Therapeutic Class Overview
Antidepressants, Other

INTRODUCTION

- Major depressive disorder (MDD) is a highly prevalent and disabling disorder characterized by symptoms such as depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (*Simon 2015*).
  - MDD is associated with higher rates of chronic disease, impaired functioning, and increased healthcare utilization. The condition is more prevalent among females and persons aged 40 to 59. From 2009 to 2012, 7.6% of Americans 12 years of age or older had depression (moderate or severe depressive symptoms in the past 2 weeks) (*Pratt and Brody 2014*).
  - Current guidelines recommend first-line treatment with a second-generation antidepressant (SGA) and/or cognitive behavioral therapy (CBT). The effectiveness of SGAs is generally comparable between and within classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). SSRIs, SNRIs, mirtazapine, and bupropion are considered optimal for the treatment of MDD in most patients (*American Psychiatric Association [APA] 2010, Qaseem et al 2016, Veteran's Affairs/Department of Defense [VA/DoD] 2016*).
    - An estimated 40% of patients do not respond to initial SGA therapy; approximately 70% do not achieve remission on initial SGA therapy. In patients who have demonstrated partial or no response to initial maximized monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another monotherapy (SGA or CBT) or augmenting with a second SGA or psychotherapy is recommended (*Gartlehner et al 2015a, VA/DoD 2016*).
- This review includes SGAs other than those classified as SSRIs. It does not include first-generation antidepressants such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). The focus of this review will be the safety and efficacy of the SNRIs, serotonin modulators, and atypical antidepressants in the treatment of MDD and other psychiatric FDA-approved indications.
  - The SNRIs approved for MDD include Cymbalta (duloxetine), Effexor (venlafaxine), Effexor XR (venlafaxine extended-release), Fetzima (levomilnacipran), Khedezla (desvenlafaxine extended-release), and Pristiq (desvenlafaxine succinate extended-release). They work by blocking presynaptic serotonin and norepinephrine transporter proteins, thereby inhibiting neurotransmitter reuptake (*Nelson 2016*).
    - Savella (milnacipran) is an SNRI approved only for fibromyalgia; therefore, it will not be included in this review. Although duloxetine is approved for other indications (ie, chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia), these indications will not be addressed in this review (*Nelson 2016*).
  - The serotonin modulators include Desyrel (trazodone), Serzone (nefazodone), Trintellix (vortioxetine), and Viibryd (vilazodone). They act as serotonin receptor antagonists and/or agonists and inhibit reuptake of postsynaptic serotonin to varying degrees (*Hirsch and Birnbaum* 2017).
    - Oleptro (trazodone extended-release) was approved in 2010 and discontinued in 2015; thus, it will not be included in this review (*Food and Drug Administration [FDA] 2017*).
  - The atypical antidepressants include bupropion and mirtazapine (*Hirsch and Birnbaum 2016*).
    - Bupropion is a monocyclic aminoketone which inhibits the presynaptic reuptake of dopamine and norepinephrine.
      - Bupropion is available a variety of formulations, including Aplenzin (bupropion hydrobromide), Forfivo XL (bupropion hydrochloride extended-release), Wellbutrin (bupropion hydrochloride), Wellbutrin SR (bupropion hydrochloride sustained-release), and Wellbutrin XL (bupropion hydrochloride extended-release). Zyban (bupropion hydrochloride sustained-release) is only indicated for smoking cessation and will not be discussed in this review.
    - Mirtazapine is a piperazinoazepine compound that acts as a potent antagonist of 5-hydroxytryptamine $(5\text{-HT})_2$, 5-HT_3, and histamine receptors and a moderate antagonist of peripheral α_1-adrenergic and muscarinic receptors.
- Some of the products included in this review have additional psychiatric indications other than MDD, including MDD with a seasonal pattern (formerly known as seasonal affective disorder), generalized anxiety disorder (GAD), panic disorder (PD), and social anxiety disorder.

