FDA Warning of Respiratory Depression for Gabapentinoids

In 2019, the Medi-Cal Drug Utilization Review (DUR) Board reported that the use of gabapentinoids has grown dramatically over the past 15 years, with gabapentin ranking as the 10th most commonly prescribed drug in the United States in 2017.[1] In the Medi-Cal population alone, there was a 118% increase in gabapentin claims from 2009 to 2018. While gabapentin and pregabalin are often prescribed as safer alternatives or adjunctive therapy to opioids for pain management, recent studies have demonstrated an increased risk of life-threatening and fatal respiratory depression associated with their use, both alone and in combination with other central nervous system (CNS) depressants.[1,2]

A 2017 population-based case-control study identified 1,256 cases of death related to opioid use. The study showed that there was a 49% greater risk of opioid-related death in patients concomitantly using gabapentin compared to those using an opioid alone. Gabapentin doses exceeding 900 mg/day were associated with approximately a 60% increase in incidence of opioid-related deaths and hospitalizations due to altered mental status or respiratory depression.[1] A review of the FDA Adverse Event Reporting System (FAERS) database from 2012 to 2017 also revealed that all gabapentinoid cases resulting in death due to respiratory depression involved either the use of a CNS depressant or a pre-existing respiratory risk factor.[2]

The FDA now mandates prescription labels to be updated with the new warning of serious breathing difficulties that may occur in patients using gabapentinoids with certain risk factors. The risk factors include concurrent use of opioids or other CNS depressants and underlying respiratory conditions that reduce lung function (i.e. chronic obstructive pulmonary disease). Elderly patients over the age of 65 are also at high risk.[3] Additionally, the FDA provided the following recommendations to providers to ensure the safe use of gabapentinoids:[2]

- Evaluate the appropriateness of gabapentinoids (FDA-approved indications are listed in Table 1)
- Use the lowest gabapentinoid dose when co-prescribed with other CNS depressants, especially opioids
- Avoid prescribing moderate-to-high gabapentin doses (≥900 mg/day) in current opioid users
- Offer naloxone to patients and/or caregivers when co-prescribing gabapentinoids and opioids
- Adjust gabapentinoid doses in patients with renal impairment
- Closely monitor for signs and symptoms of respiratory depression and sedation
- Gradually taper gabapentinoid dose over a minimum of one week prior to discontinuation

Table 1. FDA-Approved Indications of Gabapentinoids

Drug Name	FDA-Approved Indications
gabapentin (Gralise, Neurontin, Horizant)	• Postherpetic neuralgia[4,5,6] • Seizures, focal (partial) onset, adjunct (Neurontin only)[5] • Restless legs syndrome (Horizant only)[6]
pregabalin (Lyrica, Lyrica CR)	• Postherpetic neuralgia[7,8] • Neuropathic pain associated with diabetic peripheral neuropathy[7,8] • Neuropathic pain associated with spinal cord injury (Lyrica only)[7] • Fibromyalgia (Lyrica only)[7] • Seizures, focal (partial) onset, adjunct (Lyrica only)[7]

References

1. Medi-Cal DUR. Improving the Quality of Care: Risks Associated with Use of Gabapentin. https://files.medi-cal.ca.gov/pubsdoco/dur/Articles/dured_30152.pdf. Published December 2019. Accessed April 22, 2020.
2. FDA. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin. Published December 2019. Accessed April 22, 2020.
3. The American Geriatrics Society. American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. JAGS. 2019;00:1-21.
4. Gralise (package insert). Newark, CA: Depomed, Inc. 2015.
5. Neurontin (package insert). New York, NY: Parke-Davis, Division of Pfizer, Inc; 2017.
6. Horizant (package insert). Atlanta, GA: Arbor Pharmaceuticals, LLC; 2016.
7. Lyrica (package insert). New York, NY: Parke-Davis, Division of Pfizer, Inc; 2019.
8. Lyrica CR (package insert). New York, NY: Parke-Davis, Division of Pfizer, Inc; 2019.

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