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Drug Use Evaluation: Drugs for Fibromyalgia

Drugs Included: See Appendix 1.

Reason for Review:
A 2010 DUE of serotonin norepinephrine receptor inhibitor (SNRI) use found duloxetine was associated with 62% of SNRI drug costs and 22% of duloxetine patients were associated with a medical claim with a fibromyalgia ICD9 code. The goal of this DUE is to summarize current evidence for fibromyalgia drug therapies, quantify the drugs used and their cost to inform policy options.

Key Questions:
1) What are current recommendations for drug treatments for fibromyalgia?
2) Are there differences in efficacy or effectiveness of drug treatments for fibromyalgia?
3) Are there differences in harms of drug treatments for fibromyalgia?
4) Are there specific populations where specific drug treatments may be more effective or safe?
5) What diagnoses are associated with patients using these drugs in the Oregon Health Plan population?

Conclusions:
- Fibromyalgia (ICD9 729.1x – 729.2x) falls at Line 621 on the Oregon Health Plan (OHP) prioritized list and treatment is not currently funded.[1]
- Limited treatment guidelines are available and in conflict with the evidence.
- Current evidence is limited to placebo-controlled trials of about 3 months' duration studying middle-aged, white females, with duloxetine being the most studied drug. Low quality evidence suggests duloxetine, milnacipran and pregabalin, the only drugs approved by the U.S. Food and Drug Administration (FDA) for fibromyalgia, in addition to amitriptyline, may be effective at reducing pain symptoms and sleep disturbances associated with fibromyalgia at the expense of increased adverse effects. Overall treatment effects are small.
- There is low quality evidence that no differences exist between these drugs on overall treatment withdrawal.
- There is insufficient evidence to determine if there are differences in efficacy or safety of drug treatments for fibromyalgia in specific subgroups (e.g., age, sex, race, co-morbid conditions) with the exception of duloxetine, for which there is low quality evidence that it is also effective in fibromyalgia patients in these specific subgroups: concomitant major depressive disorder, aged 65 years and older, non-whites, and males.
- There is significant use of duloxetine for non-funded pain conditions (10% of patients) and cost (>$15 million annually) in the OHP population. Chronic pain syndrome, low back pain and fibromyalgia are the most prevalent non-funded conditions associated with this group of drugs.

Recommendations:
- Create comprehensive drug use criteria for high cost drugs used for fibromyalgia, chronic low back pain and chronic pain syndrome.
- Continue to require prior authorization for pregabalin and milnacipran using the new comprehensive criteria and retire the current criteria for each.
- Recommend prior authorization for duloxetine using the new comprehensive criteria; grandfather current patients and apply policy to new starts.
- Allow automatic approval for prior claims and evidence of major depression, generalized anxiety disorder and bipolar disease for duloxetine and epilepsy for pregabalin.

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Background:

Fibromyalgia is a chronic functional illness marked by widespread musculoskeletal pain often associated with other symptoms such as fatigue, sleep difficulties, cognitive dysfunction and depressed mood or depressive episodes.[2] The controversy surrounding fibromyalgia stems from the subjective nature of its complaints and lack of any defining abnormal biological findings at presentation. Women are disproportionately affected, especially in middle age.[2] Epidemiological data are limited in the United States, but the prevalence of fibromyalgia as assessed in Olmsted County, Minnesota, is 1.1% using medical records with a documented diagnosis.[3] It is unknown what may cause fibromyalgia, but proposed pathogenesis may be related to abnormal pain processing in the peripheral, central and sympathetic nervous systems and abnormal processing in the hypothalamic-pituitary-adrenal stress response axis.[2] Risk factors associated with increased risk of fibromyalgia include history of physical trauma or injury, infection (e.g., hepatitis C), stress, female sex, or having a relative with fibromyalgia.[2] Fibromyalgia is also significantly associated with a history of physical or sexual abuse, either in childhood or adulthood.[4] Patients with fibromyalgia may have substantial overlap across functional somatic syndromes such as irritable bowel syndrome, chronic pelvic pain, or chronic fatigue syndrome.[2] Patients may also have concomitant psychiatric disorders such as generalized anxiety disorder, depression, bipolar disorder or posttraumatic stress disorder.[2] Associated autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis or ankylosing spondylitis are also reported.[2] Not surprisingly, fibromyalgia reduces quality of life and is associated with functional disability, lost work time, and increased use of health care services.[5]

