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Literature Scan: Oral Antiepileptic Drugs

Date of Review: July 2016

Date of Last Review: March 2015
Literature Search: March 2015 – April 2016

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

Conclusions:

- There were no new comparative systematic reviews or evidence-based guidelines of antiepileptic drugs (AEDs) identified on which to recommend changes to the PDL class.
- Two AED medications received expanded indications in 2015. Esclicarbazepine is now approved to use as adjunctive therapy in the treatment of partial-onset seizures. Previously, it was only approved for use as monotherapy. The indications for perampanel were expanded to include treatment of primary generalized tonic-clonic seizures in patients 12 years of age and older. Perampanel was initially approved by the U.S. Food and Drug Administration (FDA) in 2012 for the treatment of partial onset seizures among epilepsy patients.
- The FDA approved a new oral suspension formulation of perampanel which provides an additional option for patients who have difficulty swallowing tablets.
- The American Academy of Neurology and the American Epilepsy Society published evidence-based guidelines for starting AEDs in adults after a first seizure. The authors found moderate evidence that immediate AED therapy as compared with no treatment is likely to reduce absolute risk by about 35% for a seizure recurrence within the subsequent 2 years.
- There is moderate quality evidence lacosamide is effective and well tolerated in the short term when used as add-on treatment for drug-resistant partial epilepsy in adults.
- There are insufficient data to address the risk-benefit balance of vigabatrin versus carbamazepine monotherapy for epilepsy in adults and children.
- There is moderate quality evidence that describes common adverse effects with lamotrigine therapy in pediatric patients. The most commonly reported adverse events include: rash, headache, fever, somnolence, vomiting, seizure aggravation, dizziness, cough, aggression, ataxia and insomnia. Children on lamotrigine monotherapy had lower incidences of adverse events compared to multiple AEDs.
- There is low quality evidence that levetiracetam is effective in reducing neuropathic pain but it is associated with an increase in adverse events and premature discontinuation due to side effects.
- There is moderate quality evidence that discontinuing an AED in children prior to at least 2 seizure-free years is associated with a higher recurrence rate than waiting 2 or more seizure-free years. The optimal time of withdrawal is not clear due to insufficient evidence. There is no evidence to guide AED discontinuation in adults.
- For all the currently marketed AEDs, there is no evidence to support the use of any of them in treating migraines. Topiramate, sodium valproate and divalproex are effective prophylactic treatments for episodic migraine in adults. There is insufficient evidence to further support the use of gabapentin in migraine prophylaxis.
- There is low quality evidence that topiramate may be effective in reducing the frequency of binge eating in patients with binge-eating disorder.

Author: Deanna Moretz, PharmD Date: July 2016

Recommendations:

- No further review or research needed at this time. After the executive session, no changes to the PDL were made.

Previous Conclusions:

- There were no new comparative systematic reviews or evidence-based guidelines of antiepileptic drugs (AEDs) identified on which to recommend changes to the PDL class.
- FDA expanded the black-boxed warnings on valproate products to include possible fetal neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, hypospadias, limb malformations) when used during pregnancy.
- There is insufficient evidence that controlled-release carbamazepine is more effective than the immediate-release formulations; however, low quality evidence suggests the controlled-release formulations may be more tolerable.
- There is insufficient evidence that felbamate is effective as add-on therapy for refractory partial-onset epilepsy.
- There is moderate quality evidence that tiagabine is effective at reducing seizure frequency but is associated with more dizziness, fatigue, nervousness and tremor when used as add-on therapy in patients with localization-related seizures who have failed at least two AEDs as monotherapy.
- There is moderate quality evidence that in the short term, adding pregabalin at doses ranging from 150-600 mg per day to AED therapy can significantly reduce seizure rates and cease seizures altogether in patients with drug-resistant partial epilepsy. There is insufficient evidence, however, for longer treatment duration and insufficient evidence comparing pregabalin against other adjunctive treatments.
- There is moderate quality evidence that in the short term, adding topiramate at doses no greater than 300 mg per day to AED therapy can significantly reduce rates and cease seizures altogether in patient with drug-resistant partial epilepsy. There is insufficient evidence, however, for longer treatment duration and insufficient evidence comparing topiramate against other adjunctive treatments.

