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Drug Class Update: Antidepressants

Date of Review: February 2026

Date of Last Review: June 2024 (antidepressants)
June 2025 (esketamine)
January 2019 (fibromyalgia)
Dates of Literature Search: 04/01/2024 - 11/24/2025

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

Purpose for Class Update:
The purpose of this update is to evaluate new literature on antidepressants since the last review and to develop evidence-based utilization management for drugs to treat current unfunded conditions (such as fibromyalgia). New evidence for generalized anxiety disorder (GAD), chronic pain, fibromyalgia and suicide prevention will be included as antidepressants, and related therapies, are used for these indications.

Plain Language Summary:
- This review looked at new research on medicines used to treat depression and other conditions. There are five main classes of antidepressants. They are called selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants.
- Antidepressants are used to help with anxiety, chronic pain, insomnia, migraine headache, fibromyalgia, bipolar disorder and obsessive-compulsive disorder (OCD).
- SNRIs may help with low back pain and TCAs help people stay active when they have low back pain.
- Some antidepressants, including SNRIs, SSRIs and vilazodone, can help improve symptoms of anxiety.
- SSRIs reduce symptoms of OCD.
- Two guidelines recommend amitriptyline to help prevent episodic migraine headache.
- One guideline recommends the combination of fluoxetine and olanzapine to treat bipolar disorder.
- One guideline recommends duloxetine and amitriptyline as treatment options to reduce pain caused by fibromyalgia.
- All antidepressants have side effects such as dry mouth, tiredness, and dizziness. Each person can respond differently to an antidepressant.
- Providers can prescribe any antidepressant they believe is best for the patient. Some antidepressants require approval, called prior authorization, due to safety concerns. The Drug Use Research and Management group does not recommend any policy changes based on this review.

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Research Questions:

1. Is there new comparative evidence related to efficacy of antidepressants for important outcomes (e.g., symptom reduction and remission rates)?
2. Is there new comparative evidence for harms for antidepressants when used to treat depression?
3. Are there specific populations based on demographic characteristics, such as age, race, ethnicity, pregnancy status, or people with certain comorbidities, for which certain antidepressants are better tolerated or more effective than other antidepressants in improving symptoms and remission of depression?
4. What is the comparative evidence for efficacy and harms for antidepressants when used to treat conditions other than depression (e.g., fibromyalgia, chronic pain, and anxiety?

Conclusions:

- This review identified three high-quality systematic reviews, six high-quality clinical practice guidelines, one randomized controlled trial (RCT), and five new safety alerts issued by the U.S. Food and Drug Administration (FDA).
- One systematic review found moderate quality evidence that serotonin norepinephrine reuptake inhibitors (SNRIs) may have a small effect at reducing low back pain intensity but not disability.[1] There is low quality evidence that they are associated with adverse events in this population. There are well documented adverse events with antidepressants when used for other indications. Tricyclic antidepressants (TCAs) may reduce disability related to low back pain but have no effect on intensity of pain based on moderate quality evidence.[1] The evidence for the efficacy of antidepressants in spine-related leg pain is unclear.[1]
- A review by the Agency for Healthcare Research and Quality (AHRQ) found that treatment with SSRIs are more effective than placebo for reduction in obsessive compulsive disorder (OCD) symptoms and global severity outcomes based on high quality evidence.[2]
- An updated guideline from the National Institute of Health and Care Excellence (NICE) recommends amitriptyline as an option for migraine prophylaxis.[3]
- American College of Physicians (ACP) recommends antidepressants for the prevention of episodic migraine headaches.[4] Venlafaxine or amitriptyline received a conditional recommendation supported by low-quality evidence.[4]
- NICE recommends fluoxetine, in combination with olanzapine, as an option to manage bipolar depression in adults.[5]
- The Scottish Intercollegiate Guidelines Network (SIGN) recommends amitriptyline and duloxetine for patients with fibromyalgia (high quality evidence; Grade A recommendation).[6] Milnacipran has similar evidence of effectiveness for the treatment of fibromyalgia but was not included in the guideline because it is not available in the UK .[6]
- The Oregon Health Authority (OHA) Mental Health Clinical Advisory Group (MHCAG) recommends initial treatment of major depressive disorder (MDD) with a selective serotonin reuptake inhibitors (SSRI), SNRI, bupropion or mirtazapine.[7] For treatment resistant depression (TRD), augmentation with a non-SSRI/SNRI antidepressant, bupropion sustained release (SR) or extended release (ER) and mirtazapine are recommended.[7] Esketamine nasal spray was also recommended for TRD as augmentation therapy.[7]
- The MHCAG recommends treatment with escitalopram, sertraline, duloxetine or venlafaxine ER for GAD.[8] Buspirone is recommended as second-line adjunct treatment option.[8]
- For the treatment of chronic insomnia in adults, specific antidepressants have demonstrated efficacy. The MHCAG recommends doxepin and trazodone as antidepressants as having evidence for use.[9]
- Antidepressants are used in the treatment of post-traumatic stress disorder (PTSD). Paroxetine, sertraline and venlafaxine ER have moderate quality evidence to support their use in PTSD and are recommended by MHCAG.[10]
- The MHCAG recommended removal of the 34-day limit on non-controlled mental health drugs and controlled IV-V mental health drugs in March of 2025.[11] This change will allow pharmacies to bill for a 100-day supply of preferred medications as currently authorized for other chronic medications.

- There is insufficient evidence on one specific antidepressant over another for specific subpopulations.

Recommendations:
- No preferred drug list (PDL) changes are recommended based on a review of the evidence.
- Update PA criteria for allow for coverage of evidence supported indications for milnacipran.
- Add at least one formulation of lithium and buspirone to the PDL to facilitate access to a 100-day supply.
- After evaluation of costs in executive session, venlafaxine tablets ER 24; lithium carbonate capsules, tablets, and tablet ER; and buspirone tablets were made preferred.

