-	-
Seizure	-	<1	-	✔	<1
Sleep disorder	-	1	-	-	-
Somnolence	≤9	13 to 20	-	✔	12 to 23
Suicide attempt/ideation	-	-	-	✔	-
Tension	-	-	<2	-	-
Trismus	-	-	-	-	✔
Vertigo	-	1	-	-	✔
Yawning	-	1	<2	-	3 to 5
Dermatological					
Acne	-	<1	-	-	-

Adverse Events	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
Alopecia	-	<1	-	-	-
Bruising	-	-	-	-	✔
Ecchymosis	-	<1	-	-	-
Eczema	-	<1	-	-	-
Erythema	-	<1	-	✔	-
Erythema multiforme	-	-	-	-	<1
Exfoliative dermatitis	-	-	-	-	<1
Dry skin	-	-	<2	-	-
Hyperhidrosis	-	6 to 8	9	9	-
Maculopapular rash	-	-	-	-	<1
Miliaria	-	-	-	-	<1
Night sweats	-	-	-	✔	-
Pruritus	-	3	<2	2	1
Rash	1	4	2	3	3
Skin atrophy	-	-	-	-	<1
Stevens-Johnson syndrome	-	<1	-	✔	<1
Toxic epidermal necrolysis	-	-	-	-	<1
Urticaria	-	<1	<2	-	-
Endocrine and Metabolic					
Bilirubin increased	-	<1	-	-	<1
Blood urea nitrogen increased	-	-	-	-	<1
Cholesterol increased	3 to 4	<1	-	-	-
Creatinine increased	-	-	-	-	<1
Diabetes mellitus	-	-	-	-	<1
Dyslipidemia	-	<1	-	-	-
Electrolyte abnormalities	-	-	-	-	<1
Hepatic steatosis	-	<1	-	-	-
Hepatitis	-	<1	-	-	<1
Hot flushes	-	2	<2	-	-
Hypercalcinuria	-	-	-	-	<1
Hyperchlorhydria	-	-	-	-	<1
Hypercholesterolemia	-	<1	-	-	<15
Hyperglycemia	-	-	-	-	<1
Hyperkalemia	-	-	-	-	<1
Hyperlipidemia	-	<1	-	-	<1
Hyperphosphatemia	-	-	-	-	<1
Hyperprolactinemia	-	-	-	✔	-
Hyperthyroidism	-	-	-	-	<1
Hypertriglyceridemia	-	<1	-	-	-
Hyperuricemia	-	-	-	-	<1
Hypocholesterolemia	-	-	-	-	<1
Hypoglycemia	-	1	-	-	<1
Hypokalemia	-	-	-	-	<1
Hyponatremia	-	<1	-	-	<1
Hypophosphatemia	-	-	-	-	<1
Hypothyroidism	-	-	-	-	<1
Increased blood cholesterol	-	-	<2	-	-
Increased liver function tests	-	-	<2	-	-
Jaundice	-	<1	-	-	<1
Kidney function abnormal	-	-	-	-	<1
Low-density lipoprotein	≤1	-	-	-	-

Adverse Events	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
increased					
Liver enzymes increased	≤2	-1	-	-	<1
Syndrome of inappropriate antidiuretic hormone secretion	-	<1	-	-	<1
Transaminase elevation	-	1	-	-	-
Triglycerides increased	-	-	-	-	✔
Weight gain	-	<1	-	-	✔
Weight loss	≤2	1 to 2	-	-	1 to 4
Gastrointestinal					
Abdominal distention	-	-	-	✔	-
Abdominal pain	-	<1	<2	3	6
Abnormal taste	-	-	-	-	2
Anorexia	5 to 8	3 to 5	-	✔	8 to 20
Aphthous stomatitis	-	<1	-	-	-
Appetite decreased	-	3 to 11	3	2	-
Appetite increased	-	-	-	-	✔
Bloody stools	-	<1	-	-	-
Cholelithiasis	-	-	-	-	<1
Colitis	-	<1	-	-	-
Constipation	9 to 11	5 to 15	9	16	8 to 15
Diarrhea	9 to 11	7 to 13	-	✔	6 to 8
Diverticulitis	-	<1	-	-	-
Dyspepsia	-	4 to 5	-	✔	7
Dysphagia	-	<1	-	-	-
Eructation	-	<1	-	-	-
Esophageal stenosis	-	<1	-	-	-
Flatulence	-	-	<2	✔	3 to 4
Gastric emptying impaired	-	<1	-	-	-
Gastric irritation	-	<1	-	-	-
Gastric ulcer	-	<1	-	-	<1
Gastritis	-	1	-	-	-
Gastroesophageal reflux disease	-	-	-	✔	-
Hematemesis	-	-	-	-	<1
Intestinal obstruction	-	-	-	-	<1
Irritable bowel syndrome	-	<1	-	-	-
Loose stools	-	2 to 3	-	-	-
Melena	-	<1	-	-	-
Nausea	22 to 26	14 to 30	17	37	21 to 58
Vomiting	≤4	1 to 6	5	7	3 to 6
Xerostomia	11 to 17	5 to 18	-	-	12 to 22
Genitourinary					
Acute kidney failure	-	-	-	✔	-
Crystalluria	-	-	-	-	<1
Cystitis	-	-	-	✔	-
Decreased libido	-	-	-	✔	-
Dysuria	-	1	-	≥2	-
Ejaculation abnormality	≤1	1 to 4	5	≥2	2 to 19
Erectile dysfunction	3 to 6	1 to 5	6	≥2	-
Hematuria	-	-	<2	-	-

