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Drug Class Update: Antidepressants

Date of Review: February 2021

Date of Last Review: July 2019
Dates of Literature Search: 04/01/2019 – 09/21/2020

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

Purpose for Class Update:
To evaluate new comparative evidence for antidepressant medications and to evaluate new Food and Drug Administration (FDA) indications for esketamine.

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 subgroups of patients based on demographics (e.g., age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one antidepressant is more effective or associated with fewer adverse events?

Conclusions:
- In children and adolescents, there is limited evidence directly comparing efficacy or safety of various antidepressants. Selective serotonin reuptake inhibitors (SSRIs), as a class may improve response and functional status in adolescents with major depressive disorder (MDD), but are associated with an increased risk of adverse events (low quality evidence).[1] Guidelines from National Institute for Health and Clinical Excellence (NICE) recommend fluoxetine as an initial treatment option in children with moderate to severe depression unresponsive to psychotherapy.[2] Recommendations are made against the use of paroxetine, venlafaxine, or tricyclic antidepressants (TCAs) in children and adolescents.[2]
- In patients with MDD and a previous treatment failure, there was evidence that augmentation of an antidepressant with cariprazine, quetiapine, or ziprasidone improves symptom severity (based on moderate to high quality evidence).[3] Use of augmentation therapy with ziprasidone or cariprazine was associated with increased rates of treatment discontinuation.[3] There was no difference in efficacy upon augmentation with olanzapine, buspirone, or mirtazapine.[3]
- Preventative use of bupropion XL in adults with a prior history of seasonal affective disorder improved the number of patients who experienced a depressive episode during winter months compared to placebo (15% vs. 27%; relative risk [RR] 0.56, 95% CI 0.44 to 0.72; moderate quality evidence).[4]
- In adults with MDD, use of antidepressants (fluoxetine or TCAs) and benzodiazepines compared to antidepressants alone improved depression severity with less than 4 weeks of treatment (standardized mean difference [SMD] -0.25; 95% CI -0.46 to 0.03; I^2=35%; n=598), with no difference in depression severity with longer follow-up (based on low quality evidence).[5]

- There is moderate quality evidence that use of SSRIs after stroke may improve depressive symptoms and risk for depression but have no impact on disability.[6]
- There is insufficient evidence for use of traditional antidepressants in patients who are pregnant or postpartum.[7]
- NICE guidelines for treatment of general anxiety disorder in adults recommend SSRIs as an initial treatment option.[8] If initial treatment is ineffective, an alternative SSRI or serotonin norepinephrine reuptake inhibitor (SNRI) is recommended.[8] In patients with panic disorder, antidepressants (including SSRIs, SNRIs or TCAs) are recommended if the disorder is long-standing or if the patient has not benefited from psychological interventions. If there is no benefit with initial treatment, an antidepressant from an alternative class should be considered.[8]
- Two randomized controlled trials (RCTs) evaluated use of esketamine in patients with MDD at high risk for suicide.[9,10] There is low quality evidence that esketamine does not decrease suicidality, but has a slight improvement in depression symptoms compared to placebo with a mean difference [MD] in the Montgomery-Asberg Depression Rating Scale (MADRS) of -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for each study.[9,10] A 2 point improvement on MADRS may be associated with a clinically significant improvement.[11] There is insufficient evidence for other outcomes including suicide attempts, hospitalizations, or hospital length-of-stay in patients with MDD and risk for suicide.

Recommendations:
- No PDL changes were made based on current clinical evidence.
- The PA for esketamine was edited for safety concerns.
- After costs reviewed in executive session, duloxetine DR capsules, bupropion HCL XL 24 hr tablets (Wellbutrin XL and generics), and desvenlafaxine succinate ER 24h tablets were made preferred on PDL. Amoxapine tablets were made voluntary non-preferred on PDL.

Summary of Prior Reviews and Current Policy:
- 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 and cost.
- Anti-depressants are designated preferred or part of the voluntary PDL. Previous recommendations are to base antidepressant treatment selection on patient characteristics and cost.
- Safety edits are currently implemented for tricyclic antidepressant use in children, esketamine which is indicated for treatment resistant depression, and brexanolone which is indicated for post-partum depression.

Background:
Historically antidepressant medications have been categorized based on mechanism and chemical structure into first-generation (TCAs and MAOIs) and second-generation antidepressants (SSRIs, SNRIs, and newer antidepressants). They are used for a wide variety of psychiatric conditions including depression, post-traumatic stress disorder (PTSD), bipolar disorder, obsessive compulsive disorder, and anxiety disorders.[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. For example in patients with PTSD, first-line recommendations from the Veterans Administration and Department of Defense 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] However, it's 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. Some of the most commonly used rating-scales and thresholds include the Montgomery-Asberg Depression Rating Scale (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. 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] Typically, a 50% improvement in symptom score from baseline is used to evaluate response to therapy.[11]

In Medicaid, antidepressants are carved out of coordinated care organizations and paid for by fee-for-service. In the second quarter of 2020, there were over 133,000 patients with claims for an antidepressant medication. The most commonly prescribed medications are available as generics and included sertraline (15%), trazodone (14%), fluoxetine (11%), escitalopram (9%), duloxetine (9%), bupropion XL (8%), and citalopram (7%).

