UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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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:

Neuropathic Agents Onset of Analgesia: A Debate

Background:
Neuropathic pain is a result of direct damage to the somatosensory nervous system, causing pain described as "shooting, burning, tingling, numb." Common neuropathic pain syndromes are diabetic neuropathy (PDN), fibromyalgia, treatment-related neuropathy, and postherpetic neuralgia (PHN). We use a variety of pharmacologic agents to combat neuropathic pain such as anticonvulsants (gabapentinoids), antidepressants (SNRIs/TCAs), and topical agents. This review will focus specifically on agents we use most commonly in practice such as gabapentin, pregabalin, venlafaxine, duloxetine, and amitriptyline.

Importance:
Neuropathic pain impacts many of our patients and reduces their quality of life. Unfortunately none of the oral agents used for neuropathic pain begin working right away. It is important for palliative care clinicians to know which agents have the quickest onset of analgesia.

The Literature:
There's a lot to review here…

Gabapentin
J Clin Oncol. 2004 Jul 15;22(14):2909-17.
- Neuropathic cancer pain
- Methods: RCT, n = 121, 10-day trial duration, Gabapentin titrated from 600mg/day to 1800mg/day (in addition to stable opioid use)
- Results:
  - Mean global pain score was less for patients taking gabapentin (4.6) than patients receiving placebo (5.4) over 10-day period, more patients in gabapentin group reached 33% pain intensity difference
  - Mean time to reach maximum dose ranged from 3.3-4.5 days depending on end dose (1200mg versus 1800mg/day)
  - Somnolence was most common ADE in gabapentin group

Pregabalin
Cochrane Database Syst Rev. 2019 Jan; 2019(1): CD007076.
- Postherpetic neuralgia, diabetic neuropathy, central neuropathic pain, mixed neuropathic pain, other neuropathic conditions
- Methods: Review; Doses ranging 75-600mg/day; many study durations were 4 weeks or longer
- Results:
  - More participants receiving pregabalin had at least 30% reduction in pain compared to placebo for PHN, PDN, and mixed neuropathic pain intensity reduction
  - Around 20 to 40 days (3-6 weeks) is needed for analgesia effects to be seen, although this data was only extractable for PHN and limited given trials did not consistent report outcomes before 4 weeks

Duloxetine
Clin J Pain. 2016 Nov;32(11):1005-1010.
- PDN
- Methods: Systematic Review (n= 8 high quality studies), majority of studies included in review had trial duration of 12 weeks, doses ranged between 20-120mg/day
- Results:
  - In one RCT, duloxetine showed greater reduction in pain versus placebo at weeks 1, 2, and 4 but not at weeks 8 and 12

J Pain Symptom Manage. 2019 Oct;58(4):645-653.
- Cancer-related neuropathic pain
- Methods: multi-center, RCT, n=70, 10-day trial duration, duloxetine 20mg/day increased to 40mg/day or placebo
- Results:
  - Mean brief pain inventory on day 10 for duloxetine patients was 4.03 versus 4.88 placebo
  - ≥ 30% reduction in pain was reported by 44% of patients treated with duloxetine versus only 18.2% in placebo group
  - 32.4% vs. 3.0% of patients in groups duloxetine and placebo, respectively reported pain reduction of ≥50%

Venlafaxine
Clin Ther. 2017 Jun; 39(6):1104-1122.
- Variety of Neuropathic Pain Syndromes
- Methods: Narrative Review (n= 10 studies), Venlafaxine doses ranged from 18.75-225mg/day, study durations ranged from 2-12 weeks
- Results:
  - Difficult to compare all the studies, outcomes reported at different time periods throughout the studies
  - Endpoints before the end of the study duration not extremely clear… making it difficult to determine if analgesia effects earlier than the study periods

Pain Med. 2017 Oct 1;19(10):1999-2012.
- Variety of Neuropathic Pain Syndromes
- Methods: Systematic review (n=13 studies), Venlafaxine dose ranges included: 18.75-225mg, study durations ranged from 10 days – 12 weeks
- Results:
  - Difficult to compare all the studies, notably 3 studies with shorter durations (days 10, 14) showing improvement in neuropathic pain

CLINICAL PEARL: Oral pharmacologic agents used for neuropathic pain do not work instantaneously, and most require at least 1-2 weeks to see onset of analgesic effect

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Amitriptyline

Cochrane Database Syst Rev. 2015 Jul 6;2015(7):CD008242.

