Therapeutic Class Overview
Selective Serotonin Reuptake Inhibitors

Therapeutic Class

- **Overview/Summary:** Antidepressants are used in the management of a variety of psychiatric disorders including mood disorders, eating disorders, premenstrual dysphoric disorders and anxiety disorders. Anxiety disorders include generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder and posttraumatic stress disorder. A mood disorder is defined as a disturbance in mood that is severe enough to impair a person's social, academic or occupational functioning for a specific duration of time.[1] Major depressive disorder and dysthymic disorder are two examples of mood disorders. Some antidepressants have also been used in nonpsychiatric conditions, such as diabetic peripheral neuropathy and nocturnal enuresis in children.

  Treatment for psychiatric disorders includes psychotherapy, pharmacotherapy or the combination of the two. The decision to implement psychotherapy is dependent upon patient willingness and severity of illness. Despite the variety of pharmacologic options available, all antidepressants appear to be equally efficacious for mood disorders. Therefore, initial treatment should depend on the individual's overall medical condition and current medication profile.[2] Pharmacology, tolerability and safety profiles differ among these classes and among individual agents. However, for all antidepressants, the Food and Drug Administration (FDA) requires manufacturers to include a black-box warning notifying prescribers of the potential for antidepressants to increase suicidal thoughts in children and adults.[3]

  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 SSRIs include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. These agents are believed to exert their effects through potentiating the serotonergic activity in the central nervous system.[1-2,5-13] All but fluvoxamine are Food and Drug Administration (FDA)-approved for the treatment of major depressive disorder.[1-19]

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
Citalopram (Celexa®*)	Depression (includes major depressive disorder),	Solution: 10 mg/5 mL Tablet: 10 mg 20 mg 40 mg	✔
Escitalopram (Lexapro®*)	Depression (includes major depressive disorder), generalized anxiety disorder,	Solution: 5 mg/5 mL Tablet: 5 mg 10 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		20 mg	
Fluoxetine (Prozac®*, Prozac Weekly®*, Sarafem®)	Bulimia nervosa, depression (includes major depressive disorder), obsessive-compulsive disorder, panic disorder, presmenstrual dysphoric disorder,	Capsule, immediate release: 10 mg 20 mg 40 mg Capsule, delayed release: 90 mg Solution: 20 mg/5 mL Tablet, immediate release: 10 mg 20 mg 60 mg	✔
Fluvoxamine (Luvox®, Luvox® CR)	Obsessive-compulsive disorder,	Capsule, extended release: 100 mg 150 mg Tablet: 25 mg 50 mg 100 mg	✔
Paroxetine hydrochloride (Paxil®*, Paxil CR®*)	Depression (includes major depressive disorder), generalized anxiety disorder*, obsessive-compulsive disorder*, panic disorder, presmenstrual dysphoric disorder†, posttraumatic stress disorder*, social anxiety disorder	Suspension, oral: 10 mg/5 mL Tablet, immediate release: 10 mg 20 mg 30 mg 40 mg Tablet, sustained release: 12.5 mg 25 mg 37.5 mg	✔
Paroxetine mesylate (Brisdelle®, Pexeva®)	Depression (includes major depressive disorder), obsessive-compulsive disorder, panic disorder, vasomotor symptoms associated with menopause; (moderate to severe)#	Capsule, immediate- release: 7.5 mg Tablet: 10 mg 20 mg 30 mg 40 mg	-
Sertraline (Zoloft®)	Depression (includes major depressive disorder), obsessive-compulsive disorder, panic disorder, presmenstrual dysphoric disorder, posttraumatic stress	Concentrate, oral: 20 mg/mL Tablet: 25 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	disorder, social anxiety disorder	50 mg 100 mg	

*Instant release only
†Sustained release only
#Brisdelle® only; Brisdelle® is not indicated for the treatment of any psychiatric condition.

Evidence-based Medicine

- Clinical trials demonstrating the safety and efficacy of the serotonin and norepinephrine reuptake - inhibitors are outlined in Table 4.[14-69]
- In one study which compared fluoxetine, imipramine and desipramine for duration of initial therapy, fluoxetine was taken for a longer period of time than desipramine or imipramine (P<0.001 for either desipramine or imipramine).[20] Statistical comparisons between the two TCAs were not done but they were numerically similar. The difference in duration of therapy was due primarily to less tolerability of desipramine and imipramine. Only 9% of the patients switched from fluoxetine due to adverse events while 27% and 28% assigned to desipramine and imipramine respectively switched due to adverse events (P<0.001 for both TCAs compared to fluoxetine).
- The overall length of antidepressant therapy (if the patient switched to another agent) was not different regardless of which agent was initiated first. In addition, response to medication as measured by the Hamilton Depression Rating Scale (HDRS) was equivalent.[21]
- One study comparing health care costs of fluoxetine versus imipramine and fluoxetine versus desipramine compared outpatient costs to primary care and to mental health. The authors found no difference in primary care visit cost in either comparison (fluoxetine versus desipramine; P=0.19 and fluoxetine versus imipramine; P=0.98). There was also no difference in mental health outpatient visit cost in either comparison group (fluoxetine versus desipramine; P=0.33 and fluoxetine versus imipramine; P=0.73).[23]
- A meta-analysis evaluated venlafaxine compared to SSRIs in treatment of major depressive disorder. Using a random effect model showed that venlafaxine was has statistically higher rates of achieving remission (odds ratio [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 with SSRIs (OR, 1.41, 95% CI, 1.10-1.79, P=0.006).[31]

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.[70-74]
  - 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.[70-71]
  - Antidepressants are recommended as first-line treatment for GAD, with the following agents considered treatment options: SSRIs, SNRIs, and nonsedating tricyclic antidepressants (TCAs).[75]

- Other Key Facts:
    - Fluoxetine is the only agent within the class that carries indications for treating bulimia nervosa, while Brisdelle® (paroxetine mesylate) is the only SSRI that is FDA-approved for the treatment of vasomotor symptoms associated with menopause.
    - All of the SSRI 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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Overview/Summary

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Treatment for psychiatric disorders includes psychotherapy, pharmacotherapy or the combination of the two. The decision to implement psychotherapy is dependent upon patient willingness and severity of illness. Despite the variety of pharmacologic options available, all antidepressants appear to be equally efficacious for mood disorders. Therefore, initial treatment should depend on the individual's overall medical condition and current medication profile.[2] Pharmacology, tolerability and safety profiles differ among these classes and among individual agents. However, for all antidepressants, the Food and Drug Administration (FDA) requires manufacturers to include a black-box warning notifying prescribers of the potential for antidepressants to increase suicidal thoughts in children and adults.[3]

The antidepressants can be classified in several ways, such as by chemical structure and/or presumed mechanism of activity. The agents included in this review belong to the category, selective serotonin-reuptake inhibitors (SSRIs).

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Citalopram (Celexa®*)	Selective Serotonin-reuptake Inhibitors	✔
Escitalopram (Lexapro®*)	Selective Serotonin-reuptake Inhibitors	✔
Fluoxetine (Prozac®*, Prozac Weekly®*, Sarafem®)	Selective Serotonin-reuptake Inhibitors	✔
Fluvoxamine (Luvox®, Luvox® CR)	Selective Serotonin-reuptake Inhibitors	✔
Paroxetine hydrochloride (Paxil®*, Paxil CR®*)	Selective Serotonin-reuptake Inhibitors	✔
Paroxetine mesylate (Brisdelle®, Pexeva®)	Selective Serotonin-reuptake Inhibitors	-
Sertraline (Zoloft®)	Selective Serotonin-reuptake Inhibitors	✔

*Generic in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indication[7-19]

Generic Name	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine hydrochloride	Paroxetine mesylate	Sertraline
Bulimia Nervosa			✔				
Depression (Includes Major Depressive Disorder)	✔	✔	✔		✔	✔	✔
Generalized Anxiety Disorder		✔			✔ *		
Obsessive-Compulsive Disorder			✔	✔	✔ *	✔	✔
Panic Disorder			✔		✔	✔	✔
Premenstrual Dysphoric Disorder			✔		✔ †		✔
Posttraumatic Stress Disorder					✔ *		✔
Social Anxiety Disorder					✔		✔
Vasomotor symptoms associated with menopause; (moderate to severe)						✔ #	

*Instant release only.
†Sustained release only.
#Brisdelle® only; Brisdelle® is not indicated for the treatment of any psychiatric condition.

A number of the selective serotonin-reuptake inhibitors (SSRIs) have been studied and used off-label for a variety of treatments.[4,5]These agents and their potential off label uses are:

- Citalopram: fibromyalgia, hot flashe, irritable bowel syndrome, pathological gambling, premenstrual disorders, stuttering, obsessive compulsive disorder, panic disorder, premenstrual dysphoric syndrome, generalized anxiety disorder, posttraumatic stress disorder
- Escitalopram: panic disorder
- Fluoxetine: borderline personality disorder, fibromyalgia, hot flashes, neuropathy (diabetic), nocturnal enuresis, Raynaud phenomenon
- Fluvoxamine: nocturnal enuresis, prevention of migraine (adults), bulimia nervosa, depression, panic disorder, social phobia
- Paroxetine hydrochloride: neuropathy, hot flashes, nocturnal enuresis, premenstrual disorders, prevention of migraine (adults), pruritus, stuttering
- Paroxetine mesylate: neuropathy, hot flashes, nocturnal enuresis, premenstrual disorders, prevention of migraine (adults), pruritus, stuttering
- Sertraline: nocturnal enuresis, extended-interval dosing, hot flashes, cholestatic pruritus

Pharmacokinetics

Table 3. Pharmacokinetics[7-19]

Generic Name	Bioavailability (%)	Metabolism	Active metabolites	Elimination (%)	Half-Life (hours)
Citalopram	≈80	Hepatic	Demethylcitalopram, didemethylcitalopram, citalopram-N-oxide, deaminated propionic acid derivative	Renal (20)	35
Escitalopram	≈80	Hepatic	S-demethylcitalopram, S-didemethylcitalopram	Renal (7)	27-32
Fluoxetine	Not Reported	Hepatic	Norfluoxetine	Hepatic	24-384
Fluvoxamine	53	Hepatic	Not reported	Renal (94)	15.6
Paroxetine hydrochloride	100	Hepatic	Not reported	Renal	21
Paroxetine mesylate	100	Hepatic	Not reported	Feces (36); renal (65)	3-65
Sertraline	Not Reported	Hepatic	N-desmethylsertraline	Feces (40-45); renal (40-45)	26; active metabolite 62-104

Clinical Trials

The selective serotonin-reuptake inhibitors (SSRIs) have been used in clinical practice for many years and studies have shown that these agents are efficacious when compared to placebo. These agents have also been shown to be as efficacious as other classes of antidepressants. Safety and efficacy appears to be comparable between the different SSRIs.

The dosing schedule of antidepressants varies according to the indication and individual being treated. Many generic antidepressants, including ones from the SSRI and tricyclic antidepressant (TCA) categories, are available in formulations that can be dosed once a day. A literature search revealed no peer-reviewed studies that reported a difference in clinical outcomes based on the antidepressant's dosing schedule or regimen. One randomized, nonblinded trial compared continued compliance rates with fluoxetine 90 mg once weekly to fluoxetine 20 mg once daily in patients who had previously received four weeks of fluoxetine 20 mg once daily.[20] At the end of 12 weeks, compliance rates significantly declined from 87% to 79% with the once daily fluoxetine; however, the effect on clinical outcomes was not measured. More patients in the once-weekly group discontinued therapy due to lack of efficacy than in the once-daily group but this difference was not statistically significant.

In one study which compared fluoxetine, imipramine and desipramine for duration of initial therapy, fluoxetine was taken for a longer period of time than desipramine or imipramine ($P<0.001$ for either desipramine or imipramine).[21] Statistical comparisons between the two TCAs were not done but they were numerically similar. The difference in duration of therapy was due primarily to less tolerability of desipramine and imipramine. Only 9% of the patients switched from fluoxetine due to adverse events while 27% and 28% assigned to desipramine and imipramine respectively switched due to adverse events ($P<0.001$ for both TCAs compared to fluoxetine). The overall length of antidepressant therapy (if the patient switched to another agent) was not different regardless of which agent was initiated first. In addition, response to medication as measured by the Hamilton Depression Rating Scale (HDRS) was equivalent.[22] The authors measured total health care costs and found no difference between the 3 groups.[23]

