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Running Out of Breath: The Diminishing Role of Gabapentinoids in Epilepsy

Gabapentinoids and Risk for Severe Exacerbation in Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study

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Background: North American and European health agencies recently warned of severe breathing problems associated with gabapentinoids, including in patients with chronic obstructive pulmonary disease (COPD), although supporting evidence is limited. Objective: To assess whether gabapentinoid use is associated with severe exacerbation in patients with COPD. Design: Time-conditional propensity score-matched, new-user cohort study. Setting: Health insurance databases from the Régie de l'assurance maladie du Québec in Canada. Patients: Within a base cohort of patients with COPD between 1994 and 2015, patients initiating gabapentinoid therapy with an indication (epilepsy, neuropathic pain, or other chronic pain) were matched 1:1 with nonusers on COPD duration, indication for gabapentinoids, age, sex, calendar year, and time-conditional propensity score. Measurements: The primary outcome was severe COPD exacerbation requiring hospitalization. Hazard ratios (HRs) associated with gabapentinoid use were estimated in subcohorts according to gabapentinoid indication and in the overall cohort. Results: The cohort included 356 gabapentinoid users with epilepsy, 9411 with neuropathic pain, and 3737 with other chronic pain, matched 1:1 to nonusers. Compared with nonuse, gabapentinoid use was associated with increased risk for severe COPD exacerbation across the indications of epilepsy (HR, 1.58 [95% CI, 1.08 to 2.30]), neuropathic pain (HR, 1.35 [CI, 1.24 to 1.48]), and other chronic pain (HR, 1.49 [CI, 1.27 to 1.73]) and overall (HR, 1.39 [CI, 1.29 to 1.50]). Limitation: Residual confounding, including from lack of smoking information. Conclusion: In patients with COPD, gabapentinoid use was associated with increased risk for severe exacerbation. This study supports the warnings from regulatory agencies and highlights the importance of considering this potential risk when prescribing gabapentin and pregabalin to patients with COPD.

Commentary

As one of the first so-called "second generation" of antiseizure medications (ASM), gabapentin appeared with promise on the not-yet-crowded field of epilepsy drugs when it was approved for use in the United States in 1994, based primarily on randomized control studies in which it was compared to placebo as an add-on therapy in pharmacoresistant focal epilepsy.[1] Its established competitors were long in the tooth, and all had complex pharmacokinetics and interactions that complicated their use. There were a few other new arrivals such as lamotrigine, but none had quite the straightforward profile of gabapentin; a 1994 review noted that the "potential advantages of gabapentin are its pharmacokinetic and toxicity profiles."[1] Doctors like drugs that are safe and simple to prescribe, as shown by the subsequent success of levetiracetam despite its psychiatric side effects. Just as levetiracetam later did, gabapentin might have been expected to eventually emerge from its position as a promising add-on to become a dominant first-line seizure therapy.

In epilepsy, gabapentin never fulfilled its promise. Over time, studies and clinical experience found it to be less efficacious for seizure control than older and newer competitors. This was emphatically demonstrated in the Standard and New Antiepileptic Drugs (SANAD) study of newly diagnosed focal epilepsy.[2] Patients were randomized to one of 5 ASMs; gabapentin performed the worst, primarily because of poor efficacy. The authors concluded that "We see no reasons to prefer gabapentin [. . .] to the standard drug carbamazepine, except where there might be individual mitigating factors."

With its dreams of dominance lost, gabapentin found a smaller role as a utility player, with its pharmacokinetic and safety profile allowing it to carve out a few niches in epilepsy. Most prominently, it was considered as an alternative for geriatric patients, who have a higher burden of comorbidities and medication interactions. An RCT comparing gabapentin,

lamotrigine, and carbamazepine in new-onset epilepsy patients 65 years and older found it to be about as efficacious as lamotrigine in preventing seizures, and less frequently stopped than carbamazepine.[3] This established gabapentin for a time as at least a reasonable alternative to lamotrigine in elderly patients, although clinical experience suggested that its side effect profile was less favorable. It has also maintained use as a (usually distant) alternative adjunctive therapy in pharmacoresistant therapy and as a choice for patients with epilepsy (or possible epilepsy) who also suffer from conditions such as tremor or neuropathic pain that might also respond to gabapentin.

