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OHSU Drug Effectiveness Review Project Summary Report – Non-Opioid Drugs to Treat Neuropathic Pain

Date of Review: July 2018 **Date of Last Review:** March 2017 (DURM); June 2011 (DERP)

Current Status of PDL Class: See **Appendix 1**.

Research Questions:

1. What is the comparative efficacy and effectiveness of anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), topical capsaicin, and topical lidocaine for neuropathic pain?
2. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, topical capsaicin, and topical lidocaine for neuropathic pain?
3. What is the comparative efficacy and effectiveness of anticonvulsants, tricyclic antidepressants, SNRIs, topical capsaicin, and topical lidocaine versus opioids for neuropathic pain?
4. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, topical capsaicin, and topical lidocaine versus opioids for neuropathic pain?
5. Are there subgroups of patients based on demographics, socioeconomic status, other medications, comorbidities, or pregnancy for which there are differences in benefits and harms of anticonvulsants, tricyclic antidepressants, SNRIs, topical capsaicin patch, topical lidocaine, and opioids when used to treat neuropathic pain?

Conclusions:

- The strength of evidence for most outcomes within the OHSU Drug Effectiveness Review Project (DERP) report is low or insufficient, as data come from single studies and are imprecise.[1]
- Nortriptyline and morphine SR were not found to differ in alleviating pain or differ in adverse event outcomes after 4 weeks of treatment for chronic sciatica in a small, fair-quality randomized controlled trial (RCT).[1]
- Pregabalin and gabapentin were not found to differ in either pain control or adverse events in 2 small, fair quality RCTs.[1]
- When pregabalin was compared to duloxetine in diabetic neuropathy, the evidence was mixed depending on the outcome measured. For reduction in pain of at least 50%, duloxetine was superior to pregabalin in a good-quality, 8-week RCT (40.3% versus 27.8%, P<0.001).[1] However, there was no difference noted between pregabalin and duloxetine in mean change in pain (using visual analog scale of 0-100) in a fair-quality, 12-week trial.[1]
- Gabapentin reduced pain scores more than amitriptyline in a fair-quality, open-label, 12-week study in patients (n=25) with diabetic neuropathy (4 point intensity scale, -1.9 vs. -1.3, P=0.026).[1] The absolute difference observed in this trial was small. In a small, fair quality trial comparing gabapentin to amitriptyline in cancer patients with neuropathic pain, there was no difference in pain control or adverse event withdrawals at 6 months.[1]
- Moderate quality evidence indicates capsaicin patch and pregabalin were not significantly different in pain response, but fewer patients on capsaicin withdrew due to adverse events.[1]
- No evidence was identified that evaluated subgroups of patients for which benefits or harms of neuropathic pain treatments might differ.

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- Lyrica® CR (pregabalin extended-release) was approved by the United States Food and Drug Administration (FDA) in October 2017 for management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN).[2]
- Qudexy® XR and Trokendi XR (topiramate extended-release) received an expanded indication from the FDA in early 2017 for prophylaxis of migraine headache in adults and adolescents 12 years of age and older.[3,4]

Recommendations:
- No further review or research at this time.
- Maintain pregabalin extended-release tablets as a non-preferred medication on the Practitioner-Managed Prescription Drug Plan (PMPDP). Apply clinical prior authorization (PA) criteria to pregabalin extended-release tablets.
- After reviewing costs in executive session, no changes were made to the Preferred Drug List (PDL).

