Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: Antidepressants

Date of Review: February 2023

Date of Last Review: February 2021
Dates of Literature Search: 01/01/2021 – 12/02/2022

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

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for the use of antidepressants and make recommendations for policy changes if supported by evidence.

Plain Language Summary:

- The reason we are doing this review is to look at the new evidence on medicines used to treat depression (antidepressants), anxiety, post-traumatic stress disorder (PTSD), and bipolar disorder. The Oregon Health Plan (OHP) fee-for-service (FFS) Medicaid program pays for all antidepressants prescribed by providers.
- Most studies compared antidepressants to the use of a sugar pill called placebo. The use of antidepressants rarely caused severe adverse events and mild adverse events, such as dizziness, headaches, and trouble sleeping, often get better after taking them for a period of time.
- Recent new evidence shows antidepressants have benefit compared to placebo for:
  - Improving sadness, interest in activities, and changes in sleep in people with depression
  - Improving sleep and feeling nervous in people with anxiety
  - Improving eating patterns and depression in people with eating disorder
  - Improving pain in people with osteoarthritis
  - Improving depression in people with called coronary artery disease (CAD)

Specific types of antidepressant medicines have shown to improve symptoms compared to placebo for these groups:

  - SSRIs for people with PTSD
  - Brexanolone for people who are close to having a baby , brexanolone decreases symptoms of depression more than treatment with placebo. Brexanolone is a type of antidepressant that is only used in persons after having a baby and has to be given by a provider.
  - Esketamine for people with moderately severe to severe depression.
- Guidelines published updated advice on the best ways to use antidepressants. The following guidelines were updated, and their recommendations support the current FFS policies: National Institute for Health and Care Excellence (NICE), Veterans Administration (VA)/Department of Defense (DOD), American Academy of Neurology (AAN) and Healthcare Improvement Scotland.

- The Drug Use Research and Management (DURM) group recommends no changes to our current policy for the use of antidepressants.

Research Questions:

1. What is the new comparative evidence for efficacy or effectiveness of antidepressants?
2. What is the new comparative evidence for safety or harms of antidepressants?
3. Are there specific subpopulations (e.g., pregnant women, children and adolescents, ethnic groups, or people with certain comorbidities) for which certain antidepressants are better tolerated or more effective than other available antidepressants when used for improvement in symptoms and remission of depression?

Conclusions:

- Evidence for this review comes from nine systematic reviews and meta-analyses, four guidelines, one randomized controlled trial (RCT), two new indications, one new formulation and three safety updates.
- A high quality systematic review and meta-analysis from the Agency for Healthcare, Research and Quality (AHRQ) found antidepressants reduced depressive symptoms more than placebo in adults with depression (standard mean difference [SMD] -0.17 to -0.50 points) (moderate quality evidence).[1] Serious adverse events were rare.
- An AHRQ report in adults found moderate quality evidence that the use of antidepressants is associated with reductions in remission of anxiety symptoms more than placebo (relative risk [RR] 0.83; 95% confidence interval [CI], 0.78 to 0.88).[1]
- There is moderate quality evidence that brexanolone, decreases depressive symptoms, based on the Hamilton Rating Scale for Depression (HAM-D), at day 30, more than placebo in women who are perinatal (least squares mean difference [LSMD] -2.6 points; p=0.02 [CI not reported]), which is lower than what is considered a clinically meaningful difference.[2] Brexanolone may cause excessive sedation and sudden loss of consciousness.
- In children and adolescents, there is low quality evidence that the use of antidepressants for the treatment of anxiety and depression results in reduced symptoms of depression and anxiety compared to placebo.[3] Treatment of anxiety with antidepressants reduced symptom scores, based on the Pediatric Anxiety Rating Scale, by 4 points (95% CI, -5.5 to -2.5 points), which is less than the eight to ten point reduction that is considered clinically me4aningful.[4] Symptom of depression were improved almost 4 points with use of escitalopram and fluoxetine in children and adolescents diagnosed with depression based on the Children's Depression Rating Scale-Revised (CDRS-R).
- A high quality Cochrane systematic review and meta-analysis found low quality evidence that fluoxetine was effective in reducing eating disorder symptom severity and depression symptoms in adolescents and adults.[5] Evidence for use of other antidepressants for eating disorders was limited and of low quality.
- In people with PTSD, treatment with SSRIs were more effective than placebo for elucidating a treatment response, 58% versus 35% (RR 0.66; 95% CI, 0.59 to 0.74) based on moderate strength of evidence.
- A systematic review and meta-analysis on the use of antidepressants for osteoarthritis pain found no clinically significant improvement in pain scores, compared to placebo, but there were more participants who were considered responders (e.g., those with a 50% or greater reduction in 24-hour mean pain) with an absolute improvement of 16% and a number needed to benefit (NNTB) of 6 (high quality evidence for both outcomes).[6]
- In people with CAD and major depressive disorder (MDD), a Cochrane review found moderate strength evidence of improved depression remission rates with antidepressant therapy, as measured by the HAM-D, compared to placebo with an incidence of 496 per 1000 people treated with antidepressants compared to 323 per 1000 people treated with placebo (odds ratio (OR) 2.06; 95% CI, 1.47 to 2.89).[7] Evidence for other outcomes was graded very low to low quality.

- A Cochrane review found esketamine use in people with unipolar MDD to be superior to placebo for remission rates based on the Montgomery-Asberg Depression Rating Scale (MADRS), 17.5% versus 7.2% (OR 2.74; 95% CI, 1.71 to 4.40) (moderate strength evidence).[8]
- A systematic review done by the Drug Effectiveness Review Project (DERP) found low quality evidence demonstrating brexanolone was more effective than placebo in people with postpartum depression (PPD) at increasing remission rates and depression symptoms at 60 hours post infusion.[9]
- Updated treatment guidelines by the NICE, VA/DOD and AAN supports current policy.[10,11,12]
- Guidelines from the Health Improvement Scotland recommend offering short-term antidepressants, in combination with psychological treatments for people with BN (Strong recommendation based on high-quality evidence).[13] Fluoxetine should be considered first-line.
- A fair quality, placebo-controlled randomized controlled trial (RCT) in adults with suicide ideation and MDD found esketamine was superior to placebo for the change in MADRS total score, from baseline to 24 hours post-first dose (least square mean difference [LSMD] -3.9 points; 95% CI, -6.6 to -1.1 points; P=0.006).[14]
- Additional studies on the effectiveness and safety of antidepressants evaluating the Medicaid population are needed.

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on the review of current evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:
- Antidepressants are designated preferred or part of the voluntary PDL.
- There is insufficient evidence of clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants. Previous recommendations are to base antidepressant treatment selection on patient characteristics, adverse effects and cost.
- Evidence reviews show esketamine does not decrease the risk of suicide but does slightly improve depressive symptoms in people with treatment-resistant depression (TRD) in adults. (1)
- • Depressive symptoms in adults with major depressive disorder (MDD) with
- acute suicidal ideation or behavior. (1).
- After presentation of the evidence and costs at the February 2021 meeting, the Pharmacy and Therapeutics Committee voted to make duloxetine DR capsules, bupropion HCL XL 24H tablets (Wellbutrin XL & associated generics), and desvenlafaxine succinate ER 24H tablets preferred; and make amoxapine tablets voluntary non-preferred.

Background:
Historically antidepressant medications have been categorized based on mechanism and chemical structure into first-generation (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) and second-generation antidepressants (SSRIs, serotonin and norepinephrine reuptake inhibitors [SNRIs], and newer antidepressants). They are used for a wide variety of psychiatric conditions including depression, PTSD, bipolar disorder, obsessive compulsive disorder, anxiety disorders and bulimia.[12] Specific antidepressants have Food and Drug Administration (FDA) labeled indications for other conditions including fibromyalgia, diabetic peripheral neuropathy, premenstrual dysphoric disorder, and smoking cessation.[12] All antidepressants have a box warning for suicide risk in young adults and can be associated a discontinuation syndrome when agents are abruptly stopped. Other notable adverse events include risk for serotonin syndrome, which increases when used in combination with other serotonergic medications, and anticholinergic adverse events.

