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Clinical Review: Off-label Use of Gabapentin and Pregabalin

Date of Review: June 2024
Generic Name: gabapentin and pregabalin
PDL Class: Antiepileptics, Outpatient

End Date of Literature Search: 3/30/2024
Brand Name (Manufacturer): Neurontin (Pfizer) and Lyrica (Viatris)
Dossier Received: No

Purpose for Drug Evaluation:

- Evaluate the evidence for compendia supported, funded, non-neuropathic, off-label uses for gabapentin and pregabalin.

Plain Language Summary:

- Should the Oregon Health Plan change the current Medicaid policy for pregabalin to cover conditions that are not approved by the Food and Drug Administration (FDA)?
- Pregabalin and gabapentin can be prescribed for nerve pain. Some studies have not shown that pregabalin or gabapentin improve pain in other pain-related conditions that are not FDA-approved.
- Pregabalin and gabapentin are commonly prescribed for conditions that are not approved by the FDA.
- Pregabalin may help decrease anxiety for people with generalized anxiety disorder if antidepressants are not working or are not tolerated.
- Currently, providers must tell Medicaid why they are prescribing pregabalin before Medicaid Open Card will pay for the prescription. This process is called prior authorization. This analysis of Medicaid data shows that prior authorization may decrease use of pregabalin for conditions where there is no benefit. But it may also delay care for people with generalized anxiety disorder or other conditions where there is benefit.
- The Mental Health Clinical Advisory Group recommended that pregabalin be available for people with generalized anxiety disorder when prescribed with an antidepressant.
- The Pharmacy and Therapeutics Committee should consider removal of prior authorization for pregabalin or automatic approval of requests for preferred pregabalin when it is prescribed for generalized anxiety disorder.

Research Questions:

1. Is there evidence demonstrating effectiveness and safety of pregabalin for use in compendia supported off-label conditions that are funded by the Oregon Health Plan (OHP)?
2. Is there evidence demonstrating effectiveness and safety of gabapentin for use in compendia supported off-label conditions that are funded by OHP?
3. Are there particular patient subgroups that would benefit more from pregabalin or gabapentin for off-label conditions?

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Conclusions:

- There is insufficient evidence (based solely on expert opinion or consensus, post-hoc analysis, case reports, or case series) evaluating the efficacy and safety of pregabalin for the following indications: familial dysautonomia, cancer-associated neuropathy, refractory cough, panic disorder, obsessive-compulsive disorder, ureteral stent-related symptoms, and vasomotor symptoms of menopause.
- There is insufficient evidence (based solely on expert opinion or consensus, post-hoc analysis, case reports, or case series) evaluating the efficacy and safety of gabapentin for the following indications: trigeminal neuralgia, generalized anxiety disorder, refractory cough, panic disorder, and social anxiety disorder.
- There is moderate quality evidence that pregabalin at doses of 300-600 mg/day may improve anxiety symptoms compared to placebo, as measured by the Hamilton Anxiety Rating Scale (HAM-A) compared to placebo based on studies of short duration (4-8 weeks) with high risk of attrition bias.[1,2] Studies demonstrate a medium effect size that is similar to the studied selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). [1]
- There is moderate quality evidence of significant effect on number of responders with social anxiety disorder with gabapentin and pregabalin compared to placebo in adults with social anxiety disorder (35.3% vs. 22.1%; risk ratio [RR]1.60; 95% confidence interval [CI] 1.16 to 2.20; 3 studies; n=532). [3]
- There is low quality evidence that pregabalin modestly reduces anxiety symptoms, based on the HAM-A, compared to placebo when used as adjunctive treatment in patients who have not adequately responded to a SSRI or SNRI over a short trial.[4]
- Pregabalin may be beneficial in generalized anxiety disorder (GAD) for those who cannot tolerate or have failed first line therapy with a SSRI and SNRI. Common side effects associated with pregabalin, risk of misuse and abuse in those at higher risk for substance use disorder, FDA warnings for respiratory depression when used in combination with opioids, and risks of use in pregnancy needs to be considered prior to use for GAD. There is insufficient data evaluating the long-term efficacy or safety of pregabalin in the treatment of GAD and insufficient data in patients with comorbid substance use or mental health disorders.
- In February 2022, the Mental Health Clinical Advisory Group (MHCAG) developed treatment algorithms for GAD. Pregabalin is recommended as first-line adjunct treatment for patient with GAD in conjunction with a SSRI/SNRI.
- There is moderate quality evidence that gabapentin improves uremic pruritus in patients with chronic kidney disease (CKD) stages 4 and 5, measured by a 10 cm Visual Analog Scale (VAS), compared to placebo (4.95 cm lower; 95% CI -5.46 to -4.44) and low-quality evidence that gabapentin may modestly reduce symptoms of uremic itch compared to antihistamines (0.44 cm lower; 95% CI -0.75 to -0.14). [5] However, the optimal dosage remains unknown and dosing interval and side effects need to be considered in patients with CKD.
- There is low quality evidence that gabapentin modestly reduces frequency of hot flashes associated with menopause compared to placebo at 12 weeks (mean difference [MD] -2.77; 95% CI -4.29 to -1.24) with no difference in duration or severity score. [6] Trials did not consistently meet the minimum clinically important difference (MCID) for vasomotor symptom frequency (3.57 per day).
- There is evidence of racial and ethnic differences in vasomotor symptoms, including an increased severity in Black women. [6] However, studies included mostly white participants. There is insufficient evidence evaluating gabapentin in Black persons and other racial groups.
- There is low quality evidence of no significant difference in improved alcohol abstinence with gabapentin at varying doses compared to placebo (RR 1.33; 95% CI 0.84 to 2.10) and no significant benefit on relapse to heavy drinking (RR 0.80; 95% CI 0.57 to 1.13). There is low quality evidence that gabapentin may reduce the percent of heavy drinking days, decrease alcohol consumption, and decrease acute alcohol withdrawal symptoms. Patients with more mild alcohol withdrawal stable enough to be treated in the outpatient setting may benefit from gabapentin.
- For all off label uses of gabapentin and pregabalin, there is a consistent trend toward higher rates of discontinuations due to adverse events compared to placebo, with the most common adverse events of dizziness, somnolence, headache, and sedation. Rates of serious adverse effects are low.