Previous Conclusions:

Efficacy

Recent comparative trials do not reveal a clear preference for one class of medications over another for management of neuropathic pain. Moderate quality evidence exists to support the use of pregabalin to manage central neuropathic pain. Moderate quality evidence shows that duloxetine is an effective agent to manage chronic low back pain (LBP). Low quality evidence supports the safety and efficacy of desipramine and amitriptyline in management of DPN or PHN. Low quality evidence supports the efficacy of carbamazepine in trigeminal neuralgia, DPN, and post-stroke pain. Moderate quality evidence shows no significant difference in analgesic efficacy between amitriptyline, duloxetine, and pregabalin in treatment of DPN. Moderate quality evidence indicates little or no effect for lamotrigine, oxcarbazepine and topiramate for treatment of neuropathic pain. There is insufficient evidence to demonstrate the efficacy of valproic acid, lacosamide, levetiracetam, and phenytoin in management of neuropathic pain.

There is insufficient evidence to evaluate the effect of antiepileptics to manage acute nonradicular LBP. There is insufficient evidence to support the use of topical lidocaine in mixed peripheral neuropathic pain. There is insufficient evidence to support the use of milnacipran for management of neuropathic pain.

Safety

There is insufficient comparative evidence in patients with neuropathic pain or chronic pain to assess comparative safety. Moderate quality evidence revealed approximately 80% of participants experienced an adverse event with an antiepileptic, but about 70% of participants receiving placebo did as well. Withdrawals due to adverse events were much higher with antiepileptics than placebo. Moderate quality evidence showed that adverse events experienced with gabapentin were significantly higher than with placebo (RR 1.25; 95% CI 1.2 to 1.3). Adverse events noted with gabapentin included somnolence, dizziness, peripheral edema and gait disturbances. Low quality evidence showed that 65% of participants experienced at least one adverse event with carbamazepine, and 27% with placebo.

Previous Recommendations:
- Revise prior authorization (PA) criteria to restrict use to funded pain conditions and include separate PA criteria for the following medications:
    - Pregabalin
    - Milnacipran
    - Lidocaine Patch
    - Topiramate Extended Release (non-preferred products)
- Add quantity limit of 3 patches/24 hours for topical lidocaine patches which is the maximum approved daily dose to insure safe use.

Methods:
The March 2018 report on non-opioid drugs to treat neuropathic pain by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:
A number of non-opioids are available for treating neuropathic pain and are broadly characterized as anticonvulsants, antidepressants, or topical analgesics.[1] **Appendix 1** lists the specific medications included in the DERP report that are also part of the Oregon Medicaid Fee-for-Service Preferred Drug List (PDL). The objective of the DERP report is to compare the effectiveness and safety of the drugs shown in **Appendix 1** for neuropathic pain, and to provide evidence for potential alternatives to opioids. The types of neuropathic pain in adults with chronic pain (3 months or greater in duration) included in the DERP summary are:

- Painful diabetic neuropathy
- Post-herpetic neuralgia
- Trigeminal neuralgia
- Cancer-related neuropathic pain
- HIV-related neuropathic pain
- Central/post-stroke neuropathic pain
- Neuropathy associated with low back pain
- Peripheral nerve injury pain
- Phantom limb pain
- Guillain-Barre syndrome
- Polyneuropathy
- Spinal cord injury-related pain
- Complex regional pain syndrome

Searches were conducted through November 2017 and included RCTs of at least 8 weeks duration, cohort or case-control studies of harms, and network meta-analyses. Thirteen RCTs and 1 systematic review with a network meta-analysis (NMA) met DERP inclusion criteria. The NMA conclusions are excluded from this report because strength of evidence based on such indirect evidence is generally considered low.[1] The RCTs included 1 trial comparing an opioid to a neuropathic pain drug, 10 trials of anticonvulsant comparisons, 1 trial of tricyclic antidepressant comparisons, and 1 trial of topical analgesic comparisons. No evidence met the DERP criteria for SNRI comparisons.