Choice in antidepressant is typically dependent on patient preference and adverse effect profile, as current evidence demonstrates little difference in efficacy between agents. Often second-generation antidepressants are recommended as first-line agents due to improved tolerability and decreased risk of adverse events compared to first-generation antidepressants and less risk for overdose. For example in patients with PTSD, first-line recommendations from the VA/DoD for pharmacotherapy include sertraline, paroxetine, fluoxetine, or venlafaxine in patients who are unable to access or choose not to engage in trauma-focused psychotherapy.[13] For the treatment of moderate to severe depression in adults, guidelines from both NICE and the American Psychiatric Association (APA) recommend combination antidepressant and psychotherapy.[14] SSRIs are recommended by NICE as a first-line option, though individual drug choice can vary depending on adverse effects.[14] APA guidelines consider SSRIs, SNRIs, mirtazapine, or bupropion as reasonable first-line treatment options.[14] It is not uncommon for first-line treatments to fail to manage depressive symptoms. It is estimated that for major depressive disorder, about two-thirds of patients have an inadequate response to initial therapy and about one-third of patients have treatment-resistant depression.[3] There is no consistent definition in the literature for treatment resistant depression, and there is little evidence to guide next steps in therapy after an initial treatment failure.[3] Common treatment options used in clinical practice include trial of a different first-line antidepressant, use of an antidepressant from a different class, and augmentation of current therapy with a second agent.

Goals of treatment for antidepressants typically focus on improvement in symptoms, function, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients treated with antidepressants. Scales vary depending on the condition. There is some evidence that measurement-based care (MBC), via depression rating scales, improves outcomes. However, the recommendation from the VA/DoD for use of these scales was weak due to lack of high quality supporting evidence.[11] Some of the most commonly used rating-scales and thresholds include the MADRS and Hamilton Depression Rating Scale (HAM-D). The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.[11] The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52). [11] Values associated with remission and minimum clinically important differences for each of these scales vary. Remission is defined as the person being free from depressive symptoms for several months after two or more depressive episodes and typically a 50% improvement in symptom score from baseline is used to evaluate response to therapy.[11] . A 2 point improvement on MADRS may be associated with a clinical improvement and HAM-D scores of 3 to 7 points may be clinically significant.[11]

In Oregon, mental health drug classes, including antidepressants, are carved out of coordinated care organizations and paid for by fee-for-service. Non-preferred products do not automatically require prior authorization, but a few specific agents do have safety criteria including esketamine, brexanolone, and TCAs in children. In the second quarter of 2022, there were over 350,000 claims for an antidepressant medications representing a substantial cost to the OHA.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. 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), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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

New Systematic Reviews:

AHRQ – Screening for Depression, Anxiety and Suicide Risk in Adults

A 2022 AHRQ review evaluated screening of primary care patients and treatment of adults with depression, anxiety, or suicide risk.[1] A literature search through September 24, 2021 identified 173 studies for inclusion. Therapies studied were the following: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine, vilazodone, nefazodone, bupropion, mirtazapine, amitriptyline, and trazodone. The findings for the use of antidepressants will be the focus of this class update.

Evidence for the use of pharmacological treatment options in adults came primarily from ten existing systematic reviews, including one high-quality systematic review consisting of 522 studies.[1] All data was from placebo-controlled comparisons. Seven of the included sources were considered good-quality. Additional studies were deemed to be of fair quality. Response to treatment was the primary outcome measured in most of the studies. Symptom severity was measured most commonly by the HAM-D and MADRAS scoring questionnaires with a 50% reduction in symptoms considered as response to treatment. Since there was variability in reporting methods, improvements in symptoms were reported in standardized units for comparison. Clinical significance of symptom changes were deemed to be a small, medium or large effect as determined by Cohen's rule of thumb correlating to sores of 0.20, 0.50, and 0.80, respectively.

All antidepressants studied, in people with depression, resulted in a treatment response, reductions in continuous symptoms and increased remission rates compared to placebo. Symptom severity was reduced from a SMD -0.17 to -0.50, suggesting small improvements in symptoms.[1] Remission rates were increased from 23% to 252% and treatment response ranged from 37% to 213% relative to placebo for all the trials included in the review. Fluoxetine had the most evidence (117 trials) and improved depression symptom severity by SMD -0.23 (95% CI, -0.28 to -0.19). Odds of remission and treatment response was also increased. Combination treatment with medication and psychotherapy decreased depression severity symptoms by a SMD of -0.46 (95% CI, -0.70 to -0.21).[1] A review of SSRIs for depressive symptoms found reductions in severity and remissions compared to placebo. An analysis of 4 trials in older adults demonstrated duloxetine had the most efficacy across all depressive outcomes and fluoxetine had the least improvement. Paroxetine was found to be effective in trials studying people of lower socioeconomic status when compared to placebo. There were few studies evaluating the long-term effects of antidepressant use. One study evaluated paroxetine use at 10 months (6 months on treatment and 4 months off of treatment) demonstrated small reductions in symptom severity (SMD -0.39; 95% CI, -0.74 to -0.04).[1] Duloxetine was also studied for longer than 12 weeks and resulted in improvements in symptom reduction but not remission. Antidepressant therapy was not shown to improve cognitive function or quality of life compared to placebo.

The risk of suicide attempts after the discontinuation of second generation antidepressants was higher with treatment compared to placebo, 0.7% versus 0.3%.[1] A study evaluating the use of duloxetine compared to placebo found that it was associated with a statistically significant greater reduction in suicidality compared to placebo in those ages 25 and older compared to those 18-24 years old.[1] In general, the number of suicide attempts was very small. Fluoxetine and venlafaxine were associated with decreased suicidal thoughts and behaviors in adults and geriatric patients.

The treatment of anxiety with antidepressants was studied in two good quality RCTs. Venlafaxine extended-release improved anxiety symptoms at 24 weeks compared to placebo. In older adults, people taking escitalopram were more likely to demonstrate a treatment response (i.e., clinician rating of improved or very much improved) compared to placebo (OR 1.87; 95% CI, 1.03 to 3.39; p=0.05).[1] The use of SSRIs and TCAs also decreased panic disorder symptoms (e.g., anxiety, panic symptoms, panic attacks, and agoraphobia) more than placebo. Antidepressants were associated with a higher likelihood of remission of anxiety symptoms (RR 0.83; 95% CI, 0.78 to 0.88).[1] For those with social anxiety disorder, use of SSRIs was more likely to result in a treatment response compared to

placebo (RR 1.65; 95% CI, 1.48 to 1.85). In people with GAD and panic disorder, anxiety symptom score improvement ranged from reductions of a SMD of -0.23 for the use of serotonin modulators to a SMD reductions of -1.84 for bupropion.[1]

Evidence on adverse events associated with antidepressant use is mostly based on observational data.[1] Low quality evidence, that was at risk of confounding due to observational data, demonstrated and increase risk of fractures with antidepressants (RR 1.67; 95% CI 1.56 to 1.79; 23 studies). All other risks (e.g., CVD, mortality, dementia, bleeding) lacked enough evidence to form strong conclusions. Serious adverse events were rare. Dropouts related to adverse events were more common in patients taking antidepressants compared to placebo. There is an increased risk of preterm birth with SSRI use in women with depressive symptoms based on observational data (OR 1.6; 95% CI, 1.0 to 2.5).[1]

There was insufficient evidence on long-term treatment with antidepressants and relapse prevention with antidepressant therapy. The most evidence for a sustained response was with combination pharmacotherapy and psychological treatment followed by psychological therapy alone.

AHRQ – Screening for Depression, Anxiety, and Suicide Risk in Children and Adolescents

A 2022 systematic review and meta-analysis evaluated the evidence for screening and treating children and adolescents in the primary care setting with a history of depression, anxiety, and suicide risk.[2] A total of 60 trials were included which evaluated treatment efficacy with behavioral therapy, medications or combination of the two. No studies evaluated the effect of pharmacotherapy on suicide risk. Duloxetine is the only therapy FDA approved for GAD in children and fluoxetine and escitalopram are the only therapies approved for MDD in children 8 and older; however, many medications are used off-label for both conditions.

Six RCTs evaluated pharmacotherapy for anxiety, and one trial evaluated combination therapy with sertraline and cognitive behavioral therapy (CBT).[2] Studies had placebo comparisons, and lasted from 8 to 12 weeks. Therapies included duloxetine, escitalopram, fluoxetine, fluvoxamine and sertraline. Participants had anxiety disorders catorgorized as general anxiety disorder (GAD), social anxiety disorder, panic disorder, agoraphobia, separation anxiety disorder and selective mutism. Pharmacotherapy improved symptom scores based on the Pediatric Anxiety Rating Scale (MD -4 points; 95% CI, -5.5 to -2.5), symptom severity based on the Clinical Global Impressions-Severity (MD -0.84; 95% CI, -1.13 to -0.55), and response rates (RR 2.11; 95% CI, 1.58 to 2.98).[2] Studies evaluating functioning at the end of treatment favored the use of pharmacotherapy.

