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Antidepressant Agents Step Therapy Criteria with Medical Diagnoses Option*

* Medical diagnoses are required for implementation of this option.

Brand	Generic	Dosage Form
Celexa [®]	citalopram	tablet ^a , oral solution ^a
Cymbalta [®]	duloxetine	delayed-release capsule
Effexor [®]	venlafaxine	tablet ^a
Effexor XR [®]	venlafaxine	extended-release capsule
Lexapro [®]	escitalopram	tablet, oral solution
Luvox [®] CR	fluvoxamine	extended-release capsule
Paxil [®]	paroxetine hydrochloride	tablet ^a , oral suspension ^a
Paxil CR [®]	paroxetine hydrochloride	controlled-release tablet ^a
Pexeva [®]	paroxetine mesylate	tablet
Pristiq [™]	desvenlafaxine	extended-release tablet
Prozac [®]	fluoxetine ^b	capsule ^a , tablet ^a , oral solution ^a
Remeron [®]	mirtazapine	tablet ^a
RemeronSolTab [®]	mirtazapine	orally disintegrating tablet ^a
venlafaxine XR	venlafaxine	extended-release tablet
Wellbutrin [®]	bupropion	tablet ^a
Wellbutrin SR [®]	bupropion	sustained-release tablet ^a
Wellbutrin XL [®]	bupropion	extended-release tablet ^a
Zoloft [®]	sertraline	tablet ^a , oral concentrate ^a

a - currently available as generic b - Prozac[®] Weekly[™] and Sarafem[®] brand are not included in this step therapy program

FDA APPROVED INDICATIONS¹⁻¹⁸

The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section "Prior Authorization Criteria for Approval."

Table 1. FDA Approved Indications¹⁻¹⁸

Available Products	Depression	OCD	PD	GAD	SAD	PMDD	PTSD	Bulimia Nervosa	Seasonal Affect Dis	DPNP	Fibro-myalgia
Celexa (citalopram)	✓										
Cymbalta (duloxetine)	✓			✓						✓	✓
Effexor (venlafaxine)	✓										
Effexor XR (venlafaxine ER)	✓		✓	✓	✓						
fluvoxamine		✓ _{≥8}									
Lexapro (escitalopram)	✓			✓							
Luvox CR (fluvoxamine CR)		✓			✓						
maprotiline	✓										
Paxil (paroxetine)	✓	✓	✓	✓	✓		✓				
Paxil CR (paroxetine CR)	✓		✓		✓	✓					
Pexeva (paroxetine mesylate)	✓	✓	✓	✓							
Pristiq (desvenlafaxine)	✓										
Prozac (fluoxetine)	✓ _{≥8 yr}	✓ _{≥7}	✓					✓			
Remeron (mirtazapine)	✓										
venlafaxine XR (tablets)	✓				✓						
Wellbutrin (bupropion)	✓										
Wellbutrin SR (bupropion SR)	✓										
Wellbutrin XR (bupropion ER)	✓								✓		
Zoloft (sertraline)	✓	✓ _{≥6}	✓		✓	✓	✓				

OCD= obsessive compulsive disorder; PD= panic disorder; GAD= generalized anxiety disorder; SAD= social anxiety disorder; PMDD= premenstrual dysphoric disorder; PTSD= post traumatic stress disorder, DPNP=diabetic peripheral neuropathic pain.

RATIONALE FOR STEP THERAPY

The intent of the step therapy criteria for Antidepressant Agents is to encourage the use of generic agents - selective serotonin reuptake inhibiting agents (SSRIs), bupropion/bupropion SR, maprotiline, mirtazapine, or venlafaxine immediate-release (IR) - prior to brand name agents (including Venlafaxine XR extended-release tablets). Guidelines for conditions such as major depressive disorder, social anxiety disorder, general anxiety disorder, panic disorder, and obsessive compulsive disorder (see tables below) show that there are first-line agents for these disorders available generically. Both efficacy and safety issues have been considered. The intent of the inclusion of Medical Diagnoses Option Criteria (see below) is to support medication adherence and continuation of therapy in patients with the high-risk diagnosis of "Major Depressive Disorder, Recurrent" (ICD-9 296.3X). In addition, the intent of the step therapy is to encourage the use of first-line generic agents before Cymbalta when prescribed for neuropathic pain or fibromyalgia.

Major Depressive Disorder

Published guidelines and systematic reviews have evaluated medications for treatment of major depressive disorder. [see Chapter 9.2C: Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRI) and Chapter 9.2E: Antidepressants: Miscellaneous].^{19,20} Recommendations for treatment of major depressive disorder are summarized in the following table:

Table 2: Recommendations for Treatment of Major Depressive Disorder^{19,20,22}

	First Line	Second Line	Third Line and Other
APA ^{19,20} (2000)	SSRIs, bupropion, venlafaxine, desipramine, nortriptyline		
VHA ^{19,20} (2000)	SSRIs, TCAs, bupropion	nefazodone, mirtazapine, venlafaxine; MAOIs; amoxapine, maprotiline, trazodone	
TIMA ^{19,20} (2000)	SSRIs, bupropion, nefazodone, venlafaxine, mirtazapine		
Prodigy (CKS) ^{19,20} (2005)	SSRI	alternate SSRI, mirtazapine; TCAs, venlafaxine	combinations, phenelzine, lithium
OHSU ²² (2006)	SSRIs, mirtazapine, bupropion, nefazodone, duloxetine, venlafaxine		
Medical Letter ^{19,20} (2006)	SSRIs		
NICE ^{19,20} (2007)	SSRI (generic)	alternate SSRI, mirtazapine; TCAs, venlafaxine	augmentation - lithium, venlafaxine if not used before, SSRI + mirtazapine; phenelzine
AHRQ ^{19,20} (2007)	SSRIs, bupropion, mirtazapine, nefazodone, trazodone, venlafaxine, duloxetine		
ICSI ^{19,20} (2007)	SSRIs, venlafaxine, duloxetine, mirtazapine, bupropion; TCAs	MAOIs; combinations or augmentation	

AHRQ – Agency for Healthcare Research and Quality; APA – American Psychiatric Association; CKS – Clinical Knowledge Summaries; ICSI – Institute for Clinical Systems Improvement; NICE – National Institute for Health and Clinical Excellence; OHSU – Oregon Health & Science University; TMAP – Texas Implementation of Medication Algorithm; VHA – Veterans Health Administration; SSRI – selective serotonin reuptake inhibitor; TCA – tricyclic antidepressant; MAOI – monoamine oxidase inhibitor

Desvenlafaxine is the newest antidepressant to be marketed. Like duloxetine and venlafaxine, it is an inhibitor of serotonin and norepinephrine reuptake (SNRI).¹⁰ According to the prescribing information¹⁰ its efficacy in the treatment of depression was established in four 8-week, randomized, double-blind, placebo-controlled, fixed-dose studies at doses of 50 mg/day to 400 mg/day in adult outpatients with major depressive disorder. Desvenlafaxine showed superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scaled for Depression (HAM-D17) total score in all four studies, and overall improvement as measured by the Clinical Global Impressions Scale-Improvement (CGI-I), in three of the four studies. In studies directly comparing 50 mg/day and 100 mg/day there was no suggestion of a greater effect with the higher dose.¹⁰ Two published phase III trials^{23,24} have reported efficacy for 100 mg/day, 200 mg/day, and 400 mg/day doses using the HAM-D17 as the primary efficacy measure, finding these dosages significantly better than placebo. CGI-I scores were also significant for these doses.^{23,24} In one study²⁴ response rates were found to be significant for 100 mg/day (51%) and 400 mg/day (48%) compared to placebo (35%); the response rate for 200 mg/day was 45%, not significantly different than placebo.²⁴

Safety and side effects of therapy should be considered before venlafaxine is prescribed. The NICE guidelines²⁵ state that the following issues should be evaluated: increased likelihood of patients discontinuing therapy due to side effects (compared with equally effective SSRIs), increased risk for discontinuation/withdrawal symptoms if abruptly stopped, toxicity in overdose. Before initiation, ECG and blood pressure measurements should be taken; monitoring cardiac function should be considered. Regular monitoring of blood pressure is suggested, especially for patients on high doses.²⁵

Anxiety Disorders – Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder, Obsessive Compulsive Disorder

Published guidelines and systematic reviews have evaluated medications for treatment of anxiety disorders, including generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder (PD), and obsessive compulsive disorder (OCD). [see Chapter 9.2C: Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRI) and Chapter 9.2E: Antidepressants: Miscellaneous].^{19,20} Recommendations for treatment of anxiety disorders are summarized in the following tables:

Table 3: Recommendations for Generalized Anxiety Disorder (GAD)^{19,20,22,26-28}

	First Line	Second Line	Third Line and Other
International Consensus ²⁸ (1998)	SSRIs, SNRIs, TCAs		
Cochrane Reviews ^{19,20} (2003)	imipramine, paroxetine, sertraline, venlafaxine		
Goodman ²⁶ (2004)	paroxetine, escitalopram, venlafaxine		
NICE ²⁷ (2004)	SSRIs	alternate SSRI	venlafaxine
BAP ^{19,20} (2005)	SSRIs, venlafaxine, imipramine, buspirone, benzodiazepines	venlafaxine or imipramine if no response to SSRI, or add benzodiazepine	
CPA ^{19,20} (2005)	SSRI, venlafaxine XR	benzodiazepines, buspirone, imipramine, pregabalin, bupropion XL	mirtazapine, trazodone; adjunctive atypical antipsychotic
Clin Evid ^{19,20} (2005)	imipramine, paroxetine, sertraline, escitalopram, venlafaxine, buspirone	benzodiazepines, trifluoperazine	
OHSU ²² (2006)	escitalopram, paroxetine, venlafaxine, sertraline		
Medical Letter ^{19,20} (2006)	SSRIs	bupropion	

BAP – British Association of Psychopharmacology; Clin Evid – Clinical Evidence; CPA – Canadian Psychiatric Association; NICE – National Institute for Health and Clinical Excellence; OHSU – Oregon Health & Science University; SSRI – selective serotonin reuptake inhibitor; SNRI – serotonin norepinephrine reuptake inhibitor; TCA – tricyclic antidepressant