Summary of Prior Reviews and Current Policy:
- Antidepressants are designated as preferred or part of the voluntary PDL. Specific antidepressants have criteria to promote safe and medically appropriate use. Because there is limited data to demonstrate clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants, previous recommendations from the Pharmacy and Therapeutics (P&T) Committee are to base antidepressant treatment selection on individual patient preference, past response to antidepressants, risk for specific harms, and cost.
- Beginning in October 2025, the Oregon Health Authority fee-for-service program began allowing enrolled pharmacies to bill preferred mental health drugs for up to a 100-day supply.
- The antidepressant class was last reviewed by the Committee in June 2024. Gepirone was maintained as voluntary non-preferred on the mental health PDL and the TCA PA criteria were updated as recommended by the MHCAG.
- Tazodone, brexanolone (no longer available) and olanzapine/fluoxetine were assigned voluntary non-preferred status after cost review in executive session.
- Esketamine was last reviewed in June 2025 and the PA criteria were updated to allow for esketamine monotherapy for people with TRD.

Background:
Antidepressant medications are categorized based on mechanism of action and chemical structure. They are classified as first-generation (TCAs and monoamine oxidase inhibitors [MAOIs]) and second-generation antidepressants (SSRIs and SNRIs, and newer antidepressants). They are used for a wide variety of psychiatric and medical conditions including depression, PTSD, bipolar disorder, obsessive compulsive disorder, and anxiety disorders. Specific antidepressants have FDA-approved indications for other conditions including fibromyalgia (which is currently not a funded diagnosis on the Oregon Health Plan), diabetic peripheral neuropathy, chronic pain, post-partum depression (PPD), PMDD, migraine, bulimia, and smoking cessation.[12] Evidence supported indications and recommended therapies are presented in **Table 1.**

Table 1. Recommendations for Antidepressant Use

Antidepressant Indication	Antidepressants with Evidence for Use	Place in Therapy
Bipolar	• Olanzapine-fluoxetine • Adding SSRI or bupropion to another mood stabilizer medication	- Lamotrigine, lithium, and quetiapine are recommended first line[13] - Avoid antidepressant monotherapy[13]
Bulimia	• Fluoxetine • Sertraline	- Fluoxetine is recommended first line[14]

	• Escitalopram • Fluvoxamine • Desipramine • Nortriptyline • Trazodone	- Paroxetine and citalopram are not recommended due to weight gain or cardiac effects[14] - Bupropion should be avoided due to risk of seizures in this population[14]
Chronic insomnia disorder	• Doxepin • Trazodone	- Non-pharmacologic therapies (i.e., sleep hygiene and psychotherapy) are recommended first line[9] - Short term (up to 4 weeks) is recommended if an antidepressant is used[9] - Mirtazapine and amitriptyline lack evidence or are associated with adverse events and are not recommended[9] - Doxepin, trazodone, lemborexant, and suvorexant recommended for sleep maintenance[9] - Zolpidem, eszopiclone, temazepam recommended for sleep onset and maintenance[9] - Triazolam recommended for sleep onset[9]
Chronic Pain	• Duloxetine	- Milnacipran may reduce pain but supported by less evidence[6] - Other antidepressants are supported by low quality evidence for effectiveness[6]
Fibromyalgia	• Duloxetine • Milnacipran • Amitriptyline • Pregabalin • Cyclobenzaprine	- Duloxetine, amitriptyline, milnacipran, cyclobenzaprine, pregabalin and gabapentin are recommended first-line drug therapy options[15] - Non-pharmacologic therapy should be tried before starting medications[15]
Generalized Anxiety Disorder	• Escitalopram • Sertraline • Duloxetine • Venlafaxine ER • Imipramine • Bupropion ER	- escitalopram, sertraline, duloxetine or venlafaxine ER are recommended as first-line[8] - imipramine has evidence of efficacy but is associated with side effects and toxicity[8]

		- Antidepressants recommended over buspirone due to slow onset and frequent daily dosing[8]
Major depressive disorder	• All except for milnacipran	- Initial treatment with SSRI, SNRI, bupropion or mirtazapine[7] - Zuranolone is the only antidepressant approved for PPD[7] - Bupropion SR or ER, mirtazapine and esketamine are recommended as antidepressant augmentation treatment options for those with TRD (failure of 2 or more antidepressants given at therapeutic doses[7]
Migraine	• Amitriptyline • Venlafaxine • Fluoxetine	- Amitriptyline and venlafaxine have the most evidence for use for migraine prevention[4]
Obsessive compulsive disorder	• Fluoxetine • Fluvoxamine • Paroxetine • Sertraline • clomipramine	- SSRIs are recommended first line.[16] - Psychotherapy is also recommended
Neuropathic pain	• Duloxetine • Venlafaxine • Amitriptyline • Nortriptyline • Desipramine	- Duloxetine, venlafaxine and amitriptyline are recommended as the first line antidepressant treatment choices[17]
Post partum depression	• Sertraline • Fluoxetine • Venlafaxine • Zuranolone	- Psychotherapy is also recommended[18]
Post-traumatic Stress Disorder (PTSD)	• Paroxetine • Sertraline • Venlafaxine XR	- Psychotherapy is recommended first line - Paroxetine, sertraline, and venlafaxine XR recommended for the treatment of PTSD[10]
Premenstrual Dysphoric Disorder	• Sertraline • Citalopram • Escitalopram	- Paroxetine is associated with weight gain and not recommended[19]

	• Fluoxetine • Venlafaxine	
Smoking Cessation	• Bupropion SR	- Treatment duration of 3 month is usually recommended[20]

Abbreviations: PPD – post-partum depression; SNRI -serotonin norepinephrine reuptake inhibitor; SSRI – selective serotonin reuptake inhibitor; TRD – treatment resistant depression; XR – extended-release.