There were 3 trials that evaluated the use of medications for depression in this population. Studies evaluated escitalopram and fluoxetine and lasted from 8 weeks to 12 months. Pharmacotherapy was shown to improve symptoms based on the CDRS-R. Treatment with antidepressants decreased symptoms by -3.76 points (95% CI, -5.95 to -1.57).[2] Differences in remission rates were not statistically different from placebo when compared to antidepressants. One study evaluating fluoxetine with CBT found higher response rates and higher remission rates compared to placebo. Compared to placebo, symptoms were improved by 8.5 points (95% CI, 13.4 to -3.6) at 6 months, response rates (defined as $\geq$50% reduction in CDRS-R score) were higher at 12 months (OR 3.3 [95% CI, 1.4 to 8.2]), and remission rates (based on Patient Health Questionnaire-9 of less than 5) were improved at 6 months (OR 5.2; 95% CI, 1.6 to 17.3).[2] In subgroup analyses, participants who were treated with antidepressants who were 12 to 17 years of age reported more improvements in functioning and symptom severity compared with those ages 6 to 11 years. There was insufficient evidence on mortality data.

AHRQ – Screening for Eating Disorders in Adolescents and Adults

A 2022 systematic review and meta-analysis evaluated screening tools as well as pharmacotherapies for the treatment of adolescents and adults with eating disorders.[5] Evidence through January 1, 2022 was included. Seventeen trials evaluated therapies to treat eating disorders. Most trials enrolled predominately adult women, mean ages 25 to 44 years.[5]

Five trials evaluated SSRIs in people with binge-eating disorder (BED). Changes in the incidence of BED were of low quality and there was no difference in scores between fluoxetine and placebo (SMD -0.29; 95% CI, -0.83 to 0.24). People with an eating disorder and depression demonstrated improvements in depression scores (SMD -0.6; 95% CI, -0.90 to -0.33).[5] In patients with bulimia nervosa, fluoxetine was found to reduce eating disorder symptom severity and depression symptoms.

Evidence is primarily applicable to adult women and patients with binge-eating disorder or bulimia nervosa. Evidence was limited by the small amount of studies included in the analysis.

AHRQ – Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Systematic Review of Perinatal Pharmacological Interventions

A systematic review and meta-analysis done by AHRQ in 2022 evaluated treatments used in people with depression and who are perinatal (pregnant and postpartum).[2] Literature was searched through June 5, 2020, identifying 164 studies. Most of the evidence came from observational studies, inferring a high risk of bias and potential for confounding.

In pregnant and postpartum people with a diagnosis of anxiety, depression, bipolar disorder or schizophrenia, there were 9 RCTs and 10 observational studies evaluating the efficacy of medications in these populations.[2] In people with depression, there was low to moderate quality evidence for the reduction in depression symptoms with antidepressants. Brexanolone at peak doses of 60 to 90 mcg/kg per hour was studied in three trials enrolling women with onset of depressive symptoms in the third trimester, with approximately 30% on concomitant antidepressant therapy. Brexanolone improved depressive symptoms within 60 hours after infusion. At 30 days after treatment based on the HAM-D when compared to placebo (-16.0 versus -14.3 points; LSMD -2.6; p=0.02 [CI not reported]) (moderate strength of evidence), which is not considered clinically significant.[2] There was low quality evidence for the use of sertraline, based on placebo comparisons, in the postpartum period for response (RR 2.24; 95% CI, 0.95 to 5.24; p= 0.01 to 0.05), remission (RR 2.51; 95% CI, 0.94 to 6.70; p=0.01 to 0.05), and improvements in depressive symptoms.[2] Results suggest sertraline may provide benefit but not all findings were significant. Discontinuation of antidepressants during pregnancy in people with bipolar resulted in an increase in depressive symptom recurrence and a shorter time to symptom recurrence (low quality evidence

Harms data for the use of antidepressants in women who are perinatal comes from 5 RCTs and 70 observational trials. Evidence was determined to be low quality.[2] Tricyclic antidepressants and SNRIs were associated with a higher risk of preeclampsia and SNRIs had an increased risk of spontaneous abortion. The use of several antidepressants may be associated with a higher risk of postpartum hemorrhage. Brexanolone was found to increase sedation and somnolence leading to dose interruptions compared to placebo, 5% versus 0%.[2] The use of SSRIs by perinatal (e.g., pregnant or up to 28 days following birth) people may be associated with the following outcomes for their child: an increased risk of respiratory issues, low Apgar scores (determinant of newborn's health), persistent pulmonary hypertension of the newborn, and depression in children.

This review was limited by inclusion of mostly low quality evidence. Due to the observational nature of the data, it is uncertain if harms were due to medications or if they were associated with the mental health diagnosis itself.

There was insufficient evidence for the comparative effectiveness of treatments for anxiety, depression, bipolar disorder or schizophrenia in women during the perinatal period.

Cochrane - Pharmacotherapy for Post-Traumatic Stress Disorder (PTSD)

A Cochrane review published in 2022 evaluated the evidence for the use of pharmacotherapy in people with PTSD.[15] Literature was search until November 2020. The review identified 66 trials, with 54 used in the meta-analysis, that met inclusion criteria. Classes studied were SSRIs, SNRIs, MAOIs, TCAs and noradrengic and specific serotonergic antidepressants (NaSSAs).[15] The majority of studies evaluated paroxetine, fluoxetine and sertraline. The primary outcome was treatment response.

In participants taking SSRIs, there was a higher treatment response compared to placebo (58% vs. 35%; RR 0.66; 95% CI, 0.59 to 0.74) based on moderate quality evidence.[15] Mirtazapine demonstrated a benefit over placebo in one small study (n=26) (RR 0.45; 95% CI, 0.22 to 0.94). Low quality evidence showed a treatment response with amitriptyline compared to placebo (50% vs. 17%; RR 0.60; 95% CI, 0.38 to 0.96).[15] Withdrawal symptoms were more common with SSRIs than placebo (RR 1.41; 95% CI, 1.07 to 1.87) (moderate quality of evidence), which was especially common with paroxetine compared to placebo (RR 1.55; 95% CI 1.05 to 2.29) . Moderate quality of evidence demonstrated the risk of dropouts due to adverse events was higher with amitriptyline compared to placebo (182 per 1000 vs. 167 per 1000; RR 0.92; 95% CI, 0.81 to 1.05).[15]

Cochrane – Antidepressants for Hip and Knee Osteoarthritis

A Cochrane review evaluated efficacy of antidepressants in adults with osteoarthritis. Literature evaluated comparisons between antidepressants and placebo, or other active therapies.[6] Participants were adults with a diagnosis of osteoarthritis and without a mental health diagnosis. Seven trials involving knee osteoarthritis and 2 trials involving knee or hip osteoarthritis lasting 8 to 16 weeks were included. The mean ages of participants included in these trials ranged from 54.5 to 65.9 years and the majority of participants were women.[6] All trials were placebo controlled, and antidepressants could be used with or without non-steroidal anti-inflammatory drugs. The primary outcomes of interest were pain, function, and harms of treatment.

Nine RCTs compared antidepressants to placebo and found a mean difference in pain reduction of -0.59 (95% CI, -0.88 to -0.31) based on a 10-point scale.[6] The absolute difference in pain improvement was 6%, suggesting a small difference which is unlikely to be clinically important (high quality evidence). The number of responders (e.g., those with a 50% or greater reduction in 24-hour mean pain) was higher in those receiving antidepressants with an absolute improvement of 16% and a NNTB of 6 (high quality evidence).[6] There was high quality evidence that physical functioning (0-100 Western Ontario and McMaster Universities Arthritis Index [WOMAC] Total score) was improved with antidepressants, compared to placebo, which was probably clinically significant (mean difference [MD] -5.65; -7.08 to -4.23).[6] There was moderate evidence of no difference in quality of life between antidepressants and placebo. There was a higher chance of withdrawal due to adverse events in participants taking antidepressants compared to placebo with a number needed to harm [NNTH] of 17 (moderate quality of evidence). Serious adverse events were similar between groups, but there was a higher incidence of total adverse events with the use of antidepressants compared to placebo (NNTH 7 based on high quality of evidence).[6]

Cochrane – Psychological and Pharmacological Interventions for Depression in Patients with Coronary Artery Disease

Cochrane performed a systematic review and meta-analysis on the effects of drug therapy and psychological interventions for the treatment of MDD in adults with CAD.[7] The evidence for the use of drug therapy will be presented. There were 21 pharmacotherapy trials that were included in the analysis. Drugs included sertraline, mirtazapine, fluoxetine, escitalopram, paroxetine and nortriptyline. Evidence was searched through August 2020.