Direct Comparisons

Neuropathic Pain Drugs compared with Opioids: Nortriptyline compared with Morphine

One small (N=55), fair-quality RCT compared nortriptyline (mean dose: 84 mg daily) with morphine sustained-release (SR) [mean dose: 62 mg daily] in patients with chronic sciatica.[5] Doses were titrated upwards over 2 weeks, then maintained at the highest tolerated dose for 2 weeks.[5] The mean duration of pain was 5 years, mean age was 53 years, and 45% of subjects were female. Using a pain rating scale of 0 to 10 (10 = worst pain), patients experienced a 14% reduction in leg pain with nortriptyline and a 7% reduction with morphine SR; this difference was not significant.[5] Average back pain was significantly better with nortriptyline compared with morphine SR (p=0.02).[5] Secondary outcomes (quality of life on the Short Form Health Survey [SF-36], depression on the Beck Depression scale, and disability on the Owestry Disability Index) were not significantly improved by either treatment.[5] Two patients withdrew due to adverse events while taking maximal doses of nortriptyline or morphine SR.[5] This evidence was insufficient for drawing conclusions because it consisted of a single small study that was not of good quality.[1]

Anticonvulsant Drug Comparisons: Pregabalin compared with Gabapentin or Gabapentin Enacarbil

Two small fair-quality trials compared pregabalin to gabapentin in patients with painful diabetic neuropathy (N=102)[6] and peripheral nerve injury (N=30) for 12 weeks.[7] There were no significant differences between drugs in pain control as evaluated by a 100-point visual analog scale (VAS) or adverse events in either of the two trials.[1]

A third fair-quality trial (n=420) compared pregabalin to 3 different doses of gabapentin enacarbil or placebo in patients with diabetic neuropathy.[8] The primary analysis in this study compared the drugs with placebo, and found no significant difference in mean change in 24-hour average pain intensity at 12 weeks.[8] The DERP analysis of head-to-head comparisons found a mixed pattern, with 1200 mg daily and 3600 mg daily of gabapentin enacarbil reducing pain scores more than pregabalin (-2.55 vs. -1.66, p=0.02; -2.54 vs. -1.66, p=0.01, respectively), while 2400 mg daily dose of gabapentin enacarbil was not significantly different from pregabalin (-1.90 vs. -1.66; p = 0.50).[1] Neither drug was significantly different compared to placebo on the SF-36 physical and mental component scores or on daily dose of rescue medications.[1] Overall, adverse events were frequent and similar between treatments, although peripheral edema was more frequent with pregabalin (p<0.01).[1] There was also a trend toward greater likelihood of discontinuing the study due to adverse events with the higher doses of gabapentin enacarbil.[1] However, evidence on adverse event withdrawals was insufficient to draw conclusions.[1]

Anticonvulsants compared with Antidepressants

Pregabalin compared with Duloxetine

One good-quality trial of patients with diabetic peripheral neuropathic pain compared standard doses of duloxetine (60 mg daily) to pregabalin (300 mg daily) in the first phase of a trial that was 8 weeks in duration (n=804).[9] Study participants in both trial phases were predominantly white (>80%) and had median pain duration of 2 years.[9] In the first phase of the trial, patients taking duloxetine experienced greater pain relief than patients taking pregabalin (40.3% of patients on duloxetine reported 50% or greater improvement on the Brief Pain Inventory Modified Short Form compared with 27.8% of patients on pregabalin, p<0.001).[1] There was no statistically significant difference in withdrawals due to adverse events (12.4% for pregabalin vs. 11.5% for duloxetine).[9] The second phase of the trial (n=339) was also 8 weeks in duration, and assessed patients not responding to standard doses of pregabalin or duloxetine. In the second phase, patients were randomized to combining the medications (duloxetine 60 mg daily and pregabalin 300 mg daily) or increasing each to its maximum recommended dose (duloxetine 120 mg daily or pregabalin 600 mg daily).[9] The trial found no significant differences in either pain control (p=0.068) or withdrawals due to adverse events (4.7% vs. 4.1%) between high-dose monotherapy compared with combination therapy.[1]

