Antidepressant Agents Step Therapy and Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

FDA APPROVED INDICATIONS AND DOSAGE[1-31,42,43]

Agent(s)	Indication(s)
Selective Serotonin Reuptake Inhibitors (SSRIs)	
Celexa® (citalopram) Tablets, Oral solution	Treatment of: – Depression
Fluoxetine 60 mg Tablets	Treatment of: – Major Depressive Disorder (MDD) – Obsessive Compulsive Disorder (OCD) – Bulimia Nervosa – Panic Disorder (PD), with or without agoraphobia
Lexapro® (escitalopram) Tablets Oral Suspension	Treatment of: – Acute and maintenance treatment of Major Depressive Disorder (MDD) in adults and adolescents aged 12-17 years – Acute Treatment of Generalized Anxiety Disorder (GAD) in adults
Paxil® (paroxetine) Tablets Oral suspension	Treatment of: – Treatment of Major Depressive Disorder (MDD) – Obsessive Compulsive Disorder – Panic Disorder (PD) – Generalized Anxiety Disorder – Social Anxiety Disorder (SAD) – Post-Traumatic Stress Disorder (PTSD)
Paxil CR® (paroxetine extended release) Tablets	Treatment of: – Major Depressive Disorder (MDD) – Panic Disorder (PD) – Social Anxiety Disorder (SAD) – Premenstrual Dysphoric Disorder (PMDD)
Pexeva® (paroxetine mesylate) Tablets	Treatment of: – Major Depressive Disorder (MDD) – Obsessive Compulsive Disorder (OCD) – Panic Disorder – Generalized Anxiety Disorder (GAD)

Agent(s)	Indication(s)
Fluoxetine Delayed Release Capsules	Treatment of: – Acute and maintenance treatment of Major Depressive Disorder (MDD)
Prozac® (fluoxetine) Tablets, Capsules, Oral solution	Treatment of: – Acute and maintenance treatment of Major Depressive Disorder (MDD) – Acute and maintenance treatment of Obsessive Compulsive Disorder (OCD) – Acute and maintenance treatment of Bulimia Nervosa – Acute treatment of Panic Disorder (PD), with or without agoraphobia
Sertraline Capsules	Treatment of: – Major depressive disorder (MDD) in adults – Obsessive-compulsive disorder (OCD) in adults and pediatric patients 6 years and older
Zoloft® (sertraline) Tablets, Oral concentrate	Treatment of: – Major Depressive Disorder (MDD) – Obsessive Compulsive Disorder (OCD – Panic disorder (PD) – Post-traumatic stress disorder (PTSD) – Social anxiety disorder (SAD) – Premenstrual dysphoric disorder (PMDD)
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	
Cymbalta® (duloxetine delayed release) Capsules	Treatment of: – Major Depressive Disorder (MDD) – Generalized Anxiety Disorder (GAD) in adults and pediatric patients 7 years of age and older – Diabetic Peripheral Neuropathic Pain (DPNP) in adults – Fibromyalgia (FM) in adults and pediatric patients 13 years of age and older Chronic Musculoskeletal Pain (CMP) in adults
Drizalma Sprinkle™ (duloxetine delayed release) Sprinkle capsules	Treatment of: – Major Depressive Disorder (MDD) – Generalized Anxiety Disorder (GAD) in adults and pediatric patients ages 7 years to 17 years old – Diabetic Peripheral Neuropathic Pain (DPNP) in adults – Chronic Musculoskeletal Pain (CMP) in adults Fibromyalgia (FM) in adults
Effexor® (venlafaxine) Tablets	Treatment of: Major Depressive Disorder (MDD)
Effexor XR® (venlafaxine extended release) Capsules	Treatment of: – Major Depressive Disorder (MDD) – Panic Disorder (MDD) – Generalized Anxiety Disorder (GAD) Social Anxiety Disorder (SAD)

Agent(s)	Indication(s)
Fetzima® (levomilnacipran ER) Capsules	Treatment of: Major Depressive Disorder (MDD)
Desvenlafaxine ER Tablets	Treatment of: Major Depressive Disorder (MDD)
duloxetine Delayed Release[b] Capsules Capsules	Treatment of: – Major Depressive Disorder (MDD) – Panic Disorder – Diabetic peripheral neuropathic pain (DPNP) – Chronic musculoskeletal pain (CMP)
Pristiq® (desvenlafaxine succinate extended release) Tablets	Treatment of: Major Depressive Disorder (MDD)
Venlafaxine ER Tablets	Treatment of: – Major Depressive Disorder Social Anxiety Disorder
Aplenzin® (bupropion extended release) Tablets	Treatment of: – Major Depressive Disorder (MDD) – Seasonal Affective Disorder (SAFD)
Other Antidepressants	
Auvelity® (dextromethorphan -bupropion extended release) Tablets	Treatment of: – Major Depressive Disorder (MDD)
Forfivo XL® (bupropion extended release) Tablets	Treatment of: – Major Depressive Disorder (MDD)
Maprotiline Tablets	Treatment of: – Major Depressive Disorder (MDD)