Treatments for fibromyalgia include drugs and non-pharmacologic therapies with goals including mitigating diffuse musculoskeletal pain, maximizing physical and cognitive function, optimizing patient self-management and managing comorbid medical and psychiatric disorders. The FDA has approved three oral medications for fibromyalgia since 2007: pregabalin, duloxetine and milnacipran. Several drugs have also been used off-label for fibromyalgia, including antidepressants, NSAIDs, opioid analgesics, and skeletal muscle relaxants.[5]

Fibromyalgia (ICD9 729.1x – 729.2x) falls at Line 621 on the Oregon Health Plan (OHP) prioritized list and treatment is not currently funded.[1] Pregabalin (April 2008) and milnacipran (January 2010) both require prior authorization to confirm use for a funded OHP condition. Duloxetine, a serotonin norepinephrine receptor inhibitor (SNRI), currently has no restriction for diagnosis and is carved-out of coordinated care plan contracts. Duloxetine is also FDA-indicated for major depressive disorder and diabetic peripheral neuropathy (Appendix 1).

Systematic Reviews:

<u>The Drug Effectiveness Review Project (DERP) Report</u>[6]

The Drug Effectiveness Review Project (DERP) conducted a systematic review on the evidence for comparative effectiveness/efficacy and comparative harms of the drugs used to treat fibromyalgia. Differences in any subgroups of patients based on demographics, socioeconomic status, other medications, or comorbidities for which any included drugs were more effective or associated with less harm were also assessed.[6] Drugs identified in eligible studies included:

<u>Tricyclic Antidepressants (TCAs)</u>

- Amitriptyline
- Nortriptyline

<u>Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)</u>

- Duloxetine
- Milnacipran

<u>Skeletal Muscle Relaxants</u>

- Cyclobenzaprine

<u>Selective Serotonin Reuptake Inhibitors (SSRIs)</u>

- Citalopram
- Fluoxetine
- Paroxetine

<u>Antiepileptics, Misc.</u>

- Gabapentin
- Pregabalin

Head-to-head evidence is sparse and low quality. Amitriptyline, pregabalin, milnacipran and duloxetine are the only drugs with sufficient number of placebo-controlled trials homogeneous enough to combine their results. These drugs are nearly always studied as monotherapy. There was no significant difference between pregabalin, milnacipran and duloxetine on response rate of 30% or 50% improvement in pain. There is no difference between amitriptyline, pregabalin, milnacipran and duloxetine on function as measured by the Fibromyalgia Impact Questionnaire (FIQ) and there is no difference between duloxetine, milnacipran, or pregabalin on the physical or mental components of the Medical Outcomes Study 36-item Short-Form Health Survey. Amitriptyline is the only drug that has sufficient evidence to report on measures of pain at 28 weeks.[6]

A recent DERP update of this review in November 2014 did not identify any new head-to-head trials for treatment of fibromyalgia. Placebo-controlled studies and post-hoc analyses continue to show relative improvement in pain and sleep disturbance symptoms for higher doses of duloxetine (60 to 120 mg daily), milnacipran (as monotherapy or adjunctive therapy to pregabalin), pregabalin, mirtazapine, and low-dose cyclobenzaprine.[7] Placebo-controlled studies show gabapentin significantly improves pain severity and response, overall impact of fibromyalgia, global status, and sleep compared to placebo, but not tender point pain threshold, depression or overall quality of life. Fluoxetine is the only SSRI, at a higher dose of 45 mg daily, that significantly improves pain, fatigue and FIQ scores compared to placebo. Paroxetine improves FIQ scores, fatigue and global status, but not pain, disability, or interestingly, not depression. Citalopram also has mixed results. Cyclobenzaprine only significantly reduced pain relative to placebo in 1 of 3 trials.[6]