One fair-quality RCT compared gabapentin 300 mg to 1800 mg daily, duloxetine 20 mg to 120 mg daily, and pregabalin 75 mg to 300 mg daily (n=152).[6] This 12-week trial was conducted in India in patients with diabetic neuropathy, with an average duration of diabetes of 8.1 years. Pain decreased in both the duloxetine and pregabalin groups over time with no difference between groups as measured by a visual analog scale (VAS scale of 0 to 100), and there were no differences in adverse events and no withdrawals due to adverse events in either study group.[6] The evidence for withdrawals due to adverse events was insufficient for drawing conclusions because it consisted of a single small study that was not of good quality.[1] The applicability of this trial to the Oregon Medicaid Fee-For-Service- population is limited due to the demographics of the study population.

Gabapentin compared with Amitriptyline

One fair-quality study compared gabapentin to amitriptyline in 25 patients with diabetes.[10] The open-label study of diabetic neuropathy treated patients for 12 weeks and measured pain intensity on a scale from 0 (no pain) to 4 (excruciating pain).[10] While both drugs showed statistically significant decreases in pain scores, the decrease was greater with gabapentin than with amitriptyline (-1.9 vs. -1.3, P=0.026), although the absolute difference was small.[1] The results of this trial cannot be considered conclusive because of the small sample size and lack of blinding.[10]

In a fair quality trial of 88 cancer patients with neuropathic pain treated for 6 months, gabapentin or amitriptyline were co-administered with tramadol.[11] There was no difference between gabapentin and amitriptyline in pain intensity using a 0 to 4 VAS scale at the end of treatment (p>0.05).[11] There was also no difference in pain scores on a 10 point VAS at any point in the course of the study, including at the end of the study (p=0.482).[11] Evidence was insufficient to compare the use of rescue analgesia between two drugs.[1] There were no serious adverse events, and no patients withdrew because of adverse events.

Anticonvulsants compared with Topical Analgesics: Capsaicin Patch compared with Pregabalin

One fair-quality trial compared the 8% capsaicin patch with pregabalin in patients (n=559) with peripheral neuropathy.[12] Authors compared scores ranging from 0 to 10 on a numeric pain rating scale (NPRS) between baseline and 8 weeks of treatment.[1] Patients with a decrease in NPRS score of 30% or more were defined as responders.[1] At 8 weeks, there was no statistically significant difference in pain response between the capsaicin patch and pregabalin (56% vs. 55%, odds ratio (OR) 1.03, 95% CI 0.72 to 1.50).[12] However, patients treated with capsaicin responded sooner than those given pregabalin (7.5 days vs. 36.0 days, hazard ratio (HR) 1.68, 95% CI 1.35 to 2.08, p<0.0001).[12] Serious adverse events were not reported. No patient in the capsaicin group discontinued treatment due to adverse events, while 8.5% (n=24) of those treated with pregabalin did so.[12] The most common adverse effects reported with pregabalin were somnolence (16%) and dizziness (20%).[12] Application site pain (24%), erythema (21%), and burning sensation (16%) were the most frequently reported adverse effects with capsaicin.[12]

In summary, this DERP report evaluated non-opioid drugs to treat neuropathic pain. The strength of evidence for most outcomes within this report was low or insufficient, as data came from single studies and were imprecise.[1] Most comparisons failed to show significant differences in outcomes related to pain control or adverse events between treatments[1]. Studies failed to report on the use of rescue analgesia, and outcomes were reported differently across studies.[1] Previously published literature reported effective analgesia for neuropathic pain with pharmacotherapy was achieved in less than half of patients.[13-15]

New Formulations or Indications:

1.Lyrica® CR (pregabalin extended-release tablets) was approved by the FDA in October 2017 for management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN).[2] The efficacy of pregabalin extended-release tablets has not been established for the management of fibromyalgia or as adjunctive therapy for adults patients with partial onset seizures.[2] Support for efficacy of pregabalin extended-release in DPN and PHN is based on the efficacy of pregabalin immediate-release for these indications along with a 19-week, placebo-controlled RCT of pregabalin extended-release in adults with PHN.[2] According to the prescribing information for pregabalin extended-release, 73.6% of patients in the pregabalin extended-release arm

achieved at least 50% improvement in pain intensity compared to 54.6% of patients in the placebo arm.[2]