Adverse Events	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
Impotence	-	-	-	-	4 to 10
Libido decreased	4 to 5	2 to 4	-	-	3 to 9
Menstrual abnormalities	-	-	-	-	<1
Micturition urgency	-	<1	-	-	-
Nocturia	-	<1	-	-	-
Pollakiuria	-	1 to 5	<2	-	-
Prostatic disorder	-	-	-	-	✔
Proteinuria	6 to 8	-	<2	-	-
Pyelonephritis	-	-	-	-	<1
Pyuria	-	-	-	-	<1
Testicular pain	-	-	4	≥2	-
Urinary frequency	-	-	-	-	3
Urinary hesitation	-	-	4	≥2	-
Urinary retention	-	<1	-	≥2	1
Urinary symptoms	≤1	1	-	-	-
Urination impaired	-	-	-	≥2	2
Hematologic					
Agranulocytosis	-	-	-	-	<1
Anemia	-	<1	-	-	-
Aplastic anemia	-	-	-	-	<1
Bleeding time increased	-	-	-	-	<1
Eosinophilia	-	-	-	-	<1
Hypoproteinemia	-	-	-	-	<1
Leukocytosis	-	-	-	-	<1
Leukoderma	-	-	-	-	<1
Leukopenia	-	<1	-	✔	<1
Lymphadenopathy	-	<1	-	-	<1
Lymphocytosis	-	-	-	-	<1
Pancytopenia	-	-	-	-	<1
Thrombocytopenia	-	<1	-	✔	<1
Thrombophlebitis	-	-	-	-	<1
Musculoskeletal					
Arthralgia	-	-	-	-	✔
Dysarthria	-	<1	-	-	-
Extrapyramidal symptoms	-	-	<2	-	<1
Hypertonia	-	-	-	-	3
Malaise	-	<1	-	-	-
Muscle cramp	-	4 to 5	-	-	-
Muscle pain	-	1 to 5	-	-	-
Muscle tightness	-	1	-	-	1 to 2
Muscle twitching	-	4	-	-	<1
Myalgia	-	1 to 3	-	-	-
Myasthenia	-	-	-	-	<1
Myopathy	-	-	-	-	<1
Neck pain/rigidity	-	-	-	-	✔
Neuroleptic malignant-like syndrome	-	-	-	-	<1
Osteoporosis	-	-	-	-	<1
Rhabdomyolysis	-	-	-	✔	<1
Rheumatoid arthritis	-	-	-	-	<1
Rigors	-	1	-	-	-

Adverse Events	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
Tendon rupture	-	-	-	-	<1
Tremor	≤3	3 to 4	-	-	4 to 10
Weakness	≤2	2 to 8	-	-	8 to 19
Respiratory					
Asthma	-	-	-	-	<1
Atelectasis	-	-	-	-	<1
Cough	-	3 to 6	-	-	✔
Dyspnea	-	-	-	2	✔
Epistaxis	<2	-	-	-	-
Nasopharyngitis	-	7 to 9	-	-	-
Pharyngitis	-	-	-	-	7
Pharyngolaryngeal pain	-	1 to 6	-	-	-
Pleurisy	-	-	-	-	<1
Pneumonia	-	-	-	-	<1
Sinusitis	-	-	-	-	2
Upper respiratory infection	-	7	-	6	-
Other					
Anaphylactic reaction	-	<1	-	-	<1
Angioneurotic edema	-	<1	-	-	-
Arteritis	-	-	-	-	<1
Bacteremia	-	-	-	-	<1
Basophilia	-	-	-	-	<1
Blurred/abnormal vision	-	1 to 3	<2	-	4 to 6
Bruxism	-	<1	<2	-	-
Cataract	-	-	-	-	<1
Catatonia	-	-	-	-	<1
Cellulites	-	-	-	-	<1
Conjunctival hemorrhage	-	-	<2	-	-
Cyanosis	-	-	-	-	<1
Deep vein thrombosis	-	-	-	-	<1
Dehydration	-	<1	-	-	<1
Diaphoresis increased	10 to 14	6	-	-	10 to 14
Embolus	-	-	-	-	<1
Facial edema	-	<1	-	-	-
Facial paralysis	-	-	-	-	<1
Fasciitis	-	-	-	-	<1
Flu-like syndrome	-	<1	-	-	6
Gingivitis	-	<1	-	-	-
Glaucoma	-	<1	-	-	<1
Homicidal ideation	-	-	-	-	<1
Hot flushes	-	2 to 3	<2	12	-
Hyperacusis	-	-	-	-	<1
Hypersensitivity reaction	<2	-	-	-	-
Infection	-	-	-	-	6
Keratoconjunctivitis sicca	-	<1	-	-	-
Larynx edema	-	-	-	-	<1
Macular degeneration	-	<1	-	-	-
Maculopathy	-	<1	-	-	-
Moniliasis	-	-	-	-	<1
Multiple myeloma	-	-	-	-	<1