There is low quality evidence that no differences exist between these drugs on overall treatment withdrawal. Overall adverse effects, especially anticholinergic-type effects, are more frequent with amitriptyline than paroxetine; and nortriptyline is associated with more overall adverse effects than amitriptyline. There are no differences between cyclobenzaprine and amitriptyline in any harms outcomes. When indirectly comparing drugs based on placebo-controlled trials, all drugs are generally well tolerated with greater adverse events (e.g., dizziness, sedation, lightheadedness, and weight gain) reported compared to placebo; pregabalin has significantly less headache, nausea and diarrhea compared to duloxetine, and significantly less headache and nausea compared to milnacipran. There are no differences between duloxetine and milnacipran in incidence of hyperhidrosis, though rates are significantly higher for both compared to placebo. Milnaciprain has significantly more tachycardia than placebo (number needed to harm 21; 95% CI, 16 to 30) and pregabalin has significantly more weight gain (relative risk, 4.58; 95% CI, 2.44 to 6.82) and peripheral edema (relative risk, 3.52; 95% CI, 2.01 to 6.18) relative to placebo. There is insufficient evidence on harms reported in placebo-controlled trials of the other drugs.[6]

There is extremely limited evidence regarding treatment of fibromyalgia in specific subgroup populations. The majority of patients in trials are middle-aged, white (84% to 91%) females (89% to 100%). Duloxetine is an exception and has been studied in different subgroups; it is no different than placebo in pain response in male patients, those 65 years of age and older, and non-white patients.[6]

The Agency for Healthcare Research and Quality (AHRQ) Report

The Agency for Healthcare Research and Quality (AHRQ) recently performed a systematic comparative effectiveness review through one of its Evidence-based Practice Centers for treatments of fibromyalgia in adult subgroups. The subgroups of interest included women, older or obese adults, individuals with coexisting mental health conditions, high severity or longer fibromyalgia duration, multiple medical comorbidities, or other chronic pain conditions. Primary outcomes included pain, symptom improvement, function, fatigue, sleep quality, participation, and health-related quality of life. Only 22 randomized controlled trials (RCTs), 8 pooled analyses of patient-level RCT data, and 4 observational studies met inclusion criteria; and only 59% were drug trials.[5]

Overall, evidence is largely insufficient to determine the effects of treatments on the subgroups studied other than duloxetine in adults with fibromyalgia. Study patients are largely middle-aged white females with moderate to severe fibromyalgia symptoms at baseline as measured by the FIQ, which is generally representative of the fibromyalgia population seen in clinical practice in the U.S. Most drug trials are placebo-controlled RCTs. Other comparators include standard care; standard care plus adjunctive therapy; normal activities; or education and information sessions. All but two individual RCTs have high risk of bias, primary due to high attrition (30-40%), and studies are overwhelmingly short-term (3 months) for a chronic, long-term condition. A meta-analysis was not conducted given the sparse evidence for specific treatments and outcomes of these subgroups.[5]

Duloxetine is the most studied drug (9 studies) and the most studied subgroup is in patients with major depressive disorder (MDD) (12 studies), followed by age (7 studies), sex (6 studies), anxiety (4 studies), obesity/body mass index (2 studies), and medical comorbidities (1 study). Less information is available on other subgroups. Outcomes other than pain, as well as non-pharmacologic interventions, are also very limited. Overall, limited, low quality evidence suggests duloxetine does not have any differential effect on pain or depression (Hamilton Depression Scale) in adults with fibromyalgia and MDD versus fibromyalgia patients without MDD. Sparse, low quality evidence suggests that the effects of duloxetine on global improvement (PGI-I) scores and FIQ scores also do not differ. Evidence is insufficient regarding the effects of milnacipran on Visual Analog Scale pain scores in adults with fibromyalgia and MDD versus the general fibromyalgia population. Limited, low quality RCT evidence for the effects of duloxetine by age (on BPI average pain and PGI-I), sex (on PGI-I) and race (on PGI-I) suggest that treatment effects do not differ in these subgroups versus the general fibromyalgia population. In general, overall treatment effects are small, and even less so when substantial placebo-group improvements are considered relative to the treatment effects. Subgroup effects parallel the magnitude and direction of overall treatment and placebo effects in mixed-sample studies. The effect of attrition within subgroups was missing so the extent to which studies could detect a difference even if one existed could not be determined, particularly since power calculations, when reported, were conducted to detect main group effects, not subgroup effects. Data are insufficient for the other treatments, including pregabalin and milnacipran, to evaluate their effects on any specific subgroups.[5]