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 2**, 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:

A recent AHRQ report evaluated pharmacologic and non-pharmacologic treatments for depressive disorders in children and adolescents.[1] For the majority of comparisons and outcomes, strength of evidence was graded as low or insufficient. Evidence was limited by high risk of bias for many included studies, small

sample sizes, lack of reporting for harms, and potential for publication bias. Many outcomes and comparisons were evaluated in only single studies leading to unknown consistency. Overall, trials were of short duration and had a wide variety of reported tools to assess symptoms and diagnose depression in adolescents. This summary will focus on review of the available comparative evidence of pharmacologic treatment options. There were 29 studies (28 RCT and one nonrandomized trial) which addressed comparative effectiveness of therapies.[1]

- SSRIs compared to placebo: Fluoxetine and escitalopram may have a small statistical improvement in symptoms for adolescents with MDD based on results from single RCTs. As a class, SSRIs may be associated with improved response (risk difference [RD] 72/1000; 95% CI 2 to 124) and functional status (SMD 0.16; 95% CI 0.03 to 0.29), but increased risk of serious adverse events (RD 20/1000; 95% CI 1 to 440) and withdrawal due to adverse events (RD 26/1000; 95% CI 6 to 45).[1] Paroxetine may be associated with increased risk of suicidal ideation and behavior in adolescents. There was insufficient data for other drugs, but authors excluded inpatients and populations without MDD.[1]
- Psychotherapy compared to pharmacotherapy: There was low quality evidence from one RCT (n=220) that fluoxetine improved clinician-reported depression symptom scores compared to cognitive behavioral therapy (CBT) in adolescents with MDD over 12 to 16 weeks (SMD 0.66; 95% CI 0.39 to 0.93; absolute mean difference in the Children's Depression Rating Scale revised (CDRS-R) of 5.76; 95% CI 3.46 to 8.06).[1] There was insufficient evidence for other comparisons or efficacy outcomes including patient-reported symptoms, function, response or remission. Psychotherapy was associated with fewer treatment-emergent psychiatric adverse events compared to pharmacotherapy in adolescents with MDD over 12 weeks (RR 0.08; 95% CI 0.01 to 0.62; RD 100 fewer out of 1000 events; CI 40 to 160 fewer cases; low quality evidence).[1] Evidence on harms for other types of depression, comparisons, or outcomes including suicide-related adverse events was insufficient. Upon subgroup analysis, CBT was inferior to fluoxetine in patients with lower family income, severe baseline depression symptoms or comorbid attention deficit hyperactivity disorder (ADHD).[1] Other patient characteristics had no effect on outcomes, however subgroup analysis is limited by small sample sizes.
- Psychotherapy plus pharmacotherapy compared to psychotherapy alone: There was low quality evidence that combination therapy with CBT and fluoxetine improved clinician-reported depression scores (MD CDRS-R -8.27; 95% CI -10.59 to -5.95), remission (RD 210/1000; 95% CI 96 to 324 more cases), and functional status (MD in the Children's Global Assessment Scale of 6.6, 95% CI 3.23 to 9.97) in adolescents with MDD compared to CBT alone.[1] Clinician-reported depression scores were also improved with combination CBT and imipramine in school-refusing adolescents with MDD and comorbid anxiety based on low strength of evidence (MD CDRS-R -11.1; 95% CI -17.68 to -4.52).[1] Evidence for other efficacy outcomes, harms, or in other populations was graded as insufficient.
- Combination psychotherapy plus pharmacotherapy compared to pharmacotherapy alone: There was insufficient evidence for outcomes of clinician-rated depression symptoms, response, recovery, relapse, and function over 8 to 28 weeks.[1] Patient-reported depressive symptoms were improved with bupropion (MD in the Beck Depression Inventory [BDI] of -5.2; 95% CI -9.31 to -1.09) or fluoxetine combined with CBT, but showed no benefit for fluoxetine, sertraline or unspecified SSRIs (SMD -0.14; 95% CI -0.36 to 0.03; n=450; I^2=0%) based on low quality evidence.[1] Remission was improved with fluoxetine combined with CBT in MDD only (RR 1.61; 95% CI 1.05 to 2.46; RD 140/1000; 95% CI 19 to 261 more cases; low strength of evidence), but evidence was insufficient for other types of depression disorders.[1] Similarly, there was insufficient evidence of harms upon comparison of combination therapy to pharmacotherapy alone. Combination treatment was significantly improved in subgroups with more mild to moderate symptoms at baseline, higher treatment expectations, or comorbid ADHD.[1]
- SSRI versus SNRIs: There was insufficient evidence from 2 studies comparing duloxetine and fluoxetine in adolescents with MDD over 10 weeks.[1] Similarly, there was insufficient evidence to support conclusions of benefit or harms upon comparison of paroxetine and imipramine or fluoxetine and desvenlafaxine in adolescents with MDD over 8 weeks.[1]
- Treatment resistant depression: There was insufficient evidence for comparative interventions for treatment-resistant depression.[1]

