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Medication Policy Manual

Policy No: dru147

Topic: Cymbalta[®], duloxetine

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Next Review Date: May 2010

IMPORTANT REMINDER

This Medical 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 medical policy is to provide a guide to coverage. Medical 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

Duloxetine (Cymbalta[®]) is a selective norepinephrine/serotonin reuptake inhibitor (SNRI) used to treat major depressive disorder, diabetic neuropathic pain, fibromyalgia and generalized anxiety disorder.

Policy/Criteria

- I. Most contracts require prior authorization approval of duloxetine prior to coverage. Duloxetine may be considered medically necessary in patients when at least two generic/preferred medications (listed in Appendix 1) have been ineffective, not tolerated, or contraindicated.

- II. Administration and Authorization Period
 - A. Regence considers duloxetine to be a self-administered medication.
 - 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

Summary

- Generically available antidepressants such as fluoxetine, paroxetine and sertraline have been extensively studied, have established effectiveness, and are the best treatment value.
- There is no evidence indicating that any one antidepressant is more effective than another in comparable doses. ^[88-94]
- Except for fluvoxamine, there is no convincing evidence of overall safety/efficacy differences among the various brand and generic antidepressants. (Fluvoxamine is used less often than other alternatives due to higher rates of reported side effects and drug interactions relative to other SSRIs.)
- Venlafaxine extended-release is a preferred/formulary option for patients who have had inadequate responses to other types of antidepressants such as SSRIs, bupropion, or mirtazapine.
- Cymbalta is sometimes used for nerve pain or fibromyalgia. However, individuals may benefit just as well from other generic medications, such as gabapentin, cyclobenzaprine (Flexeril[®]), or tricyclic antidepressants such as amitriptyline or desipramine.

Clinical Efficacy

- Many antidepressants have been approved for the treatment of mental illnesses besides depression, such as anxiety, obsessive-compulsive and panic disorders, social phobia, bulimia nervosa, and post-traumatic stress disorder. Please 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 generic SSRI provides effective treatment.

DEPRESSION ^[1-52, 74-94]

- SSRIs, SNRIs and other antidepressants such as bupropion and mirtazapine have been proven to help relieve the symptoms of depression in 55 – 70% of people who take them.
- There is no reliable evidence that any one antidepressant (including isomers and active metabolites) is generally more effective than other available antidepressant medications at comparable doses.

Multiple systematic reviews and meta-analyses have been published.^[ref] Generally these reviews have concluded that there are no significant overall differences in safety or efficacy between second-generation antidepressants in the management of major depressive disorder.^[88-93]

- * One meta-analysis concluded that sertraline and escitalopram may have advantages in efficacy and safety, but these results will need to be confirmed.^[94]
- The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial was designed to evaluate the value of switching to another antidepressant or augmenting with another antidepressant after initial unsuccessful treatment with an SSRI (citalopram).^[80, 81]
 - * Approximately one in four patients experienced a remission of symptoms after switching to another antidepressant, though there was no advantage of one agent over another.^[80]
 - * Augmentation of citalopram with either bupropion SR or buspirone both resulted in an additional 30% of patients achieving remission.^[81]

- * The STAR*D trial was not designed to evaluate the superiority of any particular medication over another. In addition, problems with trial design add uncertainty to the trial's conclusions. This study should be used with caution.

GENERALIZED ANXIETY DISORDER (GAD) ^[24,52]

- Antidepressants such as citalopram, fluoxetine, paroxetine, sertraline, Lexapro, venlafaxine (Effexor XR) and Cymbalta are recognized for their benefit in treating symptoms of generalized anxiety.
 - * The estimated number needed to treat for these antidepressants in GAD is approximately 6. This means that about 6 patients need to be treated for 1 person to have improvement in their clinical symptoms.
- Treatment discontinuation rates for the various antidepressants do not differ.

POST TRAUMATIC STRESS DISORDER (PTSD) ^[55]

- SSRIs are primary options in the treatment of post traumatic stress disorder (PTSD).
- Of the SSRIs, paroxetine and sertraline have been the most studied.
- The estimated number needed to treat to reduce the severity of symptoms in PTSD compared to placebo is about 5 patients.
 - * Treatment with Cymbalta 60 mg one or two times a day statistically significantly improved the endpoint mean pain scores from baseline and increased the proportion of patients with at least a 50% reduction in pain score from baseline.

