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Review of Off-Label Use of Gabapentin and Pregabalin

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Introduction

Gabapentinoids, including gabapentin and pregabalin, are approved by the Food Drug Administration (FDA) for the treatment of partial seizures, postherpetic neuralgia (PHN), and other neuropathic conditions (**Table 1**).[1,2] However, there is substantial use for off-label conditions (**Table 2).**[3,4] In a 2022 study, approximately 1 in 5 United States (U.S.) adults with chronic pain received a gabapentinoid.[4] This is likely a result of a need for alternatives to opioids. Center for Disease Control and Prevention (CDC) guidance includes gabapentinoids as an option for nonopioid therapy for subacute or chronic pain.[5] However, they are associated with small to moderate improvement in pain and have potential adverse events.[5]

Table 1: FDA Approved Indications.[1,2]

Indications	Gabapentin	Pregabalin
Diabetic peripheral neuropathy		✓
Fibromyalgia		✓
Partial-onset seizures	✓	✓
Postherpetic neuralgia	✓	✓
Spinal cord injury pain		✓

Gabapentin and pregabalin bind to the alpha2-delta subunit of voltage gated calcium channels resulting in anti-nociceptive and anticonvulsant effects.[1,2] Despite an increased bioavailability and faster onset of action with pregabalin compared to gabapentin, there is insufficient evidence that one agent is more effective than the other.[6] This newsletter will summarize the efficacy and safety of gabapentin and pregabalin for their use in select off-label conditions, including neuropathic pain and generalized anxiety disorder (GAD).

Neuropathic Pain

Gabapentin and pregabalin are commonly used for various types of neuropathic pain, despite differences in their labeled indications. The FDA denied approval of gabapentin for a broad neuropathic pain indication, and later approved it only for PHN based on two supportive studies .[6] A Cochrane systematic review concluded that there is moderate evidence that gabapentin is more effective than placebo over 4-12 weeks, as measured by a 50% or more reduction in pain associated with PHN (relative risk [RR]: 1.7, 95% confidence interval [CI]: 1.4-2.0) with a number needed-to-treat (NNT) of 7 (95% CI 5.5 to 9.4) and diabetic peripheral neuropathy (RR:1.7, CI: 1.4-2.0; NNT 6; 95% CI 5.0 to 9.7).[7] Despite different study populations and durations, this effect is comparable to the NNT seen with tricyclic antidepressants (NNT 3-4) and serotonin norepinephrine reuptake inhibitors (NNT 6).[8] However, in positive trials in diabetic peripheral neuropathy, gabapentin results in a difference of only about 1 point on a 1-to-10-point pain scale and there have been at least two negative studies of gabapentin in diabetic peripheral neuropathy.[3,9] A minimum clinically important difference (MCID) in the numerical pain scale is at least 2 points.[10] There is limited evidence for use of gabapentin in other neuropathic pain conditions, including central neuropathic pain, neuropathic back pain, HIV neuropathy, spinal cord injury, radicular leg pain, and cancer-related neuropathic pain.[7]

Table 2: Off-Label Uses of Gabapentinoids.

Gabapentin	Pregabalin
Compendia* supported off-label uses	
• Alcohol dependence • Diabetic peripheral neuropathy • Postoperative pain • Uremia pruritus • Vasomotor symptoms	• Generalized anxiety disorder • Postoperative pain • Restless leg syndrome** • Social anxiety disorder • Uremia pruritus
Off-label uses with insufficient or very low-quality evidence	
• Cancer related neuropathy • Fibromyalgia** • Generalized anxiety disorder • Neuropathic pain related to spinal cord injury • Panic disorder • Refractory cough • Social anxiety disorder • Trigeminal neuralgia	• Cancer-associated neuropathy • Familial dysautonomia • Obsessive-compulsive disorder • Panic disorder • Refractory cough • Ureteral stent symptoms • Vasomotor symptoms
Off-label uses with evidence of no benefit	
• HIV neuropathy • Back pain • Migraine prophylaxis	• HIV neuropathy • Back pain

*Compendia supported uses are supported by Micromedex with Level A or B evidence
**Unfunded Conditions on the Oregon Health Plan prioritized list of health services

A Cochrane systematic review concluded that pregabalin is more effective than placebo, as measured by a 50% or more reduction in pain, for the treatment of PHN based on moderate-quality evidence (pregabalin 300 mg daily RR: 2.5, CI: 1.9-3.4, NNT: 6; pregabalin 600 mg daily RR: 2.7, CI: 2.0-

3.5, NNT: 4) and peripheral diabetic neuropathy (pregabalin 300 mg daily RR: 1.3, CI: 1.2-1.5, NNT: 14; pregabalin 600 mg daily RR: 1.6, CI: 1.4-1.9, NNT: 7).[11] There is low-quality evidence for pregabalin 600 mg in central neuropathy (RR: 1.5, CI: 1.2-1.9, NNT: 8) and moderate-quality evidence that pregabalin is not more effective than placebo for the treatment of HIV neuropathy.[11] There is insufficient evidence for the efficacy of pregabalin in neuropathic cancer pain, painful polyneuropathy and back pain with radiculopathy.[11]

