Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Effectiveness Review Project (DERP) Summary Report on Second-Generation Antidepressants and Antidepressants Literature Scan

Date of Review: November 2017

Date of Last Review: July 2016
Literature Search: July 2016 – July 2017

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:

- Do any antidepressants differ in efficacy or effectiveness compared with other antidepressants for the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), or any other conditions?
- Do any antidepressants differ in harms compared with other antidepressants?
- Are there subgroups of patients based on demographics (age, racial groups, socio-demographic factors, and sex), other medications, or comorbidities for which one antidepressant medication is more effective or associated with fewer adverse events than another?

Conclusions:

- No direct comparative evidence was found for levomilnacipran, vilazodone, or vortioxetine with most other second-generation antidepressants for MDD.[1] However, network meta-analyses showed similar response rates.[1] Relative risks versus placebo were 1.41 (95% CI 1.12-1.77), 1.35 (95% CI 1.06-1.72), and 1.69 (95% CI 1.34-2.14), respectively.[1] Response to treatment in the network meta-analyses was defined as 50% improvement of scores from baseline on the Hamilton Depression Rating Scale.[1]
- Moderate quality evidence from one randomized controlled trial (RCT) demonstrated similar response rates for vilazodone and citalopram in MDD.[1]
- Low quality network meta-analyses found similar response rates for vortioxetine and duloxetine for MDD while two RCTs had conflicting data.[1] Two moderate strength RCTs also found similar remission rates and one low strength RCT showed similar improvements in functional capacity.[1] Additionally, a Cochrane review published in 2017 compared vortioxetine to placebo as well as duloxetine and venlafaxine.[2] The review of low quality evidence found that there was no significant difference between the response rates of patients treated with vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs) as a class (venlafaxine or duloxetine).[2] In individual antidepressant comparisons, response rates were significantly lower for vortioxetine compared to duloxetine (RR 0.86; 95% CI 0.79-0.94; p=0.001; ARR 6.25%; NNT 16) but no difference was seen between vortioxetine and venlafaxine.[2] However, vortioxetine was noted to have significantly lower dropout rates compared to venlafaxine (RR 0.70; 95% CI 0.52-0.93; ARR 8.1%; NNT 13).[2] The authors concluded that there was no advantage to vortioxetine compared to the SNRIs.[2]
- Moderate strength of evidence found vortioxetine and venlafaxine XR to have similar response rates after 6 weeks of treatment in severe MDD.[1]

- Low strength of evidence from one RCT demonstrated statistically non-significant yet numerically smaller response rates based on the Hamilton Anxiety Scale as well as remission rates with vortioxetine compared to duloxetine for GAD at 8 weeks.[1]
- Low strength of evidence found differences in adverse effects which included greater diarrhea (26.5% vs. 10.6%; RR 2.49; 95% CI 1.69-3.67) and vomiting (6.6% vs. 1.8%; RR 3.73; 95% CI 1.43-9.86) with vilazodone versus citalopram (one fair quality RCT), numerically lower rates of discontinuation due to adverse events with vortioxetine versus venlafaxine XR (7.0% vs. 14.2%; RR 0.49; 95% CI 0.21-1.15; one low strength RCT), and significantly lower sexual dysfunction (25% vs. 46%; RR 0.54; 95% CI 0.34-0.85 and 36% vs. 53%; RR 0.67; 95% CI 0.45-0.98; two fair quality RCT) and somnolence (5% vs. 12%; RR 0.42; 95% CI 0.19-0.02; one fair quality RCT) with vortioxetine versus duloxetine.[1] Meta-analyses demonstrated lower risks with vortioxetine compared to duloxetine for dry mouth (RR 0.69; 95% CI 0.50-0.96).[1] Other safety outcomes evaluated in the DERP report demonstrated no statistically significant difference between levomilnacipran, vilazodone, or vortioxetine and other second-generation antidepressants.[1]
- There is insufficient evidence to determine if there is a difference in various subgroup populations in efficacy or safety for levomilnacipran, vilazodone, vortioxetine, or other second-generation antidepressants.[1]
- A Cochrane review published in 2016 compared antidepressants and benzodiazepines in adults with panic disorder.[3] No significant difference was found in the primary outcome of failure to respond with tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), or antidepressants as a whole compared with benzodiazepines based on low quality evidence.[3] Low quality evidence showed a benefit for benzodiazepines in total number of dropouts (RR 1.64; 95% CI 1.03-2.63; ARR 8.8%; NNT 12; studies = 7) compared to antidepressants as a whole as well as compared to the SSRIs (RR 1.71; 95% CI 1.03-2.84; ARR 15.6%; NNT 7; studies = 1) but not the TCAs.[3]
- A Cochrane review comparing bupropion and placebo in adults with ADHD found low quality evidence that change in severity of ADHD symptoms (standard mean difference [SMD] -0.50; 95% CI -0.86 to -0.15) and proportion of patients achieving significant clinical improvement defined as a reduction of at least 30% in the severity of ADHD symptoms at baseline (48% vs. 32%; RR 1.50; 95% CI 1.13 – 1.99; ARR= 16%; NNT 7) were improved with bupropion compared with placebo.[4] Similar tolerability as measured by participants withdrawing due to adverse events was similar between the bupropion and placebo groups (RR 1.20; 95% CI 0.35 – 4.10).[4]
- A systematic review of children and adolescents with depressive disorders (DDs), anxiety disorders (ADs), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) found a significantly increased percentage of patients who discontinued studies due to adverse events in the SSRI versus placebo groups (RR 1.84; 95% CI 1.38-2.44; p<0.001; 27 trials) but not in the SNRI groups versus placebo (RR 1.56; 95% CI 0.83-2.94; p=0.17; 6 trials).[5] However, significantly higher serious adverse events were reported both in the SSRI (RR 1.71; 95% CI 1.22-2.40; p=0.002; 17 trials) and SNRI (RR 2.10; 95% CI 1.19-3.69; p=0.01; 7 trials) groups compared to placebo.[5]
- A Cochrane review published in 2016 compared antidepressants with placebo in patients over the age of 60 years in preventing relapse and recurrence.[6] At 12 months, there was a decreased risk of recurrence with antidepressants versus placebo (49% vs. 73%; RR 0.67; 95% CI 0.55-0.82; ARR 24.3%; NNT 5) based on low quality evidence.[6] However, at 24 months there was no significant difference seen in antidepressants versus placebo.[6]
- Two new guidelines, from the Department of Veterans Affairs (VA) and Department of Defense (DoD) as well as the Canadian Network for Mood and Anxiety Treatments (CANMAT), were published for the treatment of MDD.[7,8]

