University of Michigan
School of Nursing

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

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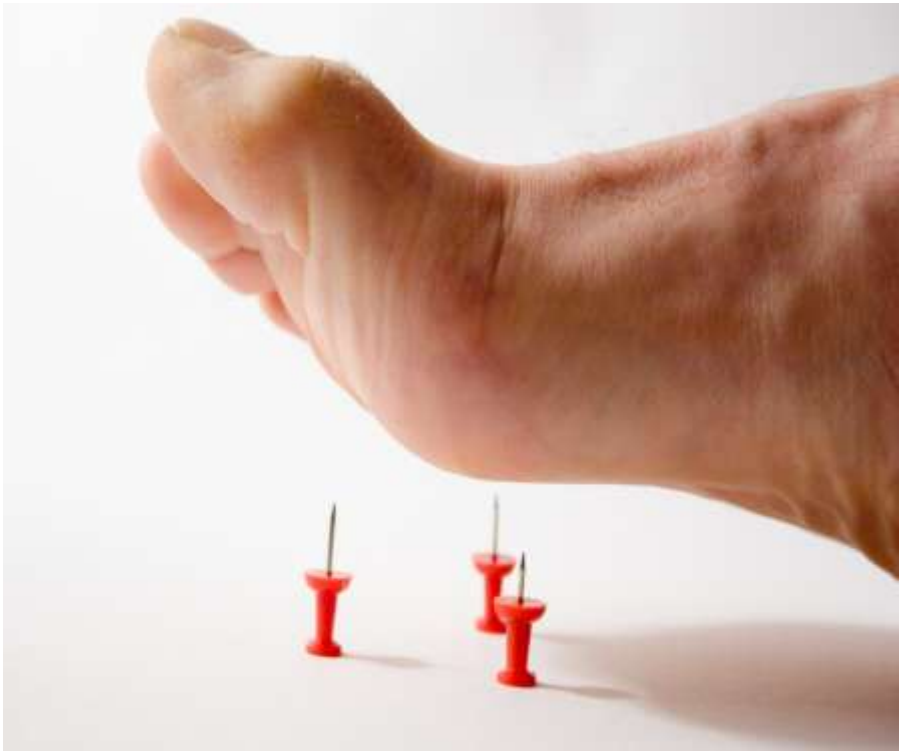
NCI Division of Cancer Prevention & Lilly Pharmaceuticals

Leading the way.

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

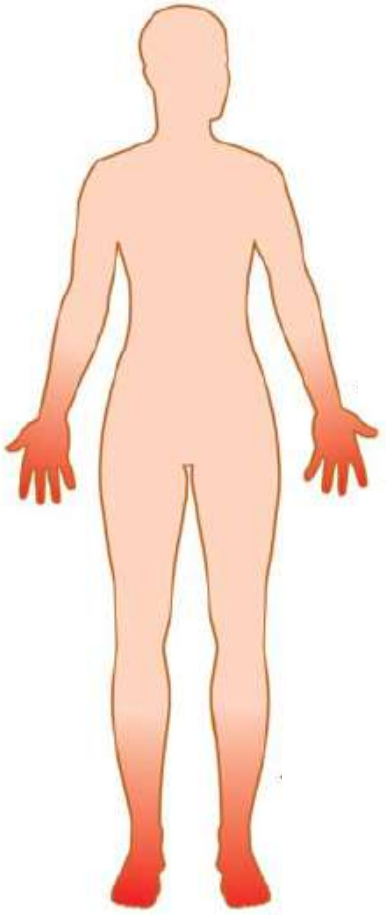
- Experienced by
  - ~ 68% in the first month after chemotherapy
  - ~ 60% at 3 months
  - ~ 30% at 6 months
  - ~ Present > 10 years later