Previous Recommendations:

- Retire current PA criteria for pregabalin which will be replaced with the PA criteria “Drugs Used for Non-funded Pain Conditions”.
- Remove PA criteria for preferred topiramate products due to cost effectiveness.
- No further review or research needed at this time.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Lacosamide Add-on Therapy for Partial Epilepsy in Adults

A Cochrane review by Weston, et al. evaluated the efficacy and tolerability of lacosamide (LCM) when used as an add-on treatment for patients with drug-resistant partial epilepsy.[1] Eligible studies were randomized, placebo, controlled trials (RCTs) in which lacosamide doses ranged from 200 to 600 mg per day.[1] Three RCTs involving 1311 subjects were included in the analysis. The participants were experiencing seizures despite taking a minimum of 2 AEDs.[1] The reviewers rated the quality of the studies as moderate to high with low risk of bias. The following outcomes were assessed: 50% or greater reduction in seizure frequency, seizure freedom, treatment withdrawal for any reason, and adverse events. Trial duration ranged from 24 to 26 weeks. The overall risk ratio (RR) for a 50% or greater reduction in seizure frequency for LCM compared with placebo was 1.70 (95% confidence interval (CI) 1.38 to 2.10); for seizure freedom for LCM compared with placebo was 2.50 (95% CI 0.85 to 7.34); and for treatment withdrawal for LCM compared with placebo was 1.88 (95% CI 1.40 to 2.52).[1] Adverse effects associated with LCM administration included abnormal coordination (RR 6.12, 99% CI 1.35 to 27.77), diplopia (RR 5.29, 99% CI 1.97 to 14.23), dizziness (RR 3.53, 99% CI 2.20 to 5.68), nausea (RR 2.37, 99% CI 1.23 to 4.58) and vomiting (RR 3.49, 99% CI 1.43 to 8.54).[1] LCM doses at 200 mg per day were well tolerated with no significant differences in withdrawal rate. [1] However, as the LCM dose was titrated up to 400 mg per day participants were almost twice as likely to withdraw due to side effects.[1] At the 600 mg dose, patients were 3-times more likely to withdraw due to side effects.[1] The authors concluded LCM is effective in the short term when used as add-on treatment for drug-resistant partial epilepsy in adults. [1] The authors noted that adverse effects with LCM were common and more likely to occur at higher doses.[1]

Vigabatrin Versus Carbamazepine Monotherapy for Epilepsy

Xiao, et al. updated their 2012 Cochrane review to investigate the efficacy and safety of vigabatrin (VGB) versus carbamazepine (CBZ) monotherapy for epilepsy in children and adults.[2] Five RCTs including a total of 734 participants compared VGB to CBZ in patients newly diagnosed with epilepsy. Subject age ranged from 6 months to 65 years.[2] The authors assessed only one study as good quality and the other 4 studies as poor quality with unclear to high risk of bias.[2] The primary outcome was time to treatment withdrawal. Secondary outcomes were time to achieve 6-month and 12-month remission after randomization, time to first seizure after randomization and adverse events. Not all studies reported the same outcomes as those identified for the review, so the authors were unable to extract aggregate data for synthesis of a meta-analysis.[2] No significant differences favored one drug over the other in terms of time to treatment withdrawal or time to achieve 6-month remission after dose stabilization.[2] Compared with CBZ, VGB was associated with more occurrences of weight gain and fewer occurrences of skin rash and drowsiness.[2] No differences in visual field defects and visual disturbances were noted.[2] The authors concluded there is insufficient data to address the risk-benefit balance of VGB versus CBZ monotherapy for epilepsy.[2]

Safety of Lamotrigine in Pediatrics

Equnsula, et al. completed a systematic review to identify adverse drug reactions associated with lamotrigine in children.[3] All studies involving pediatric patients aged 18 years or younger who had received at least one dose of lamotrigine were included.[3] The primary outcome measure was to compare the safety of lamotrigine AEDs. A secondary outcome was any adverse event observed with when lamotrigine was administered in combination with other AEDs secondary to a drug interaction.[3] A total of 78 articles involving 3783 pediatric patients were identified. The most common types of articles were case reports (n=50) followed by 12 prospective cohort trials and 9 RCTs.[3] All RCTs and cohort studies were evaluated as good quality and eligible for inclusion in the final data aggregation.[3] There were 2222 adverse events reported.[3] Rash was the most commonly reported adverse event, occurring in 7.3% of the patients, and was the most common reason for treatment discontinuation.[3] Stevens-Johnson syndrome was rarely reported, with a risk of 0.09 per 100 patients.[3] Discontinuation due to an adverse drug reaction (ADR) was noted in 72 children (1.9% of all treated patients).[3] Fifty-eight percent of treatment discontinuations were attributed to different forms of rash and 21% due to increased seizures.[3] There were significantly higher risks of dizziness (RR 4.57, 95% CI 1.88 to 11.12, $p<0.001$), abdominal pain (RR 2.53,