One study comparing health care costs of fluoxetine versus imipramine and fluoxetine versus desipramine compared outpatient costs to primary care and to mental health.[23] The authors found no difference in primary care visit cost in either comparison (fluoxetine versus desipramine; P=0.19 and fluoxetine versus imipramine; P=0.98). There was also no difference in mental health outpatient visit cost in either comparison group (fluoxetine versus desipramine; P=0.33 and fluoxetine versus imipramine; P=0.73).[23] A meta-analysis evaluated venlafaxine compared to SSRIs in treatment of major depressive disorder. Using a random effect model showed venlafaxine has statistically higher rates of achieving remission (odds ratio [OR],1.13; 95% confidence interval [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 with SSRIs (OR,1.41, 95% CI,1.10-1.79, P=0.006).[31]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Depression/Major Depressive Disorder				
Walsh et al[26] Antidepressants vs placebo	MA Adult outpatients with MDD	N=not specified 75 trials Duration not specified	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%-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[24] Antidepressants vs placebo	MA 31 trials of which 15 compared TCAs with placebo for relapse prevention of depression	N=4,410 31 trials Trials ranged in length from 6-36 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 with treatment discontinuation. The average rate of relapse on placebo was 41% compared with 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). The two-thirds reduction in risk of depressive relapse seemed to be largely independent of underlying risk of relapse, duration of treatment before randomization, or duration of the randomly allocated therapy. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Dunner et al[25] Paroxetine CR 12.5-62.5 mg vs placebo	Pooled analysis, DB, PC, RCT Adults with DSM-IV diagnosed MDD and nonsevere MDD	N=303 (4 studies) 8-12 weeks	Primary: Changes in depressive symptoms according to HAM-D-17 and CGI-I, patients achieving remission Secondary: Not reported	Primary: Statistically significant improvements in depressive symptoms in favor of paroxetine CR compared with placebo were observed in patients with both severe MDD (HAM-D treatment difference, –4.37 [95% CI, –6.31 to –2.42; P<0.001]) and nonsevere MDD (HAM-D-17 treatment difference, -1.89 [95% CI, –2.91 to –0.87; P<0.001]). The odds of CGI-I response were also significantly higher for patients receiving paroxetine CR than those receiving placebo, regardless of baseline depressive symptomatology (severe MDD: OR, 2.42 [95% CI, 1.50 to 3.91; P<0.001]; nonsevere MDD: OR, 1.63 [95% CI, 1.21 to 2.19; P<0.002]). Secondary: Not reported
Weihs et al[30] Bupropion SR tablets 100-300 mg/day vs paroxetine 10-40 mg/day	DB, MC, RCT Elderly (≥60 years) outpatients with MDD	N=100 6 weeks	Primary: HAM-D, HAM-A, CGI-I Secondary: Adverse effects	Primary: Measurements of efficacy were similar between the treatment groups, with both showing improved scores on all depression rating scales. Secondary: Somnolence and diarrhea were more common in paroxetine-treated patients (P<0.05). Headache, insomnia, dry mouth, agitation, dizziness and nausea occurred in >10% of patients in both groups.
Kavoussi et al[27] Bupropion SR tablets 100-300 mg/day vs sertraline 50-200 mg/day	DB, PG, RCT Outpatients with moderate-to-severe MDD	N=248 16 weeks	Primary: HAM-D, HAM-A, CGI-I, CGI-S Secondary: Adverse effects	Primary: Mean HAM-D, HAM-A, CGI-I and CGI-S scores improved over the course of treatment in both the bupropion SR group and the sertraline group; no between-group differences were observed on any of the scales. Secondary: Orgasm dysfunction was significantly (P<0.001) more common in sertraline-treated patients compared with bupropion SR-treated patients. The adverse events of nausea, diarrhea, somnolence and sweating were also experienced more frequently (P<0.05) in sertraline-treated patients.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No differences were noted between the two treatments for vital signs and weight.
Rocca et al[28] Citalopram 20 mg daily vs sertraline 50 mg daily	DB, RCT Patients who were non-demented outpatients, age >65 years, with minor depressive disorder or subsyndromal depressive symptomatology	N=138 8 weeks	Primary: Change in depressive symptoms and remission rates (HAM-D) Secondary: Not reported	Primary: Both treatments induced notable improvement of depressive symptoms. No statistically significant differences were found between the 2 treatments in decreases from baseline HAM-D scores. At the end of the trial, the mean total HAM-D score had fallen 55.0% in the citalopram group and 52.7% in the sertraline group (P value not reported). No significant differences in remission rates were observed between the two agents. For 1 month, 3 month and end follow-up periods; P=0.3466, 0.7570, and 0.2537, respectively. Secondary: Not reported:
Kerber et al[29] CO-MED Escitalopram 10 to 20 mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to 20 mg/day vs venlafaxine ER 150 to 300 mg/day plus mirtazapine 15 to 45 mg/day	Subgroup analysis of CO-MED Patients 18 to 75 years of age with MDD, with and without heart disease	N=665 (6% [n=40] reported having and being treated for heart disease) 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Morris et al[30] CO-MED Escitalopram 10 to 20 mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to 20 mg/day vs venlafaxine ER 150 to 300 mg/day plus mirtazapine 15 to 45 mg/day	Subgroup analysis of CO-MED Patients 18 to 75 years of age with MDD, with and without general medical conditions	N=665 (49.5% reported having no treated general medical conditions, 23.8% reported having 1, 14.8% reported having 2, and 11.9% reported having ≥3) 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, QOL, adverse events Secondary: Not reported	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: Not reported
DeSilva et al[31] Venlafaxine vs SSRIs	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Moore et al[32] Escitalopram 20 mg daily vs citalopram 40 mg daily	DB, MC, RCT Outpatients with MDD having an MADRS score of ≥30 at baseline	N=280 8 weeks	Primary: Change from baseline in the MADRS total score, adverse events, response to treatment, remission rate Secondary: Not reported	Primary: Escitalopram group exhibited a greater improvement in the MADRS score compared to the citalopram arm (–22.4 vs –20.3; P<0.05). There were more treatment responders with escitalopram than with citalopram (76.1% vs 61.3%; P<0.01). Remission rate was higher among patients on escitalopram compared with the citalopram group (56.1% vs 43.6%; P<0.05). Tolerability was similar in both treatment groups (P value not reported). Secondary: Not reported
Lam et al[33] Escitalopram 10-20 mg daily vs citalopram 20-40 mg daily	MA 3 DB, MC, R trials consisting of outpatients with MDD	N=1,321 3 trials 8 weeks	Primary: MADRS, response rate Secondary: CGI-I, CGI-S, HAMD	Primary: The analysis of pooled data demonstrated that the difference between citalopram and placebo was approximately constant; however, the difference between escitalopram and placebo (P=0.0010) and escitalopram and citalopram (P=0.0012) became greater the more severely depressed the patient was at baseline. No significant difference in response rate between the 2 treatment groups was seen at week 8. Secondary: Similar results were seen in the secondary outcomes.
Colonna et al[34] Escitalopram 10 mg daily vs	DB, RCT Patients with moderate-to-severe MDD	N=357 24 weeks	Primary: Change from baseline in MADRS	Primary: No significant difference was observed between groups in the MADRS at week 24 (P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
citalopram 20 mg daily			Secondary: Change from baseline in CGI-S	Escitalopram patients had significantly better scores on the CGI-S at week 24 compared to citalopram patients (P value not reported).
Gorman et al[35] Escitalopram 10-20 mg daily vs citalopram 20-40 mg daily	MA 3 MC, R trials consisting of outpatients with MDD	N=1,321 3 trials 8 weeks	Primary: MADRS, CGI-I Secondary: Not reported	Primary: Mean change in MADRS score from baseline at week 8 was significantly improved in both treatment groups compared to baseline (P<0.05). Mean change in MADRS score from baseline at week 8 was significantly improved in the escitalopram group compared to the citalopram group (P<0.05). Mean change in CGI-I score from baseline at week 8 was significantly improved in both treatment groups compared to baseline (P<0.05). No significant difference in CGI-I scores between the 2 treatment groups was reported at week 8 (P>0.05). Secondary: Not reported
Boulenger et al[36] Escitalopram 20 mg daily vs paroxetine 40 mg daily	DB, MC, R Patients with MDD and a baseline MADRS≥30	N=459 24 weeks	Primary: Change in MADRS score, withdrawal Secondary: HAM-A, CGI-S, remitters	Primary: The difference in MADRS scores at 24 weeks compared to baseline was –25.2 for the escitalopram treated patients compared to –23.1 for the paroxetine-treated patients (P=0.0105). Significantly more patients withdrew from the study in the paroxetine group (32%) compared to the escitalopram group (19%; P<0.05). Secondary: The difference in HAM-A scores at 24 weeks compared to baseline was –15.1 for the escitalopram-treated patients compared to –13.2 for the paroxetine-treated patients (P=0.01). The difference in CGI-S scores at 24 weeks compared to baseline was –2.8 for the escitalopram-treated patients compared to –2.6 for the paroxetine-treated patients (P=0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				After 24 weeks of treatment the proportion of remitters was 75% in the escitalopram group compared to 66.8% in the paroxetine group (P<0.05).
Ventura et al[37] Escitalopram 10 mg daily vs sertraline 50-200 mg daily	MC, RCT Patients 18-80 years of age with a diagnosis of depression	N=212 8 weeks	Primary: Change from baseline in MADRS scores using the LOCF method Secondary: Not reported	Primary: No significant differences were observed between groups in the change from baseline in MADRS scores at week 8 (P value not reported). Secondary: Not reported
Thase et al[38] Imipramine(mean dosage, 221 mg/day) vs sertraline (mean dosage, 163 mg/day)	DB, SS Patients with chronic major depression who failed to respond to 12 weeks of treatment with either imipramine or sertraline	N=168 12 weeks	Primary: HAM-D, CGI Secondary: Not reported	Primary: Response was defined as a 50% decrease in the 24 item HAM-D. The 2 groups were equal in response rates for completers, 63% and 55% for the sertraline and imipramine groups, respectively (P=0.16). However, in the ITT analysis there was a statistically better outcome for the sertraline group (P=0.03). Those patients going from sertraline to imipramine experienced significant increases in 8 adverse events and significant reductions in 3 adverse events while those patients going from imipramine to sertraline experienced a significant reduction in 7 adverse events and no increase in any adverse event. Secondary: Not reported
Versiani et al[39] Mirtazapine 15-60 mg daily vs fluoxetine 20-40 mg daily	DB, RCT Adult patients 18-65 years old with DSM-IV diagnosis for major depressive episode	N=297 8 weeks	Primary: Change from baseline in HAM-D-17 score Secondary: MADRS, CGI	Primary: No statistically significant differences were noted between the two groups in change from baseline HAM-D-17 score at any time point. Secondary: Mirtazapine treatment was associated with greater change in MADRS score at day 14 (–10.9 vs –8.5; P=0.006) and the proportion of patients with ≥50% decrease in MADRS score (21.4% vs 10.9%; P=0.031).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				On the CGI, the proportion of "much/very much improved" patients tended to be greater with mirtazapine (significant at day 7; 9.7% vs 3.4%; P=0.032). No significant between-group differences were observed for the majority of quality-of-life measures. Mirtazapine produced significantly better improvements on "sleeping assessment 1" (14.9±5.2 vs 13.7±5.4; P=0.028) and "sleeping assessment 2" (P=0.013) than fluoxetine. Both agents were generally well tolerated but mirtazapine-treated patients experienced a mean weight gain of 0.8±2.7 kg compared with a mean decrease in weight of 0.4±2.1 kg for fluoxetine-treated patients (P<0.001).
Wheatley et al[40] Mirtazapine 15-60 mg/day vs fluoxetine 20-40 mg/day	DB, MC, RCT Patients with MDD aged 18 to 75 years	N=123 6 weeks	Primary: HAM-D Secondary: Not reported	Primary: The mean HAM-D-17 scores were no different at week 6 for the two groups; although at week 3 (the estimated treatment difference was -3.40 in favor of mirtazapine; 95% CI, –6.10 to –0.76; P=0.006) and week 4 (the estimated treatment difference was -3.80 in favor of mirtazapine: 95% CI, –6.61 to –1.02; P=0.009), statistical significance reported for mirtazapine. No other assessment endpoints were statistically different between the two groups at week 6. Secondary: Not reported
Behke et al[41] Mirtazapine orally disintegrating tablets 30-45 mg/day vs sertraline 50-150 mg/day	DB, RCT Patients with MDD	N=345 8 weeks	Primary: HAM-D Secondary: CSFQ	Primary: Mirtazapine was significantly (P<0.05) more effective than sertraline at all assessments during the first 2 weeks of the study. After this time, HAM-D total scores were similar in both groups. Secondary: The CSFQ revealed a greater improvement in sexual functioning with mirtazapine than with sertraline at all assessments in both females and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				males. The differences were not statistically significant.
Rossini et al[42] Sertraline 150 mg daily vs fluvoxamine 200 mg daily	DB, RCT Patients >59 years of age with DSM-IV MDD	N=88 7 weeks	Primary: Response rate (HAM-D) Secondary: Not reported	Primary: Response rates were 55.6% for sertraline and 71.8% for fluvoxamine. No significant difference in final response rates were observed between treatment groups (P=0.12). Secondary: Not reported
Llorca et al[43] Escitalopram 10-20 mg daily vs citalopram 20-40 mg daily vs placebo	MA Patient between 18 and 80 years old with depression	N=506 (3 clinical trials) 8 weeks	Primary: MADRS Secondary: HAM-D, CGI-I, CGI-S	Primary: Mean change from baseline in MADRS total scores was significantly higher in the escitalopram-treated group compared with the citalopram-treated group (P=0.003). Response rates to escitalopram were 56% compared to 41% with citalopram (P=0.007). Secondary: The mean change in HAM-D from baseline between escitalopram and citalopram was in favor of escitalopram at endpoint (P=0.007). On both the CGI-I and CGI-S scales, patients showed a significant improvement at treatment endpoint in favor of escitalopram when compared with citalopram treatment (P=0.01 and P=0.001 for CGI-I and CGI-S, respectively).
Burke et al[44] Escitalopram 10 mg daily vs escitalopram 20 mg daily vs citalopram 40 mg daily	DB, MC, RCT Outpatients between the ages of 18 and 65, meeting DSM-IV criteria for a major depressive episode of ≥4 weeks in duration, with MADRS score of	N=491 9 weeks (1 week run-in; 8 weeks treatment phase)	Primary: Change from baseline in the MADRS total score at week 8 Secondary: Change from baseline in the MADRS total score at weeks	Primary: Mean changes from baseline for the MADRS score were significantly greater compared with placebo in the two escitalopram groups (P<0.01) and in the citalopram group (P≤0.05). There were no significant differences in the mean change of MADRS score from baseline to endpoint between the escitalopram 20 mg daily and citalopram 40 mg daily groups (P=0.09). Secondary: Patients randomized to the two escitalopram groups and the citalopram

