UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

March 10, 2023 Vol. 3, No. 4

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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:

Chemotherapy-Induced Peripheral Neuropathy: A Review of the Evidence

Background:
Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a debilitating, dose-dependent adverse effect that may arise when patients undergo chemotherapy. CIPN may persist months and years beyond the completion of chemotherapy. Currently, there are no FDA-approved medications for CIPN; duloxetine is the only agent supported by ASCO and NCCN guidelines.

- Other medications are used for peripheral neuropathy:
  - Tricyclic antidepressants (TCAs), Serotonin Norepinephrine Receptor Inhibitors (SNRIs), anticonvulsants, and corticosteroids all of which are mentioned in NCCN guidelines, although noted that evidence is extrapolated from non-cancer neuropathic pain syndromes

Importance:
Chemotherapy-induced peripheral neuropathy persistence post-therapy is common for specific chemotherapy agents (e.g. taxanes and platinum-based agents) and has a negative impact on patients' quality of life. A question arose regarding available evidence for other antidepressants (other than duloxetine) use in CIPN. Palliative care clinicians should be aware of the evidence surrounding treatment options specifically for CIPN.

The Literature:

JAMA. 2013 Apr 3; 309(13): 1359-1367.

Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial.

Objective: Study goal was to determine the effect of duloxetine 60 mg daily reduce average CIPN pain severity

Methods: Phase III double-blind placebo-controlled crossover trial

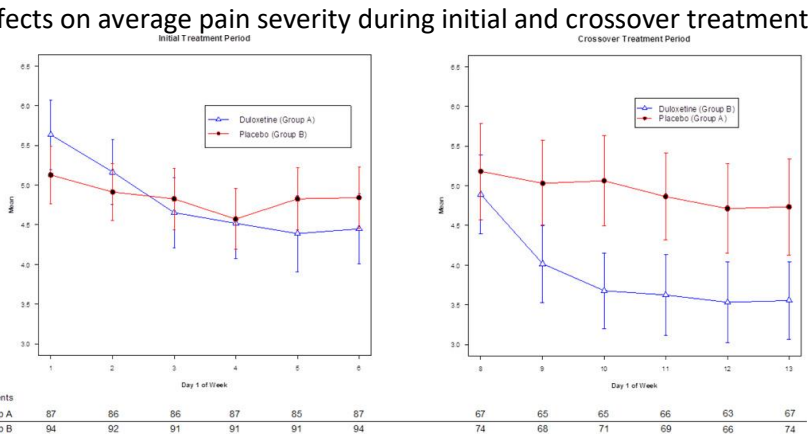
- Grade 1 sensory CIPN on CTCAE 3.0 scale AND 4/10 average CIPN-related neuropathic pain > 3 months beyond completion of chemotherapy
- 1:1 allocation ratio to two groups: 60 mg oral duloxetine daily or placebo
  - 5-week initial period, then crossover at week 8-12 (two-week washout)

Outcomes:

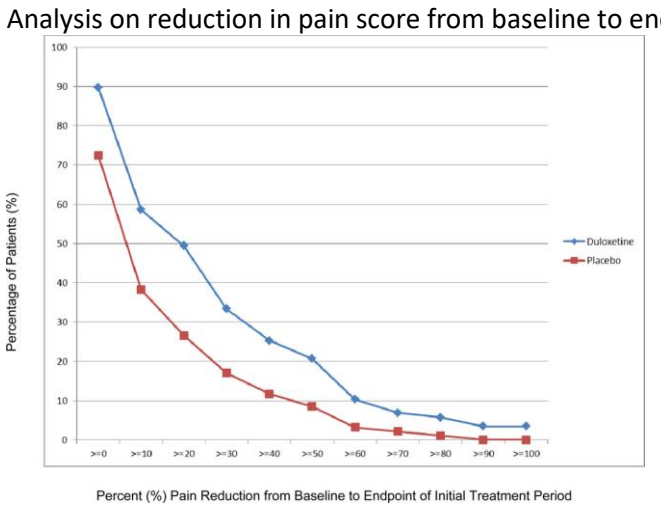
- Primary: change in average pain based on BPI severity scale from week 1-5
- Secondary: changes in CIPN-related quality of life via FACT/GOG-NTX and degree of pain-related functional interference

Results: N= 231; mean age = 59 (+/- 10.5)

- Effects on average pain severity during initial and crossover treatment period



- Analysis on reduction in pain score from baseline to end of initial period



Discussion:

- Fatigue, nausea, and insomnia were most common reported ADEs for duloxetine
- 27% of patients in duloxetine group discontinued concomitant drugs by end of initial period compared to 19% of patients in the placebo group
- Observed mean difference was larger in groups that received platinum-based chemotherapy

Conclusion: 5-week course of duloxetine resulted in greater pain reduction compared to placebo.

Annals of Oncology. 2012; 23:200-205.

Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial

Objective: percentage of patients with 100% pain relief under treatment

Methods: Phase III randomized double-blind, placebo-controlled trial at six French university hospitals

- Oxaliplatin-related neuropathy, ECOG performance status <2, histologically proven cancer, concomitant medication use
- Groups: Venlafaxine 50 mg once prior to infusion, venlafaxine 37.5 mg BID post-infusion, or placebo

Outcomes:

- Primary: percentage of patients with 100% relief of acute neuropathy
- Secondary: percentage of patients with >50% pain relief, mean NPSI (Neuropathic Pain Symptom Inventory) score variation; grade 0 or grade 3 neuropathy at 3 months

CLINICAL PEARL:
Generally, SNRIs are safe and effective for CIPN. Duloxetine remains 1st-line.