The recommended initial dose of pregabalin extended-release is 165 mg once daily after the evening meal. The dose may be titrated up to 330 mg per day within 1 week.[2] If patients with PHN do not experience significant pain relief following 2 to 4 weeks of treatment with pregabalin extended-release 330 mg per day, the dose may be increased to 660 mg per day as tolerated.[2] The maximum recommended dose of pregabalin extended-release for management of DPN is 330 mg per day and for PHN is 660 mg per day.[2] There is no evidence that the higher dose of pregabalin immediate-release confers additional significant benefit and this dose was less well tolerated in clinical trials.[2] Pregabalin extended-release tablets are not recommended for patients with creatinine clearance less than 30 mL/min or who are undergoing hemodialysis.[2] Due to extensive renal excretion, dosing adjustments of pregabalin extended-release are recommended for patients with creatinine clearance between 30 and 60 mL/min.[2] Pregabalin extended release tablets are available as 82.5 mg, 165 mg and 330 mg tablets.[2]

2.Qudexy® XR (topiramate extended-release) capsules received an expanded indication from the FDA in March 2017 for prophylaxis of migraine headache in adults and adolescents 12 years of age and older.[3] Another formulation of topiramate extended-release capsules (Trokendi XR®) received the expanded indication for migraine prophylaxis in adults and adolescents aged 12 years and older in April 2017.[4] Topamax® (topiramate immediate-release) capsules have been FDA-approved for migraine prophylaxis in adults and adolescents aged 12 years and older since March 2014.[16] Janssen, the manufacturer of Topamax® held exclusivity for migraine prophylaxis in the adolescent population until the patent expired in March 2017. The recommended dose for migraine prophylaxis with topiramate extended-release is 25 mg once daily at nighttime for the first week, followed by weekly dose increases increments of 25 mg to a maximum dose of 100 mg once daily.[3]

New FDA Safety Alerts:
No new safety alerts identified**.**

References:

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12. Haanpaa M, Cruccu G, Nurmikko TJ, et al. Capsaicin 8% patch versus oral pregabalin in patients with peripheral neuropathic pain. *Eur J Pain.* 2016;20(2):316-328.
13. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc.* 2010;85(3 Suppl):S3-14.
14. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain.* 2010;150(3):573-581.
15. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med.* 2009;122(10 Suppl):S22-32.
16. Topamax® (topiramate) tablets. Prescribing Information. Titusville, NJ; Janssen Pharmaceuticals, Inc. 3/14.

