Title: Antidepressant Agents

- Prime Therapeutics will review Prior Authorization requests.

Prior Authorization Form:

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional
Original Effective Date: January 1, 2008
Revision Date(s): December 31, 2009;
May 20, 2011; February 1, 2012;
August 30, 2012; October 1, 2013;
April 1, 2014; July 1, 2014;
September 17, 2014; June 10, 2015;
October 1, 2015; June 1, 2016;
July 1, 2016; April 1, 2017; July 1, 2017
Current Effective Date: July 1, 2017

Institutional
Original Effective Date: January 1, 2008
Revision Date(s): December 31, 2009;
May 20, 2011; February 1, 2012;
August 30, 2012; October 1, 2013;
April 1, 2014; July 1, 2014;
September 17, 2014; June 10, 2015;
October 1, 2015; June 1, 2016;
July 1, 2016; April 1, 2017; July 1, 2017
Current Effective Date: July 1, 2017

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.
DESCRIPTION
The intent of the Antidepressant Agents Prior Authorization program is to encourage the use of generic antidepressant agents - selective serotonin reuptake inhibiting agents (SSRIs), serotonin norepinephrine reuptake inhibiting agents (SNRIs), bupropion/bupropion extended-release, or mirtazapine [or generic trazodone extended-release if it becomes available] - prior to brand antidepressant agents and to accommodate for use of brand antidepressant agents when generic prerequisite agents cannot be used due to previous trial, documented intolerance, FDA labeled contraindication, or hypersensitivity. The criteria for Cymbalta also encourage its use for neuropathic pain after trial of amitriptyline, nortriptyline, imipramine, desipramine, or gabapentin, for fibromyalgia (FM) after a trial of amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, tramadol, or gabapentin, and for chronic musculoskeletal pain (CMP; for example, osteoarthritis or chronic low back pain) after a trial of acetaminophen, oral NSAID, topical NSAID, or any other prerequisite for FM or neuropathic pain already listed. The criteria for duloxetine (delayed release capsule, brand product) and Irenka also encourage its use for neuropathic pain after trial of amitriptyline, nortriptyline, imipramine, desipramine, or gabapentin; and for chronic musculoskeletal pain (CMP; for example, osteoarthritis or chronic low back pain) after a trial of acetaminophen, oral NSAID, topical NSAID, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, tramadol, or gabapentin. Requests for brand antidepressant agents will be reviewed when patient-specific documentation has been provided.

Target Drugs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplenzin™ (bupropion)</td>
<td>Maprotiline (tablets, brand product)</td>
</tr>
<tr>
<td>Trintellix™ (vortioxetine)</td>
<td>Oleptro™ (trazodone extended-release) b</td>
</tr>
<tr>
<td>Celexa® (citalopram) a</td>
<td>Paxil® (paroxetine hydrochloride) a</td>
</tr>
<tr>
<td>Cymbalta® (duloxetine) a</td>
<td>Paxil CR® (paroxetine extended-release) a</td>
</tr>
<tr>
<td>Desvenlafaxine (ER tablets, brand product)</td>
<td>Pexeva® (paroxetine mesylate)</td>
</tr>
<tr>
<td>Desvenlafaxine fumarate (ER tablets, brand product)</td>
<td>Pristiq® (desvenlafaxine succinate) a</td>
</tr>
<tr>
<td>Duloxetine 40 mg (delayed release capsule, brand product)</td>
<td>Prozac® (fluoxetine) a</td>
</tr>
<tr>
<td>Effexor® (venlafaxine) a</td>
<td>Prozac® Weekly™ (fluoxetine delayed-release) a</td>
</tr>
<tr>
<td>Effexor XR® (venlafaxine extended-release) a</td>
<td>Remeron® (mirtazapine) a</td>
</tr>
<tr>
<td>Fetzima™ (levomilnacipran extended-release)</td>
<td>Remeron SolTab® (mirtazapine) a</td>
</tr>
<tr>
<td>fluvoxamine extended release a</td>
<td>Venlafaxine ER (tablets, brand product) a</td>
</tr>
<tr>
<td>Fluoxetine 60 mg (tablets, brand product)</td>
<td>Viibryd™ (vilazodone)</td>
</tr>
<tr>
<td>Forfivo XL® (bupropion extended–release)</td>
<td>Wellbutrin® (bupropion) a</td>
</tr>
<tr>
<td>Irenka™ (duloxetine delayed release)</td>
<td>Wellbutrin SR® (bupropion extended-release) a</td>
</tr>
<tr>
<td>Khedezla™ (desvenlafaxine extended release)</td>
<td>Wellbutrin XL® (bupropion extended-release) a</td>
</tr>
<tr>
<td>Lexapro® (escitalopram) a</td>
<td>Zoloft® (sertraline) a</td>
</tr>
</tbody>
</table>