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Results: N= 48; median age = 67.6
- Proportion of patients with full relief of acute neuropathy: 31.3% v 5.3% (venlafaxine v placebo); p = 0.03
- Pain relief > 50%: 68.8% v 26.3% (venlafaxine v placebo); p = 0.02
- End points favoring venlafaxine: cold-induced pain, functional status

Conclusion: Venlafaxine use results in greater pain relief than placebo for *acute* neuropathy due to oxaliplatin administration.

Journal of Pain and Symptom Management. 2008 Jan; 35(1):31-39.

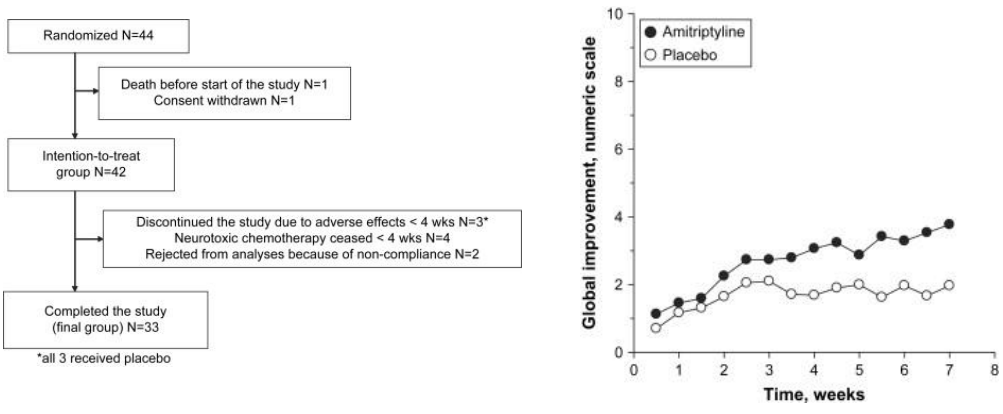
Amitriptyline in the Treatment of Chemotherapy-Induced Neuropathic Symptoms

Objective: show whether amitriptyline has efficacy on CIPN compared to placebo

Methods: eight-week, double-blind, randomized, placebo-controlled parallel group study
- Patients age 20-65 years with CIPN pain >3/10
- Starting dose = 10 mg/day; titrate up by 10 mg/week to 50 mg/day if tolerated then stable dose for >4 weeks

Outcomes:
- Primary: relief of neuropathic symptoms with amitriptyline compared to placebo
- Secondary: severity of other neuropathic symptoms, mood, sleep, quality of life

Results: N= 33; mean age = 53 (35-67)
- Mean SD for global improvement was 3.4 ± 3.6 in the amitriptyline group and 1.9 ± 3.1 in the placebo group
- (L) Study enrollment process; (R) Mean global improvement measured (twice weekly)



Discussion:
- No difference in neuropathy severity and physical activity; QoL improvement only temporary for amitriptyline
- Sleep disturbance is common at baseline; less nighttime awakening in amitriptyline group (9/10)

Conclusion: Amitriptyline improved QoL and tended to improve symptoms of chemotherapy-induced neuropathy

Bottom Line:

- Current literature lacks head-to-head trials between SNRIs and TCAs, so it's hard to deduce if one medication (or class) truly works better than the other
- **Duloxetine has consistent favorable outcomes for CIPN; making it first-line treatment option for CIPN. This recommendation is backed by ASCO.**
- Venlafaxine and Amitriptyline trial above had smaller N than duloxetine study, so although on the surface findings look promising… might be hard to generalize these two studies. Above venlafaxine study looked specifically at *acute* neuropathy…
- Mixed results exist for venlafaxine efficacy for CIPN. Some studies that did not show benefit used lower doses (like 37.mg daily). This makes sense as venlafaxine primarily acts on serotonin receptors at low doses. If planning to try venlafaxine for CIPN, would try using higher doses (≥150mg/day).
- Although TCAs are utilized commonly for neuropathic pain, studies specifically examining their use in CIPN did not have favorable results. Given their high incidence of side effects, we need more evidence before concluding benefit outweighs risk for use in CIPN.
- In fact, a trial examining nortriptyline for use in treating cisplatin-induced paresthesia resulted in quick symptom resolution of CIPN due to chemotherapy discontinuation so findings not clinically relevant
- Timing of pain score can influence the reported pain score when assessing for efficacy

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3. NCCN Adult Cancer Pain. 2022 Jun 27.
4. Kautio A, Haanpaa M, Saarto T, et al. Amitriptyline in the Treatment of Chemotherapy-Induced Neuropathic Symptoms. *Journal of Pain and Symptom Management.* 2008 Jan; 35(1): 31-39.
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6. Desforges AD, Hebert CM, Spence AL. Treatment and diagnosis of chemotherapy-induced peripheral neuropathy: An update. *Biomedicine & Pharmacotherapy.* 2022 Mar; 147:112671.
7. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. *J Clin Oncol.* 2020; 38:3325-3348.

CLINICAL PEARL:

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