All antidepressants have an FDA boxed warning for suicide risk in young adults and can be associated with 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.[21]

Goals of treatment for depression typically include symptom and function improvement, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients living with depression. Scales vary depending on the condition. Some of the most commonly used rating scales 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.[12] The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52) with scores of 10-13 indicating mild depression, 14-17 indicating mild to moderate depression and 17 and greater indicating moderate to severe depression.[12] The FDA has stated that this tool is valuable in the study of depressive symptoms but may be associated with a higher representation of evaluation of somatic symptoms (e.g., insomnia and somatic anxiety) compared to other tools.[22] Remission is defined as the person being free from depressive symptoms for several months after two or more depressive episodes, and response to therapy is typically defined as a 50% improvement in symptom score from baseline.[12] A 2-point improvement on the MADRS may be associated with a minimum clinically important improvement and HAM-D scores of 3 to 7 points may be clinically significant.[12]

In patients with GAD the Hamilton Anxiety Rating Scale (HAM-A) is used to assess efficacy. The HAM-A is a 14 item scale which rates symptoms on a 5-point scale from 0 to 4 with total scores ranging from 0-56.[23] Anxiety rating are minimal (0-7), mild (8-14), mild to moderate (15-24), moderate to severe (25-30), and severe to very severe (31-56).[23]

In Oregon, mental health drug classes, including antidepressants, are carved out from the coordinated care organizations (CCOs) and paid for by FFS. Non-preferred products do not automatically require prior authorization, but safety criteria are in place for esketamine, zuranolone and TCAs in children. antidepressant medication claims for OHP fee-for-service (FFS) members. There were over 400,000 antidepressant claims in quarter 2 of 2025. Milnacipran requires prior authorization to ensure that it is prescribed for an OHP-funded diagnosis in adults with evidence supporting it use in that condition.

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, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) 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:

Cochrane – Antidepressants for Low Back Pain and Spine-related Leg Pain

A 2024 Cochrane review evaluated treatments used for low back pain and spine-related leg pain in participants that were 18 years and older.[1] Type of pain included non-specific low back pain or spine-related pain of any duration. Patients with low back pain because of spinal fracture, inflammatory disease, aortic dissection, malignancy or infection were excluded. The main outcomes studied were pain intensity and disability, measured during short-term follow-up between 4 weeks to 14 weeks, and adverse events.[1] Twenty-six randomized trials, all of which were placebo-controlled, were included. Studies of non-specific low back pain accounted for 18 studies and 7 studies evaluated spine-related leg pain.[1] One study included patients with either condition. The mean duration of pain was 18 months to 20 years.[1] Participant's ages ranged from 27-59 years. Antidepressants studied were SNRIs (8 studies of duloxetine and milnacipran), SSRIs (2 studies of paroxetine), TCAs (14 studies of amitriptyline, clomipramine, desipramine, imipramine and nortriptyline), and 2 studies of other antidepressants (i.e., bupropion and trazodone).[1]

The results are presented in **Table 2** for studies evaluating non-specific low back pain and **Table 3** for studies of spine-related leg pain. Other antidepressants were not studied for the outcome of disability in non-specific low back pain. There were no studies of SSRIs or other antidepressants that studied spine-related leg pain. One of the main limitations was high attrition bias in 69% of the studies.[1] This may bias the results by creating differences in the participant groups leading to underestimation or overestimation of antidepressant effects for low back pain and spine-related pain.

Table 2. Non-Specific Low Back Pain[1]

Outcome	Result	Certainty of Evidence	Interpretation
SNRIs - duloxetine and milnacipran (4 studies)			
Pain Intensity†	MD -5.25; 95% CI, -7.17 to -3.34	Moderate	Likely a small benefit
Disability‡	MD -0.91; 95% CI, -1.30 to -0.51	Moderate	Likely a trivial effect
SSRIs – paroxetine (3 studies for pain; 1 for disability)			
Pain Intensity†	MD 1.20; 95% CI, -4.90 to 7.30	Low	Little to no effect
Disability*	MD -2.20; 95% CI, -8.11 to 3.71	Low	Little to no effect
TCAs – amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline (4 studies)			
Pain Intensity	MD -2.00; 95% CI, -7.25 to 3.24	Moderate	Little to no effect
Disability‡	MD -1.76; 95% CI, -2.70 to -0.82	Moderate	Small effect
Other Antidepressants – bupropion (1 study)			
Pain intensity	MD -5.40; 95% CI, -23.08 to 12.28	Very low	Little to no effect

Key: *Disability scale of 0-100 scale; † Pain scale of 0-100; ‡ Disability scale of 0-24.

Abbreviations: CI = confidence interval; MD = mean difference; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

Table 3. Spine-Related Leg Pain[1]

Outcome	Result	Certainty of Evidence	Interpretation
SNRI - Milnacipran (1 study)			
Pain Intensity	MD -46.10; 95% CI, -89.29 to -2.91	Very low	Evidence is uncertain
Disability*	MD -4.40; 95% CI, -20.25 to 11.45	Very low	Evidence is uncertain
TCA – amitriptyline (1 study)			
Pain Intensity†	MD -23.00; 95% CI, -32.12 to -13.88	Low	May have a large effect
Disability*	MD -13.00; 95% CI, -19.42 to -6.58	Moderate	May have a moderate effect

Key: *Disability scale of 0-100; † Pain scale of 0-100.
Abbreviations: CI = confidence interval; MD = mean difference; SNRIs = serotonin norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants.

When evaluating harms data, all the evidence was considered low or very low quality except for the SNRIs. There is limited evidence for antidepressant use for these indications, which influenced the evidence rating. SNRIs probably increase the risk of adverse events (relative risk [RR] 1.17; 95% CI, 1.07 to 1.27) with short-term use over 4 to 14 weeks based on moderate quality evidence.[1] Adverse events for TCAs and SSRIs were not statistically different than placebo in short term RCTs, lasting 4-14 weeks, but the data is unclear and estimates we inprecise.[1] There were no data on the adverse events of other antidepressants.