a-available as a generic; generic included as a prerequisite in prior authorization program
b-generic product anticipated
## FDA Approved Indications and Dosage

<table>
<thead>
<tr>
<th>Drug</th>
<th>MDD</th>
<th>OCD</th>
<th>PD</th>
<th>GAD</th>
<th>SAD</th>
<th>PDD</th>
<th>PTSD</th>
<th>Bulimia</th>
<th>Other Diagnoses</th>
<th>Dosing Range (adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors (SSRIs)</strong></td>
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<tr>
<td>Celexa (citalopram) Tablets, Solution</td>
<td>✔</td>
<td></td>
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<td>MDD: 20 mg/day up to 40 mg/day; doses above 40 mg/day are not recommended due to the risk of QT prolongation. 20 mg/day is maximum recommended dose for CYP2C19 poor metabolizers, patients taking cimetadine or another CYP2C19 inhibitor, with hepatic impairment, or age &gt;60</td>
</tr>
<tr>
<td>Fluoxetine 60 mg</td>
<td>✔  ✔  ✔  ✔</td>
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<td></td>
<td></td>
<td>✔</td>
<td>MDD, OCD, PD, Bulimia: 60 mg/day</td>
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<tr>
<td>Fluvoxamine Tablets</td>
<td></td>
<td>✔</td>
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<td>OCD: 50 mg/day as a single dose titrated up to 100-300 mg/day (divided twice daily)</td>
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<tr>
<td>Fluvoxamine Extended Release Capsules</td>
<td></td>
<td>✔</td>
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<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>OCD: 100-300 mg/day</td>
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<tr>
<td>Lexapro (escitalopram) Tablets, Solution</td>
<td>✔</td>
<td>✔</td>
<td></td>
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<td></td>
<td>MDD: 10-20 mg/day</td>
</tr>
<tr>
<td>Paxil (paroxetine) Tablets, Suspension</td>
<td>✔  ✔  ✔  ✔  ✔  ✔</td>
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<td></td>
<td>MDD: 20-50 mg/day</td>
</tr>
<tr>
<td>Paxil CR (paroxetine) Controlled Release Tablets</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td>PD: 10-60 mg/day (target 40 mg/day)</td>
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<tr>
<td>Prozac (fluoxetine) Tablets, Capsules, Solution</td>
<td></td>
<td>✔</td>
<td>✔</td>
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<td></td>
<td>MDD: 20-50 mg/day</td>
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<tr>
<td>Prozac Weekly (fluoxetine) Once Weekly Capsules</td>
<td>✔</td>
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<td></td>
<td>MDD: 90 mg once weekly</td>
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<tr>
<td>Prozac Weekly (fluoxetine) Once Weekly Capsules</td>
<td>✔</td>
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<td></td>
<td>MDD, OCD: 20-80 mg/day</td>
</tr>
<tr>
<td>Zoloft (sertraline) Tablets, Concentrate</td>
<td>✔  ✔  ✔  ✔</td>
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<td></td>
<td>✔</td>
<td>MDD, OCD: Initially 50 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

