**Medication Policy Manual**

**Policy No:** dru352

**Date of Origin:** May 9, 2014

**Committee Approval Date:** September 9, 2016

**Next Review Date:** May 2017

**Effective Date:** January 1, 2017

**IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

_Benefit determinations should be based in all cases on the applicable contract language._ To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Desvenlafaxine-containing medications (Khedezla, Pristiq®), levomilnacipran (Fetzima™), milnacipran-containing medications (generic, Savella®), vilazodone (Viibryd®), vortioxetine (Brintellix®, Trintellix®), bupropion hydrobromide (Aplenzin™), and bupropion XL (Forfivo XL™) are oral medications used to treat major depressive disorder (MDD) and other mental health conditions. Many of these medications may also be used to treat other conditions such as neuropathic pain, fibromyalgia, and musculoskeletal pain. This policy also addresses certain high cost antidepressants in which comparable, yet lower cost, generic products are available.
Policy/Criteria

I. Most contracts require prior authorization approval of certain high cost antidepressants prior to coverage. High cost antidepressants may be considered medically necessary when criterion A or B below is met.

A. Desvenlafaxine, levomilnacipran, milnacipran, vilazodone, vortioxetine, bupropion hydrobromide, and bupropion XL may be considered medically necessary when at least two low-cost generic/preferred medications (examples listed in Appendix 1) have been ineffective, not tolerated, or contraindicated.

OR

B. Antidepressants included in Table 1 may be considered medically necessary when there is an intolerance or contraindication to an inactive ingredient in all specified alternative(s) listed in Table 1.

Table 1. High cost antidepressants with AB-rated alternatives

<table>
<thead>
<tr>
<th>High Cost Drug</th>
<th>Alternative(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effexor XR</td>
<td>venlafaxine HCL ER</td>
</tr>
<tr>
<td>Elavil</td>
<td>amitriptyline</td>
</tr>
<tr>
<td>Lexapro</td>
<td>escitalopram oxalate</td>
</tr>
<tr>
<td>Wellbutrin SR</td>
<td>bupropion HCL SR</td>
</tr>
<tr>
<td>Wellbutrin XL</td>
<td>bupropion HCL XL</td>
</tr>
<tr>
<td>Zoloft</td>
<td>sertraline HCL</td>
</tr>
</tbody>
</table>

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers all drugs in this policy to be self-administered medications.

B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

Position Statement

- Desvenlafaxine, levomilnacipran, and milnacipran are in a class of medications called selective serotonin and norepinephrine reuptake inhibitors (SNRIs). There are low-cost generic treatment options (e.g. venlafaxine) available within the class.

- Vortioxetine and vilazodone work by affecting the activity of serotonin in multiple ways, including by inhibiting its reuptake. There are many generically available antidepressants that exhibit their effects by interfering with serotonin activity, and are called selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine, paroxetine, sertraline).

- Bupropion hydrobromide and bupropion XL are in a class of medications called aminoketone antidepressants. There are generically available alternatives (e.g., bupropion hydrochloride SR and bupropion hydrochloride XL) available within the class.
High-cost antidepressant medications have not demonstrated superior efficacy, safety, or tolerability relative to generically available treatment options for the same condition. AB-rated generic products are lower cost and considered to be pharmaceutical equivalents of the branded products, with the same clinical effect and safety profile when administered to patients under the conditions specified in the package labelling. Patients who are adherent, yet do not respond to equivalent doses of the generic/OTC product(s) are not likely to respond to the branded product.

Appendix 1 includes examples of numerous low-cost generically available treatment options for each diagnosis that desvenlafaxine, levomilnacipran, milnacipran, vilazodone, and vortioxetine are commonly used to treat.

Clinical Efficacy

Many antidepressants have been approved for the treatment of mental health conditions other than depression, such as anxiety, obsessive-compulsive and panic disorders, social phobia, bulimia nervosa, and post-traumatic stress disorder (see Appendix 2). Larger doses of each can improve the chances of response, though not in all cases. Additionally, the potential benefits of larger doses need to be weighed against the risk of side effects.

For the majority of patients with these conditions, a low-cost generic antidepressant (e.g. SSRI, SNRI, bupropion) provide effective treatment.

