UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

May 28, 2021 Vol. 1, No. 10

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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 for Cancer-Related Neuropathy

Background:

Gabapentinoids, anticonvulsants such as pregabalin (Lyrica®) and gabapentin (Neurontin®), are widely used to manage neuropathic pain. Gabapentinoids bind to voltage gated calcium channels, which decreases the release of glutamate, noradrenaline (norepinephrine), and substance P. This mechanism contributes to their anticonvulsant, analgesic, and anxiolytic actions. Pregabalin and gabapentin are used for a variety of neuropathic pain syndromes, and their evidence differs based on the individual neuropathic syndrome.

Importance:

In the last issue we discussed that the most evidence for gabapentinoid use in neuropathic pain is specific for diabetic neuropathy or post-herpetic neuralgia. Gabapentinoids are commonly used in the oncology setting for cancer-related neuropathy. Although not much data exists to include in the Cochrane reviews, palliative care clinicians should be aware of the limited evidence behind their use in this setting.

The Literature:

Am J Hosp Palliat Care. 2012 May;29(3):177-82.

A Comparative Efficacy of Amitriptyline, Gabapentin, and Pregabalin in Neuropathic Cancer Pain: A Prospective Randomized Double-Blind, Placebo-Controlled Study

Methods: placebo- controlled RCT, patients with cancer having neuropathic pain (n=120)

- Dose titrations were as follows over a 3-week period: Amitriptyline 100mg/day, gabapentin 1800mg/day, pregabalin 600mg/day
- Morphine utilized for breakthrough pain

Outcomes:

- Primary: Pain Score (VAS 0-100mm) daily
- Secondary: intensity of burning, shooting/lancinating, and dysesthesia/allodynia on numerical rating scale (0-10), ECOG, Adverse effects intensity (mild-severe), maximum tolerated dose of study drugs

Results:

- Efficacy:
  - VAS significantly less in each visit as compared to previous visits. VAS was significantly less in pregabalin group than amitriptyline group at visits 3 and 4, and significantly less than gabapentin group at visit 4.

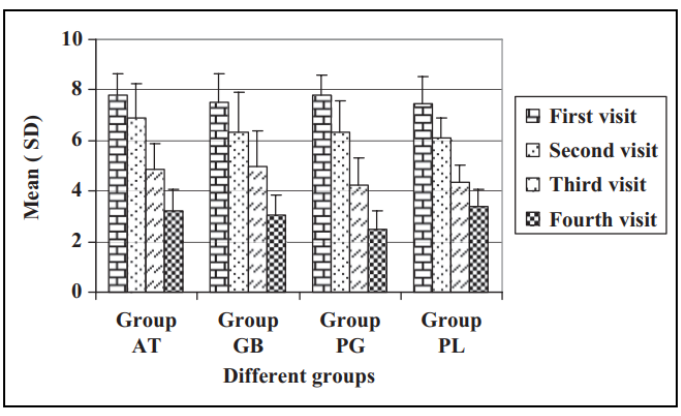

Figure 1. Comparison of pain score in different groups at different time periods

  - All arms, except for placebo, required less morphine breakthrough doses
  - Decrease in percentage of patients with allodynia was maximum in gabapentin group
  - Maximum improvement in ECOG scoring was found after 4 visits in pregabalin group
  - Most patients tolerated 600mg/day of pregabalin, tolerance of gabapentin or amitriptyline dose escalations not individually reported
- Safety:
  - Most common ADE: somnolence, dizziness, dry mouth, nausea, constipation, with less severe ratings of adverse effects in pregabalin group

Conclusion:

- Amitriptyline and gabapentinoids are effective in relieving neuropathic pain in patients with cancer, although pregabalin may reduce neuropathic pain compared to other medications

Asia Pac J Clin Oncol. 2017 Apr;13(2):e57-e64.