Contains Public Information
<table>
<thead>
<tr>
<th>Drug</th>
<th>MDD</th>
<th>OCD</th>
<th>PD</th>
<th>GAD</th>
<th>SAD</th>
<th>PD</th>
<th>PTSD</th>
<th>Bulimia</th>
<th>Other Diagnoses</th>
<th>Dosing Range (adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)</strong></td>
<td></td>
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<tr>
<td>Cymbalta (duloxetine) Delayed Release Capsules</td>
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<td></td>
<td>✓ DPNP, FM, CMP</td>
<td>MDD: 20 mg twice daily to 60 mg/day (once or divided twice daily); may titrate from 30 to 60 mg once daily GAD: 60 mg/day (titrate from 30 mg/day) MDD, GAD: 120 mg/day shown effective but no evidence of added benefit and more adverse effects from doses &gt;60 mg/day DPNP: 60 mg/day FM, CMP: 30 mg/day x one week; then 60 mg/day no evidence of added benefit and more adverse effects from doses &gt;60 mg/day</td>
</tr>
<tr>
<td>Desvenlafaxine, Desvenlafaxine fumarate ER Tablets</td>
<td>✓</td>
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<td></td>
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<td></td>
<td>MDD: 50 mg/day (range 50-400 mg/day); no evidence of additional benefit and more adverse effects from doses &gt;50 mg/day</td>
</tr>
<tr>
<td>Duloxetine Delayed Release Capsules</td>
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<td></td>
<td>✓ DPNP CMP</td>
<td>MDD: 40 mg/day – 120 mg/day; no evidence of additional benefit for doses &gt;60 mg/day GAD: 30 mg/day – 120 mg/day; no evidence of additional benefit for doses &gt;60 mg/day DPNP: 60 mg/day; no evidence of additional benefit for doses &gt;60 mg/day CMP: 30 mg/day – 60 mg/day; no evidence of additional benefit for doses &gt;60 mg/day</td>
</tr>
<tr>
<td>Effexor (venlafaxine) Tablets</td>
<td>✓</td>
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<td>MDD: In 2-3 divided doses, 75-225 mg/day (moderately depressed outpatients); up to 350 mg/day (severely depressed inpatients) Maximum 375 mg/day in divided doses</td>
</tr>
<tr>
<td>Effexor XR (venlafaxine ER) ER Capsules</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td></td>
<td>MDD, GAD, PD: Initially 37.5 mg/day for 7 days; then range of 75-225 mg/day SAD: 75 mg/day</td>
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<tr>
<td>Fetzima (levomilnacipran) ER capsules</td>
<td>✓</td>
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<td>MDD: Initial 20 mg once daily, then 40 mg once daily. Based on efficacy/tolerability, increase in increments of 40 mg at intervals of &gt;2 days. Range 40 mg to 120 mg once daily. Maximum recommended dose is 120 mg once daily.</td>
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<tr>
<td>Irenka (duloxetine delayed release)</td>
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<td></td>
<td>✓ DPNP CMP</td>
<td>MDD: 40 mg/day – 120 mg/day; no evidence of additional benefit for doses &gt;60 mg/day GAD: 30 mg/day – 120 mg/day; no evidence of additional benefit for doses &gt;60 mg/day DPNP: 60 mg/day; no evidence of additional benefit for doses &gt;60 mg/day CMP: 30 mg/day – 60 mg/day; no evidence of additional benefit for doses &gt;60 mg/day</td>
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<tr>
<td>Khedezla (desvenlafaxine) ER tablets</td>
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<td></td>
<td></td>
<td>✓</td>
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<td>MDD: 50 mg/day (range 50-400 mg/day); no evidence of additional benefit and more adverse effects from doses &gt;50 mg/day</td>
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<tr>
<td>Pristiq (desvenlafaxine succinate) ER Tablets</td>
<td>✓</td>
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<td></td>
<td></td>
<td></td>
<td>MDD: 50 mg/day (range 50-400 mg/day); no evidence of additional benefit and more adverse effects from doses &gt;50 mg/day</td>
</tr>
<tr>
<td>Drug</td>
<td>MDD</td>
<td>OCD</td>
<td>PD</td>
<td>GAD</td>
<td>SAD</td>
<td>PDD</td>
<td>PTSD</td>
<td>Bulimia</td>
<td>Other Diagnoses</td>
<td>Dosing Range (adults)</td>
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<tr>
<td>Venlafaxine ER</td>
<td>✓</td>
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<td></td>
<td></td>
<td>MDD: Initially 37.5 to 75 mg/day; range of 75-225 mg/day</td>
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<tr>
<td>ER Tablets</td>
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<td>SAD: 75 mg/day</td>
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<tr>
<td>Other Antidepressants</td>
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<tr>
<td>Aplenzin (bupropion)</td>
<td>✓</td>
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<td>MDD: Initially, 174 mg/day; usual target dose is 348 mg/day; consider maximum dose 522 mg/day if no response to 348 mg</td>
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<tr>
<td>ER Tablets</td>
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<tr>
<td>Forfivo XL (bupropion)</td>
<td>✓</td>
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<td>MDD: Initially start with another formulation of bupropion until a patient has been on 300mg of bupropion per day for at least 2 weeks, and requires a dosage of 450mg per day</td>
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<tr>
<td>ER Tablets</td>
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<tr>
<td>Maprotiline Tablets</td>
<td>✓</td>
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<td>MDD: 25 mg three times daily; may increase by 25-50 mg/day at weekly intervals depending on response. Usual dose: 75-150 mg/day (single dose at bedtime or divided). Maximum of 150-220 mg/day (1-3 doses)</td>
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<tr>
<td>Oleptro (trazodone)</td>
<td>✓</td>
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<td></td>
<td>MDD: Initially 150 mg once daily; increase by 75 mg/day; maximum 375 mg/day</td>
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<tr>
<td>ER Tablets</td>
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<tr>
<td>Remeron, Remeron SolTab (mirtazapine) Tablets, ODT Tablets</td>
<td>✓</td>
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<td></td>
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<td></td>
<td></td>
<td>MDD: Initially 15 mg/day; range 15-45 mg/day</td>
</tr>
<tr>
<td>Trintellix (vortioxetine) Tablets</td>
<td>✓</td>
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<td></td>
<td>MDD: Initially, 10 mg once daily; increase to 20 mg/day as tolerated. Efficacy and safety of doses above 20 mg/day have not been evaluated</td>
</tr>
<tr>
<td>Viibryd (vilazodone) Tablets, Starter Kit</td>
<td>✓</td>
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<td></td>
<td></td>
<td>MDD: Initially, 10 mg/day for 7 days; then 20 mg/day for 7 days; then 40 mg/day (recommended dose).</td>
</tr>
<tr>
<td>Wellbutrin, Wellbutrin SR (bupropion) Tablets, ER Tablets</td>
<td>✓</td>
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<td></td>
<td>MDD: Wellbutrin: Initially 100 mg twice daily; may increase to 100 mg three times daily; Maximum of 450 mg/day (divided doses &lt;150 mg each) MDD: Wellbutrin SR: Initially 150 mg once daily; then 150 mg twice daily as early as day 4; Maximum of 200 mg twice daily.</td>
</tr>
<tr>
<td>Wellbutrin XL (bupropion) ER Tablets</td>
<td>✓</td>
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<td></td>
<td>MDD: 150 mg/day titrated to 300 mg/day as early as day 4; Maximum 450 mg/day. SAFD: 150 mg/day for one week; then 300 mg/day (target dose).</td>
</tr>
</tbody>
</table>