Recommendations:

- No new evidence in the DERP report or literature search suggests changes should be made to the PDL based on clinical differences between agents.
- Due to clinical concerns with the Initial Pediatric SSRI Antidepressant – Daily Dose Limit PA that has not yet been implemented, evaluate for potential intervention (possibly education, retro-DUR, or case management focused) to be brought back to the committee and implemented instead of a PA.
- After evaluation of comparative costs in executive session, no changes to the PDL were recommended.

Previous Conclusions:

- A Cochrane review published in 2014 compared the efficacy and tolerability profile of paroxetine to tricyclic antidepressants (TCAs), other selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants. Most of the studies included in the analysis were at unclear or high risk of bias due to poor reporting of study characteristics or incomplete outcome reporting. Although some possibly meaningful differences between paroxetine and other antidepressants (ADs) were noted, no definitive conclusions can be drawn regarding the preference of one AD over another. There is no new comparative evidence between antidepressants that changes the previous conclusions.
- The Agency for Healthcare Research and Quality (AHRQ) funded a systematic review to evaluate the benefits and harms of second generation antidepressants (SGAs) compared to non-pharmacologic interventions such as cognitive behavioral therapy (CBT) or herbal supplements such as St. John's wort. The authors found low quality evidence with a high risk of bias and concluded both CBT and SGAs are reasonable choices for first line treatment of adults with depression.
- Several systematic reviews evaluated the safety and efficacy of antidepressants in specific populations such as post-partum women and patients with cancer, epilepsy or end stage renal disease. In the absence of robust and reliable evidence the authors were unable to draw effective conclusions regarding the impact of antidepressants in managing depression in these unique populations. More studies in each of these populations is needed to guide clinical practice.
- Two systematic evaluations focused on antidepressant therapy in pediatric patients concluded that selective serotonin reuptake inhibitors (SSRIs) are better tolerated with superior efficacy compared to TCA therapy. One systematic review concluded fluoxetine was best tolerated and the most effective for treating depression in children and adolescents. However, the quality of the studies ranged from low to moderate quality with unclear to high risk of bias.
- A retrospective cohort study conducted in children enrolled in the Tennessee Medicaid program found no evidence of increased suicide risk for sertraline, paroxetine, citalopram, escitalopram or venlafaxine compared with fluoxetine in children and adolescents.
- Vilazodone received an expanded indication from the Food and Drug Administration (FDA) in March 2015 for a lower 20 mg dose to treat MDD. An additional Phase III trial demonstrated the efficacy of the 20mg dose in treating MDD.
- New safety warnings were issued by the FDA after reports of orthostatic hypotension, falls and syncope were reported with therapeutic doses of duloxetine. An analysis of patients from all placebo controlled trials revealed that patients treated with duloxetine reported a higher rate of falls compared to patients treated with placebo.

Previous Recommendations:

- There is no evidence of a difference in safety or efficacy between antidepressants and preference can be established on cost and patient specific factors. Evaluate comparative antidepressant costs in Executive Session.

Second Quarter 2017 Utilization:

Second quarter (4/1/2017-7/28/2017) utilization data for the antidepressants show that there were 123,006 claims with the majority (68%) of the utilization for preferred agents. The most utilized agents overall were sertraline and trazodone (14% each) followed by fluoxetine (11%) and citalopram (10%).

Methods:

The April 2017 Drug Class Review on second-generation antidepressants by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1] In addition, new systematic

reviews and RCTs published on antidepressants since completion of the last literature scan in July 2016 which were not included in the DERP report were identified. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The DERP is part of the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University. The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports. The original DERP report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The primary focus of the evidence outside of the DERP report is on high quality systematic reviews and evidence-based guidelines. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

DERP Report Findings:

In April 2017, DERP released a drug class update on second-generation antidepressants with an emphasis on levomilnacipran, vilazodone, and vortioxetine compared with other second-generation antidepressants.[1] The report focused on adult populations with MDD or GAD and included 7 head-to-head trials.[1] A network meta-analysis based on response to treatment on the Hamilton Depression Rating Scale was also completed utilizing 119 RCTs which included all placebo- and active-controlled RCTs that contained homogeneous populations and outcomes.[1] Network meta-analysis is a procedure that allows inferences into the comparative effectiveness of interventions that may or may not have been studied directly.[9] The results of network meta-analyses should be interpreted with caution as this is indirect evidence.[9,10]

Table 1. Second-generation Antidepressants Included in the DERP Review.[1]

Generic Name	U.S. Trade Name	Usual Daily Dosing Range	Frequency
Bupropion	Wellbutrin®	200-450 mg	Three times daily
	Wellbutrin SR®	150-400 mg	Twice daily
	Wellbutrin XL®	150-450 mg	Once daily
Citalopram	Celexa®	20-40 mg	Once daily
Desvenlafaxine	Pristiq®	50 mg	Once daily
Duloxetine	Cymbalta®	40-60 mg	Once or twice daily
Escitalopram	Lexapro®	10-20 mg	Once daily
Fluoxetine	Prozac®	10-80 mg	Once or twice daily
	Prozac Weekly®	90 mg	Once weekly
Fluvoxamine	Luvox®	50-300 mg	Once or twice daily

Levomilnacipran	Fetzima®	40-120 mg	Once daily
Mirtazapine	Remeron®	15-45 mg	Once daily
	Remeron Sol tab®	15-45 mg	Once daily
Nefazodone	Serzone®	200-600 mg	Twice daily
Paroxetine	Paxil®	20-60 mg	Once daily
	Paxil CR®	12.5-75 mg	Once daily
Sertraline	Zoloft®	50-200 mg	Once daily
Trazodone	Desyrel®	150-400 mg	Three times daily
Venlafaxine	Effexor®	75-375 mg	Two to three times daily
	Effexor XR®	75-225 mg	Once daily
Vilazodone	Viibryd®	40 mg	Once daily
Vortioxetine	Trintellix®	10-20 mg	Once daily

Key Question 1: For outpatients with major depressive disorder (MDD) or generalized anxiety disorder (GAD), do levomilnacipran, vilazodone, or vortioxetine differ in efficacy or effectiveness compared with one another or other second-generation antidepressants?

