

Chemotherapy-Induced Neuropathy: Standard and Innovative Treatment Approaches

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Potential Conflicts of Interest

- Competitive Technologies provided a machine and supplies for research
- Pfizer provided funding for a study
- I have spoken to many interested companies
- Virtually all of which I discuss will not be FDA approved

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The latest version is at <http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.54.0914>

JOURNAL OF CLINICAL ONCOLOGY

A S C O S P E C I A L A R T I C L E

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

- 1,225 potentially relevant citations
- 250 examined in detail
- 48 eligible for guideline evidentiary basis
 - 42 for CIPN prevention
 - 6 for CIPN treatment

Treatment agents reviewed

- Duloxetine
- Gabapentin
- Topical BAK
- Tricyclic antidepressants
- Acetyl-L-carnitine
- Lamotrigine

Treatment agents recommended against

- Duloxetine
- Gabapentin
- Topical BAK
- Tricyclic antidepressants
- Acetyl-L-carnitine
- Lamotrigine

Treatment agent recommended

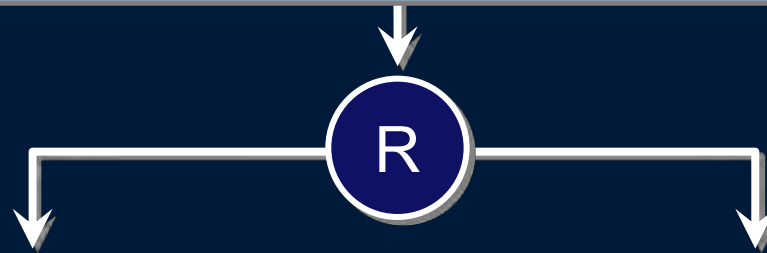
- Duloxetine
- Gabapentin
- Topical BAK
- Tricyclic antidepressants
- Acetyl-L-carnitine
- Lamotrigine

A PHASE III DOUBLE BLIND TRIAL OF ORAL
DULOXETINE FOR TREATMENT OF PAIN
ASSOCIATED WITH CHEMOTHERAPY-INDUCED
PERIPHERAL NEUROPATHY (CIPN)

Ellen Smith, Tim Ahles, Ethan Basch et al

Smith et al JAMA; 2013;309:1359-67

Chemotherapy-induced neuropathy



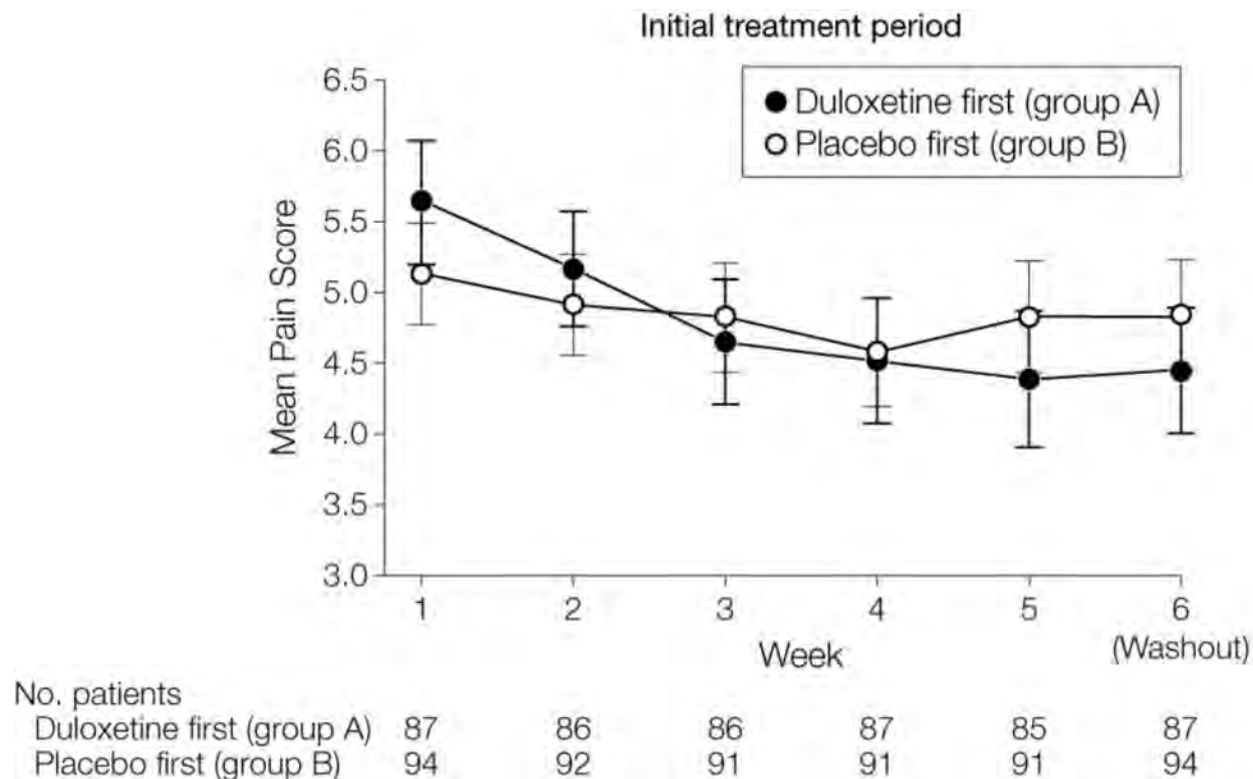
Duloxetine
30 mg/d for 1 week
60 mg/d for 4 weeks