- For most off-label uses, there is significant heterogeneity in dosing among studies, inconsistent dose-response demonstrated for efficacy, high rates of attrition, and little guidance on optimal dose.

Recommendations:

- Modify prior authorization criteria to allow use of pregabalin for generalized anxiety disorder in those who have trialed or have a contraindication to first line treatment with a SSRI and SNRI without a prior trial of gabapentin.

Background:

Use of gabapentinoids, including pregabalin and gabapentin, has been rising. Between 2012 and 2016, spending on pregabalin grew from $2 billion to nearly $4.5 billion. In a 2022 study, approximately 1 in 5 U.S. adults with chronic pain were receiving a gabapentinoid.[7,8] Much of the increased use has been attributed to the search for alternatives to opioids for the management of chronic pain. New guidance from the Centers for Disease Control calls for even greater use of non-opioid analgesics, including gabapentinoids.[9] The guidelines suggest considering gabapentin or pregabalin for certain chronic pain conditions, including diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia.[9] The guidelines also indicate that they are associated with only small to moderate improvements and are not without adverse events such as blurred vision, cognitive effects, sedation, weight gain, dizziness, peripheral edema, and risks of respiratory depression and overdose when used in combination with opioids.[9]

Evidence directly comparing gabapentin to pregabalin is limited and is generally of poor quality with small sample sizes.[4] Among the small trials for chronic neuropathic pain, results are inconsistent with some trials showing small differences between gabapentin and pregabalin and the majority showing them to be equal in efficacy.[10] Overall, there is insufficient evidence to discern the superiority of one agent over another. Adverse events can include blurred vision, negative cognitive effects, sedation, weight gain, dizziness, peripheral edema, and risks when used in combination with opioids. The Food and Drug Administration (FDA) issued a warning in 2019 of an increased risk of respiratory depression when used with opioids or other CNS depressants.[11] Observational studies have shown an association between concurrent use of gabapentinoids and opioids versus opioids alone and increased risk for overdose, with higher risks at increased gabapentinoid doses. Pregabalin is a schedule V controlled substance, defined as a drug with low potential for abuse and dependence.

FDA approved indications for immediate-release pregabalin include neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, neuropathic pain associated with spinal cord injury, fibromyalgia, and treatment of partial-onset seizures. Extended-release formulations are only FDA approved to treat neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Gabapentin is only FDA approved for postherpetic neuralgia and seizures. It is used primarily off-label and has become standard of care for neuropathic pain conditions.

For FDA approved indications, overall effect size of pregabalin in clinical studies is small.[10] Five studies were submitted to FDA for approval for diabetic peripheral neuropathy. Of those, the FDA rated three as being supportive, one as partly supportive and one as negative. Overall, the reduction in pain is modest, as measured on a 11-point Likert scale (ranging from 0-10). Additionally, the placebo response was at least 50% as large as the response to any pregabalin dose. For the treatment of fibromyalgia, there was a small difference seen in mean pain score with pregabalin 300 mg/day, 450 mg/day and 600 mg/day compared to placebo (difference of -0.71 to -1.0) with little additional benefit with the highest dose but more discontinuations due to adverse events.[10] Finally, cognitive adverse effects was a significant concern of FDA and most trials excluded patients from using other centrally acting medications during the study period, including opioids, which may underestimate adverse effects.

There have been negative studies showing no significant benefit with pregabalin over placebo for various chronic pain conditions, including sciatica pain, human immunodeficiency virus (HIV) neuropathy, chronic sickle cell pain, acute zoster pain, and back pain.[12-14] The manfuacturer has sought FDA approval of pregabalin for GAD both in 2004 and 2009. Both times, the FDA determined there was not sufficient evidence for FDA approval.

In the OHP fee-for-service (FFS) program, prior authorization (PA) is required for pregabalin (**Appendix 2**). The goal of the PA is to limit use to FDA-approved and OHP-funded indications. Common conditions that are unfunded on the prioritized list include restless leg syndrome, fibromyalgia, and some polyneuropathies. Gabapentin tablets and capsules are currently preferred products and are available without PA.

In February 2022, the MHCAG developed treatment algorithms for GAD. Pregabalin is recommended as first-line adjunct treatment for patient with GAD in conjunction with a SSRI/SNRI. The MHCAG discussed the role of pregabalin in the OHP FFS program and made the following recommendations to the Pharmacy and Therapeutics (P & T) Committee for consideration:[11]

- Recommendation 1: Remove OHP FFS PA for pregabalin immediate-release (IR) capsule products.
- Recommendation 2: Should the P & T Committee not agree with the MHCAG's first recommendation, the MHCAG asks that the P & T Committee consider this alternative: Add GAD to Table 1 of OHP FFS PA for pregabalin IR and do not require prior treatment or intolerance to gabapentin.

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 for gabapentin and pregabalin for off-label compendia (i.e. Micromedex) supported and OHP funded indications.
The following compendia-supported off-label uses were identified for possible inclusion.