Adverse Events	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
Mydriasis	2	-	-	-	2
Nephropathy	-	<1	-	-	-
Night sweats	-	1	-	-	-
Oropharyngeal edema	-	<1	-	-	-
Phlebitis	-	<1	-	-	-
Retinal detachment	-	<1	-	-	-
Serotonin syndrome	-	-	-	-	<1
Stomatitis	-	<1	-	-	-
Suicidal ideation/attempt	-	<1	-	-	<1 to 2
Thirst	-	<1	<2	-	-
Tinnitus	2	-	-	-	2
Trauma	-	-	-	-	2
Trismus	-	-	-	-	✔
Visual disturbance	-	<1	-	-	-
Withdrawal syndrome	-	<1	-	-	<1

✔ Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications[1-2,5-13]

Contraindication	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
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 desvenlafaxine[1,5-7]

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

Black Box Warning for duloxetine[1,8]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk of suicidal thoughts and

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

Black Box Warning for levomilnacipran[1,9]

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

Black Box Warning for milnacipran[1,10]

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

Black Box Warning for venlafaxine, venlafaxine extended-release[1,10-12]

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

Warnings/Precautions

Table 8. Warnings and Precautions[1-2,5-13]

Warning/Precaution	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
Abnormal bleeding; use may increase the risk of bleeding events	✔	✔	✔	✔	✔
Activation of mania/hypomania has been reported in clinical trials	✔	✔	✔	-	✔
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	✔	✔	✔	-	✔
Controlled narrow-angle glaucoma; use with caution	-	✔	-	-	-
Discontinuation of treatment; abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms	✔	✔	✔	✔	✔
Elevated blood pressure (and potentially hear rate); increases in blood pressure were observed in clinical trials	✔	✔	✔	✔	-
Glycemic control may be worsened in some patients with diabetes	-	✔	-	-	-
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	✔	✔	✔	-	✔

Warning/Precaution	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
inappropriate antidiuretic hormone secretion					
Inhibitors of CYP1A2 or thioridazine should not be administered with this agent	-	✔	-	-	-
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	✔	-	-	-	✔
Male patients with a history of obstructive uropathies may experience higher rates of genitourinary adverse events	-	-	-	✔	-
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	✔	✔	✔	✔	✔

Warning/Precaution	Des-venlafaxine	Duloxetine	Levo-milnacipran	Milnacipran	Venla-faxine
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	-	✔	-	-	-
Suicidality; monitor for worsening of depressive symptoms and suicide risk	-	-	-	✔	-
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 cautiously in patients with conditions that slow gastric emptying	-	✔	-	-	-
Use in patients with concomitant illness; clinical experience is limited	-	-	-	-	✔

Drug Interactions

Table 9. Drug Interactions[1]

Generic Name	Interacting Medication or Disease	Potential Result
Serotonin-norepinephrine reuptake inhibitors	Anticoagulants	The risk of bleeding with Anticoagulants may be potentiated with concomitant use of these serotonin-norepinephrine reuptake inhibitors and patients are at an increased risk of bleeding. The mechanism of this interaction is unknown.
Duloxetine, levomilnacipran, venlafaxine	Monoamine oxidase inhibitors	Serotonin syndrome may occur.
Duloxetine, levomilnacipran, venlafaxine	Selective 5-HT1 receptor agonists	Serotonin syndrome may occur.
Desvenlafaxine, venlafaxine	Narcotic analgesics	The toxic effects of desvenlafaxine and venlafaxine with narcotic analgesics may be additive resulting in the development of serotonin syndrome.
Desvenlafaxine, venlafaxine	Salicylates	The risk of upper gastrointestinal bleeding may be increased with concurrent administration of salicylates and desvenlafaxine or venlafaxine. The mechanism is unknown. Prolonged use of desvenlafaxine or venlafaxine may lead to depletion of serotonin, which is thought to play an important role in hemostasis.