Seretny et al., 2014

Clinical Manifestations

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



Park, et al., 2013

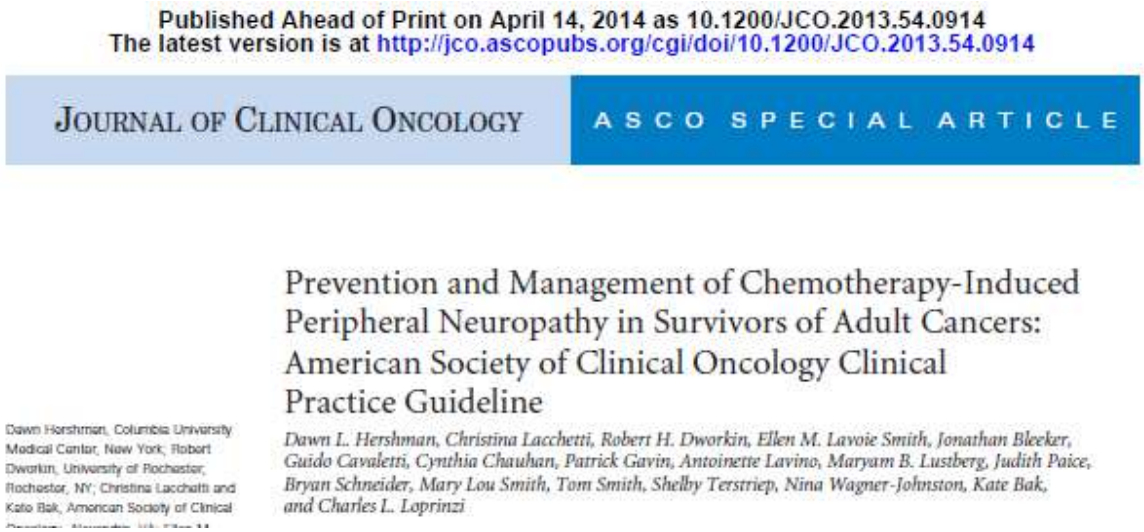
CIPN Outcomes

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

https://pixabay.com/en/seminar-motivation-joy-of-life-743932/

Seretney et al., 2014; Argyriou, 2014; Smith, et al., 2013, Mols, et al., 2013

The Search for Relief



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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Dawn L. Hershman, Christina Lacchetti, Robert H. Dworkin, Ellen M. Lavoie Smith, Jonathan Bleeker, Guido Cavaletti, Cynthia Chauhan, Patrick Gavin, Antoinette Lavino, Maryam B. Lustberg, Judith Paice, Bryan Schneider, Mary Lou Smith, Tom Smith, Shelby Terstriep, Nina Wagner-Johnston, Kate Bak, and Charles L. Loprinzi

Dawn Hershman, Columbia University Medical Center, New York; Robert Dworkin, University of Rochester, Rochester, NY; Christina Lacchetti and Kate Bak, American Society of Clinical

47 of 48 RCTs published between 1992 - 2013 failed to reveal an effective intervention for painful and non-painful CIPN.

Hershman et al., 2014.

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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for the Alliance for Clinical Trials in Oncology

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.

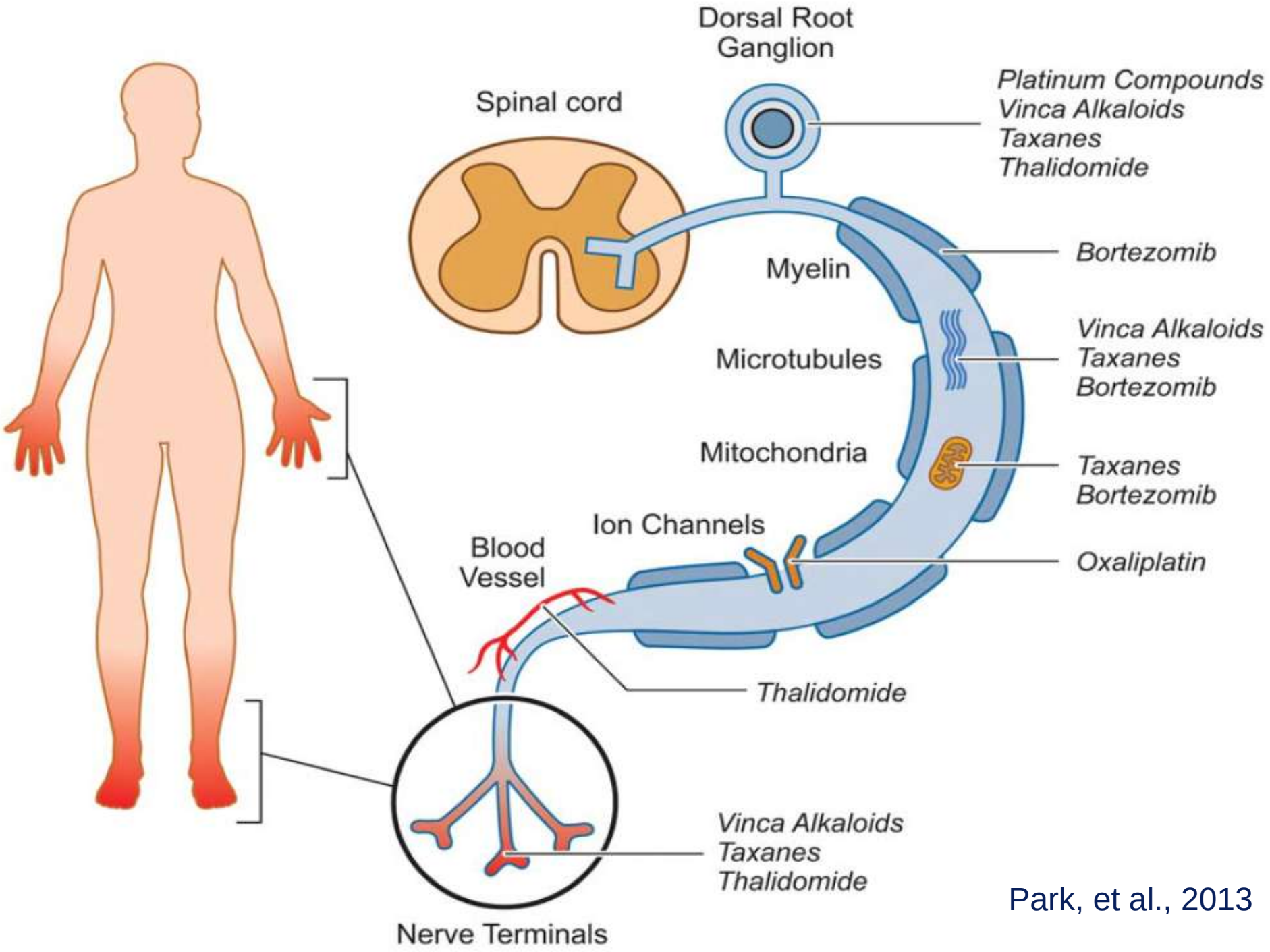
Main Outcome Measures The primary hypothesis was that duloxetine would be more