Placebo
1/d for 1 week
2/d for 4 weeks

Smith et al JAMA; 2013;309:1359-67

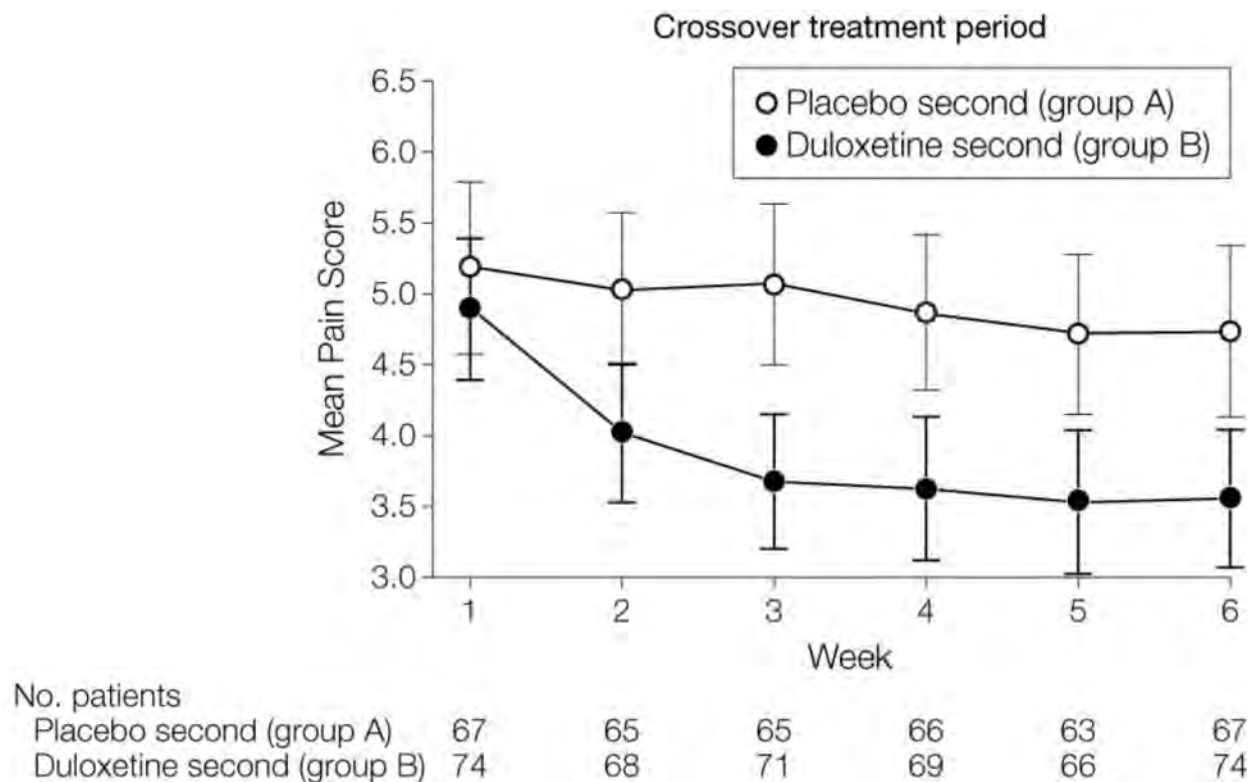
From: **Effect of Duloxetine on Pain, Function, and Quality of Life Among Patients With Chemotherapy-Induced Painful Peripheral Neuropathy: A Randomized Clinical Trial**