Generic Name	Interacting Medication or Disease	Potential Result
Duloxetine, levomilnacipran	Nonsteroidal anti-inflammatory drugs	The risk of upper gastrointestinal bleeding may be increased.
Duloxetine, venlafaxine	Sympathomimetics	Increased sensitivity to sympathomimetic effects and increased risk of serotonin syndrome.
Duloxetine	β blockers	Excessive β blockade (bradycardia) may occur.
Duloxetine	Phenothiazines	Plasma concentrations and pharmacologic effects of phenothiazines may be increased by duloxetine. The possibility of serious ventricular dysrhythmias should be considered. Inhibition of CYP2D6 isoenzymes by duloxetine may decrease the metabolic elimination of phenothiazines; the combination should be avoided.
Duloxetine	Tri-cyclic antidepressants	Plasma concentrations of tri-cyclic antidepressants may be increased by duloxetine. Inhibition of cytochrome CYP2D6 isoenzymes by duloxetine may decrease the metabolic elimination of tri-cyclic antidepressants.
Levomilnacipran	Strong CYP3A4 Inhibitors (e.g. ketoconazole)	Concomitant use may result in increased exposure of levomilnacipran. A maximum dose of 80 mg/day is recommended.
Venlafaxine	Azole antifungals	Venlafaxine plasma levels may be elevated, increasing the adverse effects.
Desvenlafaxine, venlafaxine	Selegiline	The combination of these serotonin-norepinephrine reuptake inhibitors and selegiline may produce unexpected toxicity, characterized by manic-like behavior, shivering, diaphoresis, hypertension and ataxia. The mechanism of this interaction is unknown.
Duloxetine, venlafaxine	Linezolid	Serotonin syndrome may occur.
Duloxetine, venlafaxine	St. John’s wort	Unexpected toxicity may occur when St. John's wort and desvenlafaxine/venlafaxine are coadministered; the mechanism is unknown.
Duloxetine, venlafaxine	Tramadol	Serotonin syndrome may occur.
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	Tamoxifen	Pharmacologic effects of tamoxifen may be decreased by duloxetine. Coadministration of duloxetine with tamoxifen may increase the risk of breast cancer recurrence.
Duloxetine	Thioridazine	Thioridazine plasma concentrations may be elevated, increasing the risk of life-threatening ventricular arrhythmias and sudden death.
Levomilnacipran	Alcohol	Consumption of alcohol may interfere with the delayed release mechanism of levomilnacipran.
Levomilnacipran	Grapefruit juice	Concomitant use may result in increased levomilnacipran exposure.
Venlafaxine	Bupropion	Venlafaxine plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.

Generic Name	Interacting Medication or Disease	Potential Result
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 Administration[1-2,5-13]

Generic Name	Adult Dose	Pediatric Dose	Availability
Desvenlafaxine	Treatment of major depressive disorder: Extended-release tablet: 50 mg once-daily	Safety and efficacy in children have not been established.	Extended-release tablet: 50 mg 100 mg
Duloxetine	Management of chronic musculoskeletal pain: Delayed-release capsule: initial, 30 mg/day; maintenance, 60 mg once-daily; maximum, 60 mg/day Management of fibromyalgia: Delayed-release capsule: initial, 30 mg/day; maintenance, 60 mg once-daily; maximum, 60 mg/day Management of neuropathic pain associated with diabetic peripheral neuropathy: Delayed-release capsule: 60 mg once-daily Treatment of generalized anxiety disorder: Delayed-release capsule: initial, 60 mg/day; maintenance, 60 mg once-daily; maximum, 120 mg/day Treatment of major depressive disorder: 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;	Safety and efficacy in children have not been established.	Delayed-release capsule: 20 mg 30 mg 60 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	maximum, 120 mg/day		
Levomilnacipran	Treatment of major depressive disorder: Extended-release capsule: initial, 20 mg once daily for two days, then increase to 40 mg once daily; maintenance, 40 to 120 mg once daily; maximum, 120 mg once daily	Safety and efficacy in children have not been established.	Extended-release capsules: 20 mg 40 mg 80 mg 120 mg
Milnacipran	Management of fibromyalgia: Tablet: initial, 12.5 mg once daily for one day, then 12.5 mg twice daily for two days, then 25 mg twice daily for four days; maintenance, 50 mg twice daily; maximum, 200 mg/day	Safety and efficacy in children have not been established.	Tablet: 12.5 mg 25 mg 50 mg 100 mg
Venlafaxine	Treatment of generalized anxiety disorder: Extended-release capsule: initial, 75 mg once-daily; maximum, 225 mg/day Treatment of major depressive disorder: Extended-release capsule: initial, 75 mg once-daily; maximum, 225 mg/day Extended-release tablet: 37.5 to 75 mg/day; maximum, 225 mg/day Tablet: initial, 75 mg/day administered in two or three divided doses; maintenance, 150 to 225 mg/day; maximum, 375 mg/day Treatment of panic disorder, with or without agoraphobia: Extended-release capsule: initial, 37.5 mg once-daily for one week; maximum, 225 mg/day Treatment of social anxiety disorder: Extended-release capsule, extended-release tablet: 75 mg once-daily	Safety and efficacy in children have not been established.	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 37.5 mg 50 mg 75 mg 100 mg

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**	Acute phase • Pharmacotherapy: o An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder (MDD) and definitely should be provided for those with severe MDD. o Due to the fact that the effectiveness of antidepressant

Clinical Guideline	Recommendations
(2010)[112]	medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects; the safety or tolerability of these side effects; pharmacological properties of the medication and additional factors such as medication response in prior episodes, cost and patient preference. o For the majority of patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), bupropion or mirtazapine is optimal. o In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) should be restricted to patients who do not respond to other treatments. o During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy. o If side effects do occur, an initial strategy is to lower the dose of the antidepressants or to change to an antidepressant that is not associated with those side effects. • Assessing the adequacy of treatment response: o It is important to establish that treatment has been administered for a sufficient duration and at a sufficient frequency or, in the case of medication, dose. o Generally, four to eight weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention. • Strategies to address non-response: o For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely, as an incomplete response to treatment is often associated with poor functional outcomes. o If at least a moderate improvement in symptoms is not observed within four to eight weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed and the treatment plan adjusted. o It is important to assess the quality of the therapeutic alliance and treatment adherence. o If medications are prescribed, the psychiatrist should determine whether pharmacokinetic or pharmacodynamic factors suggest a need to adjust medication dose. o After an additional four to eight weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan. o There are a number of strategies available when a change in treatment seems necessary. ▪ For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached. ▪ In patients who have shown minimal improvement or experienced significant medication side effects, other