Compendia supported and funded off-label indications for pregabalin reviewed for inclusion:

- Familial dysautonomia
- Generalized anxiety disorder
- Obsessive-compulsive disorder
- Peripheral neuropathy due to antineoplastic therapy
- Postoperative Pain
- Restless legs syndrome
- Social phobia
- Uremic pruritus
- Ureteral stent-related symptom; Prophylaxis

Compendia supported and funded off-label indications for gabapentin reviewed for inclusion:

- Alcohol dependence
- Fibromyalgia
- Hemodialysis associated pruritus
- Vasomotor symptoms of menopause
- Neuropathic pain – spinal cord injury

- Neuropathic pain with diabetes mellitus
- Peripheral neuropathy due to antineoplastic therapy
- Postoperative pain
- Trigeminal neuralgia

Off-label uses with only Category C evidence (based on data derived from Expert onion or consensus, case reports or case series) were excluded as were unfunded conditions (fibromyalgia and restless leg syndrome). Since postoperative pain studies focus on short term treatment in the immediate postoperative period, usually prior to discharge and outcomes are short-term only (i.e. 24-72 hours postoperatively)[15] , this off-label indication was also excluded from the evidence review. Lastly, treatment for neuropathic pain is reviewed separately by the Pharmacy & Therapeutics Committee.[16]

The Medline search strategies used for this review are available in **Appendix 1,** which includes dates, search terms and limits used. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.
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.

Results:

Off-label uses with insufficient evidence
There is insufficient evidence for pregabalin use in the following indications and are based solely on expert opinion or consensus, post-hoc analysis, case reports, or case series: familial dysautonomia[17], cancer-associated neuropathy, refractory cough, panic disorder, and vasomotor symptoms.

There is insufficient evidence for gabapentin use in the following indications and are based solely on expert opinion or consensus, post-hoc analysis, case reports, or case series: trigeminal neuralgia, generalized anxiety disorder, refractory cough, panic disorder, and social anxiety disorder.

Off-label uses with very low-quality evidence
Based on a literature search, there is very low quality evidence supporting pregabalin for obsessive compulsive disorder based on only one small (n=42) poor quality study.[18] There is very low quality evidence supporting pregabalin for ureteral stent-related symptoms. Two open-label, small randomized controlled trials were identified showing benefit when pregabalin was used in combination with an anticholinergic medication and a small benefit over control in a 38-question subjective questionnaire.[19,20]

Generalized and Social Anxiety Disorder: Pregabalin

Systematic Reviews
Five systematic reviews were excluded after further review due to study design (network meta-analysis)[21,22], and poor quality (no risk of bias assessment[23-25], inclusion of non-randomized studies[26]). One Cochrane systematic review evaluated pharmacotherapy for anxiety and comorbid alcohol use disorders but no studies of pregabalin in this population were identified.[27]

- A 2015 systematic review included placebo-controlled, randomized controlled studies of patients with GAD, social anxiety disorder, and panic disorder using the HAM-A.[1] HAM-A measures the severity of anxiety symptoms and consists of 14 items with a total score ranging from 0-56. For the counterpart used to evaluate depression (Hamilton Rating Scale for Depression; HAM-D), a clinically meaningful important difference has been defined as a change of 3 to 7, but no MCID has been established for the anxiety scale. Study quality was assessed using the Scottish Intercollegiate Guidelines Network (SIGN). Due to high heterogeneity, a random-effects model was used in the analysis. In total, 234 studies (n=37,333) were included. Effect size was expressed as the Cohen's d, which classifies effect sizes as small (d=0.2), medium (d=0.5), and large (d ≥ 0.8). [1] Overall, there was higher efficacy with medications compared to psychotherapies. Eight studies included pregabalin and showed it to be more effective than placebo (d=0.55; 95% CI 0.37 to 0.74) with a medium effect size similar to the studied SSRIs and SNRIs.[1] The authors identified large effect size heterogeneity and limited head-to-head data as major limitations.

- Another systematic review identified studies of gabapentin and pregabalin in bipolar disorder, anxiety disorders and insomnia that compared to placebo or active control.[2] The primary outcome for anxiety studies was change in validated and standardized anxiety rating scales and risk of bias was assessed independently by 4 authors using the Cochrane risk of bias tool. The risk of bias was unclear for most studies, and many had high risk of attrition bias. For anxiety, 42 double-blind RCTs were included with 3,539 patients randomized to pregabalin and 525 to gabapentin. Gabapentinoids were significantly more effective than placebo across different outcomes with standardized mean differences ranging from -2.25 to -0.25 on various scales. In studies of pregabalin in GAD only (10 studies), pregabalin was significantly more effective than placebo (standard mean difference [SMD] -0.37; 95% CI -0.46 to -0.29).[2] Pregabalin reduced the risk of dropouts due to lack of efficacy (RR 0.44; 95% CI 0.28 to 0.70) but trended toward an increased risk of dropouts due to adverse events (RR 1.30; 95 % CI 0.99 to 1.71) and the most common adverse events were drowsiness and dizziness.[2]

- A Cochrane Collaboration review assessed the effects of pharmacotherapy for social anxiety disorder in adults.[3] Placebo-controlled RCTs in adults with social anxiety disorder were included. The primary outcome was response to treatment, as assessed by the Clinical Global Impressions Improvement scale (CGI-I), which ranges from 1 to 7. Responders were defined as having a change of 1 (very much improved) or 2 (much improved). A total of 66 RCTs comparing pharmacotherapy to placebo were included. Thirty-four of the RCTs included SSRIs. Only 3 studies included gabapentin (1 study) or pregabalin (2 studies). [3] All 3 studies had unclear risk of bias in most bias categories. There was moderate quality evidence of significant effect on number of responders in CGI-I compared to placebo in adults with social anxiety disorder (35.3% vs. 22.1%; RR 1.60; 95% CI 1.16 to 2.20; 3 studies; n=532).[3] There was a nonsignificant increase in discontinuations due to adverse effects compared to placebo (17% vs. 6% RR 2.90; 95% CI 0.92 to 9.14).[3]

Randomized Controlled Trials

A total of 8 RCTs were identified through the literature search. Three of these were excluded due to poor quality (open label[28], wrong indication[29], not designed or powered for statistical comparisons.[30] The remaining study details are included in **Table 1**.

Table 1. Randomized Controlled Trial Evidence Table.