- MDD with a seasonal pattern is characterized by a regular temporal relationship between particular periods of the year and the onset and remission of depressive symptoms (*APA 2010*).
- GAD is characterized by excessive anxiety and worry. Symptoms of GAD include restlessness, being easily fatigued, irritability, difficulty concentrating, muscle tension, and sleep disturbances (*Bandelow et al 2012*).
- PD is characterized by recurrent unexpected panic attacks followed by concern about subsequent panic attacks or maladaptive change in behavior related to the attacks. Panic attacks are discrete periods of intense fear or discomfort accompanied by somatic and psychic symptoms (eg, palpitations, sweating, trembling, dyspnea, chest pain, nausea) (*APA 2009, Bandelow et al 2012*).
- Social anxiety disorder is characterized by persistent fear of being observed or evaluated negatively by others in social performance or interaction situations. Patients with social anxiety disorder often avoid social interactions or endure them with intense anxiety or distress (*Bandelow et al 2012*).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Atypical agents	
Aplenzin (bupropion hydrobromide)	-
Forfivo XL (bupropion hydrochloride extended-release)	-
Remeron (mirtazapine)	✔
Remeron SolTab (mirtazapine ODT)	✔
Wellbutrin (bupropion hydrochloride)	✔
Wellbutrin SR (bupropion hydrochloride sustained-release)	✔
Wellbutrin XL (bupropion hydrochloride extended-release)	✔
SNRIs	
Cymbalta (duloxetine)	✔
Effexor XR (venlafaxine extended-release)	✔
Fetzima (levomilnacipran)	-
Khedezla (desvenlafaxine extended-release)	✔
Pristiq (desvenlafaxine succinate extended-release)	✔
venlafaxine*	✔
Serotonin modulators	
nefazodone*	✔
trazodone*	✔
Trintellix (vortioxetine)	-
Viibryd (vilazodone)	-

* Branded Effexor (venlafaxine), Serzone (nefazodone), and Desyrel (trazodone) are no longer marketed.

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. FDA Approved Indications for Atypical Agents

Indication	Aplenzin (bupropion hydrobromide)	Forfivo XL (bupropion hydrochloride extended-release)	Remeron (mirtazapine)	Remeron SolTab (mirtazapine ODT)	Wellbutrin (bupropion hydrochloride)	Wellbutrin SR (bupropion hydrochloride sustained-release)	Wellbutrin XL (bupropion hydrochloride extended-release)
MDD	✔	✔	✔	✔	✔	✔	✔
Prevention of seasonal major depressive episodes in patients with a diagnosis of seasonal affective disorder	✔						✔

(*Prescribing information: Aplenzin 2017, Forfivo XL 2017, Remeron 2016, Remeron SolTab 2016, Wellbutrin 2017, Wellbutrin SR 2017, Wellbutrin XL 2017*)

Table 3. FDA Approved Indications for SNRIs

Indication	Cymbalta (duloxetine)	Effexor XR (venlafaxine extended-release)	Fetzima (levomilnacipran)	Khedezla (desvenlafaxine extended-release)	Pristiq (desvenlafaxine succinate extended-release)	venlafaxine
MDD	✔	✔	✔	✔	✔	✔
Chronic musculoskeletal pain	✔					
Diabetic peripheral neuropathy	✔					
Fibromyalgia	✔					
GAD	✔	✔				
PD		✔				
Social anxiety disorder		✔				

(*Prescribing information: Cymbalta 2017, Effexor XR 2017, Fetzima 2017, Khedezla 2017, Pristiq 2017, venlafaxine 2016*)

Table 4. FDA Approved Indications for Serotonin Modulators

Indication	nefazodone	trazodone	Trintellix (vortioxetine)	Viibryd (vilazodone)
MDD	✔	✔	✔	✔

(*Prescribing information: nefazodone 2015, trazodone 2016, Trintellix 2017, Viibryd 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