Table 4: Recommendations for Social Anxiety Disorder (SAD)^{19,20,22,28,29}

	First Line	Second Line	Third Line and Other
International Consensus ²⁸ (1998)	SSRIs (paroxetine, sertraline, fluvoxamine, fluoxetine, citalopram)		
Cochrane ²⁹ (2000)	SSRIs (fluoxetine, fluvoxamine, escitalopram, paroxetine, sertraline)		
CPA ^{19,20} (2005)	SSRI, venlafaxine XR	benzodiazepines, gabapentin, pregabalin, phenelzine	bupropion, mirtazapine, divalproex, topiramate, atypical antipsychotics
BAP ^{19,20} (2005)	effective - SSRIs, phenelzine, venlafaxine, olanzapine, benzodiazepines, anticonvulsants	switch to venlafaxine or add buspirone or benzodiazepine if no response to SSRI	
OHSU ²² (2006)	citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine ER,		

BAP – British Association of Psychopharmacology; CPA – Canadian Psychiatric Association; OHSU – Oregon Health & Science University; SSRI – selective serotonin reuptake inhibitor

Luvox CR (fluvoxamine extended-release) is newly available for SAD. According to the prescribing information,⁶ the effectiveness of fluvoxamine ER in SAD was demonstrated in two 12-week, multicenter, placebo-controlled studies of adult outpatients with SAD. Patients in these trials were titrated in 4 50 mg increments over the first six weeks of the study on the basis of response and tolerance from a dose of 100 mg/day to a dose within a range of 100 mg to 300 mg once-a-day (mean daily doses were 236 mg and 204 mg). On the basis of change from baseline in the Liebowitz Social Anxiety Scale (LSAS), fluvoxamine ER demonstrated statistically significant superiority over placebo at the primary endpoint at week 12.⁶ Published 12-week clinical trials also showed efficacy of fluvoxamine ER compared with placebo using the LSAS.^{30,31} In a published trial of a 12-week extension phase of one placebo-controlled trial, subjects who demonstrated some improvement at the end of a 12-week acute-phase trial were allowed to continue for a further 12 weeks under double-blind conditions.³² Results showed that subjects treated with fluvoxamine ER had a numerically greater decrease in LSAS total score than subjects treated with placebo. Although the magnitude of changes was smaller in the extension phase than in the acute phase, fluvoxamine ER-treated subjects continued to show improvement compared with placebo-treated subjects.³²

Table 5: Recommendations for Panic Disorder (PD)^{19,20,22,27,33,34}

	First Line	Second Line	Third Line and Other
APA ³³ (1998)	SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine), TCAs, benzodiazepines	MAOIs	
Clin Evid ^{19,20} (2004)	SSRIs, TCAs	benzodiazepines	
NICE ²⁷ (2004)	SSRIs	TCAs (imipramine, clomipramine)	
BAP ^{19,20} (2005)	effective - SSRIs, TCAs, benzodiazepines, venlafaxine	switch or combine effective therapies	
CPA ^{19,20} (2005)	SSRI, venlafaxine XR	alternate first line therapy; TCAs, mirtazapine, benzodiazepines	Divalproex, gabapentin, phenelzine, atypical antipsychotics, pindolol
APA – Practice Watch ³⁴ (2006)	above (APA 1998) plus citalopram, escitalopram, venlafaxine ER		
OHSU ²² (2006)	fluoxetine, paroxetine, sertraline		

APA – American Psychiatric Association; BAP – British Association of Psychopharmacology; Clin Evid – Clinical Evidence; CPA – Canadian Psychiatric Association; NICE – National Institute for Health and Clinical Excellence; OHSU – Oregon Health & Science University; SSRI – selective serotonin reuptake inhibitor; TCA – tricyclic antidepressant; MAOI – monoamine oxidase inhibitor

Table 6: Recommendations for Obsessive Compulsive Disorder (OCD)^{19,20}

	First Line	Second Line	Third Line and Other
BAP ^{19,20} (2005)	effective - SSRIs, clomipramine	switch or combine effective therapies; augment with antipsychotic or pindolol	
CPA ^{19,20} (2005)	SSRI	clomipramine, mirtazapine, venlafaxine XR	MAOIs; adjunctive second line or atypical antipsychotic, haloperidol, pindolol, topiramate
NICE ^{19,20} (2005)	SSRIs	a second SSRI or clomipramine	
Clin Evid ^{19,20} (2006)	SSRIs, clomipramine		
APA ^{19,20} (2007)	SSRIs, clomipramine		

APA – American Psychiatric Association; BAP – British Association of Psychopharmacology; Clin Evid – Clinical Evidence; CPA – Canadian Psychiatric Association; NICE – National Institute for Health and Clinical Excellence; SSRI – selective serotonin reuptake inhibitor

Fluvoxamine ER has been shown to be effective in OCD in a 12-week, multicenter, placebo-controlled study of adult outpatients with moderate to severe OCD.⁶ As in the SAD studies, doses were started at 50 mg/day and titrated up to a final dose within the range of 100 mg/day to 300 mg/day. The mean daily dose at the end of the study was 261 mg/day. Patients receiving fluvoxamine ER demonstrated statistically significant improvement over placebo patients at the primary endpoint (week 12) compared to baseline on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).⁶