A recent Cochrane review evaluated therapy for treatment-resistant depression in adults.[3] Nine of the 10 included studies were conducted in the outpatient setting, and all were located in high-income countries (4 in the United States).[3] Treatment resistance for this review was broadly defined as patients without response to at least 4 weeks of an adequately-dosed antidepressant.[3] Only one study evaluated patients with previous failure of at least 2 antidepressant from different classes, and 2 studies excluded participants inadequate response to 3 or more antidepressants.[3] Included patients were primarily female and, on average, 42 to 50 years of age.[3] Identified studies evaluated augmentation of current antidepressant therapy with a second drug over 8 to 12 weeks (either mirtazapine, buspirone, or a second-generation antipsychotic).[3] Risk of bias was graded as either low or unclear based on lack of reported methods. About half of included studies had unclear risk for selection bias based on lack of reported methods for randomization or allocation concealment.[3] Attrition ranged from 14% to 41% without significant imbalances between groups.[3] Most studies used a last observation carried forward methodology to evaluate missing data.[3] Risk for selective reporting was rated as unclear or high for all except one study.[3] Results for primary efficacy and safety outcomes are summarized in **Table 1**. The most common reason for treatment discontinuation were inability to tolerate treatment (approximately 8% of all patients).[3]

Table 1. Antidepressant augmentation versus placebo in treatment-resistant depression[3]

Baseline therapy/ Duration	Augmenting agent	Outcome/Results	Quality of Evidence	Evidence Conclusion
SSRI/SNRI 1 RCT 12 weeks	mirtazapine	BDI-II (range 0 to 64): MD -1.7 (95% CI -4.03 to 0.63) Treatment discontinuation: RR 0.50 (95% CI 0.15 to 1.62) Quality of life (EQ-5D-5L): MD -0.01 (95% CI -0.06 to 0.04)	High High High	No difference between groups
SSRI 1 RCT 6 weeks	buspirone	MADRS: MD -0.3% from baseline (95% CI -9.48 to 8.88) Treatment discontinuation: RR 0.60 (95% CI 0.23 to 1.53)	Low	No difference between groups
Various antidepressants 1 RCT 8 weeks	cariprazine	MADRS: MD -1.5 (95% CI -2.74 to -0.25) Treatment discontinuation: RR 1.68 (95% CI 1.16 to 2.41); 81 per 1000 patients (95% CI 19 to 168) Response: RR 1.27 (95% CI 1.07 to 1.52); 103 per 1,000 (95% CI 27 to 199) Remission (MADRS ≤10): RR 1.07 (95% CI 0.86 to 1.33)	High Moderate Moderate Moderate	Statistical improvement in symptoms which did not achieve a minimum clinical difference vs. placebo; improvement in the proportion of patients with a response to treatment but not in remission. More patients discontinued treatment vs. placebo.
Fluoxetine 1 RCT 8 weeks	olanzapine	HAM-D: MD -7.9 (95% CI -16.76 to 0.96) MADRS: MD -12.4 (95% CI -22.44 to 2.36) Treatment discontinuation: RR 0.33 (95% CI 0.04 to 2.69)	Low Low Low	No difference between groups
Various antidepressants 3 RCTs	quetiapine	MADRS or HAM-D: SMD -0.32 (95% CI -0.46 to -0.18) Treatment discontinuation: RR 1.33 (95% CI 0.90 to 1.95) Response: RR 1.25 (95% CI 1.09 to 1.44); 110 per 1000 (95% CI 40 to 194) Remission MADRS score ≤8/HAM-D ≤ 7): RR 1.53 (95% CI 1.23 to 1.90); 123 per 1000 (95% CI 54 to 210) Quality of Life (Q-LES-Q-SF): MD 0.57 (95% CI -1.52 to 2.65)	High Moderate Moderate Moderate Moderate	Improved depression symptoms, patients with response and with remission, no difference in dropouts or quality of life

SSRI 2 RCTs 6 to 8 weeks	ziprasidone	HAM-D: MD -2.73 (95% CI -4.53 to -0.93) Treatment discontinuation: RR 1.60 (95% CI 1.01 to 2.55); 136 per 1,000 (95% CI 2 to 352) Response: RR 1.80 (95% CI 1.07 to 3.04); 145 more per 1,000 (95% CI 13 to 371) Remission (clinician-rated): OR 1.46 (95% CI 0.75 to 2.86)	Moderate Moderate Moderate Moderate	Improved depression symptoms and proportion of patients with a response (50% improvement), but remission did not achieve statistical significance. More patients discontinued treatment compared to placebo.

