UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

# THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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## TODAY'S TOPIC:

### Gabapentin: Updated Safety Concerns

#### Background:

Gabapentinoids, e.g., gabapentin (Gralise, Neurontin) and pregabalin (Lyrica)), are commonly used for numerous indications in clinical practice, including neuropathic pain, as well as other less common indications like for seizures. In 2019, the FDA issued a warning about the risk of gabapentinoinds causing serious, life threatening, and fatal respiratory depression, and the literature was assessed in Vol. 1, issue 11 of the tablet. That article largely emphasized the risk of respiratory depression when used concomitantly with opioids. Gabapentin is increasingly associated with safety risks like poor respiratory outcomes, neurocognitive changes in older adults, and increasing fall risk. Unfortunately, there are few medications that can be used for neuropathic pain, and gabapentinoids are one of the more effective treatments, especially for post-herpetic neuralgia and diabetic neuropathy. As new literature emerges regarding gabapentinoid safety, this information can better inform the risks and benefits for individual patients.

#### Importance:

Despite increasing safety concerns, gabapentinoid use is prevalent, in part due to lack of efficacious alternatives. Despite limited efficacy, the emergence of new safety data for gabapentinoids may lead to a re-evaluation of risks and benefits of gabapentin for some patients.

#### The Literature:

Ann Intern Med. 2024 Feb;177(2):144-154.

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

Objectives:

- Assess if gabapentinoid (pregabalin or gabapentin) use was associated with an increased risk of COPD exacerbation

Methods:

- Researchers used a matched cohort of time-conditional propensity scores of 3 Quebecer databases from 1994-2015. Patients were followed until they had a severe COPD exacerbation resulting in hospitalization, death, end of prescription coverage, or the end of the trial period.
- Patients had to be ≥55 years old, taking select COPD medications without diagnosed asthma.
- Patients were matched based on indication for gabapentinoids (epilepsy, neuropathic pain, other chronic pain), age, sex, calendar year, and time since start of COPD.

Outcomes:

- Primary: Severe COPD exacerbation requiring hospitalizations
- Secondary: Hazard ratios by indication for gabapentinoid use

Results:

- Of the 7117,014 patients (n=13,504 in the gabapentinoid user group and n=13,504 in the gabapentinoid nonuser group), overall patients experienced more severe COPD exacerbations.

| Exposure | Patient (n) | Events (n) | Person Years (n) | Incidence (95% CI) | Adjusted HR (95% CI) |
|---|---|---|---|---|---|
| Epilepsy | | | | | |
| Nonuse | 356 | 90 | 838 | 10.7 (8.7-13.2) | 1.00 |
| Gabapentinoid Use | 356 | 46 | 205 | 22.4 (16.8-29.9) | 1.58 (1.08-2.30) |
| Neuropathic Pain | | | | | |
| Nonuse | 9411 | 2142 | 24645 | 8.7 (8.3-9.1) | 1.00 |
| Gabapentinoid Use | 9411 | 712 | 4646 | 15.3 (14.2-14.6) | 1.35 (1.24-1.48) |
| Other Chronic Pain | | | | | |
| Nonuse | 3737 | 756 | 10298 | 7.3 (6.8-7.9) | 1.00 |
| Gabapentinoid Use | 3737 | 258 | 1842 | 14.0 (12.4-15.8) | 1.49 (1.27-1.73) |
| Overall Cohort | | | | | |
| Nonuse | 13504 | 2988 | 35780 | 8.3 (8.0-8.6) | 1.00 |
| Gabapentinoid Use | 13504 | 1016 | 6693 | 15.1 (14.2-16.1) | 1.39 (1.29-1.50) |

- Across all indications for gabapentinoid use, (age, sex, prior COPD exacerbation, and use of benzodiazepines) researchers consistently found significantly higher hazard ratios.

Conclusion:

- Results from this population-based cohort trial support existing literature and affirm the additional safety risks of gabapentinoid use in patients with existing respiratory comorbidities.
- While researchers acknowledged that other trials have found gabapentinoid adverse effects to be dose-dependent, ***dosages of all medications were not assessed in this trial.***

Front Pharmacol. 2022 Nov 25;13:910719.

**The association of gabapentin initiation and neurocognitive changes in older adults with normal cognition**

Objectives:

- Assess changes in cognition, motor decline, and functional status in older adults taking gabapentin

Methods:

- Using a matched cohort study from the the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS) from 2005-2021, researchers completed a retrospective analysis.
- Gabapentin use was determined via patient disclosure in the interview in data set.
- For patients ≥65 years old with normal cognitive function, new gabapentin users were matched with non-users, and results were compared at annual visits for the next two years.
- For the data set looking at motor changes, researchers also excluded those with gait/movement disorders at baseline.
- Researchers used stabilized inverse probability of treatment weights and stabilized inverse probability of censoring weights to adjust for confounding variables.
    - Covariate assessment was very thorough, including age, sex, education, race, body mass index, smoking history, comorbidities, medications, and APOEe4 allele status.