There was low quality evidence that the use of antidepressants, compared to placebo, helps to reduce symptoms of depression in the short term (SMD of 0.83 points lower than placebo).[7] Remission rates for depression, as measured by the Hamilton Rating Scale for Depression, were lower with antidepressant therapy with an incidence of 496 per 1000 people treated with antidepressants compared to 323 per 1000 people treated with placebo (OR 2.06; 95% CI, 1.47 to 2.89) (moderate quality evidence).[7] The evidence for mortality outcomes and risk of myocardial infarction (MI) was based on very low quality evidence, and therefore, strong conclusions could not be drawn. There was insufficient evidence for head-to-head comparisons between treatments.

There is a need for additional evidence demonstrating improvement in depressive symptoms in those treated with antidepressants that have CAD and MDD.

Cochrane – Ketamine and other Glutamate Receptor Modulators for Depression in Adults with Unipolar Major Depressive Disorder

A high quality systematic review and meta-analysis evaluated the evidence for the use of ketamine (22 trials), esketamine (8 trials), memantine (2 trials), atomoxetine (1 trial), and riluzole (1 trial) for the treatment of unipolar MDD.[8] Participants in the trials were 18 and older and had a diagnosis of moderate depression (29 trials), severe depression (17), and mild-moderate depression (5). Twenty percent of the included trials enrolled patients with treatment-resistant depression (defined as inadequate response to at least two antidepressants).[8] The primary outcome was the number of participants with response to treatment. The included RCTs were considered to have low risk of bias or unclear risk of bias. The non-randomized trials were deemed to be at high risk of bias.

Ketamine was studied as a single, IV dose in most studies and esketamine was given intranasally twice weekly for four weeks in most studies.[8] Ketamine was shown to possibly increase response and remission of depression symptoms more than placebo or midazolam, but all evidence was considered to be of very low quality. Esketamine was compared to placebo and found to increase remission rates (based on MADRS) at 24 hours (17.5% vs. 7.2%; OR 2.74; 95% CI, 1.71 to 4.40) (moderate strength of evidence).[8] At 24 hours the response rate was also higher in those treated with esketamine compared to placebo, but the evidence was low quality (OR 2.11; 95% CI, 1.20 to 3.68).[8] There was moderate evidence that esketamine improved depression rating scale scores more than placebo based on 4 RCTs (n=824) with a SMD of 0.31 points lower (95% CI, -0.45 to -0.17). Treatment discontinuation was higher with esketamine compared to placebo based on moderate evidence (12.9% versus 4.3%). There was insufficient evidence for the use of memantine, atomoxetine, or riluzole for the use in unipolar MDD.

DERP – Intravenous Brexanolone (Zulresso) and SAGE-217 (Zuranolone) to Treat Postpartum Depression

The evidence for the use of brexanolone and SAGE-217 (not approved in the US) was reviewed by DERP in March of 2021.[9] Brexanolone is indicated for women with PPD and is delivered by the IV route via a 60-hour infusion. Three studies placebo-controlled trials were available for inclusion. Trial duration lasted up to 30 days post-infusion.[9]

Evidence regarding benefit of brexanolone was mixed and dependent on the specific outcome, timepoint, and population. Disease remission was higher with brexanolone compared to placebo at 60 hours based on low quality evidence, but no different at 30-days post infusion.[9] At 60 hours, depression symptoms were improved, based on HAM-D scores (low quality of evidence), but not different when evaluated using the Edinburgh Postnatal Depression Scale (EPDS) based on very low quality of evidence. At 30-days post infusion, there were significant improvements in depression scores based on the HAM-D in women with severe PPD but not in those with moderate PPD, as determined by DERP.[9]

Brexanolone has a Risk Evaluation and Mitigation Strategy program required for use due to the risk of excessive sedation and sudden loss of consciousness. Studies found no significant difference between placebo and brexanolone in treatment-emergent adverse events up to 7 days after therapy initiation.[9]

After review, 280 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[16–26, 17,27–38, 39–46]

New Guidelines:
High Quality Guidelines:

NICE – Depression in Adults: Treatment and Management
In June of 2022 NICE updated their guidance on treating adults with antidepressants.[10] This updates the original guidance from 2009. Pharmacological recommendations will be included, as this is the focus of this updated; however, there are recommendations included in the guidance for the benefits of psychological and psychosocial therapies. Guidelines recommend discussing the choices of therapy, dose and dose adjustments, expected benefits, and potential harms prior to starting therapies. Reviewing expected benefits of treatment, time to effect (approximately 4 weeks), instructions on administration, and withdrawal symptoms should be discussed between patient and provider.[10]

The treatment choice should be guided by the needs and preferences of the individual with depression, taking into account any previous treatments, sedative effects, concomitant illness or medications, and suicide risk.[10] Treatment should be assessed 2 to 4 weeks after starting treatment. SSRIs are recommended as a first-line option for treatment of depression. Other treatment options include SNRIs, TCAs, or combination therapy with CBT.[10] TCAs are dangerous in overdose and should be used with caution in certain populations. If depressive symptoms have a limited response to treatment, the dose can be increased or the treatment can be changed to another medication (in the same class in a different class). Vortioxetine should be reserved for patients that have tried at least 2 previous antidepressants without a desired response due to lack of superiority to other antidepressants and it's high cost.[10] People with ongoing depressive symptoms should be referred to a specialist and may be a candidate for the addition of a second antidepressant from another class or addition of a second-generation antipsychotic.

If treatment is discontinued it should be done after a conversation with the prescriber and the patient should be cautioned on risk of unsteadiness, altered sensation, altered feelings such as irritability, restlessness or agitation, problems sleeping, sweating, abdominal symptoms, and palpitations. All antidepressants can be associated with withdrawal symptoms, especially commonly used treatments such as paroxetine and venlafaxine. Withdrawing therapy may take weeks to months to complete and medications such as paroxetine and venlafaxine are most likely to be associated with withdrawal symptoms.[10] Specific recommendations related to discontinuing fluoxetine include alternate day dosing in those taking fluoxetine 20 mg a day and slow dose tapers every 1-2 weeks for people taking higher doses of 40 to 60 mg daily so effects can be evaluated.[10]

VA – Management of Major Depressive Disorder
The VA published guidance on the treatment of MDD in 2022 with literature searched through January of 2021.[11] The guideline is intended for management of adult patients, 18 and older, with a diagnosis of MDD of any severity. Guideline recommendations range from weak to strong based on evidence. Recommendations related to antidepressant pharmacotherapy will be included.

A collaborative/integrated care model is strongly recommended to treat MDD.[11] The guideline recommends that patients with a history of MDD be evaluated via a quantitative measure for depression severity to guide treatment management. There is a strong recommendation for psychotherapy or pharmacotherapy for treatment of MDD, based on patient preference. Other factors that should be considered are treatment response, severity and chronicity. Certain treatment strategies (e.g., augmentation, combination treatment, switching treatment, and second-line treatments) may be appropriate, depending upon patient

characteristics. Recommendations for initial therapy include bupropion, mirtazapine, SSRIs, trazodone, vilazodone, vortioxetine, or SNRIs (weak recommendation).[11] The following treatments are not recommended as first-line therapies: esketamine, ketamine, MAOIs, nefazodone, and TCAs (weak recommendation). Combination therapy with medication and psychotherapy is weakly recommended for those with severe MDD (PHQ-9 greater than 20 points), persistent major depressive disorder (greater than 2 years), and recurrent depression with more than 2 episodes. There was insufficient evidence for the use of bupropion for augmentation therapy as an add on treatment to an SSRI.[11] A weak recommendation for the use of ketamine or esketamine as augmentation is recommended for people who have MDD and have not responded to several pharmacological therapy trials. The use of antidepressants during pregnancy should be considered and the risks and balances should be weighed in people who responded to therapy prior to pregnancy (strong recommendation). St. John's wort is weakly recommended as monotherapy for pregnant patients with mild MDD who prefer herbal treatments, and are not on therapy that could interact with St. John's wort.[11] There is a strong recommendation that treatment should be continued for 6 months beyond remission to prevent relapse.