Abbreviations: BDI-II = Beck depression inventory II (range 0 to 63); CI = confidence interval; HAM-D = Hamilton Depression Rating Scale (range 0 to 52); MADRS = Montgomery Asberg depression rating scale (range 0 to 60); MD = mean difference; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

A Cochrane review evaluating preventative antidepressant treatment for seasonal affective disorder (SAD) in adults identified 3 RCTs (n=1100) which evaluated efficacy of bupropion XL compared to placebo.[4] All trials enrolled adults with a history of seasonal affective disorder and no depressive symptoms at the time of enrollment.[4] Participants were primarily female (70%), white (89%) and had an average of 13 prior episodes of SAD.[4] Compared to placebo, fewer patients treated with bupropion experienced a depressive episode during the winter season (15% vs. 27%; ARR 12%; RR 0.56, 95% CI 0.44 to 0.72; moderate quality evidence).[4] The overall rate of adverse events (85% vs. 83%; RR 1.02, 95% CI 0.97 to 1.08) and discontinuation due to adverse events (9% vs. 5%; RR 1.68, 95% CI 0.74 to 3.79) was similar between groups.[4] However, patients treated with bupropion had a statistically increased chance for headaches (34% vs. 27%; RR 1.26, 95% CI 1.02 to 1.56), insomnia (20% vs. 13%; RR 1.46, 95% CI 1.10 to 1.93), and nausea (13% vs. 8%; RR 1.63, 95% CI 1.12 to 2.38) based on low to moderate quality evidence.[4] Evidence was limited by high attrition rates in all studies, and risk for reporting bias.[4] All three included studies were funded by the manufacturer of bupropion XL.[4]

A 2019 Cochrane review evaluated the effect of pharmacological and psychological continuation and maintenance treatments for persistent depressive disorder (illness duration >2 years).[15] Ten studies (n=840) were included, 7 RCTs and 3 non-randomized controlled trials.[15] Treatment interventions included both continuation (16 to 26 weeks) and maintenance (52 to 104 weeks) of pharmacotherapy and psychotherapy.[15] Overall, there was insufficient evidence comparing pharmacotherapy or antidepressant therapy when used as monotherapy or in combination compared to either therapy alone.[15] Evidence was primarily limited by small sample sizes, clinical heterogeneity, and moderate or high risk of bias. Risk of bias for non-randomized studies included risk of selective reporting, and for RCTs, included lack of blinding for outcome assessment and study funding. Five studies compared antidepressant medication to placebo. Compared to placebo, antidepressants reduced risk of relapse (33.8% vs. 13.9%; RR 0.41; 95% CI 0.21 to 0.79; I^2=54%; n=383; moderate quality evidence), but there was no difference between groups upon exclusion of studies with a high risk of bias.[15] Similarly, patients treated with antidepressants had lower symptom severity compared to placebo (MD in HAM-D –4.79, 95% CI –8.49 to –1.09; RCTs = 3; n = 333; I^2 = 60%).[15] Treatment discontinuation due to other reasons was similar compared to placebo (23.0% vs. 25.5%, RR 0.90, 95% CI 0.39 to 2.11; RCTs =4; n = 386; I^2 = 64%, low quality evidence).[15]

A recently updated Cochrane review evaluated evidence of combination antidepressants and benzodiazepines compared to antidepressants alone in adults with MDD.[5] Trials in the review included patients with comorbid anxiety and depression. Trials which evaluated concurrent psychosocial therapies were excluded. Primary outcomes included depression severity and acceptability of treatment. Secondary outcomes included response (50% improvement in severity scores), remission (usually defined as 7 or lower on HRSD or 11 or lower on MADRS), anxiety severity, insomnia severity, and adverse events.[5] Trials were at least 4 weeks in duration and outcomes were evaluated over several periods less than 4 weeks, 5-12 weeks, and more than 12 weeks.[5] There were 10 RCTs included in the review which evaluated fluoxetine (n=2) or a TCA (n=8).[5] Only one trial assessed treatment longer than 12 weeks. All trials were published prior to 2002 and had either high or unclear risk of bias for all risk of bias assessments.[5] Attrition was very high in 4 studies (34 to 41% of patients discontinuing treatment).[5] There

was moderate quality evidence that depression severity was improved with combination treatment with less than 4 weeks of treatment (SMD -0.25; 95% CI -0.46 to -0.03; I^2=35%; n=598), with no difference in depression severity with longer follow-up (low quality evidence).[5] Similarly response (RR 1.34; 95% CI 1.13 to 1.58; I^2=0%; NNT 9; 95% CI 6 to 24) and remission (RR 1.39, 95% CI 1.03 to 1.90; I^2=2%) were improved with combination therapy compared to monotherapy at less than 4 weeks, but demonstrated no statistical difference between treatment groups with longer duration of therapy.[5] Acceptability of treatment evaluated by treatment discontinuation for any reason was no different with combination therapy compared to antidepressant monotherapy (RR 0.76; 95% CI 0.54 to 1.07; I^2=36%; moderate quality evidence).[5] Patients prescribed combination therapy were less likely to discontinue treatment due to adverse events compared to monotherapy (RR 0.54, 95% CI 0.32 to 0.90; 64 dropouts [95% CI 38 to 107] vs. 119 dropouts with monotherapy per 1000 patients; moderate quality evidence), but were more likely to experience at least one adverse event (RR 1.12, 95% CI 1.01 to 1.23; moderate quality evidence).[5]