Cochrane – Antidepressants versus Placebo for Generalized Anxiety Disorder

A 2025 Cochrane review evaluated the safety and efficacy of antidepressants for treatment of GAD in adults.[24] Thirty-seven placebo-controlled RCTs (n=12,226) were included. All participants had a diagnosis of moderate to severe GAD. Settings included inpatient and outpatient populations with treatment lasting from four to 28 weeks.[24] Drugs studied were duloxetine, escitalopram, imipramine, paroxetine, sertraline, venlafaxine, vilazodone and vortioxetine.[24] Participants with severe medical comorbidities were excluded. The main outcomes studied were change in HAM-A rating and discontinuations due to adverse effect or lack of efficacy.

Results are presented in **Table 4**. There were four categories of comparison: all antidepressants, SSRIs, SNRIs and 'other' antidepressants (e.g., vilazodone).[24] Among the different classes of antidepressants, all medication classes are more effective than placebo in a reduction of at least 50% on the HAM-A (i.e., treatment response). For the comparisons of all antidepressants to placebo the treatment response was statistically and clinically significant with a reported number needed-to-treat [NNT] of 7.[24]

Table 4. Antidepressants Compared to Placebo[24]

Outcome	Result	Certainty of Evidence	Interpretation
All Antidepressants			
Treatment Response* (follow-up 6-24 weeks)	RR 1.41; 95% CI, 1.29 to 1.55	High	Antidepressants improved symptoms more than placebo

Total number of dropouts (follow-up 4-28 weeks)	RR 1.03 ; 95% CI, 0.93 to 1.14	High	There was no difference between groups
Dropouts due to lack of efficacy (follow-up 6-28 weeks)	RR 0.41; 95% CI 0.33 to 0.50	High	Treatment with an antidepressant decreased the risk of dropping out of the study due to lack of efficacy
Dropouts due to adverse events (follow-up 6-28 weeks)	RR 2.18; 95% CI, 1.81 to 2.61	High	Antidepressants were more likely to cause discontinuations due to adverse events compared to placebo
SSRIs			
Treatment Response* (follow-up 8-12 weeks)	RR 1.51; 95% CI, 1.20 to 1.90	High	Treatment with antidepressants improved symptoms more than placebo
Total number of dropouts (follow-up of 4-12 weeks)	RR 1.06; 95% CI, 0.95 to 1.19	High	No difference between groups
Dropouts due to lack of efficacy (follow-up 8-12 weeks)	RR 0.55; 95% CI, 0.38 to 0.79)	High	Treatment with an SSRI decreased the risk of dropping out of the study due to lack of efficacy
Dropouts due to adverse events (follow-up 8-12 weeks)	RR 1.98; 95% CI, 1.51 to 2.61	High	SSRIs were more likely to cause discontinuations due to adverse events compared to placebo
SNRIs			
Treatment Response* (follow-up 8-24 weeks)	RR 1.34; 95% CI, 1.21 to 1.47	High	Treatment with SNRIs improved symptoms more than placebo
Total number of dropouts (follow-up of 8-28 weeks)	RR 1.03; 95% CI, 0.87 to 1.21	High	No difference between groups
Dropouts due to lack of efficacy (follow-up 8-28 weeks)	RR 0.33; 95% CI, 0.25 to 0.43	High	Treatment with an SNRIs decreased the risk of dropping out of the study due to lack of efficacy
Dropouts due to adverse events (follow-up 8-28 weeks)	RR 2.42; 95% CI, 1.81 to 3.22	High	SNRIs were more likely to cause discontinuations due to adverse events compared to placebo
Other Antidepressants			
Treatment Response* (follow-up 8-12 weeks)	RR 1.54; 95% CI, 1.14 to 2.08	High	Treatment with 'other' antidepressants improved symptoms more than placebo
Total number of dropouts (follow-up of 8-12 weeks)	RR 0.90; 95% CI, 0.60 to 1.34	High	No difference between groups
Dropouts due to lack of efficacy (follow-up 8-12 weeks)	RR 0.52; 95% CI, 0.28 to 0.95	High	Treatment with 'other' antidepressants decreased the risk of dropping out of the study due to lack of efficacy
Dropouts due to adverse events (follow-up 8-12 weeks)	RR 2.29; 95% CI, 1.31 to 4.01	High	'Other' antidepressants were more likely to cause discontinuations due to adverse events compared to placebo
Key: * Treatments response was defined as a reduction in 50% or more on the HAM-A			

Abbreviations: CI = confidence interval; HAM-A = Hamilton Anxiety Rating Scale; RR = relative risk; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors

AHRQ – Diagnosis and Management of Obsessive-Compulsive Disorder in Children

A 2025 review for the diagnosis and management of OCD in children and adolescents was done by AHRQ.[2] The review focused on assessment and diagnostic tools and efficacy and harms of treatments (behavioral and pharmacotherapy were evaluated). Literature was searched up to May 2024. The focus of this review will be on the evidence of pharmacological treatments, in which 24 studies were included, and behavioral and pharmacological treatment combinations which included 17 studies. Placebo-controlled comparisons included SSRIs (8 studies) and TCAs (2 studies).[2] Six studies compared a SSRI to a TCA. Outcomes were analyzed via a network meta-analysis.

The review found that treatment with SSRIs is more effective than placebo for reduction in OCD symptoms and global severity outcomes based on high quality evidence.[2] Exposure and response prevention (ERP) (i.e., cognitive behavioral therapy for OCD) is probably more effective than SSRIs for OCD symptom reduction based on moderate quality evidence. Combination ERP and SSRI treatment is as effective as ERP alone for symptom reduction and remission based on high quality evidence.[2] The TCA clomipramine is more effective than placebo for OCD symptoms based on moderate quality evidence. Studies comparing SSRIs to clomipramine found they were no differences in effectiveness (moderate quality evidence).[2] Evidence for harms of SSRIs and clomipramine were not fully reported making conclusions difficult.

After review, 26 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).[25–34,27,35–43, 44–51]

New Clinical Guidelines:

High Quality Guidelines:

National Institute for Health and Care Excellence – Headache

Guidance from NICE was updated in June 2025 for the diagnosis and management of headaches.[3] This guidance updates a previous review done in September 2012. The focus of this guideline summary will be on the use of antidepressants for headache.