MDD

- Although there is conflicting evidence, most meta-analyses and systematic reviews conclude that the SNRIs, serotonin modulators, and atypical antidepressants have comparable efficacy to SSRIs and to one another in the treatment of MDD. No robust or replicated results have established a clinically meaningful difference in efficacy among classes or within a class (*Simon 2015*).
- A 2011 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review evaluated bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine in the treatment of adults with depressive disorders (*Gartlehner et al 2011*).
  - Results from direct and indirect comparisons based on 61 head-to-head trials and 31 placebo-controlled (PC) trials did not detect any substantial differences in efficacy among the SGAs for MDD (moderate strength of evidence).
  - While the overall adverse event (AE) profiles and rates of discontinuation are similar among SGAs, the incidence of specific AEs varies among agents (high strength of evidence).
    - Venlafaxine was associated with higher rates of nausea and vomiting than SSRIs based on a meta-analysis of 15 studies (high strength of evidence).
    - Mirtazapine was associated with higher weight gain than citalopram, fluoxetine, paroxetine, and sertraline based on results from 7 trials (high strength of evidence).
    - Sertraline was associated with a higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine based on results of 15 studies (moderate strength of evidence).
    - Trazodone was associated with a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine based on results from 6 trials (moderate strength of evidence).
    - Bupropion was associated with lower rates of sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline based on results from 6 trials (high strength of evidence).
  - Results from 7 trials suggest that mirtazapine has a significantly faster onset of action compared to citalopram, fluoxetine, paroxetine, and sertraline (moderate strength of evidence).
  - Separate meta-analyses of the available head-to-head trials also suggested comparable efficacy between SGAs. The clinical significance of the marginal but statistically significant differences reflected in certain head-to-head comparisons remains to be determined.
    - A meta-analysis of 6 studies (n = 1197) directly comparing venlafaxine to fluoxetine demonstrated a significantly higher odds ratio [OR] of response (defined as ≥ 50% reduction of symptoms from baseline) with venlafaxine (OR 1.47; 95% confidence interval [CI], 1.16 to 1.86).
    - A meta-analysis of 3 studies (n = 470) directly comparing sertraline to venlafaxine demonstrated similar rates of response (OR 1.18; 95% CI, 0.81 to 1.72).
    - A meta-analysis of 3 studies (n = 849) directly comparing paroxetine to duloxetine also demonstrated similar rates of response (OR 0.84; 95% CI, 0.63 to 1.12).
- The newer SGAs, levomilnacipran, vilazodone, and vortioxetine, were not included in the 2011 AHRQ review but were included in the 2015 AHRQ comparative effectiveness review which evaluated SGAs and nonpharmacological treatments for adult patients with MDD. The available evidence did not warrant the selection of one SGA over another based on efficacy in initial therapy, switching SGAs, or augmenting SGAs for MDD (*Gartlehner et al 2015a*).
  - Two direct comparisons (n = 1123) with patients who did not achieve remission following an initial adequate SGA trial and were switched to another SGA did not demonstrate a substantial differences in response rates between SGAs (moderate strength of evidence). Additionally, results from one of those studies (n = 727) did not demonstrate a substantial difference between the SGAs in remission rates, decrease in severity of depression, overall risk of AEs, or suicidal ideas or behaviors (low strength of evidence).
  - One direct comparison (n = 565) with patients who did not achieve remission following an initial adequate SGA trial and were treated with add-on therapy with another SGA did not demonstrate substantial differences in the rates of response or remission between SGAs (low strength of evidence).
- In a Cochrane review of 15 studies (n = 7746) with vortioxetine for MDD, patients on vortioxetine were more likely to respond to therapy than those on placebo (Mantel-Haenszel risk ratio [RR] 1.35; 95% CI, 1.22 to 1.49; 14 studies, 6220 participants) with a low quality of evidence. The response rate for vortioxetine was comparable to that of SNRIs as a class (RR 0.91; 95% CI, 0.82 to 1.00; 3159 participants) but lower compared with duloxetine alone (RR 0.86; 95% CI,

0.79 to 0.94; 6 studies, 2392 participants), with a very low quality of evidence. The clinical implications of these results are unclear (*Koesters et al 2017*).

- A multiple-treatments meta-analysis of 117 randomized controlled trials (RCTs) (n = 25,928) found clinically important differences when comparing bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine (not approved in the United States), sertraline, and venlafaxine for the acute treatment of adults with MDD. Mirtazapine, escitalopram, venlafaxine, and sertraline were among the most efficacious antidepressants, while escitalopram, sertraline, bupropion, and citalopram were better tolerated than the other remaining antidepressants (*Cipriani et al 2009*).
  - Patients on mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more likely to respond to therapy than those on duloxetine (OR 1.39, 1.33, 1.30 and 1.27, respectively), fluoxetine (OR 1.37, 1.32, 1.28, and 1.25, respectively), fluvoxamine (OR 1.41, 1.35, 1.30, and 1.27, respectively), and paroxetine (OR 1.35, 1.30, 1.27, and 1.22, respectively).