Major Depressive Disorder

Levomilnacipran Compared with Other Second-Generation Antidepressants

- Comparative evidence was not found.[1]
- No statistically significant differences were found in terms of response rates in network meta-analyses.[1]

Vilazodone Compared with Other Second-Generation Antidepressants

- One fair quality RCT showed no difference in Montgomery Asberg Depression Rating Scale scores (-17.6 vs. -17.5 points) or response rates (64.6% vs. 62.9%; RR 1.03; 95% CI 0.90-1.16) between vilazodone 40 mg and citalopram 40 mg groups (n=580 total) at 10 weeks.[1] The network meta-analyses results for response rates were similar to those in the RCT (RR 1.01; 95% CI 0.72-1.41).[1]
- No other direct comparative evidence was available for vilazodone, and no statistically significant differences were found for response rates in the network meta-analyses when comparing vilazodone to other second-generation antidepressants.[1]

Vortioxetine Compared with Duloxetine

- Evidence from two fair-quality phase III trials provided differing results in terms of response rate.[1]
- One trial (n=614) compared vortioxetine 15 mg and 20 mg with duloxetine 60 mg. Fewer patients in both the vortioxetine groups achieving response to treatment at 8 weeks compared to duloxetine 60 mg (44.1% vs. 44.2% vs. 54.8%; RR 0.81; 95% CI 0.67-0.98).[1] The percent of responders in the placebo group was 39.2%.[11] Neither of the treatment groups showed significantly greater improvements in Sheehan Disability Score compared to the placebo group.[1]
- Another trial (n=602) comparing flexible-dose vortioxetine (10-20mg/day) to duloxetine 60 mg resulted in similar rates of response (50.9% vs. 54.5%; RR 0.98; 95% CI 0.92-1.19).[1]

- No statistically significant differences were found in terms of response rates in network meta-analyses (RR 1.22; 95% CI 0.95-1.56).[1]

Vortioxetine Compared with Venlafaxine XR

- One fair-quality phase II trial (n=429) reported similar reductions in Montgomery Asberg Depression Rating Scale scores from baseline to week 6 (-22.9 vs. -23.4 points), response rates on the Hamilton Depression Rating Scale (69.0% vs. 72.0%; RR 0.98; 95% CI 0.82-1.16), and remission rates on the Hamilton Depression Rating Scale (45.0% vs. 46.0%; RR 0.98; 95% CI 0.73-1.31) between vortioxetine 10 mg per day and venlafaxine 225 mg per day.[1] Placebo response rates and remission rates on the Hamilton Depression Rating Scale were 40% and 28%, respectively, indicating a significant improvement with both vortioxetine 10 mg and venlafaxine 225 mg for both outcomes.[12]
- No statistically significant differences were found in terms of response rates in network meta-analyses (RR 1.15; 95% CI 0.91-1.45).[1]

Vortioxetine Compared with Other Second-Generation Antidepressants

- No direct comparative evidence was found aside from the evidence presented above for vortioxetine versus duloxetine and vortioxetine versus venlafaxine XR.[1]
- Upon indirect comparison with network meta-analyses, vortioxetine was associated with significantly greater response rates compared to bupropion (RR 1.33; 95% CI 1.02-1.74) and fluoxetine (RR 1.35; 95% CI 1.05-1.73).[1] However, results were significantly impacted by inclusion or exclusion of studies with high risk of bias in the meta-analysis which decreases confidence in these results. Upon addition of studies with high risk of bias to the meta-analyses, the bupropion versus vortioxetine comparison no longer achieved statistically significant differences. Additionally, upon removal of a single vortioxetine versus placebo trial from the model which reported substantially greater response rates for vortioxetine, the response rates were not statistically significant for either comparison.[1]

Generalized Anxiety Disorder

- No comparative evidence was found for levomilnacipran or vilazodone compared to other second-generation antidepressants.[1]

Vortioxetine Compared with Duloxetine

- Vortioxetine is not FDA-approved for GAD.[1]
- A fair-quality phase III trial (n=781) showed statistically similar results in the change of Hamilton Anxiety Scale ratings from baseline to week 8 (-11.66 for vortioxetine 10 mg; -13.87 for duloxetine 60 mg).[1] Response rates (44.8% vs. 51%; RR 0.88; 95% CI 0.69-1.12) and remission rates (20.1% vs. 28.2%; RR 0.71; 95% CI 0.48-1.07) were statistically similar but numerically lower for patients on vortioxetine 10 mg compared to duloxetine.[1] The response rate for placebo was 42.2%.[13]

Key Question 2: For outpatients with major depressive disorder or generalized anxiety disorder: do levomilnacipran, vilazodone, or vortioxetine differ in harms compared with other second-generation antidepressants?