95% CI 1.12 to 5.70, p=0.03) and nausea (RR 5.94, 95% CI 1.59 to 22.13, p=0.008) with lamotrigine than placebo.[3] Headache (5.3% with monotherapy and 8.3% with polytherapy, p=0.02), somnolence (1.5% with monotherapy and 18.6% with polytherapy , p<0.001), nausea (0.9% with monotherapy and 4.3% with polytherapy, p=0.01), vomiting (0% with monotherapy and 8.7% with polytherapy, p<0.001), dizziness (1.2% with monotherapy and 10.7% with polytherapy, p<0.001) and abdominal pain (1.5% with monotherapy and 5.1% with polytherapy, p=0.01) were significantly lower among children on monotherapy.[3] Rash was the most common adverse effect that resulted in lamotrigine treatment discontinuation. [3]The authors concluded children on lamotrigine monotherapy had lower incidences of adverse events compared with the patients receiving multiple AEDs.[3]

Early Versus Late Antiepileptic Drug Withdrawal For People With Epilepsy In Remission

Strozzi, et al. updated a 2001 Cochrane review to evaluate optimal timing of AED discontinuation to reduce adverse effects associated with long-term use of AEDs.[4] The primary outcome was difference in seizure relapse rates between early and late withdrawal of AEDs in epileptic patients in remission.[4] Five randomized trials including 924 children were included in the analysis.[4] Due to the difficulties of simulating withdrawal of medication, none of the studies were blinded.[4] All of the study participants were pediatric epileptic patients 16 years and younger at randomization.[4] The pooled risk ratio for seizure relapse after AED withdrawal after two years of therapy was 1.34 (95% CI 1.13 to 1.59, p=0.0007).[4] Early discontinuation was associated with greater relapse rates in children with partial seizures (RR 1.51; 95% CI 0.97 to 2.35, p=0.07).[4] Variables associated with higher risk of seizure relapse were abnormal EEG findings (RR 1.44, 95% CI 1.13 to 1.83, p=0.003), especially epileptiform activity (RR 2.58, 95% CI 2.03 to 3.28, p<0.0001); epilepsy onset before 2 years or after 10 years of age; history of status epilepticus; intellectual disability (IQ < 70); and high seizure frequency before and during treatment.[4] The authors concluded that discontinuing AED medication in children prior to at least 2 seizure-free years is associated with a higher recurrence rate than waiting 2 or more seizure-free years.[4] The optimal time of withdrawal is not clear due to insufficient evidence.[4] There is no evidence to guide AED discontinuation in adults who have been seizure-free.[4]

Levetiracetam For Neuropathic Pain in Adults

A Cochrane review completed by Wiffen, et al. assessed the analgesic efficacy and adverse events of levetiracetam use in adults with chronic neuropathic pain conditions.[5] Primary outcomes included: participant-reported pain relief ≥30%, participant-reported pain relief ≥50%, and Patient Global Impression of Change (PGIC) improvement (moderate to substantial). The authors included 6 studies: 5 small, cross-over studies with 174 participants, and one parallel group study with 170 participants.[5] Participants were treated with levetiracetam (2000 mg to 3000 mg daily) or placebo between 4 and 14 weeks.[5] Each study included participants with a different type of neuropathic pain; central pain due to multiple sclerosis, pain following spinal cord injury, painful polyneuropathy, central post-stroke pain, postherpetic neuralgia, and post-mastectomy pain. The evidence was very low quality, downgraded because of the small size of the treatment arms, and because studies reported results using last observation carried forward (LOCF) imputation for withdrawals or using only participants who completed the study according to the protocol, where there were greater than 10% withdrawals.[5] There were insufficient data for a pooled efficacy analysis in particular neuropathic pain conditions, but individual studies did not show any analgesic effect of levetiracetam compared with placebo.[5] The authors pooled results for any outcome considered substantial pain relief (≥50% pain intensity reduction or “complete” or “good” responses on the verbal rating scale) for 4 studies with dichotomous data; response rates across different types of neuropathic pain was similar with levetiracetam (10%) and placebo (12%), with no statistical difference (RR 0.9; 95% CI 0.4 to1.7).[5] Data were pooled across different conditions for adverse events and withdrawals.[5] Based on very limited data, significantly more participants experienced an adverse event with levetiracetam than with placebo (number needed to treat for an additional harmful event (NNH) 8.0 (95% CI 4.6 to 32)).[5] There were significantly more adverse event withdrawals with levetiracetam (NNH 9.7 (6.7 to 18)).[5] The amount of evidence for levetiracetam in neuropathic pain conditions was very small and potentially biased because of the methods of analysis used in the studies.[5] There was no indication that levetiracetam was effective in reducing neuropathic pain, but it was associated with an increase in adverse events and withdrawal from therapy due to adverse events.[5]