MDD with a Seasonal Pattern: extended-release bupropion

- A Cochrane review of 3 RCTs (n = 1100) evaluated SGAs for the prevention of seasonal affective disorder in adults. Extended-release bupropion was shown to be an effective intervention compared to placebo (RR 0.56; 95% CI, 0.44 to 0.72) for the prevention of depressive episodes in patients with MDD with a seasonal pattern, with a moderate quality of evidence. Bupropion therapy was also associated with a greater incidence of headaches, insomnia, and nausea compared to placebo. There was insufficient evidence to compare bupropion to other SGAs or to other interventions such as light therapy, psychotherapy, or melatonin (*Gartlehner et al 2015b*).

GAD: duloxetine and extended-release venlafaxine

- A non-inferiority RCT (n = 984) randomized adults with GAD to receive duloxetine, extended-release venlafaxine, or placebo. The primary outcome of response to therapy was defined as ≥ 50% reduction from baseline in Hamilton Anxiety Rating Scale (HAMA) total score. Response rates for duloxetine, extended-release venlafaxine, and placebo were 56%, 58%, and 40%, respectively. Duloxetine and extended-release venlafaxine both demonstrated superiority over placebo ($p \leq 0.001$ for both). The authors concluded that duloxetine met all statistical and clinical criteria for non-inferiority and exhibited a similar tolerability profile compared to extended-release venlafaxine for the treatment of adults with GAD (*Allgulander et al 2008*).

PD: extended-release venlafaxine

- A Cochrane review of 35 double-blind RCTs (n = 6785) evaluated antidepressants and benzodiazepines as monotherapy for adults with PD. An analysis of 2 studies (n = 1316) directly comparing paroxetine with venlafaxine demonstrated similar response rates for PD (RR 0.96; 95% CI, 0.75 to 1.23; 2 studies; 991 participants; $I^2 = 1\%$; high quality of evidence). Additionally, no difference in response rate was detected between antidepressants and benzodiazepines for PD (RR 0.99; 95% CI, 0.67 to 1.47; 2 studies; 215 participants; low quality of evidence) (*Bighelli et al 2016*).
- In a meta-analysis of 50 studies (n = 5236) of antidepressants for PD, the following antidepressants demonstrated superiority over placebo in the reduction from baseline of overall anxiety symptoms (in increasing order of effectiveness): citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine for panic symptoms and paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine (*Andrisano et al 2013*).

Social Anxiety Disorder: extended-release venlafaxine

- A systematic review and meta-analysis of 51 RCTs (n = 9914) evaluated pharmacotherapies for social anxiety disorder. Venlafaxine demonstrated a superior response rate, assessed by the Clinical Global Impressions Improvement (CGI-I) scale, vs. placebo (RR 1.59; 95% CI, 1.38 to 1.83; 4 studies; 1173 participants) (*Ipser et al 2008*).
- Another systematic review and meta-analysis of 3 head-to-head trials and 15 PC trials did not reveal significant differences in the efficacy of SGAs for social anxiety disorder. Pooled evidence from PC trials supported the superiority over placebo in the CGI-I response of escitalopram (relative benefit [RB] 1.3; 95% CI, 1.2 to 1.5), paroxetine (RB 1.9; 95% CI, 1.5 to 2.3), sertraline (RB 1.8; 95% CI, 1.5 to 2.2), and venlafaxine (RB 1.7; 95% CI, 1.5 to 1.9) for social anxiety disorder. While the network meta-analysis did not find significant differences in efficacy among the SGAs, there were differences in the AE profiles (*Hansen et al 2008*).