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	>22 and a minimum score of 2 on item 1 (depressed mood) of the HAM-D score		1,2,4 and 6, change from baseline in the HAM-D, CGI-S, CGI-I, HAM-A, QOL, and CES-D	arm exhibited significantly greater improvement in the HAM-D score from baseline compared with placebo (P<0.01 and P≤0.05, respectively). Response to treatment was observed in 50.0% of escitalopram 10 mg, 51.2% of escitalopram 20 mg, and 45.6% of citalopram 40 mg groups; the difference in response rate was significantly greater than that of placebo group (P<0.01) but not statistically different among the three active groups (P value not reported). There were no significant differences in the mean change of CGI-I, HAM-D and CGI-S scores from baseline to endpoint between the escitalopram 20 mg daily and citalopram 40 mg daily groups (P=0.09). All three treatment groups exhibited significantly improved HAM-D depressed mood scores from baseline to endpoint (P≤0.01). Patients randomized to the escitalopram 10 mg and 20 mg group exhibited significantly greater improvement in the HAM-A score from baseline compared with placebo (P=0.04 and P<0.01, respectively). Mean changes from baseline for the QOL score were significantly greater compared with placebo in the escitalopram 10 mg group (P=0.04) and in the escitalopram 20 mg group (P<0.01). Mean changes from baseline for the CES-D score were significantly greater compared with placebo in the escitalopram 10 mg group (P=0.02) and in the escitalopram 20 mg group (P<0.01). There was no statistically significant difference in the discontinuation rates due to adverse events between the escitalopram 10 mg and placebo groups (P value not reported); however, escitalopram 20 mg and citalopram 40 mg groups had significantly greater discontinuation rates compared to placebo (P≤0.05). The rate of adverse effects was not significantly different between the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				escitalopram 10 mg group and placebo (79.0% vs 70.5%; P=0.14). Escitalopram 20 mg and citalopram 40 mg groups were associated with significantly greater adverse event rates compared to placebo (85.6% vs 86.4%; P<0.01).
Goldstein et al[45] Duloxetine 20-40 mg twice a day vs paroxetine 20 mg daily vs placebo	DB, PC, RCT Patients with depression in the outpatient setting	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-item total change by 3.62 points (95% CI, 1.38 to 5.86; P=0.002). Duloxetine at 40 mg/day was also significantly more efficacious than placebo by 2.43 points (95% CI, 0.19 to 4.66; P=0.034), while paroxetine was not (1.51 points; 95% CI, -0.55 to 3.56; P=0.150). 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).
Fava et al[46] Fluoxetine 20 mg daily vs sertraline 50 mg daily vs paroxetine 20 mg daily	DB, MC, RCT Patients with depression at least 18 years of age	N=284 10 to 16 weeks	Primary: HAM-D-17 scores Secondary: Improvement in insomnia/sleep disturbances	Primary: As indicated by baseline-to-endpoint improvement on the HAM-D-17, there were no statistically significant differences between fluoxetine, sertraline and paroxetine on all outcome measures (P=0.365). Secondary: Insomnia improvement when using the sleep disturbance factor was similar in all patients with no significant difference between groups (P=0.868).
Cipriani et al[47]	MA	N=9,311	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluoxetine 20-80 mg daily vs sertraline 50-200 mg daily vs nortriptyline 50-175 mg daily vs amitriptyline 75-300 mg daily vs venlafaxine 75-200 mg daily vs imipramine 75-300 mg daily vs nefazodone 200-500 mg daily vs citalopram 20-40 mg daily vs desipramine 125-250 mg daily	Study participants were diagnosed with depression	132 studies Duration varied	Number of patients who responded to treatment (HAM-D, MADRS) Secondary: Tolerability	On a dichotomous outcome fluoxetine was less effective than sertraline (PetoOR, 1.40; 95% CI, 1.11 to 1.76), mirtazapine (PetoOR, 1.64; 95% CI, 1.01 to 2.65) and venlafaxine (PetoOR, 1.40; 95% CI, 1.15 to 1.70; P value 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs paroxetine 20-60 mg daily vs placebo vs pramipexole* 5 mg daily vs fluvoxamine 100-150 mg daily vs trazodone 50-400 mg daily vs bupropion 225-450 mg daily vs clomipramine 50-200 mg daily vs duloxetine 20-120 mg daily vs mirtazapine 30-60 mg daily				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs doxepin 100-225 mg daily				
Bull et al[48] Continuation of an SSRI vs discontinuation of an SSRI vs switching of an SSRI	RETRO Adult patients diagnosed with a depressive disorder, taking an SSRI for at least 6 months were interviewed over the phone; prescribing physicians were asked to complete a survey	N=137,401 physicians and patients, respectively ~6 months	Primary: Patient-physician communication about therapy duration and adverse effects, therapy discontinuation or switching of medication within 3 months of SSRI use, BDI-FS, depression symptoms Secondary: Not reported	Primary: While 72% of physicians reported instructing their patients on taking SSRIs for a minimum of 6 months, only 34% of patients acknowledged receiving this information from their physician and 56% reported receiving no instructions at all (P value not reported). Patients instructed to continue therapy for < 6 months were 3 times more likely to discontinue therapy prematurely compared to therapy for a longer duration (OR, 3.12; 95% CI, 1.21 to 8.07; P<0.001). Patients informed about adverse effects common with their medication were less likely to discontinue therapy than patients who did not have this discussion with their physician (OR, 0.49; 95% CI, 0.25 to 0.95). Patients who discussed adverse effects with their physicians were more likely to switch medications (RR, 5.60; 95% CI, 2.31 to 13.60). Patients experiencing adverse effects were 3 times more likely to switch their medication (OR, 3.09; 95% CI, 1.30 to 7.31). Less than three follow-up visits, and lack of therapeutic response to medication at 3 months were also associated with a higher incidence of therapy discontinuation (P=0.002, P<0.001, respectively). Patients who continued to have severe symptoms, based on the BDI-FS scale, were 6 times more likely to switch their medication (OR, 6.15; 95% CI, 2.11 to 17.89). Secondary: Not reported
Anderson et al[49]	MA	N=10,706	Primary: HAM-D, MADRS	Primary: Efficacy was based on 102 studies (5,533 SSRI patients and 5,173 TCA