Appendix 1: Current Preferred Drug List

Antiepileptics

Route	Form	Brand	Generic	PDL	Carveout
ORAL	CAPSULE	DILANTIN	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	PHENYTOIN SODIUM EXTENDED	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	PHENYTEK	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	ORAL SUSP	DILANTIN-125	PHENYTOIN	Y	
ORAL	ORAL SUSP	PHENYTOIN	PHENYTOIN	Y	
ORAL	TAB CHEW	DILANTIN	PHENYTOIN	Y	
ORAL	TAB CHEW	PHENYTOIN	PHENYTOIN	Y	
ORAL	SOLUTION	DEPAKENE	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	SOLUTION	VALPROIC ACID	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	CAPSULE	DEPAKENE	VALPROIC ACID	Y	Y
ORAL	CAPSULE	VALPROIC ACID	VALPROIC ACID	Y	Y
ORAL	CAP DR SPR	DEPAKOTE SPRINKLE	DIVALPROEX SODIUM	Y	Y
ORAL	CAP DR SPR	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
ORAL	TABLET DR	DEPAKOTE	DIVALPROEX SODIUM	Y	Y
ORAL	TABLET DR	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
ORAL	TAB ER 24H	DEPAKOTE ER	DIVALPROEX SODIUM	Y	Y
ORAL	TAB ER 24H	DIVALPROEX SODIUM ER	DIVALPROEX SODIUM	Y	Y
ORAL	ORAL SUSP	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	ORAL SUSP	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	TABLET	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	TABLET	EPITOL	CARBAMAZEPINE	Y	
ORAL	TABLET	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	TAB CHEW	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	TAB ER 12H	CARBAMAZEPINE ER	CARBAMAZEPINE	Y	
ORAL	TAB ER 12H	TEGRETOL XR	CARBAMAZEPINE	Y	
ORAL	TABLET	LAMICTAL	LAMOTRIGINE	Y	Y
ORAL	TABLET	LAMOTRIGINE	LAMOTRIGINE	Y	Y
ORAL	CAPSULE	GABAPENTIN	GABAPENTIN	Y	
ORAL	CAPSULE	NEURONTIN	GABAPENTIN	Y	
ORAL	TABLET	GABAPENTIN	GABAPENTIN	Y	
ORAL	TABLET	NEURONTIN	GABAPENTIN	Y	
ORAL	TABLET	TOPAMAX	TOPIRAMATE	Y	

ORAL	TABLET	TOPIRAMATE	TOPIRAMATE	Y	
ORAL	TABLET	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	TABLET	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	ORAL SUSP	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	ORAL SUSP	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	TABLET	KEPPRA	LEVETIRACETAM	Y	
ORAL	TABLET	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	TABLET	ROWEEPRA	LEVETIRACETAM	Y	
ORAL	SOLUTION	KEPPRA	LEVETIRACETAM	Y	
ORAL	SOLUTION	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	TABLET	VIMPAT	LACOSAMIDE	Y	
ORAL	TB CHW DSP	LAMICTAL	LAMOTRIGINE	V	Y
ORAL	TB CHW DSP	LAMOTRIGINE	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMICTAL (BLUE)	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMICTAL (GREEN)	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMICTAL (ORANGE)	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMICTAL ODT	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMOTRIGINE ODT	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT (ORANGE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMOTRIGINE ODT (ORANGE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT (BLUE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMOTRIGINE ODT (BLUE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT (GREEN)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMOTRIGINE ODT (GREEN)	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMICTAL XR	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMOTRIGINE ER	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR (BLUE)	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR (GREEN)	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR (ORANGE)	LAMOTRIGINE	V	Y
ORAL	TAB ER 24H	GRALISE	GABAPENTIN	N	
ORAL	CPMP 12HR	CARBAMAZEPINE ER	CARBAMAZEPINE	N	
ORAL	CPMP 12HR	CARBATROL	CARBAMAZEPINE	N	
ORAL	SOLUTION	GABAPENTIN	GABAPENTIN	N	
ORAL	SOLUTION	NEURONTIN	GABAPENTIN	N	
ORAL	CAP SPRINK	TOPAMAX	TOPIRAMATE	N	
ORAL	CAP SPRINK	TOPIRAMATE	TOPIRAMATE	N	
ORAL	CAP ER 24H	TROKENDI XR	TOPIRAMATE	N	
ORAL	CAP SPR 24	QUDEXY XR	TOPIRAMATE	N	
ORAL	CAP SPR 24	TOPIRAMATE ER	TOPIRAMATE	N	
ORAL	TAB ER 24H	OXTELLAR XR	OXCARBAZEPINE	N	