CLINICAL GUIDELINES

MDD

- **Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of MDD** (*2016*)
  - As first-line treatment for uncomplicated mild to moderate MDD, evidence-based psychotherapy or evidence-based pharmacotherapy should be offered. Selection should be based on patient preference, safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications, cost of medication, and provider training/competence.
    - Evidence-based pharmacotherapy includes SSRIs (except fluvoxamine), SNRIs, mirtazapine, and bupropion.
    - The evidence does not support recommending a specific psychotherapy or pharmacotherapy over another.
    - In patients who have demonstrated partial or no response to initial maximized monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another monotherapy (medication or psychotherapy) or augmenting with a second medication or psychotherapy is recommended.
  - In cases of severe MDD, combined pharmacotherapy and psychotherapy is recommended if initial monotherapy with an antidepressant did not achieve a response or remission. In patients who have demonstrated a partial response and are tolerating the current antidepressant, augmentation with another medication or psychotherapy is reasonable.
- **Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With MDD: A Clinical Practice Guideline From the American College of Physicians (ACP)** (*Qaseem et al 2016*)
  - Clinicians are recommended to select between either CBT or SGAs to treat patients with MDD after discussing treatment effects, AE profiles, cost, accessibility, and preferences with the patient (Grade: Strong recommendation, moderate-quality evidence).
  - There are reported differences among SGAs in mild (constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence) to major (sexual dysfunction and suicidality) AEs. Bupropion is associated with a lower rate of sexual AEs than fluoxetine and sertraline, whereas paroxetine has higher rates of sexual dysfunction than fluoxetine, fluvoxamine, nefazodone, and sertraline. Physicians and patients should discuss AE profiles before selecting a medication.
- **American Psychiatric Association (APA) Practice Guideline for the Treatment of MDD: 3rd Edition** (*2010*)
  - The effectiveness of antidepressant medications is generally comparable between classes and within classes of medications. Thus, the initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference.
  - For most patients, an SSRI, an SNRI, mirtazapine, or bupropion is optimal.
  - In general, the use of nonselective MAOIs (eg, phenelzine, tranylcypromine, isocarboxazid) should be restricted to patients who do not respond to other treatments.

MDD with a Seasonal Pattern

- Light therapy may be suggested for adult patients with mild to moderate MDD with a seasonal pattern. While there is limited evidence supporting the effectiveness of light therapy, the benefits outweigh the risks. For severe seasonal MDD, pharmacological intervention with an antidepressant is recommended, and light therapy may be considered as adjunctive therapy. Extended-release bupropion is FDA approved for use in patients with MDD with seasonal pattern (*APA 2010, VA/DoD 2016*).

GAD

- According to the World Federation of Societies of Biological Psychiatry (WFSBP), the first-line pharmacologic therapies for GAD are SSRIs, SNRIs and pregabalin. Other treatment options include buspirone and hydroxyzine. Benzodiazepines should only be used for long-term treatment when other drugs or CBT have failed (*Bandelow et al 2012*).

PD

- The WFSBP recommends SSRIs or venlafaxine as first-line pharmacotherapies for PD. For severe acute panic attacks, short-acting benzodiazepines may be needed. Treatment should continue for at least several months after remission in order to prevent relapses (*Bandelow et al 2012*).
- For the initial treatment of PD, the use of an SSRI, SNRI, TCA, benzodiazepine (appropriate as monotherapy only in the absence of a co-occurring mood disorder), or CBT is strongly supported by evidence of efficacy in numerous RCTs.

There is insufficient evidence to recommend any of the pharmacological or psychosocial interventions as superior to the others, or to routinely recommend a combination of therapies over monotherapy (*APA 2009*).

Social Anxiety Disorder

- The WFSBP recommends SSRIs and venlafaxine for first-line pharmacologic therapy for social anxiety disorder. There is insufficient evidence to recommend benzodiazepines or TCAs. Exposure therapy and CBT are also effective psychotherapies (*Bandelow et al 2012*).

SAFETY SUMMARY

Contraindications

- In general, antidepressants are contraindicated in patients with concurrent administration of MAOIs (trazodone and nefazodone have this listed as a warning rather than a contraindication). The risk for serotonin syndrome is increased with the use of MAOIs, including linezolid and intravenous methylene blue.
- Bupropion products are additionally contraindicated in the following: seizure disorder; current or prior diagnosis of bulimia or anorexia; abrupt discontinuation of alcohol, benzodiazepines, barbiturates, antiepileptic drugs.
- Nefazodone is additionally contraindicated in patients who were withdrawn from nefazodone due to liver injury and in patients concurrently on terfenadine, astemizole, cisapride, pimozide, carbamazepine, or triazolam.

Warnings

- All antidepressants carry a boxed warning for suicidal thoughts and behaviors. The risk of suicidal thinking and behavior is increased in children, adolescents, and young adults taking antidepressants.
- Nefazodone labeling also contains a boxed warning for life-threatening hepatic failure and recommends that prescribers consider the risk of hepatic failure associated with nefazodone treatment when deciding among the various treatment options available for MDD. In many cases, this would lead to the conclusion that other drugs should be tried first.
- Neonates exposed to SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with venlafaxine tablets during the third trimester, the potential risks and benefits of treatment should be carefully considered.