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
TCAs vs SSRIs	Patients with depression	102 studies Duration varied	Secondary: Adverse events	patients). Efficacy was determined by comparing the mean reduction in depression scores based upon the HAM-D or the MADRS. There was no statistical difference in efficacy between the two groups (effect size, –0.03; 95% CI, –0.09 to 0.03). TCAs did appear more effective for inpatients (–0.23; 95% CI, –0.40 to -0.05). Secondary: SSRIs were better tolerated with discontinuations due to adverse effects significantly greater in the TCA group (12.4% vs 17.3%; P<0.0001).
MacGillivray et al[50] TCAs vs SSRIs	MA Patients with depression in primary care	N=2,951 11 studies Duration varied	Primary: HAM-D, MADRS Secondary: Tolerability	Primary: Efficacy between SSRIs and TCAs did not differ significantly (SMD, fixed effects 0.07; 95% CI, –0.02 to 0.15; P<0.11). Secondary: Significantly more patients receiving a TCA withdrew from treatment (RR, 0.78; 95% CI, 0.68 to 0.90; P<0.0007) and withdrew specifically because of side effects (RR, 0.73; 0.60 to 0.88; P<0.001).
Steffens et al[51] TCAs vs SSRIs	MA Patients with depression	N=not specified 34 studies Duration varied	Primary: HAM-D Secondary: Frequency of side effects	Primary: Overall, the response rate to treatment for patients who completed a trial was 63.2% for SSRIs and 68.2% for TCAs (P=0.038). For the ITT groups, these rates dropped to 48.0% and 48.6% (P=NS), respectively. Significantly more TCA-treated than SSRI-treated subjects dropped out due to either lack of efficacy or adverse reactions (30.0% vs 24.7%; P=0.01). Secondary: Patients taking SSRIs experienced significantly more gastrointestinal problems and sexual dysfunction, whereas treatment with TCAs produced significantly more complaints of sedation, dizziness and anticholinergic symptoms.
Generalized Anxiety Disorder				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Davidson et al[52] Escitalopram 10-20 mg daily	FD, MC, OL extension study Patients who completed an 8-week, DB, PC, lead-in and were diagnosed with GAD were eligible to enter extension	N=526 24 week	Primary: CGI-I, HAM-A score ≤7 Secondary: Safety	Primary: Ninety two percent of the patients were considered responders. Secondary: Adverse events led to study withdrawal in 9.9% of patents. The most frequent adverse events leading to study withdrawal were ejaculations disorder (1.6%), insomnia (1.3%) and nausea (1.0%). Serious adverse events were reported by 2.1% of patients, including 1 completed suicide.
Goodman et al[53] Escitalopram 10-20 mg daily vs placebo	DB, MC, PC Patients 18-80 years of age with DSM-IV defined GAD	N=850 8 weeks	Primary: HAM-A Secondary: CGI-S, CGI-I	Primary: Escitalopram significantly improved mean HAM-A total scores (the primary efficacy measure) relative to placebo with the mean change from baseline to week 8 in HAM-A total score –10.1±0.3 for escitalopram and –7.6±0.3 for placebo (P<0.001). Secondary: Escitalopram led to statistically significant improvements compared to placebo in both HAM-A subscales: psychic anxiety (–5.8+0.2 vs –3.9±0.2; P<0.001; and somatic anxiety (–4.3±0.2 vs –3.7±0.2; P=0.02). At endpoint, 47.5% of escitalopram-treated patients and 28.6% of placebo-treated patients were responders (P<0.001), and 26.4% of escitalopram-treated patients and 14.1% of placebo-treated patients were remitters (P<0.001). CGI-I response rates at endpoint were 52% for escitalopram and 37% for placebo (P<0.001).
Dahl et al[54] Sertraline 50-150 mg daily vs placebo	DB, MC, RCT Patients were out-patients who met DSM-IV criteria for GAD based on clinical assessment	N=373 12 weeks	Primary: The change from baseline to endpoint in HAM-A total score of the ITT population	Primary: Sertraline treatment was associated with significant improvement (P<0.001) in the HAM-A psychic anxiety factor. Significant separation from placebo in primary endpoint was significant by week 4 for sertraline (52%) compared to placebo (34%; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and a structured interview		Secondary: CGI-S, CGI-I, MADRS, Q-LES-Q	Clinically meaningful improvement (≥30% reduction in psychic symptom severity) was achieved by week 4 in the majority of patients (P=0001). Secondary: Global improvement was modestly but consistently better correlated with improvement in psychic anxiety (P value not reported). The degree of correlation was similar, regardless of study treatment. Quality of life was significantly improved in the sertraline group compared with placebo with improvement seen in 51% of patients on sertraline compared with 35% on placebo (P<0.01).
Bielski, Bose et al[55] Escitalopram 10 to 20 mg daily vs paroxetine 20 to 50 mg daily	DB, RCT Patients diagnosed with GAD via the DSM-IV criteria	N=121 24 weeks	Primary: Mean change from baseline in HAM-A scores at week 24, treatment-emergent adverse effects Secondary: Not reported	Primary: After 24 weeks of treatment, patients receiving escitalopram had significantly greater improvement in the HAM-A scores compared to the paroxetine group (–15.3 vs –13.3; P=0.13). Significantly fewer patients withdrew from escitalopram than paroxetine treatment due to adverse events (6.6% vs 22.6%; P=0.02). Significantly more paroxetine than escitalopram patients experienced treatment-related adverse events (88.7% vs 77.0%). The following adverse events were noted to occur more frequently in the paroxetine group compared to the escitalopram-treated patients: insomnia (25.8% vs 14.8%), constipation (14.5% vs 1.6%), ejaculation disorder (30.0% vs 14.8%), anorgasmia (26.2% vs 5.9%) and decreased libido (22.6% vs 4.9%); (P value not reported). In contrast, diarrhea and upper respiratory tract infection were reported more frequently with escitalopram than paroxetine (21.3% vs 8.1%, and 14.8% vs 4.8%, respectively; P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ball et al[56] Paroxetine 10-40 mg daily vs sertraline 25-100 mg daily	DB, FD, PG Patients with primary GAD	N=55 8 weeks	Primary: HAM-A scores as well as responder and remission rates based on CGI Secondary: Improvement in IU-GAM	Primary: Both sertraline and paroxetine groups displayed significant reductions in HAM-A scores from baseline to end of treatment (P<0.001). The mean percent reduction in HAM-A scores was 57.3%+27.6% for the paroxetine group and 55.9%+27.6% for the sertraline group. With treatment response defined as 50.0% reduction in HAM-A from baseline to posttreatment, the percent of treatment responders was 68.0% in the paroxetine group and 61.0% in the sertraline group (P value not reported). Secondary: Both sertraline and paroxetine groups displayed significant reductions in IU-GAMS scores from baseline to end of treatment (P<0.001). With treatment response defined as a reduction of greater than 50% in IU-GAMS scores from baseline to posttreatment, 40% of the paroxetine group responded compared to 25% of the sertraline group (P value not reported).
Schmitt et al[57] Venlafaxine 37.5 mg daily vs venlafaxine 75 mg daily vs venlafaxine 150 mg daily vs placebo	MA All randomized controlled trials assessing the use of antidepressants in GAD, non-randomized trials and those that included patients with both GAD and another Axis I comorbidity were excluded	N=2,238 Duration of study varied from 8-28 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	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs paroxetine 20 mg daily vs imipramine 143 mg daily vs trazodone 225 mg daily vs diazepam 26 mg daily vs venlafaxine 225 mg daily vs imipramine 50-100 mg daily vs paroxetine 20 mg daily vs sertraline			dropping out during the trial	For paroxetine the calculated RR was 0.72 (95% CI, 0.56 to 0.92), and the calculated NNT was 6.72 (95% CI, 3.90 to 24.70). For paroxetine vs imipramine the calculated RR was 1.73 (95% CI, 0.31 to 9.57). Secondary: No significant differences were found between antidepressants and placebo with regard to drop out rate. The RR for dropout for any antidepressant was 0.95 (95% CI, 0.84 to 1.09). Similarly, when individual antidepressants were considered, no differences were found between individual treatments and the placebo group: imipramine: RR, 0.71 (95% CI, 0.41 to 1.24); venlafaxine: RR, 0.86 (95% CI, 0.72 to 1.02); sertraline: RR, 0.45 (95% CI, 0.03 to 5.84); paroxetine: RR, 1.15 (95% CI, 0.74 to 1.78); and paroxetine vs imipramine: RR, 1.62 (95% CI, 0.58 to 4.48).
Obsessive-compulsive Disorder				
Mundo et al[58] Fluvoxamine 100-300 mg daily	RCT Patients with OCD	N=30 10 weeks	Primary: NIMH-OC, Y-BOCS, HAM-D,	Primary: No significant differences were noted between the treatment groups (P=0.000).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs paroxetine 20-60 mg daily vs citalopram 20-60 mg daily			CGI Secondary: Not reported	Results performed on NIMH-OC and Y-BOCS obsessions, compulsions, and total scores did not show any significant effect of the variable group (treatment) but only a significant effect of time (NIMH-OC; P=0.000, Y-BOCS obsessions; P=0.000, Y-BOCS compulsions; P=0.000, Y-BOCS total; P=0.000) and no significant effect of their interaction. Similar results were derived from the ANOVA with repeated measures performed on HAM-D total scores (time effect: P=0.000). Secondary: Not reported
Panic Disorder				
Sheehan et al[59] Paroxetine CR 25-75 mg daily vs placebo	DB, MC, PC, RCT Patients with DSM-IV panic disorder with or without agoraphobia	N=889 10 weeks	Primary: Patients free of panic attacks in the 2 weeks prior to endpoint Secondary: CGI-I, HAM-A	Primary: Paroxetine CR was statistically more effective compared to placebo on the primary outcome measure: 63% vs 53%; P<0.005. Secondary: Paroxetine CR was statistically more effective compared to placebo in the proportion of patients with improved CGI-I (79% vs 55%; P<0.001). Paroxetine CR was statistically more effective compared to placebo in alleviating general anxiety symptoms as measured by HAM-A; P<0.001. Adverse events leading to study withdrawal occurred in 11% of patients in the paroxetine CR group and 6% of patients in the placebo group.
Stahl, Gergel et al[60] Citalopram vs escitalopram vs	DB, PC, RCT Patients 18-80 years of age diagnosed with panic disorder	N=366 10 weeks	Primary: Frequency of panic attacks at week 10 assessed by the Modified Sheehan Panic and Anticipatory Anxiety Scale	Primary: A significant decrease in the frequency of panic attacks was observed in both the escitalopram and citalopram groups compared to placebo (P≤0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			Secondary: Not reported	
Rampello et al[61] Escitalopram vs citalopram	OL Elderly patients diagnosed with panic attacks	N=40 8 weeks	Primary: Weekly rate of panic attacks Secondary: Change from baseline in HAM-A, HAM-D, Cooper Disability Scale scores	Primary: No significant difference was observed at 8 weeks in the weekly rate of panic attacks (P value not reported). Secondary: No significant differences were observed at 8 weeks in the HAM-A and HAM-D and in the Cooper Disability Scale scores (P value not reported). A significant improvement from baseline in outcome measures was observed in the escitalopram at 2 weeks and in the citalopram group at 4 weeks (P<0.001 and P<0.01 respectively).
Bandelow et al[62] Sertraline 50-150 mg daily vs paroxetine 40-60 mg daily	DB, MC, PG, RCT Patients with panic disorder between the ages of 18 and 65 years	N=225 12 weeks	Primary: Clinician-rated PAS Secondary: CGI-I score	Primary: Treatment with sertraline and paroxetine resulted in equivalent levels of improvement on the primary outcome measure from baseline, the PAS total score (P=0.749). The efficacy of sertraline and paroxetine was equivalent (P=0.487) with regard to the PAS across the agoraphobia and nonagoraphobia subtypes. Secondary: Global response (CGI-I score ≤2) was achieved by 82% of the efficacy-evaluable population treated with sertraline compared with 78% of patients treated with paroxetine (P=0.320).
Ballenger et al[63] Paroxetine 10 mg daily vs paroxetine 20 mg daily	DB, PC, PG, RCT Patients with panic disorder 18 years of age or older	N=278 10 weeks	Primary: Change in panic attacks from baseline, CGI-S Secondary: Marks-Sheehan Phobia Scale,	Primary: The percent of subjects free of panic attacks were 86.0% (40 mg), 65.2% (20 mg) and 67.4% (10 mg) (P<0.019 at weeks 4 and 10). No significant differences were noted between groups in mean change from baseline in number of full panic attacks. No significant differences were reported between groups in percentage of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs paroxetine 40 mg daily			HAM-A, MADRS	subjects with a 50% reduction from baseline in number of full panic attacks. The mean CGI global and severity ratings were 81.2% (40 mg), 75.4% (20 mg), 57.8% (10 mg), 51.5% (placebo) (significantly higher with 40 and 20 mg, P<0.019). Secondary: The mean score for public avoidance on the Marks-Sheehan Phobia Scale declined nonsignificantly in all groups. Significant improvement in the score on the HAM-A (total) was observed for the 40-mg paroxetine group (in the end-point but not completer analysis). Improvement in depressive symptoms (MADRS) was significantly greater for the 40-mg paroxetine group than for the placebo group at week 10.
Posttraumatic Stress Disorder				
Davidson et al[64] Fluoxetine 10-60 mg daily vs placebo	OL, RCT Patients diagnosed with PTSD, between ages of 18 and 70; patients were excluded if history of bipolar, schizophrenia, organic brain disease, alcohol or drug abuse, or mental retardation were present	N=123 6 months	Primary: Rate of relapse defined by a change in CGI-I score that reverted back to no improvement relative to baseline or worse, CGI-I score which increased by at least 2 points Secondary: CGI-S	Primary: On the CGI-I, there was a significantly higher number of relapses in the group who received placebo (50.0%) compared to the group that received fluoxetine (22.2%; P=0.029). Secondary: Differences between the fluoxetine and the placebo group failed to meet significance for CGI-S (P=0.08).
Friedman et al[65]	DB, PC, RCT	N=169	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Sertraline 25-200 mg daily vs placebo	Patients had DSM-III-R diagnosis of combat-related PTSD and scored 50 or higher on CAPS-2 at the end of a 1 week placebo run in period	12 weeks	Mean change in CAPS-2 total severity score from baseline to endpoint Secondary: IES, CGI-S	The adjusted mean changes on the CAPS-2 total severity score for the sertraline and placebo groups were –13.1 and –15.4, respectively; the difference was not statically different (P=0.26). Secondary: The adjusted mean changes for the IES total score were –8.7 and –8.1 for the sertraline and placebo groups, respectively. The difference was not statistically significant (P=0.28). For the CGI-S scale, there was no statically significant difference between treatment groups in changes from baseline to endpoint. The mean changes from baseline to endpoint were –0.5 and –0.6, respectively (P=0.41).
Premenstrual Dysphoric Disorder				
Pearlstein et al[66] Paroxetine CR 12.5 or 25 mg daily vs placebo	DB, MC, PC, RCT Patients with PMDD aged 18-45 years with regular menstrual cycles	N=47 3 menstrual cycles	Primary: VAS-Mood Secondary: VAS-Total	Primary: A statistically significant difference was observed in favor of paroxetine CR 25 mg vs placebo on the VAS-Mood (P<0.001) and for paroxetine CR 12.5 mg vs placebo (P=0.013). Secondary: Paroxetine CR demonstrated greater mean reduction in VAS-Total scores compared with placebo at each time point. At the treatment cycle 3 last-observation-carried-forward endpoint, statistically significant differences in mean changes were observed in favor of paroxetine CR 25 mg vs placebo (P<0.001) as well as for paroxetine CR 12.5 mg vs placebo (P=0.011).
Steiner et al[67] Paroxetine CR 12.5 mg daily vs paroxetine CR 25 mg daily	DB, MC, PC, RCT Female patients aged 18-45 years who had regular menstrual cycles and who met the criteria for PMDD	N=373 3 menstrual cycles	Primary: VAS-Mood Secondary: Change form baseline to treatment cycle 3 in the sum of the	Primary: A statistically significant difference was demonstrated in favor of paroxetine CR 25 mg and 12.5 mg compared with placebo (paroxetine CR 25 mg vs placebo: adjusted mean difference, –10.79 mm; 95% CI, –16.46 to –5.12; P<0.001; paroxetine CR 12.5 mg vs placebo: adjusted mean difference, –7.66 mm; 95% CI, –13.25 to –2.08; P=0.007) for change from baseline in mean luteal phase VAS-Mood score at the treatment cycle 3 last-observation-carried-forward endpoint.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	as outlined in DSM-IV		11 VAS symptoms; change from baseline in the PMTS-O total score	Secondary: The mean change from baseline in the VAS-Total score, (paroxetine CR 25 mg vs placebo -77.82 mm; P=0.006; paroxetine CR 12.5 mg vs placebo –73.13 mm; P=0.009) The mean change from baseline in the PMTS-O total score (paroxetine CR 25 mg vs placebo –3.21 mm; P=0.005; paroxetine CR 12.5 mg vs placebo –1.78 mm; P=0.093), the CGI-S (paroxetine CR 25 mg vs placebo –0.61 mm; P=0.004; paroxetine CR 12.5 mg vs placebo –0.27 mm; P=0.177). The mean change from baseline in the SDS total score (paroxetine CR 25 mg vs placebo –2.74 mm; P=0.016; paroxetine CR 12.5 mg vs placebo –2.33 mm; P=0.028) was greater compared with placebo.
Multiple Disease				
Mullins et al[68] Sertraline vs paroxetine vs citalopram	RETRO Patients with depression, PTSD or social anxiety disorder	N=14,933 Data gathered from 1/1/99-6/30/02	Primary: Persistence, switching, discontinuation Secondary: Not reported	Primary: Compared with patients receiving sertraline and citalopram, those receiving paroxetine had lower rates of persistence (23.79% for paroxetine vs 25.96% for sertraline [P=0.0093] and 26.56% for citalopram [P=0.0022]) and higher rates of switching (3.55% for paroxetine vs 3.32% for sertraline [P=0.5076] and 2.78% for citalopram [P=0.0359]) and discontinuation (72.66% for paroxetine vs 70.72% for sertraline [P=0.0258] and 70.66% for citalopram [P=0.0334]). Survival curves showed that persistence rates with sertraline and citalopram were significantly greater than with paroxetine (P<0.05). Secondary: Not reported
Stein et al[69] Cochrane Review, including 17 SSRI trials, 3 MAOI (phenelzine) trials, 9 trials with	MA 36 randomized controlled trials for social anxiety	N=5,264 36 trials Duration	Primary: CGI-I scale Secondary: LSAS	Primary: Summary statistics for responder status (assessed using the CGI from 25 short-term comparisons demonstrated a higher degree of efficacy of various medications over placebo (RR of non-response, 0.63; 95% CI, 0.55 to 0.72).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
RIMAs (including moclobemide*, brofaromine*), 9 trials with "other medications" including benzodiazepines, beta blocker, buspirone, gabapentin, and olanzapine in social anxiety disorder	disorders 25 trials were short term (≤14 weeks or less); 7 trials had maintenance component; 8 trials had a relapse component; trials were completed prior to 2003	varied		Response to treatment by SSRIs (N=11; RR, 0.67; 95% CI, 0.59 to 0.76), MAOIs (N=3; RR, 0.43; 95% CI, 0.24 to 0.76) and RIMAs (N=6; RR, 0.74; 95% CI, 0.59 to 0.91) supported the value of these agents. However, the SSRIs were significantly more effective than the RIMAs (P<0.00001). Secondary: LSAS showed a statistically significant difference between medication and placebo (weighed mean difference, –15.56; 95% CI, –17.95 to -13.16), with this effect once again most evident for the SSRIs. Medication was also significantly more effective compared to placebo in reducing symptom clusters, comorbid depressive symptoms, and associated disability. The value of long-term medication treatment in treatment responders was supported by 3 comparisons from maintenance studies (RR, 0.58; 95% CI, 0.39 to 0.85) and 5 comparisons from relapse prevention studies (RR, 0.33; 95% CI, 0.22 to 0.49).