Amitriptyline is recommended for migraine prophylactic treatment.[3] The continuing need for prophylaxis should be reassessed 3 to 6 months after initiating therapy. This recommendation is the same as previous guidance.

American College of Physicians – Prevention of Episodic Migraine: Pharmacologic Treatments in the Outpatient Setting

A 2025 guideline by ACP outlines treatment recommendations for the management of episodic migraines.[4] Several classes of medications are evaluated. The focus of this review will be reviewing antidepressants used for migraine: SSRI (fluoxetine), SNRI (venlafaxine), and TCA (amitriptyline).

A systematic review and network meta-analysis were used to evaluate findings. Randomized clinical trials that were at least 12 weeks long and assessed the benefits and harms for episodic migraine prevention were evaluated.[4] Most participants had an average of 7-8 headaches per month and had a history of

previous preventative migraine treatment failure.[4] The certainty of evidence was graded from low to high and strength of recommendations are rated as strong (ACP recommends) and conditional (ACP suggests). Recommendations are for nonpregnant and nonlactating adults.

Monotherapy for episodic migraine prevention is recommended with a medication from one of the following classes based on a conditional recommendation supported by low-quality evidence: beta-adrenergic blocker (metoprolol or propranolol), valproate, venlafaxine or amitriptyline.[4] No preference for one therapy over another was provided. Comparative evidence was limited; however, low certainty of evidence suggests that venlafaxine may reduce migraine duration compared to amitriptyline.[4] There was insufficient evidence for the use of fluoxetine for the outcomes studied to draw strong conclusions of efficacy. Fluoxetine may be considered if there is intolerance or inadequate response to other recommended therapies.[4]

Adverse effects associated with antidepressants used for migraine are pain, paresthesia, reduced physical activity, rash and dizziness.[4]

NICE – Management of Bipolar Disorder

Guidance from NICE was updated in September 2025 on the management of bipolar disorder in children, young people and adults.[5] Pharmacotherapy is recommended in adults who have moderate to severe bipolar depression. Fluoxetine combined with olanzapine or quetiapine monotherapy are recommended as the initial treatments of choice.[5] Lamotrigine or olanzapine monotherapy can also be offered.[5] If there is an inadequate response to fluoxetine combined with olanzapine, or quetiapine monotherapy, then lamotrigine monotherapy can be tried.[5]

SIGN – Management of Chronic Pain

An updated guideline on the management of chronic pain was completed by SIGN in 2019.[6] Antiepileptics, non-opioid analgesics (NSAIDs and acetaminophen), topical capsaicin, topical lidocaine, topical rubefacients (i.e., methyl salicylate), opioids, and antidepressants were included in the guidance.[6] Evidence was graded based on level of evidence (1+++[high quality] to 4 [expert opinion]) (**Table 5**) and grades of recommendation (A [high quality] to D [extrapolated evidence]).[6]

Table 5. SIGN Levels of Evidence[6]

LEVELS OF EVIDENCE	
1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Antidepressants with noradrenaline, serotonin and noradrenergic mechanisms of action, such as TCAs and SNRIs, have demonstrated superior efficacy to SSRIs for neuropathic pain.[6] Tricyclic antidepressants were found to not be significantly different from placebo in pain relief in patients with chronic low back pain.

Evidence Supporting Guideline Recommendations (all based on high quality evidence):

- For the treatment of fibromyalgia, TCAs improved pain scores (SMD -0.43; 95% CI, -0.55 to -0.30; p<0.001) and depression (SMD -0.26; 95% CI, -0.39 to -0.12; p<0.001).[6] Sleep disturbances and health-related quality of life (HRQOL) were also significantly improved with TCAs.[6]
- Amitriptyline reduced pain in patients with fibromyalgia (SMD -1.64; 95% CI, -2.57 to -0.71; p<0.001) and sleep disturbances (weighted mean difference [WMD] -1.84; 95% CI, -2.62 to -1.06; p<0.001).[6]
- Duloxetine 60-120 mg has been shown to be effective for the treatment of chronic low back pain based on bodily pain scores.[6]
- In patients with fibromyalgia, duloxetine produced better pain control compared to placebo for the outcome of 50% improvement (RR 1.60; 95% CI, 1.22 to 2.10; p=0.0007) and 30% improvement (RR 1.52; 95% CI, 1.24 to 1.86; p<0.0001).[6]
- Duloxetine and milnacipran reduced pain by 50% or more in patients with fibromyalgia compared to placebo (SMD -0.23; 95% CI, -0.29 to -0.18; p-value not provided).[6]
- Milnacipran 100 mg or 200 mg provided 30% or more pain relief compared to placebo in 40% patients with fibromyalgia. More adverse events occurred in the milnacipran group compared to placebo.[6]
- Duloxetine 60 mg reduced painful diabetic neuropathy with a 50% or more pain reduction with a NNT of 6 over 12 weeks.[6]
- Knee osteoarthritis was improved with duloxetine compared to placebo based on improvement of 30% or more in pain reduction (65.3% vs. 44.1%; p≤ 0.001). A 50% reduction in pain was not different between duloxetine and placebo.[6]
- Evidence from a meta-analysis found fluoxetine and paroxetine to be effective for pain relief in patients with fibromyalgia (SMD -0.39; 95% CI, -0.77 to -0.01; p=0.04) (paroxetine only accounted for one study).[6]

Guideline Recommendations (All high-quality evidence and Grade A recommendation unless noted)