**CLINICAL PEARL: While gabapentinoids are a mainstay of therapy for neuropathic pain, new literature may change the risk/benefit balance in specific patient populations.**

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Outcomes:
- Cognitive Decline: Clinical Dementia Rating Global Score (CDRGLOB) and sum of boxes (CDR-SB) – measured using higher CDRGLOB score and 1-point increase in CDR-SB score
- Functional Status: Functional Activities Questionnaire – measured using ≥3 point increase in sum or ≥0.3 point increase in mean, indicating increased impairment
- Motor Function: measured using clinician ratings of gait disorders, falls, and slowness

Results:
- The final populations for the cognitive impairment and functional status groups included 4,800 patients (n=480 gabapentin new users with normal cognition, and n=4,320 non-users), and the motor function group included 4,590 patients (n=459 gabapentin new users with normal cognition, and n=4,131 non-users). Access to the data set itself is limited.

| Outcome | OR (95% CI) +1 year | OR (95% CI) +2 years |
|---|---|---|
| Clinical Dementia Rating – Global (CDRGLOB) | 1.55 (1.07-2.25) | 1.26 (0.84-1.89) |
| Clinical Dementia Rating – Sum of Boxes (CDR-SB) | 1.94 (1.22-3.09) | 1.57 (0.99-2.47) |
| Sum of Functional Assessment Questionnaire (FAQ) | 1.50 (0.76-2.96) | 1.55 (0.86-2.97) |
| Mean FAQ | 1.56 (0.93-2.63) | 1.78 (1.12-2.83) |
| Gait Disorder | 0.97 (0.44-2.15) | 1.10 (0.54-2.24) |
| Falls | 1.42 (0.61-3.31) | 2.51 (1.19-5.31) |
| Slowness | 1.44 (0.70-2.97) | 1.39 (0.66-2.92) |

- Based on these results, there was a significant decrease in cognitive decline in the first year, with no significant differences in other variables.
- By the second year, changes in cognition were no longer statistically significant, though there were significant changes in the average quality of life scale and fall risk.

Conclusion:
- There is some evidence to suggest that gabapentin can decrease cognitive function, at least within the first year of therapy. Also, after a couple of years of therapy, patients may have reduced quality of life and increased fall risk compared to those who do not use gabapentin.

Am Surg. 2023 Jan;89(1):61-68. doi: 10.1177/00031348211011114.

**A Case-Control Study of Accidental Falls During Surgical Hospitalization**

Objectives:
- Determine incidence/specifications of in-hospital falls within 3 days of operation and assess risk factors (e.g., perioperative hypnotics, benzodiazepines, opioids, and gabapentinoids-pregabalin or gabapentin)

Methods:
- Researchers collected retrospective chart review data on those who had been issued sedative perioperative prescriptions (home medications, procedural medications, and if they were taking select medications prior to falling), and matched patient cases with controls based on age, sex, and procedure type.
- Data came from a major academic medical center looking at postoperative falls (suddenly descending from standing/sitting/supine position within the first 72 hours of surgery) in adult patients from January 1, 2010 to April 30, 2018.
- Researchers presented a median for continuous variables, and percentage for nominal variables, and results are presented in odds ratios.

Outcomes:
- Injury from falls, assessing preoperative and perioperative medication use

Results:
- During this observation period, there were 17.1 falls for every 10,000 patients.
- No procedural midazolam, opioids, gabapentin, or ketamine was associated with fall risk.
- Patients using gabapentinoids at home made up 16.0% of the proportion of patients who fell, and 11% of the proportion of controls. In patients who had a post operative fall, 18.1% received gabapentinoids, while only 9.9% of controls did, which was significant ($p<0.001$).
- Notably, non-benzodiazepine hypnotics/z-drug use at home/receiving them in the post-surgical period was associated with a significantly higher risk of falling.

| Characteristic | Cases (n=343) | Controls (n=686) | OR (95% CI) | P val |
|---|---|---|---|---|
| Age | 67 [55, 75] | 67 [56, 75] | --- | --- |
| Home Opioids | 112 (32.7) | 205 (29.9) | 1.07 (0.79-1.44) | .678 |
| Home Benzodiazepines | 48 (14.0) | 93 (13.6) | 0.92 (0.61, 1.37) | .677 |
| Home Gabapentinoids | 55 (16.0) | 77 (11.2) | 1.20 (0.77, 1.05) | .138 |
| Home Z-hypnotics | 31 (9.0) | 27 (3.9) | 2.68 (1.47, 4.88) | .001 |
| Prior to fall Non-benzodiazepine hypnotics | 22 (6.4) | 11 (1.6) | --- | <0.001 |
| Prior to fall Gabapentinoids | 62 (18.1) | 68 (9.9) | --- | <0.001 |
| Prior to fall Opioids | 93 (27.1) | 148 (21.6) | --- | 0.051 |
| Prior to Fall benzodiazepines | 56 (16.3) | 109 (15.9) | --- | 0.857 |

Conclusion:
- The conclusions of this trial support existing literature suggesting that gabapentinoid use is associated with increased fall risk.

## Sydney's thoughts:

- There are very few medications available to treat neuropathic pain, and gabapentinoids are a mainstay of therapy.
- Gabapentinoids are associated with an increased risk of respiratory adverse effects in patients with existing COPD, even independent of concomitant opioid use.
- There is increasing evidence to suggest that gabapentin may lead to worsening cognition in older adults, increase fall risk for patients receiving gabapentin after surgery.

## Bottom Line:

- Gabapentinoids should be used cautiously in patients with pre-existing COPD, in older adults at risk for cognitive impairment, and in those at higher risk for falls – as more literature emerges, the risk-benefit balance may be less favorable than originally thought.
- If patient has had adequate trial of gabapentinoid (~1 month) with appropriate titrations to reach target dose of 1800mg/day of gabapentin equivalent (or maximum tolerated dose) for neuropathic pain, without improvement in pain outcomes, would have a low threshold to discontinue to avoid ongoing risks of gabapentinoid therapy.

**CLINICAL PEARL: While gabapentinoids are a mainstay of therapy for neuropathic pain, new literature may change the risk/benefit balance in specific patient populations.**