A Cochrane review evaluated impact of SSRIs compared to placebo or usual care on recovery after stroke.[6] Sixty-three trials (n=9168) were identified which evaluated symptom improvement within 1 year of their stroke.[6] The most common drugs evaluated included fluoxetine, paroxetine, citalopram and escitalopram.[6] The primary pre-specified analysis included only trials which had a low risk of bias (3 RCTs, n=3249).[6] In these trials, participants were not required to have depression symptoms upon enrollment. Overall, upon completion of treatment with an SSRI (74 to 180 days), there was no improvement in disability, neurological deficit score, death, or number of seizures based on moderate to high quality evidence.[6] Compared to placebo, SSRIs were associated with an improvement in depression severity (SMD -0.11; 95% CI -0.19 to -0.04; I^2=69%; moderate quality evidence) and risk of depression at the end of treatment (13.4% vs. 17.2%; RR 0.78, 95% CI 0.66 to 0.92).[6] Gastrointestinal adverse events were more common with treatment compared to placebo or usual care (RR 2.19; 95% CI 1.00 to 4.76; 234 per 1000 patients; 95% CI 107 to 508; moderate quality evidence).[6] Sensitivity analyses were conducted which evaluated outcomes for all identified trials regardless of risk of bias score. Twenty-six trials had sufficient data for meta-analysis and demonstrated a significant improvement in disability score compared to placebo with significant heterogeneity between trials (SMD 0.23, 95% CI 0.18 to 0.29; I^2=92%).[6] However, authors noted that studies with higher risk of bias (particularly lack of blinding for outcome assessors) were more likely to report favorable outcomes from treatment. Overall, they conclude that SSRIs do not affect disability or independence after stroke, but reduce risk of future depression and are associated with an increased risk of adverse gastrointestinal events.[6]

A systematic review conducted for the US Preventative Services Task Force evaluated interventions to prevent depression during pregnancy and the postpartum period.[7] Trials were included if they were at least 6 weeks in duration and evaluated recurrence rates of depression in high-risk patients.[7] Only 2 small studies evaluating the use of nortriptyline (n=58) and sertraline (n=22) were identified in the literature search.[7] Trials had mixed results and evidence for use of antidepressants was rated as insufficient overall.[7]

After review, the following systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria)[16-24] and wrong study design of included trials (e.g., observational, evaluation of non-drug therapy).[25,26]

New Guidelines:

High Quality Guidelines:

A 2011 NICE guideline on general anxiety and panic disorder in adults was updated in July 2019.[8] General recommendations for anxiety disorder include the following:[8]

- In patients with general anxiety disorder and marked functional impairment or in patients whose symptoms have not improved with psychoeducation or individual self-help, either drug treatment or individual high-intensity psychotherapy is recommended. Treatment choice is based on patient preference as there is no evidence that either option is more beneficial.

- Recommended initial drug treatments include SSRIs. Recommendations are made to assess for cocaine use when prescribing SSRIs and to avoid concurrent use of multiple concurrent serotonergic agents. Concomitant use of cocaine and citalopram may increase risk of bleeding which may be life-threatening.
- If initial treatment is ineffective, offer an alternative SSRI or SNRI. Anxiolytic effect may Treatment choice should consider potential for discontinuation syndrome (especially with paroxetine and venlafaxine), side effect profile, drug interactions, risk of suicide or overdose (especially venlafaxine), and prior treatment experience. Combination therapy with psychotherapy and drug therapy may be considered with failure of either therapy alone.
- If the patient is unable to tolerate SSRIs or SNRIs, consider offering pregabalin with careful evaluation for risk of abuse or dependence.
- Recommendations are made against use of benzodiazepines, except as a short-term measure during crisis, or antipsychotics in primary care.
- Referral to a specialist is recommended in patients with risk of self-harm, significant comorbidities, self-neglect, or inadequate response to pharmacotherapy or an SSRI.
- In patients with harmful comorbid substance use, treatment of the substance use disorder may significantly improve anxiety symptoms and is generally recommended before treatment of the anxiety disorder.

For patients with panic disorder, recommendations remain mostly unchanged from initial guidance in 2004.[8]

- Antidepressants (including SSRIs, SNRIs or TCAs) are recommended if the disorder is long-standing or if the patient has not benefited from psychological interventions. If there is no benefit with initial treatment, an antidepressant from an alternative class should be considered.
- Recommendations are made to consider a SSRI as initial treatment and either imipramine or clomipramine may be considered as alternative options if there is no improvement after 12 weeks.
- Benzodiazepines, sedating antihistamines, or antipsychotics are not recommended for panic disorder.

In 2019, NICE guidelines for identification and management of depression in children and adolescents age 5 to 18 years were updated.[2] Pharmacotherapy is not recommended except in combination with concurrent psychotherapy and should include careful, frequent monitoring and assessment (e.g., weekly contact for the first 4 weeks of treatment).[2] The following recommendations are based on symptom severity and age:[2]