Anticonvulsants in Migraine Prophylaxis

Mulleners, et al. updated their 2013 Cochrane review evaluating the efficacy and tolerability of several AEDs in preventative treatment of episodic migraine headaches in adults.[6] Prospective, controlled trials of AEDs taken regularly to prevent the occurrence of migraine attacks, to improve migraine-related quality of life, or both, were included in the review.[6] Thirty-seven published and 3 unpublished studies were evaluated.[6] The specific AEDs studied included: topiramate, valproate, gabapentin, pregabalin, lamotrigine, carbamazepine, clonazepam, levetiracetam, oxcarbazepine, vigabatrin and zonisamide.[6] Outcomes measured in the analysis included headache frequency, quality of life and adverse events.[6] The studies were rated as low to moderate quality evidence with moderate to high risk of bias. Mean headache frequency was reduced by 4 days with valproate and by 1 day with topiramate when compared to placebo.[6] There was no evidence of efficacy in preventing migraine headaches for any of the other AEDs.[6] The reviewers found insufficient evidence to further support the use of gabapentin in migraine prophylaxis.[6]

Anticonvulsants in Binge-Eating Disorder

Binge-eating disorder (BED) involves the recurrent consumption of an amount of food that is larger than most people would consume under similar circumstances.[7] McElroy and colleagues have evaluated the short- and long-term effects of topiramate in treating BED associated with obesity.[9,10] In a double blinded, 14-week trial, 61 outpatients with BED and a body mass index (BMI) ≥30 kg/m^2 were randomly assigned to receive topiramate (n=30) or placebo (n=31).[9] A total of 26 patients (42%) did not complete the 14 weeks of treatment. Nine patients withdrew from the study because of adverse events (TPM: n=6; PBO: n=3), 3 because of lack of efficacy (TPM: N=1; PBO: N=2), 13 because of nonadherence with the study protocol (TPM: n=6; PBO: n=7) and one participant withdrew because of an exacerbation of a previous medical condition.[9] Patients in the topiramate arm were more likely to withdraw from the study due to adverse effects than patients in the placebo arm. The authors noted a greater reduction from baseline in binge frequency with the TPM group (94%) relative to PBO (46%) in the intent-to-treat group (p=0.02). Thirty-one patients entered an open label, 42-week extension period: 15 patients received TPM and 16 patients continued on PBO. Twenty-one (67%) patients discontinued the extension trial due to nonadherence (TPM n=5, PBO n = 6), adverse events (TPM n=1, PBO = 7), or lack of efficacy (TPM n=2).[10] Ten patients completed 56 weeks of TPM therapy. Mean binge frequency was statistically significantly decreased from baseline in the 10 patient completer group (mean change = -5 binges/week, p=0.002).[10] The authors concluded long term (56 weeks) treatment with TPM was associated with sustained reductions in binge-eating frequency.[10] The extension trial was in a small population, open label, nonrandomized, and not controlled which contribute to significant weaknesses of the study. Furthermore, the study had a high attrition rate in both the short term and extension phases. Finally, patients with bipolar disorder, active substance abuse, psychosis or severe personality disorders were excluded from the study, which limits the ability to generalize these findings to all patients with BED.[10] Further long term studies that evaluate the safety and efficacy of topiramate in treating BED are warranted.

New Guidelines:

The American Academy of Neurology and the American Epilepsy Society published evidence-based guidelines for starting AEDs in adults after a first seizure. Based on data from studies including mixed cohorts of both AED-treated and untreated subjects, an adult with an unprovoked first seizure is at greatest risk of a recurrence relatively early, within the first 2 years (21%–45%), and especially in the first year, and this risk appears to be lower for patients treated with AEDs.[11] Immediate AED therapy as compared with no treatment is likely to reduce absolute risk by about 35% for a seizure recurrence within the subsequent 2 years.[11] However, immediate AED treatment as compared with treatment delayed until a second seizure occurs is unlikely to improve the chance of attaining sustained seizure remission over the longer term (>3 years). [11] Studies of the nature and incidence of adverse events indicate a wide range of predominantly mild and

reversible adverse events that occur in approximately 7% to 31% of patients.[11] General consensus remains that initiating AED therapy should be individualized based upon patient characteristics after an in depth risk-benefit analysis.

New Formulations/Indications:

Perampanel (Fycompa) was initially approved by the FDA in 2012 for the treatment of partial onset seizures among epilepsy patients aged 12 and older.[8] In 2015 the indications were expanded to include treatment of primary generalized tonic-clonic (PGTC) seizures in patients 12 years of age and older. The efficacy of perampanel as adjunctive therapy in patients with idiopathic generalized epilepsy experiencing PGTC seizures was established in one multicenter RCT conducted at 78 sites in 16 countries.[12] Eligible patients on a stable dose of 1 to 3 AEDs experiencing at least 3 PGTC seizures during the 8-week baseline period were randomized to either perampanel or placebo. Efficacy was analyzed in 162 patients (perampanel n=81, placebo n=81) who received medication and at least one post-treatment seizure assessment. Compared with placebo, perampanel showed a greater median percent change in PGTC seizure frequency per 28 days (−38.4% vs. −76.5%; $p < 0.0001$) and greater 50% PGTC seizure responder rate (39.5% vs. 64.2%; $p = 0.0019$).[12] During maintenance, 12.3% of placebo-treated patients and 30.9% of perampanel-treated patients achieved PGTC seizure freedom. For the safety analysis, the most frequent treatment-emergent adverse events with perampanel were dizziness (32.1%) and fatigue (14.8%).[12]