Agent(s)	Indication(s)
Remeron®, Remeron SolTab® (mirtazapine) Tablets Orally Disintegrating Tablets	Treatment of: – Major Depressive Disorder (MDD)
Trintellix® (vortioxetine) Tablets	Treatment of: – Major Depressive Disorder (MDD)
Viibryd® (vilazodone) Tablets	Treatment of: – Major Depressive Disorder (MDD)
Wellbutrin® (bupropion)**, Wellbutrin SR®** (bupropion sustained release) Tablets	Treatment of: – Major Depressive Disorder (MDD)
Wellbutrin XL® (bupropion extended release) Tablets	Treatment of: – Major Depressive Disorder (MDD) – Seasonal Affective Disorder (SAFD)

a- Generic equivalent available
b- Available as a generic only

CLINICAL RATIONALE

Depression

No antidepressant has been clearly shown to be superior to another. All FDA-approved antidepressant medications should be considered potentially appropriate for first-line treatment. Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, and several newer agents are typically used as first-line medications because their safety and tolerability may be preferable to patients and clinicians compared to those of tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors[32]. Many clinical features and medication characteristics influence the choice of a first-line antidepressant. There are no absolutes, and relative differences between medications are small, hence, selecting an antidepressant involves an individualized needs assessment for each patient[33].

Anxiety Disorders

Guidelines for treatment of anxiety include several anxiety-related conditions: generalized anxiety disorder (GAD), panic disorder (PD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and social anxiety disorder (SAD). SSRIs are generally

considered first-line therapy for GAD and PD. In the treatment of PD, TCAs are as effective as SSRIs, but adverse effects may limit the use of TCAs in some patients. Extended-release venlafaxine is effective and well tolerated for GAD and PD, whereas duloxetine has been adequately evaluated only for GAD. Due to the typical delay in onset of action, medications should not be considered ineffective until they are titrated to the high end of the dose range and continued for at least four weeks. Once symptoms have improved, medications should be used for 12 months before tapering to limit relapse. Some patients will require longer treatment[34]. OCD has a highly selective response to serotonergic medications. SSRIs are preferred for initial therapy. There is insufficient evidence to show that one SSRI is superior, and the choice should be individualized, taking into account potential drug interactions and tolerability. Dosage should be increased over four to six weeks until maximum dose is achieved. Trial of therapy should continue for eight to 12 weeks, with at least four to six weeks at the maximum tolerable dosage. It usually takes at least four to six weeks for patients to note any significant improvement in symptoms; it may take 10 weeks or longer for some. If successful, medication should be continued for at least one to two years, if not indefinitely[35]. Among adult patients with PTSD, fluoxetine, paroxetine, sertraline, and venlafaxine are appropriate choices, with none showing improved efficacy over the others[36]. For SAD, SSRIs and SNRIs venlafaxine are the clear first-line pharmacotherapy treatment based on demonstrated efficacy in randomized controlled trials and meta-analyses. Medications in these classes that have been FDA-approved in the U.S. are paroxetine (immediate-release and controlled release), sertraline, fluvoxamine controlled release, and venlafaxine extended release. Other medications in these classes with evidence of efficacy from randomized controlled trials include citalopram, escitalopram, and vilazodone. Fluoxetine has had mixed results in randomized controlled trials. SNRIs should be used with caution in patients at risk for suicide due to greater toxicity in overdose. No individual medication within this class has been consistently shown to be superior to another in this class[37].

Neuropathic Pain
First-line treatment for neuropathic pain include TCAs, gabapentin, pregabalin, and SNRI antidepressants (duloxetine [most studied], venlafaxine) as first-line therapies.[38] For patients with diabetic neuropathy, only two medications, pregabalin and duloxetine, have been approved by the FDA. However, in addition to those two medications, gabapentin and amitriptyline are considered first-line therapy. SNRIs such as venlafaxine and desvenlafaxine are considered second-line therapy. SSRIs such as citalopram, paroxetine, and escitalopram are considered third-line therapy[39].