*Product not available in the United States.
Study abbreviations: DB=double-blind, FD=fixed dose, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SS=switch study
Miscellaneous abbreviations: ANOVA=analysis of variance, BDI-FS=Beck Depression Inventory Fast Screen, CAPS-S=Clinician -Administered PTSD Scale, CES-D=Center for Epidmiological Studies-Depression Scale, CGI=Clinical Global Impression, CGI-I=Clinical Global Impression, Improvement, CGI-S=Clinical Global Impression, Severity, CI=confidence interval, CR=controlled release, CSFQ=Changes in Sexual Functioning Questionnaire, DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, ER=extended-releaseGAD=generalized anxiety disorder, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, IES= Impact of Event Scale, ITT-Intent-to-Treat Analysis, IU-GAM= Indiana University Generalized Anxiety Measurement Scale, LOCF=last observation carried forward, LSAS=Liebowitz Social Anxiety Scale, MADRS=Montgomery-Åsberg Depression Rating Scale, MAOIs=Monoamine Oxidase Inhibitors, MDD=major depressive disorder, NIMH-OC=National Institute of Mental Health-Obsessive-Compulsive Scale, NNT=number needed to treat, OCD=obsessive compulsive disorder, PAS=Panic and Agoraphobia Scale, PMDD=premenstrual dysphoric disorder, PMTS=Premenstrual Tension Scale, PTSD=Posttraumatic Stress Disorder, QOL=Quality of Life, Q-LES-Q=Quality of Life, Enjoyment, and Satisfaction Questionnaire, RIMAs=reversible monoamine oxidase inhibitors, RR=relative risk, SMD=standard mean difference, SR=sustained release, SSRIs=Selective Serotonin-reuptake Inhibitors, TCAs=tricyclic antidepressants, VAS=Visual Analog Scale, Y-BOCS=Yale-Brown Obsessive-Compulsive Scale

Special Populations

Table 5. Special Populations[5-19]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Citalopram	No overall differences in safety or efficacy have been routinely observed in the elderly compared to younger individuals. Safety and efficacy in children have not been established.	No dosage adjustment required, use with caution.	Use with caution.	C	Yes, % not reported.
Escitalopram	No overall differences in safety or efficacy have been routinely observed in the elderly compared to younger individuals. Safety and efficacy in children have not been established.	No dosage adjustment required, use with caution.	Use with caution.	C	Yes, % not reported.
Fluoxetine	No overall differences in safety or efficacy have been routinely observed in the elderly compared to younger individuals. The safety and efficacy in children younger than 8 years of age in major depressive disorder and younger than 7 years of age in obsessive compulsive disorder have not been established.	No dosage adjustment required.	Use a lower or less frequent dose in patients with cirrhosis.	C	Yes, % not reported.
Fluvoxamine	No overall differences in safety were observed between elderly and younger patients. Safety and effectiveness in the pediatric population other than pediatric patients with obsessive compulsive disorder have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Yes, % not reported.
Paroxetine hydrochloride	Reduce the initial dosage in elderly patients.	Reduce the initial dosage.	Reduce the initial dosage.	D	Yes, % not reported.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children have not been established.				
Paroxetine mesylate	Reduce the initial dosage in elderly patients (Pexeva®). No dosage adjustment is needed in elderly patients (Brisdelle®). Safety and efficacy in children have not been established.	Reduce the initial dosage.	Reduce the initial dosage.	D (Pexeva®) X* (Brisdelle®)	Yes, % not reported.
Sertraline	No overall differences in safety were observed between elderly and younger patients. The effectiveness of sertraline in pediatric patients with major depressive disorder, panic disorder, post traumatic stress disorder, premenstrual dysphoric disorder, or social anxiety disorder has not been established.	No dosage adjustment required.	Use a lower or less frequent dose.	C	Unknown

*Brisdelle® contraindicated in pregnant women because menopausal VMS does not occur during pregnancy and paroxetine can cause fetal harm.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[5-19]

Adverse Event	Citalo-pram	Escitalo-pram	Fluox-etine	Fluvox-amine	Parox-etine	Ser-traline
Cardiovascular						
Angina	-	-	<1	-	-	-
Arrhythmia	-	-	<1	-	-	-
Atrial arrhythmia	-	-	-	-	-	<1
Atrial fibrillation	-	<1	-	-	-	-
Atrioventricular block	-	-	-	-	-	<1
Bradycardia	-	<1	-	-	-	<1
Chest pain	-	1-10	1-10	-	3	1-10
Chest tightness	-	<1	-	-	-	-
Congestive heart failure	-	-	<1	-	-	-
Electrocardiogram abnormal	-	<1	-	-	-	-
Hemorrhage	-	-	1-10	<1	-	-
Hypertension	-	1-10	1-10	-	✔	-

Adverse Event	Citalo-pram	Escitalo-pram	Fluox-etine	Fluvox-amine	Parox-etine	Ser-traline
Myocardial infarct	-	-	<1	-	-	-
Palpitation	-	1-10	1-10	-	2-3	1-10
Postural hypotension	-	-	<1	-	-	-
Pulmonary hypertension	-	-	-	-	-	<1
QT_c prolongation	<1	<1	<1	-	-	<1
Syncope	-	<1	<1	-	-	-
Tachycardia	-	<1	-	-	✔	-
Torsades de pointes	<1	<1	<1	-	-	<1
Vasculitis	-	-	-	-	-	<1
Vasodilation	-	-	1-5	-	2-4	-
Ventricular arrhythmia	<1	<1	-	-	-	-
Ventricular tachycardia	-	-	<1	-	-	<1
Central Nervous System						
Abnormal dreams	-	1-10	1-5	-	3-4	-
Abnormal thinking	-	-	2	-	-	-
Aggression	-	<1	-	-	-	-
Agitation	<10	-	1-10	16	3-5	1-10
Amnesia	-	-	1-10	-	-	-
Anxiety	<10	<1	6-15	5	5	1-10
Apathy	-	<1	-	-	-	-
Asthenia	-	-	-	14	-	-
Auditory hallucination	-	<1	-	-	-	-
Blurred vision	-	1-10	-	-	-	-
Chills	-	-	1-10	-	>1	-
Concentration impaired	-	1-10	-	-	3-4	-
Confusion	-	<1	1-10	-	>1	-
Delirium	<1	<1	-	-	-	-
Depersonalization	-	<1	-	-	3	-
Depression	-	<1	-	<1	-	-
Dizziness	-	5	9	11	6-14	>10
Emotional lability	-	<1	1-10	-	>1	-
Euphoria	-	-	<1	-	-	-
Excitability	-	<1	-	-	-	-
Fatigue	-	5-8	-	-	-	>10
Fever	-	1-10	2	-	-	-
Grand mal seizure	-	<1	-	-	-	-
Hallucinations	-	<1	<1	-	-	<1
Headache	-	24	21	22	17-18	>10
Hypoesthesia	-	-	-	-	-	1-10
Hypomania	-	-	-	<1	-	-
Insomnia	>10	9-12	10-33	21	11-24	>10
Irritability	-	1-10	-	-	-	-
Lethargy	-	1-10	-	-	-	-
Lightheadedness	-	1-10	-	-	-	-
Malaise	-	<1	-	-	-	1-10
Mania	-	-	-	<1	-	-
Migraine	-	1-10	-	-	-	-
Nervousness	-	-	8-14	12	4-9	1-10
Nystagmus	-	<1	-	-	-	-
Panic reaction	-	<1	-	-	-	-

Adverse Event	Citalo-pram	Escitalo-pram	Fluox-etine	Fluvox-amine	Parox-etine	Ser-traline
Paresthesia	-	1-10	-	-	-	1-10
Psychiatric disturbances	-	-	-	-	-	<1
Seizure	-	-	-	<1	-	-
Sleep disorder	-	-	1-10	-	-	-
Somnolence	>10	6-13	5-17	22	15-24	>10
Tremors	-	-	-	4	-	>10
Vertigo	-	1-10	-	-	>1	-
Dermatological						
Angioedema	-	-	-	-	-	<1
Epidermal necrolysis	<1	<1	-	-	-	-
Erythema multiforme	<1	<1	-	-	-	-
Erythema nodosum	-	-	<1	-	-	-
Exfoliative dermatitis	-	-	<1	-	-	-
Photosensitivity	-	-	<1	-	-	<1
Pruritis	<10	-	4	-	>1	-
Rash	<10	1-10	2-6	-	2-3	1-10
Stevens-Johnson syndrome	-	-	<1	-	-	<1
Endocrine and Metabolic						
Galactorrhea	-	-	-	-	-	<1
Gynecomastia	-	-	-	-	5	<1
Hepatic failure	-	-	<1	-	-	<1
Hepatic necrosis	<1	<1	<1	-	-	-
Hepatitis	-	<1	-	-	-	<1
Hepatomegaly	-	-	-	-	-	<1
Hot flashes	-	1-10	-	-	-	-
Hypercholesterolemia	-	<1	-	-	-	-
Hyperglycemia	-	<1	-	-	-	<1
Hyperprolactinemia	-	-	<1	-	-	<1
Hyponatremia	-	-	<1	<1	-	-
Hypothyroidism	-	-	-	-	-	<1
Jaundice	-	-	<1	-	-	<1
Prolactinemia	-	<1	-	-	-	-
Transaminase elevation	-	-	-	-	-	<1
Gastrointestinal						
Abdominal cramps	-	1-10	-	-	-	-
Abdominal pain	<10	2	-	-	4	<1
Constipation	-	3-5	5	10	5-16	1-10
Diarrhea	<10	8	8-18	11	9-12	>10
Dyspepsia	<10	-	6-10	-	2-5	1-10
Flatulence	-	1-10	3	-	4	1-10
Gastroenteritis	-	1-10	-	-	-	-
Gastroesophageal reflux	-	1-10	-	-	-	-
Heartburn	-	1-10	-	-	-	-
Indigestion	-	3	-	10	-	-
Nausea	>10	15	12-29	40	19-26	>10
Pancreatitis	<1	<1	<1	-	-	<1
Vomiting	<10	1-10	3	5	2-3	1-10
Xerostomia	>10	6-9	4-12	14	9-18	>10
Genitourinary						
Urinary frequency	-	1-10	1-10	-	2-3	-

Adverse Event	Citalo-pram	Escitalo-pram	Fluox-etine	Fluvox-amine	Parox-etine	Ser-traline
Urinary tract infection	-	1-10	-	-	2	-
Hematologic						
Agranulocytosis	-	-	-	-	-	<1
Anemia	-	<1	-	-	-	-
Aplastic anemia	-	-	-	-	-	<1
Bilirubin increased	-	<1	-	-	-	<1
Hemolytic anemia	<1	<1	<1	-	-	-
Increased bleeding	-	-	-	-	-	<1
Leukopenia	-	-	-	-	-	<1
Pancytopenia	-	-	<1	-	-	-
Prothrombin decreased	-	<1	-	-	-	-
Thrombocytopenia	-	<1	<1	-	-	<1
Thrombocytopenic purpura	-	-	<1	-	-	-
Thrombosis	-	<1	-	-	-	-
Musculoskeletal						
Akathisia	-	<1	-	-	-	-
Arthralgia	<10	1-10	-	-	>1	-
Back pain	-	-	-	-	3	1-10
Choreoathetosis	-	<1	-	-	-	-
Dyskinesias	<1	-	<1	-	-	-
Dystonia	-	-	-	-	-	<1
Extrapyramidal symptoms	-	-	<1	-	-	<1
Hyperreflexia	-	<1	-	-	-	-
Hypertonia	-	-	-	-	-	1-10
Involuntary muscle contractions	-	<1	-	-	-	-
Limb pain	-	1-10	-	-	-	-
Muscle cramp	-	1-10	-	-	-	-
Myalgia	<10	1-10	-	-	2-4	1-10
Neck/shoulder pain	-	1-10	-	-	-	-
Neuroleptic malignant syndrome	<1	-	<1	-	-	-
Rhabdomyolysis	<1	<1	-	-	-	-
Tics	-	<1	-	-	-	-
Tremor	<10	1-10	3-13	-	4-11	-
Weakness	-	<1	7-21	-	12-22	1-10
Respiratory						
Asthma	-	-	<1	-	-	-
Bronchitis	-	1-10	-	-	-	-
Cough	<10	1-10	-	-	-	-
Eosinophilia pneumonia	-	-	<1	-	-	-
Laryngospasm	-	-	<1	-	-	-
Nasal congestion	-	1-10	-	-	-	-
Pharyngitis	-	-	3-11	-	4	-
Pulmonary embolism	-	<1	<1	-	-	-
Pulmonary fibrosis	-	-	<1	-	-	-
Pulmonary hypertension	-	-	<1	-	-	-
Rhinitis	<10	5	-	-	3	1-10
Sinus headache	-	1-10	-	-	-	-
Sinusitis	<10	3	1-6	-	4	-
Upper respiratory infection	-	-	-	4	7	-
Other						

Adverse Event	Citalo-pram	Escitalo-pram	Fluox-etine	Fluvox-amine	Parox-etine	Ser-traline
Abnormal vision	-	-	-	-	-	1-10
Acute renal failure	<1	<1	<1	-	-	<1
Allergic reaction	-	<1	-	-	-	<1
Allergy	-	1-10	<1	-	-	-
Alopecia	-	-	<1	-	-	-
Anaphylaxis	<1	<1	<1	-	-	<1
Angioedema	<1	<1	-	-	-	-
Anorexia	<10	-	4-11	-	5-9	>10
Anorgasmia	-	2-6	-	2	>1	-
Appetite decreased	-	3	-	4	-	-
Appetite increased	-	1-10	1-10	-	-	1-10
Blindness	-	-	-	-	-	<1
Carbohydrate craving	-	<1	-	-	-	-
Cataract	-	-	<1	-	-	<1
Diaphoresis	>10	4-5	2-8	7	5-14	>10
Dysphagia	-	-	<1	-	-	-
Ear ache	-	1-10	1-10	-	-	-
Ecchymosis	-	<1	-	-	-	-
Ejaculation disorder	-	9-14	<7	7	10-28	>10
Esophagitis	-	-	<1	-	-	-
Flu-like syndrome	-	5	3-10	-	-	-
Gout	-	-	<1	-	-	-
Gum hyperplasia	-	-	-	-	-	<1
Impotence	-	3	<7	-	2-9	1-10
Libido decreased	-	3-7	1-11	-	3-15	>10
Lupus-like syndrome	-	-	<1	-	-	<1
Menstrual cramps	-	1-10	-	-	-	-
Menstrual disorder	-	1-10	-	-	-	-
Neuroleptic malignant syndrome	-	-	-	-	-	<1
Oculogyric crisis	-	-	-	-	-	<1
Optic neuritis	-	-	<1	-	-	<1
Pain	-	-	-	-	-	1-10
Priapism	<1	<1	<1	-	-	<1
Serotonin syndrome	<1	<1	<1	<1	-	<1
Serum sickness	-	-	-	-	-	<1
Sexual dysfunction	<10	-	-	-	-	-
Spontaneous abortion	-	<1	-	-	-	-
Suicidal tendency	-	<1	-	<1	-	-
Syndrome of inappropriate antidiuretic hormone secretion	<1	<1	-	-	-	<1
Taste alteration	-	<1	1-10	2	2	-
Tinnitus	-	1-10	1-10	-	>1	1-10
Tooth ache	-	1-10	-	-	-	-
Vasculitis	-	-	<1	-	-	-
Visual difficulty	-	<1	2	-	2-4	1-10
Weight gain	<10	1-10	1-10	-	>1	1-10
Weight loss	-	1-10	2	✔	-	-
Withdrawal syndrome	<1	<1	-	-	-	-
Yawning	<10	1-10	<11	2	2-4	1-10

✔ Percent not specified.