Of the SSRI agents, Celexa (citalopram), Paxil immediate-release (paroxetine hydrochloride), Paxil CR (paroxetine hydrochloride controlled-release), Prozac (fluoxetine), and Zoloft (sertraline) are available as AB-rated generics in the oral solid dosage forms; an exception is Prozac Weekly (90 mg fluoxetine extended-release capsules). Fluvoxamine immediate-release is available as a generic only; brand Luvox[®] is no longer being marketed. The oral solutions of Prozac and Celexa are available as AA-rated generics; the generic sertraline oral concentrate is AB-rated to Zoloft oral concentrate; the generic paroxetine hydrochloride oral suspension is AB-rated to Paxil. Lexapro (escitalopram), Luvox CR (fluvoxamine extended-release), and Pexeva (paroxetine mesylate) are not available in generic formulations. For the non-SSRIs there are AB-rated generics for bupropion tablets, bupropion SR tablets, bupropion ER tablets, mirtazapine tablets, mirtazapine orally disintegrating tablets, and venlafaxine IR tablets.

For psychiatric indications, the following table summarizes the FDA-approved uses for AB-rated generic products and the SSRIs that have accepted unlabeled uses documented in the pharmaceutical compendia, USP/DI (accepted indications) and Micromedex DrugDex (treatment considered useful in some or most cases), and also systematic reviews such as Clinical Evidence Concise 2005 (beneficial or likely to be beneficial), or practice guidelines.³⁵⁻⁴⁴

Table 7. Generically-available SSRIs, FDA Approved Indications and Unlabeled Uses

Indication	FDA-approved agents ¹⁻¹⁸	Accepted Unlabeled agents ³⁵⁻⁴⁴
Depression	citalopram, fluoxetine, paroxetine, sertraline, bupropion, venlafaxine	
OCD	fluvoxamine, fluoxetine, paroxetine, sertraline	citalopram ³⁹
PD	fluoxetine, paroxetine, sertraline	citalopram ^{35,37,39} , fluvoxamine ^{35,37,39}
GAD	paroxetine	sertraline ^{35,40,44}
SAD	paroxetine, sertraline	fluvoxamine ^{35,37,44}
PMDD	sertraline	citalopram ^{37,41} , fluvoxamine ⁴¹ , paroxetine ⁴¹
PTSD	paroxetine, sertraline	fluoxetine ^{7,37,42,43,44}
Bulimia	fluoxetine	fluvoxamine ³⁷

*OCD= obsessive compulsive disorder; PD= panic disorder; GAD= generalized anxiety disorder; SAD= social anxiety disorder or social phobia; PMDD= premenstrual dysphoric disorder; PTSD= post traumatic stress disorder.

Neuropathic Pain

Published guidelines and systematic reviews have evaluated medications for treatment of neuropathic pain syndromes. [see Chapter 9.2E: Antidepressants: Miscellaneous and Chapter 9.2B: Antidepressants: Tricyclic Antidepressants (TCAs)].^{20,21} Recommendations for treatment of neuropathic pain are summarized in the following table:

Table 8: Recommendations for Treatment of Neuropathic Pain^{20,21,45-51}

	First Line	Second Line	Third Line and Other
AAN ^{20,21} (2004)	amitriptyline, nortriptyline, desipramine, maprotiline, gabapentin, pregabalin, topical lidocaine, opioids		
Duby et al ^{20,21} (2004)	desipramine, amitriptyline, capsaicin, tramadol, gabapentin, bupropion, venlafaxine	opioids, NSAIDs	citalopram, paroxetine, lamotrigine, oxcarbazepine
Cochrane Reviews ⁴⁷⁻⁴⁹ (2004, 2005)	TCAs	gabapentin, other anticonvulsants	