Fibromyalgia
Pharmaceutical therapy recommendations depend on the source of the guideline. Guidelines are available from the European League Against Rheumatism (EULAR-2016), the Canadian Pain Society (2012) and the Association of the Scientific Medical Societies in Germany (AWMF-2012). Recommendations from these guidelines include amitriptyline, pregabalin, gabapentin, SNRIs (including duloxetine and milnacipran), and SSRIs. Amitriptyline, pregabalin, and duloxetine are used most commonly[40].

Chronic Musculoskeletal Pain
Antidepressants are options for the treatment of chronic pain. Meta-analyses of randomized controlled trials indicate that TCAs and SNRIs provide effective pain relief for a variety of chronic pain etiologies[41]. Duloxetine is FDA approved for chronic musculoskeletal pain[13].

Adverse Effects
All of the above listed agents have had a black box warning issued by the FDA. The warning concerns suicidal thoughts and behaviors. Since there are small differences between the

warnings, they are not listed here. Please see the respective agent's prescribing information for the warning.

References

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Antidepressant Agents Step Therapy

TARGET AGENT(S)

Aplenzin® (bupropion)
Auvelity™ (dextromethorphan/bupropion ER)
Celexa® (citalopram)[a]
Citalopram (capsules)[b]
Cymbalta® (duloxetine)[a]
Desvenlafaxine ER (tablets)[b]
Drizalma Sprinkle™ (duloxetine delayed release sprinkle capsule)
Effexor® (venlafaxine)[a]
Effexor XR® (venlafaxine extended release)[a]
Fetzima® (levomilnacipran extended release)
Fluoxetine 60 mg (tablets)[ab]
Forfivo XL® (bupropion extended release)
Lexapro® (escitalopram)[a]
Maprotiline (tablets)[b]
Paxil® (paroxetine hydrochloride)[a]
Paxil CR® (paroxetine extended release)[a]
Pexeva® (paroxetine mesylate)
Pristiq® (desvenlafaxine succinate)[a]
Prozac® (fluoxetine)[a]
Fluoxetine delayed release (capsules)[b]
Remeron® (mirtazapine)[a]
Remeron SolTab® (mirtazapine)[a]
Sertraline (capsules)[b]
Trintellix® (vortioxetine)
Venlafaxine ER (tablets)[b]
Viibryd® (vilazodone)[a]
Wellbutrin® (bupropion)[a]
Wellbutrin SR® (bupropion extended release)[a]
Wellbutrin XL® (bupropion extended release)[a]
Zoloft® (sertraline)[a]

a - available as a generic; generic included as a *prerequisite* in step therapy program
b – branded generic product(s) available; targeted in the step therapy program

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Brand Antidepressant Agents (except Cymbalta and Drizalma) will be approved when ONE of the following are met:

1. Information has been provided that indicates the patient has been treated with the requested agent within the past 180 days
   OR
2. The prescriber states that the patient has been treated with the requested agent within the past 180 days AND is at risk if therapy is changed
   OR
3. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   A. A statement by the prescriber that the patient is currently taking the requested agent
      AND
   B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
   C. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

4. The request is for Auvelity AND ONE of the following:
    A. The patient's medication history includes TWO generic antidepressant agents (i.e., SSRI, SNRI, bupropion, mirtazapine, or vilazodone) use, intolerance, or hypersensitivity

    OR

    B. BOTH of the following:
        i. The prescriber has stated that the patient has tried TWO generic antidepressant agents (i.e., SSRI, SNRI, bupropion, mirtazapine, or vilazodone) **AND**
        ii. BOTH generic antidepressant agents (i.e., SSRI, SNRI, bupropion, mirtazapine, or vilazodone) were discontinued due to lack of effectiveness or an adverse event

    OR

    C. The patient has an FDA labeled contraindication to ALL generic antidepressant agents (i.e., SSRI, SNRI, bupropion, mirtazapine, or vilazodone)

    OR

    D. The prescriber has provided documentation that ALL generic antidepressant agents (i.e., SSRI, SNRI, bupropion, mirtazapine, or vilazodone) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

OR

5. The request is for a medication other than Auvelity AND ONE of the following:
    A. The patient's medication history includes generic antidepressant agent (i.e., SSRI, SNRI, bupropion, mirtazapine, or vilazodone) use, intolerance, or hypersensitivity

    OR

    B. BOTH of the following:
        i. The prescriber has stated that the patient has tried a generic antidepressant agent (i.e., SSRI, SNRI, bupropion, mirtazapine, or vilazodone)

        AND

        ii. The generic antidepressant agent (i.e., SSRI, SNRI, bupropion, mirtazapine, or vilazodone) was discontinued due to lack of effectiveness or an adverse event

    OR

    C. The patient has an FDA labeled contraindication to ALL generic antidepressants (i.e., SSRI, SNRI, bupropion, mirtazapine, and vilazodone)

    OR

    D. The prescriber has provided documentation that ALL generic antidepressant agents (i.e., SSRI, SNRI, bupropion, mirtazapine, and vilazodone) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.