AEs

- Common AEs with the antidepressants included in this review are outlined in Table 5 below.

Table 5. AEs of antidepressant medications

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Atypical agents								
Bupropion	0	0	2+ (IR) 1+ (SR)	0	1+	1+	0	0
Mirtazapine	1+	4+	0	0	1+	0	4+	1+
SNRIs†,‡								

* Risk of QTc prolongation or torsades de pointes is also elevated with advanced age, female sex, heart disease, congenital long QT syndrome, hypokalemia or hypomagnesemia, elevated serum drug concentrations (eg, drug overdose, interacting drugs, organ failure) and combination of drugs with QTc prolonging effects. Refer to topic on acquired long QT syndrome.

† All SSRIs and SNRIs are associated with transient nausea and gastrointestinal discomfort upon initiation or dose increase.

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Desvenlafaxine§	0	0	1+	0	0	2+	unknown	1+
Duloxetine	0	0	1+	0	0	2+†	0-1+	1+
Levomilnacipran§	0**	0	0-1+	0-1+	0	2+†	0	1+
Venlafaxine§	0	1+	1+	0	1+	2+	0-1+	3+
Serotonin modulators								
Nefazodone††	1+	2+	0	1+	0	2+	0	0
Trazodone‡‡	0	4+	0	3+	2+	3+	1+	1+§§
Vilazodone	0	0	2+	0	0	4+***	0	2+
Vortioxetine	0	0	0	0	0	3+	0	1+

Abbreviations: IR = immediate release; SNRI = serotonin-norepinephrine reuptake inhibitor; SR = sustained release.
Scale: 0 = none; 1+ = slight; 2+ = low; 3+ = moderate; 4+ = high; ND = inadequate data.

‡ None of the SNRIs have anticholinergic activity. However, SNRIs can produce anticholinergic-like effects (which appear to be mediated by noradrenergic effects on the autonomic nervous system) such as dry mouth and constipation, and should be used with caution in narrow angle glaucoma. In addition, levomilnacipran is associated with urinary hesitancy.
§ May cause persistent dose-related increases in blood pressure (primarily diastolic) and heart rate. Monitor blood pressure regularly.
** Levomilnacipran has dose dependent effects on urinary hesitancy.
†† Caution: can cause liver failure. Not available in Europe, Canada, and several other countries.
‡‡ Side effect scale is displayed for the antidepressant dose of trazodone.
§§ Trazodone is associated rarely with priapism, which is considered a medical emergency.
*** Vilazodone is associated with higher rates of nausea, vomiting, and diarrhea.

(*Hirsch and Birnbaum 2017, Nelson 2016*)

DOSING AND ADMINISTRATION

- In general, the dose of antidepressants should be gradually reduced prior to complete discontinuation to avoid withdrawal.

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Atypical agents				
Aplenzin (bupropion hydrobromide)	Extended-release tablets	Oral	Daily	Increase dose gradually to reduce seizure risk. Dose adjustments may be required in renal or hepatic impairment.
Forfivo XL (bupropion hydrochloride)	Extended-release tablets	Oral	Daily	Not recommended in patients with renal or hepatic impairment due to higher dose. Bupropion treatment should not be initiated with Forfivo XL. Another bupropion formulation should be used for initial dose titration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Remeron (mirtazapine)	Tablets	Oral	Daily	Administered in the evening prior to sleep. Caution is advised in renal or hepatic insufficiency.
Remeron SolTab (mirtazapine)	Orally-disintegrating tablets	Oral	Daily	
Wellbutrin (bupropion hydrochloride)	Tablets	Oral	3 times daily	Dose adjustments may be required in renal or hepatic impairment.
Wellbutrin SR (bupropion hydrochloride)	Sustained-release tablets	Oral	Twice daily	
Wellbutrin XL (bupropion hydrochloride)	Extended-release tablets	Oral	Daily	
SNRIs				
Cymbalta (duloxetine)	Delayed-release capsules	Oral	Daily or twice daily	
Effexor XR (venlafaxine)	Extended-release capsules	Oral	Daily	Take with food. Dose adjustments may be required in renal or hepatic impairment.
Fetzima (levomilnacipran)	Extended-release capsules	Oral	Daily	Adjust dose in moderate or severe renal impairment.
Khedezla (desvenlafaxine)	Extended-release tablets	Oral	Daily	Dose adjustments may be required in renal or hepatic impairment. Increased risk of orthostatic hypotension for patients ≥ 65 years.
Pristiq (desvenlafaxine succinate)	Extended-release tablets	Oral	Daily	
venlafaxine*	Tablets	Oral	2 or 3 times daily	Take with food. Dose adjustments may be required in renal or hepatic impairment.
Serotonin modulators				
nefazodone*	Tablets	Oral	Twice daily	Not recommended in active liver disease or elevated baseline serum transaminases.
trazodone*	Tablets	Oral	3 times daily	Take shortly after a meal or light snack. Caution is advised in renal or hepatic impairment.
Trintellix (vortioxetine)	Tablets	Oral	Daily	
Viibryd (vilazodone)	Tablets	Oral	Daily	Take with food.