The only drug recommended by ASCO for treatment of painful CIPN

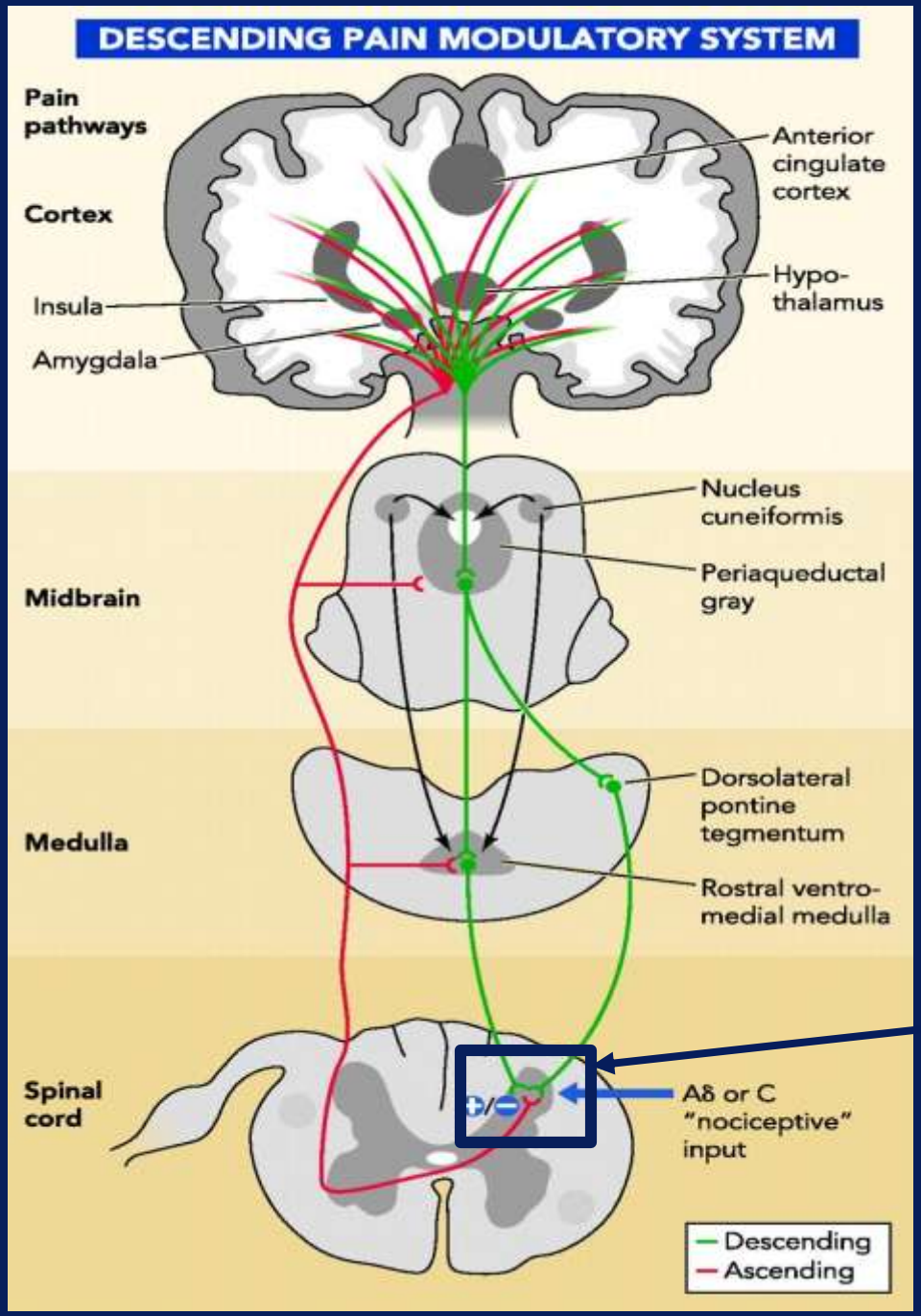
Hershman, et al., 2014, Smith, et al., 2013