Extensive exclusion criteria in these studies likely contribute to the lack of data in these subgroups. The fibromyalgia evidence is largely insufficient to determine subgroup effects for drug treatments other than duloxetine in patients with MDD. Unfortunately, patients with fibromyalgia and multi-morbid conditions are a clinical reality. Thus, the limitations of the primary literature preclude any change of policy or practice based on these findings.[5]

Guidelines:

Evidence-based guidelines for the management of fibromyalgia are primarily limited to the *Canadian Guidelines for the Diagnosis and Management of Fibromyalgia Syndrome in Adults*,[8] which is endorsed by the Canadian Pain Society and the Canadian Rheumatology Association. Some of the recommendations presented in the guideline conflict with the systematic reviews presented here.

The grading system for its recommendations is based on guidance provided by the Oxford Centre for Evidence-based Medicine and consists of levels of evidence and grades of recommendation[8]:

- Level 1 - systematic review of randomized trials
- Level 2 - randomized trial or (exceptional) observational study with dramatic effect
- Level 3 - nonrandomized controlled cohort/follow-up study
- Level 4 - systematic review of case-control studies or historically controlled studies
- Level 5 - opinion

- Grade A - consistent Level 1 studies
- Grade B - consistent Level 2 or Level 3 studies, or extrapolations from Level 1 studies
- Grade C - Level 4 studies or extrapolations from Level 2 or Level 3 studies
- Grade D - Level 5 evidence or concerning, inconsistent or inconclusive studies of any level
- Consensus - opinion

Though studies commonly evaluate drugs like duloxetine and milnacipran as monotherapy, this guideline recommends choice of drug therapy be guided by symptoms, which may require combination of medications (Level 1, Grade A).[8]

Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) may be used to treat pain and other symptoms, such as fatigue and depression, in patients with fibromyalgia (Level 1, Grade A).[7] The guideline does not provide detailed recommendations regarding specific antidepressants, dosing and step therapy, but the following antidepressants have been most studied[2,8]:

- Amitriptyline 25-50 mg nightly (TCA)
- Cyclobenzaprine 10-30 mg nightly (TCA properties)
- Duloxetine 60 mg daily (SNRI)
- Milnacipran 50 mg twice daily (SNRI)
- Paroxetine and fluoxetine (SSRIs)

Analgesics such as acetaminophen may be useful at safe doses (Level 5, Consensus). NSAIDs should only be prescribed at the lowest dose for the shortest time period possible to avoid adverse effects (Level 5, Grade D). Opioid therapy should be reserved for patients with moderate-to-severe pain that is unresponsive to other treatments; but treatment should be started with a weak opioid such as tramadol (Level 2, Grade D).[8] Lastly, antiepileptic drugs may be effective for their pain-modulating properties; both pregabalin and gabapentin may reduce pain and other symptoms of fibromyalgia (Level 1, Grade A).[8]

Methods:

A cross-section of patients with a paid fee-for-service (FFS) or encounter paid drug claim in calendar year 2014 for any drug in Appendix 1 were included. Patients with Medicare Part D coverage as identified with benefit package BMM or BMD were excluded. The study population was those with $\geq$ 75% days of eligibility of 365 days prior to index claim for a drug of interest. The comparison group was the total population without the eligibility exclusion. Patients were flagged for diagnoses of interest in Appendix 2 if there was a paid FFS or encounter claim with the diagnosis code from 1 year prior to index drug claim through 2014.

Results:

Table 1 displays the demographics of the patients on fibromyalgia drugs. The majority of patients on the drugs of interest were female (66-70%), 26-64 years old (85-89%) and Caucasian (78-80%).