Study	Drug Regimens/ Duration	Patient Population	Primary Outcome	Results	Limitations
Kasper et al.[31] DB, PC, RCT	Pregabalin 300-600 mg/day vs. Venlafaxine XR 75-225 mg/day vs. Placebo	Adult with GAD without other psychiatric conditions, including major depressive disorder.	Improvement in the Hamilton Anxiety Rating Scale (HAM-A)	Change in HAM-A from baseline (LS mean): Pregabalin: -14.5 Venlafaxine: -12.0	• High attrition rates (27% - 33%) • Short duration of 8 weeks may not allow for sufficient response with venlafaxine.

	8 weeks	(n=374)		Placebo: -11.7 Pregabalin vs. placebo: p=0.028 Venlafaxine vs. placebo = 0.97 <u>Response Rate (> 50% reduction in HAM-A)</u> Pregabalin: 59% Venlafaxine: 44% Placebo: 46% P=0.05 for pregabalin vs. venlafaxine and vs. placebo	• Exclusion criteria limits applicability to patients with comorbid mental health conditions, including major depressive disorder, or concomitant mental health medications and renal dysfunction (CrCl < 60 ml/min), and to use of alcohol, opiates, and those with substance use disorders. • High rates of dizziness (21%) and vertigo (13%) in pregabalin group • Low HAM-A scores at baseline • High placebo response rates • Study was funded by Pfizer and many study authors had financial conflicts. • There was no significant effect seen on quality-of-life outcomes
Feltner[32] MC, DB, PC, PG, RCT	Pregabalin titrated up to 450 mg/day vs. placebo. Study consisted of 1 week screening phase, 8-week open label acute treatment phase, 24 weeks double-blind relapse prevention phase, 2-week discontinuation assessment phase	Adults with GAD without other psychiatric conditions other than depression (n=339)	Time to relapse	<u>Relapse:</u> Pregabalin: 42.3% Placebo: 65.3% Efficacy in time to relapse was superior with pregabalin (p<0.0001) <u>D/C due to AE:</u> Pregabalin: 5.9% Placebo: 2.4%	• Only subjects who sustained a clinical response with pregabalin during open-label phase were recruited into double-blind phase and randomized to continue pregabalin vs. placebo. • 45.7% of participants from open-label acute phase did not meet criteria for double-blind study. • High rates of attrition in both groups • Exclusion criteria excluded common comorbidities associated with GAD.
Montgomery, et al.[33] DB, PG, PC, RCT	Pregabalin 400 mg/day Pregabalin 600 mg/day Venlafaxine 75 mg/day Placebo 6 weeks	Adults with GAD without other psychiatric conditions other than depression	Change from baseline in the HAM-A	<u>Change from baseline in HAM-A</u> Pre 400 mg: -14.7 Pre 600 mg: -14.1 Venlafaxine: -14.1 Placebo: -11.6 *All comparisons significant compared to placebo (p<0.05) <u>Response rate (> 50% reduction in HAM-A)</u> Pre 400mg: 61% Pre 600 mg: 58% Venlafaxine: 62% Placebo: 45% *Significant for pregabalin 400 mg vs. placebo (p=0.02) and venlafaxine vs. placebo (p=0.01) but not for	• High attrition rates (20% - 30%) in each group with significantly more dropouts in the venlafaxine group compared to pregabalin (p<0.05) • Study was funded by Pfizer and many study authors had financial conflicts. • Exclusion criteria limits applicability to patients with comorbid mental health conditions, on concomitant mental health medications, and those with alcohol and substance use disorders. • Venlafaxine dosing was not titrated to allow for comparable doses used in clinical practice. • Short duration of 6 weeks may not allow for sufficient response with venlafaxine.

				pregabalin 600 mg vs. placebo (p=0.06) <u>D/C due to adverse events:</u> Pre 400mg: 6% Pre 600 mg: 14% Venlafaxine: 20% Placebo: 7%	• 99% of patients enrolled in the study were white, limiting generalizability to other races and ethnicities. • No dose response seen with pregabalin. • Higher rates of dizziness and somnolence with pregabalin 400 mg (22.7% and 13.4%) and 600 mg (26.4% 13.6%) compared with venlafaxine and placebo.
Pande et al.[34] DB, PC, RCT	Pregabalin 150 mg/day Pregabalin 600 mg/day Lorazepam 6 mg/day Placebo 4 weeks	Adults with GAD without other psychiatric conditions other than mild depression (n=277)	Change from baseline in the HAM-A	<u>Change from baseline in HAM-A</u> Pre 150 mg: -9.2 Pre 600 mg: -10.25 Lorazepam: -11.96 Placebo: -6.8 *All comparisons significant compared to placebo (p<0.05) Pre 150 vs. pre 600 mg: p=0.36 Pre 600 mg vs. lorazepam: p=0.13 <u>Response rate (> 50% reduction in HAM-A)</u> Pre 600 mg: 46% Lorazepam: 61% Placebo: 28% *Significant for pregabalin 600 mg vs. placebo and lorazepam vs. placebo (p< 0.05) but not for pregabalin 150mg vs. placebo <u>D/C due to adverse events:</u> Pre 150mg: 2.9% Pre 600 mg: 20% Lorazepam 27.9% Placebo: 10%	• More females in placebo and lorazepam groups at baseline • High and variable attrition rates in each group (10-27%) • 14 patients were missing efficacy assessments and not included in the analysis. • Exclusion criteria limits applicability to patients with comorbid mental health conditions, including major depressive disorder, and on concomitant mental health medications, and those with alcohol and substance use disorders. • Higher rates of dizziness with pregabalin and higher rates of discontinuations due to adverse events in the high dose pregabalin and lorazepam groups • Higher doses of lorazepam without room for flexibility compared to doses used in clinical practice
Rickels, et al.[35] DB, PC, RCT	Pregabalin 300 mg/day Pregabalin 450 mg/day Pregabalin 600mg/day Alprazolam 1.5 mg/day Placebo 4 weeks	Adults with GAD without other psychiatric conditions or psychiatric medications and without alcohol or substance use disorders	Change from baseline in the HAM-A	<u>Change from baseline in HAM-A</u> Pre 300 mg: -12.25 Pre 450 mg: -11.0 Pre 600 mg: -11.79 Alprazolam: -10.91 Placebo: -8.35 P<0.05 for all comparisons versus placebo	• High attrition bias with rates of attrition between 11 and 20% and significantly more with higher doses of pregabalin and alprazolam compared to 300 mg pregabalin • Mostly white participants (74%) with no details race and ethnicity of remaining participants • Short duration of 4 weeks