PREMENSTRUAL SYNDROME (PMS)/PREMENSTRUAL DYSPHORIC DISORDER (PMDD) ^[56, 95]

- SSRIs have evolved in their use as front-line therapy for premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD).

- SSRIs are effective in reducing the overall symptomatology of PMS, including PMDD. ^[56, 95]
- However, discontinuation of an SSRI due to side effects were 2.5 times more likely than placebo, particularly at higher doses.

BULIMIA NERVOSA ^[54]

- Of the available antidepressants, fluoxetine and bupropion are recognized for their efficacy in treating bulimia nervosa.
- Other options include tricyclic antidepressants (imipramine, desipramine and amitriptyline), the monoamine oxidase inhibitor Nardil, and trazodone.
- There are no proven differences in efficacy among these various antidepressants in treating bulimia nervosa.
 - * Remission: The pooled RR for remission of binge episodes was 0.87 (95% CI 0.81-0.93; p<0.001) favoring these agents. The NNT for 1 patient to achieve remission over a mean treatment duration of 8 weeks compared to placebo is approximately 9 patients (95% CI 6 - 16).
 - * Clinical Improvement (50% reduction or more in binge episodes): The pooled RR for clinical improvement is 0.63 (95% CI 0.55-0.74). The NNT for 1 patient to achieve a reduction of 50% or more in binge episodes over a mean treatment duration of 9 weeks is approximately 4 patients (95% CI 3 - 6).
 - * Patients treated with antidepressants were more likely to interrupt prematurely the treatment due to adverse events.
- Discontinuation rates for antidepressants in bulimia nervosa are very high. Fluoxetine has the lowest potential for discontinuation of treatment relative to other antidepressants and placebo. Therefore, fluoxetine may be a more viable option when considering treatment option.

NEUROPATHIC PAIN CONDITIONS ^[56-58, 65-70]

- Antidepressants are effective for a variety of neuropathic pain conditions caused by herpes infection or diabetes. These include tricyclic antidepressants (amitriptyline, desipramine) and SNRIs like Cymbalta.
- Other proven treatment options in neuropathic pain conditions include anticonvulsants (gabapentin, carbamazepine and phenytoin) and tramadol.
- None of the SSRIs are recognized as effective in treating neuropathic pain symptoms.
- The benefit and risks of the antidepressants in the treatment of diabetic neuropathic pain and/or postherpetic neuralgia are summarized in Appendix 3.

FIBROMYALGIA ^[81-86]

- The studies that evaluated duloxetine in fibromyalgia compared it to placebo (sugar pill). There is no information that shows how well duloxetine works relative to standard therapies such as amitriptyline, cyclobenzaprine, or gabapentin.
- The efficacy of duloxetine in patients with fibromyalgia (with or without MDD) has been studied in three published, randomized, controlled trials. ^[84-86]
 - * Overall, about 1 out of every 6 to 7 patients will experience a 30% decrease in pain when treated with duloxetine 60 mg or 120 mg a day, as compared to treatment with a placebo.
 - * When patients are treated with 120 mg per day, about 1 in 7 patients will experience a 50% reduction in pain compared to treatment with a placebo.
- The unlabeled use of the following therapies is supported by randomized controlled trials and several guidelines on the management of fibromyalgia (Goldenberg DL, et al. *JAMA* 2004; Buckhardt CS, et al. American Pain Society 2005): ^[81-83]
 - * Medications: amitriptyline, cyclobenzaprine, and gabapentin.
 - * Non-medication therapies: aerobic exercise, muscle strengthening, patient education, and cognitive behavior therapy.

- Similar to duloxetine, these medications (amitriptyline, cyclobenzaprine, and gabapentin) provide modest benefit to some patients with fibromyalgia pain.
- A recent study funded by the National Institutes of Health found that **gabapentin** (Neurontin) given in doses of 1,200 mg/day to 2,400 mg/day over 12 weeks decreased pain in patients with fibromyalgia better than placebo in 1 patient out of 5, a rate similar to that observed with duloxetine in other trials.^[82, 84-86]

Safety ^[1-35, 38-51, 53-71]