The FDA approved a new oral suspension formulation of perampanel which provides an additional option for patients who have difficulty swallowing tablets. The liquid formulation has been designated as bioequivalent to the tablet formulation by the FDA. Perampanel can be abused or lead to drug dependence so it has been designated by the US Drug Enforcement Administration (DEA) as a federally controlled substance (CIII). The oral suspension is available in a concentration of 0.5 mg/mL.

Eslicarbazepine (Aptiom) was approved in 2013 by the FDA as adjunctive therapy for treatment of partial-onset seizures.[12] In 2015 the indications were expanded to include the use of esclicarbazepine as monotherapy in the treatment of partial-onset seizures based on results of 2 RCTs.[12] In these trials patients were randomized 2:1 to receive eslicarbazepine 1200mg or 1600mg once per day with historical data used as control. The primary efficacy endpoint was the exit rate for patients meeting specified critieria signifying worsening seizure control. Overall, a reduction in seizure frequency from baseline was noted in the monotherapy arm compared to placebo arms of the historical trials. The most common adverse effects were dizziness, somnolence, nausea, headache, and diplopia.[12]

New FDA Safety Alerts:

Ezogabine [FDA Drug Safety Communication]: FDA determines that risk of retinal abnormalities, potential vision loss, and skin discoloration associated with ezogabine requires additional study. Based on reviews of additional safety reports from patients treated with ezogabine, the FDA determined that potential risks of vision loss due to pigment changes in the retina and of skin discoloration can be adequately managed by following the current recommendations in the official Potiga labeling. To further explore any potential long-term consequences of these pigment changes, the FDA has required the Potiga manufacturer, GlaxoSmithKline, to conduct a long-term observational study.[17]

References:

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVEOUT
ORAL	CAP SPRINK	DEPAKOTE SPRINKLE	DIVALPROEX SODIUM	Y	Y
ORAL	CAP SPRINK	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
ORAL	CAPSULE	CELONTIN	METHSUXIMIDE	Y	
ORAL	CAPSULE	DEPAKENE	VALPROIC ACID	Y	Y
ORAL	CAPSULE	DILANTIN	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	ETHOSUXIMIDE	ETHOSUXIMIDE	Y	
ORAL	CAPSULE	GABAPENTIN	GABAPENTIN	Y	
ORAL	CAPSULE	NEURONTIN	GABAPENTIN	Y	
ORAL	CAPSULE	PHENYTEK	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	PHENYTOIN SODIUM EXTENDED	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	VALPROIC ACID	VALPROIC ACID	Y	Y
ORAL	CAPSULE	ZARONTIN	ETHOSUXIMIDE	Y	
ORAL	CAPSULE	ZONEGRAN	ZONISAMIDE	Y	
ORAL	CAPSULE	ZONISAMIDE	ZONISAMIDE	Y	
ORAL	ORAL SUSP	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	ORAL SUSP	DILANTIN-125	PHENYTOIN	Y	
ORAL	ORAL SUSP	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	ORAL SUSP	PHENYTOIN	PHENYTOIN	Y	
ORAL	ORAL SUSP	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	ORAL SUSP	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	SOLUTION	DEPAKENE	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	SOLUTION	ETHOSUXIMIDE	ETHOSUXIMIDE	Y	
ORAL	SOLUTION	KEPPRA	LEVETIRACETAM	Y	
ORAL	SOLUTION	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	SOLUTION	VALPROIC ACID	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	SOLUTION	ZARONTIN	ETHOSUXIMIDE	Y	
ORAL	TAB CHEW	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	TAB CHEW	DILANTIN	PHENYTOIN	Y	
ORAL	TAB CHEW	PHENYTOIN	PHENYTOIN	Y	
ORAL	TAB ER 12H	CARBAMAZEPINE ER	CARBAMAZEPINE	Y	
ORAL	TAB ER 12H	TEGRETOL XR	CARBAMAZEPINE	Y	
ORAL	TAB ER 24H	DEPAKOTE ER	DIVALPROEX SODIUM	Y	Y
ORAL	TAB ER 24H	DIVALPROEX SODIUM ER	DIVALPROEX SODIUM	Y	Y
ORAL	TABLET	BANZEL	RUFINAMIDE	Y	