The Problem

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

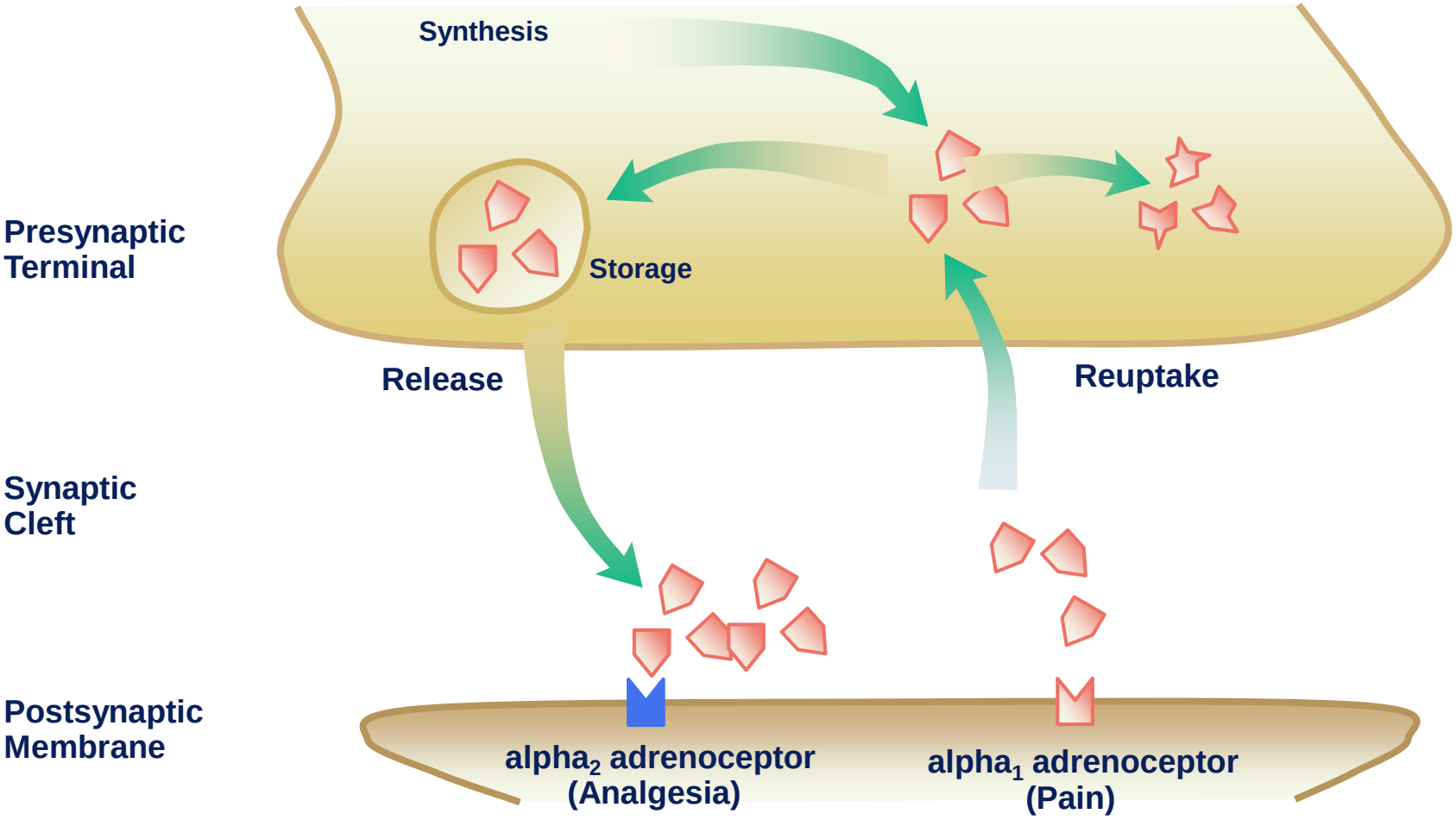


Park, et al., 2013

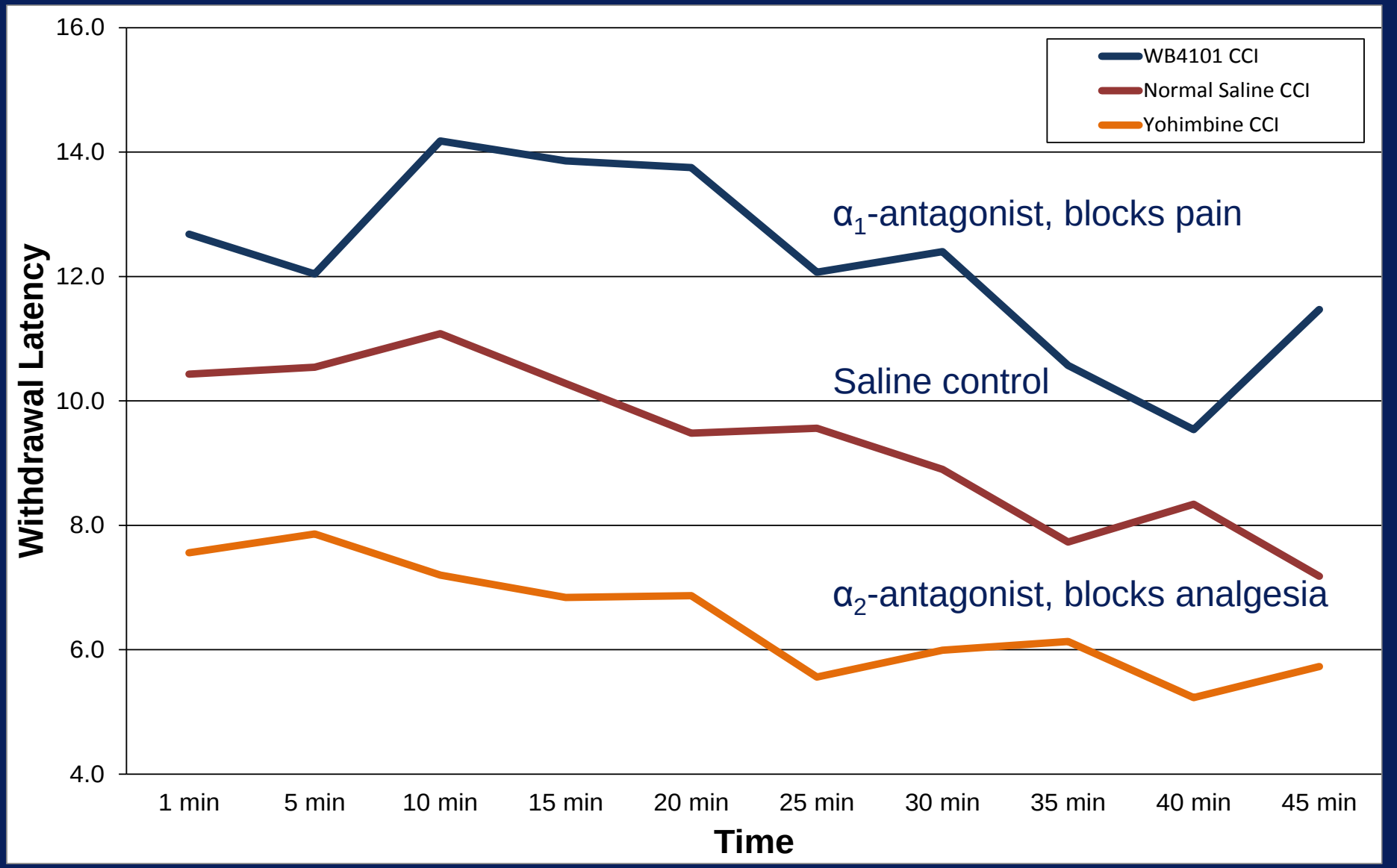


Spinal Cord
Dorsal Horn