Clinical Guideline	Recommendations
	options include augmenting the antidepressant with a depression-focused psychotherapy or with other agents or with changing to another non-MAOI antidepressant. ▪ Patients may be changed to an antidepressant from the same pharmacological class or to one from a different class. ▪ Patients who have not responded to an SSRI, may respond to SNRI. ▪ Augmentation of antidepressant medications can utilize another non-MAOI antidepressant, generally from a different pharmacological class, or a non-antidepressant medication, such as lithium, thyroid hormone or a second generation antipsychotic. <u>Continuation phase</u> • During the continuation phase of treatment, the patient should be carefully monitored for signs of possible relapse. • Systematic assessment of symptoms, side effects, adherence and functional status is essential and may be facilitated through the use of clinician- and/or patient-administered rating scales. • To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for four to nine months. • In general, the dose used in the acute phase should be used in the continuation phase. • To prevent a relapse of depression in the continuation phase, depression-focused psychotherapy is recommended, with the best evidence available for cognitive behavioral therapy (CBT). <u>Maintenance phase</u> • In order to reduce the risk of a recurrent depressive episode, patients who have had three or more prior MDD episodes or who have chronic MDD should proceed to the maintenance phase of treatment after completing the continuation phase. • Maintenance therapy should also be considered for patients with additional risk factors for recurrence. • Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes, the persistence of depressive symptoms after recovery and the presence of co-occurring disorders. Such factors also contribute to decisions about the duration of the maintenance phase. • For many patients, some form of maintenance treatment will be required indefinitely. • An antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose. • For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression-focused psychotherapy but who have shown a response to electroconvulsive therapy (ECT), maintenance ECT may be considered. • Due to the risk of recurrence, patients should be monitored systematically

Clinical Guideline	Recommendations
	and at regular intervals during the maintenance phase. Discontinuation of treatment • When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks. • To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home. • A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome when discontinuing antidepressants or reducing antidepressant doses. • Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms. • After discontinuation of medications, patients should continue to be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur.
National Institute for Health and Clinical Excellence: **Treatment and Management of Depression in Adults (Update) (2009)**[113]	Persistent subthreshold depressive symptoms or mild to moderate depression • Do not use antidepressants routinely to treat persistent subthreshold depressive symptoms or mild depression. • Consider antidepressants for the following people: o A past history of moderate or severe depression. o Initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least two years). o Subthreshold depressive symptoms or mild depression that persist(s) after other interventions. Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression • For patients with persistent subthreshold depressive symptoms or mild to moderate depression who have not benefited from a low-intensity psychosocial intervention, discuss the relative merits of different interventions with the person and provide: o An antidepressant (normally an SSRI) or a high intensity psychosocial intervention. • For people with moderate or severe depression, provide a combination of an antidepressant medication and a high intensity psychological intervention. • The choice of intervention should be influenced by the duration of the episodes of depression and the trajectory of symptoms, previous course of depression and response to treatment, likelihood of adherence to treatment and any potential adverse effects and the patient's treatment preference and priorities. Antidepressant drugs • Choice of antidepressant: o Discuss the choice of antidepressant with the patient, including any anticipated adverse events and potential drug interactions, and their perception of the efficacy and tolerability of any antidepressant they have previously taken. o When an antidepressant is used, it should normally be an SSRI in a generic form. The SSRIs are equally effective as other

Clinical Guideline	Recommendations
	antidepressants and have a favorable risk-benefit ratio. Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs, and paroxetine is associated with a higher incidence of discontinuation symptoms than other SSRIs. o Take into account toxicity in overdose when choosing an antidepressant for people at significant risk for suicide. Be aware that compared to other equally effective antidepressants routinely used in primary care, venlafaxine is associated with a greater risk of death from overdose, and tri-cyclic antidepressants (TCAs), except lofepramine, are associated with the greatest risk in overdose. o When prescribing drugs other than SSRIs, take the following into account: the increased likelihood of the person stopping treatment because of side effects with duloxetine, venlafaxine and TCAs, the specific cautions, contraindications and monitoring requirements for some drugs, that non-reversible MAOIs should normally be prescribed only by specialists. • Starting and initial phase of treatment: o When prescribing antidepressants, explore any concerns the patient has. Explain the gradual development of the full antidepressant effect, the importance of taking the medication as prescribed, the need to continue treatment after remission, potential side effects, the potential for interactions with other medications, the risk and nature of discontinuation symptoms with all antidepressants and how these symptoms can be minimized and the fact that addiction does not occur with antidepressants. o If side effects develop early in antidepressant treatment, provide appropriate information and consider one of the following strategies: monitor symptoms closely where side effects are mild and acceptable to the patient, stop the antidepressant, change to a different antidepressant if the person prefers or consider short term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic (this should usually be for no longer than two weeks in order to prevent the development of dependence). o Patients who start on low dose TCAs and who have clear clinical response can be maintained on that dose with careful monitoring. o If the patient's depression shows no improvement after two to four weeks with the first antidepressant, check that the drug has been taken regularly and in the prescribed dose. o If response is absent or minimal after three to four weeks of treatment with a therapeutic dose of an antidepressant, increase the level of support and consider increasing the dose in line with the summary of product characteristics if there are no significant side effects or switching to another antidepressant. • If the patient's depression shows some improvement by four weeks, continue treatment for another two to four weeks. Consider switching to another antidepressant if response is still not adequate, there are side effects or the person prefers to change treatment.
American College of Physicians: **Clinical Practice**	Treatment of MDD • When treating acute-phase MDD, the second-generation antidepressants did not significantly differ in efficacy, effectiveness, or quality of life