1. Duloxetine 60 mg daily should be considered in people with chronic pain.[52]
2. Amitriptyline 25-125 mg daily should be considered for treatment of patients with fibromyalgia and neuropathic pain (excluding HIV-related neuropathic pain).[6]
3. Duloxetine 60 mg daily should be considered in patients with diabetic neuropathic pain if response is inadequate to first- or second-line therapies, such as lifestyle therapies and physical therapy.[6]
4. Duloxetine 60 mg daily should be considered in patients with fibromyalgia or osteoarthritis.[6]
5. Fluoxetine (20-80 mg daily) should be considered for the treatment of fibromyalgia (high quality evidence; Grade B recommendation).[6]
6. Adequate treatment of moderate depression in patients with chronic pain and comorbid depression should be considered.[6]
7. Combination therapy should be considered for patients with neuropathic pain, such as gabapentinoids, TCAs and SNRIs.[6]

MHCAG – Medication Treatment for Adults with Generalized Anxiety Disorders

In February of 2023 of the MHCAG created recommendations for the management of GAD.[8] First-line treatment with escitalopram, sertraline, duloxetine, and venlafaxine XR are recommended for GAD symptom reduction and remission. The SSRIs, escitalopram and sertraline, are tolerated at higher doses compared to SNRIs.[8] If first-line treatments are not effective or contraindicated then imipramine and bupropion XR can be considered. Adjunctive therapy may be required for adults with GAD. First-line adjunct treatment recommendations are for pregabalin, to be used with an SSRI or SNRI.[8] There is low-quality evidence that

buspirone may be effective for GAD; however, it has a slow onset and frequent dosing limiting use. Additional adjunct treatment options are quetiapine XR, hydroxyzine, diazepam and lorazepam.[8]

MHCAG – Treatment of Chronic Insomnia Disorders in Adults

The MHCAG published recommendations for the treatment of chronic insomnia disorders in July of 2024.[9] A key point in insomnia management is educate patients on sleep hygiene that may produce better sleep. Psychotherapy is recommended first line cognitive behavioral therapy for insomnia in person and online and mobile apps. If pharmacotherapy is needed then no more than 4 weeks is recommended.[9] There are many classes of medications recommended for chronic insomnia treatment. Antidepressants that are recommended are doxepin (3-6 mg) and trazodone (50-150 mg).[9] Other treatment options are lemborexant, suvorexant, eszopiclone and zolpidem. Short term use, 7-10 days of triazolam or temazepam can be tried.[9]

MHCAG – Recommendations on Extending Days' Supply for Mental Health Drugs

A review was done in March 2025 by the MHCAG on the benefits and risks of the current dispensing limits of 34 days per prescription claim for psychotropic medications.[11] While there is risk of intentional overdose (IOD) with 90-day supplies of mental health medications, there may be a benefit for some patients. The MHCAG recommends that a risk tool be published to assist providers in determining risk of IOD with psychotropic medications. The group recommended removal of the 34-day limit for non-controlled mental health drugs and controlled IV-V mental health drugs.[11]

New Formulations or Indications:

None identified.

New FDA Safety Alerts:

Table 6. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Paroxetine[53]	PAXIL	November 2024	Warnings and Precautions	Meta-analysis of epidemiological studies demonstrate exposure to paroxetine in the first trimester of pregnancy is associated with a less than 2-fold increase in the rate of cardiovascular malformations among infants. Paroxetine should be initiated only after consideration of other treatment options for women who intend to become pregnant or who are in their first trimester of pregnancy.
Amitriptyline/ chlordiazepoxide[54]	LIMBITROL	June 2025	Warnings and Precautions	Risk of serotonin syndrome alone and more commonly when used with other serotonergic drugs and with drugs that impair the metabolism of serotonin. Hyponatremia has also been reported often due to syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Bupropion and bupropion SR[55]	WELLBUTRIN	August 2025	Warnings and Precautions	Risk of aseptic meningitis.

	WELLBUTRIN SR			
Desipramine[56]	NORPRAMIN	June 2025	Warnings and Precautions	Risk of hyponatremia has been reported often due to syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Doxepin[57]	SINEQUAN	July 2025	Boxed Warnings	Increased risk of suicidal thoughts and behaviors in pediatric and young adults taking antidepressants. Doxepin is not approved in pediatric patients.

Randomized Controlled Trials:

A total of 355 citations were manually reviewed from the initial literature search. After further review, citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 7. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Janik, et al[58] DB, PC, Phase 4, RCT	Esketamine NS 56 mg monotherapy twice weekly x 4 weeks* Esketamine NS 84 mg monotherapy twice weekly x 4 weeks* Placebo NS twice weekly x 4 weeks	Adults with MDD without psychotic features who experienced an inadequate response (≤25% improvement) to ≥2 oral antidepressants during current depressive episode (n=378)	Change in MADRS from baseline at day 28	Esketamine 56 mg: -12.7 Esketamine 84 mg: -13.9 Placebo: -7.0 Esketamine 56 mg vs. Placebo LSMD -5.1 (95% CI, -7.91 to -2.33; p<0.001) Esketamine 84 mg vs. Placebo LSMD -6.8 (95% CI, -9.48 to -4.07; p<0.001)	Mean baseline MADRS score was 37.3 indicating severe depression. Onset of esketamine efficacy around 24 hours. Results were clinically meaningful with a MADRS change greater than 2. Limitations included short study duration, exclusion of patients with other mental health comorbidities, and possible unblinding due to adverse effects of esketamine. Adverse events were similar between groups.

Key: * Fixed doses of esketamine with no option for titration.

Abbreviations: CI = confidence interval; DB = double blind; LSMD = least-square mean difference; MADRS = Montgomery-Asberg Depression Rating Scale Total Score; MDD = major depressive disorder; NS = nasal spray; PC = placebo-controlled; RCT = randomized clinical trial.