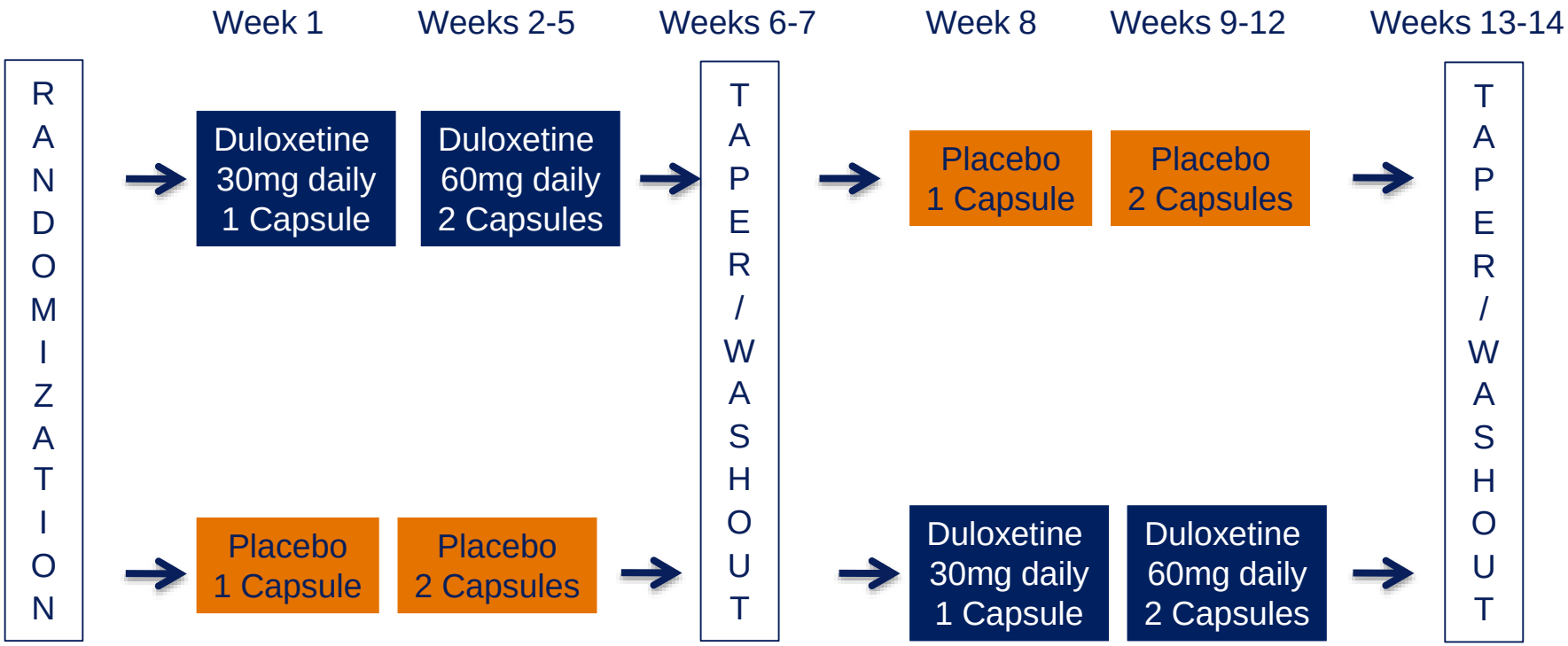
(Modified from: Bingel & Tracey, 2008)


Presynaptic Terminal
Synaptic Cleft
Postsynaptic Membrane
Synthesis
Storage
Release
Reuptake
alpha2 adrenoceptor (Analgesia)
alpha1 adrenoceptor (Pain)