Levomilnacipran Compared with Other Second-Generation Antidepressants

- No eligible studies were found.[1]

Vilazodone Compared with Other Second-Generation Antidepressants

- One RCT was found comparing vilazodone with citalopram.[1]
  - The overall risks of adverse events and overall discontinuations were similar between vilazodone and citalopram groups.[1]
  - The discontinuation rates due to adverse events and risk of suicidal ideation were similar between groups, and the data are insufficient to determine differences for these outcomes.[1] One attempted suicide was documented in the vilazodone group.[1]
  - There is insufficient data to determine differences in the comparative risk of serious adverse events between vilazodone and citalopram.[1]
  - While risks for specific adverse events were similar, the vilazodone groups documented significantly more diarrhea (26.5% vs. 10.6%; RR 2.49; 95% CI 1.69-3.67) and vomiting (6.6% vs. 1.8%; RR 3.73; 95% CI 1.43-9.86) compared to those treated with citalopram.[1]

Vortioxetine Compared with Duloxetine

- Overall risk of adverse events was similar between groups based on 3 fair-quality trials and a meta-analysis.[1]
- Evidence from a random-effects meta-analysis showed similar risks of overall discontinuation and discontinuation due to adverse events.[1]
- Serious side effects were rare, and difference in comparative risk between groups could not be determined.[1] Suicidal ideation (n=1) and a suicide attempt (n=1) were documented in patients randomized to vortioxetine.[1] Angina pectoris (n=1) and somnolence (n=1) were reported in the duloxetine groups.[1,13]
- In terms of specific adverse events, there were lower risks with vortioxetine for dry mouth (RR 0.69; 95% CI 0.50-0.96) based on meta-analyses, as well as for sexual dysfunction (25% vs. 46%; ARR 21%; RR 0.54; 95% CI 0.34-0.85 and 36% vs. 53%; ARR 17%; RR 0.67; 95% CI 0.45-0.98 [two trials]) and somnolence (5% vs. 12%; RR 0.42; 95% CI 0.19-0.02; one trial) based on RCTs.[1] For decreased appetite and fatigue, one RCT showed a decreased risk while another RCT did not.[1] Similar risks were found for diarrhea, dizziness, nausea, vomiting, and constipation.[1]

Vortioxetine Compared with Venlafaxine XR

- Based on one RCT, vortioxetine-treated patients and venlafaxine XR-treated patients experienced a similar risk of overall adverse events and overall discontinuation.[1]
- Discontinuation rates due to adverse events were not statistically significant but were numerally smaller for the vortioxetine group (7.0% vs. 14.2%; RR 0.49; 95% CI 0.21-1.15).[1]
- There are insufficient data to determine comparative risks of serious adverse events as only 3 patients experienced serious adverse events (worsening of MDD and varicella zoster infection in the vortioxetine group and brain tumor in the venlafaxine XR group).[1]
- No significant difference in specific adverse events was reported and data were limited by wide confidence intervals.[1] Compared to venlafaxine XR, vortioxetine-treated patients experienced numerically more nausea (38.0% vs. 33.6%) and vomiting (9.0% vs. 3.5%) but numerically less constipation (3.0% vs. 9.7%) and excessive sweating (10.0% vs. 15.0%).[1] None of these adverse effects achieved statistically significant differences between treatments.

Key Question 3: Are there subgroups of patients based on demographics (age, racial groups, socio-demographic factors, and sex), other medications, or comorbidities for which 1 drug (levomilnacipran, vilazodone, or vortioxetine) is more effective or associated with fewer adverse events than another?

Major Depressive Disorder

No available evidence regarding differences in subgroups was found.[1]

Generalized Anxiety Disorder
No available evidence regarding differences in subgroups was found.[1]

New Systematic Reviews:
Comparative Assessments
Vortioxetine Compared with Placebo and Other Antidepressant Drugs
A 2017 Cochrane review sought to determine the efficacy and acceptability of vortioxetine compared with placebo and other antidepressants for the treatment of acute depression in adults.[2] The primary outcomes were response to treatment and total number of dropouts.[2] Fifteen randomized, double-blinded studies including 7746 patients were identified for inclusion in the review.[2] In the combined studies, 4134 patients were randomized to vortioxetine, 2299 were randomized to placebo, and 1313 were randomized to SNRIs (344 to venlafaxine and 969 to duloxetine).[2] All included patients were 18 years of age or older with a diagnosis of MDD and no other comorbid psychiatric disorders.[2] Compared to placebo, vortioxetine had a greater response rate (48.1% vs. 35.6%; RR 1.35; 95% CI 1.22-1.49; ARR 12.5%; NNT 8; low quality evidence) with no difference in the number of dropouts (RR 1.05; 95% CI 0.93-1.19; moderate quality evidence).[2] In the class effect comparison of vortioxetine and SNRIs (venlafaxine or duloxetine), no significant difference was found in response to treatment (RR 0.91; 95% CI 0.82-1.00).[2] Response rates were significantly lower for vortioxetine compared to duloxetine (RR 0.86; 95% CI 0.79-0.94; p=0.001; ARR 6.25%; NNT 16) but no difference was seen between vortioxetine and venlafaxine (RR 1.03; 95% CI 0.85-1.25).[2] Upon comparison of discontinuation rates, no significant difference was seen with vortioxetine compared to the two SNRIs as a group (RR 0.89; 95% CI 0.73-1.08) or duloxetine alone (RR 0.96; 95% CI 0.76-1.21), but significantly lower dropout rates were seen for vortioxetine compared to venlafaxine (RR 0.70; 95% CI 0.52-0.93; ARR 8.1%; NNT 13).[2] This evidence was rated as very low quality due to high dropout rates and substantial statistical heterogeneity in the 8 included studies.[2] The authors concluded that while vortioxetine was more effective than placebo, there was no advantage to vortioxetine compared to SNRIs.[2] Additionally, there were no available studies to compare vortioxetine to SSRIs which are most often recommended as first-line therapy for treatment.[2] Therefore, the place in therapy for acute depression remains unclear and additional direct comparisons to SSRIs are needed.[2]