MDD=major depressive disorder; OCD=obsessive compulsive disorder; PD=panic disorder; GAD=generalized anxiety disorder; SAD=social anxiety disorder or social phobia; PDD=premenstrual dysphoric disorder; PTSD=post traumatic stress disorder; DPNP=diabetic peripheral neuropathic pain; FM=fibromyalgia; CMP=chronic musculoskeletal pain; SAFD=seasonal affective disorder; ER=extended release; ODT=orally disintegrating.
POLICY

Prior Authorization Criteria for Approval

A. **Brand Antidepressant Agents** (except Cymbalta, Duloxetine (delayed release capsule, brand product), and Irenka, see below) will be approved when BOTH of the following are met:
   1. The patient has not filled a prescription for a monoamine oxidase (MAO) inhibitor in the past 30 days
   AND
   2. ONE of the following:
      a. The patient’s medication history includes use of a generic antidepressant agent - SSRI, SNRI, bupropion, or mirtazapine [or generic trazodone extended-release if it becomes available] in the past 365 days
      OR
      b. There is documentation that the patient is currently using the requested agent
      OR
      c. The prescriber states that the patient is using the requested agent AND is at risk if therapy is changed
      OR
      d. The patient has a history of a documented intolerance, FDA-labeled contraindication, or hypersensitivity to a generic antidepressant agent - SSRI, SNRI, bupropion, or mirtazapine, [or generic trazodone extended-release if it becomes available]

