INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Gabapentinoids***
-August 2026-

Background:
The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of gabapentinoid agents (i.e., gabapentin and pregabalin). Prior to this review, gabapentin was listed on the IHS National Core Formulary (NCF); pregabalin, extended-release gabapentin (Gralise®), and the prodrug gabapentin enacarbil (Horizant®) were not. Following clinical review and analysis, the NPTC voted to **remove gabapentin** from the NCF.

Discussion:
Gabapentinoid prescribing has expanded dramatically over the past two decades, largely driven by off-label use; population prevalence rose from 1.2% in 2002 to 4.7% in 2021, with gabapentin accounting for 83% of that growth.[1] American Indian and Alaska Native (AI/AN) patients carry the highest documented burden of chronic pain of any racial/ethnic group in the United States (approximately 4 times higher prevalence) and the highest drug overdose death rate nationally, roughly double the United States (U.S.) average, often involving concurrent fentanyl and methamphetamine.[2,3] Because AI/AN patients are more likely to be prescribed a gabapentinoid for chronic pain and are simultaneously at the highest population-level risk for polysubstance overdose, the safety margin for this drug class is disproportionately narrow in this population.

Misuse, Overdose, and Respiratory Depression: Gabapentinoid misuse occurs in approximately 1% of the general population but rises to as high as 20% among patients with opioid use disorder, typically to potentiate opioid euphoria or self-treat withdrawal.[4] A cohort study from the United Kingdom (UK) found gabapentinoid exposure was associated with substance misuse (HR=2.40; 95% CI: 2.25-2.55) and overdose (HR=2.99; 95% CI: 2.56-3.49), and concurrent opioid use amplified these[5]. Overdose was more common with pregabalin compared to gabapentin.[5] In 2019, the U.S. Food and Drug Administration strengthened the warnings and precautions for gabapentinoids after data showed markedly increased respiratory depression when gabapentinoids are combined with opioids, benzodiazepines, or other CNS depressants.[6] Perioperative use of gabapentin has also been independently associated with increased odds of postoperative respiratory depression (OR=1.47; 95% CI: 1.22-1.76; p<0.001).[6]

Lack of Efficacy for Common Off-Label Uses: Chronic low back pain, one of the most frequent off-label indications for gabapentin, is not supported by evidence.[7,8] Both systematic reviews and meta-analyses showed no effect versus placebo for chronic low back pain (MD=-0.0; 95% CI: -0.8 to 0.7) or lumbar radicular pain (MD=-0.1; 95% CI: -0.7 to 0.5), with 14 of 15 comparisons negative, while adverse effects increased significantly.[7,8] A 2020 meta-analysis of perioperative use (281 RCTs, n=24,682) found reductions in postoperative pain below the minimally important difference at every time point, no chronic pain prevention benefit, and increased dizziness/visual disturbance, which supported that routine perioperative use is not recommended.[9] The UK's National Institute for Health and Care Excellence (NICE) guidelines recommend against gabapentinoids for low back pain, citing no benefit and evidence of harm.[10]

Adverse Effects and Adherence: Dizziness (up to 40%) and somnolence (up to 25%) are common adverse effects and frequently a reason for discontinuation.[11,12] These adverse effects are dose-limiting; however, the real-world discontinuation rate reaches 85% due to side effects or lack of benefit.[11,12] Emerging data also raise concern for cardiovascular events, severe COPD exacerbation (HR=1.39; 95% CI: 1.29-1.50), and Alzheimer's disease/related dementia (OR=1.28; 95% CI: 1.10-1.50) with long-term use.[13,14]

Where Evidence Supports Use: This is not a blanket statement of inefficacy. Cochrane reviews support gabapentin and pregabalin for postherpetic neuralgia and diabetic peripheral neuropathy (NNT 7–9), and there is strong evidence for gabapentin enacarbil and pregabalin for restless leg syndrome (RLS responders 61% vs. 37%; RR=1.66).[15-17] Pregabalin outperforms gabapentin head-to-head for neuropathic pain (SMD=-0.47 pain; OR=0.50 lower opioid use) but is a federal controlled substance and had stronger overdose data compared to the non-controlled gabapentin.[18]

Gabapentin may be considered a second-line agent for management of alcohol use disorder, although addictive potential should be considered.

Alternative Agents for Neuropathic Pain: Clinicians should consider agents already on the NCF: duloxetine (first-line, American Academy of Neurology/American Diabetes Association, diabetic neuropathy), amitriptyline/nortriptyline (first-line

tricyclic antidepressant per NICE; caution in older adults/cardiac disease), venlafaxine, topical lidocaine or capsaicin (localized pain, minimal systemic risk), and topiramate (second-line, useful in comorbid migraine or alcohol use disorder).[19,20]

Non-Pharmacologic Treatment Options: Structured physical therapy, cognitive-behavioral therapy for chronic pain, sleep hygiene, glycemic control in diabetic neuropathy, and integrative pain programs carry no misuse potential and should be emphasized, particularly for chronic low back pain.[20]

Guideline Alignment: The U.S. Department of Veterans Affairs and Department of Defense remain neutral on gabapentinoids for chronic low back pain and recommend against gabapentin for episodic migraine prevention, favoring nonopioid pharmacotherapy broadly.[21] The U.S. Centers for Disease Control and Prevention similarly reserves gabapentinoids for defined neuropathic pain syndromes, not general chronic pain.[22] These more conservative positions on gabapentinoid use still allow access to alternative medications and therapies that have equal or stronger evidence to support their use.

Findings:

Removal of gabapentin from the NCF is supported by (1) the disproportionate AI/AN chronic pain and overdose burden, which narrows the safety margin for a drug class with documented misuse and CNS-depression risk; (2) lack of benefit for chronic low back pain and routine perioperative use, commonly prescribed off-label; (3) high real-world discontinuation (up to 85%); and (4) increased respiratory depression, overdose, and trauma risk when combined with opioids or benzodiazepines. For patients with an appropriate indication (e.g., postherpetic neuralgia, diabetic peripheral neuropathy, RLS), providers should consider use of alternative agents that already exist on the NCF. For patients currently on gabapentin but will stop use, the medication should be tapered over at least one week rather than stopped abruptly, to minimize the risk of withdrawal. This transition should include reassessment of pain diagnosis, screening for opioid/benzodiazepine co-prescribing, and selection of an evidence-based alternative for the indication.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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