Clinical Guideline	Recommendations
Guideline: Using Second-Generation Antidepressants to Treat Depressive Disorders (2008)[114]	among the SSRIs, SNRIs, selective serotonin norepinephrine reuptake inhibitors (SSNRIs), or other second-generation antidepressants. • Mirtazapine had a significantly faster onset of action; however, after four weeks, most response rates were similar. • Second-generation antidepressants did not differ in the rate of achieving remission. • First-generation antidepressants (TCAs and MAOIs) are less commonly used than second-generation antidepressants, which have similar efficacy to and lower toxicity in overdose than first-generation antidepressants. Treatment of depression in patients with accompanying symptom clusters • When treating symptom clusters in patients with accompanying depression, second-generation antidepressants did not differ in efficacy in treating accompanying anxiety, pain, and somatization. • Limited evidence suggests that some agents may be more effective in treating insomnia. Treatment of depression in selected patient populations • Second-generation antidepressants did not differ in efficacy among subgroups and special populations categorized according to age, sex, race or ethnicity, or comorbid conditions. Risk for harms and adverse events • Most of the second-generation antidepressants had similar adverse effects. • The most commonly reported adverse events were constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence. Nausea and vomiting were the most common reasons for discontinuation in efficacy studies. • Paroxetine was associated with an increased risk for sexual dysfunction. • SSRIs resulted in an increased risk for nonfatal suicide attempts. Recommendations • Clinicians should select second-generation antidepressants on the basis of adverse effect profiles and patient preferences. • Clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within one to two weeks of initiation of therapy. • Clinicians should modify treatment if the patient does not have an adequate response to pharmacotherapy within six to eight weeks of the initiation of therapy for major depressive disorder. • Clinicians should continue treatment for four to nine months after a satisfactory response in patients with a first episode of major depressive disorder. For patients who have had two or more episodes of depression, an even longer duration of therapy may be beneficial.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and**	All Types of childhood/adolescent depression • All patients with depression should receive therapy in the acute (six to 12 weeks) and continuation phases (six to 12 months); 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.

Clinical Guideline	Recommendations
Adolescents with Depressive Disorders (2007)[115]	• Medication regimen may be optimized or augmented in partial responders; while switching to another regimen may be appropriate in non-responders. Uncomplicated depression/brief depression/mild psychosocial impairment • Initial management: education, support, and case management. Reevaluate if no response after four to six weeks. Moderate-to-severe depression • 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 hyperactivity deficit disorder (ADHD). • TCAs should not be used as 1st line therapy for child/adolescent depression due to poor efficacy (not statistically different from placebo) and unfavorable side-effect profile. Psychotic depression • SSRIs combined with atypical antipsychotics are the treatment of choice. Seasonal affective disorder (SAD) • Bright light therapy is recommended as treatment of SAD in youths. Bipolar disorder • 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)[116]**	Stepped care for people with generalized anxiety disorder (GAD)
	• 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:
	  o Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine).
	  o The side-effect profile and the potential for drug interactions.
	  o The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine).
	  o 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.

Clinical Guideline	Recommendations
	• Do not offer an antipsychotic for the treatment of GAD in primary care. Panic disorder general considerations • 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: o Psychological therapy (i.e., cognitive behavioral therapy, structured problem solving, psychoeducation). o Pharmacological therapy (antidepressant therapy). o Self-help interventions (i.e., bibliotherapy, support groups, exercise, CBT 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.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)**[117]	• 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

Clinical Guideline	Recommendations
	other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic. • 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. • MAOIs 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.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders (2007)**[118]	• 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: o Need for acute symptom reduction in a moderately to severely anxious child. o A comorbid disorder that requires concurrent treatment. o 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