B. **Cymbalta, Duloxetine (delayed release capsule, brand product), and Irenka** will be approved when BOTH of the following are met:
   1. The patient has not filled a prescription for a monoamine oxidase (MAO) inhibitor in the past 30 days
   AND
   2. ONE of the following:
      a. The patient’s medication history includes use of a generic antidepressant agent - SSRI, SNRI, bupropion, or mirtazapine [or generic trazodone extended-release if it becomes available] in the past 365 days
      OR
      b. The patient has a diagnosis of neuropathic pain and the medication history includes use of amitriptyline, nortriptyline, desipramine, imipramine, or gabapentin in the past 90 days
      OR
c. For Cymbalta only, the patient has a diagnosis of fibromyalgia and the medication history includes use of amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, gabapentin, or tramadol in the past 90 days
   **OR**

d. The patient has a diagnosis of chronic musculoskeletal pain and the medication history includes use of acetaminophen, oral NSAID, topical NSAID, tramadol, amitriptyline, nortriptyline, desipramine, imipramine, cyclobenzaprine, or gabapentin in the past 90 days
   **OR**
e. There is documentation that the patient is currently using the requested agent
   **OR**
f. The prescriber states that the patient is using the requested agent AND is at risk if therapy is changed
   **OR**
g. The patient has a history of a documented intolerance, FDA-labeled contraindication, or hypersensitivity to a prerequisite for the requested diagnosis

**Length of approval:** 12 months

**RATIONALE**

**Depression**
Selective serotonin reuptake inhibitors (SSRIs) along with serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, and mirtazapine are considered first line treatment options for adults with major depressive disorder (MDD). The choice of medication is based on side effect profiles, history of prior response, family history of response, type of depression, concurrent medical illnesses, concurrently prescribed medications, and cost of medication. Although all these drugs may have similar efficacy, they differ significantly in their side effect profiles. Patients who cannot tolerate one agent may do well with another.44-47

**Anxiety Disorders**
Guidelines for treatment of anxiety include several anxiety-related conditions: obsessive compulsive disorder (OCD), panic disorder (PD), social anxiety disorder (SAD), post-traumatic stress disorder (PTSD), and generalized anxiety disorder (GAD). Most guidelines on treatment of anxiety disorders consider SSRIs or SNRIs (e.g. venlafaxine) the first line treatment for these conditions. Although all these drugs may have similar efficacy, they differ significantly in their side effect profiles. 48

**Neuropathic Pain**
For patients with diabetic neuropathy, an antidepressant (e.g., amitriptyline, duloxetine, venlafaxine) or anticonvulsant (e.g., pregabalin) is recommend as initial therapy. Available evidence suggests these agents have similar modest benefit, though few high-quality
comparative trials have been done. Among these options, the preference is to start with amitriptyline, particularly in younger healthier patients. Patients who fail to improve with a reasonable trial of one of these agents can be switched to monotherapy with another agent. For patients who do not improve on one drug, suggest combination therapy employing two drugs from different medication classes as the next step in the treatment paradigm. For patients who are unable to tolerate any of these drugs, alternative treatments include capsaicin cream, lidocaine patch, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation.49

A meta-analysis (2015; 225 RCTs) evaluated pharmacotherapy for treatment of neuropathic pain (including painful neuropathy [PDN]). Studies published in peer-reviewed journals reported greater effects than did unpublished studies. Trial outcomes were generally modest: in particular, combined NNTs (50% pain relief) were 6.4 for SNRIs, mainly including duloxetine (nine of 14 studies); 7.7 for pregabalin; 7.2 for gabapentin, and 10.6 for capsaicin high-concentration patches. NNTs were lower for TCAs, strong opioids, tramadol, and botulinum toxin A, and undetermined for lidocaine patches. Based on grade, final quality of evidence was moderate or high for all treatments apart from lidocaine patches; tolerability and safety, and values and preferences were higher for topical drugs; and cost was lower for TCAs and tramadol. These findings permitted a strong recommendation for use and proposal as first-line treatment in neuropathic pain for TCAs, SNRIs, pregabalin, and gabapentin; a weak recommendation for use and proposal as second line for lidocaine patches, capsaicin high-concentration patches, and tramadol; and a weak recommendation for use and proposal as third line for strong opioids and botulinum toxin A. Topical agents and botulinum toxin A are recommended for peripheral neuropathic pain only.22