Table 1 - Demographics

	Total		Study	
N=	87,572	%	51,434	%
Female	57,915	66.1%	35,740	69.5%
Mean age (range)	41.9	(1-92)	40.9	(1-92)
<= 12	488	0.6%	439	0.9%
13-25	9,981	11.4%	7,192	14.0%
26-65	76,877	87.8%	43,612	84.8%
>65	226	0.3%	191	0.4%
Caucasian	68,045	77.7%	41,305	80.3%

Over $25 million was paid to pharmacies for these drugs in 2014 for all OHP patients. Using an assumed 30% rebate rate, the net cost is estimated to be $17.5 million annually. Table 2 reveals duloxetine is associated with more than 60% of pharmacy reimbursed drug costs within this group of drugs while only 10% of patients (Table 3). Gabapentin is associated with 10% of drug costs and 23% of patients, whereas pregabalin is associated with 9% of costs and just 1% of patients. There is almost no use of milnacipran.

Table 4 categorizes patients as those who have only non-funded conditions (fibromyalgia, low back pain or chronic pain syndromes), those that have a funded condition (e.g. major depression, anxiety or neuropathy) or those with none of the selected diagnoses in Appendix 2 for each drug. Those with both a funded and non-funded condition were placed in the funded group. Drugs with the highest rates of only non-funded conditions were the tricyclic antidepressants (7.6% - 36.7%), gabapentin (20.6%), pregabalin (11.4%) and duloxetine (10.6%). Chronic pain syndrome or chronic back pain is the most prevalent non-funded conditions for all drugs.

Table 2 – Total Fibromyalgia Drug Utilization and Cost (Amount Paid on Claim) CY 2014

			Total Patients				Study Patients			
Class Group	**HSN**	**Generic Name**	**Sum Claim Count**	**Sum Claim Cost**	**Market Share by Cost**	**Mean Cost / claim**	**Sum Claim Count**	**Sum Claim Cost**	**Market Share by Cost**	**Mean Cost / claim**
AED	08831	gabapentin	137,154	$2,541,765	10%	$19	85,037	$1,675,950	10%	$20
AED	26470	pregabalin	7,525	$2,185,954	8%	$290	5,358	$1,562,327	9%	$292
SNRI 1	08847	venlafaxine HCl	60,287	$1,970,282	8%	$33	34,470	$1,184,855	7%	$34
SNRI 1	21229	milnacipran HCl	49	$7,895	0%	$161	19	$3,091	0%	$163
SNRI 1	26521	duloxetine HCl	75,559	$15,884,328	61%	$210	49,042	$10,663,069	62%	$217
SNRI 2	35420	desvenlafaxine succinate	5,764	$1,255,337	5%	$218	3,873	$859,118	5%	$222
SNRI 2	40202	desvenlafaxine	260	$43,813	0%	$169	114	$20,641	0%	$181
SNRI 2	40632	levomilnacipran HCl	1,067	$239,801	1%	$225	652	$143,810	1%	$221
SNRI 2	40692	desvenlafaxine fumarate	6	$876	0%	$146	6	$876	0%	$146
TCA	01641	imipramine HCl	3,712	$65,807	0%	$18	2,805	$49,166	0%	$18
TCA	01642	imipramine pamoate	184	$57,246	0%	$311	134	$40,760	0%	$304
TCA	01643	amitryptyline HCl	64,850	$793,822	3%	$12	40,904	$519,244	3%	$13
TCA	01644	nortriptyline HCl	19,440	$234,162	1%	$12	11,498	$141,253	1%	$12
TCA	01645	desipramine HCl	779	$59,606	0%	$77	566	$45,690	0%	$81
TCA	01950	cyclobenzaprine HCl	114,626	$490,204	2%	$4	69,048	$299,722	2%	$4
		Totals	491,262	$25,830,898			303,526	$17,209,571		

AED = Alpha2-ligand Anti-Epileptic Drugs; SNRI-1 = 1st generation Serotonin Norepinephrine Receptor Inhibitor; SNRI-2 = 2nd generation Serotonin Norepinephrine Receptor Inhibitor; TCA = Tri-Cyclic Antidepressants