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>who have a significant reduction in anxiety or depressive symptoms on an SSRI and maintain stability in these symptoms for one year.
• 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.</td></tr>
<tr><td>A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society:
Diagnosis and Treatment of Low Back Pain (2007)[119]</td><td>• 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>
<tr><th colspan="4">Interventions for the Management of Low Back Pain</th></tr>
<tr><th colspan="2">Intervention Type</th><th>Acute pain (duration <4 weeks)</th><th>Subacute or chronic pain (duration >4 weeks)</th></tr>
<tr><td rowspan="3">Self-care</td><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Application of superficial heat</td><td>Yes</td><td>No</td></tr>
<tr><td>Book, handouts</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="7">Pharmaco-logic Therapy</td><td>Acetaminophen</td><td>Yes</td><td>Yes</td></tr>
<tr><td>TCA</td><td>No</td><td>Yes</td></tr>
<tr><td>Benzodiazepines</td><td>Yes</td><td>Yes</td></tr>
<tr><td>NSAIDs</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Skeletal muscle relaxants</td><td>Yes</td><td>No</td></tr>
<tr><td>Tramadol, opioids</td><td>Yes</td><td>Yes</td></tr>
<tr><td></td><td>Acupuncture</td><td>No</td><td>Yes</td></tr>
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<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td rowspan="8">Non-pharmaco-logic Therapy</td><td>Cognitive behavior therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Exercise therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Massage</td><td>No</td><td>Yes</td></tr>
<tr><td>Progressive relaxation</td><td>No</td><td>Yes</td></tr>
<tr><td>Spinal manipulation</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Yoga</td><td>No</td><td>Yes</td></tr>
<tr><td>Intensive interdisciplinary rehabilitation</td><td>No</td><td>Yes</td></tr>
</table>
Adapted with permission from Chou R, 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 [published correction appears in Ann Intern Med. 2008;148(3):247-8]. Ann Intern Med. 2007;147(7):482.

• 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.</td></tr>
<tr><td>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)[120]</td><td><u>Nonpharmacologic recommendations for the management of hand osteoarthritis</u>
• It is recommended that health professionals should:
o Evaluate the ability to perform activities of daily living.
o Instruct in joint protection techniques.
o Provide assistive devices, as needed, to help patients perform activities of daily living.
o Instruct in use of thermal modalities.
o Provide splints for patients with trapeziometacarpal joint osteoarthritis.

<u>Pharmacologic recommendations for the initial management of hand osteoarthritis</u></td></tr>
</table>

Clinical Guideline	Recommendations
	• It is recommended that health professionals should use one or more of the following: o Topical capsaicin. o Topical NSAIDs, including trolamine salicylate. o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors. o Tramadol. • It is conditionally recommend that health professionals should not use the following: o Intraarticular therapies. o Opioid analgesics. • It is conditionally recommend that: o In persons ≥75 years of age should use topical rather than oral NSAIDs. o In persons <75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. Nonpharmacologic recommendations for the management of knee osteoarthritis • It is strongly recommend that patients with knee osteoarthritis do the following: o Participate in cardiovascular (aerobic) and/or resistance land-based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with knee osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Use medially directed patellar taping. o Wear medially wedged insoles if they have lateral compartment osteoarthritis. o Wear laterally wedged subtalar strapped insoles if they have medial compartment osteoarthritis. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. o Participate in tai chi programs. o 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). o 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:

Clinical Guideline	Recommendations
	o Participation in balance exercises, either alone or in combination with strengthening exercises. o Wearing laterally wedged insoles. o Receiving manual therapy alone. o Wearing knee braces. o Using laterally directed patellar taping. Pharmacologic recommendations for the initial management of knee osteoarthritis • It is conditionally recommend that patients with knee osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Topical NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. • It is conditionally recommend that patients with knee osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. o Topical capsaicin. • No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. Nonpharmacologic recommendations for the management of hip osteoarthritis • It is strongly recommend that patients with hip osteoarthritis do the following: o Participate in cardiovascular and/or resistance land based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with hip osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Participation in tai chi. o Receiving manual therapy alone. Pharmacologic recommendations for the initial management of hip osteoarthritis • It is conditionally recommend that patients with hip osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Tramadol. o Intraarticular corticosteroid injections.

Clinical Guideline	Recommendations
	• It is conditionally recommend that patients with hip osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. • No recommendation is made regarding the use of the following: o Topical NSAIDs. o Intraarticular hyaluronate injections. o Duloxetine. • Opioid analgesics.
American Academy of Orthopedic Surgeons: **Clinical Practice Guideline on Osteoarthritis of the Knee (2013)**[121]	• Conservative treatments o It is recommended that patients with symptomatic osteoarthritis of the knee participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education; and engage in physical activity consistent with national guidelines. o Weight loss for patients with symptomatic osteoarthritis of the knee and a body mass index ≥25 is recommended. o The guideline cannot recommend acupuncture in patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning manual therapy in patients with symptomatic osteoarthritis of the knee. o The guideline cannot suggest a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning a lateral wedge insoles be used for patients with symptomatic medial compartment osteoarthritis of the knee. o The guideline cannot recommend using glucosamine and chondroitin for patients with symptomatic osteoarthritis of the knee. • Pharmacologic treatments o NSAIDs; oral or topical or tramadol for patients with symptomatic osteoarthritis of the knee are recommended. o No recommendation can be made concerning the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee. • Procedural treatments o No recommendation can be made concerning the use of intraarticular corticosteroids for patients with symptomatic osteoarthritis of the knee. o The guideline cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee. o The guideline cannot suggest that the practitioner use needle lavage for patients with symptomatic osteoarthritis of the knee. • Surgical treatments o The guideline cannot recommend performing arthroscopy with lavage and/or debridement in patients with a primary diagnosis