ORAL	TABLET	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	TABLET	EPITOL	CARBAMAZEPINE	Y	
ORAL	TABLET	GABITRIL	TIAGABINE HCL	Y	
ORAL	TABLET	KEPPRA	LEVETIRACETAM	Y	
ORAL	TABLET	LAMICTAL	LAMOTRIGINE	Y	Y
ORAL	TABLET	LAMOTRIGINE	LAMOTRIGINE	Y	Y
ORAL	TABLET	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	TABLET	MYSOLINE	PRIMIDONE	Y	
ORAL	TABLET	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	TABLET	PEGANONE	ETHOTOIN	Y	
ORAL	TABLET	PRIMIDONE	PRIMIDONE	Y	
ORAL	TABLET	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	TABLET	TIAGABINE HCL	TIAGABINE HCL	Y	
ORAL	TABLET	TOPAMAX	TOPIRAMATE	Y	
ORAL	TABLET	TOPIRAMATE	TOPIRAMATE	Y	
ORAL	TABLET	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	TABLET	VIMPAT	LCM	Y	
ORAL	TABLET DR	DEPAKOTE	DIVALPROEX SODIUM	Y	Y
ORAL	TABLET DR	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
RECTAL	KIT	DIASTAT	DIAZEPAM	Y	
RECTAL	KIT	DIASTAT ACUDIAL	DIAZEPAM	Y	
ORAL	ELIXIR	PHENOBARBITAL	PHENOBARBITAL	Y	
ORAL	TABLET	PHENOBARBITAL	PHENOBARBITAL	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 DS PK	LAMOTRIGINE	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMICTAL XR	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMOTRIGINE ER	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMICTAL ODT	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMOTRIGINE ODT	LAMOTRIGINE	V	Y
ORAL	TB CHW DSP	LAMICTAL	LAMOTRIGINE	V	Y
ORAL	TB CHW DSP	LAMOTRIGINE	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	TB RD DSPK	LAMICTAL ODT (BLUE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT (GREEN)	LAMOTRIGINE	V	Y

ORAL	TB RD DSPK	LAMICTAL ODT (ORANGE)	LAMOTRIGINE	V	Y
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	CAP SPRINK	TOPAMAX	TOPIRAMATE	N	
ORAL	CAP SPRINK	TOPIRAMATE	TOPIRAMATE	N	
ORAL	CAPSULE	LYRICA	PREGABALIN	N	
ORAL	CPMP 12HR	CARBAMAZEPINE ER	CARBAMAZEPINE	N	
ORAL	CPMP 12HR	CARBATROL	CARBAMAZEPINE	N	
ORAL	ORAL SUSP	BANZEL	RUFINAMIDE	N	
ORAL	ORAL SUSP	FELBAMATE	FELBAMATE	N	
ORAL	ORAL SUSP	FELBATOL	FELBAMATE	N	
ORAL	ORAL SUSP	ONFI	CLOBAZAM	N	
ORAL	POWD PACK	SABRIL	VIGABATRIN	N	
ORAL	SOLUTION	GABAPENTIN	GABAPENTIN	N	
ORAL	SOLUTION	LYRICA	PREGABALIN	N	
ORAL	SOLUTION	NEURONTIN	GABAPENTIN	N	
ORAL	SOLUTION	VIMPAT	LCM	N	
ORAL	TAB ER 24H	KEPPRA XR	LEVETIRACETAM	N	
ORAL	TAB ER 24H	LEVETIRACETAM ER	LEVETIRACETAM	N	
ORAL	TAB ER 24H	OXTELLAR XR	OXCARBAZEPINE	N	
ORAL	TABLET	APTIOM	ESLICARBAZEPINE ACETATE	N	
ORAL	TABLET	FELBAMATE	FELBAMATE	N	
ORAL	TABLET	FELBATOL	FELBAMATE	N	
ORAL	TABLET	FYCOMPA	PERAMPANEL	N	
ORAL	TABLET	GABAPENTIN	GABAPENTIN	N	
ORAL	TABLET	NEURONTIN	GABAPENTIN	N	
ORAL	TABLET	ONFI	CLOBAZAM	N	
ORAL	TABLET	POTIGA	EZOGABINE	N	
ORAL	TABLET	SABRIL	VIGABATRIN	N	
RECTAL	KIT	DIAZEPAM	DIAZEPAM	N	
ORAL	TABLET ER	HORIZANT	GABAPENTIN ENACARBIL	N	
ORAL	SYRINGE	VALPROIC ACID	VALPROIC ACID (AS SODIUM SALT)	N	Y
ORAL	TAB ER 24H	GRALISE	GABAPENTIN	N	
ORAL	TABLET	ONFI	CLOBAZAM	N	
ORAL	TABLET ER	HORIZANT	GABAPENTIN ENACARBIL	N	