Efficacy in Specific Populations
Panic Disorder
A 2016 Cochrane review sought to assess the evidence of antidepressants and benzodiazepines in adults with panic disorder.[3] The primary outcomes investigated were treatment failure and total number of dropouts. Thirty-four RCTs were included in the meta-analysis.[3] These trials included mainly comparators of TCAs (clomipramine, desipramine, imipramine) and SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) from the antidepressant class.[3] Of note, no TCAs are FDA approved for panic disorder and only three SSRIs (fluoxetine, paroxetine, and sertraline) have this indication while the remaining SSRIs (citalopram, escitalopram, fluvoxamine, vortioxetine, and vilazodone) do not.[14] There was no significant difference in the primary outcome of failure to respond with TCAs versus benzodiazepines (RR 1.03; 95% CI 0.63-1.67; participants = 61; studies = 1), SSRIs versus benzodiazepines (RR 0.93; 95% CI 0.48-1.80; participants = 154; studies = 1), or antidepressants as a whole (consisting of the TCAs and SSRIs) versus benzodiazepines (RR 0.99; 95% CI 0.67-1.47; participants = 215; studies = 2).[3] The quality of this evidence was low due to wide confidence intervals, an unclear risk of bias, and a limited population.[3] For the comparison of total number of dropouts, very low quality evidence with wide confidence intervals and a considerable degree of heterogeneity (I^2 = 75%) showed a benefit for benzodiazepines compared to antidepressants (RR 1.64; 95% CI 1.03-2.63; ARR 8.8%; NNT 12; studies = 7).[3] A benefit was also seen for the benzodiazepines versus the SSRIs (RR 1.71; 95% CI 1.03-2.84; ARR 15.6%; NNT 7; studies = 1) but not compared to the TCAs (RR 1.67; 95% CI 0.93-2.99).[3] The authors concluded that due to the small effect differences seen and small number of participants enrolled in the majority of studies, this review cannot firmly recommend the choice of treatment for patients with panic disorder.[3] The choice of treatment should be made based on an individual basis with each patient.[3]

Attention Deficit Hyperactivity Disorder (ADHD) in Adults

A 2017 Cochrane review sought to assess the safety and efficacy evidence of bupropion in adults with ADHD.[4] A total of six RCTs involving 438 participants were included which compared long-acting versions of bupropion (150 mg – 450 mg daily) to placebo.[4] The primary efficacy outcomes were change in severity of ADHD symptoms from baseline (using various standardized instruments) and proportion of participants achieving a significant clinical improvement, defined as a reduction of at least 30% in severity of symptoms or a score of one or two on the Clinical Global Impression (CGI)-Improvement scale.[4] Tolerability was also analyzed as the proportion of participants withdrawn from the studies due to any adverse effect.[4] 62% of the patients in the included studies were male and the mean age ranged from 32.2 to 41.4 years of age.[4] The mean study intervention length was 7.2 weeks (range: 6-10 weeks).[4] In the analysis of risk of bias, 75% of all assessed items were unclear.[4] A significant benefit was seen in the primary outcome in change of severity of ADHD between bupropion and placebo (SMD -0.50; 95% CI -0.86 to -0.15; I^2 = 0%) as well as in the proportion of participants achieving a significant clinical improvement (48% vs. 32%; RR 1.50; 95% CI 1.13 – 1.99; ARR= 16%; NNT 7; I^2 = 27%; studies = 4).[4] In terms of safety and the number of participants withdrawn due to adverse events, the pooled, fixed-effect RR was 1.20 (95% CI 0.35 – 4.10; I^2 = 49%).[4] These results suggest a significant benefit for both primary efficacy outcomes as well as a non-significant difference in withdrawals due to adverse effects.[4] However, due to the methodological limitations, poor reporting, and lack of precision, this evidence is of low quality and indicates uncertainty in the results.[4]

Children and Adolescents

A 2017 systematic review and meta-analysis sought to determine the efficacy and safety of SSRIs, SNRIs, and placebo in the treatment of children and adolescents younger than 18 years of age with depressive disorders (DDs), anxiety disorders (ADs), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD).[5] A total of 36 trials involving 6778 participants were included which compared SSRIs or SNRIs with placebo.[5] The outcomes in trials varied but were required to use well-validated, disorder specific or general severity scales including Children's Depression Rating Scale-Revised, Multidimensional Anxiety Scale for Children, Children's Yale-Brown Obsessive Compulsive Scale, or Clinical Global Impression-Severity Scale.[5]

Hedges *g*, a method of reporting effect size, was utilized for the efficacy endpoints.[5,15] Hedges *g* is similar to Cohen's *d*, another method of interpreting effect sizes, with a correction for small sample size.[15,16] If the value is greater than zero, the number reports the degree of greater efficacy for one treatment over another.[16] Generally, a Cohen's *d* of 0.2 indicates a small difference, 0.5 indicates a medium difference, and 0.8 indicates a large difference.[16] This effect size methodology is limited and should be interpreted with caution as it may not have direct clinical applicability due to only reporting the magnitude of clinical effect sizes and not assessing direction and relevance of the effect.[16]

The review found a small drug-placebo difference across all of the included disorders (*g*=0.32; 95% CI 0.25-0.40; p<0.001) but the drug-placebo responses differed based on disorder.[5] Both AD and OCD were found to have greater drug-placebo responses (AD vs. DD: p<0.001; OCD vs. DD: p=0.02) compared to the DD group (*g*=0.20; 95% CI 0.13-0.27; p<0.001).[5]

In contrast to the efficacy endpoints, risk ratios were reported for the safety analyses.[5] A significantly increased percentage of patients were found to have discontinued the study due to adverse events in the SSRI groups versus placebo (RR 1.84; 95% CI 1.38-2.44; p<0.001; 27 trials) but not in the SNRI groups versus placebo (RR 1.56; 95% CI 0.83-2.94; p=0.17; 6 trials).[5] However, significantly higher serious adverse events were reported both in the SSRI (RR 1.71; 95% CI 1.22-2.40; p=0.002; 17 trials) and SNRI (RR 2.10; 95% CI 1.19-3.69; p=0.01; 7 trials) groups compared to placebo.[5] This article did not report specific adverse events such as suicidal attempts or ideation.[5]

Older Patients (defined as >60 years of age)