Generalized Anxiety Disorder

In February 2022, the Oregon Health Authority Mental Health Clinical Advisory Group (MHCAG) developed treatment guidance for GAD.[12] The algorithm is included in **Appendix 1** and the full guidance can be found here: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/Pages/MHCAG-Recommendations.aspx.[13] The algorithm recommends pregabalin as first-line adjunct treatment for patients with GAD in conjunction with a selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).[12]

Moderate-quality evidence shows 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), based on studies of short duration (4-8 weeks) with high risk of attrition bias.[14] HAM-A measures the severity of anxiety symptoms and consists of 14 items with a total score ranging from 0-56. No MCID has been established for the HAM-A.[14] Studies demonstrate a medium effect size for anxiety reduction that is similar to SSRIs and SNRIs. One study evaluated pregabalin as adjunctive treatment in patients who had not adequately responded to a SSRI or SNRI over 8 weeks.[15] Subjects on pregabalin had a higher responder rate on the HAM-A than those on placebo (47.5% vs. 35.2%; odds ratio [OR] 1.77; 95% CI 1.12-2.79).[15] There are limited data evaluating the efficacy or safety of pregabalin for GAD in patients with comorbid substance use or other mental health disorders. There is also insufficient evidence supporting the use of gabapentin for the use of GAD.

Non-Neuropathic Pain

A systematic review of perioperative gabapentinoid for postoperative pain found a statistically significant reduction in postoperative pain compared to placebo at all time points from 6 hours to 48 hours postoperatively.[16] However, the mean difference was not clinically meaningful. The mean difference in pain score on a 100-point scale ranged from 2 to 10 with most relief seen within 6 hours.[16] The investigators noted that a difference of at least 10 points is needed for a MCID.

Another systematic review found limited evidence of no benefit with gabapentin and pregabalin for the treatment of chronic low back pain.[17] Overall, there is limited evidence to support the use of gabapentin and pregabalin in non-neuropathic pain indications in both acute and chronic settings.

Other

Vasomotor Symptoms

There is low-quality evidence that gabapentin 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 of vasomotor symptoms.[18] Trials did not consistently meet the MCID for vasomotor symptom frequency (3.57 per day).[19] The North American Menopause Society recommends gabapentin for menopausal women who cannot tolerate hormone therapy.[20]

Alcohol Dependence

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).[21] Low-quality evidence shows that gabapentin may reduce the percentage of heavy drinking days, decrease alcohol consumption, and decrease acute alcohol withdrawal symptoms.[22,23] Patients with more mild alcohol withdrawal symptoms that are stable enough to be treated in an outpatient setting may benefit from gabapentin.

Safety and Tolerability

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. Additional adverse events can include blurred vision, negative cognitive effects, sedation, weight gain, peripheral edema and increased risks of these events when used in combination with opioids. Rates of serious adverse effects in published trials are low.

The FDA issued a warning in 2010 of increased risk of respiratory depression when gabapentinoids are used with opioids or other central nervous system (CNS) depressants.[24] 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 doses.[24] Pregabalin is a Schedule V controlled substance, defined as a drug with low potential for abuse and dependence. Although there may be low abuse potential in the general population, data suggests this risk is much higher among patients with substance use disorders, particularly opioid use disorder.[25,26]

Current Policies

In the Oregon Health Plan (OHP) fee-for-service (FFS) Medicaid program, prior authorization (PA) is required for

pregabalin. The goal of the PA is to limit use to FDA-approved and OHP-funded indications. Common conditions that are unfunded on the Health Evidence Review Commission (HERC) prioritized list include restless leg syndrome, fibromyalgia, and some polyneuropathies. Gabapentin is currently a preferred product and available without PA. In June 2024, the PA criteria was modified to allow use of pregabalin for GAD as adjunct to first-line treatment with a SSRI or SNRI, consistent with the MHCAG GAD treatment guidance.

Conclusion

Gabapentin and pregabalin are commonly used for off-label indications with limited evidence. Trials are short in duration (4-12 weeks), often have high placebo response rates, and result in modest benefit with a relatively small effect size. For the treatment of GAD, adjunctive pregabalin may be beneficial for those who cannot tolerate or have not benefit on first-line therapy alone.

Providers and patients should weigh the potential benefit of gabapentinoids with their side effects, risk of misuse and abuse in those at high risk for substance use disorder, risk for respiratory depression when used in combination with opioids, and risk of fetal harm when used in pregnancy.

When determined that it is appropriate to use a gabapentinoid off-label in clinical practice, patient education should be provided regarding limited evidence and potential adverse events. A reasonable time frame to evaluate clinical effects (6-8 weeks) of the medication should be determined, and if no clinical benefit is observed, the drug should be deprescribed.

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Appendix 1: Oregon Health Authority Mental Health Clinical Advisory Group Generalized Anxiety Disorder Treatment-Resistant Algorithm