	First Line	Second Line	Third Line and Other
Irving ⁵¹ (2005)	gabapentin	TCAs, venlafaxine, duloxetine, bupropion, lidocaine patch, carbamazepine, lamotrigine, topiramate, oxcarbazepine, valproate, tramadol, opioids	
Hempenstall et al ^{20,21} (2005)	TCAs, gabapentin, tramadol, pregabalin, opioids		
Maizels et al ^{20,21} (2005)	TCAs, gabapentin	bupropion, venlafaxine	opioids, tramadol
Mayo Clinic ^{20,21} (2006)	TCAs (amitriptyline, desipramine), pregabalin, duloxetine, oxycodone CR	carbamazepine, gabapentin, lamotrigine, tramadol, venlafaxine ER	topical capsaicin cream, lidocaine patches
Clin Evid ^{20,21} (2006)	TCAs, gabapentin		topical counterirritants or anesthetics, opioids
EFNS ^{20,21} (2006)	TCAs, gabapentin, pregabalin	duloxetine, venlafaxine, lamotrigine, tramadol, topical lidocaine	
Gilron et al ^{20,21} (2006)	TCAs, gabapentin, pregabalin, SNRIs		
Cochrane Reviews ^{20,21} (2007)	TCAs, venlafaxine		
Dworkin ⁵⁰ (2007)	TCAs, SNRIs (venlafaxine, duloxetine), gabapentin, pregabalin	opioids, tramadol	carbamazepine, lamotrigine, valproic acid, oxcarbazepine, topiramate, bupropion, citalopram, paroxetine, mexiletine, capsaicin
AACE ⁴⁶ (2007)	duloxetine, pregabalin, TCAs, capsaicin, anticonvulsants		
Prodigy (CKS) ^{20,21} (2007)	TCAs (amitriptyline, nortriptyline, desipramine), gabapentin, pregabalin, lidocaine patch, tramadol, duloxetine, venlafaxine	paroxetine, citalopram, bupropion, lamotrigine, carbamazepine	
Wong et al ^{20,21} (2007)	capsaicin and/or TCAs	sodium valproate, carbamazepine	pregabalin, gabapentin, duloxetine, opioids
CPS ^{20,21} (2007)	TCAs, gabapentin, pregabalin	SNRIs, topical lidocaine	Tramadol, opioids, lamotrigine, topiramate, valproic acid
ADA ^{20,21,45} (2005, 2008)	TCAs (amitriptyline, imipramine), duloxetine	gabapentin, pregabalin, lamotrigine, topiramate, carbamazepine	tramadol, oxycodone, capsaicin

AAN – American Academy of Neurology; AACE – American Association of Clinical Endocrinologists;

ADA – American Diabetes Association; Clin Evid – Clinical Evidence; CKS – Clinical Knowledge Summaries;

CPS – Canadian Pain Society; EFNS – European Federation of Neurological Societies;

SSRI - selective serotonin reuptake inhibitor, SNRI – serotonin norepinephrine reuptake inhibitor TCAs - tricyclic antidepressants

Duloxetine is approved for treatment of pain associated with diabetic peripheral neuropathy (DPNP).¹ There are no trials comparing duloxetine with other agents used to treat peripheral neuropathy. The VA review of duloxetine use in painful diabetic neuropathy and fibromyalgia⁵² states that: “Given (1) the lack of direct evidence of the relative treatment benefits of duloxetine in patients with diabetic peripheral neuropathy and fibromyalgia, (2) the indirect evidence suggesting that duloxetine is not better

than alternative formulary agents, as well as, (3) the lack of long-term (>1 year) safety trials, duloxetine should generally be used as a second-line agent after adequate trials of alternative oral, non-opioid formulary agents.⁵² The 2005 review by the Medical Letter on Drugs and Therapeutics⁵³ concludes that duloxetine has efficacy in treatment of pain, but that there are no studies comparing duloxetine with other drugs used for pain due to diabetic neuropathy. Duloxetine was more effective than placebo in clinical trials, but the duration of trials was relatively short; and long-term effectiveness remains unclear.⁵³

Although carbamazepine is considered by some to have “stood the test of time” as far as effectiveness in neuropathic pain,⁴⁷ recent evaluations consider carbamazepine to be highly effective for trigeminal neuralgia but not always beneficial for other types of neuropathic pain.^{20,21,47,49}

Dworkin et al.⁵⁰ state that most randomized controlled trials of chronic neuropathic pain have examined only 2 pain syndromes, DPNP and PHN. These authors suggest that while the applicability of the results of clinical trials for one chronic neuropathic pain syndrome to others cannot be determined, most of the first-line therapies have been tested with multiple types of neuropathic pain and have shown similar results.⁵⁰ Because of this, the PA Criteria for Approval for use of duloxetine for neuropathic pain will include as possible pre-requisites the generic agents included as first-line therapy in the guidelines and reviews listed above—amitriptyline, nortriptyline, imipramine, desipramine, and gabapentin. Oxycodone ER and tramadol will not be included due to their higher potential for overuse, abuse, and dependence.

Fibromyalgia

Fibromyalgia is a disease characterized by widespread pain for longer than 3 months and bilateral sites of amplified tenderness.⁵⁴⁻⁶² In most patients, fibromyalgia is associated with fatigue, sleep dysfunction, stiffness, depression, anxiety, cognitive disturbance, or exercise intolerance. The etiology and pathophysiology of fibromyalgia remain unclear; current hypotheses center on atypical sensory processing in the CNS and dysfunction of skeletal muscle nociception and the hypothalamic-pituitary-adrenal axis.^{54,56,60} Randomized controlled trials are generally difficult due to factors such as a lack of understanding of the pathophysiology and a heterogeneous fibromyalgia patient population.⁵⁴⁻⁶²

The American College of Rheumatology (ACR) currently has “criteria for classification” of fibromyalgia, but no guidelines for treatment.⁵⁴ Recommendations for treatment of fibromyalgia are summarized in the following table; some are based on expert opinion, due to the limitations in currently published literature; some reviews do not designate first line agents but rather list agents shown to be effective:

Table 9: Recommendations for Treatment of Fibromyalgia

	First Line	Second Line	Third Line and Other
APS ⁵⁵ (2005)	TCA's, (specifically amitriptyline, cyclobenzaprine)	SSRIs, tramadol	NSAIDs combined with TCA's or SSRIs, opioids
Goldernberg ⁵⁶ , (2004) Rocks ⁵⁷ (2007)	amitriptyline, cyclobenzaprine	SSRIs, duloxetine, pregabalin, venlafaxine, tramadol	
	Effective Agents		Comments
Fibromyalgia Fact Sheet (ACR) ⁵⁸ (2006)	TCA's, cyclobenzaprine, venlafaxine, duloxetine, tramadol, SSRIs, bupropion, trazodone, mirtazapine, gabapentin, pregabalin, benzodiazepine, opioids		opioids and benzodiazepines are usually reserved for those who haven't responded to other therapies
Borg-Stein ⁶⁰ (2006) Mease ⁶¹ , (2005) Henningsen ⁶² (2007)	TCA's, doxepin, SSRIs, venlafaxine, duloxetine, milnacipran gabapentin, pregabalin, opioids, tramadol, NSAIDs, sedative-hypnotics		NSAIDs, sedative-hypnotics efficacy primarily in combination with other agents
EULAR ⁵⁹ (2008)	tramadol, amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide, pirlindol, tropisetron, pramipexole, pregabalin, acetaminophen, weak opioids		acetaminophen, weak opioids recommendation based mainly on expert opinion

ACR - American College of Rheumatology; APS – American Pain Society; EULAR - European League Against Rheumatism

The efficacy of duloxetine for the management of fibromyalgia was established in two, randomized, double-blind, placebo-controlled, fixed-dose studies in adult patients meeting the American College of Rheumatology (ACR) criteria for fibromyalgia (a history of widespread pain for three months, and pain present at 11 or more of the 18 specific tender point sites).^{63,64} In a 12 week study 354 female patients with primary fibromyalgia with or without MDD were randomized to duloxetine 60 mg once daily (n=118), duloxetine 60 mg twice daily (n=116), or placebo (n=120).⁶³ The primary outcome was the Brief Pain Inventory (BPI) average pain severity score.⁶³ Response to treatment was defined as $\geq 30\%$ reduction in this score. At study end, when compared to placebo, a significantly higher percentage of duloxetine-treated patients had a decrease of $\geq 30\%$ in the BPI score; duloxetine 60 mg once daily (55%; $p < 0.001$); duloxetine 60 mg twice daily (54% ($p = 0.002$); placebo (33%).⁶³ In a second 24-week study, 520 male and female patients with fibromyalgia were randomized to duloxetine 20 mg once daily, duloxetine 60 mg once daily, duloxetine 120 mg once daily, or placebo (after three months, the duloxetine 20 mg daily group was titrated to 60 mg once daily).⁶⁴ The co-primary outcome measures were the BPI average pain severity score and Patient Global Impression of Improvement score.⁶⁴ Compared with placebo-treated patients, both the duloxetine 60 mg daily and the duloxetine 120 mg daily treatment groups improved significantly more on the co-primary outcome measures at three months and at six months.⁶⁴

The *PA Criteria for Approval* for use of duloxetine for fibromyalgia will include as prerequisites the generic agents with clinical support for use in fibromyalgia in the guidelines and reviews listed above, including TCAs, doxepin, SSRIs, cyclobenzaprine, gabapentin, and tramadol. Some of the prerequisite agents are included in the automatic electronic edit if they are also appropriate treatment options for neuropathic pain or a generic SSRI. Doxepin, cyclobenzaprine, and tramadol are not included in the electronic edit for duloxetine. These agents are widely used for indications other than fibromyalgia. Agents effective when used in combination with agents already listed (NSAIDs and sedative-hypnotics) will not be included in the prerequisites list.

Medical Diagnoses Option Criteria

The intent of the identification of patients with certain medical diagnoses is to allow coverage of brand antidepressants and venlafaxine in members at high risk for disease morbidity and mortality. This is an enhancement to the basic step therapy edit program, which utilizes pharmacy claims data only. The medical diagnosis "Major Depressive Disorder, Recurrent" (ICD-9 296.3X) will be used to identify patients for pre-approval of brand antidepressants or venlafaxine through the implementation process. The utilization management step therapy program for antidepressants will not be required for these patients.

The diagnosis of Major Depressive Disorder, Recurrent requires the following criteria:⁶⁵

1. Presence of two or more major depressive episodes (each separated by at least 2 months in which criteria are not met for a major depressive episode)
2. The major depressive episodes are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified
3. There has never been a manic episode, a mixed episode, or a hypomanic episode⁶⁵

Patients with the diagnosis Major Depressive Disorder, Recurrent are known to be at high risk for significant disease morbidity, repeat hospitalizations, suicidal thoughts, and social and occupational disruptions.⁶⁵⁻⁷⁴ Practice guidelines from the APA for treatment of patients with major depressive disorder⁶⁵ state "There have been over 20 trials of pharmacotherapy in the maintenance phase, and results from these have generally demonstrated the effectiveness of antidepressant medication for relapse prevention; these trials have mainly been of tricyclic antidepressant medications." More recently, the guideline watch⁶⁶ confirms that "...more recent studies have confirmed the benefits of continuation and maintenance treatment with antidepressants in other classes [beyond the tricyclic antidepressants] (e.g., sertraline, venlafaxine, and mirtazapine) in decreasing the likelihood of recurrence."⁶⁶

