

Patient Safety Tip of the Week

September 27, 2022

More Bad News for Gabapentin

We neurologists have used gabapentin for many years as a very useful anticonvulsant. But, over the past couple decades, gabapentin and gabapentinoids have been far more often used in management of pain. At the beginning, they were used primarily for neuropathic pain. But now we see them used for almost any sort of pain.

Over the past 5 years, we’ve seen more and more examples of the downside of gabapentinoids (see our prior columns listed below). There were several reports of increased risk of respiratory depression when gabapentinoids were used in conjunction with opioids.

In our February 25, 2020 Patient Safety Tip of the Week [“More on Perioperative Gabapentinoids”](#) we described 2 studies ([Ohnuma 2019](#), [Yan 2019](#)) that showed gabapentinoids were associated with more post-operative respiratory depression and no significant reduction in opioid use. Also, a systematic review and meta-analysis on perioperative use of gabapentinoids ([Verret 2019](#)) found no clinically significant analgesic effect for the perioperative use of gabapentinoids, with low level of evidence, and an increased risk of adverse events with moderate level of evidence. The authors concluded that their results do not support the use of gabapentinoids for the management postoperative acute pain in adult patients.

Now another study has looked at perioperative gabapentin use among older patients undergoing major surgery. Park et al. ([Park 2022](#)) looked at almost 1 million patients aged 65 and older who underwent major surgery and were not on gabapentin prior to admission. The rate of perioperative gabapentin use was 12.3% in these patients. They used propensity score matching to reduce confounding when comparing events in those who received gabapentin compared to those who did not. Compared with nonusers, gabapentin users had increased risk of delirium (3.4% vs 2.6%), new antipsychotic use (0.8% vs 0.7%), and pneumonia (1.3% vs 1.2%). There was no significant difference in in-hospital death (0.3% vs 0.2%) between the groups. Risk of delirium among gabapentin users was greater in subgroups with high comorbidity burden than in those with low comorbidity burden.

The Park study and the two studies mentioned above were not randomized, controlled trials. Nevertheless, the evidence is growing that patients receiving perioperative gabapentinoids have an increased risk of complications, particularly postoperative opioid-related respiratory depression and delirium.

In the editorial accompanying the Park study, Bongiovanni et al. ([Bongiovanni 2022](#)) question whether the use of gabapentinoids as part of multimodal pain management is wise in older patients. They note that most studies showing a reduction in opioid use when gabapentinoids are used were done in patients of all ages. So, perhaps they are useful in younger patients undergoing surgery but should be used with caution in older patients. They also note that in the Park study 80% of gabapentin users received gabapentin on the day of surgery, suggesting that it was started prior to any patient report of pain. They suggest this might represent an opportunity to de-escalate gabapentin use for some patients.

One thing we were struck by was the low incidence of delirium in the Park study. 76.4% of the patients in that study had orthopedic surgery. Yet the incidence of delirium was only 3.4% and 2.6%, respectively, in the two groups. That incidence is far below what we'd expect in elderly patients undergoing major orthopedic surgery. The authors acknowledge that as well. They note that the claims-based algorithm used for delirium detection in this patient population had high specificity but low sensitivity. They further speculate that the delirium identification algorithm was better at identifying hyperactive delirium than hypoactive or normoactive delirium and that this might lead to their risk difference estimates even being underestimated.

Our January 2020 What's New in the Patient Safety World column "[FDA Warning on Gabapentinoids](#)" summarized some of our previous concerns about gabapentinoids and discussed a new warning on gabapentinoids from the FDA ([FDA 2019](#)). The FDA warns that "serious breathing difficulties may occur in patients using gabapentin (Neurontin, Gralise, Horizant) or pregabalin (Lyrica, Lyrica CR) who have respiratory risk factors. These include the use of opioid pain medicines and other drugs that depress the central nervous system, and conditions such as chronic obstructive pulmonary disease (COPD) that reduce lung function. The elderly are also at higher risk."

The FDA notes that gabapentinoids are often being combined with CNS depressants (including opioids, anti-anxiety medicines, antidepressants, and antihistamines), which increases the risk of respiratory depression. It acknowledges that there is less evidence supporting the risk of serious breathing difficulties in healthy individuals taking gabapentinoids alone.

Note that the [American Geriatrics Society Beers Criteria®](#) now lists gabapentin as a potentially inappropriate medication (PIM) in the elderly because of its risk of sedation and respiratory depression, especially when used in combination with opioids.

We think it is pretty unlikely that a randomized, controlled trial of gabapentin or gabapentinoids will ever be done on elderly patients undergoing major surgery. But the

evidence from the observational and cohort studies and meta-analyses certainly suggests that caution should be used in such patients, particularly when opioids are also used. We concur with Bongiovanni et al. that multimodal pain management pathways for older adults should be reconsidered, keeping in mind both pain reduction and complications.

Some of our prior columns on safety issues with gabapentinoids:

- November 2017 “[Bad Combination: Gabapentin and Opioids](#)”
- March 2019 “[Gabapentin and Pregabalin on the Radar Screen](#)”
- January 2020 “[FDA Warning on Gabapentinoids](#)”
- February 25, 2020 “[More on Perioperative Gabapentinoids](#)”
- January 2021 “[Gabapentinoids Again](#)”
- June 2022 “[Gabapentin and Overdoses](#)”

References:

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(Bongiovanni 2022)

FDA (US Food and Drug Administration). FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR) When used with CNS depressants or in patients with lung problems. FDA 2019; 12-19-2019

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