Clinical Guideline	Recommendations
	of symptomatic osteoarthritis of the knee. o No recommendation can be made concerning arthroscopic partial meniscectomy in patients with osteoarthritis of the knee with a torn meniscus. o The practitioner might perform a valgus producing proximal tibial osteotomy in patients with symptomatic medial compartment osteoarthritis of the knee. • In the absence of reliable evidence, it is the opinion of the work group not to use the free-floating (un-fixed) interpositional device in patients with symptomatic medial compartment osteoarthritis of the knee.
European League Against Rheumatism: **Evidence-based Recommendations for the Management of Fibromyalgia Syndrome (2007)**[122]	• 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. • Tropisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia.
American Pain Society: **Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children (2005)**[123]	Pharmacologic therapies • Use multiple strategies and include both pharmacologic and nonpharmacologic therapies in the management of fibromyalgia syndrome. • For initial treatment of fibromyalgia syndrome, prescribe a TCA for sleep, in particular 10 to 30 mg amitriptyline or cyclobenzaprine at bedtime. • Use SSRIs such as fluoxetine, alone or in combination with TCAs, for pain relief. • Do not use NSAIDs as the primary pain medication for people with fibromyalgia syndrome. There is no evidence that NSAIDs are effective when used alone to treat fibromyalgia syndrome patients. NSAIDs, including cycloixegenase-2 selective agents and acetaminophen, may provide some analgesia when used with other medications. • Use tramadol (50 to 100 mg two or three times daily) for pain relief in people with fibromyalgia syndrome. Tramadol can be used alone or in combination with acetaminophen. • Use opioids for management of fibromyalgia syndrome pain only after all other pharmacologic and nonpharmacologic therapies have been exhausted. • Use sleep and anti-anxiety medications such as trazodone, benzodiazepines, nonbenzodiazepine sedatives, or L-dopa and carbidopa in fibromyalgia syndrome, especially if sleep disturbances such as restless leg syndrome are prominent. • Do not use corticosteroids in the treatment of fibromyalgia syndrome unless there is concurrent joint, bursa, or tendon inflammation. Fibromyalgia syndrome in children and adolescents • Utilize pharmacologic and nonpharmacologic strategies in the management of juvenile fibromyalgia syndrome. • Use CBT to reduce pain and psychological disability by enhancing self-efficacy, self-management, and skills for coping with pain. • Use aerobic exercise to minimize pain, improve sleep quality, enhance self-efficacy and increase positive mood.

Clinical Guideline	Recommendations
	• Emphasize sleep hygiene as part of the treatment plan, using both pharmacologic and nonpharmacologic techniques. • Treat anxiety and depression aggressively with both pharmacologic and nonpharmacologic approaches. • Fluoxetine should be the first antidepressant agent used to treat depression in children and adolescents; however, all of these medications should be used only with extreme caution and extensive parental education.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[124]	Painful polyneuropathy • 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 SNRIs (duloxetine, venlafaxine). • Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain. • 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. Post herpetic neuropathy • 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.
American Academy of Neurology/American Association of Neuromuscular and Electrodiagnostic Medicine/American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[125]	Anticonvulsants • 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. Antidepressants • 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. Opioids • Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other.

Clinical Guideline	Recommendations
	Other pharmacologic options • 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. Nonpharmacologic options • 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.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)**[126]	Diabetic neuropathy • Diabetic painful neuropathy is diagnosed clinically and must be differentiated from other painful conditions. • Interventions that reduce oxidative stress, improve glycemic control, and/or improve dyslipidemia and hypertension might have a beneficial effect on diabetic neuropathy. • Exercise and balance training may also be beneficial. • TCAs, anticonvulsants, and serotonin and norepinephrine reuptake inhibitors are useful treatments. • Large-fiber neuropathies are managed with strength, gait, and balance training; pain management; orthotics to treat and prevent foot deformities; tendon lengthening for pes equinus from Achilles tendon shortening; and/or surgical reconstruction and full contact casting as needed. • Small-fiber neuropathies are managed with foot protection (e.g., padded socks), supportive shoes with orthotics if necessary, regular foot and shoe inspection, prevention of heat injury, and use of emollient creams; however, for pain management, the medications mentioned above must be used.
American Diabetes Association: **Diabetic Neuropathies (2005)**[127]	Algorithm for the management of symptoms diabetic polyneuropathy • 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.
American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[128]	• 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.

Clinical Guideline	Recommendations
	• Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit. • The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, 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.

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.[1-12] Immediate- and extended-release formulations of venlafaxine are available generically; however, dexvenlafaxine (Pristiq®), duloxetine and levomilnacipran 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.[112-115] 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.[112-115]Antidepressants are recommended as first-line treatment for GAD, with the following agents considered treatment options: SSRIs, SNRIs, and nonsedating tricyclic antidepressants (TCAs).[116-118] For the treatment of neuropathic pain, the SNRIs are recommended as initial therapy along with TCAs and anticonvulsants.[124-128]

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 head to head trials in the class is limited.[14-111]

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