A 2016 Cochrane review sought to determine the efficacy of antidepressants and psychological therapies in preventing relapse and recurrence of depression in older people.[6] Six studies involving 708 participants were included which compared antidepressants with placebo [6] The antidepressants compared against placebo were tricyclic antidepressants (TCA) including nortriptyline and dothiepin (not currently available in the U.S.[14]) and selective serotonin reuptake inhibitors (SSRI) including escitalopram, citalopram, and sertraline.[6] The primary outcome studied was the recurrence rate of depression at 12 months as defined by depression symptom rating scales.[6] The authors found a decreased risk of recurrence at 12 months with antidepressants (49%) compared with placebo (73%) based on low quality evidence from 3 RCTs (RR 0.67; 95% CI 0.55-0.82; ARR 24.3%; NNT 5).[6] Marked clinical heterogeneity and significant numbers of drop-outs were noted.[6] At 24 months, there was not a statistically significant benefit in antidepressants versus placebo based on 4 RCTs (RR 0.78; 95% CI 0.61-1.01) The authors concluded that due to the low grade of evidence and small number of participants, no firm recommendation on the duration of antidepressant maintenance therapy in older adults can be made.[6]

New Guidelines:

Department of Veterans Affairs (VA) and Department of Defense (DoD)

In 2009, the VA and DoD first published a clinical practice guideline for the management of MDD, and the most recent update of this guideline was completed in 2016.[7] New and updated recommendations regarding management of MDD include:

- to utilize one of the following treatments for first-line treatment of mild to moderate MDD: evidence-based psychotherapy or evidence-based pharmacotherapy (SSRIs, SNRIs, mirtazapine, or bupropion).[7] However, none of these therapies are recommended over another (strong recommendation).[7]
- to switch to another monotherapy and to augment with a second therapy if a patient has partial or no response to maximized initial pharmacotherapy monotherapy.[7] These therapies can be either medication or psychotherapy (strong recommendation).[7]
- to use a combination of pharmacotherapy and psychotherapy if MDD is characterized as severe, chronic, or recurrent (weak recommendation).[7]
- to create a monitoring plan which should include assessment symptoms, adherence, and adverse effects at least monthly until the remission is achieved (strong recommendation).[7]
- to continue the medication for at least 6 months once remission is achieved with a medication (strong recommendation).[7]
- to continue pharmacologic therapy for at least 12 months, or possibly indefinitely, in patients who are at high risk for recurrent depressive episodes (strong recommendation).[7]

Canadian Network for Mood and Anxiety Treatments (CANMAT)

An update to the 2009 CANMAT guidelines for the management of adults with MDD was published in 2016.[8] The guideline provides recommendations on a variety of aspects of treatment, but this update has focused on second-generation antidepressants as there is limited new information on the older medications.[8] While this guideline was rated as high quality based on the Agree II Global Rating Scale, it is limited by industry financial conflicts of interest for about half of the guideline work group.[17-19] Selected recommendations included in this review are limited to level I evidence which is defined as meta-analysis with narrow confidence intervals and/or 2 or more RCTs with adequate sample size, preferably placebo controlled.[8]

Recommended treatments based on level I evidence:

- First line: agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mianserin, milnacipran, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine.[8]
- Second line: amitriptyline, clomipramine, levomilnacipran, moclobemide, quetiapine, selegiline transdermal, trazodone, and vilazodone.[8]

- Third line: phenelzine, tranylcypromine, and reboxetine.[8]

The importance of selecting an antidepressant based on clinical features and medication characteristics on an individual patient basis is also emphasized.[8]

New FDA Drug Approvals: No new drug approvals were identified.

New Formulations/Indications: No new formulations or indications were identified.

New FDA Safety Alerts:
January 2017: A new addition was made to the Warnings and Precautions section of SSRI and SNRI medications to include amphetamines as a serotonergic drug that may lead to the development of serotonin syndrome when used concomitantly with these classes of medications.[20-29]

May 2017: New warnings and precautions describe neuropsychiatric adverse events and suicide risk in smoking cessation treatment with Zyban which has the same active ingredient of bupropion.[30]

May 2017: A new warning was added to the approved drug label of Anafranil (clomipramine hydrochloride) stating that rare cases of drug rash with eosinophilia and systemic symptoms (DRESS) have been reported. It is recommended to discontinue therapy immediately and institute appropriate treatment in the event of severe acute reactions such as DRESS.[31]

References:

1. Gartlehner G WG, Schultes M, et al. Drug Class Review Second-generation Antidepressants Levomilnacipran, Vilazodone, and Vortioxetine Compared with Other Second-generation Antidepressants Targeted Update Final Report.
2. Koesters M, Ostuzzi G, Guaiana G, Breilmann J, Barbui C. Vortioxetine for depression in adults. *Cochrane Database Syst Rev.* 2017;7:CD011520.
3. Bighelli I, Trespidi C, Castellazzi M, et al. Antidepressants and benzodiazepines for panic disorder in adults. *Cochrane Database Syst Rev.* 2016;9:CD011567.
4. Verbeeck W, Bekkering GE, Van den Noortgate W, Kramers C. Bupropion for attention deficit hyperactivity disorder (ADHD) in adults. *Cochrane Database Syst Rev.* 2017;10:CD009504.
5. Locher C, Koechlin H, Zion SR, et al. Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: A Systematic Review and Meta-analysis. *JAMA Psychiatry.* 2017.
6. Wilkinson P, Izmeth Z. Continuation and maintenance treatments for depression in older people. *Cochrane Database Syst Rev.* 2016;9:CD006727.
7. Department of Veterans Affairs, Department of Defense. VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Version 3.0. April 2016.
8. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Can J Psychiatry.* 2016;61(9):540-560.
9. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ.* 2013;346:f2914.
10. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health.* 2011;14(4):417-428.
11. Mahableshwarkar AR, Jacobsen PL, Chen Y, Serenko M, Trivedi MH. A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. *Psychopharmacology (Berl).* 2015;232(12):2061-2070.
12. Alvarez E, Perez V, Dragheim M, Loft H, Artigas F. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol.* 2012;15(5):589-600.
13. Mahableshwarkar AR, Jacobsen PL, Chen Y, Simon JS. A randomised, double-blind, placebo-controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine in the acute treatment of adults with generalised anxiety disorder. *Int J Clin Pract.* 2014;68(1):49-59.
14. Lexicomp Online. Lexi-Comp, Inc. Accessed August 3, 2017.
15. Turner HM and Bernard RM. Calculating and Synthesizing Effect Sizes. Contemporary Issues in Communication Science and Disorders. 2006; 33:42-55.
16. McGough JJ and Faraone SV. Estimating the Size of Treatment Effects: Moving Beyond P Values. Psychiatry (Edgemont) 2009;6(10):21-29.
17. Depression Work Group for the 2016 Clinical Guidelines for the Management of Adults with MDD. Canadian Network for Mood and Anxiety Treatments. http://www.canmat.org/AAfiles/publications/CANMAT%20MDD%20Work%20Group%202016.pdf. Accessed 12 October 2017.
18. Agree II-GRS Instrument. Agree Trust Website. http://www.agreetrust.org/resource-centre/agree-ii-grs-instrument/. Accessed 12 October 2017.
19. Lam RW, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Introduction and Methods. *Can J Psychiatry.* 2016;61(9):506-509.
20. Celexa (citalopram hydrobromide) Drug Safety Lableling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=712. Accessed 6 September 2017.