Rickels, et al.[4] DB, MC, PC, RCT	Pregabalin 150-600 mg/day vs. placebo On background treatment with SSRIs and SNRIs 8 weeks	Adults with GAD who failed to respond optimally (partially responders) to a previous GAD treatment during 8-week open label phase (N=356)	Change from baseline in HAM-A	<u>Change from baseline in HAM-A</u> Pre: -7.6 Placebo: -6.4 Mean difference -1.2; 95% CI -2.15 to -0.27 P=0.01 <u>HAM-A responder rates</u> Pre: 47.5% Placebo: 35.2% OR 1.77; 95% CI 1.12-2.79 P=0.01	• Those with depressive disorder, social anxiety disorder, substance dependence, psychiatric conditions were excluded • 8-weel open label treatment optimization phase limits generalizability • Only those who had partially responded during open label treatment were randomized. However, 8 weeks may not be sufficient for response. • Short duration study
Abbreviations: AE: adverse events; CrCl: creatinine clearance; DB: double-blinded; D/C: discontinuations; GAD: generalized anxiety disorder; HAM-A: Hamilton Anxiety Rating Scale; MC = multicenter; OR: odds ratio; Pre: pregabalin; PC: placebo controlled; PG: parallel group; RCT: randomized controlled trial, SNRIs: selective-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors.					

<u>Clinical Guidelines</u>

Clinical Guidelines from the National Institute for Health and Care Excellence (NICE)[36] were updated in 2020 and recommend the following for drug treatment:

- If a person with GAD chooses treatment, offer a SSRI as first line. Consider sertraline as first line.
- If sertraline or other first line SSRI is ineffective, offer an alternative SSRI or a SNRI.
- If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin
    - Pregabalin is associated with increased risk of abuse and dependence. Prior to prescribing pregabalin, evaluate patients carefully for a history of drug abuse and observe patients for development of signs of abuse and dependence.
    - Based on new data suggesting pregabalin may slightly increase the risk of congenital malformations if used in pregnancy. Patients should continue to use effective contraception during treatment and avoid use in pregnancy unless clearly necessary.
- Do not offer a benzodiazepine in primary care except as a short-term measure during crises.
- Do not offer an antipsychotic for treatment of GAD in primary care.

Uremic Pruritus: Gabapentin and Pregabalin

Pruritus, or itching, may occur in individuals with CKD, particularly in those receiving hemodialysis. The exact mechanism of gabapentin and pregabalin in treating pruritus is not clear but may be related to the interference of C-fibre mediated nociceptive sensations to the brain.

<u>Systematic Reviews:</u>

One systematic review was excluded due to design (network meta-analysis)[37].

- One Cochrane systematic review evaluated the benefits and harms of intervention for the treatment of uremic pruritus in patients with CKD, including GABA analogues (gabapentin and pregabalin).[5] All RCTs and quasi-RCTs in patients with CKD stages 4 or 5 were excluded. A total of 92 studies (n=4466) were identified evaluating 43 different interventions (oral and topical). There were 12 studies (n=618) that included either oral gabapentin or pregabalin. Compared to placebo, 5 studies included dosages of gabapentin 300 mg–400 mg twice weekly or pregabalin 75 mg twice weekly. Studies reported itch on a 10 cm VAS. Subjects were trained to evaluate severity with 10 horizontal lines marked from 0 to 10, with 0 meaning no pruritus and 10 for worst possible itch. Five studies with overall low risk of bias compared GABA analogues to placebo demonstrating high quality evidence that GABA analogues resulted in a greater reduction in the VAS Score compared to placebo (4.95 cm lower; 95% CI -5.46 to -4.44).[5] An additional 5 studies compared gabapentin (at doses of 100 to 200 mg daily and 300 mg three times weekly) to antihistamines, including loratadine, hydroxyzine and dexchlorpheniramine. Low certainty evidence suggests gabapentin may reduce symptoms of uremic itch compared to antihistamines (0.44 reduction; 95% CI 0.75 to 0.14 lower).[5] One study showed no significant difference in itch reduction between gabapentin and pregabalin. [5] Mild adverse effects (somnolence, dizziness, and fatigue) occurred in <5% of patients and no moderate or severe adverse effects were reported. The authors concluded that GABA analogues achieved the largest effect size of all studied interventions and ondansetron was not associated with a reduction in pruritus compared to placebo. Most of the evidence was for gabapentin. There is insufficient evidence to give recommendations regarding optimal dosing and the clinical significance of the resulting effect size on the VAS remains unclear.