- Variety of Neuropathic Pain Syndromes
- Methods: Review, (n=17 studies), study duration at least 4 weeks; Amitriptyline dose range used: 10-150mg/day
- Results:
  - Unable to determine onset of analgesia, given study durations ≥ 4 weeks, and outcomes prior to the end of the study period were not discussed

Venlafaxine versus Gabapentin

J pain Res. 2010 Apr 1;3:33-49.0

- Polyneuropathy
- Methods: Prospective, nonrandomized cohort, n=223, after 3 and 6 months, mean dose of venlafaxine was ~220mg/day, mean dose of gabapentin was 2400mg/day
- Results:
  - VAS reported only at 0, 3, and 6-month intervals
  - Unable to determine from this which works "faster"
  - More sedation, dizziness in gabapentin group

Duloxetine versus Gabapentin

Drug Des Devel Ther. 2019 Jun 17;13:1985-1992.

- Diabetic peripheral neuropathy
- Methods: Double-blind RCT, 8-week study period, n = 104, gabapentin 300mg titrated to 900mg/day based on tolerability, duloxetine 30mg titrated to 60mg/day
- Results:
  - Gabapentin group had greater VAS reduction in 1 week versus duloxetine
  - Both groups had reduction over study period at weeks 4 and 8

Duloxetine versus pregabalin

J Pain Res. 2018 Sep 13;11:1857-1868.

- Diabetic peripheral neuropathy
- Methods: RCT, n = 303, duloxetine 40-60mg/day versus pregabalin 300-600mg/day, 12 weeks duration
- Results:
  - Both groups showed similar reduction in 24-hour pain reported via numeric rating scale across each week for the 12 weeks duration
  - No difference in analgesic onset based on these results, both showed improvement as soon as week 1

What else do we know from a pharmacologic standpoint/anecdotal evidence?? (although adequate trial data is lacking to back up these)

- TCAS: Analgesic onset can 4 to 6 weeks, including 2 weeks at the highest dosage tolerated
- Duloxetine: Analgesic onset after 1-2 weeks with maximum effect at about 4 weeks
- Venlafaxine: Analgesic onset can occur at 2 weeks at doses as low as 75mg/day, but target dose is ~150mg/day
- Gabapentin: Analgesic onset can be seen as early as 1-2 weeks of therapy when titration is rapid (which can cause more somnolence); peak effect usually occurs approximately two weeks after a target dose (~1800mg/day) is achieved
- Pregabalin: Analgesic onset may begin within 1-2 weeks, as starting dose of ~150/day has been found to be efficacious and requires less dose titration

Bottom Line:

- It is difficult to determine onset of analgesia versus peak analgesia from these trials' data, as onset of analgesia is not well-reported in these studies
- Additionally, heterogeneity of doses/dose titration schedules, type of neuropathy treated, and outcome timepoints makes it difficult to deduce onset of analgesia
- Most trials were investigating the analgesic outcomes surrounding the peak effect for these medications (durations of 4-12 weeks), so it remains unclear which oral agent used for neuropathic pain works "quickest"
- Generally speaking, agents that require less dose titrations will likely reach therapeutic peak faster, and therefore "peak" analgesic effect quicker (ie. duloxetine, pregabalin)
- Of course patients can notice *some* relief after initiating these therapies without reaching "target dose"… we see this all the time after starting gabapentin at low doses like 300mg/day
- Rapid titration of gabapentin over a period of days could shorten the interval it takes to reach max therapeutic benefit, but this comes at a cost… usually quicker titration results in greater somnolence & patients may be unwilling to escalate the doses further…

CLINICAL PEARL: Oral pharmacologic agents used for neuropathic pain do not work instantaneously, and most require at least 1-2 weeks to see onset of analgesic effect