

# THE TABLET: PALLIATIVE CARE PHARMACY TIPS

June 4, 2021

Vol. 1, No. 11



## Palliative Care Pharmacy Team:

### Clinical Pharmacy Specialist:

**Maria Felton Lowry,  
PharmD, BCPS, BCGP**  
Assistant Professor  
University of Pittsburgh  
School of Pharmacy,  
Department of Pharmacy  
and Therapeutics  
Palliative  
Care Clinical Pharmacy  
Specialist  
UPMC Palliative and  
Supportive Institute

Cell: 412-627-8473  
Office: 412-864-2899  
Email: lowrymf@upmc.edu

If you have a topic you  
would like the pharmacy  
team to answer, please  
send your suggestions to:  
lowrymf@upmc.edu

## TODAY'S TOPIC: Gabapentinoids and Respiratory Depression

### Background:

Gabapentinoids, such as pregabalin (Lyrica®) and gabapentin (Neurontin®), are widely used for a variety of neuropathic pain syndromes. We learned that their evidence is strongest for neuropathy related to diabetes and postherpetic neuralgia, however they remain in our toolbox for treating other neuropathic syndromes seen commonly in palliative care. Literature regarding the peri-operative use of gabapentin for opioid-sparing effects first described respiratory depression associated with the combination of gabapentinoids and opioids. This interaction is thought to be a result of both pharmacodynamic and pharmacokinetic reactions; it likely reflects additive respiratory depression when using both opioids and gabapentinoids concomitantly. Additionally, for gabapentin: absorption occurs in the upper small intestine, and slowing of GI transit by opioids could prolong gabapentin's bioavailability. Pregabalin is also absorbed in the proximal colon so the latter interaction may be less relevant for pregabalin.

### Importance:

Gabapentinoids are used commonly in our seriously ill population, many of which have underlying respiratory conditions or take concomitant opioids or other CNS depressants. In December 2019, the FDA added a warning to gabapentinoids' drug labeling highlighting the risk of respiratory depression for those with underlying respiratory risk factors citing mostly peri-operative cases of respiratory depression. Palliative care clinicians should be aware of this warning, other data behind this warning, and its implications for clinical practice.

### Known Respiratory Risk Factors:

- Underlying lung disease (COPD, asthma, OSA)
- Older adults  $\geq$  65 years
- Co-administration of medications that also suppress CNS
  - Opioids, benzodiazepines, sedative hypnotics ("Z drugs"), antihistamines, sedating antidepressants/antipsychotics

### FDA Adverse Event Reporting System (FAERS) Search:

- January 1, 2012, to October 26, 2017
  - Identified 49 cases of respiratory depression with gabapentinoids (n=15 gabapentin, n=34 pregabalin)
    - 92% of cases reported had at least one respiratory risk factors listed above
  - 24% of cases resulted in death, all of which reported at least one known respiratory risk factor listed above

### The Literature:

[PLoS Med. 2017 Oct 3;14\(10\):e1002396.](#)

#### Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case control study

Methods: population-based nested case-control study (n=1256 cases, n=4619 controls)

- Patients using opioids who died of an opioid-related cause (excluding suicides/homicides) matched with 4 controls who also used opioids, primary exposure being gabapentin use within 120 days preceding "index" date (ie. death)
  - *Exclusion: prior diagnosis of cancer, or patients receiving palliative care services in the 6 month prior to index date*
- Gabapentin exposure defined as 1 Rx in the 120 days preceding index date

Objective:

- To investigate whether co-Rx of opioids + gabapentin is associated with increased risk of accidental opioid-related mortality
- Secondary dose-response analysis (low:<900mg, moderate:900-1799mg, high: $\geq$ 1800mg)

Results:

- Odds of an opioid-related death was 49% higher among individuals recently exposed to gabapentin and opioids concomitantly compared to those exposed to opioids (adjusted for potential confounders, including opioids dose)
- Moderate (900-1799mg) or High ( $\geq$ 1800mg) gabapentin dose was associated with almost 60% increased odds of opioid-related death compared to exposure to opioids alone

Conclusion:

- Co-prescription of gabapentin and opioids was associated with 50% increase in risk of dying of opioid-related causes, and this increase in risk is likely dose-dependent.

[J Pain Res. 2017 Nov 10;10:2635-2641.](#)

#### Risk of respiratory depression with opioids and concomitant gabapentinoids

Methods: Retrospective cohort study of two groups who received naloxone therapy: Opioids versus Opioids + Gabapentinoids (n=125; n=36 gabapentinoid group)

- Total of 153 episodes of naloxone administration occurred during study period

Outcomes: Respiratory depression (defined as RR <8 BPM, and oxygen saturation either below 92% or a decrease of more than 5% from baseline), association of oversedation and risk factors

Results:

- No significant difference in incidence of respiratory depression between groups
- Average opioid requirements in gabapentinoid group were slightly higher than non-gabapentinoid group (~25mg OME/day)
- Of note, majority of patients in gabapentinoid group received low dose (<1800mg gabapentin or <300mg pregabalin)

Conclusion:

- No significant association of respiratory depression with gabapentinoid group versus non-gabapentinoid group
- Still possible that dose-dependent effect on respiratory depression exists, given that most patients in gabapentinoid group were receiving low doses

### Bottom Line:

- Clinicians should consider carefully whether to co-prescribe opioids and gabapentinoids especially in those with other underlying respiratory risk factors.
- Gabapentinoids might have dose-related effect on respiratory depression (and remember... our target dose for pain mgmt. is ~1800mg/day, considered "high dose")
- Because of this, would have a very low threshold to discontinue gabapentin if not receiving meaningful benefit as risk may outweigh benefit at that point
- These results might be falsely low for our seriously ill patient population

**CLINICAL PEARL:** Gabapentinoids prescribed (especially at high doses) with opioids may increase risk for respiratory depression. If patient does not perceive gabapentinoid as beneficial, would have a low threshold for discontinuation as risk may outweigh benefit.