21. Pristiq (desvenlafaxine succinate) Drug Safety Labeling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=366. Accessed 6 September 2017.
22. Cymbalta (duloxetine hydrochloride) Drug Safety Labeling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=384. Accessed 6 September 2017.
23. Lexapro (escitalopram oxalate) Drug Safety Labeling Changes. Food and Drug Administration. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=715. Accessed 6 September 2017.
24. Prozac (fluoxetine hydrochloride) Drug Safety Labeling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=705. Accessed 6 September 2017.
25. Luvox (fluvoxamine maleate) Drug Safety Labeling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=687. Accessed 6 September 2017.
26. Fetzima (levomilnacipran hydrochloride) Drug Safety Labeling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=742. Accessed 6 September 2017.
27. Paxil (paroxetine hydrochloride) Drug Safety Labeling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=709. Accessed 6 September 2017.
28. Effexor XR (venlafaxine hydrochloride) Drug Safety Labeling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=65. Accessed 6 September 2017.
29. Viibryd (vilazodone hydrochloride) Drug Safety Labeling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=394. Accessed 6 September 2017.
30. Wellbutrin (bupropion hydrochloride) Drug Safety Labeling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=172. Accessed 6 September 2017.
31. Anafranil (clomipramine hydrochloride) Drug Safety Labeling Changes. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=1082. Accessed 6 September 2017.

Appendix 1: Current Status on Preferred Drug List

Brand	Generic	Formulation	PDL	Carveout
FLUOXETINE HCL	FLUOXETINE HCL	CAPSULE	Y	Y
PROZAC	FLUOXETINE HCL	CAPSULE	Y	Y
SERTRALINE HCL	SERTRALINE HCL	ORAL CONC	Y	Y
ZOLOFT	SERTRALINE HCL	ORAL CONC	Y	Y
CITALOPRAM HBR	CITALOPRAM HYDROBROMIDE	SOLUTION	Y	Y
FLUOXETINE HCL	FLUOXETINE HCL	SOLUTION	Y	Y
CELEXA	CITALOPRAM HYDROBROMIDE	TABLET	Y	Y
CITALOPRAM HBR	CITALOPRAM HYDROBROMIDE	TABLET	Y	Y
ESCITALOPRAM OXALATE	ESCITALOPRAM OXALATE	TABLET	Y	Y
FLUOXETINE HCL	FLUOXETINE HCL	TABLET	Y	Y
FLUVOXAMINE MALEATE	FLUVOXAMINE MALEATE	TABLET	Y	Y
LEXAPRO	ESCITALOPRAM OXALATE	TABLET	Y	Y
PAROXETINE HCL	PAROXETINE HCL	TABLET	Y	Y
PAXIL	PAROXETINE HCL	TABLET	Y	Y
SARAFEM	FLUOXETINE HCL	TABLET	Y	Y
SERTRALINE HCL	SERTRALINE HCL	TABLET	Y	Y
ZOLOFT	SERTRALINE HCL	TABLET	Y	Y
ANAFRANIL	CLOMIPRAMINE HCL	CAPSULE	Y	Y
DOXEPIN HCL	DOXEPIN HCL	CAPSULE	Y	Y
NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	CAPSULE	Y	Y
PAMELOR	NORTRIPTYLINE HCL	CAPSULE	Y	Y
SURMONTIL	TRIMIPRAMINE MALEATE	CAPSULE	Y	Y
DOXEPIN HCL	DOXEPIN HCL	ORAL CONC	Y	Y
NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	SOLUTION	Y	Y
AMITRIPTYLINE HCL	AMITRIPTYLINE HCL	TABLET	Y	Y
DESIPRAMINE HCL	DESIPRAMINE HCL	TABLET	Y	Y
IMIPRAMINE HCL	IMIPRAMINE HCL	TABLET	Y	Y
MAPROTILINE HCL	MAPROTILINE HCL	TABLET	Y	Y
NORPRAMIN	DESIPRAMINE HCL	TABLET	Y	Y
PROTRIPTYLINE HCL	PROTRIPTYLINE HCL	TABLET	Y	Y
TOFRANIL	IMIPRAMINE HCL	TABLET	Y	Y