Table 3 - Index Drug Patient Distribution

Class Group	HSN	Generic Name	N=	Total 87,572	%	Study 51,434	%
AED	00883	gabapentin		20,750	23.7%	11,961	23.3%
AED	02647	pregabalin		655	0.7%	472	0.9%
SNRI 1	00884	venlafaxine HCl		7,997	9.1%	4,387	8.5%
SNRI 1	02122	milnacipran HCl		4	0.0%	1	0.0%
SNRI 1	02652	duloxetine HCl		8,677	9.9%	5,404	10.5%
SNRI 2	03542	desvenlafaxine succinate		744	0.8%	480	0.9%
SNRI 2	04020	desvenlafaxine		35	0.0%	13	0.0%
SNRI 2	04063	levomilnacipran HCl		163	0.2%	98	0.2%
SNRI 2	04069	desvenlafaxine fumarate		1	0.0%	1	0.0%
TCA	00164	amitryptyline HCl		10,229	11.7%	6,256	12.2%
TCA	00164	desipramine HCl		151	0.2%	105	0.2%
TCA	00164	imipramine HCl		593	0.7%	436	0.8%
TCA	00164	imipramine pamoate		20	0.0%	14	0.0%
TCA	00164	nortriptyline HCl		3,320	3.8%	1,956	3.8%
TCA	00195	cyclobenzaprine HCl		34,233	39.1%	19,850	38.6%

AED = Alpha2-ligand Anti-Epileptic Drugs; SNRI-1 = 1st generation Serotonin Norepinephrine Receptor Inhibitor; SNRI-2 = 2nd generation Serotonin Norepinephrine Receptor Inhibitor; TCA = Tri-Cyclic Antidepressants

Table 4 – Diagnosis Distribution by Index Drug - Study Group Only

AED Drugs	gabapentin		pregabalin	
N=	11,961	%	472	%
#1) Only Not-Funded - FIBROMYALGIA	133	1.1%	7	1.5%
#2) Only Not-Funded – BACK / CHRONIC PAIN	1,864	15.6%	24	5.1%
Only Group #1 & #2 present	463	3.9%	23	4.9%
Total patients with only non-funded diagnosis present	14,421	20.6%	526	11.4%
Patients with selected funded diagnosis present	8,298	69.4%	399	84.5%
No selected diagnosis present	1,203	10.1%	19	4.0%

SNRI 1 Drugs	duloxetine		milnacipran		venlafaxine	
N=	5,404	%	1	%	4,387	%
#1) Only Not-Funded - FIBROMYALGIA	59	1.1%		0.0%	15	0.3%
#2) Only Not-Funded – BACK / CHRONIC PAIN	350	6.5%		0.0%	191	4.4%
Only Group #1 & #2 present	163	3.0%		0.0%	38	0.9%
Total patients with only non-funded diagnosis present	572	10.6%	0	0.0%	244	5.6%
Patients with selected funded diagnosis present	4,500	83.3%	1	100.0%	3,747	85.4%
No selected diagnosis present	332	6.1%		0.0%	396	9.0%

SNRI 2 Drugs	desvenlafaxine		des. fumarate		des. succinate		levomilnacipran	
N=	13	%	1	%	480	%	98	%
#1) Only Not-Funded - FIBROMYALGIA		0.0%		0.0%		0.0%		0.0%
#2) Only Not-Funded – BACK / CHRONIC PAIN	1	7.7%		0.0%	17	3.5%	3	3.1%
Only Group #1 & #2 present		0.0%		0.0%	3	0.6%	1	1.0%
Total patients with only non-funded diagnosis present	1	7.7%	0	0.0%	20	4.2%	4	4.1%
Patients with selected funded diagnosis present	11	84.6%	1	100.0%	422	87.9%	89	90.8%
No selected diagnosis present	1	7.7%		0.0%	38	7.9%	5	5.1%