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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	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
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
nefazodone HCl	NEFAZODONE HCL	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
sertraline HCl	SERTRALINE HCL	ORAL CONC	Y
sertraline HCl	ZOLOFT	ORAL CONC	Y
sertraline HCl	SERTRALINE HCL	TABLET	Y
sertraline HCl	ZOLOFT	TABLET	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 HCl	BUPROPION XL	TAB ER 24H	V
bupropion HCl	FORFIVO XL	TAB ER 24H	V
citalopram hydrobromide	CITALOPRAM HBR	CAPSULE	V
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	V
clomipramine HCl	ANAFRANIL	CAPSULE	V
clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	V
dextromethorphan HBr/bupropion	AUVELITY	TAB IR ER	V
duloxetine HCl	DRIZALMA SPRINKLE	CAP DR SPR	V
escitalopram oxalate	ESCITALOPRAM OXALATE	CAPSULE	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
gepirone HCl	EXXUA	TAB 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
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	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
phenelzine sulfate	NARDIL	TABLET	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	V
protriptyline HCl	PROTRIPTYLINE HCL	TABLET	V
selegiline	EMSAM	PATCH TD24	V
sertraline HCl	SERTRALINE HCL	CAPSULE	V
tranylcypromine sulfate	TRANYLCYPROMINE SULFATE	TABLET	V
trazodone HCl	RALDESY	SOLUTION	V
trazodone HCl	TRAZODONE HCL	TABLET	V
trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	V
venlafaxine besylate	VENLAFAXINE BESYLATE ER	TAB ER 24	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	V
vilazodone HCl	VIIBRYD	TABLET	V
vilazodone HCl	VILAZODONE HCL	TABLET	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	V
zuranolone	ZURZUVAE	CAPSULE	V
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	

Miscellaneous Agents for Depression, Anxiety, and Fibromyalgia

Generic	Brand	Form
buspirone HCl	BUCAPSOL	CAPSULE
buspirone HCl	BUSPIRONE HCL	TABLET
lithium carbonate	LITHIUM CARBONATE	CAPSULE
lithium carbonate	LITHIUM CARBONATE	TABLET
lithium carbonate	LITHIUM CARBONATE ER	TABLET ER
lithium carbonate	LITHOBID	TABLET ER
lithium citrate	LITHIUM CITRATE	SOLUTION
milnacipran HCl	SAVELLA	TAB DS PK
milnacipran HCl	SAVELLA	TABLET

Appendix 2: Abstracts of Comparative Clinical Trials

Esketamine Monotherapy in Adults With Treatment-Resistant Depression: A Randomized Clinical Trial
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Importance: Esketamine nasal spray, administered in conjunction with an oral antidepressant, is approved for treatment-resistant depression (TRD). However, the efficacy of esketamine nasal spray administered as monotherapy for patients with TRD has not yet been evaluated.
Objective: To assess the efficacy and safety of esketamine monotherapy compared to placebo in reducing depressive symptoms in patients with TRD.
Design, setting, and participants: This phase 4, double-blind, placebo-controlled randomized clinical trial was conducted from November 2020 to January 2024 at 51 outpatient centers in the US. Adults with major depressive disorder (DSM-5 criteria) without psychotic features who experienced inadequate response (≤25% improvement) to 2 or more oral antidepressants during the current depressive episode were eligible for inclusion. Data analyses were conducted from March 1, 2024, to July 8, 2024.
Interventions: After a 2-week or longer antidepressant-free period, participants were randomized at a 1:1:2 ratio to fixed-dose intranasal esketamine (56 mg or 84 mg) or matching intranasal placebo, administered twice weekly for 4 weeks.
Main outcomes and measures: Change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to day 28 (primary efficacy end point) and to 24 hours post-first dose (day 2; key secondary efficacy end point) were analyzed by a mixed-effects model using repeated measures.
Results: In this multicenter randomized clinical trial, 378 participants who met prerandomization MADRS severity criteria received 1 or more study drug doses (esketamine, 56 mg [n = 86]; esketamine, 84 mg [n = 95]; or placebo [n = 197]). Mean (SD) participant age was 45.4 (14.1) years, 231 participants (61.1%) were female, and baseline mean (range) MADRS total score was 37.3 (28-50). At day 28, the least-square (LS) mean difference (SE) between esketamine and placebo was -5.1 (1.42) (95% CI, -7.91 to -2.33) for the 56-mg dose and -6.8 (1.38) (95% CI, -9.48 to -4.07) for the 84-mg dose (for each, 2-sided P < .001). Observed effect sizes were 0.48 and 0.63 for the 56-mg and 84-mg dose groups, respectively. At day 2 (approximately 24 hours post-first dose), the between-group difference was significant for both esketamine doses: -3.8 (1.29) (95% CI, -6.29 to -1.22; 2-sided P = .004) for 56 mg and -3.4 (1.24) (95% CI, -5.89 to -1.00; 2-sided P = .006) for 84 mg. The most common treatment-emergent adverse events reported for esketamine (combined doses) were nausea (56 participants [24.8%]), dissociation (55 [24.3%]), dizziness (49 [21.7%]), and headache (43 [19.0%]).
Conclusions and relevance: According to results of this multicenter, double-blind randomized clinical trial, esketamine monotherapy may expand treatment options for adult patients with TRD by addressing an unmet need of patients experiencing treatment-limiting tolerability concerns and nonresponse with oral antidepressants.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to October 24, 2025
Search Strategy:

#	Searches	Results
1	Amitriptyline/ or amitriptyline.mp.	10333
2	bupropion.mp. or Bupropion/	6145

3	citalopram.mp. or Citalopram/	8180
4	desipramine.mp. or Desipramine/	8052
5	desvenlafaxine.mp. or Desvenlafaxine Succinate/	604
6	duloxetine.mp. or Duloxetine Hydrochloride/	3731
7	doxepin.mp. or Doxepin/	1589
8	escitalopram.mp. or Escitalopram/	3788
9	fluoxetine.mp. or Fluoxetine/	16694
10	Fluvoxamine.mp. or Fluvoxamine/	3508
11	imipramine.mp. or Imipramine/	13717
12	mirtazapine.mp. or Mirtazapine/	3036
13	nefazodone.mp.	821
14	nortriptyline.mp. or Nortriptyline/	3397
15	paroxetine.mp. or Paroxetine/	7217
16	sertraline.mp. or Sertraline/	6709
17	venlafaxine.mp. or Venlafaxine Hydrochloride/	5429
18	amoxapine.mp. or Amoxapine/	499
19	clomipramine.mp. or Clomipramine/	4221
20	dextromethorphan.mp. or Dextromethorphan/	3391
21	esketamine.mp.	1642
22	isocarboxazid.mp. or Isocarboxazid/	424
23	levomilnacipran.mp. or Levomilnacipran/	117
24	phenelzine.mp.	1709
25	protriptyline.mp. or Protriptyline/	419
26	selegiline.mp. or Selegiline/	3093
27	tranylcypromine.mp. or Tranylcypromine/	2353