- An additional systematic review of RCTs of gabapentin compared to placebo or other medications for the treatment of uremic pruritus in CKD patients on hemodialysis identified seven RCTs (n=315).[38] Four studies were able to be combined in a quantitative meta-analysis. Ten cm VAS was used in six of the studies. Five studies had moderate risk of bias and two had high risk of bias. Allocation concealment was unclear in five studies. Dosing included 100 mg daily, 100–300 mg three times weekly after hemodialysis, and 400 mg two times weekly after hemodialysis. The primary outcome review was ≥ 50% reduction in pruritus scores. In the pooled analysis, treatment with gabapentin at varying doses was associated with a significantly decreased severity of uremic pruritus compared to placebo (RR 0.18; 95% CI 0.09 to 0.33; p<0.0001; I^2=4%; 4 studies).[38] Treatment with gabapentin was also associated with a higher incidence of adverse drug reactions compared to both active comparators and placebo, but results were not statistically significant (RR 1.3; 95% CI 0.81 to 2.11; p=0.28; 6 studies). [38]

Randomized Controlled Trials

Three RCTs were excluded due to poor quality (open-label, high risk of bias, or lack of placebo[39-41]) and the remaining were included in the Cochrane Systematic Review detailed above and will not be reviewed individually.[42-48]

Vasomotor Symptoms Associated with Menopause: Gabapentin

Systematic Reviews:

Three meta-analyses were excluded (network meta-analysis[49,50], lack of high quality methodology[51]).

- One systematic review and meta-analysis included prospective RCTs and randomized crossover studies examining the effects of gabapentin or pregabalin on vasomotor symptoms in women experiencing menopause because of natural or medical reasons.[6] Primary outcomes included reduction in frequency, severity, or duration of hot flashes. Studies were assessed for risk of bias using the Cochrane risk of bias tool. A total of 19 RCTs and 2

crossover trials were identified (n=3519). Participants in studies discontinued hormonal therapy. The most common dose of gabapentin was 900 mg and majority of studies were 12 weeks in duration. Moderate risk of bias in randomization was reported. Four studies had high risk of detection bias and the majority had unclear other bias due to conflicts of interest among authors and funding from pharmaceutical companies. Overall, the authors concluded the certainty of the evidence ranged from very low to moderate due to risk of bias, inconsistency, and imprecision. Low to moderate quality evidence was identified for the comparison of gabapentin to placebo. Other comparisons (estrogen, tibolone, isoflavone, hypnotherapy, and antidepressants) will not be discussed due to lower quality evidence and significant heterogeneity. Compared with placebo, moderate quality evidence demonstrated a reduction in the frequency of hot flashes at week 4 from baseline (mean difference [MD] -1.62; 95% CI -1.98 to -1.26; 8 RCTs) and low-quality evidence at week 12 (MD -2.77; 95% CI -4.29 to -1.24; 7 RCTs).[6] There was low quality evidence of no difference in reduction in duration of hot flashes or severity score. Compared to placebo, there was low to moderate quality evidence of a higher risk of dizziness (RR 4.45; 95% CI 2.50-794) and somnolence (RR 3.29; 95% CI 1.97 to 5.48) compared to placebo and more participants discontinued treatment due to adverse events in the gabapentin group (RR 1.99; 95% CI 1.50 to 2.62).[6] The authors noted several limitations to consider with these results, including heterogeneity, small sample size in many studies, variable information about baseline hot flashes, and lack of data testing long-term efficacy of treatment. There was insufficient evidence to evaluate pregabalin for the treatment of vasomotor symptoms.

Randomized Controlled Trials

An additional 3 RCTs were identified. One was excluded due to overall risk of bias and quality.[52] The remaining 2 are included in Table 2.

Table 2. Randomized Controlled Trial Evidence Table.

Study	Drug Regimens/ Duration	Patient Population	Primary Outcome	Results	Limitations
Guttuso et al.[53] DB, PC, RCT	Gabapentin 900 mg daily vs. placebo N=59	Postmenopausal women with an average of 7 or more hot flashes per day accompanied by sweating not on HRT.	Percent reduction in frequency at week 12	% change in frequency Gabapentin: -45% (SD=31.5) Placebo -29% (SD=32.1) Difference-20.9%; 95% CI 2.7 % to 34% P=0.02 Daily mean difference -1.9	• 93.2% white • Natural menopause rates not reported • Wide confidence intervals suggesting large variance
Pinkerton et al.[54] DB, PC, RCT	Gabapentin gastroretentive formulation 1800 mg daily versus placebo N=600	Healthy postmenopausal women who experienced 7 or more moderate-to severe hot flashes per day during a 14-day baseline not on HRT.	Mean change in frequency and severity of hot flashes at week 12	Mean change in frequency Gabapentin: -7.64 Placebo: -6.50 Difference -1.14; 95% CI -1.8 to -0.48; p=0.0007 Mean change in severity Gaba: -0.65 Placebo; -0.46 Difference -0.19; 95% CI -0.33 to -0.04; p=0.012	• High attrition bias (33.8% discontinued from the study early) • Exclusion criteria of note: substance abuse within the past year; any serious medical condition • 69.5% white
Abbreviations: CI = Confidence Interval; DB: double-blinded; HRT: hormone replacement therapy; PC: placebo controlled; RCT: randomized controlled trial; SD = Standard Deviation					

Alcohol Dependence: Gabapentin and Pregabalin

Systematic Reviews

Two systematic reviews was excluded due to lack of high-quality methodology[55] (no risk of bias assessment[56]).

- A 2014 Cochrane Systematic review concluded there was insufficient evidence to conclude anticonvulsants as a class are effective in treating alcohol dependence.[57] A total of 25 studies were included, many with unclear risk of bias due to lack of blinding and/or unclear allocation concealment. Overall, there was no significant effect on abstinence (RR.1.21; 95% CI 0.97 to 1.52; 8 studies; moderate quality evidence) or dropping out of treatment (RR 0.94; 95% CI 0.74 to 1.19); 16 studies; moderate quality evidence) compared to placebo. There was moderate quality evidence of a decrease in mean drinks/day with anticonvulsants compared to placebo (mean difference -1.49 fewer drinks; 95% CI -2.32 to -0.65).[57] There were 5 studies including gabapentin, with doses ranging from 600 to 1500 mg/day and 1 study with pregabalin. There was no significant difference between gabapentin and placebo in treatment dropouts (RR 0.62; 95% CI 0.33 to 1.16) based on 4 studies or continuous abstinence (RR 1.12; 95% CI 0.30 to 4.24) based on 2 studies. There was a decrease in alcohol use (MD -2.14; 95% CI -4.21 to -0.06) that was not significant when the study with high risk of bias was excluded from the analysis. [57]