See the current prescribing information for full details

CONCLUSION

- Despite conflicting evidence, most meta-analyses and systematic reviews conclude that the SNRIs, serotonin modulators, and atypical antidepressants have comparable efficacy to SSRIs and to one another in the treatment of MDD. No robust or replicated results have established a clinically meaningful difference in efficacy among classes of SGAs or within a class (*Simon 2015*).
- While the AE profiles and discontinuation rates are similar among SGAs, the incidence of specific AEs varies among agents (*Gartlehner et al 2011*). Therefore, the overall safety is comparable between the SNRIs, serotonin modulators, and atypical antidepressants, with the exception of nefazodone, which carries a boxed warning for life-threatening hepatic failure.

- According to clinical practice guidelines, CBT and SGAs are equally effective first-line monotherapies in the initial treatment of patients with MDD. There is insufficient evidence to recommend a specific psychotherapy or pharmacotherapy over another. The effectiveness is generally comparable between classes and within classes of SGAs. Thus, the initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference (*APA 2010, Qaseem et al 2016, VA/DoD 2016*).
  - An estimated 40% of patients do not respond to initial SGA therapy; approximately 70% do not achieve remission on initial SGA therapy. For patients with an insufficient response to initial SGA monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another SGA, augmenting with a second SGA, or augmenting with CBT are all reasonable options (*Gartlehner et al 2015a, VA/DoD 2016*).