ORAL	TAB ER 24H	KEPPRA XR	LEVETIRACETAM	N
ORAL	TAB ER 24H	LEVETIRACETAM ER	LEVETIRACETAM	N
ORAL	TAB SUSP	SPRITAM	LEVETIRACETAM	N
ORAL	CAPSULE	LYRICA	PREGABALIN	N
ORAL	SOLUTION	LYRICA	PREGABALIN	N
ORAL	SOLUTION	VIMPAT	LACOSAMIDE	N
ORAL	TABLET	APTIOM	ESLICARBAZEPINE ACETATE	N
ORAL	TABLET	FYCOMPA	PERAMPANEL	N
ORAL	ORAL SUSP	FYCOMPA	PERAMPANEL	N
ORAL	SOLUTION	BRIVIACT	BRIVARACETAM	N
ORAL	TABLET	BRIVIACT	BRIVARACETAM	N
ORAL	TABLET ER	HORIZANT	GABAPENTIN ENACARBIL	N
ORAL	TABLET ER 24H	LYRICA CR	PREGABALIN	N

Antidepressants: Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) and Tricyclic Antidepressants

Route	Form	Brand	Generic	PDL	Carveout
ORAL	TABLET	IMIPRAMINE HCL	IMIPRAMINE HCL	Y	Y
ORAL	TABLET	TOFRANIL	IMIPRAMINE HCL	Y	Y
ORAL	TABLET	AMITRIPTYLINE HCL	AMITRIPTYLINE HCL	Y	Y
ORAL	CAPSULE	NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	Y	Y
ORAL	CAPSULE	PAMELOR	NORTRIPTYLINE HCL	Y	Y
ORAL	SOLUTION	NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	Y	Y
ORAL	TABLET	DESIPRAMINE HCL	DESIPRAMINE HCL	Y	Y
ORAL	TABLET	NORPRAMIN	DESIPRAMINE HCL	Y	Y
ORAL	TABLET	PROTRIPTYLINE HCL	PROTRIPTYLINE HCL	Y	Y
ORAL	CAPSULE	DOXEPIN HCL	DOXEPIN HCL	Y	Y
ORAL	ORAL CONC	DOXEPIN HCL	DOXEPIN HCL	Y	Y
ORAL	TABLET	VENLAFAXINE HCL	VENLAFAXINE HCL	Y	Y
ORAL	CAP ER 24H	EFFEXOR XR	VENLAFAXINE HCL	Y	Y
ORAL	CAP ER 24H	VENLAFAXINE HCL ER	VENLAFAXINE HCL	Y	Y
ORAL	CAPSULE	IMIPRAMINE PAMOATE	IMIPRAMINE PAMOATE	V	Y
ORAL	TAB ER 24	VENLAFAXINE HCL ER	VENLAFAXINE HCL	V	Y
ORAL	CAPSULE DR	CYMBALTA	DULOXETINE HCL	V	Y
ORAL	CAPSULE DR	DULOXETINE HCL	DULOXETINE HCL	V	Y
ORAL	TAB ER 24H	DESVENLAFAXINE SUCCINATE ER	DESVENLAFAXINE SUCCINATE	V	Y
ORAL	TAB ER 24H	PRISTIQ	DESVENLAFAXINE SUCCINATE	V	Y
ORAL	TAB ER 24H	DESVENLAFAXINE ER	DESVENLAFAXINE	V	Y

ORAL	TAB ER 24	DESVENLAFAXINE ER	DESVENLAFAXINE	V	Y
ORAL	TAB ER 24	KHEDEZLA	DESVENLAFAXINE	V	Y
ORAL	CAP SA 24H	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	CAP24HDSPK	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	TAB ER 24	DESVENLAFAXINE FUMARATE ER	DESVENLAFAXINE FUMARATE	V	Y

Miscellaneous

Route	Form	Brand	Generic	PDL	Carveout
PO	TABLET	SAVELLA	MILNACIPRAN HCL		
PO	TAB DS PK	SAVELLA	MILNACIPRAN HCL		