- In patients with mild depression, antidepressants are not recommended. Treatment options include watchful waiting or psychotherapy.
- In patients with moderate to severe depression, initial treatment recommendations include psychotherapy. In patients unresponsive to psychotherapy, fluoxetine may be added. Fluoxetine can be offered to patients 12 to 18 years of age following multidisciplinary review if the patient is unresponsive to psychotherapy after 4-6 sessions. Fluoxetine can be cautiously considered in patients 5 to 11 years of age though there is limited evidence of efficacy in this age group. Fluoxetine is the only antidepressant in which clinical trial evidence demonstrates benefits outweigh risks.
- Intensive psychotherapy is recommended with or without medication therapy in patients with depression unresponsive to combined psychotherapy and fluoxetine, recurrent depression, or psychotic depression. Options for second-line antidepressant therapy include sertraline and citalopram. These medications should only be considered when the following criteria have been met:
    - Informed consent regarding likely risks and benefits of therapy
    - Sufficiently severe symptoms to justify another medication trial (e.g., weight loss, suicidal behavior)
    - Clear evidence of failure for combined psychotherapy and fluoxetine (including assessment of adherence to therapy)
    - Reassessment of diagnosis and cause of depression (including comorbidities)
    - Consultation with a child and adolescent psychiatrist
- Recommendations are made against the use of paroxetine, venlafaxine, or TCAs in children and adolescents due to unfavorable risk benefit ratio. Both paroxetine and venlafaxine lack an FDA indication in children and may be associated with severe adverse events including suicidal thoughts and behaviors.

- For children or adolescents with psychotic depression, augmentation with an antipsychotic may be considered though the optimal dose and duration of therapy are unknown. There is limited data on use of antipsychotics in MDD for children, and choice of antipsychotic is based primarily on evidence in other conditions (e.g., psychosis, schizophrenia).
- Drug therapy should be continued for at least 6 months after remission (defined as absence of symptoms for at least 8 weeks) in people with a response to treatment.

New Formulations or Indications:

In July 2020, esketamine nasal spray received an expanded indication for depressive symptoms in adults with MDD and acute suicidal ideation or behavior. Esketamine was previously approved for treatment-resistant depression. Approval was based on 2 identical double-blind, 4-week, multicenter RCTs in adults.[10] These trials enrolled a total of 456 patients from the United States, Europe, Asia, South Africa, South America, and Canada.[9,10] Participants had a diagnosis of MDD, suicidal ideation within the 24 hours prior to randomization with need for hospitalization due to imminent suicide risk, and a MADRS score greater than 28 indicating at least moderate depression.[9,10] Patients received comprehensive standard of care treatment including an initial 5 to 14 day hospitalization in a psychiatric unit.[9,10] Esketamine, administered twice weekly, was initiated upon enrollment with standard antidepressant optimization during the first 2 weeks of each trial.[9,10] Pharmaceutic standards of care could include either antidepressant monotherapy or an antidepressant plus augmentation therapy (second antidepressant, atypical antipsychotic or mood stabilizer).[9] Patients with clinically significant comorbidities were excluded from the studies (e.g., bipolar disorder, OCD, personality disorder, moderate to severe substance use disorder, psychotic disorder, renal or liver insufficiency, uncontrolled hypertension, history of malignancy, or clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic or metabolic disease).[9,10] The primary endpoint was change in depressive symptom severity evaluated with the MADRS score from baseline to 24 hours.[9,10] The key secondary outcome was symptom severity using the Clinical Global Impression of Severity of Suicidality - Revised scale (CGI-SS-r; range 0 to 6) which is a one-item, clinician-rated assessment of suicide severity.[9,10]

Overall, 78-89% of patients receiving esketamine and 82-83 % of patients receiving placebo completed 4 weeks of treatment, and about 72% of patients in each study completed the 90 day follow-up.[9,10] Baseline mean MADRS score was 40-41 indicating severe depressive symptoms, clinician-rated suicidality based on CGI-SS-r was moderate to extremely suicidal for 90-91% of patients.[9,10] Over 60% of patients in each study had a prior suicide attempt. In the first study, 28% had a recent attempt in the past month.[9] Common antidepressant therapy included venlafaxine, escitalopram, duloxetine, quetiapine, mirtazapine, and sertraline.[9,10] About 67-75% of patients received concomitant benzodiazepines, though use was not permitted within 8 hours of esketamine dosing.[9,10] Most baseline characteristics were balanced between groups. However, in the first study more males were randomized to esketamine compared to placebo (42% vs. 34%) and a slightly higher proportion of patients randomized to esketamine were prescribed antidepressant plus augmentation therapy compared to placebo (47% vs. 42%).[9] In the second study, the proportion of patients with a recent suicide attempt within the past 28 days at baseline differed between groups with more patients in the esketamine group with a recent suicide (31.6%) compared to placebo (21.2%).[10] A prior suicide attempt is a known risk factor for subsequent attempts which may indicate that patients randomized to treatment had more severe suicidality than those given placebo.

There was a substantial difference in MADRS from baseline to 24 hours for both esketamine and placebo groups. Patients given esketamine had mean improvements in MADRS of 16.4 (SD 11.95) and 15.7 (SD 11.56) points while patients randomized to placebo improved by 12.8 (SD 10.73) and 12.4 (SD 10.43) points in each study.[9,10] The mean difference from placebo at 24 hours was -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for Study 1 and 2, respectively. A 2-point change in MADRS may correspond with clinically meaningful improvements in symptoms. The difference from placebo was maintained at 4 weeks. Both placebo and esketamine groups had a decrease in acute suicidality (median 1 point improvement on CGI-SS-r from baseline to 24 hours), and there was no statistical difference compared to placebo indicating that hospitalization and standard therapy had a greater impact on acute suicidality.[9,10]