REFERENCES

- Allgulander C, Nutt D, Detke M, et al. A non-inferiority comparison of duloxetine and venlafaxine in the treatment of adult patients with generalized anxiety disorder. *J Psychopharmacol*. 2008;22(4):417-25. doi: 10.1177/0269881108091588.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition. November 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed July 1, 2017.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition. January 2009. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf. Accessed July 1, 2017.
- Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: a meta-analysis. *Int Clin Psychopharmacol*. 2013;28(1):33-45. doi: 10.1097/YIC.0b013e32835a5d2e.
- Aplenzin [package insert], Bridgewater, NJ: Valeant Pharmaceuticals North America LLC.; May 2017.
- Bandelow B, Sher L, Bunevicius R,et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84. doi: 10.3109/13651501.2012.667114.
- Bighelli I, Trespidi C, Castellazzi M, et al. Antidepressants and benzodiazepines for panic disorder in adults. *Cochrane Database Syst Rev*. 2016;9:CD011567. doi: 10.1002/14651858.CD011567.pub2.
- Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746-58. doi: 10.1016/S0140-6736(09)60046-5.
- Cymbalta [package insert], Indianapolis, IN: Lilly USA, LLC; January 2017.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed July 1, 2017.
- Effexor XR [package insert], Philadelphia, PA: Wyeth Pharmaceuticals Inc.; March 2017.
- Fetzima [package insert], Irvine, CA: Allergan USA, Inc.; January 2017.
- Food and Drug Administration. Determination that Tensilon and Tensilon Preservative Free (edrophonium chloride) injectable and other drug products were not withdrawn from sale for reasons of safety or effectiveness. *Federal Register.* 2015;80(210):66911.
- Forfivo XL [package insert], Pine Brook, NJ: Almatica Pharma, Inc.; May 2017.
- Gartlehner G, Gaynes BN, Amick HR, et al. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder. Agency for Healthcare Research and Quality (AHRQ) Web site. December 2015a. http://www.effectivehealthcare.ahrq.gov/ehc/products/568/2155/major-depressive-disorder-report-151202.pdf. Accessed July 1, 2017.
- Gartlehner G, Hansen RA, Morgan LC, et al. Second-generation antidepressants in the pharmacologic treatment of adult depression: an update of the 2007 comparative effectiveness review. Agency for Healthcare Research and Quality (AHRQ) Web site. December 2011. https://effectivehealthcare.ahrq.gov/ehc/products/210/863/CER46_Antidepressants-update_20111206.pdf. Accessed July 1, 2017.
- Gartlehner G, Nussbaumer B, Gaynes BN,et al. Second-generation antidepressants for preventing seasonal affective disorder in adults. *Cochrane Database Syst Rev*. 2015b;11:CD011268. doi: 10.1002/14651858.CD011268.pub2.
- Hansen RA, Gaynes BN, Gartlehner G, et al. Efficacy and tolerability of second-generation antidepressants in social anxiety disorder. *Int Clin Psychopharmacol*. 2008;23(3):170-9. doi: 10.1097/YIC.0b013e3282f4224a.
- Hirsch M, Birnbaum RJ. Atypical antidepressants: Pharmacology, administration, and side effects. UpToDate Web site. www.uptodate.com. Updated September 14, 2016. Accessed July 1, 2017.
- Hirsch M, Birnbaum RJ. Serotonin modulators: Pharmacology, administration, and side effects. UpToDate Web site. www.uptodate.com. Updated June 12, 2017. Accessed July 1, 2017.
- Ipser JC, Kariuki CM, Stein DJ. Pharmacotherapy for social anxiety disorder: a systematic review. *Expert Rev Neurother*. 2008;8(2):235-57. doi: 10.1586/14737175.8.2.235.
- Khedezla [package insert], Marietta, GA: Osmotica Pharmaceutical US LLC; January 2017.
- Koesters M, Ostuzzi G, Guaiana G, Breilmann J, Barbui C. Vortioxetine for depression in adults. *Cochrane Database Syst Rev*. 2017;7:CD011520. doi: 10.1002/14651858.CD011520.pub2.
- Nefazodone [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc.; September 2015.
- Nelson C. Serotonin-norepinephrine reuptake inhibitors (SNRIs): Pharmacology, administration, and side effects. UpToDate Web site. www.uptodate.com. Updated April 4, 2016. Accessed July 1, 2017.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed July 1, 2017.
- Pratt LA, Brody DJ. Depression in the U.S. household population, 2009-2012. Nations Center for Health Statistics (NCHS) data brief, no 172. 2014. https://www.cdc.gov/nchs/data/databriefs/db172.htm. Accessed July 1, 2017.
- Pristiq [package insert], Philadelphia, PA: Wyeth Pharmaceuticals Inc.; January 2017.

- Qaseem A, Barry MJ, Kansagara D, et al. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;164(5):350-9. doi: 10.7326/M15-2570.
- Remeron [package insert], Whitehouse Station, NJ: Merck and Co, Inc.; July 2016.
- Remeron SolTab [package insert], Whitehouse Station, NJ: Merck and Co, Inc.; July 2016.
- Simon G. Unipolar major depression in adults: Choosing initial treatment. UpToDate Web site. www.uptodate.com. Updated December 23, 2015. Accessed July 1, 2017.
- Trazodone [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc.; September 2016.
- Trintellix [package insert], Deerfield, IL: Takeda Pharmaceuticals America, Inc.; April 2017.
- Venlafaxine [package insert], Dayton, NJ: Aurobindo Pharma USA, Inc.; October 2017.
- Veteran's Affairs/Department of Defense (VA/DoD) clinical practice guidelines for the management of major depressive disorder. Department of Veterans Affairs Web site. April 2016. https://www.healthquality.va.gov/guidelines/MH/mdd/. Accessed July 1, 2017.
- Viibryd [package insert], Irvine, CA: Allergan USA, Inc.; January 2017.
- Wellbutrin [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2017.
- Wellbutrin SR [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2017.
- Wellbutrin XL [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2017.

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