American Academy of Neurology - Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary

A 2022 guideline published by the AAN provides recommendations for the treatment of painful diabetic neuropathy (PDN).[12] Literature was searched up until April 2020 and evidence was graded using a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.[12] Conflicts of interest were noted for some guideline authors; however, criteria for dealing with conflicts with industry were clearly outlined. Five classes of medications were included in the update: gabapentinoids, SNRIs, TCAs, sodium channel blockers, and SNRI/opioid dual mechanism agents (e.g., tramadol and tapentadol).[12] All pain outcomes were converted to an effect size estimate for efficacy, with a SMD of 0.5 demonstrating a moderate effect. Since the focus of this review is for the use of antidepressants, evidence for their use will be presented.

Evidence for the use of antidepressants for PDN are presented in **Table 2**. Comparisons of therapies found venlafaxine to be similar to carbamazepine for pain intensity (SMD -0.02; 95% CI, -0.32 to 0.35; p>0.05) (moderate quality of evidence).[12] There is moderate evidence that pregabalin is more effective at reducing pain compared to venlafaxine (SMD 0.84; 95% CI, 0.48 to 1.20). Amitriptyline was shown to have similar efficacy to gabapentin for pain intensity (SMD 0.33; 95% CI, -0.32 to 0.98) based on low quality evidence.[12] Combination therapy with duloxetine and pregabalin has similar efficacy to the monotherapy components. A comparison between duloxetine and nortriptyline found duloxetine to be more likely to improve pain (SMD 1.64; 95% CI, 0.63 to 2.65) (low quality of evidence). However, overall TCAs, compared to placebo, demonstrated the largest benefit on pain scores; based on low quality evidence.

The guidelines recommend that all patient with PDN should be given the option of a TCA, SNRIs, gabapentinoids, and/or sodium channel blockers (e.g., anticonvulsants) to help manage pain symptoms (Level B evidence).[12] Evidence for efficacy between the different therapies show similar effects on pain, all with a medium effect size (SMD 0.5). Adverse effect profiles should be considered as well as costs and patient preferences. Due to adverse effects and limited evidence on efficacy in PND, opioids, tramadol and tapentadol should not be used for pain control in PDN (Level C).[12]

Table 2. Recommendations for the Use of Antidepressants for Diabetic Polyneuropathy[12]

Class	Effect size for pain reduction	Grade	Notes
SNRIs (9 studies)	SMD 0.47 (95% CI, 0.34 to 0.60)	Moderate quality of evidence	Most evidence comes from venlafaxine, desvenlafaxine and duloxetine.
TCAs (3 studies)	SMD 0.95 (95% CI, 0.15 to 1.8)	Low quality of evidence	All evidence was for amitriptyline.

SNRI/Opioids (4 studies)	SMD 0.78 (95% CI, 0.54 to 1.03)	Low quality of evidence	Opioids not recommended due to adverse effects.

Abbreviations: CI – confidence interval; SMD – standard mean difference; SNRIs – selective norepinephrine reuptake inhibitors; TCA – tricyclic antidepressants.

Health Improvement Scotland – Eating Disorders

An August 2022 guideline was published to provide evidence for the management of eating disorders.[13] Healthcare Improvement Scotland produces high quality clinical guidelines accredited by NICE. Recommendations are based on the quality of evidence, ranging from 1 to 4. Level 1 evidence is considered high-quality and Level 4 is expert opinion. Eating disorders covered in the guideline are anorexia nervosa (AN), bulimia nervosa (BN) and BED.

Recommendations pertaining to the treatment of eating disorders with antidepressant medications will be presented. Psychological therapies are a cornerstone of treating eating disorders but are out of the scope of this review. Pharmacotherapy with antidepressants is not recommended for treating AN. The guidelines recommend offering antidepressants short-term, in combination with psychological treatments for people with BN (Strong recommendation based on high quality evidence).[13] Fluoxetine is the only FDA treatment approved for the treatment of BN and should be considered first-line (Strong recommendation based on high quality evidence). Other antidepressants can be considered if fluoxetine is not an option.[13] In people with BED, treatment of comorbidities should be treated but evidence does not support the use of medication for BED alone. People with comorbid anxiety and depression should be treated with evidence-based treatment in addition to the eating disorder.

Additional Guidelines for Clinical Context:
No guidelines were excluded due to poor quality.

New Formulations or Indications:

Brexanolone (Zulresso®): A new indication for brexanolone was approved in June of 2022 which expanded use for patients 15 years and older diagnosed with postpartum depression.[47] Brexanolone was previously approved in adults for this indication.

Dextromethorphan and bupropion (Auvelity®): A new dosage formulation, available as a combination product of dextromethorphan and bupropion, was approved in August of 2022.[48] The product is a combination of an uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist (dextromethorphan) and sigma-1 receptor agonist and aminoketone and CYP450 2D6 inhibitor (bupropion) indicated for MDD in adults. Approval was based on one placebo-controlled trial and one trial comparing the combination product to bupropion. Both studies were 6 week studies enrolling adult patients. Dextromethorphan/bupropion improved depression symptoms compared to placebo with a decrease in MADRS score of -3.9 points (95% CI, -6.4 to -1.4) more than placebo. The mean baseline MADRS score of participants was 33.4 indicating moderate depression for most patients.[48] Specific results were not available for the second study.

Duloxetine (Drizalma Sprinkle®): In July of 2021, duloxetine received an expanded indication for the use for fibromyalgia in adults with a starting dose of 30 mg a day and a target dose of 60 mg a day.[49] Approval was based on two, double-blind, placebo-controlled RCTs.[49] Treatment with duloxetine 60 mg or 120 mg once daily resulted in improved pain scores as measured by the primary outcome of the proportion of patients with at least a 50% reduction in scores from baseline. The 120 mg dose was not superior to the 60 mg dose and was associated with more adverse reactions.[49] Other formulations of duloxetine are also approved for fibromyalgia.[50]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change	Addition or Change and Mitigation Principles (if applicable)
Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)[51]	Not Applicable	September 2021	Warnings and Precautions	There is an association between the use of SSRIs and SNRIs and the occurrence of sexual dysfunction that should be included in all labeling.
Vortioxetine tablets[52]	Trintellix®	January 2021	Box Warning	Revised box warning to include increased risk of suicidal thinking and behaviors in pediatric and young adult patients which should be closely monitored. Updated labeling is in response to a pooled analysis which found that treatment in patients 24 years and younger was associated with an increased incidence of suicidal thoughts and behaviors compared to placebo treated patients.
Venlafaxine extended release capsules[53]	Effexor XR®	November 2021	Warnings and Precautions	Post marketing reports suggest an increased risk of serious symptoms upon discontinuation of venlafaxine XR, reported as protracted and severe. Symptoms range from suicide, suicidal thoughts, aggression, violent behavior, visual changes and increased blood pressure after stopping or reducing the dose of venlafaxine XR.

Randomized Controlled Trials:

A total of 312 citations were manually reviewed from the initial literature search. After further review, 311 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Ionescu, et al[14] ASPIRE II	1. Esketamine 84 mg nasal spray twice weekly*	Adults (ages 18 to 64 years) with MDD and active	Change from baseline to 24 hours post-first dose in MADRS total score	1. -15.7 points 2. -12.4 points Esketamine vs. Placebo	Results are most applicable to inpatient treatment of patients with severe disease.

DB, Phase 3, RCT	2. Placebo nasal spray twice weekly* Study duration: 4 weeks	suicidal ideation with intent		LSMD -3.9 (95% CI, -6.6 to -1.1) P=0.006	

Key: * All patients received standard of care (e.g., 5 or more days hospitalization and newly initiated or optimized oral antidepressant[s])
Abbreviations: CI = confidence interval; LSMD = least square mean difference; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; RCT = randomized clinical trial.

References:

1. O'Connor E, Henniger M, Perdue L, et al. Screening for Depression, Anxiety and Suicide Risk in Adults: A Systematic Evidence Review for the U.S. Preventative Task Force. Agency for Healthcare Research and Quality Comparative Effectiveness Review. August 2022; Number 223.