The Effects of Alpha Adrenoceptor Antagonists



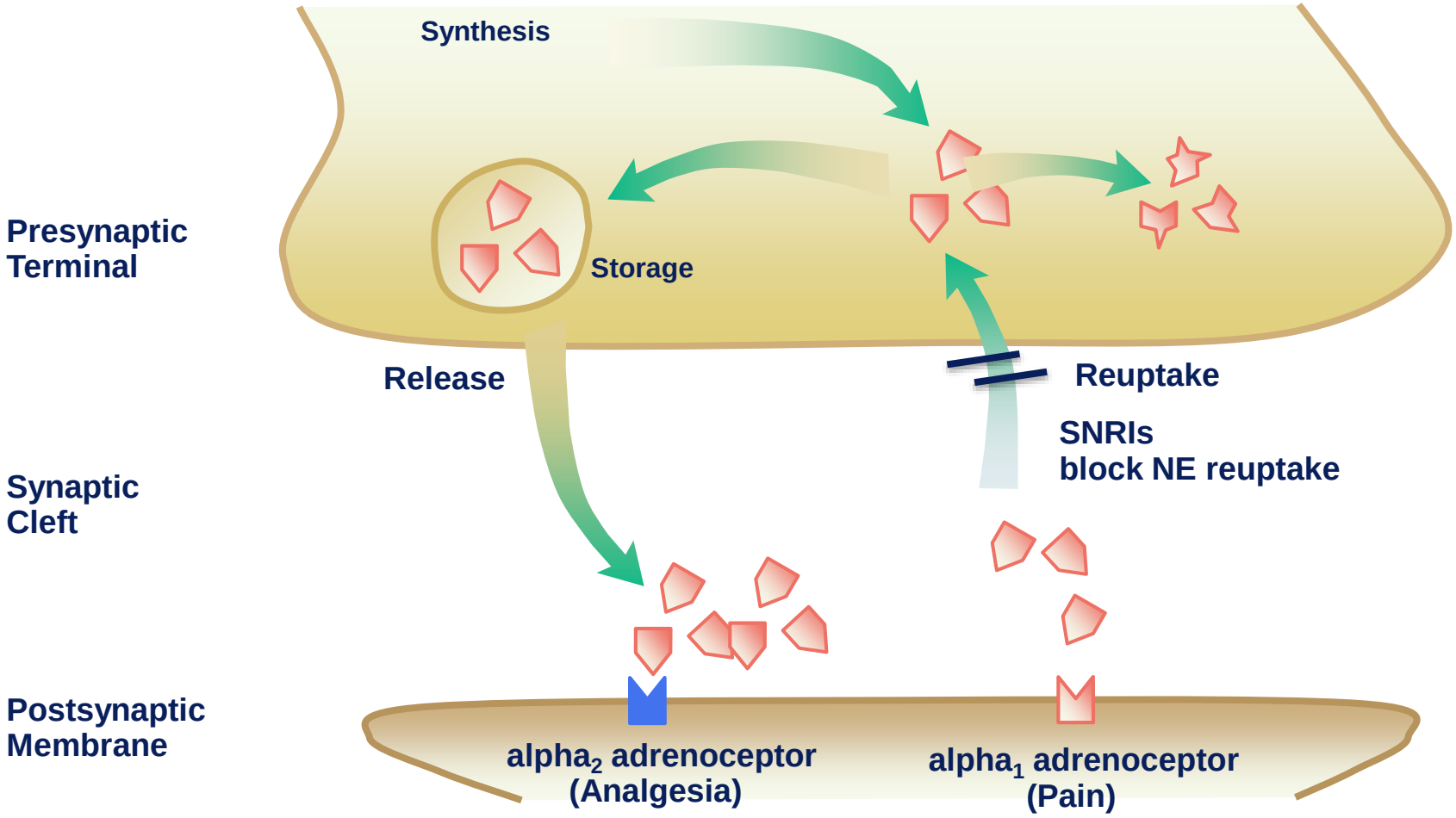
Duloxetine For Painful CIPN



Stratification Factors: Chemotherapy Class & CIPN Risk

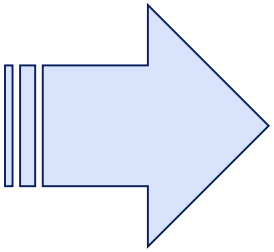
Smith, et al., 2013. *JAMA.*

Duloxetine's Central Effects



Bedside to Bench

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

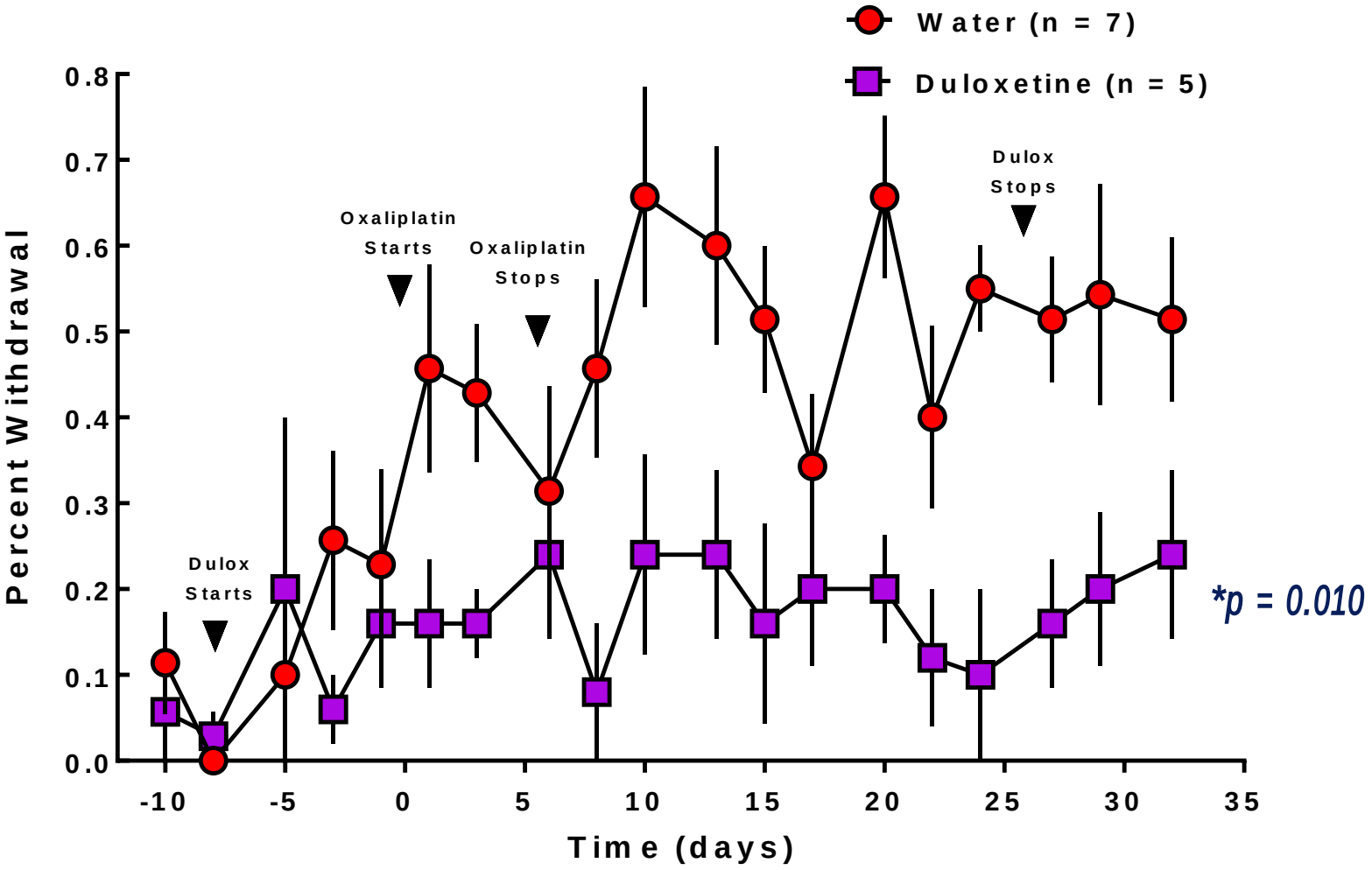
Design

- 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