- All antidepressants carry risk of side effects.
- The individual side effect profiles for these products may differ, but overall discontinuation rates from all causes are relatively similar based on individual clinical trials, meta-analysis, or persistency data.
 - * The vast majority of people who take an antidepressant (90%) experience at least one side effect.
 - * Most individuals tolerate the mild side effects without much difficulty.
 - * About 20% of individuals discontinue antidepressants because of intolerable side effects.
- Sexual dysfunction is a common side effect among all antidepressants.
 - * The incidence is reported as anywhere from 5% - 70%. (This difference is likely due to studies that did not measure sexual dysfunction in the same way).
 - * Bupropion may have less potential for sexual sided effects, but trade-offs include risk of the elevating seizure threshold at higher doses or in patients with history of seizures.
- All antidepressants carry the black box warning for suicidal thoughts in children, adolescents and young adults.
- Of all the antidepressants, only fluoxetine carries FDA labeling for use in pediatric patients for treatment of depression. Fluvoxamine is indicated for the treatment of Obsessive-Compulsive disorder in patients as young as 8 years.

Appendix 1: Generic Medication Alternatives

Condition	Generic Alternatives
<p>Mental Health Conditions including, but not limited to:</p> <ul style="list-style-type: none"> - major depression - social anxiety disorder - generalized anxiety disorder - panic disorder - bulimia - post-traumatic stress disorder - premenstrual dysphoric disorder 	<ul style="list-style-type: none"> - citalopram (Celexa[®]) - fluoxetine (Prozac[®]) - fluvoxamine (Luvox[®]) - paroxetine (Paxil[®]) sertraline (Zoloft[®]) - bupropion SR/XL (Wellbutrin SR[®], Wellbutrin XL[®] 300mg) - mirtazapine (Remeron[®]) - venlafaxine (Effexor[®]) - venlafaxine SR tablets
<p>Neuropathic Pain</p>	<ul style="list-style-type: none"> - gabapentin (Neurontin[®]) - tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline)
<p>Fibromyalgia</p>	<ul style="list-style-type: none"> - gabapentin (Neurontin[®]) - tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline) - cyclobenzaprine (Flexeril[®])

Appendix 2: FDA-approved indications for selected antidepressants. ^[41-51,72,73,87]

Indication	Selective Serotonin Reuptake Inhibitors (SSRIs)						Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)				Miscellaneous		
	citalopram	fluoxetine	fluvoxamine	paroxetine	sertraline	Lexapro	Effexor XR	Pristiq	Cymbalta	Savella	Bupropion SR	Bupropion XL	mirtazapine
Depression	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓
Generalized anxiety disorder				✓		✓	✓		✓				
Obsessive-compulsive disorder		✓	✓	✓	✓								
Panic disorder		✓		✓	✓		✓						
Premenstrual dysphoric disorder		✓		✓	✓								
Posttraumatic stress disorder				✓	✓								
Social anxiety disorder				✓	✓		✓						

Appendix 2: FDA-approved indications for selected antidepressants. ^[41-51,72,73,87]

Indication	Selective Serotonin Reuptake Inhibitors (SSRIs)						Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)				Miscellaneous		
	citalopram	fluoxetine	fluvoxamine	paroxetine	sertraline	Lexapro	Effexor XR	Pristiq	Cymbalta	Savella	Bupropion SR	Bupropion XL	mirtazapine
Bulimia Nervosa		✓											
Seasonal Affective Disorder												✓	
Fibromyalgia									✓	✓			

✓ = FDA approved indication

Medications in **BOLD** are generically available.

Appendix 3: Benefit and risks of the antidepressants in the treatment of diabetic neuropathic pain and/or postherpetic neuralgia [57,-59,66-68,70,71]

	NNT moderate pain relief or better	NNH minor harm	NNH major harm
TCAs	2 (95% CI 1.7 to 2.5)	4.6	16
	NNT (achieving 50% reduction in pain)	NNH minor harm	NNH major harm
carbamazepine	2.3	3.7	Not significant
gabapentin	3.8	2.5	Not significant
phenytoin	2.1	3.2	Not significant
	NNT (defined as achieving 50% reduction in pain)	NNH _{DC} due to adverse events	
tramadol	3.4	7.7	
Cymbalta	5	13	

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Cross References
Lexapro [®] ; escitalopram dru148
Effexor XR [®] ; venlafaxine extended release dru146
Luvox CR [®] ; fluvoxamine extended-release capsules dru153
Pristiq [®] , desvenlafaxine dru154
Lyrica [®] , pregabalin dru122
Savella [™] , milnacaprin dru175

Codes	Number	Description
N/A		