Cymbalta and Drizalma Sprinkle will be approved when ONE of the following are met:

1. Information has been provided that indicates the patient has been treated with the requested agent within the past 180 days

    OR

2. The prescriber states the patient has been treated with the requested agent within the past 180 days AND is at risk if therapy is changed
   OR
3. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   A. A statement by the prescriber that the patient is currently taking the requested agent
      AND
   B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
   C. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR
4. The patient's medication history includes use of a generic antidepressant agent - SSRI, SNRI, bupropion, mirtazapine, or vilazodone
   OR
5. BOTH of the following:
   A. The prescriber has stated that the patient has tried a generic antidepressant agent – SSRI, SNRI, bupropion, or mirtazapine
      AND
   B. The generic antidepressant agent – SSRI, SNRI, bupropion or mirtazapine was discontinued due to lack of effectiveness or an adverse event

   OR
6. The patient has a diagnosis of neuropathic pain and ONE of the following:
   A. The patient's medication history includes amitriptyline, nortriptyline, desipramine, imipramine, or gabapentin use, intolerance, or hypersensitivity
      OR
   B. BOTH of the following:
      i. The prescriber has stated that the patient has tried amitriptyline, nortriptyline, desipramine, imipramine, or gabapentin
         AND
      ii. Amitriptyline, nortriptyline, desipramine, imipramine, or gabapentin was discontinued due to lack of effectiveness or an adverse event

      OR
   C. The patient has an FDA labeled contraindication to ALL prerequisite agents (i.e., amitriptyline, nortriptyline, desipramine, imipramine, and gabapentin)
      OR
   D. The prescriber has provided documentation that amitriptyline, nortriptyline, desipramine, imipramine, and gabapentin cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

   OR
7. For Cymbalta only, the patient has a diagnosis of fibromyalgia and ONE of the following:
   A. The patient's medication history includes amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, gabapentin, or tramadol use, intolerance, or hypersensitivity
      OR
   B. BOTH of the following:
      i. The prescriber has stated that the patient has tried amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, gabapentin, or tramadol
         AND

ii. Amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, gabapentin, or tramadol was discontinued due to lack of effectiveness or an adverse event

OR

C. The patient has an FDA labeled contraindication to ALL prerequisite agents (i.e., amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, gabapentin, and tramadol)

OR

D. The prescriber has provided documentation that amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, gabapentin and tramadol cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

OR

8. The patient has a diagnosis of chronic musculoskeletal pain and ONE of the following:
   A. The patient's medication history includes acetaminophen, oral NSAID, topical NSAID, tramadol, amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, or gabapentin use, intolerance, or hypersensitivity

   OR

   B. BOTH of the following:
      i. The prescriber has stated that the patient has tried acetaminophen, oral NSAID, topical NSAID, tramadol, amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, or gabapentin

      AND

      ii. Acetaminophen, oral NSAID, topical NSAID, tramadol, amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, or gabapentin were discontinued due to lack of effectiveness or an adverse event

   OR

   C. The patient has an FDA labeled contraindication to ALL prerequisite agents (i.e., acetaminophen, oral NSAID, topical NSAID, tramadol, amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, and gabapentin

   OR

   D. The prescriber has provided documentation that acetaminophen, oral NSAID, topical NSAID, tramadol, amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, and gabapentin cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

OR

9. If using for a diagnosis other than neuropathic pain, fibromyalgia for Cymbalta only, or musculoskeletal pain ONE of the following:
   A. The patient has an intolerance or hypersensitivity to a generic antidepressant - SSRI, SNRI, bupropion, mirtazapine, or vilazodone

   OR

   B. The patient has an FDA labeled contraindication to ALL generic antidepressants - SSRI, SNRI, bupropion, mirtazapine, and vilazodone

   OR

   C. If using for a diagnosis other than neuropathic pain, fibromyalgia for Cymbalta only, or musculoskeletal pain: The prescriber has provided documentation that ALL generic antidepressant agents – SSRI, SNRI, bupropion, mirtazapine, and vilazodone cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.