- Event not reported or incidence <1%.

Contraindications

The Food and Drug Administration (FDA) requires manufacturers to include a black-box warning notifying prescribers of the potential of antidepressants to increase suicidal thoughts in children and adolescents.[3] In addition, the FDA issued a public health advisory cautioning that adults being treated with antidepressant medications, particularly those being treated for depression, should be watched closely for worsening of depression and for increased suicidal thinking or behavior.

Table 7. Contraindications[5-19]

Contraindications	Citalo-pram	Escitalo-pram	Fluox-etine	Fluvox-amine	Parox-etine	Ser-traline
Concurrent use of alosetron				✔		✔ †
Concurrent use of MAOIs intended to treat psychiatric disorders within 14 of starting therapy	✔	✔	✔	✔	✔	✔
Concurrent use of MAOIs (strong; linezolid or intravenous methylene blue).	✔	✔	✔	✔	✔	✔
Concurrent use of pimozide	✔	✔	✔	✔	✔	✔
Concurrent use of thioridazine			✔	✔	✔	
Concurrent use of tizanidine				✔		
Hypersensitivity to the drug or any of the inactive ingredients	✔	✔			✔	✔
Pregnancy					✔ *	

MAOIs=monoamine oxidase inhibitors
*Brisdelle® only.
†Sertaline oral concentrate only)

Black Box Warning for the Antidepressants[7-19]

WARNING
Suicidality and Antidepressant Drugs Antidepressants, including selective serotonin reuptake inhibitors (SSRIs) 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 [Insert established name] 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. [Insert Drug Name] is not approved for use in pediatric patients. [The previous sentence would be replaced with the sentence, below, for the following drugs: Prozac: Prozac is approved for use in pediatric patients with MDD and obsessive-compulsive disorder (OCD). Zoloft: Zoloft is not approved for use in pediatric patients except for patients with obsessive-compulsive disorder (OCD). Fluvoxamine: Fluvoxamine is not approved for use in pediatric patients except for patients with obsessive-compulsive disorder (OCD).] (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

Warnings and Precautions

Table 8. Warnings and Precautions[5-19]

Warnings and Precautions	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Appetite altered and weight loss, especially in underweight depressed or bulimic patients			✔			✔
Akathisia has been reported					✔	
Angle closer glaucoma attack may be trigged by pupillary dilation in patients with anatomically narrow angles who does not have a patent iridectomy	✔ (tablet)	✔	✔	✔	✔	✔
Anxiety and insomnia have been reported			✔			
Bleeding, abnormal, have been reported	✔	✔	✔	✔	✔	✔
Bone fracture has been reported					✔	
Coadministration with tamoxifen; uncertain effect on tamoxifen efficacy					✔ #	
Hepatic impairment				✔		
Hyponatremia	✔	✔	✔	✔	✔	✔
Long elimination half-life; changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment			✔ †			
Mania/hypomania activation, use with caution in patients with a history of mania; screen for bipolar disorder	✔	✔	✔	✔	✔	✔
QT prolongation and Torsade de Pointes; dose-dependent	✔	✔	✔			
Rash and allergic reactions, including anaphylaxis have been reported			✔			
Pregnancy, first trimester; increased risk of congenital malformations, particularly cardiovascular malformations					✔	
Suicide risk; may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior	✔	✔	✔	✔	✔	✔
Seizures; not studied, use with care	✔	✔	✔	✔	✔	✔
Serotonin syndrome; increased risk with use of other serotonergic drugs and with drugs that impair metabolism of serotonin	✔	✔	✔	✔	✔	✔
Withdrawal symptoms; gradual reduction in dose is recommended	✔	✔	✔	✔	✔	✔

Warnings and Precautions	Citalo-pram	Escitalo-pram	Fluox-etine	Fluvox-amine	Parox-etine	Ser-traline
Uric acid decreased; clinical significance unknown						✔
Use in patients with concomitant systemic illnesses; experience in patients with certain concomitant systemic illnesses is limited.*	✔	✔	✔	✔	✔	✔

*Certain cardiac conditions, hepatic impairment, severe renal impairment.
†Fluoxetine tablet, weekly capsule, and oral suspension only.
#Brisdelle® only.

Drug Interactions

Table 9. Drug Interactions[5-19]

Generic Name	Interacting Medication or Disease	Potential Result
Fluoxetine	Carbamazepine	Serum carbamazepine levels may be increased, producing possible toxicities by an unknown mechanism. However, fluoxetine is known to inhibit the metabolism of other drugs, suggesting that this may be a potential mechanism involved in the interaction. The close monitoring of serum carbamazepine levels during concurrent administration of fluoxetine is recommended. Adjustment of carbamazepine dose advised.
Fluoxetine	Hydantoins (ethotoin, fosphenytoin, phenytoin)	Serum hydantoin concentrations may be elevated, producing an increase in the pharmacologic and toxic effects, possibly by the inhibition of hydantoin metabolism by fluoxetine. Close monitoring of hydantoin levels and observing patients for toxicity or loss of therapeutic activity if fluoxetine is started or stopped is advised. Adjustment of the hydantoin dose as needed is recommended.
Fluoxetine	Phenothiazines (chlorpromazine, thioridazine)	Phenothiazine plasma concentrations may be elevated, increasing the risk of life-threatening cardiac arrhythmias, including torsades de pointes. Fluoxetine may inhibit the metabolism of phenothiazines through the CYP2D6 system. Thioridazine is contraindicated in patients already receiving fluoxetine. Closely monitor electrocardiograms (ECGs) when coadministering fluoxetine and a phenothiazine.
Fluoxetine	Ritonavir	The area under the curve (AUC) of ritonavir may be increased. Serotonin syndrome (eg, central nervous system irritability, increased muscle tone, myoclonus, and altered consciousness) may occur as a result of coadministration. Fluoxetine and ritonavir may inhibit the CYP2D6 metabolism of each other, resulting in the need for close monitoring of adverse effects. Serotonin syndrome requires immediate medical attention, including withdrawal of fluoxetine and supportive care.
Fluvoxamine	Methadone	Increased serum methadone concentrations with possible toxicity may result. Fluvoxamine may inhibit the hepatic metabolism of methadone. As a result the

Generic Name	Interacting Medication or Disease	Potential Result
		starting and stopping of fluvoxamine therapy should be handled with caution in patients receiving methadone maintenance treatment.
Fluvoxamine	Tacrine	Plasma tacrine concentrations may be elevated, increasing the pharmacologic and adverse effects, possibly by the CYP1A2 inhibition of tacrine metabolism by fluvoxamine. If this combination cannot be avoided, monitor for side effects, including hepatotoxicity, when fluvoxamine is initiated in patients receiving tacrine or if both drugs are started concomitantly. Other selective serotonin-reuptake inhibitors that are not metabolized by CYP1A2 might be safer alternatives.
Fluvoxamine	Theophyllines (aminophylline, theophylline)	Increased theophylline serum concentrations with possible toxicities. Fluvoxamine inhibits the hepatic metabolism (CYP1A2) of theophylline, so close monitoring of theophylline levels is warranted when fluvoxamine therapy is started or stopped. Adjustments to the theophylline dosing should be manipulated as needed. A 33% reduction in theophylline dose has been recommended when starting theophylline in patients receiving fluvoxamine.
Fluvoxamine	Tizanidine	Tizanidine plasma concentrations may be elevated, increasing the pharmacologic and adverse reactions (eg, hypotension). Inhibition of tizanidine metabolism (CYP1A2) by fluvoxamine is suspected as a potential mechanism. Coadministration of tizanidine and fluvoxamine is contraindicated.
Paroxetine	Digoxin	Digoxin serum concentrations may be elevated, increasing the pharmacologic and toxic effects. Inhibition of renal tubular P-glycoprotein excretion of digoxin by paroxetine is suspected, therefore, patients receiving digoxin, closely monitor digoxin serum levels and observe the patient for signs of digitalis toxicity when paroxetine is coadministered. Adjustment of the digoxin dose should be altered as needed. Since citalopram and venlafaxine have less of an effect on P-glycoprotein, they may be less likely to interact with digoxin.
Paroxetine	Phenothiazines (chlorpromazine, fluphenazine, methotrimeprazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, thioridazine, trifluoperazine)	Phenothiazine plasma levels may be elevated, increasing the pharmacologic and adverse effects, including the risk of life-threatening cardiac arrhythmias with thioridazine, secondary to the decreased metabolism (CYP2D6) of the phenothiazine. Thioridazine is contraindicated in patients receiving paroxetine, and it may be necessary to decrease the usual starting dose of other phenothiazines in patients whose paroxetine therapy is at steady-state. In patients receiving a phenothiazine, careful observation of the clinical response when starting, stopping, or changing the dose of paroxetine is necessary. Adjust the phenothiazine dose as needed.
Serotonin reuptake	Cyproheptadine	Decreased pharmacologic effects of SRIs may result.

Generic Name	Interacting Medication or Disease	Potential Result
inhibitors (SRIs) (citalopram, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)		Since cyproheptadine is a serotonin antagonist, the interaction may occur at the receptor level. If a loss of the antidepressant efficacy occurs, consider discontinuing cyproheptadine therapy.
SRIs (citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	Linezolid	Serotonin syndrome (eg, agitation, altered consciousness, ataxia, overactive reflexes, shivering) may occur as a result of excessive accumulation of serotonin. The coadministration of linezolid and SRIs should be handled with caution. Since linezolid has Monoamine oxidase inhibitor (MAOI) activity, allow at least 2 weeks between stopping linezolid and starting an SSRI.
SRIs (fluoxetine, fluvoxamine, nefazodone)	Phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil, vardenafil)	PDE5 inhibitor plasma levels may be elevated as a result of the inhibition of PDE5 inhibitor metabolism (CYP3A4) by certain SRIs, thus increasing the risk of adverse reactions. Until more clinical data are available, administer PDE5 inhibitors with caution to patients receiving certain SRIs. Consider reducing the initial dose of the PDE5 inhibitor if coadministration cannot be avoided.
SRIs (citalopram, duloxetine, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	Selective 5-HT_1 receptor agonists (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)	Serotonin syndrome, including agitation, overactive reflexes, ataxia, shivering, myoclonus, and altered consciousness, may occur in some patients as a result of rapid accumulation of serotonin in the central nervous system. If coadministration of these agents is indicated, lower starting dosages and close monitoring is recommended. Readiness to provide supportive care, stop the serotonergic agent, and give an antiserotonergic agent (eg, cyproheptadine) is necessary.
SRIs (fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	Sibutramine	A “serotonin syndrome,” including central nervous system irritability, motor weakness, shivering, myoclonus, and altered consciousness, may occur, since the serotonergic effects of these agents may be additive. Concomitant administration of these agents is not recommended by the manufacturer. If concurrent use cannot be avoided, carefully monitor the patient for adverse effects. The serotonin syndrome requires immediate medical attention.
SRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, venlafaxine)	Sympathomimetics (amphetamine, amphetamine/ dextroamphetamine, benzphetamine, dextroamphetamine,	Increased sensitivity to sympathomimetic effects and increased risk of serotonin syndrome are possible, through an unknown mechanism. If these agents must be used concurrently, monitor for increased central nervous system effects and adjust therapy as needed.

Generic Name	Interacting Medication or Disease	Potential Result
	diethylpropion, methamphetamine, phendimetrazine, phentermine)	
SRIs (citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	Tramadol	Serotonin syndrome (eg, agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering) may occur, as the serotonergic effects of these agents may be additive. Close monitoring for adverse reactions is advised. Serotonin syndrome requires immediate medical attention, including withdrawal of the serotonergic agent and supportive care.
Selective serotonin reuptake inhibitors (SSRIs) (citalopram, fluoxetine, fluvoxamine, sertraline)	Clozapine	Serum clozapine levels may be elevated, resulting in increased pharmacologic and toxic effects. Certain SSRIs inhibit clozapine hepatic metabolism, resulting in the need to monitor clozapine serum levels and closely observe the clinical response. Clozapine dose adjustments should be made as needed.
SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline)	Cyclosporine	Serotonin-reuptake inhibitors may increase cyclosporine concentrations via the CYP3A4 inhibition of cyclosporine metabolism, resulting in various toxicities. Close monitoring of cyclosporine trough whole blood concentrations when adding or discontinuing a serotonin-reuptake inhibitor is warranted, with the subsequent adjustment of the cyclosporine dose as needed.
SSRIs (fluoxetine, paroxetine)	Metoclopramide	Metoclopramide plasma concentrations may be elevated, secondary to the inhibition of metoclopramide metabolism (CYP2D6) by certain serotonin-reuptake inhibitors, increasing the risk of adverse reactions. Close monitoring for adverse reactions to metoclopramide during coadministration of certain serotonin-reuptake inhibitors is warranted. Adjustment of the metoclopramide dose as needed is recommended.
SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	Nonsteroidal anti-inflammatory drugs (NSAIDS) (diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone,	The risk of upper gastrointestinal bleeding may be increased, although the specific mechanism is unknown. If coadministration of these agents cannot be avoided, consider shortening the NSAID treatment duration, decreasing the dose, or replacing the NSAID with acetaminophen, or the SSRI with a tricyclic antidepressant (TCA). If GI adverse reactions occur, consider interventional therapy (eg, proton pump inhibitor) or discontinuing the SSRI or NSAID and giving an alternative therapy.