2. Viswanathan M, Cook Middleton J, Stuebe A, et al. *Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Systematic Review of Perinatal Pharmacologic Interventions*. Agency for Healthcare Research and Quality (AHRQ); 2021. doi:10.23970/AHRQEPCCER236

3. Viswanathan M, Wallace IF, Cook Middleton J, et al. Screening for Anxiety in Children and Adolescents: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2022;328(14):1445-1455. doi:10.1001/jama.2022.16303

4. Caporino NE, Brodman DM, Kendall PC, et al. Defining Treatment Response and Remission in Child Anxiety: Signal Detection Analysis Using the Pediatric Anxiety Rating Scale. *J Am Acad Child Adolesc Psychiatry*. 2013;52(1):57-67. doi:10.1016/j.jaac.2012.10.006

5. Feltner C, Peat C, Reddy S, et al. Screening for Eating Disorders in Adolescents and Adults: An Evidence Review for the U.S. Preventative Services Task Force. Agency for Healthcare Research and Quality Comparative Effectiveness Review. March 2022; Number 212.

6. Leaney AA, Lyttle JR, Segan J, et al. Antidepressants for hip and knee osteoarthritis. *Cochrane Database of Systematic Reviews*. 2022;(10). doi:10.1002/14651858.CD012157.pub2

7. Tully PJ, Ang SY, Lee EJ, et al. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database of Systematic Reviews*. 2021;2021(12). doi:10.1002/14651858.cd008012.pub4

8. Dean RL, Hurducas C, Hawton K, et al. Ketamine and other glutamate receptor modulators for depression in adults with unipolar major depressive disorder. *Cochrane Database of Systematic Reviews*. 2021;(9). doi:10.1002/14651858.CD011612.pub3

9. The Drug Effectiveness Review Project. Intravenous Brexanolone (Zulresso) and SAGE-217 (Zuranolone) to Treat Postpartum Depression: Clinical Evidence and Management Strategies Systematic Review. March 2021.

10. National Institute for Health and Care Excellence. Depression in adults: treatment and management. NICE Guideline; June 2022. Available at: www.nice.org.uk/guidance/ng222. Accessed on November 18, 2022:113.

11. Department of Veterans Affairs/Department of Defense. VA/DoD clinical practice guidelines for the management of major depressive disorder. Version 3.0-20167. The Management of Major Depression Disorder Working Group. April 2016.

12. Price R, Smith D, Franklin G, et al. Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary: Report of the AAN Guideline Subcommittee. *Neurology*. 2022;98(1):31-43. doi:10.1212/WNL.0000000000013038

13. Scottish Intercollegiate Guidelines Network (SIGN). Eating disorders 2022. (SIGN publication no. 164). [January 2022]. Available from URL: http://www.sign.ac.uk. Accessed December 13, 2022.

14. Ionescu DF, Fu DJ, Qiu X, et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *Int J Neuropsychopharmacol*. 2021;24(1):22-31. doi:10.1093/ijnp/pyaa068

15. Williams T, Phillips NJ, Stein DJ, Ipser JC. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane Database of Systematic Reviews 2022. Issue 3. Art No: CD002795. Accessed November 8, 2022.

16. Witt KG, Hetrick SE, Rajaram G, et al. Pharmacological interventions for self-harm in adults. *Cochrane Database of Systematic Reviews*. 2021;(1). doi:10.1002/14651858.CD013669.pub2

17. Kalbouneh HM, Toubasi AA, Albustanji FH, Obaid YY, Al-Harasis LM. Safety and Efficacy of SSRIs in Improving Poststroke Recovery: A Systematic Review and Meta-Analysis. [Review]. *Journal of the American Heart Association*. 2022;11(13):e025868. doi:10.1161/JAHA.122.025868

18. Razali NA, Sidi H, Choy CL, Roos NAC, Baharudin A, Das S. The Role of Bupropion in the Treatment of Women with Sexual Desire Disorder: A Systematic Review and Meta-Analysis. *Current Neuropharmacology*. 2022;20(10):1941-1955. doi:10.2174/1570159X20666220222145735

19. Leeuwen EV, Driel ML van, Horowitz MA, et al. Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults. *Cochrane Database of Systematic Reviews*. 2021;2021(4). doi:10.1002/14651858.cd013495.pub2

20. Brown JVE, Wilson CA, Ayre K, et al. Antidepressant treatment for postnatal depression. *Cochrane Database of Systematic Reviews*. 2021;2021(2). doi:10.1002/14651858.cd013560.pub2

21. Nussbaumer-Streit B, Thaler K, Chapman A, et al. Second-generation antidepressants for treatment of seasonal affective disorder. *Cochrane Database of Systematic Reviews*. 2021;(3). doi:10.1002/14651858.CD008591.pub3

22. Bruijn CMA de, Rexwinkel R, Gordon M, Benninga MA, Tabbers MM. Antidepressants for functional abdominal pain disorders in children and adolescents. *Cochrane Database of Systematic Reviews*. 2021;2021(2). doi:10.1002/14651858.cd008013.pub3

23. Hetrick SE, McKenzie JE, Bailey AP, et al. New generation antidepressants for depression in children and adolescents: a network meta-analysis. *Cochrane Database of Systematic Reviews*. 2021;(5). doi:10.1002/14651858.CD013674.pub2

24. Hoffman J, Williams T, Rothbart R, et al. Pharmacotherapy for trichotillomania. *Cochrane Database of Systematic Reviews*. 2021;2021(9). doi:10.1002/14651858.cd007662.pub3

25. Allida S, House A, Hackett ML. Pharmaceutical interventions for emotionalism after stroke. *Cochrane Database of Systematic Reviews*. 2022;(11). doi:10.1002/14651858.CD003690.pub5

26. Kruizinga J, Liemburg E, Burger H, et al. Pharmacological treatment for psychotic depression. *Cochrane Database of Systematic Reviews*. 2021;2021(12). doi:10.1002/14651858.cd004044.pub5

27. Kampling H, Baumeister H, Bengel J, Mittag O. Prevention of depression in adults with long-term physical conditions. *Cochrane Database of Systematic Reviews*. 2021;2021(3). doi:10.1002/14651858.cd011246.pub2

28. Nakhaee H, Zangiabadian M, Bayati R, Rahmanian M, Ghaffari Jolfayi A, Rakhshanderou S. The effect of antidepressants on the severity of COVID-19 in hospitalized patients: A systematic review and meta-analysis. *PLoS ONE [Electronic Resource]*. 2022;17(10):e0267423. doi:10.1371/journal.pone.0267423

29. Marquez MC, Sanchez JM, Salazar AM, Martinez CV, Valderrama F, Rojas-Gualdron DF. Efficacy and safety of antipsychotics and antidepressants in the treatment of anorexia nervosa: a systematic review. [Review]. *Revista Colombiana De Psiquiatria*. 2022;51(3):227-235. doi:10.1016/j.rcpeng.2022.08.007

30. Park JH, Nunez NA, Gardea-Resendez M, et al. Short Term Second-Generation Antidepressant Monotherapy in Acute Depressive Episodes of Bipolar II Disorder: A Systematic Review and Meta-Analysis. [Review]. *Psychopharmacology Bulletin*. 2022;52(2):45-72.

31. Baldwin DS, Necking O, Schmidt SN, Ren H, Reines EH. Efficacy and safety of vortioxetine in treatment of patients with major depressive disorder and common co-morbid physical illness. *Journal of Affective Disorders*. 2022;1:588-594. doi:10.1016/j.jad.2022.05.098

32. Bhuta S, Khokher W, Kesireddy N, et al. Fluvoxamine in Nonhospitalized Patients With Acute COVID-19 Infection and the Lack of Efficacy in Reducing Rates of Hospitalization, Mechanical Ventilation, and Mortality in Placebo-Controlled Trials: A Systematic Review and Meta-Analysis. *American Journal of Therapeutics*. 2022;29(3):e298-e304. doi:10.1097/MJT.0000000000001496

33. Naji L, Dennis B, Rosic T, et al. Mirtazapine for the treatment of amphetamine and methamphetamine use disorder: A systematic review and meta-analysis. [Review]. *Drug & Alcohol Dependence*. 2022;1:109295. doi:10.1016/j.drugalcdep.2022.109295

34. Feng RF, Ma R, Wang P, et al. Efficacy of escitalopram for poststroke depression: a systematic review and meta-analysis. *Scientific Reports*. 2022;12(1):3304. doi:10.1038/s41598-022-05560-w