SNRIs and other antidepressants such as tricyclic antidepressants (TCAs; e.g. amitriptyline) can be used on-label or off-label to treat some pain conditions including neuropathic pain, fibromyalgia, and musculoskeletal pain.

For the majority of patients with these conditions, low-cost generic SNRIs, TCAs, and other low-cost generic medications such as non-steroidal anti-inflammatory drugs (NSAIDs; e.g. ibuprofen, naproxen) or gabapentin provide effective treatment.

MENTAL HEALTH CONDITIONS

Depression [2-13]

SSRIs, SNRIs, and other antidepressants (e.g. bupropion, TCAs, mirtazapine) have been shown to improve symptoms of depression relative to placebo.

There is insufficient evidence to establish that any one antidepressant is safer or more effective overall than any other for the treatment of major depressive disorder.

Generalized Anxiety Disorder (GAD) [14,15]

Antidepressants such as SSRIs (e.g. citalopram, fluoxetine, paroxetine, sertraline) and SNRIs (e.g. duloxetine, venlafaxine) have demonstrated efficacy in the treatment of GAD.

There is insufficient evidence to establish that any one antidepressant medication is superior in terms of efficacy, safety, or tolerability relative to any other for the treatment of GAD.

Posttraumatic Stress Disorder (PTSD) [16]

SSRIs are primary options in the treatment of PTSD. Paroxetine and sertraline have the largest body of evidence for the treatment of PTSD.

There is insufficient evidence to establish the comparative efficacy of antidepressant or any other treatment options for PTSD.
Premenstrual Syndrome (PMS)/Premenstrual Dysphoric Disorder (PMDD) [17,18]
- SSRIs are commonly used as front-line therapy for premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) because they have demonstrated efficacy in reducing symptoms.
- There is insufficient evidence to establish the relative safety, efficacy, and tolerability of treatments for PMS and PMDD.

Bulimia Nervosa [19]
- Many antidepressants are recognized for their efficacy in treating bulimia nervosa, including fluoxetine, tricyclic antidepressants (imipramine, desipramine and amitriptyline), the monoamine oxidase inhibitor (MAOI) phenelzine (Nardil), and trazodone.
- There are no proven differences in efficacy among these various antidepressants in treating bulimia nervosa.

PAIN CONDITIONS

Neuropathic Pain [20-25]
- Antidepressants are effective for a variety neuropathic pain conditions caused by herpes infection or diabetes. These include tricyclic antidepressants (amitriptyline, desipramine) and SNRIs like duloxetine.
- Other proven treatment options for neuropathic pain conditions include anticonvulsants (gabapentin, carbamazepine and phenytoin) and tramadol.
- None of the SSRIs are recognized as effective in treating neuropathic pain symptoms.
- There is insufficient evidence to establish overall differences in safety, efficacy, or tolerability among treatment options for neuropathic pain.

Fibromyalgia [26-30]
- Medications used for the treatment of fibromyalgia include cyclobenzaprine, duloxetine, gabapentin, and tricyclic antidepressants among others.
- Non-medication therapies include aerobic exercise, muscle strengthening, patient education, and cognitive behavioral therapy.
- There is insufficient evidence to establish the superiority of any one medication for treating fibromyalgia relative to other options.

Chronic Musculoskeletal Pain
- Medications used for the treatment of chronic musculoskeletal pain include centrally-acting analgesics such as tramadol or codeine, duloxetine, and non-steroidal anti-inflammatory drugs (NSAIDs).
- There is insufficient evidence to establish overall differences in safety, efficacy, or tolerability among treatment options for chronic musculoskeletal pain.

Safety [1]
- All antidepressants carry risk of side effects. In general, the types of common adverse events reported are similar among antidepressants; however, the frequency and severity of adverse events may differ.
- Sexual dysfunction is a common side effect among all antidepressants.
  * The incidence is reported as anywhere from 5% - 70%. The wide range of reported incidence is likely due to differences in how sexual dysfunction was measured.
  * Bupropion may have less potential for sexual sided effects, but an added risk is for elevating the seizure threshold at higher doses or in patients with history of seizures.

- All antidepressants carry the boxed warning for suicidal thoughts in children, adolescents and young adults.