Several societies and associations have strong recommendations for TCAs, gabapentin, pregabalin, and SNRI antidepressants (duloxetine [most studied], venlafaxine) as first-line therapies. 21

AAN recommendations for treatment of PDN include pregabalin (level A evidence, established as effective); and gabapentin, sodium valproate, venlafaxine, duloxetine, amitriptyline, dextromethorphan, maprotiline, tramadol, oxycodone, capsaicin, isosorbide dinitrate, electrical stimulation, percutaneous nerve stimulation (level B evidence, considered probably effective).36

**Fibromyalgia**

Nonpharmacological therapy should be first-line therapy and then if there is a lack of effect, therapy should be individualized according to patient need, which may include pharmacological therapy. Pharmacologic therapies include: duloxetine, milnacipran, tramadol, pregabalin, cyclobenzaprine. Strength of recommendation for all these options is weak.23,50 A review (2015) suggests pharmaceuticals (e.g., pregabalin, duloxetine, milnacipran) will provide clinically meaningful improvement without any major adverse events for a relatively small subset of patients only. In many other patients, the benefits do not outweigh the adverse effects, while the remainder do not experience any symptom improvement or even get worse.23,51

Pharmacological therapy should be guided by predominant symptoms that accompany pain. All patients should have a good therapeutic trial of a low-dose tricyclic compound (e.g., cyclobenzaprine, amitriptyline, or nortriptyline). Patients with comorbid depression or fatigue should next try a serotonin norepinephrine reuptake inhibitor (SNRI). Patients with comorbid
anxiety or sleep issues should next try a gabapentinoid. It is often necessary to use several
classes of drugs together. Use of opioids is discouraged. Nonsteroidal antiinflammatory drugs
(NSAIDs) and acetaminophen can be used to treat comorbid peripheral pain generators.25

**Chronic Musculoskeletal Pain**
The American Psychiatric Association recommends the use of TCAs and SNRIs for treating
chronic pain and comorbid depression.28,42 SNRIs, which target both serotonin and
norepinephrine, have a greater analgesic effect than antidepressants targeting either
neurotransmitter alone. Duloxetine and venlafaxine have effectively reduced symptoms in
patients with pain disorders and comorbid depression.38

Duloxetine is indicated for the management of chronic musculoskeletal pain, which was
established in studies of patients with chronic low back pain and chronic pain due to
osteoarthritis (OA).13 A guideline on treatment of chronic noncancer pain including neuropathic,
somatic, myofascial and visceral types of pain (American Society of Anesthesiologists, 2010)
includes anticonvulsants, antidepressants (TCAs and SNRIs), benzodiazepines, NMDA receptor
antagonists, NSAIDs, opioids, skeletal muscle relaxants, and topical agents as part of a
multimodal strategy for a variety of patients with chronic pain.31

**Adverse Effects**

**SSRIs**
SSRIs commonly cause nausea, vomiting, diarrhea, nervous activation (e.g., insomnia,
restlessness, anxiety), and headaches and these may dissipate over time. Although sexual
dysfunction (e.g., loss of libido, erectile/ejaculatory problems) can occur with any antidepressant,
this appears to be more common with SSRIs, and may also disappear with time. Paroxetine is
associated with a higher incidence of weight gain than other SSRIs. Serotonin syndrome is
associated with simultaneous use of SSRIs plus other serotonergic agents (e.g., mono
amine oxidase inhibitors [MAOIs]) and should be avoided. SSRIs should not be abruptly discontinued to
avoid discontinuation syndrome; most likely with paroxetine, least likely with fluoxetine.28

Citalopram doses above 40 mg/day are not recommended due to the risk of QT prolongation; 20
mg/day is the maximum recommended dose for CYP2C19 poor metabolizers or those patients
taking a CYP2C19 inhibitor.4 Citalopram should not be used in patients with QT syndrome,
bradycardia, hypokalemia, hypomagnesemia, recent acute myocardial infarction, uncompensated
heart failure, or with other drugs that prolong the QTc interval. Patients at risk for electrolyte
disturbances should have baseline serum potassium and magnesium checked with periodic
monitoring.4,24