TCA Drugs	amitryptyline		cyclobenzaprine		desipramine		imipramine		imipramine pamoate		nortriptyline	
N=	6,256	%	19,850	%	105	%	436	%	14	%	1,956	%
#1) Only Not-Funded - FIBROMYALGIA	72	1.2%	151	0.8%	1	1.0%	2	0.5%		0.0%	29	1.5%
#2) Only Not-Funded – BACK / CHRONIC PAIN	873	14.0%	6,497	32.7%	15	14.3%	24	5.5%		0.0%	274	14.0%
Only Group #1 & #2 present	198	3.2%	631	3.2%		0.0%	7	1.6%	1	7.1%	75	3.8%
Total patients with only non-funded diagnosis present	1,143	18.3%	7,279	36.7%	16	15.2%	33	7.6%	1	7.1%	378	19.3%
Patients with selected funded diagnosis present	4,002	64.0%	9,700	48.9%	70	66.7%	262	60.1%	10	71.4%	1,183	60.5%
No selected diagnosis present	1,111	17.8%	2,871	14.5%	19	18.1%	141	32.3%	3	21.4%	395	20.2%

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Appendix 1 – Drugs indicated for fibromyalgia

Therapeutic Class	HSN	Generic Name	Major Depressive Disorder	Seizure	Fibromyalgia	Peripheral Herpetic Neuropathy	Diabetic Peripheral Neuropathy	Other Peripheral Neuropathy
Tricyclic Antidepressants	001643	amitryptyline HCl	x		?	?		?
Tricyclic Antidepressants	001950	cyclobenzaprine HCl			?			
Tricyclic Antidepressants	001645	desipramine HCl	x		?			
Tricyclic Antidepressants	001641	imipramine HCl	x				?	
Tricyclic Antidepressants	001642	imipramine pamoate	x				?	
Tricyclic Antidepressants	001644	nortriptyline HCl	x			?		
SNRI-1 Antidepressants	026521	duloxetine HCl	x		x		x	?
SNRI-1 Antidepressants	021229	milnacipran HCl	?		x			
SNRI-1 Antidepressants	008847	venlafaxine HCl	x		?			
SNRI-2 Antidepressants	040202	desvenlafaxine	x					
SNRI-2 Antidepressants	040692	desvenlafaxine fumarate	x					
SNRI-2 Antidepressants	035420	desvenlafaxine succinate	x					
SNRI-2 Antidepressants	040632	levomilnacipran HCl	x					
Alpha2-ligand AED	008831	gabapentin		x	?		?	
Alpha2-ligand AED	026470	pregabalin		x	x	x	x	x

X = FDA indication ?=reported off-label use in Micromedex 2.0, Dynamed or UpToDate

Appendix 2 – Diagnoses of Interest

Not-Funded Diagnosis Group #1	ICD9
DISORDERS OF SOFT TISSUE	
Myalgia and myositis, unspecified	7291x
Neuralgia, neuritis, and radiculitis, unspecified	7292x
Not-Funded Diagnosis Group #2	ICD9
ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT	
Syringomyelia and syringobulbia	3360x
Disorders of meninges, not elsewhere classified	3492x
Sacroiliitis, not elsewhere classified	7202x
Inflammatory spondylopathies in diseases classified elsewhere	72081
Cervical spondylosis without myelopathy	7210x
Thoracic spondylosis without myelopathy	7212x
Lumbosacral spondylosis without myelopath	7213x
Traumatic spondylopathy	7217x
Other allied disorders of spine	7218x
Spondylosis of unspecified site, without mention of myelopathy	72190
Intervertebral disc disorders	722xx
Cervicalgia	7231x
Brachial neuritis or radiculitis NOS	7234x
Other disorders of cervical region	7236x - 7239x
Pain in thoracic spine/Lumbago	7241x-7242x
Backache, unspecified	7244x-7249x
Nonallopathic lesions not elsewhere classified	739xx
Other specified congenital anomalies of spinal cord	74259
Congenital musculoskeletal deformities of sternocleidomastoid muscle	7541x
Closed dislocation thoracic and lumbar vertebra	8392x
Sprains and strains of other and unspecified parts of back	847xx
CHRONIC PAIN (EXCLUDED DIAGNOSES)	
Chronic pain d/t trauma	33820-33821
Other chronic pain	33829
Chronic pain syndrome	3384x

Funded Diagnosis Group #3	ICD9
Hereditary and idiopathic peripheral neuropathy	356xx
Diabetes with neurological manifestations	2506x
Herpes zoster with nervous system complications	0531x
MDD or Depressive disorder, NOS	311xx
Major Depressive Disorder	2962x; 2963x
Anxiety disorders	300xx
Epilepsy and recurrent seizures	345xx

Appendix 3 Proposed new PA criteria

Drugs Used for Non-Funded Pain Conditions

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature (e.g. major depressive disorder, epilepsy, diabetic neuropathy, post-herpetic neuralgia).