Generic Name	Interacting Medication or Disease	Potential Result
	naproxen, oxaprozin, piroxicam, sulindac, tolmetin)	
SSRIs (citalopram, sertraline)	Pimozide	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased, although the precise mechanism is unknown. The concurrent administration of pimozide with citalopram or sertraline is contraindicated.
SSRIs (duloxetine, fluoxetine, paroxetine, sertraline)	Propafenone	Plasma propafenone levels may be elevated, increasing the pharmacologic and adverse reactions. Certain SRIs may inhibit the metabolism (CYP2D6) of propafenone, so careful monitoring of cardiac function if SRIs are coadministered with propafenone. Citalopram does not inhibit CYP2D6 and may be a safer alternative.
SSRIs (fluoxetine, paroxetine, sertraline)	Risperidone	Risperidone plasma concentrations may be elevated, increasing the risk of side effects. Serotonin syndrome (eg, altered consciousness, central nervous system irritability, increased muscle tone, myoclonus) may occur. The CYP2D6 inhibition of risperidone metabolism by fluoxetine and paroxetine is suspected, as a rapid accumulation of serotonin in the central nervous system may occur. Close observation of the clinical response to risperidone when starting, stopping, or changing the dose of fluoxetine or paroxetine, or when giving high sertraline doses (more than 100 mg/day) should be employed. Dose adjustments of risperidone should be managed as needed.

Dosage and Administration

Table 10. Dosing and Administration[5-19]

Generic Name	Adult Dose	Pediatric Dose	Availability
Citalopram	Depression: Oral: initial, 20 mg/day, generally with an increase to 40 mg/day; doses of more than 40 mg are not usually necessary; should a dose increase be necessary, it should occur in 20 mg increments at intervals of no less than one week; maximum dose, 60 mg/day Elderly: Oral: initial, 10-20 mg once daily; increase dose to 40 mg/day only in nonresponders	Safety and efficacy in children have not been established.	Solution: 10 mg/5 mL Tablet: 10 mg 20 mg 40 mg
Escitalopram	Depression/Generalized Anxiety Disorder: Oral: initial, 10 mg/day; dose may be increased to 20 mg/day after at least one week	Safety and efficacy in children have not been established.	Solution: 5 mg/5 mL Tablet:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Elderly: Oral: initial, 5-10 mg/day; doses may be increased by 5-10 mg/day after at least one week		5 mg 10 mg 20 mg
Fluoxetine	Bulimia Nervosa: Oral, immediate release: 20 mg/day in the morning (lower doses of 5-10 mg/day have been used for initial treatment); may increase after several weeks by 20 mg/day increments; usual dose range: 60-80 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Depression: Oral, immediate release: 20 mg/day in the morning (lower doses of 5-10 mg/day have been used for initial treatment); may increase after several weeks by 20 mg/day increments; usual dose range, 20-40 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Capsule, delayed release: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed-release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose Elderly: Oral, immediate release: some patients may require an initial dose of 10 mg/day with dosage increases of 10 mg and 20 mg every several weeks as tolerated; should not be taken at night unless patient experiences sedation Obsessive-Compulsive Disorder: Oral, immediate release: 20 mg/day in the morning (lower doses of 5-10 mg/day have been used for initial treatment); may increase after several weeks by 20 mg/day increments; usual dose range, 40-80 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Panic Disorder: Oral, immediate release: initial, 10 mg/day; after one week, increase to 20 mg/day; may increase after several weeks; doses	Depression: Children 8-18 years: Oral, immediate release: 10-20 mg/day; lower-weight children can be started on 10 mg/day, may increase to 20 mg/day after one week if needed Obsessive-Compulsive Disorder: Children 7-18 years: Oral, immediate release: 10 mg/day; in adolescents and higher-weight children, dose may be increased to 20 mg/day after two weeks; range, 10-60 mg/day	Capsule, immediate release: 10 mg 20 mg 40 mg Capsule, delayed release: 90 mg Solution: 20 mg/5 mL Tablet, immediate release: 10 mg 20 mg 60 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	>60 mg/day have not been evaluated Premenstrual Dysphoric Disorder: Oral, immediate release: 20 mg/day continuously, or 20 mg/day starting 14 days prior to menstruation and through first full day of menses (repeat with each cycle)		
Fluvoxamine	Obsessive-Compulsive Disorder: Tablet: initial, 50 mg at bedtime; adjust dose in 50 mg increments at four- to seven-day intervals; usual dose range: 100-300 mg/day; divide total daily dose into 2 doses; administer larger portion at bedtime; when total daily dose exceeds 50 mg, the dose should be given in two divided doses Elderly: Tablet: reduce dose; titrate slowly	Obsessive-Compulsive Disorder: Children 8-17 years: initial, 25 mg at bedtime; adjust in 25 mg increments at four- to seven-day intervals, as tolerated, to maximum therapeutic benefit, range, 50-200 mg/day; maximum dose, children 8-11 years 200 mg/day and adolescents 300 mg/day; lower doses may be effective in female versus male patients; when total daily dose exceeds 50 mg, the dose should be given in two divided doses	Capsule, extended release: 100 mg 150 mg Tablet: 25 mg 50 mg 100 mg
Paroxetine hydrochloride	Depression: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; maximum dose, 50 mg/day Tablet, sustained release: initial, 25 mg once daily; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 62.5 mg/day Elderly: Oral, immediate release: initial, 10 mg/day; increase if needed by 10 mg/day increments at intervals of at least one week; maximum dose, 40 mg/day Elderly: Tablet, sustained release: initial, 12.5 mg/day; increase if needed by 12.5 mg/day increments at intervals of at lease one week; maximum dose, 50 mg/day	Safety and efficacy in children have not been established.	Suspension, oral: 10 mg/5 mL Tablet, immediate release: 10 mg 20 mg 30 mg 40 mg Tablet, sustained release: 12.5 mg 25 mg 37.5 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Generalized Anxiety Disorder: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; doses of 20-50 mg/day were used in clinical trials; however, no greater benefit was seen with doses >20 mg Obsessive-Compulsive Disorder: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose, 40 mg/day; range, 20-60 mg/day; maximum dose, 60 mg/day Panic Disorder: Oral, immediate release: initial, 10 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose, 40 mg/day; range: 10-60 mg/day; maximum dose, 60 mg/day Tablet, sustained release: initial, 12.5 mg once daily in the morning; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 75 mg/day Premenstrual Dysphoric Disorder: Tablet, sustained release: initial, 12.5 mg once daily in the morning; dose may be increased to 25 mg/day; dosing changes should occur at intervals of at least one week; may be given daily throughout the menstrual cycle or limited to the luteal phase Posttraumatic Stress Disorder: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; range, 20-50 mg; limited data suggest doses of 40 mg/day were not more efficacious than 20 mg/day		

Generic Name	Adult Dose	Pediatric Dose	Availability
	Social Anxiety Disorder: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; recommended dose, 20 mg/day; range, 20-60 mg/day; doses >20 mg/day may not have additional benefit Tablet, sustained release: initial, 12.5 mg once daily, preferably in the morning; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose: 37.5 mg/day		
Paroxetine mesylate	Depression: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; maximum dose, 50 mg/day Elderly: Oral, immediate release: initial, 10 mg/day; increase if needed by 10 mg/day increments at intervals of at least one week; maximum dose, 40 mg/day Obsessive-Compulsive Disorder: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose, 40 mg/day; range: 20-60 mg/day; maximum dose, 60 mg/day Panic Disorder: Oral, immediate release: initial, 10 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose, 40 mg/day; range: 10-60 mg/day; maximum dose, 60 mg/day Vasomotor symptoms associated with menopause, moderate to severe: Immediate-release capsule (Brisdelle®), 7.5 mg once daily	Safety and efficacy in children have not been established.	Capsule, immediate-release: 7.5 mg Tablet: 10 mg 20 mg 30 mg 40 mg
Sertraline	Depression/Obsessive-Compulsive Disorder: Oral: initial, 50 mg/day; may increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if	Obsessive-Compulsive Disorder: Children 6-12 years: Oral: initial, 25 mg once daily	Concentrate, oral: 20 mg/mL Tablet:

Generic Name	Adult Dose	Pediatric Dose	Availability
	somnolence is noted, give at bedtime Elderly: Oral: initial, 25 mg/day in the morning; increase by 25 mg/day increments every two to three days if tolerated to 50-100 mg/day; additional increases may be necessary; maximum, 200 mg/day Panic Disorder/Posttraumatic Stress Disorder/Social Anxiety Disorder: Oral: initial, 25 mg once daily; increased after one week to 50 mg once daily Premenstrual Dysphoric Disorder: Oral: 50 mg/day either daily throughout menstrual cycle or limited to the luteal phase of menstrual cycle; patients not responding to 50 mg/day may benefit from dose increases (50 mg increments per menstrual cycle) up to 150 mg/day when dosing throughout menstrual cycle or up to 100 mg/day when dosing during luteal phase only; if 100 mg/day has been established with luteal phase dosing, a 50 mg/day titration step for three days should be utilized at the beginning of each luteal phase dosing period	Children 13-17 years: Oral: initial, 50 mg once daily May increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime	25 mg 50 mg 100 mg

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Major Depressive Disorder (2000)**[70]	• The following are recommendations for the treatment of patients older than 18 years of age and who have been diagnosed with major depressive disorder, for which other causes have been eliminated. • Treatment of major depressive disorder can be divided into the acute phase (remission is achieved, usually lasting 6-8 weeks), continuation phase (remission is preserved, usually lasting 16-20 weeks) and the maintenance phase (susceptible patient is protected against recurrence). • Selecting an agent should be driven by anticipated side effects, tolerability, patient preference, and quantity and quality of available clinical data. • The effectiveness of antidepressants is usually comparable within medication classes and comparable between medication classes. • Selection of medication can be influenced by prior positive response, severity of symptoms, sleep and/or appetite disturbances or the anticipation of the requirement for maintenance therapy. • These medications that can be considered first-line therapy for most patients and should be initiated during the acute phase: selective serotonin-reuptake inhibitors (SSRIs), desipramine, nortriptyline,

Clinical Guideline	Recommendation
	bupropion and venlafaxine. • Due to the risk of serious side effects, monoamine oxidase inhibitors (MAOIs) should be reserved for patients who are unresponsive to other available medications. • Secondary amine tricyclic antidepressants (TCAs) may not be the best treatment choice for patients with concomitant cardiovascular disease, close-angle glaucoma, urinary retention or significant prostatic hypertrophy. • All SSRIs have some risk of sexual side effects. • For patients who present with significant psychosocial stressors, intrapsychic conflict, interpersonal difficulties or axis II comorbidity, psychotherapy may be considered as initial monotherapy. • Patients who present with psychosocial issues as well as moderate-to-severe major depressive disorder (MDD) may benefit from combination psychotherapy and antidepressant medication. • Therapy should be assessed after 4-8 weeks of therapy to judge response to treatment. If there is no response or partial response at this time, a change in therapy should be considered, including changing the dose (if partial response), changing the antidepressant, adding psychotherapy or electroconvulsive therapy (ECT). • Switching to a different non-MAOI antidepressant to another within the same class, or to one in a different class are both effective strategies. • The antidepressant medication used to induce remission during the acute phase should be continued through the continuation phase, 16-20 weeks after remission, and through the maintenance phase in patients who are at risk for relapse. • Discontinuation of treatment after maintenance phase may be considered by the prescriber and the patient. Attention should be paid to the probability of relapse, detection of symptoms should they return, and the potential for adverse events upon stopping the antidepressant.
APA: **Guideline Watch: Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 2nd Edition (2005)**[71]	• A black-box warning for liver toxicity and failure was added to nefazodone, due to an incidence of 3-4 times the baseline. Patients with pre-existing liver failure should not be treated with nefazodone. • Patients with major depressive disorder are at increased risk of suicide. Continued cautFion should be used when initiating and treating these patients. • A black-box warning was added to all antidepressants, highlighting the increased risk of suicide and suicidal thoughts, changes in behavior, as well as other safety concerns, when antidepressants are used in children and adolescents. • Escitalopram and duloxetine are new antidepressants approved since the previous guideline. • Escitalopram is an SSRI approved for the acute and maintenance treatment of MDD and has shown comparable efficacy and tolerability to other antidepressants, including citalopram and venlafaxine. • Duloxetine is a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), approved for the treatment of depression, that has shown comparable efficacy to SSRIs. • A combination product of olanzapine and fluoxetine was approved for the treatment of episodes of bipolar depression. It has been found useful in the treatment of major depression with psychotic features and in treatment-resistant depression.

Clinical Guideline	Recommendation
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameters for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007)**[72]	All Types of Childhood/Adolescent Depression • All patients with depression should receive therapy in the acute (6-12 weeks) and continuation phases (6-12 months); some will require maintenance treatment (longer than 12 months). During each phase, treatment should be accompanied by psychotherapy, education, as well as family and school involvement. • Treatment should encompass the management of comorbid conditions. • Medication regimen may be optimized or augmented in partial responders; while switching to another regimen may be appropriate in non-responders. Uncomplicated Depression/Brief Depression/Mild Psychosocial Impairment • Initial management: education, support and case management. Reevaluate if no response after 4-6 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. Non-Responsive Depression • Consider unrecognized or untreated comorbid psychiatric or medical disorders. • Switching to another antidepressant plus cognitive behavioral therapy (CBT) may result in a better response than a switch to another antidepressant without additional psychotherapy. • Open small studies using augmentation with lithium or MAOIs have shown contradictory results.
National Institute for	Mild Depression

Clinical Guideline	Recommendation
Health and Clinical Excellence (NICE): **Management of Depression in Primary and Secondary Care (2004)**[73]	• Due to a low risk-benefit ratio, antidepressants are not recommended for the initial treatment of mild depression. • Antidepressants may be used when mild depression is resistant to other interventions, when depression is associated with psychosocial or medical problems or in patients with a past history of moderate-to-severe depression. <u>Moderate-to-Severe Depression</u> • Patients at risk of harming themselves or others should be immediately referred to a specialist. • Antidepressants should be routinely offered to patients with moderate depression before psychological interventions are attempted. <u>Pharmacological Treatment of Major Depressive Disorder (MDD)</u> • Therapy should be continued for at least 6 months following remission; longer treatment duration may be appropriate for some patients. • SSRIs are recommended as the initial treatment of depression. If agitation occurs early into treatment, benzodiazepines may be used for management of this adverse event. • In case of an inadequate response to the standard dose of an SSRI, gradual dose escalation may be appropriate. • Lack of response after 1 month of therapy may warrant switching to another antidepressant. Decision to switch therapy may be postponed for 6 weeks after initiation of drug if the patient is experiencing a partial response to the medication. • Recommended choices for a second antidepressant include a different SSRI, mirtazapine and TCAs. • SSRIs should not be discontinued abruptly due to the risk of withdrawal symptoms and a gradual reduction of the dose over a 4-week period is appropriate (fluoxetine may be stopped sooner). <u>Pharmacological Treatment of Atypical Depression</u> • SSRIs should be used to treat atypical depression based on consensus opinion. <u>Chronic Depression</u> • Combination of pharmacological and CBT is appropriate. <u>Treatment-Resistant Depression</u> • Combination of pharmacological and CBT is appropriate. • Augmentation with lithium or another antidepressant (i.e. mirtazapine) may be considered for patients failing several antidepressants. • Augmentation with carbamazepine, lamotrigine, buspirone, pindolol, valproate or thyroid medication is not recommended. • Augmentation with benzodiazepines is not recommended due to insufficient evidence. • Venlafaxine may be considered after an adequate trial of 2 other antidepressants. <u>Recurrent Depression</u> • Patients with a history of at least 2 recent severe depressive episodes should continue antidepressant therapy for 2 years.