Appendix 2: New Clinical Trials

A total of 107 citations were manually reviewed from the literature search. After further review, 105 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 2 trials are briefly described in the table below. Full abstracts are included in **Appendix 3.**

Table 1: Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Razazian, et al. Randomized, double-blind, parallel group design 4 weeks	Carbamazepine 200 mg po bid vs Pregabalin 75mg po bid vs Venlafaxine 75mg po bid	Adults over 18 years of age, metabolically stable type 1 or 2 diabetes with peripheral diabetic neuropathic pain for at least 3 months with visual analog score ≥ 40	Subjective pain as assessed by the visual analogue scale (VAS).	Carbamazepine: Mean VAS baseline: 74.5, mean VAS score on day 35: 39.6 ($p< 0.0001$) Pregablin: Mean VAS baseline: 82.3, mean VAS score on day 35: 33.4 ($p< 0.0001$)
Werhahn, et al. Randomized, double-blind, parallel group design 58 weeks	Carbamazepine controlled release 200-1200mg per day vs Lamotrigine 50-300mg per day vs Levetiracetam 500- 3000mg per day Flexible dosing	Patients ≥60 years with new-onset focal epilepsy	Primary outcome was the retention to treatment at week 58.	Retention Rates at week 58: Carbamazepine CR 45.8% Lamotrigine 55.6% Levetiracetam 61.5%

Appendix 3: Abstracts of Clinical Trials

Razazian N, Baziyar M, Moradian N, Afshari D, Bostani A, Mahmoodi M. Evaluation of the efficacy and safety of pregabalin, venlafaxine, and carbamazepine in patients with painful diabetic peripheral neuropathy. A randomized, double-blind trial. *Neurosciences*. 2014 Jul; 19(3):192-8

Background. To evaluate the efficacy and safety of carbamazepine, pregabalin, and venlafaxine in patients with painful diabetic neuropathy (PDN)
Methods. Randomized, double-blind, parallel-group clinical trial between December 2012 and December 2013 at Kermanshah University of Medical Sciences, Kermanshah, Iran. Two hundred and fifty-seven patients with clinically definite PDN were randomized to receive, carbamazepine, venlafaxine, or pregabalin. The primary outcome was subjective pain as assessed by the visual analogue scale (VAS). Secondary outcomes consisted of sleep, mood, and work interference assessments, and a percentage of patients achieving at least 50% reduction in pain intensity.
Results. Means of VAS scores for carbamazepine, pregabalin, and venlafaxine treatment groups at the baseline (74.5, 82.3, and 74.5) and endpoint (39.6, 33.4, and 46.6) revealed significant reduction, although pregabalin was more efficacious than carbamazepine, and venlafaxine. Improvements in means scores of sleep, mood, and work interferences were identified in all treatment groups.
Conclusions. This study showed the efficacy of venlafaxine, pregabalin, and carbamazepine in pain reduction in patients with diabetic neuropathy, although pregabalin was shown to be superior to carbamazepine, and venlafaxine in relieving pain, no significant superiority was shown between carbamazepine, and venlafaxine.

Konrad J. Werhahn, Eugen Trinka, et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia*. Volume 56, Issue 3, pages 450–459, March 2015.

Background. To compare the effectiveness of controlled-released carbamazepine (CR-CBZ) to levetiracetam (LEV) and to lamotrigine (LTG) in elderly patients with newly diagnosed focal epilepsy.
Methods. Randomized, double-blind, parallel-group trial conducted between January 2007 and August 2011, in 47 ambulatory or hospital sites in Germany, Austria, or Switzerland. Eligible participants were aged ≥60, had new-onset epilepsy, had no acute illness as the cause of their seizures, and had no contraindication to the drugs in the trial. Patients were randomized 1:1:1 to CR-CBZ, LTG, or LEV. Doses were up-titrated for 6 weeks and could be maintained or adjusted depending on seizure relapse or tolerability over an additional period of 52 weeks. Primary outcome was the retention to treatment at week 58; secondary measures related to seizure and adverse event frequency.
Results. Of 361 randomized patients, 359 were included (CR-CBZ n = 121, LTG n = 117, LEV n = 122) in the modified intent-to-treat population (mean age [range] 71.4 [60–95] years). At week 58, the retention rate for LEV was significantly higher than for CR-CBZ (61.5% vs. 45.8%, p = 0.02), and similar to LTG (55.6%). Seizure freedom rates at weeks 30 and 58 were not different across the groups. Twice as many patients receiving CR-CBZ discontinued due to adverse events or death compared to those in the LEV group (32.2% vs. 17.2%; odds ratio 2.28, 95% confidence interval [CI] 1.25–4.19, p = 0.007), whereas discontinuation was intermediate for LTG (26.3%). Median daily doses of completers (n = 195) were CR-CBZ 380.0 mg/day (333.0–384.0), LTG 95 mg/day (94.0–97.0), and LEV 950 mg/day (940.0–985.0).
Conclusions. In the initial monotherapy of focal epilepsy in the elderly, 1-year retention to LEV was higher compared to CR-CBZ due to better tolerability. Retention of LTG was intermediate and close to LEV, but did not differ significantly from either comparators.