The course of Major Depressive Disorder, Recurrent is variable. Some people have episodes separated by many years of normal functioning, others have clusters of episodes, and still others have increasingly frequent episodes as they grow older.⁶⁵ In patients with Major Depressive Disorder, Recurrent it is important to support medication adherence and to prevent delay or discontinuation of therapy. At the start of a new depressive episode, a patient may not have a record of past antidepressant therapy in the pharmacy claims system. Generic SSRIs, bupropion, maprotiline, and mirtazapine are not subject to the step therapy edit, but the brand name products and venlafaxine would be blocked if prerequisites are not

seen in the pharmacy claims data. Previous identification of patients with Major Depressive Disorder, Recurrent would eliminate the requirements of the step therapy program.

Medical claims data will be used to identify plan members with ICD-9 codes included in the following table:

EVENT	ICD-9CM Code*
Major Depressive Disorder, Recurrent	296.3, 296.3X

*The Medical Diagnoses Criteria will approve ICD-9 codes of three or more digits as applicable to ensure that members who have been assigned incomplete codes will be included.

These patients would be exempt from the prior authorization process for prescriptions for any antidepressant included in this program.

ELECTRONIC EDITS

The overall process for step therapy requires that another drug or drugs be tried in a specific previous time period before the claim drug. If the patient has met any of the requirements outlined below, the requested step therapy medication will be paid under the patient's current prescription benefit.

Table 3: Summary of Antidepressant Step Therapy

Targeted Agent(s)	GPIs	Prerequisite(s)	GPIs
Celexa	58160020*****, MSC M, N, O	Any generic SSRI, generic bupropion, generic maprotiline, generic mirtazapine, generic venlafaxine IR	5816*****, MSC Y
Effexor	581800901003**, MSC M, N, O		58300040*****, MSC Y
Effexor XR	581800901070**, MSC M, N, O		58300010*****, MSC Y
Lexapro	58160034*****, MSC M, N, O		5803*****, MSC Y
Luvox CR	581600451070**, MSC M, N, O		581800901003**, MSC Y
Paxil	581600600003** and 581600600018**, MSC M, N, O		
Paxil CR	581600600075**, MSC M, N, O		
Pexeva	581600603003**, MSC M, N, O		
Pristiq	58180020*****, MSC M, N, O		
Prozac	58160040*****, MSC M, N, O		
Remeron, RemeronSolTab	58030050*****, MSC M, N, O		
Venlafaxine XR (tablet)	581800901075**, MSC M, N, O		
Wellbutrin, Wellbutrin SR, Wellbutrin XL	58300040*****, MSC M, N, O		
Zoloft	58160070*****, MSC M, N, O		
Cymbalta	58180025*****, MSC M, N, O	Any generic SSRI, generic bupropion, generic maprotiline, generic mirtazapine, generic venlafaxine IR OR gabapentin. amitriptyline. nortriptyline, imipramine. or desipramine	5816*****, MSC Y 58300040*****, MSC Y 58300010*****, MSC Y 5803*****, MSC Y 581800901003**, MSC Y 7260003000*****, MSC M, N, O, Y 58200010*****, MSC M, N, O, Y 58200060*****, MSC M, N, O, Y 58200050*****, MSC M, N, O, Y 58200030*****, MSC M, N, O, Y

MSC = multi-source code

Is auto-grandfathering implemented? (with look-back time frame)	Y - 90 day ^a look-back timeframe
Number of prerequisites required	1
Prerequisite look-back time frame for generic antidepressants (SSRIs, bupropion, maprotiline, mirtazapine, venlafaxine IR)	365 days ^b
Prerequisite look-back time frame for generic agents for neuropathic pain (gabapentin, TCAs) for Cymbalta	90 days ^a
Age-related edit?	N/A
Additional Comment	1) Major Depressive Disorder, Recurrent will allow target drugs to pay IF Medical Diagnosis option is implemented 2) Prozac [®] Weekly [™] and Sarafem [®] brand are not included in this step therapy program

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

b - The system searches for a claim with a days supply that begins or ends in the past 365 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 395 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 455 days (assuming claims history data extends back this far).

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

The intent of the *Prior Authorization (PA) Criteria for Approval* is to provide a manual review process for claims that do not meet the electronic edit criteria and are not automatically paid. The criteria for approval through the PA process are identical to those set up in the electronic edit.

The PA criteria for approval will ensure that patients who require a brand antidepressant and who have not met the electronic step therapy criteria will be evaluated for use of the target drug. The PA criteria for these agents will approve the requested agent for the patient who has tried and failed a generic antidepressant. The target drug will also be approved when the patient is allergic to or intolerant of generic agents; if the patient has contraindications to the available generic second generation agents; if the patient has responded to the target drug in the past; or if the patient is currently on the targeted brand, has had an adequate response, and switching may cause harm or health risk. Initiation of a brand antidepressant prescribed for other indications will be evaluated through the prior authorization process if the prescriber submits information documenting use of the target drug to treat the patient's condition.