Pregabalin, the other gabapentinoid which shares structural, mechanistic, and clinical characteristics with gapapentin, was approved by the FDA in 2005 and has carved out a similar profile as an ASM with some efficacity against focal seizures, usually as an adjunctive therapy in specific circumstances.[4]

But if gabapentinoids were a disappointment in the ASM field, they have become a booming success in the treatment of many other conditions, some with more evidence than others. American Academy of Neurology (AAN) guidelines cite gabapentin as having Level B evidence in support for the treatment of essential tremor[5] and insufficient evidence to recommend for migraine prevention,[6] and the gabapentinoid class as probably more likely than placebo to improve pain from diabetic polyneuropathy.[7]

With sometimes limited evidence, physicians seized on the apparent versatility of gabapentinoids to extend their use to many other conditions such as chronic pain, leading to a dramatic increase in off-label prescriptions. One suspects that its apparently simple pharmacokinetic profile and the perception that it can cause no dangerous adverse effects, the qualities that initially brought gabapentin to the ASM market with such hope, have played a crucial role in its expansion. I recall that when I attended my first AAN meeting as a medical student in 2008, one speaker jokingly described gabapentin as so safe it could be put in drinking water.

The present study by Rahman et al challenges this rationale for gabapentinoid use.[8] Inspired by reports that gabapentinoids can be responsible for severe adverse events including respiratory distress leading to multiple warnings by regulatory agencies, the authors investigated the risk of exacerbation of chronic obstructive pulmonary disease (COPD) associated with gabapentinoid prescription.

Making use of several large health databases in Québec, Canada, including hospitalization data and prescription records from its public prescription drug insurance plan, the authors created a cohort of patients 55 years and over suffering from COPD, identified primarily based on prescriptions of respiratory drugs. Of these, patients who were prescribed gabapentinoids for epilepsy, neuropathic pain, or other chronic pain were identified and matched 1:1 across multiple demographic and health variables to other individuals from the cohort. Looking primarily at the outcome of hospitalization or death due to COPD exacerbation, they compared patients prescribed gabapentinoids to those without, using a time-conditional propensity score matched design.

The database identified 13 504 COPD patients prescribed gabapentinoids. Interestingly, less than 3% of these were for the indication of epilepsy, reflecting their limited role in epilepsy care. Across all indications, gabapentinoid prescription was associated with higher risk of severe COPD exacerbation, with a hazard ratio (HR) of 1.39. Within the small subset of epilepsy patients, the HR was highest, at 1.58. The authors conclude that, taken together with other forms of accumulating evidence on this topic, their study supports the notion that the risk of COPD exacerbation should be carefully considered when prescribing gabapentinoids.

As with all large database studies, the results should be interpreted with care. Many clinical variables including COPD were identified using definitions that, although often validated by other studies, remain surrogates for their gold standards. Inevitably, some patients will be mislabeled, although hopefully not enough to significantly affect the bottom line. Furthermore, it is possible that unmeasured but relevant factors could have made the compared groups systematically different, thus introducing bias in the results. In this vein, the authors cite the inability to determine whether patients were smokers as a potential limitation.

Nevertheless, the signal identified in the study is strong, and we cannot expect an RCT to help us resolve this question. These are the best data that we have on this question. At minimum, it is incumbent upon neurologists to seriously consider the risk of COPD exacerbation prior to gabapentinoid prescription. Even further, this study reminds us that perceived safety or ease of prescription is hardly justification for the selection of a medication. As use of a medication expands, unsuspected dangers may emerge that are not justified by the risk-reward ratio, especially in the absence of proven benefit.

In epilepsy, gabapentinoids have failed to gain a large foothold mostly due to their relative lack of efficacy. Now, with increasing understanding of their risks, even their niche as a simple and "safe" treatment of elderly patients or patients with polypharmacy will need to be reconsidered.

Samuel Lapalme-Remis, MDCM
Centre hospitalier de l'Université de Montréal (CHUM)

ORCID iD

Samuel Lapalme-Remis https://orcid.org/0000-0003-0909-9513

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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