Appendix 4: Medline Search Strategy

Ovid Medline (R) without Revisions 1996 to April Week 1 2016

1 exp Epilepsy/dt [Drug Therapy] 18598
2 exp Anticonvulsants/ad, ae, ct, pk, pd, tu, to [Administration & Dosage, Adverse Effects, Contraindications, Pharmacokinetics, Pharmacology, Therapeutic Use, Toxicity] 45806
3 1 and 2 15473
4 (2015 or 2016*).dp. 530554*
5 3 and 4 613
6 exp Carbamazepine 5333
7 3 and 4 and 6 50
8 Clobazam.mp 394
9 3 and 4 and 8 17
10 Diazepam/ 4342
11 3 and 4 and 10 19
12 valproic acid/ 7128
13 limit 12 to humans 5656
14 3 and 4 and 13 63
15 Eslicarbazepine.mp 141
16 limit 15 to humans 141
17 3 and 4 and 16 7
18 Ethosuximide/ 259
19 limit 18 to humans 120
20 3 and 4 and 19 1
21 Ethotoin.mp 2
22 Ezogabine.mp 0
23 Felbamate.mp 464
24 limit 23 to humans 359
25 Gabapentin.mp 4445
26 limit 25 to humans 3563
27 3 and 4 and 26 7
28 LCM.mp 402
29 limit 28 to humans
30 3 and 4 and 29 23
31 Lamotrigine.mp 3882
32 limit 31 to humans 3366
33 3 and 4 and 32 42
34 Levetiracetam.mp 2027
35 limit 34 to humans
36 3 and 4 and 35 61

37 Methsuximide.mp 17
38 limit 37 to humans 15
39 Oxcarbazepine.mp 1161
40 limit 39 to humans 1161
41 3 and 4 and 40 18
42 Perampanel.mp 115

43 limit to humans 104
44 3 and 4 and 43 17
45 Phenobarbital/ 2916
46 limit 45 to humans 1333
47 3 and 4 and 46 13
48 Phenytoin/ 3107
49 limit 48 to humans 2339
50 3 and 4 and 49 24
51 Pregablin.mp 8
52 limit 51 to humans 7
53 Primidone/ 155
54 limit 53 to humans 118
55 3 and 4 and 54 0
56 Rufinamide.mp 155
57 limit 56 to humans 145
58 3 and 4 and 57 4
59 Tiagabine.mp 785
60 limit 59 to humans
61 3 and 4 and 60 1
62 Topiramate.mp 3486
63 limit 62 to humans 3091
64 3 and 4 and 63 23
65 Valproic Acid.mp 8562
66 limit 65 to humans 6840
67 3 and 4 and 65 90
68 Vigabatrin/ 998
69 limit to 68 to humans 745
70 3 and 4 and 69 11
71 Zonisamide.mp 909
72 limit 71 to humans 773
73 3 and 4 and 71 13
74 limit 5 to (humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 107
75 6 or 8 or 10 or 12 or 15 or 18 or 21 or 22 or 23 or 25 or 28 or 31 or 34 or 37 or 39 or 42 or 45 or 48 or 51 or 53 or 56 or 59 or 59 or 62 or 65 or 68 or 71 33738
76 limit 75 to ((clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews) and last 2 years) 551

Clobazam

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- 12 months

Requires PA:

- Clobazam

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 patients have a diagnosis of Lennox-Gastaut syndrome and is 2 years of age or older?	**Yes:** Go to #3.	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness

Limitations of Use:

• Clobazam is not indicated for other epilepsy syndromes other than Lennox-Gastaut.

P&T Review: *7/16 (DM); 3/15; 5/12*
Implementation: *8/12*

Topiramate

Goal(s):

- Approve topiramate only for covered diagnoses (above the line) 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 (ICD-10 G40101-G40311; G40401-G40509; G40802; G40804; G40901-G40919; R569 or S069X9S)?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine (ICD10 G43001-G43919; G43A0; G43B0; G43C0; G43D0; G43A1; G43B1; G43C1; G43D1)?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder? • ICD-10 F30.10-F33.9 and subsets • ICD-10 F259 and subsets	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
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: *7/16 (DM); 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*