Efficacy and Safety of Pregabalin in Patients with Neuropathic Cancer Pain Undergoing Morphine Therapy

Methods: RCT placebo-controlled crossover, patients with cancer (n=40) experiencing cancer-related or cancer
treatment-related neuropathic pain, having been treated with morphine for over 3 months

- Randomized to receive morphine/pregabalin or morphine/placebo for 2-week period
- Pregabalin titrated from 150mg/day to 300mg/day

Outcomes:

- Primary: Decrements in morphine dose, including daily and rescue doses
- Secondary: Quantitative sleep assessment, Constipation, and other ADE

Results:

- Efficacy:
  - Mean morphine dose was significantly lower (~20% lower) in the pregabalin group than in placebo group and from baseline (prior to treatment arms)
  - Pregabalin group had significantly lower scores for sleep disturbance, sleep problems and longer hours of sleep.
- Safety
  - Most common ADE: Dry mouth, somnolence

Conclusion:

- Use of pregabalin in patients with neuropathic cancer pain either reduces the need for morphine dose escalation or allows the use of lower doses.

CLINICAL PEARL: Gabapentinoids can be trialed for cancer-related neuropathy, although data is very limited. Discontinue gabapentinoid if no relief after adequate trial (~4 weeks and targeted dose achieved).

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J Clin Oncol. 2004 Jul 15;22(14):2909-17.

Gabapentin for Neuropathic Cancer Pain: A Randomized Controlled Trial from the Gabapentin Cancer Pain Study Group

Methods: multicenter, placebo-controlled RCT, patents with neuropathic pain due to cancer, partially controlled on systemic opioids (n=121)

- Randomized to receive Placebo or Gabapentin titrated from 600mg/day to 1800mg/day

Outcomes:

- Primary: average pain score at follow up on numerical rating scale 0-10 (10 days)
- Secondary: Intensity of burning pain, shooting/lancinating pain, dysesthesias, number of daily episodes of lancinating pain, presence of allodynia, extra doses of opioid analgesics, ADEs

Results:

- Efficacy
  - Mean follow up global pain score was lower for patients taking gabapentin (4.6) than for patients receiving placebo (5.4)
  - Dysesthesias were less severe in gabapentin group (4.3 vs. 5.2), but other symptoms did not show significant differences
  - Max daily doses for gabapentin were 600mg (7.5%), 1200mg (22.7%), and 1800mg (69.6%)
- Safety
  - 4 patients had severe side effects leading to discontinuation of gabapentin
  - Most common ADE: somnolence, dizziness

Conclusion:

- Gabapentin could play a role as an adjuvant to opioids for neuropathic cancer pain

Maria's Reflections:

- Except for the last article, it is unclear if neuropathy was secondary to cancer, cancer-directed therapy, or another underlying etiology which hinders the assessment of actual utility in "cancer-related" neuropathy
- The longest study period referenced above is 4 weeks in only one of the studies… adequate trial, like mentioned last week, is at least 4 weeks on highest tolerated dose
- On the surface a reduction of pain scores seems promising, however these reductions hardly would be considered clinically significant
- Outcomes differed between these three studies, so it is difficult to combine the evidence to formulate stronger opinions about the use of gabapentinoids in cancer-related neuropathy

Bottom Line (no new revelations based on the evidence above):

- Limited evidence exists for efficacy of gabapentinoids in cancer-related neuropathy
- Adequate trial of gabapentin could be defined as: dose titration to >1800mg/day or highest tolerated dose if below 1800mg/day and continuation for at least 4 weeks after reaching max tolerated dose
- Adequate trial of pregabalin could be defined as: dose titration to ~300mg/day, or maximum tolerated dose for at least 4 weeks
- Discontinue if patients perceive little or no benefit after adequate trial
- Counsel patients on side effects of gabapentinoids such as somnolence or dizziness and beware of prescribing other sedating medications concomitantly

CLINICAL PEARL: Gabapentinoids can be trialed for cancer-related neuropathy, although data is very limited. Discontinue gabapentinoid if no relief after adequate trial (~4 weeks and targeted dose achieved).