MIRTAZAPINE	MIRTAZAPINE	TAB RAPDIS	Y	Y
REMERON	MIRTAZAPINE	TAB RAPDIS	Y	Y
MIRTAZAPINE	MIRTAZAPINE	TABLET	Y	Y
REMERON	MIRTAZAPINE	TABLET	Y	Y
EFFEXOR XR	VENLAFAXINE HCL	CAP ER 24H	Y	Y
VENLAFAXINE HCL ER	VENLAFAXINE HCL	CAP ER 24H	Y	Y
VENLAFAXINE HCL	VENLAFAXINE HCL	TABLET	Y	Y
BUPROPION HCL SR	BUPROPION HCL	TAB ER 12H	Y	Y
WELLBUTRIN SR	BUPROPION HCL	TAB ER 12H	Y	Y
BUPROPION HCL	BUPROPION HCL	TABLET	Y	Y
EMSAM	SELEGILINE	PATCH TD24	V	Y
FLUVOXAMINE MALEATE ER	FLUVOXAMINE MALEATE	CAP ER 24H	V	Y
BRISDELLE	PAROXETINE MESYLATE	CAPSULE	V	Y
FLUOXETINE DR	FLUOXETINE HCL	CAPSULE DR	V	Y
PAXIL	PAROXETINE HCL	ORAL SUSP	V	Y
ESCITALOPRAM OXALATE	ESCITALOPRAM OXALATE	SOLUTION	V	Y
PAROXETINE CR	PAROXETINE HCL	TAB ER 24H	V	Y
PAROXETINE ER	PAROXETINE HCL	TAB ER 24H	V	Y
PAXIL CR	PAROXETINE HCL	TAB ER 24H	V	Y
PEXEVA	PAROXETINE MESYLATE	TABLET	V	Y
CLOMIPRAMINE HCL	CLOMIPRAMINE HCL	CAPSULE	V	Y
IMIPRAMINE PAMOATE	IMIPRAMINE PAMOATE	CAPSULE	V	Y
FETZIMA	LEVOMILNACIPRAN HCL	CAP SA 24H	V	Y
FETZIMA	LEVOMILNACIPRAN HCL	CAP24HDSPK	V	Y
CYMBALTA	DULOXETINE HCL	CAPSULE DR	V	Y
DULOXETINE HCL	DULOXETINE HCL	CAPSULE DR	V	Y
IRENKA	DULOXETINE HCL	CAPSULE DR	V	Y
DESVENLAFAXINE ER	DESVENLAFAXINE	TAB ER 24	V	Y
DESVENLAFAXINE FUMARATE ER	DESVENLAFAXINE FUMARATE	TAB ER 24	V	Y
KHEDEZLA	DESVENLAFAXINE	TAB ER 24	V	Y
VENLAFAXINE HCL ER	VENLAFAXINE HCL	TAB ER 24	V	Y
DESVENLAFAXINE ER	DESVENLAFAXINE	TAB ER 24H	V	Y
DESVENLAFAXINE SUCCINATE ER	DESVENLAFAXINE SUCCINATE	TAB ER 24H	V	Y

PRISTIQ	DESVENLAFAXINE SUCCINATE	TAB ER 24H	V	Y
APLENZIN	BUPROPION HBR	TAB ER 24H	V	Y
BUPROPION XL	BUPROPION HCL	TAB ER 24H	V	Y
WELLBUTRIN XL	BUPROPION HCL	TAB ER 24H	V	Y
NEFAZODONE HCL	NEFAZODONE HCL	TABLET	V	Y
MARPLAN	ISOCARBOXAZID	TABLET	V	Y
NARDIL	PHENELZINE SULFATE	TABLET	V	Y
PARNATE	TRANYLCYPROMINE SULFATE	TABLET	V	Y
PHENELZINE SULFATE	PHENELZINE SULFATE	TABLET	V	Y
TRANYLCYPROMINE SULFATE	TRANYLCYPROMINE SULFATE	TABLET	V	Y
VIIBRYD	VILAZODONE HCL	TAB DS PK	V	Y
VIIBRYD	VILAZODONE HCL	TABLET	V	Y
TRINTELLIX	VORTIOXETINE HYDROBROMIDE	TABLET	V	Y
SAVELLA	MILNACIPRAN HCL	TAB DS PK		
SAVELLA	MILNACIPRAN HCL	TABLET		
AMOXAPINE	AMOXAPINE	TABLET		Y
TRAZODONE HCL	TRAZODONE HCL	TABLET		Y

Appendix 2: New Clinical Trials

A total of 85 citations were manually reviewed from the literature search. After further review, all 85 trials were excluded because of wrong study design (observational), comparator (placebo), outcome studied (non-clinical), or inclusion in a past review.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 2 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 19, 2017
1 exp Depressive Disorder, Major/dt [Drug Therapy] 6994
2 exp Depression/dt [Drug Therapy] 8361
3 exp Depression, Postpartum/dt [Drug Therapy] 311
4 exp Long-Term Synaptic Depression/ 1570
5 exp Anxiety/dt [Drug Therapy] 3300
6 exp Premenstrual Dysphoric Disorder/dt [Drug Therapy] 11
7 exp Amitriptyline/ 2009
8 exp Bupropion/ 2415
9 exp Citalopram 3863
10 exp Clomipramine/ 1055
11 exp Desipramine/ 1391
12 exp Desvenlafaxine Succinate/ 241
13 exp Doxepin/ 283
14 exp Duloxetine Hydrochloride/ 1320
15 escitalopram.mp. 1891
16 exp Fluoxetine/ 6211
17 exp Fluvoxamine/ 1344
18 exp Imipramine/ 2036
19 exp Isocarboxazid/ 9
20 levomilnacipran.mp. 55
21 exp Maprotiline/ 154
22 mitrazapine.mp. 1862
23 nefazodone.mp. 666
24 exp Nortriptyline/ 742
25 exp Paroxetine/ 3177
26 exp Phenelzine/ 189
27 exp Protriptyline/ 20
28 exp Selegiline/ 1177
29 exp Sertraline/ 2411
30 exp Tranylcypromine/ 283
31 exp Trazodone/ 499

32 exp Trimipramine/ 75
33 exp Venlafaxine Hydrochloride/ 2213
34 exp Vilazodone Hydrochloride/ 86
35 vortioxetine.mp. 214
36 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 30044
37 limit 36 to (English language and humans and yr="2016-Current") 688
38 1 or 2 or 3 or 4 or 5 or 6 19506
39 limit 38 to (English language and humans and yr="2016-Current") 714
40 37 and 39 175
41 limit 40 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews) 85