Clinical Guideline	Recommendation
	• Lithium is not recommended for the prevention of recurrent depressive episodes. Psychotic Depression • Augmentation with antipsychotic should be considered.
Texas Department of State Health Services: **Texas Implementation of Medication Algorithms (2008)**[74]	• First-line pharmacotherapy for a major depressive episode without psychotic features is a trial of a single antidepressant agent. Choices include: SSRIs, SNRIs (eg, venlafaxine, duloxetine), bupropion and mirtazapine. • Patients who do not respond to or tolerate the first agent may need a trial of an alternative agent among the first-line choices, often with a different mechanism of action. • Patients who do not respond to or tolerate successive trials of first-line antidepressant monotherapy may be candidates for combination treatments or monotherapy with MAOIs or TCAs.

NICE: **Management of Anxiety (Panic Disorder, With or Without Agoraphobia, and Generalized Anxiety Disorder) in Adults in Primary, Secondary and Community Care (2004)**[75]	Panic Disorder General Considerations
	• Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder. More effective options are outlined below.
	• Sedating antihistamines or antipsychotics should not be prescribed for panic disorder.
	
	Panic Disorder Treatment Options
	• Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  • Psychological therapy (i.e., CBT, structured problem solving, psychoeducation).
	  • Pharmacological therapy: antidepressants.
	  • Self-help interventions (i.e., bibliotherapy, support groups, exercise, CBT via a computer interface).
	
	Panic Disorder Additional Considerations for Pharmacologic Therapy
	• Antidepressants should be the only pharmacologic intervention used in the long term.
	• Two types of medication are considered in the guideline for the treatment of panic disorder; TCAs and SSRIs.
	• Unless otherwise indicated, an SSRI (eg, paroxetine, fluvoxamine, citalopram) licensed in the United Kingdom for panic disorder should be offered; if an SSRI is not suitable, the TCAs imipramine or clomipramine may be considered.
	• Side effects with the initiation of antidepressants may be minimized by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved.
	• If the patient is showing improvement, the medication should be continued for at least 6 months after optimal dose is reached, after which the dose may be tapered slowly over an extended period of time to minimize the risk of discontinuation/withdrawal symptoms.
	• If there is no improvement after a 12-week course with an SSRI and if a further medication is appropriate, imipramine or clomipramine may be considered, or another form of therapy may be offered.

Clinical Guideline	Recommendation

	Generalized Anxiety Disorder (GAD) General Considerations
	• Benzodiazepines may be used for acute treatment, but they should not usually be used beyond 2 to 4 weeks.
	
	GAD Treatment Options
	• Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  • Psychological therapy (eg, CBT, structured problem solving, psychoeducation).
	  • Pharmacological therapy: antidepressants.
	  • Self-help interventions (eg, bibliotherapy, support groups, exercise, CBT via a computer interface).
	
	GAD Additional Considerations for Pharmacologic Therapy
	• Unless otherwise indicated, an SSRI should be offered; if one SSRI is not suitable, another SSRI should be offered.
	• Side effects with the initiation of antidepressants may be minimized by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved.
	• If the patient is showing improvement the medication should be continued for at least 6 months after optimal dose is reached, after which the dose may be tapered slowly over an extended period of time to minimize the risk of discontinuation/withdrawal symptoms.
	• If there is no improvement after a 12 week course with an SSRI and if a further medication is appropriate, another SSRI may be considered, or another form of therapy may be offered.
	• If venlafaxine is being considered, an initial electrocardiogram (ECG) and blood pressure measurement should be undertaken and the dose should be no higher than 75 mg per day; treatment should be initiated and managed under the supervision of specialist mental health medical practitioners and regular monitoring of cardiac status is advised.
	• A number of different drugs are considered for the treatment of GAD in the guideline, including SSRIs (eg, paroxetine, fluvoxamine, citalopram), TCAs (eg, imipramine, clomipramine), benzodiazepines (eg, diazepam, alprazolam, clonazepam, lorazepam), sedating antihistamines (eg, hydroxyzine), SNRIs (eg, venlafaxine) and buspirone.
	• Antidepressants are preferred over benzodiazepines due to the potential for abuse and because antidepressants may treat comorbid depression.
	• The evidence is that the following are not effective for people with GAD: MAOIs, beta blockers, antipsychotic medication.

APA: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007)**[77]	• Obsessive-compulsive disorder (OCD) is a chronic illness which typically waxes and wanes. • Patients who have symptoms interfering with daily functioning should be treated. • Clinical remission and recovery may not always occur and will not occur rapidly. • Goals of treatment include improving symptoms, patient functioning, and quality of life. • The choice of treatment depends on the patient's ability to comply with therapy, whether psychotherapy, pharmacotherapy, or both. • First-line treatments include CBT, serotonin-reuptake inhibitors (SRIs), or

Clinical Guideline	Recommendation
	a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • CBT or SRI therapy may be used alone or in combination, and combination therapy may be considered in patients who do not respond fully to monotherapy, those with severe symptoms, those with comorbid psychiatric illnesses for which an SRI is indicated, or in patients who wish to limit SRI exposure. • Clomipramine, fluoxetine, fluvoxamine, paroxetine and sertraline are FDA-approved for the treatment of OCD. • Meta-analyses and placebo-controlled trials suggest better efficacy for clomipramine compared to fluoxetine, fluvoxamine and sertraline though head-to-head trials do not support this claim. • All SRIs appear to be equally effective, though patients may respond to agents differently. • Prescribers should consider the safety, side effects, FDA warnings, drug interactions, past response to treatment, and comorbid medical conditions when choosing a medication for treatment. • Most patients do not experience a significant improvement until 4-6 weeks after treatment initiation, and some may ultimately respond after as many as 10-12 weeks. • Patients not responding after 10-12 weeks may respond to a higher dose of the same medication. • There is only weak support for the use of MAOIs in OCD.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder (2012)**[76]	• The psychiatric assessment of children and adolescents should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors. • If screening suggests obsessive-compulsive symptoms, clinicians should fully evaluate the child using the DSM-IV-TR criteria and scalar assessment. • A complete psychiatric evaluation should be performed, including information from all available sources and compromising standard elements of history and a mental state examination, with attention to the presence of commonly occurring comorbid psychiatric disorders. • It is possible that three out of four children with obsessive-compulsive disorder (OCD) meet criteria for at least one comorbid diagnosis, and these children have lower response rates to CBT than children without comorbid diagnoses. • Identification of MDD and bipolar disorder is very important before initiating treatment with a SSRI. • Comorbid eating disorders are infrequent in younger children; however, comorbid eating disorders become more prevalent in adolescents. • A full medical, developmental, family and school history should be included with the psychiatric history and examination. • CBT is the first-line treatment for mild to moderate OCD in children, whenever possible. • For moderate to severe OCD, medication is indicated in addition to CBT. • Serotonin reuptake inhibitors (SRIs) are the first-line medications recommended for OCD in children, including clomipramine (a TCA) and certain SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline). • There is no SRI that is proven to be more efficacious over another.

Clinical Guideline	Recommendation
	• The modality of assigned treatment should be guided by empirical evidence on the moderators and predictors of treatment response. • Multimodal treatment with CBT and medication is recommended if CBT fails to achieve a clinical response after several months or in more severe cases. • Medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy. • Adding clomipramine to an SSRI is a useful medication augmentation strategy. • Augmenting with an atypical neuroleptic is also a strategy employed by experts (e.g., haloperidol and risperidone combined) based on studies in adults with OCD; however, controlled data for the use of atypical antipsychotics in children with OCD does not exist. • A minimum of two adequate SSRI trials or an SSRI and clomipramine trial is recommended before atypical augmentation. • Empirically validated medication and psychosocial treatments for comorbid disorders should be considered.
NICE: **Obsessive-Compulsive Disorder (2005)**[78]	• Initial pharmacological treatment of OCD in adults should be an SSRI (fluoxetine, fluvoxamine, paroxetine, sertraline or citalopram). • The dose of SSRI may be increased after 4-6 weeks in adults not fully responding to treatment. • Other drugs including TCAs (other than clomipramine), SSRIs, SNRIs, MAOIs, anxiolytics and antipsychotics should not be routinely used in patients without comorbidities. • Patients not responding to an SSRI or a combination of and SSRI and CBT (or in patients who can not engage in CBT), another SSRI or clomipramine may be offered. • Clomipramine may also be used as a first-line agent in patients who have had a previous good response to it.
APA: **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2004)**[79]	• Goals of treatment for patients with Posttraumatic Stress Disorder (PTSD) and Acute Stress Disorder (ASD) include lessening the severity of symptoms and preventing trauma-related comorbid conditions. • Clinical trial data and randomized studies are limited and difficult to perform. • Treatment includes pharmacotherapy, psychotherapy and supportive measures. • SSRIs are first-line therapy for PTSD and ASD and if found effective, treatment should be continued in order to continue to see benefit. • Second-line treatment agents include TCAs (specifically amitriptyline and imipramine, but not desipramine) and MAOIs. • Benzodiazepines should not be used as monotherapy but may be effective as sedatives and anxiolytics. • Atypical antipsychotics may be necessary for patients experiencing psychotic symptoms. • Anticonvulsants (divalproex, carbamazepine, topiramate and lamotrigine) have produced mixed results for treating PTSD and ASD but may prove to be beneficial. • Limited data exists for the use of adrenergic inhibitors and their use is not part of the guideline at this time. • An adequate trial of therapy requires a minimum of three months of

Clinical Guideline	Recommendation
	treatment. If treatment is effective, it should be continued for up to 12 months or longer.
American College of Obstetricians and Gynecologists (ACOG): **Practice Bulletin: Premenstrual Syndrome (2000)**[80]	• SSRIs have been proven effective in treating premenstrual syndrome (PMS). • Current evidence does not support the use of natural progesterone or primrose oil for the treatment of PMS. • Gonadotropin-releasing hormone (GnRH) agonists and surgical oophorectomy have been shown to be effective, but side effects limit usefulness in most patients. • Alprazolam may be useful in some patients, but side effects prevent it from being used as a first-line agent. • Calcium supplements may be effective. • Magnesium, vitamin B6, and vitamin E are minimally effective in treating PMS.
APA: **Practice Guideline for the Treatment of Patients with Eating Disorders (2006)**[81]	• Patients with eating disorders should be treated with nutritional rehabilitation. • Psychosocial therapy should be used in the treatment of anorexia. • SSRIs may be considered in the treatment of anorexia. • Bupropion should be avoided in patients with eating disorders. • Atypical antipsychotics may be used in patients with severe symptoms. • SSRIs, TCAs and MAOIs may be considered in patients with bulimia because of demonstrated efficacy in controlled clinical trials; however, MAOIs are potentially dangerous in patients with chaotic eating and purging habits, and therefore should be used with caution.

Conclusions

The antidepressants are indicated to treat a number of psychological disease states including but not limited to depression, anxiety disorders, obsessive compulsive disorders, and eating disorders. There are many agents in this class and most of them are available generically. National and international treatment guidelines do address the use of these agents for their respective Food and Drug Administration (FDA)-approved indications. 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 medication classes, and comparable between medication classes.[70] Guidelines also state that medications that can be considered first-line therapy for most patients include selective serotonin-reuptake inhibitors (SSRIs), desipramine, nortriptyline, bupropion and venlafaxine, while monoamine oxidase inhibitors (MAOIs) should be reserved for patients who are unresponsive to other available medications. These guidelines do not recommend one SSRI or MAOI over another.[70,71]

For the treatment of generalized anxiety disorder, antidepressants are recommended as first-line treatment, with the following agents considered treatment options: SSRIs, serotonin- and norepinephrine-reuptake inhibitors (SNRIs), and nonsedating tricyclic antidepressants (TCAs). Benzodiazepines may be used as adjunct agents in acute exacerbations of GAD and buspirone has also demonstrated efficacy in GAD in most clinical trials, although it has not shown efficacy against comorbid conditions and therefore is not recommended as first-line treatment for GAD. First-line treatments for obsessive-compulsive disorder (OCD) include cognitive-behavioral therapy (CBT), SSRIs, or a combination of the two. Clomipramine, fluoxetine, fluvoxamine, paroxetine and sertraline are also FDA approved for the treatment of OCD. Guidelines do note that all SSRIs appear to be equally effective, though patients may respond to agents differently.[72]

Although some studies have shown a benefit when one agent is compared to another, these results have not been consistently demonstrated. 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 SSRIs, almost all of which are available generically, appear to be better tolerated than the tricyclic and other norepinephrine-reuptake inhibitors but the long term risk of relapse is comparable. All are statistically better than placebo.

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