Length of Authorization:

90 days to lifetime (criteria specific)

Requires PA:

- duloxetine, milnacipran, pregablin

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the drug requested pregablin AND does client have a diagnosis of epilepsy? (ICD-9 code 345.0-345.9, 780.39, or 907.0)	Yes: Approve for lifetime (until 12-31-2036)	No: Go to #3.
3. Is the drug requested duloxetine AND does the client have an anxiety disorder or depressive disorder (ICD9 296xx, 300xx, 309xx, 311xx)?	Yes: Approve for lifetime (until 12-31-2036)	No: Go to #4.
4. Is the diagnosis funded on the OHP list of prioritized services (See Table below for examples)?	Yes: Approve for 90 days to 1 year.	No: Pass to RPH; Go to #5.

Approval Criteria

5. Pass to RPH
   - For Bipolar affective disorder: there are no data to support use of any of these drugs for this indication (Deny Medical Appropriateness). Recommend other alternatives (lithium, valproate, carbamazepine, lamotrigine).
   - For Migraine prophylaxis: there are no data to support use of any of these drugs for this indication (Deny Medical Appropriateness). Recommend other alternatives (beta-blockers, calcium channel blockers, valproate, gabapentin, TCAs). Refer to American Academy of Neurology Guideline.
   - If clinically warranted, may DENY yesterday's date (Medical Appropriateness) and use clinical judgment to APPROVE for 1 month starting today to allow time for appeal.

   All other indications need to be evaluated to see if diagnosis is funded:
   - Funded neuropathies found in table (list is not all-inclusive) may be approved for 90 days with subsequent approvals dependent on documented positive response (documented response means that follow-up and response is noted in client's chart per clinic staff).
   - **Forward any neuropathy/neuralgia ICD-9 codes not found in the Table to the Lead Pharmacist. These codes will be forwarded to DMAP for consideration.**

Table

Not-Funded Diagnoses	ICD9
DISORDERS OF SOFT TISSUE	
Myalgia and myositis, unspecified (includes fibromyalgia syndromes)	7291x
Neuralgia, neuritis, and radiculitis, unspecified	7292x
ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT	
Syringomyelia and syringobulbia	3360x
Disorders of meninges, not elsewhere classified	3492x
Sacroiliitis, not elsewhere classified	7202x
Inflammatory spondylopathies in diseases classified elsewhere	72081
Cervical spondylosis without myelopathy	7210x
Thoracic spondylosis without myelopathy	7212x
Lumbosacral spondylosis without myelopath	7213x
Traumatic spondylopathy	7217x
Other allied disorders of spine	7218x
Spondylosis of unspecified site, without mention of myelopathy	72190
Intervertebral disc disorders	722xx

Cervicalgia	7231x
Brachial neuritis or radiculitis NOS	7234x
Other disorders of cervical region	7236x - 7239x
Pain in thoracic spine/Lumbago	7241x-7242x
Backache, unspecified	7244x-7249x
Nonallopathic lesions not elsewhere classified	739xx
Other specified congenital anomalies of spinal cord	74259
Congenital musculoskeletal deformities of sternocleidomastoid muscle	7541x
Closed dislocation thoracic and lumbar vertebra	8392x
Sprains and strains of other and unspecified parts of back	847xx
CHRONIC PAIN (EXCLUDED DIAGNOSES)	
Chronic pain d/t trauma	33820-33821
Other chronic pain	33829
Chronic pain syndrome	3384x
Funded Diagnoses	ICD9
Hereditary and idiopathic peripheral neuropathy	356xx
Diabetes with neurological manifestations	2506x
Herpes zoster with nervous system complications	0531x

P&T / DUR Action: *3/26/15; 5/09; 9/07; 11/07*
Revision(s): *TBD; 1/11; 1/10*
Initiated: *4/08*