28	trimipramine.mp. or Trimipramine/	555
29	vilazodone.mp. or Vilazodone Hydrochloride/	312
30	vortioxetine.mp. or Vortioxetine/	879
31	trazodone.mp. or Trazodone/	2556
32	gepirone.mp.	310
33	zuranolone.mp.	146
34	buspirone.mp. or Buspirone/	3226
35	lithium.mp. or Lithium/	85025
36	milnacipran.mp. or Milnacipran/	826
37	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 or 33 or 34 or 35 or 36	176189
38	limit 37 to (english language and humans and yr="2024 -Current")	3426
39	limit 38 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	355

Appendix 4: Key Inclusion Criteria

Population	Patients with an indication for antidepressant use (e.g., depression, anxiety, pain)
Intervention	Antidepressant treatment
Comparator	Placebo or active treatment comparison
Outcomes	Reduction in symptoms of depression, pain, anxiety
Setting	Outpatient

Appendix 5: 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 in Children

Drug	FDA-Approved Indications	Maximum Daily 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 (150 mg for 10-19 years of age)	10
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	225 mg	18

	Dysthymia Mixed anxiety and depressive disorder		
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. Does the dose exceed the maximum FDA-approved dose (**Table 1**)?	**Yes:** Go to #3	**No:** Go to #4
3. Is there documentation that the prescriber is monitoring blood levels to support use of the prescribed dose?	**Yes:** Go to #4	**No:** Go to #6
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: 2/26; 6/24 (KS); 12/23, 2/23, 2/21(SS) 11/19
Implementation:7/1/24; 2/1/2020

Esketamine (Spravato)

Goal(s):

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

Length of Authorization:

- Up to 6 months

Requires PA:

- Esketamine (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 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 #4
4. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Is the member currently engaged in or been referred for psychotherapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is there prescriber attestation or documentation of treatment-resistant depression based on all the following criteria: a. Diagnosis of unipolar major depressive disorder b. Patient has tried at least 2 different antidepressants in which: i. There has been inadequate response after at least 6 weeks of treatment at an average minimum therapeutic dose or greater; or ii. The patient has not been able to continue treatment for at least 6 weeks due to intolerable side effects. Minimum therapeutic doses can be found here: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Switching-Between-Anti-Depressant-Medications.pdf	**Yes:** Go to #9	**No:** Go to #7
7. Is the request for treatment of major depressive disorder in the setting of acute suicidal ideation or behavior?	**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.

Approval Criteria		
8. Is there a documented plan to optimize oral antidepressant treatment in one of the following ways: a. Titrating the dose of the current antidepressant to a therapeutic level b. Switching to a different antidepressant OR c. Adding oral augmentation therapy (e.g., a second antidepressant, an atypical antipsychotic, or mood stabilizer)?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. 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 up to 28 days for induction (either 56 mg and/or 84 mg for titration) not to exceed 24 units total to be covered within the approved time window. The approved time window typically spans 60 days to accommodate scheduling visits.

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. Is the request for administration of esketamine once weekly or every 2 weeks?	**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 (total 28 days of treatment with a maximum of 24 nasal spray devices (each device contains 28 mg of esketamine)

P&T/DUR Review: 2/26 (KS); 6/25(SS);6/24(KS);2/24; 12/23; 2/23, 10/21; 2/21; 7/19
Implementation 8/1/25; 7/1/24; 1/1/22; 3/1/21; 8/19/19

Zuranolone (Zurzuvae)

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

Length of Authorization:
- One time use only.

Requires PA:
- Zuranolone requires a prior authorization approval due to safety concerns.

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 and age (e.g., ≥18 years)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Does the patient have moderate to severe post-partum depression? Note: Zuranolone is not indicated for major depressive disorder but can be covered for depression meeting the clinical diagnosis of post-partum depression (e.g., moderate to severe depression with peripartum onset).	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient been previously treated with zuranolone for severe post-partum depression related to their most recent pregnancy?	**Yes:** Pass to RPh. Deny; medical appropriateness. Multiple courses of zuranolone have not been studied.	**No:** Approve for a single 14-day treatment.

P&T/DUR Review: 2/26 (KS); 6/24 (KS); 12/23
Implementation: 1/1/24

Milnacipran

Goal(s):
- Restrict use to OHP-funded and evidence-supported diagnoses.

Length of Authorization:
- Up to 12 months

Requires PA:
- Milnacipran

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 the request for renewal of previously approved milnacipran therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis an OHP-funded diagnosis (see Table 1 below)?	**Yes:** Go to #4	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded. **If eligible for EPSDT review: Go to #4**
4. Is this an FDA approved or evidence-supported indication and age (see Table 1 below)?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient had an inadequate response (i.e., appropriate dose and duration of at least 6-8 weeks) and/or intolerance/contraindication to 2 preferred treatments?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend a trial of amitriptyline or duloxetine

Renewal Criteria		
1. Is there provider attestation of a reduction or stabilization in pain symptoms related to fibromyalgia since starting milnacipran?	**Yes**: Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend alternative therapy for pain control.

Table 1. OHP Funded or Non-Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Milnacipran
Funded	
Diabetic Neuropathy	
Postherpetic Neuropathy	

Painful Polyneuropathy	
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	≥18 years

P&T Review: 2/26 (KS); 7/18 (DM); 3/17
Implementation: 4/1/17