In general subgroup analyses were comparable to the overall treatment effect with little variability between groups. The largest variability in MADRS score was observed based on baseline MADRS scores greater or less than the median score and in patients with or without a prior suicide attempt with a trend toward improved scores in patients with higher MADRS values or patients with a prior suicide attempt.[9] Subgroup analyses showed little difference between groups for the second study.[10]

The overall rate of suicide attempts during and after the study was low compared to current epidemiological data which authors attribute to the comprehensive clinical care and frequent follow-up required as part of the study. Nineteen percent (n=21) and 11% (n=13) of patients in studies 1 and 2, respectively, had a dose reduction due to intolerance.[9,10] In total, suicide-related adverse events (including suicidal ideation) occurred in 12 patients in the 4-week treatment period and were generally balanced between groups.[9,10] Eight suicide attempts occurred during therapy (4 in each group) on treatment.[9,10] During the 90 day follow-up period while on standard therapy, 10 patients had suicide attempts (7 with prior esketamine and 3 with prior placebo) during the follow-up period.[9,10] One patient, previously randomized to esketamine, completed suicide.[9] In most cases, patients with a suicide attempt after enrollment also had an attempt prior to enrollment.[9,10]

There is limited applicability to outpatient treatment, particularly during initiation of treatment in patients with suicidal ideation. The mean length of hospital stay in the second study was 21.6 days (SD 20.6) for patients receiving esketamine and 19.1 days (SD 19.6) for placebo indicating that the majority of the trial occurred during an inpatient stay.[10] Hospital duration was not reported in the first study. Both groups had a decrease in acute suicidality with no difference from placebo indicating that standard therapy, including hospitalization and greater clinical follow-up, likely continues to be the most effective treatment for suicidal symptoms. Psychotherapy was permitted, but less than 5% of patients received psychotherapy during the 4-week treatment phase.[10]

There is no evidence available from these studies which suggests that esketamine decreases suicidality, suicide attempts, hospitalizations, or hospital length-of-stay in patients with MDD and risk for suicide.

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts[27]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Escitalopram Levomilnacipran Paroxetine Vilazodone	Lexapro Fetzima Paxil CR Viibryd	8/2020 10/2019 9/2019 1/2020	Warnings/Precautions Boxed Warning	Clarification of warnings regarding risk of suicidal thoughts and behaviors in adolescents and young adults. Language was updated to include information on a pooled analyses of placebo-controlled trials which included approximately 77,000 adult patients and 4,500 pediatric patients. Patients 24 years of age and younger had greater risk of suicidal thoughts and behaviors compared to placebo. Close monitoring is recommended.
Escitalopram	Lexapro	8/2020	Warnings/Precautions	Use of escitalopram can cause activation of mania or hypomania. Language in the labeling was updated to recommend screening for personal or family history prior to use.

Nortriptyline	Pamelor	4/2019	Warnings/Precautions	Post-marking reports indicate a use of nortriptyline may unmask Brugada Syndrome, a disorder characterized by syncope, abnormal electrocardiographic (ECG) findings, and a risk of sudden death. Use is not recommended in patients with a history of Brugada Syndrome.
Clomipramine	Anafranil	5/2019	Warnings/Precautions	Clomipramine therapy has been associated with hyponatremia primarily as a result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Patients who are elderly or volume-depleted may be at greater risk for this adverse event. Monitoring is recommended.

Randomized Controlled Trials:

A total of 89 citations were manually reviewed from the initial literature search. After further review, all individual trials were excluded because of wrong study design (eg, observational or post-hoc analysis)[28-33] or comparator (eg, no control or placebo-controlled).[34-40]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
amitriptyline HCl	AMITRIPTYLINE HCL	TABLET	PO	Y
amitriptyline HCl	ELAVIL	TABLET	PO	Y
bupropion HCl	BUPROPION HCL SR	TAB SR 12H	PO	Y
bupropion HCl	WELLBUTRIN SR	TAB SR 12H	PO	Y
bupropion HCl	BUPROPION HCL	TABLET	PO	Y
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	PO	Y
citalopram hydrobromide	CELEXA	TABLET	PO	Y
citalopram hydrobromide	CITALOPRAM HBR	TABLET	PO	Y
desipramine HCl	DESIPRAMINE HCL	TABLET	PO	Y
desipramine HCl	NORPRAMIN	TABLET	PO	Y
doxepin HCl	DOXEPIN HCL	CAPSULE	PO	Y
doxepin HCl	DOXEPIN HCL	ORAL CONC	PO	Y
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	PO	Y
escitalopram oxalate	LEXAPRO	TABLET	PO	Y
fluoxetine HCl	FLUOXETINE HCL	CAPSULE	PO	Y
fluoxetine HCl	PROZAC	CAPSULE	PO	Y
fluoxetine HCl	FLUOXETINE HCL	SOLUTION	PO	Y
fluoxetine HCl	FLUOXETINE HCL	TABLET	PO	Y
fluoxetine HCl	SARAFEM	TABLET	PO	Y
fluvoxamine maleate	FLUVOXAMINE MALEATE	TABLET	PO	Y
imipramine HCl	IMIPRAMINE HCL	TABLET	PO	Y
imipramine HCl	TOFRANIL	TABLET	PO	Y
maprotiline HCl	MAPROTILINE HCL	TABLET	PO	Y
mirtazapine	MIRTAZAPINE	TAB RAPDIS	PO	Y
mirtazapine	REMERON	TAB RAPDIS	PO	Y
mirtazapine	MIRTAZAPINE	TABLET	PO	Y
mirtazapine	REMERON	TABLET	PO	Y
nortriptyline HCl	NORTRIPTYLINE HCL	CAPSULE	PO	Y
nortriptyline HCl	PAMELOR	CAPSULE	PO	Y
nortriptyline HCl	NORTRIPTYLINE HCL	SOLUTION	PO	Y
paroxetine HCl	PAROXETINE HCL	TABLET	PO	Y
paroxetine HCl	PAXIL	TABLET	PO	Y
protriptyline HCl	PROTRIPTYLINE HCL	TABLET	PO	Y
sertraline HCl	SERTRALINE HCL	ORAL CONC	PO	Y
sertraline HCl	ZOLOFT	ORAL CONC	PO	Y
sertraline HCl	SERTRALINE HCL	TABLET	PO	Y
sertraline HCl	ZOLOFT	TABLET	PO	Y
trimipramine maleate	SURMONTIL	CAPSULE	PO	Y

trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	PO	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	PO	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	PO	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	PO	Y
bupropion HBr	APLENZIN	TAB ER 24H	PO	V
bupropion HCl	BUPROPION XL	TAB ER 24H	PO	V
bupropion HCl	FORFIVO XL	TAB ER 24H	PO	V
bupropion HCl	WELLBUTRIN XL	TAB ER 24H	PO	V
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	PO	V
clomipramine HCl	ANAFRANIL	CAPSULE	PO	V
clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	PO	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	PO	V
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	PO	V
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	PO	V
duloxetine HCl	DRIZALMA SPRINKLE	CAP DR SPR	PO	V
duloxetine HCl	CYMBALTA	CAPSULE DR	PO	V
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	PO	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	PO	V
esketamine HCl	SPRAVATO	SPRAY	NS	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	PO	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	PO	V
imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	PO	V
isocarboxazid	MARPLAN	TABLET	PO	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	PO	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	PO	V
nefazodone HCl	NEFAZODONE HCL	TABLET	PO	V
paroxetine HCl	PAXIL	ORAL SUSP	PO	V
paroxetine HCl	PAROXETINE CR	TAB ER 24H	PO	V
paroxetine HCl	PAROXETINE ER	TAB ER 24H	PO	V
paroxetine HCl	PAXIL CR	TAB ER 24H	PO	V
paroxetine mesylate	PEXEVA	TABLET	PO	V
phenelzine sulfate	NARDIL	TABLET	PO	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	PO	V
selegiline	EMSAM	PATCH TD24	TD	V
tranylcypromine sulfate	TRANYLCYPROMINE SULFATE	TABLET	PO	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	PO	V
vilazodone HCl	VIIBRYD	TAB DS PK	PO	V
vilazodone HCl	VIIBRYD	TABLET	PO	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	PO	V
amoxapine	AMOXAPINE	TABLET	PO	

brexanolone	ZULRESSO	VIAL	IV
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	PO
olanzapine/fluoxetine HCl	SYMBYAX	CAPSULE	PO
trazodone HCl	TRAZODONE HCL	TABLET	PO

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to September 18, 2020

1	brexanolone.mp.	63
2	esketamine.mp.	204
3	escitalopram.mp.	2570
4	nefazodone.mp.	772
5	exp Antidepressive Agents, Second-Generation/	66705
6	exp Antidepressive Agents, Tricyclic/	31134
7	exp desvenlafaxine succinate/ or exp duloxetine hydrochloride/ or exp isocarboxazid/ or exp levomilnacipran/ or exp mirtazapine/ or exp phenelzine/ or exp selegiline/ or exp sertraline/ or exp tranylcypromine/ or exp vilazodone hydrochloride/ or exp vortioxetine/	11928
8	exp Depression/	120224
9	exp Depression, Postpartum/	5611
10	exp Suicide/	63293
11	exp Anxiety Disorders/	79634
12	exp Anxiety/	86039
13	exp Stress Disorders, Post-Traumatic/	32979
14	8 or 9 or 10 or 11 or 12 or 13	330834
15	1 or 2 or 3 or 4 or 5 or 6 or 7	102538
16	14 and 15	14061
17	limit 16 to (english language and humans and yr="2019 -Current")	268
18	limit 17 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	89

Appendix 3: 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 4: Prior Authorization Criteria

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.
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.

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.	
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 a history of substance abuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7

Approval Criteria		
7. Does the patient have treatment resistant depression (failure of two antidepressants which were each given for at least 6-8 weeks at FDA approved doses)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
8. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
9. Does the patient have documentation of any of the following: • Aneurysmal vascular disease or arterial venous malformation OR • Intracerebral hemorrhage OR • Pregnancy OR • Uncontrolled hypertension	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for induction phase only: 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)

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 #3
2. 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.

Renewal Criteria		
3. 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 (84 mg twice weekly for a maximum of 28 days)

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

Approval Criteria		
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: 2/21(SS); 7/19 (KS)
Implementation: 8/19/19