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Gabapentin and Opioids a Potentially Deadly Combination



Patients taking prescription opioids and gabapentin concomitantly have a 49% greater risk for opioid-related death than those treated with opioids only, according to a new Canadian study.

A team of researchers led by Tara Gomes, PhD, MHSc, principal investigator of the Ontario Drug Policy Research Network (ODPRN), used administrative databases to compare opioid users who died of an opioid-related cause (n=1,256) with controls (n=4,619) who were selected in a 4:1 ratio and matched on age, sex, year of index date,

history of chronic kidney disease and a disease risk index (*PLoS Med* 2017;14:e1002396). The primary exposure was concomitant gabapentin use during the 120 days preceding the index date.

Among opioid users with an opioid-related death, 12.3% (155/1,256) were prescribed gabapentin during the previous 120 days, compared with 6.8% of controls (313/4,619).

The researchers found that the combination of opioids and gabapentin was associated with a 49% increased odds of opioid-related death (odds ratio [OR], 1.99; 95% CI, 1.61-2.47; $P < 0.001$; adjusted OR [aOR], 1.49; 95% CI, 1.18-1.88; $P < 0.001$), over an opioid prescription alone. The increased risk persisted after multivariable adjustment for confounders such as opioid dose, use of other medications, number of other drugs being taken, alcohol use, and illnesses such as diabetes or chronic lung disease.

The researchers also conducted a secondary analysis that categorized gabapentin dose into low (<900 mg daily), moderate (900-1,799 mg daily) or high ($\geq 1,800$ mg daily). They found that exposure to moderate- or high-dose gabapentin was associated with a nearly 60% increased risk for opioid-related death over exposure to opioids alone (moderate doses: aOR, 1.56; 95% CI, 1.06-2.28; $P = 0.024$; high doses: aOR, 1.58; 95% CI, 1.09-2.27; $P = 0.015$). However, the association between a low gabapentin dose and an increased risk for opioid-related death was not statistically significant (aOR, 1.32; 95% CI, 0.89-1.96; $P = 0.174$).

A sensitivity analysis comparing the combination of opioids and nonsteroidal anti-inflammatory drugs with exposure to opioids alone found no significant association.

“Our finding that even moderate doses of gabapentin were associated with a 60% increased risk of opioid-related death was important, and the fact that this increases to a twofold higher risk among people getting very high doses is concerning,” Dr. Gomes said.

Although the mechanism for the increased risk for death in patients taking a combination of opioids and gabapentin is unclear, “it seems likely that both pharmacodynamic and pharmacokinetic interactions between these drugs are responsible,” she explained. “Some studies have suggested that use of an opioid with

gabapentin can slow the transit of gabapentin through the gut, leading to increased absorption and thus increased sedation and respiratory depression, leading to risks of fatal overdoses.”

Commenting on the study, Alyssa Peckham, PharmD, assistant professor of pharmacy practice at Midwestern University, in Glendale, Ariz., said it “echo[es] the alarming findings” her team found of “the increased risk of respiratory depression when gabapentin is overused, specifically in concert with opioid overuse” (*Drug Saf* 2017 Sep 27. [Epub ahead of print]).

The study “provides an additional important contribution: Because these investigators could measure mortality, they have provided a direct link between gabapentin/opioid misuse and risk of death,” Dr. Peckham said. The findings “call for reevaluation of the non-scheduled status of gabapentin at the federal and international level.”

Dr. Gomes agreed and added, “My hope is that physicians become aware of the potential risks of prescribing opioids and gabapentin together, and take this into consideration when treating patients with these products.” If the coprescription is clinically necessary, doses should be “adjusted accordingly” and physicians should “carefully monitor their patients to ensure they aren’t at risk of serious side effects from using this combination of drugs.”

—Batya Swift Yasgur, MA, LSW