**SNRIs**
SNRI side effects are similar with those of SSRIs (nausea, vomiting, nervous activation, sexual
dysfunction) and may attenuate with continued use. SNRI effects are also more likely to reflect
noradrenergic activity (increased pulse, dilated pupils, dry mouth, excess sweating, and
constipation). All three SNRIs have a risk of increased blood pressure, especially at higher doses.
As with SSRIs, serotonin syndrome is associated with simultaneous use of SNRIs plus other
serotonergic agents (e.g., MAOIs) and should be avoided. Like SSRIs, SNRIs should not be
abruptly discontinued to avoid discontinuation syndrome; more likely with venlafaxine and
desvenlafaxine than duloxetine.28
Vortioxetine
Most common adverse reactions in patients on vortioxetine were nausea, constipation and vomiting.  

Vilazodone
Most common adverse effects of vilazodone in clinical trials were diarrhea, nausea, vomiting, and insomnia. Vilazodone is an SSRI and partial serotonergic 5-HT_{1a} agonist. Like SSRIs and SNRIs, the drug is associated with serotonin and discontinuation syndromes, and should not be given with other serotonergic agents or discontinued abruptly.

Bupropion
Bupropion has fewer sexual side effects than other antidepressants. Neurologic adverse effects include headache, tremors, and seizures. Risk of seizures is minimized by avoiding high doses, avoiding rapid titration, using divided dosing schedules, avoiding use in patients at risk of seizures. Other side effects may include agitation/nervousness, mild cognitive dysfunction, insomnia, gastrointestinal upset.

Mirtazapine
Most common side effects of mirtazapine include dry mouth, sedation, and weight gain (greater risk than other antidepressants). Mirtazapine is often given at bedtime and may be chosen for depressed patients with initial insomnia and weight loss. Mirtazapine increases serum cholesterol levels in some patients.

Trazodone
The most common side effect with trazodone is sedation; this may be an advantage in patients with initial insomnias. Trazodone can also cause cardiovascular side effects, including orthostasis, particularly among elderly patients or those with preexisting heart disease. Use of trazodone has also been associated with life-threatening ventricular arrhythmias in several case reports. Trazodone also can cause sexual side effects, including erectile dysfunction in men; in rare instances, priapism occurs, which might require surgical correction.

Maprotiline
Side effects with maprotiline may be similar to those seen with tricyclic antidepressants (TCAs), and can include cardiovascular effects including arrhythmias, anticholinergic effects, sedation, orthostatic hypotension, weight gain and seizures at therapeutic doses. Potentially dangerous interactions, including hypertensive crises and serotonin syndrome, can develop when TCAs are administered with MAOIs.

Serotonin Syndrome
Serotonin syndrome is presumed to result from high levels of serotonin in the brain. Features of serotonin syndrome include abdominal pain, diarrhea, flushing, sweating, hyperthermia, lethargy, mental status changes, tremor and myoclonus, rhabdomyolysis, renal failure, cardiovascular shock, and possibly death. Although it can occur with administration of one or more serotonergic medications, it is most severe when an MAOI is coadministered with another serotonergic medication (such as an antidepressant).

Other antidepressants should not be used in patients concomitantly taking an MAOI.
**REVISIONS**