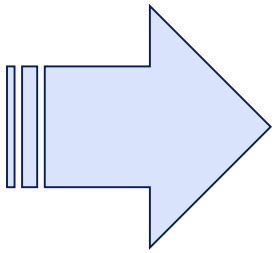
Monofilament Size	Target Force (Grams)
1.65	0.008
2.36	0.02
2.44	0.04
2.83	0.07
3.22	0.16
3.61	0.4
3.84	0.6
4.08	1
4.17	1.4
4.31	2
4.56	4
4.74	6
4.93	8
5.07	10
5.18	15
5.46	26
5.88	60
6.10	100
6.45	180
6.65	300

Female Hyperalgesia



Bench to Bedside: Phase II – III RCT

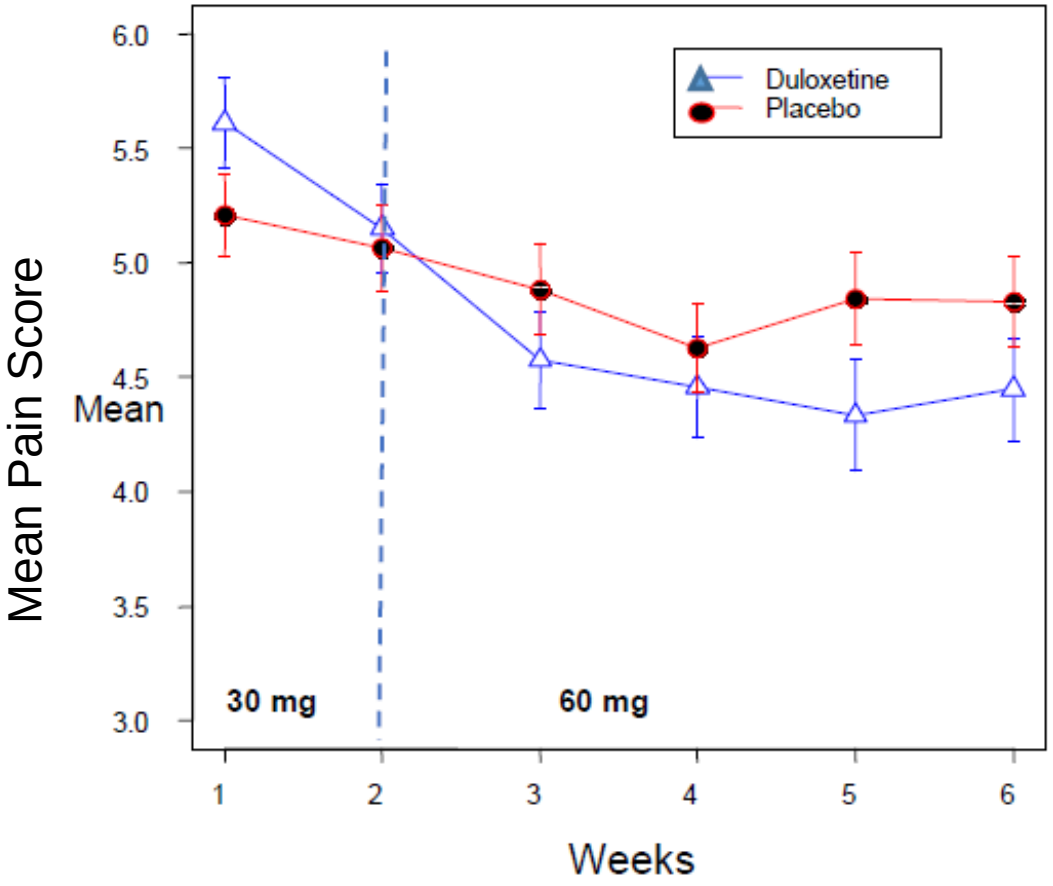
Can duloxetine prevent oxaliplatin-induced peripheral neuropathy in patients with stage II – III colorectal cancer?