35. Baethge C, Braun C, Rink L, Schwarzer G, Henssler J, Bschor T. Dose effects of tricyclic antidepressants in the treatment of acute depression - A systematic review and meta-analysis of randomized trials. [Review]. *Journal of Affective Disorders*. 2022;1:191-198. doi:10.1016/j.jad.2022.03.075

36. Hu Y, Zhang H, Wang H, Wang C, Kung S, Li C. Adjunctive antidepressants for the acute treatment of bipolar depression: A systematic review and meta-analysis. [Review]. *Psychiatry Research*. 2022;1:114468. doi:10.1016/j.psychres.2022.114468

37. Xiang Y, Cuijpers P, Teng T, et al. Comparative short-term efficacy and acceptability of a combination of pharmacotherapy and psychotherapy for depressive disorder in children and adolescents: a systematic review and meta-analysis. *BMC Psychiatry*. 2022;22(1):139. doi:10.1186/s12888-022-03760-2

38. Wen XJ, Wang LM, Liu ZL, Huang A, Liu YY, Hu JY. Meta-analysis on the efficacy and tolerability of the augmentation of antidepressants with atypical antipsychotics in patients with major depressive disorder. *Brazilian Journal of Medical and Biological Research*. 2014;47(7):605-616. doi:10.1590/1414-431X20143672

39. Vazquez GH, Bahji A, Undurraga J, Tondo L, Baldessarini RJ. Efficacy and Tolerability of Combination Treatments for Major Depression: Antidepressants plus Second-Generation Antipsychotics vs. Esketamine vs. Lithium. *Journal of Psychopharmacology*. 2021;35(8):890-900. doi:10.1177/02698811211013579

40. Ko YC, Lee CH, Wu CS, Huang YJ. Comparison of efficacy and safety of gabapentin and duloxetine in painful diabetic peripheral neuropathy: A systematic review and meta-analysis of randomised controlled trials. *International Journal of Clinical Practice*. 2021;75(11):e14576. doi:10.1111/ijcp.14576

41. Cheng DK, Lai KSP, Pico-Espinosa OJ, et al. Interventions for Depressive Symptoms in People Living with Chronic Pain: A Systematic Review of Meta-Analyses. *Pain Medicine*. 2022;23(5):934-954. doi:10.1093/pm/pnab248

42. Kato H, Koizumi T, Takeuchi H, Tani H, Mimura M, Uchida H. Effects of Discontinuation of Drugs Used for Augmentation Therapy on Treatment Outcomes in Depression: A Systematic Review and Meta-analysis. *Pharmacopsychiatry*. 2021;54(3):106-116. doi:10.1055/a-1330-8587

43. Xiong J, Lipsitz O, Chen-Li D, et al. The acute antisuicidal effects of single-dose intravenous ketamine and intranasal esketamine in individuals with major depression and bipolar disorders: A systematic review and meta-analysis. [Review]. *Journal of Psychiatric Research*. 2021;1:57-68. doi:10.1016/j.jpsychires.2020.12.038

44. Maguire MJ, Marson AG, Nevitt SJ. Antidepressants for people with epilepsy and depression. *Cochrane Database of Systematic Reviews*. 2021;(4). doi:10.1002/14651858.CD010682.pub3

45. Js J, R K, Op A, Gj H. Risk of Fractures in Stroke Patients Treated With a Selective Serotonin Reuptake Inhibitor: A Systematic Review and Meta-Analysis. *Stroke*. 2021;52(9). doi:10.1161/STROKEAHA.120.032973

46. Hm F, I Y, H G, I S, Ja D, T E. Comparison of Amitriptyline and US Food and Drug Administration-Approved Treatments for Fibromyalgia: A Systematic Review and Network Meta-analysis. *JAMA network open*. 2022;5(5). doi:10.1001/jamanetworkopen.2022.12939

47. Zulresso (brexanolone) [prescribing information]. Cambridge, MA; Sage Therapeutics, Inc. June 2022.

48. Auvelity (dextromethorphan hydrobromide and bupropion hydrochloride) [prescribing information]. New York, NY; Axsome Therapeutics, Inc. August 2022.

49. Drizalma Sprinkle (duloxetine) [prescribing information]. Sun Pharmaceuticals Industries, Inc; Cranbury, NJ. July 2021.

50. Cymbalta (duloxetine delayed release capsules) [prescribing information]. Indianapolis, IN; Lilly USA, LLC. July 2021.

51. Viibryd (vilazodone) [prescribing information]. Madison, NJ; Allergan. September 2021.

52. Trintellix (vortioxetine) [prescribing information]. Deerfield, IL; Takeda Pharmaceuticals America, Inc. January 2021.

53. Effexor XR (venlafaxine extended-release capsules) [prescribing information]. Philadelphia, PA; Pfizer, Inc., November 2021.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
amitriptyline HCl	AMITRIPTYLINE HCL	TABLET	Y
amitriptyline HCl	ELAVIL	TABLET	Y
bupropion HCl	BUPROPION XL	TAB ER 24H	Y
bupropion HCl	WELLBUTRIN XL	TAB ER 24H	Y
bupropion HCl	BUPROPION HCL SR	TAB SR 12H	Y
bupropion HCl	WELLBUTRIN SR	TAB SR 12H	Y
bupropion HCl	BUPROPION HCL	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	Y
citalopram hydrobromide	CELEXA	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	TABLET	Y
desipramine HCl	DESIPRAMINE HCL	TABLET	Y

desipramine HCl	NORPRAMIN	TABLET	Y
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	Y
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	Y
doxepin HCl	DOXEPIN HCL	CAPSULE	Y
doxepin HCl	DOXEPIN HCL	ORAL CONC	Y
duloxetine HCl	CYMBALTA	CAPSULE DR	Y
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	Y
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	Y
escitalopram oxalate	LEXAPRO	TABLET	Y
fluoxetine HCl	FLUOXETINE HCL	CAPSULE	Y
fluoxetine HCl	PROZAC	CAPSULE	Y
fluoxetine HCl	FLUOXETINE HCL	SOLUTION	Y
fluoxetine HCl	FLUOXETINE HCL	TABLET	Y
fluvoxamine maleate	FLUVOXAMINE MALEATE	TABLET	Y
imipramine HCl	IMIPRAMINE HCL	TABLET	Y
mirtazapine	MIRTAZAPINE	TAB RAPDIS	Y
mirtazapine	REMERON	TAB RAPDIS	Y
mirtazapine	MIRTAZAPINE	TABLET	Y
mirtazapine	REMERON	TABLET	Y
nortriptyline HCl	NORTRIPTYLINE HCL	CAPSULE	Y
nortriptyline HCl	PAMELOR	CAPSULE	Y
nortriptyline HCl	NORTRIPTYLINE HCL	SOLUTION	Y
paroxetine HCl	PAROXETINE HCL	TABLET	Y
paroxetine HCl	PAXIL	TABLET	Y
protriptyline HCl	PROTRIPTYLINE HCL	TABLET	Y
sertraline HCl	SERTRALINE HCL	ORAL CONC	Y
sertraline HCl	ZOLOFT	ORAL CONC	Y
sertraline HCl	SERTRALINE HCL	TABLET	Y
sertraline HCl	ZOLOFT	TABLET	Y
trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	Y
amoxapine	AMOXAPINE	TABLET	V
bupropion HBr	APLENZIN	TAB ER 24H	V
bupropion HCl	BUPROPION XL	TAB ER 24H	V
bupropion HCl	FORFIVO XL	TAB ER 24H	V
citalopram hydrobromide	CITALOPRAM HBR	CAPSULE	V
clomipramine HCl	ANAFRANIL	CAPSULE	V

clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	V
duloxetine HCl	DRIZALMA SPRINKLE	CAP DR SPR	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	V
esketamine HCl	SPRAVATO	SPRAY	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	V
imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	V
isocarboxazid	MARPLAN	TABLET	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	V
nefazodone HCl	NEFAZODONE HCL	TABLET	V
paroxetine HCl	PAROXETINE HCL	ORAL SUSP	V
paroxetine HCl	PAXIL	ORAL SUSP	V
paroxetine HCl	PAROXETINE CR	TAB ER 24H	V
paroxetine HCl	PAROXETINE ER	TAB ER 24H	V
paroxetine HCl	PAXIL CR	TAB ER 24H	V
paroxetine mesylate	PEXEVA	TABLET	V
phenelzine sulfate	NARDIL	TABLET	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	V
selegiline	EMSAM	PATCH TD24	V
sertraline HCl	SERTRALINE HCL	CAPSULE	V
tranylcypromine sulfate	TRANYLCYPROMINE SULFATE	TABLET	V
venlafaxine besylate	VENLAFAXINE BESYLATE ER	TAB ER 24	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	V
vilazodone HCl	VIIBRYD	TAB DS PK	V
vilazodone HCl	VIIBRYD	TABLET	V
vilazodone HCl	VILAZODONE HCL	TABLET	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	V
brexanolone	ZULRESSO	VIAL	
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	
olanzapine/fluoxetine HCl	SYMBYAX	CAPSULE	
trazodone HCl	TRAZODONE HCL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II)
Ionescu D, Dong-Jing Fu, Xin Qiu, Rosanne Lane, Pilar Lim, Siegfried Kasper, David Hough, Wayne C Drevets, Husseini Manji, Carla M Canuso
Background: Patients with major depressive disorder (MDD) having active suicidal ideation with intent require immediate treatment.
Methods: This double-blind study (ASPIRE II) randomized adults (aged 18-64 years) with MDD having active suicidal ideation with intent to esketamine 84 mg or placebo nasal spray twice weekly for 4 weeks, given with comprehensive standard of care (hospitalization ≥5 days and newly initiated or optimized oral antidepressant[s]). Change from baseline to 24 hours post-first dose in Montgomery-Asberg Depression Rating Scale total score (primary efficacy endpoint) was analyzed using ANCOVA. Clinical Global Impression-Severity of Suicidality-revised (key secondary endpoint) was analyzed using ANCOVA on ranks of change.
Results: Of 230 patients who were randomized (115 per arm), 227 received study drug and were included in efficacy/safety analyses; 184 (80.0%) completed double-blind treatment. Greater improvement in Montgomery-Asberg Depression Rating Scale total score was observed with esketamine (mean [SD]: -15.7 [11.56]) vs placebo (-12.4 [10.43]), each with standard of care, at 24 hours (least-squares mean difference [SE]: -3.9 [1.39], 95% CI: -6.60, -1.11; 2-sided P = .006). This was also noted at the earlier (4-hour) timepoint (least-squares mean difference -4.2, 95% CI: -6.38, -1.94). Patients in both treatment groups experienced rapid reduction in Clinical Global Impression-Severity of Suicidality-revised score; the between-group difference was not statistically significant. The most common adverse events among esketamine-treated patients were dizziness, dissociation, nausea, dysgeusia, somnolence, headache, and paresthesia.
Conclusion: This study confirmed rapid and robust reduction of depressive symptoms with esketamine nasal spray in severely ill patients with MDD who have active suicidal ideation with intent. Trial Registration: Clinical Trials.gov identifier: NCT03097133.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 18, 2022
Search Strategy:

#	Searches	Results
1	Amitriptyline/ or amitriptyline.mp.	9780
2	bupropion.mp. or Bupropion/	5461
3	citalopram.mp. or Citalopram/	7584
4	desipramine.mp. or Desipramine/	7952
5	desvenlafaxine.mp. or Desvenlafaxine Succinate/	517
6	doxepin.mp. or Doxepin/	1512
7	duloxetine.mp. or Duloxetine Hydrochloride/	3140
8	escitalopram.mp. or Escitalopram/	3078
9	fluoxetine.mp. or Fluoxetine/	15314
10	fluvoxamine.mp. or Fluvoxamine/	3225

11	imipramine.mp. or Imipramine/	13487
12	mirtazapine.mp. or Mirtazapine/	2632
13	nortriptyline.mp. or Nortriptyline/	3231
14	paroxetine.mp. or Paroxetine/	6725
15	protriptyline.mp. or Protriptyline/	415
16	sertraline.mp. or Sertraline/	5829
17	trimipramine.mp.	544
18	venlafaxine.mp. or Venlafaxine Hydrochloride/	4861
19	amoxapine.mp. or Amoxapine/	482
20	clomipramine.mp. or Clomipramine/	4096
21	esketamine.mp.	559
22	isocarboxazid.mp. or Isocarboxazid/	415
23	levomilnacipran.mp. or Levomilnacipran/	98
24	nefazodone.mp.	794
25	phenelzine.mp. or Phenelzine/	1677
26	selegiline.mp. or Selegiline/	2982
27	tranylcypromine.mp. or Tranylcypromine/	2300
28	vilazodone.mp. or Vilazodone Hydrochloride/	250
29	vortioxetine.mp. or Vortioxetine/	613
30	brexanolone.mp.	117
31	olanzapine.mp. or Olanzapine/	10259
32	trazodone.mp. or Trazodone/	2279
33	1 or 2 or 3 or 4 or 5 or 6 or 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	89226
34	limit 33 to (english language and humans and yr="2021 -Current")	2814
35	limit 34 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	312

Appendix 4: Key Inclusion Criteria

Population	Patients with depression, anxiety, or post-traumatic stress disorder
Intervention	Antidepressants listed in **Appendix 1**
Comparator	Antidepressants listed in **Appendix 1** or other active comparator (e.g., psychological therapy)
Outcomes	Function, quality of life, symptoms, morbidity, mortality, significant adverse events
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Esketamine (Spravato)

Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression.

Length of Authorization:

- Up to 6 months

Requires PA:

- Esketamine requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims).

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Does the patient have treatment resistant depression (failure of two separate antidepressant trials which were each given for at least 6 weeks at target doses)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
7. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
8. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve requested doses (either 56 mg and/or 84 mg for titration) not to exceed 23 units total.

Renewal Criteria		
1. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?	**Yes:** Go to #2	**No**: Go to #4
2. Is the request for administration of esketamine once weekly or every 2 weeks?	**Yes:** Go to #3	**No**: Pass to RPh. Deny; medical appropriateness.
3. Has the patient been adherent to oral antidepressant therapy?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has the patient been on therapy for at least 4 weeks?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for completion of induction phase (total 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)

P&T/DUR Review: 2/23 (KS), 10/21 (SS); 2/21(SS); 7/19 (KS)
Implementation: 1/1/22; 3/1/21; 8/19/19

Brexanolone (Zulresso)

Goal(s):
To ensure appropriate use of brexanolone in patient with post-partum depression.

Length of Authorization:
- One time use only.

Requires PA:
Brexanolone requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP
4. Is the patient an adult with moderate to severe post-partum depression?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient had an adequate trial (6-8 weeks) of an oral antidepressant?	**Yes:** Approve for a single, continuous, intravenous infusion over 60 hours (titrated per prescribing recommendations)	**No:** Pass to RPh. Deny; recommend trial of oral antidepressant

P&T/DUR Review: 2/23 (KS), 2/21(SS); 7/19 (KS)
Implementation: 8/19/19

Tricyclic Antidepressants

Goal(s):

- Ensure safe and appropriate use of tricyclic antidepressants in children less than 12 years of age
- Discourage off-label use not supported by compendia

Length of Authorization:

- Up to 12 months

Requires PA:

- Tricyclic antidepressants in children younger than the FDA-approved minimum age (new starts)
- Auto-PA approvals for:
  - Patients with a claim for an SSRI or TCA in the last 6 months
  - Prescriptions identified as being written by a mental health provider

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Indications of Tricyclic Antidepressants

Drug	FDA-Approved Indications	Maximum Dose	Minimum FDA-Approved Age
amitriptyline HCl	Depression	50 mg	12
amoxapine	Depression	400 mg	18
clomipramine HCl	Obsessive-compulsive disorder	200 mg	10
desipramine HCl	Depression	300 mg	18
doxepin HCl	Depression Anxiety	150 mg	12
imipramine HCl	Depression Nocturnal enuresis	75 mg	6
imipramine pamoate	Depression	200 mg	18
maprotiline HCl	Depression Bipolar depression Dysthymia Mixed anxiety and depressive disorder	225 mg	18
nortriptyline HCl	Depression	50 mg	12
protriptyline HCl	Depression	60 mg	12
trimipramine maleate	Depression	100 mg	12

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
3. Does the dose exceed the maximum FDA-approved dose (**Table 1**)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the request for an FDA-approved indication and age (**Table 1**)?	**Yes:** Approve for up to 6 months	**No:** Go to #5
5. Is the request for prophylactic treatment of headache or migraine and is the therapy prescribed in combination with cognitive behavioral therapy?	**Yes**: Approve for up to 6 months	**No:** Go to #6
6. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., mental health specialist, neurologist, etc.)?	**Yes**: Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 2/23 (KS), 2/21(SS); 11/19
Implementation: 2/1/2020