In addition, the PA criteria will allow for evaluation of Cymbalta/duloxetine for the treatment of neuropathic pain and fibromyalgia. Duloxetine will also be approved if the patient has tried and failed a first-line agent for neuropathic pain (amitriptyline, nortriptyline, imipramine, desipramine, gabapentin) or fibromyalgia (TCA, doxepin, SSRI, cyclobenzaprine, gabapentin, or tramadol), and also when the patient is allergic to, intolerant of, or has contraindications to these first-line agents; if the patient has been initiated on duloxetine, has had an adequate response, and switching may cause harm or health risk; or if the prescriber has considered all first-line agents for neuropathic pain or fibromyalgia and determined that duloxetine will best treat the patient.

All brand second generation antidepressants will be approved for 12 months at a time in patients meeting criteria.

Step Therapy PA Criteria for Approval

BRAND products: Celexa (citalopram), Effexor (venlafaxine), Effexor XR (venlafaxine extended-release), Lexapro (escitalopram), Luvox CR (fluvoxamine extended-release), Paxil (paroxetine hydrochloride), Paxil CR (paroxetine controlled-release), Pexeva (paroxetine mesylate), Pristiq (desvenlafaxine), Prozac (fluoxetine), RemeronSolTab (mirtazapine), Remeron (mirtazapine), Venlafaxine XR (tablets), Wellbutrin (bupropion), Wellbutrin SR (bupropion sustained-release), Wellbutrin XL (bupropion extended-release), Zoloft (sertraline)

Initial and Renewal Evaluation

1. Is the patient's diagnosis Major Depressive Disorder, Recurrent (ICD-9 296.3X)?
If yes, approve for 12 months. If no, continue to 2.
2. Has the patient previously responded to the requested drug or is the patient currently receiving and responding to the requested drug and switching could potentially cause harm or a health risk?
If yes, approve for 12 months. If no, continue to 3.
3. Does the patient's past prescription history include the use of a generic SSRI, bupropion, maprotiline, mirtazapine, or venlafaxine IR for treatment in this patient?
If yes, approve for 12 months. If no, continue to 4.
4. Is the patient allergic to, intolerant of, or have a contraindication to generic SSRIs, bupropion, maprotiline, mirtazapine, or venlafaxine IR?
If yes, approve for 12 months. If no, continue to 5.
5. Has the prescriber submitted documentation in support of the requested therapeutic use for a brand second generation antidepressant in this patient?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

Cymbalta (duloxetine)

Initial and Renewal Evaluation

1. Is the patient's diagnosis Major Depressive Disorder, Recurrent (ICD-9 296.3X)?
If yes, approve for 12 months. If no, continue to 2.
2. Has the patient previously responded to Cymbalta (duloxetine) or is the patient currently receiving and responding to Cymbalta (duloxetine) and switching could potentially cause harm or a health risk?
If yes, approve for 12 months. If no, continue to 3.
3. Does the patient's past prescription history include the use of a generic SSRI, bupropion, maprotiline, mirtazapine, or venlafaxine IR for treatment in this patient?
If yes, approve for 12 months. If no, continue to 4.
4. Is the patient allergic to, intolerant of, or have a contraindication to generic SSRIs, bupropion, maprotiline, mirtazapine, or venlafaxine IR?
If yes, approve for 12 months. If no, continue to 5.
5. What is the patient's diagnosis?
 - a. Neuropathic pain
 - b. Fibromyalgia
 - c. OtherIf a, continue to 6. If b, continue to 8. If c, continue to 10.

6. Has the patient tried and failed one of the following agents; a tricyclic antidepressant (amitriptyline, nortriptyline, desipramine or imipramine) or gabapentin?
If yes, approve for 12 months. If no, continue to question 7.
7. Does the patient have an allergy, intolerance, or contraindication to one of the agents listed above in question 6?
If yes, approve for 12 months. If no, continue to 10.
8. Has the patient tried and failed one of the following agents: an antidepressant (TCA, doxepin, SSRI), cyclobenzaprine, gabapentin, or tramadol?
If yes, approve for 12 months. If no, continue to 9.
9. Does the patient have an allergy, intolerance, or contraindication to one of the agents listed above in question 8?
If yes, approve for 12 months. If no, continue to 10.
10. Has the prescriber submitted documentation in support of the requested therapeutic use for Cymbalta (duloxetine) in this patient?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

SUMMARY

Step therapy electronic edits are designed to identify patients electronically by their medication history. The Antidepressant Step Therapy edit allows for automatic payment of claims when the patient's medication history indicates prior use of a generic SSRI, bupropion, maprotiline, mirtazapine, or venlafaxine IR, bypassing the manual PA process. The edit also allows for automatic payment if a medical diagnosis of Major Depressive Disorder, Recurrent is documented. The PA process provides a member-specific review process where practitioner provided patient-specific parameters are taken into consideration when reviewed. The step therapy protocol for Antidepressants optimizes the utilization of generic second generation antidepressants or generic alternatives for neuropathic pain or fibromyalgia for the individual benefit plan.

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