- One systematic review was identified that evaluated gabapentinoids and their effects on abstinence rates in alcohol use disorder (AUD).[58] The Cochrane risk of bias tool was used to evaluate quality of each study independently by three investigators. The primary outcome was effect on achieving abstinence or reducing alcohol consumption. A Hedge's g was used to measure the effect size between treatment and control for dichotomous outcomes (abstinence rates). A Hedge's g is interpreted as small (0.2), medium (0.5) and large (0.8). A total of 16 studies were included in the quantitative synthesis, including only two studies of pregabalin. For the primary outcome of reducing alcohol consumption, based on 8 studies (n=413), there was no significant effect on abstinence with gabapentin compared to placebo or treatment as usual (effect estimate 0.0725; 95% CI -0.2655 to 0.4105; p=0.6743) with high heterogeneity (I^2 = 64.9%).[58] There was a significant effect on percentage of heavy drinking days (effect estimate 0.55; 95% CI 0.0145 to 1.08; p=0.0441) and withdrawal symptoms (effect size 0.2885; 95% CI 0.03 to 0.55; p=003) and no effect on craving, symptoms of sleep disturbance, or depression.[58] When adding the two studies using pregabalin, similar results were produced. There was no difference in the incidence of side effects between gabapentinoids and placebo (odds ratio [OR] 1.07; 95% CI 0.91 to 1.25; p=0.4). The authors concluded that gabapentin may decrease alcohol consumption and acute alcohol withdrawal symptoms but not effect abstinence and the small number of studies and heterogeneity limit the quality of the results.

- Another systematic review included placebo controlled RCTs of gabapentin for alcohol use disorder in reducing drinking or sustaining abstinence. Studies focused on withdrawal symptoms or with active comparators were excluded. A total of 7 studies were included and they were all assessed for risk of bias using the Cochrane risk of bias tool. Studies included maximum gabapentin doses ranging from 300-3600 mg/day and trial duration was from 3-26 weeks. Like other studies, the percentage of participants completing the trial varied and was often low (33-80%). Risk of bias in most studies was low, with one study largely with unclear risk of bias due to missing information. This meta-analysis showed no significant effect on abstinence (RR 1.33; 95% CI 0.84-2.10; p=0.23) or relapse to heavy drinking (RR 0.80; 95% CI 0.57-1.13; p=0.21). There were no serious adverse effects but more total adverse effects with gabapentin compared to placebo.

- A systematic review and meta-analysis identified placebo controlled RCTs of gabapentin monotherapy in alcohol use disorder, excluding studies focusing on withdrawal symptoms and insomnia and when used in combination with other medications.[59] The Cochrane risk of bias tool was used to assess the quality of included studies. A total of seven RCTs with 32 different effect measures were included. Gabapentin doses varied from 300-3600 mg/day and trial duration was between 3 and 26 weeks. Trial completion was overall low and varied from 33-80% among the studies. Most studies were good quality, with too much missing data to assess in one study. The authors concluded there was no evidence that gabapentin significantly improved abstinence compared to placebo (RR 1.33; 95% CI 0.84-2.10; p=0.23) with no significant heterogeneity and no effect on relapse to heavy drinking with gabapentin compared to placebo (RR. 0.80; 95% CI 0.57-1.13; p=0.21).[59] The only significant positive finding for gabapentin was in reducing the percent of heavy drinking days, with an effect size (Hedges g) of -0.64; 95% CI -0.64 to -0.06; p=0.03), demonstrating a moderate effect (hedges g = 0.5). There was not a significant increase in serious adverse events and a 10% greater frequency of overall adverse events with gabapentin compared to placebo.

Clinical Guidelines

Guidelines updated in 2021 from the United States Department Veterans Affairs recommend naltrexone and topiramate and suggest acamprosate and disulfiram for AUD.[60] Gabapentin is considered a second line option for AUD based on a weak recommendation when first line treatments were ineffective or are contraindicated. Gabapentin is also given a weak recommendation as an option for alcohol withdrawal in patients for whom risks of benzodiazepines outweigh benefits. The guidelines note there are few studies with substantial limitations that suggest gabapentin is at least moderately effective and it remains unknown if it is equivalent to benzodiazepines for preventing withdrawal delirium or withdrawal seizures. For AUD, the weak recommendation for gabapentin is based on small single-site studies with high dropout rates and overall low-quality evidence. They concluded the benefits of reduced alcohol consumption slightly outweighed the potential harms, mainly potential for misuse and CNS depressant effects.

Randomized Controlled Trials:

Five RCTs were excluded due to poor quality (single center, dose ranging[61], open label design[62], high risk of bias[63,64]) and for use of a non-clinical outcome[65]. The remaining trials are summarized in Table 3.

Table 3. Randomized Controlled Trial Evidence Table.