Topical Analgesics

Route	Form	Brand	Generic	PDL	Carveout
TOPICAL	CREAM (G)	CAPSAICIN	CAPSAICIN	Y	
TOPICAL	CREAM (G)	ARTHRITIS PAIN RELIEVING	CAPSAICIN	Y	
TOPICAL	LIQUID	CAPSAICIN	CAPSAICIN	N	
TOPICAL	CREAM (G)	LIDOCAINE	LIDOCAINE	N	
TOPICAL	OINT. (G)	LIDOCAINE	LIDOCAINE	N	
TOPICAL	ADH. PATCH	LIDOCAINE	LIDOCAINE	N	
TOPICAL	ADH. PATCH	LIDODERM	LIDOCAINE	N	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 2 2018 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March Week 2 2018

1.	brivaracetam.mp.	130
2.	eslicarbazepine.mp.	192
3.	perampanel.mp.	184
4.	gabapentin.mp.	5147
5.	PREGABALIN/	1581
6.	oxcarbazepine.mp.	1600
7.	levetiracetam.mp.	2466
8.	topiramate.mp.	3880
9.	lamotrigine.mp	4519
10.	gabapentin enacarbil.mp.	69
11.	Valproic Acid/	11561
12.	CARBAMAZEPINE/	10436
13.	PHENYTOIN/	13025
14.	levomilnacipran.mp.	48
15.	milnacipran.mp.	582
16.	Desvenlafaxine Succinate/	254
17.	Duloxetine Hydrochloride/	1366
18.	Venlafaxine Hydrochloride/	2338
19.	doxepin.mp. or DOXEPIN/	1300
20.	protriptyline.mp.	398
21.	IMIPRAMINE/	9792
22.	AMITRIPTYLINE/	6372
23.	nortritpyline.mp.	2
24.	desimpramine.mp.	3
25.	CAPSAICIN/	9722
26.	LIDOCAINE/	23161
27.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	93906
28.	limit 27 to (english language and humans and yr="2017 -Current" and "all adult (19 plus years)" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	222
29.	Neuralgia/	11530
30.	28 and 29	15

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin and pregabalin extended release

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for pregabalin?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is the request for pregabalin immediate release?	**Yes:** Go to #4	**No:** Go to #5
4. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to #5

Approval Criteria		
5. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; not funded by the OHP.
6. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of gabapentin for 90 days
Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X
Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	
Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	

Non-funded		
Fibromyalgia	X	

P&T Review: *7/18 (DM); 3/18; 3/17*
Implementation: *8/15/18; 4/1/17*

Milnacipran

Goal(s):
- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:
- 90 days

Requires PA:
- Milnacipran

Covered Alternatives
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Approve for 90 days	**No:** Pass to RPh. Deny; not funded by the OHP

Table 1. OHP Funded or Non-Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Milnacipran
Funded	

Diabetic Neuropathy	
Postherpetic Neuropathy	
Painful Polyneuropathy	
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	X

P&T Review: *7/18 (DM); 3/17*
Implementation: *4/1/17*

Lidocaine Patch

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to 12 months (criteria specific)

Requires PA:

- Lidocaine Patch

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1.What diagnosis is being treated?	Record ICD10 code	
2.Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (refer to Table 1 for examples).	**Yes:** Go to # 3	**No:** Pass to RPh. Deny; not funded by the OHP
3.Is this a request for renewal of a previously approved prior authorization for lidocaine patch?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 4
4.Is the prescription for Lidoderm patch greater than 3 patches/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 90 days
Renewal Criteria		
1. Does the patient have documented improvement from lidocaine patch?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness.

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Lidocaine Patch
Funded	
Diabetic Neuropathy	X
Postherpetic Neuropathy	X
Painful Polyneuropathy	X
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	

Non-funded	
Fibromyalgia	

P&T Review: *7/18 (DM); 3/17*
Implementation: *4/1/17*

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Non-preferred topiramate products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.*	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #7
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: “Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal.”	

P&T Review: *7/18 (DM); 3/18; 3/17; 7/16; 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*