- SNRIs are contraindicated for concomitant use with monoamine oxidase inhibitors (MAOIs) due to an increased risk of serotonin syndrome. Some are also contraindicated in patients with narrow-angle glaucoma.

### Appendix 1: Lower-cost Generic Medication Alternatives

<table>
<thead>
<tr>
<th>Condition</th>
<th>Lower-cost Generic Alternatives</th>
</tr>
</thead>
</table>
| **Mental Health Conditions** including, but not limited to: | - citalopram (generic Celexa®)  
- duloxetine (generic Cymbalta®)  
- escitalopram (generic Lexapro®)  
- fluoxetine (generic Prozac®)  
- fluvoxamine (generic Luvox®)  
- paroxetine (generic Paxil®)  
- sertraline (generic Zoloft®)  
- bupropion SR/XL (generic Wellbutrin SR*, Wellbutrin XL® 300mg)  
- mirtazapine (generic Remeron®)  
- trazodone  
- venlafaxine (generic Effexor®)  
- venlafaxine SR tablets |
| - major depression  
- social anxiety disorder  
- generalized anxiety disorder  
- panic disorder  
- bulimia  
- post-traumatic stress disorder  
- premenstrual dysphoric disorder |
| **Neuropathic Pain** | - gabapentin (generic Neurontin®)  
- tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline) |
| **Fibromyalgia** | - gabapentin (generic Neurontin®)  
- tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline)  
- cyclobenzaprine (generic Flexeril®) |
| **Chronic Musculoskeletal Pain** | - generic prescription non-steroidal antiinflammatories (diclofenac, diflunisal, etodolac, fenoprofen*, flurbiprofen, indomethacin, ketoprofen, ketorolac, meclofenamate*, meloxicam, nabumetone, oxaprozin*, piroxicam, sulindac, tolmetin)  
- generic prescription centrally-acting analgesics, alone or in combination (codeine, hydrocodone, morphine, meperidine, oxycodone, propoxyphene, tramadol) |

* Most contracts require prior authorization approval prior to coverage.

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Appendix 2: FDA-approved indications for selected antidepressants. [1]

<table>
<thead>
<tr>
<th>Indication</th>
<th>Selective Serotonin Reuptake Inhibitors (SSRIs)</th>
<th>Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)</th>
<th>Miscellaneous</th>
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<tbody>
<tr>
<td></td>
<td>citalopram</td>
<td>fluoxetine</td>
<td>fluvoxamine</td>
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<tr>
<td>Depression</td>
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<td>✓</td>
<td>✓</td>
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<tr>
<td>Generalized anxiety disorder</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
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<tr>
<td>Panic disorder</td>
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<td>✓</td>
<td>✓</td>
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<tr>
<td>Premenstrual dysphoric disorder</td>
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<tr>
<td>Posttraumatic stress disorder</td>
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<td></td>
<td>✓</td>
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<tr>
<td>Social anxiety disorder</td>
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<td>✓</td>
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<tr>
<td>Bulimia Nervosa</td>
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<td>Seasonal Affective Disorder</td>
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<tr>
<td>Neuropathic pain</td>
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<tr>
<td>Fibromyalgia</td>
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<tr>
<td>Musculo-skeletal pain</td>
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Cross References

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
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<tbody>
<tr>
<td>Lyrica®, pregabalin, Medication Policy Manual, Policy No. 122</td>
<td></td>
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<tr>
<td>High cost nonsteroidal anti-inflammatory drugs (NSAIDs), dru447</td>
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Codes

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<th>Description</th>
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References


**Revision History**

<table>
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<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/09/16</td>
<td>Added Elavil and antidepressants that were previously included in dru420 (Effexor XR, Lexapro, Wellbutrin SR, Wellbutrin XR, Zoloft). Policies reorganized, no true criteria changes.</td>
</tr>
<tr>
<td>05/13/2016</td>
<td>Added bupropion hydrobromide (Aplenzin), bupropion XL (Forfivo XL), and generic milnacipran to the policy Updated alternatives in Appendix I</td>
</tr>
<tr>
<td>02/12/2016</td>
<td>Delete duloxetine (generic and brand) from the list of “High-Cost Antidepressant Medications”</td>
</tr>
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