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:

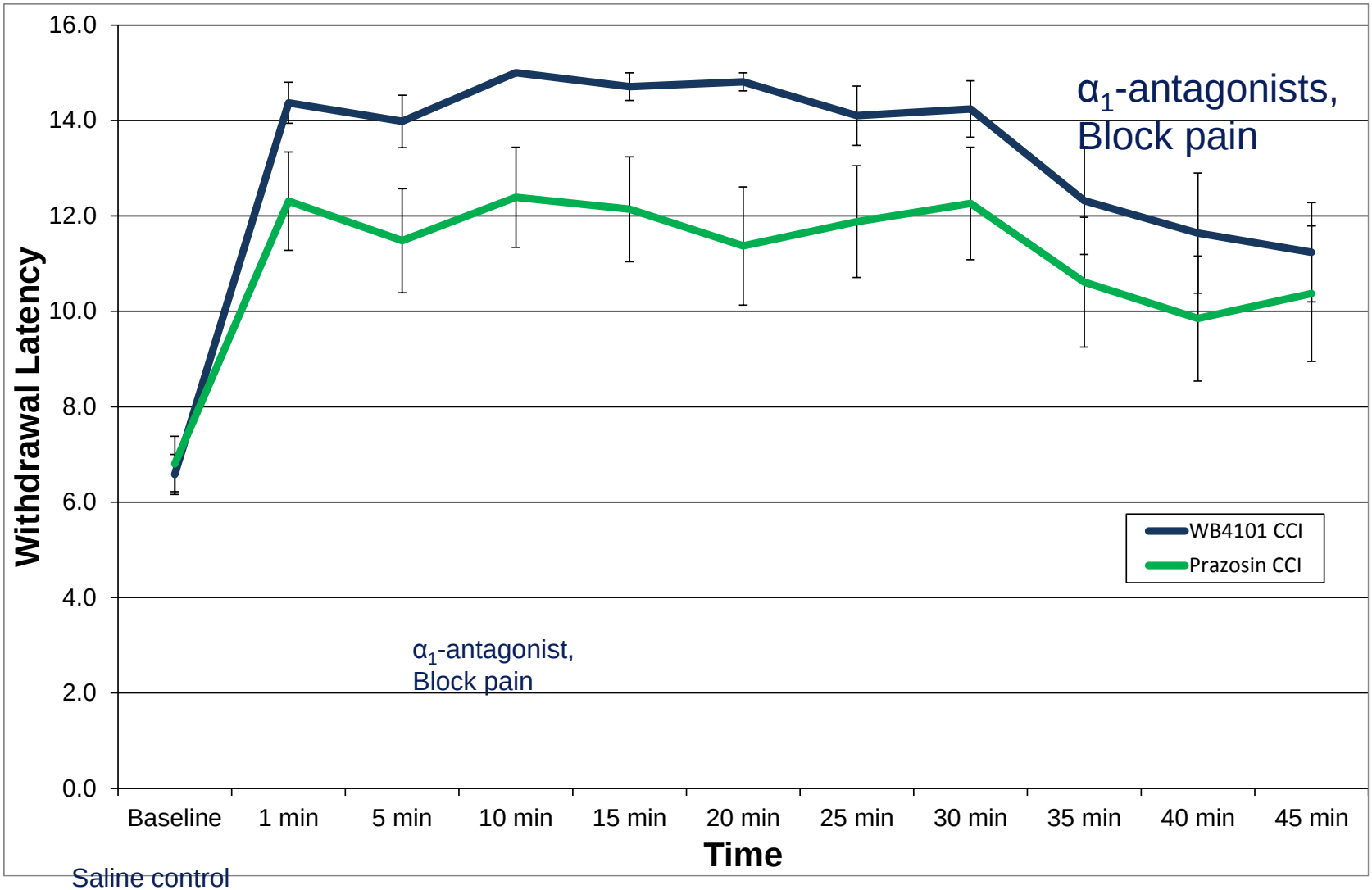
- Co-Primary Aims: Demonstrate that the most promising dosage of duloxetine identified in the Phase II component will be more effective than placebo at preventing
  - ~ OIPN during oxaliplatin treatment
  - ~ Chronic neuropathic pain after oxaliplatin treatment

Duloxetine Limitations

It didn't work in 44%.

The mean decrease in average pain = 1.06 (95% CI, 0.72-1.40)

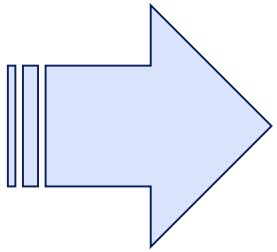
Effects of Prazosin IT



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