<table>
<thead>
<tr>
<th>Date</th>
<th>Revision Details</th>
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  In Description section:  
  ▪ Added to Target Drugs: Brintellix™ (vortioxetine), Khedezla (Desvenlafaxine ER tablets), and Fetzima™ (levomilnacipran extended-release)  
  ▪ Updated FDA Approved Indications and Dosage References updated |
| 07-01-2014 | Administrative Update  
  In Description section:  
  ▪ Added target drugs: Desvenlafaxine (ER tablets, brand product) and Desvenlafaxine fumarate (ER tablets, brand product)  
  ▪ FDA Approved Indications and Dosage chart updated References updated |
| 09-17-2014 | Description section updated  
  ▪ Target Drugs chart revised.  
  ▪ FDA Approved Indications and Dosage chart updated to add Fluoxetine and correct dosage for Brintellix  
  In Policy section:  
  ▪ In Items A 2 a, A 2 d, and B 2 a added "antidepressant agent" "generic", and "if it becomes available" to read, "... antidepressant agent - SSRI, SNRI, bupropion, or mirtazapine [or generic trazodone extended-release if it becomes available]"  
  ▪ In Items A 2 c and B 2 f removed "prescribing physician" and added "provider" to read, "The prescriber states the patient..."  
  Rationale section updated  
  In Coding section  
  ▪ HCPCS Codes confirmed  
  In Revision section  
| 06-10-2015 | Description section updated  
  FDA Approved Indications and Dosage chart updated  
  In Policy section:  
  ▪ In Items A 2 c and B 2 f, grammar corrections made.  
  Rationale section updated  
  Coding section removed  
  References updated |
  Description section updated to include addition of "Duloxetine 40 mg (brand)" and "Irenka (duloxetine delayed release)" drug to Target Drugs chart and "Irenka (duloxetine delayed release)" to the FDA Approved Indications and Dosage chart.  
  In Policy section:  
  ▪ In Item A added “and Irenka" to read, "Brand Antidepressant Agents (except Cymbalta and Irenka, see below) will be approved when BOTH of the following are met:...”  
  ▪ In Item B added “and Irenka” to read, “Cymbalta and Irenka will be approved when BOTH of the following are met:...”  
  ▪ In Item B 2 c added “For Cymbalta only,” to read, "For Cymbalta only, the patient has a diagnosis of fibromyalgia and..."  
  ▪ In Item B 2 e added “the requested agent” and removed “Cymbalta (duloxetine)” to read, “There is documentation that the patient is currently using the requested agent”  
  ▪ In Item B 2 f added “the requested agent” and removed “Cymbalta (duloxetine)” to read, “The prescriber states that the patient is using the requested agent AND...” |
**REVISIONS**

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<tr>
<td>06-01-2016</td>
<td>Published 05-25-2016. Effective 06-01-2016. Description section updates to Target Drugs and FDA Approved Indications and Dosage charts.</td>
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<td>In Policy section:</td>
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<td>- In Item A added &quot;Duloxetine (delayed release capsule, brand product),&quot; to read &quot;Brand Antidepressant Agents (except Cymbalta, Duloxetine (delayed release capsule, brand product), and Irenka, see below) will be approved when BOTH of the following are met:&quot;</td>
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<td>- In Item A 2 a, B 2 a, B 2 b, and B 2 c added &quot;in the past 365 days&quot;</td>
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<td>- In Item B added &quot;Duloxetine (delayed release capsule, brand product),&quot; to read &quot;Cymbalta, Duloxetine (delayed release capsule, brand product), and Irenka will be approved when BOTH of the following are met:&quot;</td>
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<td>07-01-2016</td>
<td>Published 07-20-2016. Retro-effective to 07-01-2016. The Brand drug name Brintellex was changed to Trintellix to avoid confusion with the antiplatelet drug Brilinta (ticagrelor).</td>
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<td>In Description section:</td>
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<td>- Trintellix added to Target Drugs; FDA Approved Indications and Dosage charts.</td>
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<td>In Revision section:</td>
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<td>- Removed Revision narratives for the following revision dates: 02-01-2012, 08-30-2012, 10-01-2013</td>
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<tr>
<td>04-01-2017</td>
<td>In Description section:</td>
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<tr>
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<td>- Noted availability of first generic drug for Pristiq in Target Drugs chart.</td>
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<tr>
<td>07-01-2017</td>
<td>In Description section:</td>
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<tr>
<td></td>
<td>- Target Drugs updated to remove Brintellix and Luvox CR and add fluvoxamine extended release</td>
</tr>
<tr>
<td></td>
<td>- FDA Approved Indications and Dosage updated to reflect Target Drugs updates</td>
</tr>
<tr>
<td></td>
<td>In Policy section:</td>
</tr>
<tr>
<td></td>
<td>- In Item A 2 b and A 2 c removed &quot;brand antidepressant&quot; and added &quot;agent&quot; to read &quot;...the patient is currently using the requested agent...&quot;</td>
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<td>- In Item B 2 b, B 2 c, and B 2 d revised &quot;365 days&quot; to &quot;90 days&quot;.</td>
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</tbody>
</table>

**REFERENCES**

52. Up to Date (2017): Treatment of fibromyalgia in adults not responsive to initial therapies. Current through Dec 2016.