Study	Drug Regimens/ Duration	Patient Population	Primary Outcome	Results	Limitations
Anton, et al.[66] DB, PC, RCT	Gabapentin 300 mg/day on day 1, 600 mg/day on day 2, 300 mg TID on day 3, then 1200 mg daily on days 5-112 vs. placebo 16 weeks	Medically stable adults with AUD and withdrawal symptoms, abstinent ≥ 3 days without psychiatric conditions and not on psychotropic medications (n=96)	Percentage with no heavy drinking days (≥ 5 drinks/day for men and ≥ 4 drinks/day for women)	% no heavy drinking: Gabapentin 27% Placebo: 13% 14.2% difference; 95% CI -2.1 to 30.6, p=0.09* Abstinence Gabapentin 21% Placebo 4% 16.1% difference, 95% CI 2.8-9.4, p=0.02; NNT 6.2	• 94% of participants were White • High attrition rates (30% in gabapentin group vs. 39% in placebo group). • Patients taking psychotropic medications or with psychiatric conditions and with other substance use disorders excluded • More mild to moderate dizziness with gabapentin vs. placebo

				*Results were statistically significant when verbal response was confirmed by %dCDT (NNT 5.4)	
Myrick et al.[67] DB, RCT	Gabapentin 900 mg daily vs. 1200 mg daily tapered down at day 4 vs. lorazepam 2 mg TID	Adults with alcohol dependence and withdrawal, CIWA-Ar ≥ 10, stable for treatment in the outpatient setting (n=84)	CIWA at follow up (after day 4)	<u>Mean CIWA</u> Gabapentin 900: 1.79 (0.32) Gabapentin 1200: 1.03 (0.31) Lorazepam: 2.53 (0.31) High dose gabapentin vs. lorazepam: p=0.009 Low dose gabapentin vs. lorazepam: p=NS	• Recruited treatment-seeking patients through newspaper ads may limit generalizability • Included only those with mild to moderate alcohol withdrawal stable for outpatient treatment • Not placebo-controlled • Single site • Other substance use disorders excluded
Abbreviations: AUD = alcohol use disorder; DB: double-blinded; CI = Confidence Interval; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol–Revised;; PC: placebo controlled; RCT: randomized controlled trial; TID = three times daily; %dCDT: Disialo carbohydrate-deficient transferrin (blood test for alcohol use)					

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Appendix 1: Medline Search Strategies

Ovid MEDLINE(R) ALL <1946 to December 20, 2023>

1 pregabalin.mp. or Pregabalin/ 4784
2 gabapentin.mp. or Gabapentin/ 8340
3 Substance Withdrawal Syndrome/ or alcohol withdrawal.mp. or Alcohol Withdrawal Delirium/ 26015
4 Alcohol Abstinence/ 907
5 1 or 2 11557
6 3 or 4 26859
7 5 and 6 200
8 limit 7 to (english language and humans and (controlled clinical trial or meta analysis or randomized controlled trial or "systematic review")) 48
9 alcohol dependence.mp. or Alcoholism/ 84488
10 3 or 4 or 9 106403
11 5 and 10 262
12 8 and 11 48
13 from 12 keep 1-3,8,10-13,19,21,28,31-33,35,38 16
14 from 13 keep 5-12,14-16 11

Ovid MEDLINE(R) ALL <1946 to December 20, 2023>

1 pregabalin.mp. or Pregabalin/ 4784
2 Anxiety Disorders/ or generalized anxiety disorder.mp. or Anxiety/ 145413
3 1 and 2 294
4 limit 3 to (english language and humans and (controlled clinical trial or meta analysis or randomized controlled trial or "systematic review")) 67
5 from 4 keep 3,9-10,16,20,33,38-39,41-42,48,55,61,63,65-67 17
6 from 5 keep 1-2,4,7-9,11,13-17 12

Ovid MEDLINE(R) ALL <1946 to December 28, 2023>

1 pregabalin.mp. or Pregabalin/ 4791
2 obsessive compulsive disorder.mp. or Obsessive-Compulsive Disorder/ 22282
3 1 and 2 18

4 limit 3 to (english language and humans and (controlled clinical trial or meta analysis or randomized controlled trial or "systematic review")) 3

Ovid MEDLINE(R) ALL <1946 to December 28, 2023>

1 pregabalin.mp. or Pregabalin/ 4791
2 uremic pruritis.mp. 9
3 ureteral stent.mp. 2631
4 2 or 3 2640
5 1 and 4 2

Ovid MEDLINE(R) ALL <1946 to February 01, 2024>

1 pregabalin.mp. and Pregabalin/ 2551
2 Pruritus/ or uremic pruritus.mp. 14397
3 gabapentin.mp. or Gabapentin/ 8476
4 1 or 3 10388
5 2 and 4 174
6 limit 5 to (english language and humans and (controlled clinical trial or meta analysis or randomized controlled trial)) 35
7 from 6 keep 2,4,6-8,11-15,19,22,26-27,35 15
8 from 7 keep 2,5-6,9-10,12-15 9

Ovid MEDLINE(R) ALL <1946 to February 02, 2024>

1 ureteral stent-related symptoms.mp. 55
2 pregabalin.mp. or Pregabalin/ 4896
3 1 and 2 2
4 from 3 keep 2 1

Ovid MEDLINE(R) ALL <1946 to March 08, 2024>

1 gabapentin.mp. or Gabapentin/ 8480
2 Menopause/ and vasomotor symptoms.mp. 1185
3 1 and 2 44
4 limit 3 to (english language and humans and (controlled clinical trial or meta analysis or randomized controlled trial)) 4

Appendix 2: Prior Authorization Criteria

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
5. Is the request for an OHP-funded diagnosis?	**Yes:** Go to #7	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP. For current age < 21 years: Go to #6

Approval Criteria		
6. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	**Yes**: Go to #7	**No:** Pass to RPh; Deny; medical necessity.
7. Is the request for an FDA-approved or evidence-supported diagnosis (see Table 1 below for examples)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the request for generalized anxiety disorder?	**Yes:** Go to #9	**No:** Go to #10
9. Has the patient tried and failed to have benefit from, or have a contraindication to, first line treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness.
10. Has the patient tried and failed, or have contraindications or intolerance to, gabapentin therapy for 90 days?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny; medical appropriateness. 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; medical appropriateness

Table 1. Pregabalin formulations for specific indications based on available evidence

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	
Generalized Anxiety Disorder	X	
Non-funded		
Fibromyalgia	X	

P&T Review: *6/24 (MH); 4/23; 10/22 (SF); 10/21 (DM); 10/20; 1/19; 7/18; 3/18; 3/17*
Implementation: *7/1/24; 10/1/18; 8/15/18; 4/1/17*