Bedside to Bench to Bedside: Managing Painful Chemotherapy-Induced Peripheral Neuropathy

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Chemotherapy-Induced Peripheral Neuropathy (CIPN)

- Experienced by
  - ~ 68% in the first month after chemotherapy
  - ~ 60% at 3 months
  - ~ 30% at 6 months
  - ~ Present > 10 years later

Seretny et al., 2014
Clinical Manifestations

- Stocking/glove distribution
- Sensory Symptoms
- Motor Symptoms
- Autonomic Symptoms

Park, et al., 2013
CIPN Outcomes

- Impaired function
- Diminished quality of life
- Chemotherapy dosage modifications

Seretney et al., 2014; Argyriou, 2014; Smith, et al., 2013, Mols, et al., 2013
47 of 48 RCTs published between 1992 - 2013 failed to reveal an effective intervention for painful and non-painful CIPN.
Duloxetine (SNRI)

Effect of Duloxetine on Pain, Function, and Quality of Life Among Patients With Chemotherapy-Induced Painful Peripheral Neuropathy
A Randomized Clinical Trial

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Importance
There are no known effective treatments for painful chemotherapy-induced peripheral neuropathy.

Objective
To determine the effect of duloxetine, 60 mg daily, on average pain severity.

Design, Setting, and Patients
Randomized, double-blind, placebo-controlled crossover trial at 8 National Cancer Institute (NCI)-funded cooperative research networks that enrolled 231 patients who were 25 years or older being treated at community and academic settings between April 2008 and March 2011. Study follow-up was completed July 2012. Stratified by chemotherapeutic drug and comorbid pain risk, patients were randomized to receive either duloxetine followed by placebo or placebo followed by duloxetine. Eligibility required that patients have grade 1 or higher sensory neuropathy according to the NCI Common Terminology Criteria for Adverse Events and at least 4 on a scale of 0 to 10, representing average chemotherapy-induced pain, after paclitaxel, other taxane, or oxaliplatin treatment.

Interventions
The initial treatment consisted of taking 1 capsule daily of either 30 mg of duloxetine or placebo for the first week and 2 capsules of either 30 mg of duloxetine or placebo daily for 4 additional weeks.

Main Outcome Measures
The primary hypothesis was that duloxetine would be more effective than placebo in reducing pain intensity among patients with chemotherapy-induced peripheral neuropathy.

Hershman, et al., 2014, Smith, et al., 2013

The only drug recommended by ASCO for treatment of painful CIPN
The Problem

We have failed to find effective interventions for CIPN because we do not fully understand the underlying mechanisms.
Spinal Cord
Dorsal Horn

(Modified from: Bingel & Tracey, 2008)
Presynaptic Terminal

Synaptic Cleft

Postsynaptic Membrane

Synthesis

Release

Storage

Reuptake

$\alpha_2$ adrenoceptor (Analgesia)

$\alpha_1$ adrenoceptor (Pain)

Adapted from: Wilkie, Diana, TNEEL
The Effects of Alpha Adrenoceptor Antagonists

- **α<sub>1</sub>-antagonist, blocks pain**
- **α<sub>2</sub>-antagonist, blocks analgesia**

**Diagram:**
- WB4101 CCI
- Normal Saline CCI
- Yohimbine CCI

**Graph:**
- Withdrawal Latency over Time
- Y-axis: Withdrawal Latency
- X-axis: Time (1 min to 45 min)
Duloxetine For Painful CIPN

Stratification Factors: Chemotherapy Class & CIPN Risk

Smith, et al., 2013. JAMA.
Duloxetine’s Central Effects

Presynaptic Terminal

Storage

Synthesis

Release

Reuptake

SNRIs block NE reuptake

Synaptic Cleft

Postsynaptic Membrane

alpha$_{2}$ adrenoceptor (Analgesia)

alpha$_{1}$ adrenoceptor (Pain)

Adapted from: Wilkie, Diana, TNEEL
Can duloxetine prevent oxaliplatin-induced peripheral neuropathy (OIPN) in pre-clinical studies?
Why might duloxetine prevent OIPN?

Duloxetine blocks Nav1.7 sodium channel-triggered peripheral nerve impulses from traveling from the periphery to the CNS.

Wang, S. et al., 2010; Wang, C. et al., 2015
Translational Study

- Rat model of Painful Oxaliplatin-Induced CIPN
- Oral duloxetine
- Test for hyperalgesia and allodynia
Design

- Rats receiving dose of oxaliplatin (2mg/kg)
  - 2 treatment groups
    1. Control (water) n= 13
    2. Duloxetine (15mg/kg) n= 6 -preventative

- Von Frey testing
  - 15 g fiber for hyperalgesia
  - 4 g fiber for allodynia

- The higher the withdrawal response, the greater the pain.
Von Frey Filaments

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<th>Monofilament Size</th>
<th>Target Force (Grams)</th>
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Female Hyperalgesia

- *p = 0.010

Time (days)

Percent Withdrawal

Duloxetine (n = 5)

Water (n = 7)

Dulox Starts

Oxaliplatin Starts

Dulox Stops

Oxaliplatin Stops

*p = 0.010

Leading the way.
Can duloxetine prevent oxaliplatin-induced peripheral neuropathy in patients with stage II – III colorectal cancer?
Phase II

- Using a **Phase II** 3-arm, randomized, double-blind, placebo-controlled design:

- **Primary Aim:** Identify the most promising dosage of duloxetine (i.e., 30 mg or 60 mg daily) to prevent OIPN.
Phase III

- Using a **Phase III** 2-arm randomized, double blind, placebo-controlled design:

- **Co-Primary Aims:** Demonstrate that the most promising dosage of duloxetine identified in the Phase II component will be more effective than placebo at preventing
  - OIPN during oxaliplatin treatment
  - Chronic neuropathic pain after oxaliplatin treatment
Duloxetine Limitations

It didn’t work in 44%.

The mean decrease in average pain $= 1.06$ (95% CI, 0.72-1.40)
Effects of Prazosin IT

α₁-antagonists, Block pain

Saline control
Bedside to Bench

Does oral prazosin prevent CIPN pain in pre-clinical studies?

Does oral prazosin plus duloxetine work better than duloxetine alone?
Concluding Remarks

- Duloxetine can reduce painful CIPN but its effect to prevent CIPN (N, T, P) is unknown.
  - Pre-clinical studies suggest that duloxetine might prevent OIPN.

- Clinically, duloxetine’s effect is modest.
  - Ongoing pre-clinical studies aim to determine if duloxetine plus prazosin might work better than duloxetine alone.

- Future research is needed to identify and test mechanism-targeted interventions to ameliorate and prevent CIPN.
Thank you!

DISCUSSION