JAMA. 2013;309(13):1359-1367. doi:10.1001/jama.2013.2813



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

JAMA. 2013;309(13):1359-1367. doi:10.1001/jama.2013.2813



2014 ASCO/MASCC Palliative Care: Yasuo Hirayama et al J Clin Oncol 32, 2014 (suppl 31; abstr 181)

- Japanese pts randomized to receive duloxetine followed by vitamin B12 **versus** vitamin B12 followed by duloxetine
- 34 cases
- 5 cases dropped out because of adverse effects
- Significant differences in changes of VAS were observed between duloxetine group and VB12 group for:
 - numbness ($p=0.02$)
 - pain ($p=0.03$)

Duloxetine in symptomatic chemotherapy-induced peripheral neuropathy: Single-center experience beyond the clinical trial

Roser Velasco et al

University Hospital of Bellvitge, Barcelona,
Spain;

ASCO 2015; Abstract e20713

- Single-institution consecutive cancer patients with CIPN
- Treated with duloxetine in 2014
- Prospectively collected data

Study aim was to evaluate:

- Drug efficacy
- Rate of compliance
- Adverse-effects profile

- 73 pts treated:
 - 45 (62%) patients discontinued duloxetine related to:
 - Side-effects (38%)
 - Ineffectiveness (23%)

Drug dosing details not provided.

Conclusions Regarding Duloxetine

- It does work
- Benefit is limited
- Toxicity is a problem for some

Treatment agents endorsed

- Duloxetine
- Gabapentin
- Topical BAK
- Tricyclic antidepressants
- Acetyl-L-carnitine
- Lamotrigine

Responses to questions re use of gabapentin

Medical Oncologists

Have you been using gabapentinoids for treatment of established neuropathy?	What percentage of patients get mild or more benefit?	What percentage of patients get marked benefit?
N	--	--
N	--	--
N	--	--
N	--	--
N	--	--
N	10%	0
N	5-10%	0
Rarely	--	--
Rarely	--	--
Rarely	5%	0%
Occasionally	10-20%	0%
Occasionally	--	--
Occasionally	20%	5%
Occasionally	10-20%	<10%
Occasionally	20%	10%
Y	20%	0%
Y	10-40%	<10%
Y	30-50%	10-20%
Y	45%	>50%

Responses to questions re use of gabapentin Hematologists

Have you been using gabapentinoids for treatment of established neuropathy?	What percentage of patients get mild or more benefit?	What percentage of patients get marked benefit?
Rarely	--	--
Y	25%	5%
Y	20%	10%
Y	40-50%	10-20%
Y	25%	20%
Y	20%	30-40%
Y	50%	50%

The first known report regarding the use of gabapentin for chemotherapy-induced neuropathy:

Oxaliplatin-induced Neuropathy: Could Gabapentin be the Answer?

- Mariani et al
- 2000 ASCO annual meeting

- Gabapentin used in 7 patients receiving oxaliplatin who developed neuropathy
- With the initiation of neuropathy, gabapentin was given at a dose of 100 mg twice per day
- Increased to 100 mg three times daily if symptoms did not resolve with the lower daily dose
- Disappearance of neuropathy symptoms that continued even with the use of up to 14 total oxaliplatin doses
- Not available in manuscript form

- 2006 report on two sequential cohorts of patients who received similar oxaliplatin treatments for metastatic colorectal cancer
- The second cohort also received gabapentin, 300 mg daily initially....allowed to be increased to 600 mg three times daily
- Similar degrees of neurotoxicity were seen on both arms
- No differences in the relative dose intensities of oxaliplatin

- 2009, Czech Republic manuscript
- Pregabalin use in 30 children (mean age of 13.5 years) in an open label trial design
- Variety of neurotoxic chemotherapy drugs and had a pain score of at least 4/10 when entered on trial
- Mean VAS decreased by 59%
- 86% of the evaluable patients had long-lasting pain relief

Vondracek P et al: EJPN : official journal of the European Paediatric Neurology Society 13:332-6, 2009

- In 2010, a report of 23 patients treated with pregabalin for oxaliplatin-induced neuropathy
- Appears to be a clinical practice experience, as opposed to a prospective clinical trial
- Authors felt that 40% of the patients responded to therapy, as judged by a neuropathy improvement of 1-2 grades
- Quite a few toxicities

Saif MW, et al: Role of pregabalin in treatment of oxaliplatin-induced sensory neuropathy. Anticancer Research 30:2927-33, 2010

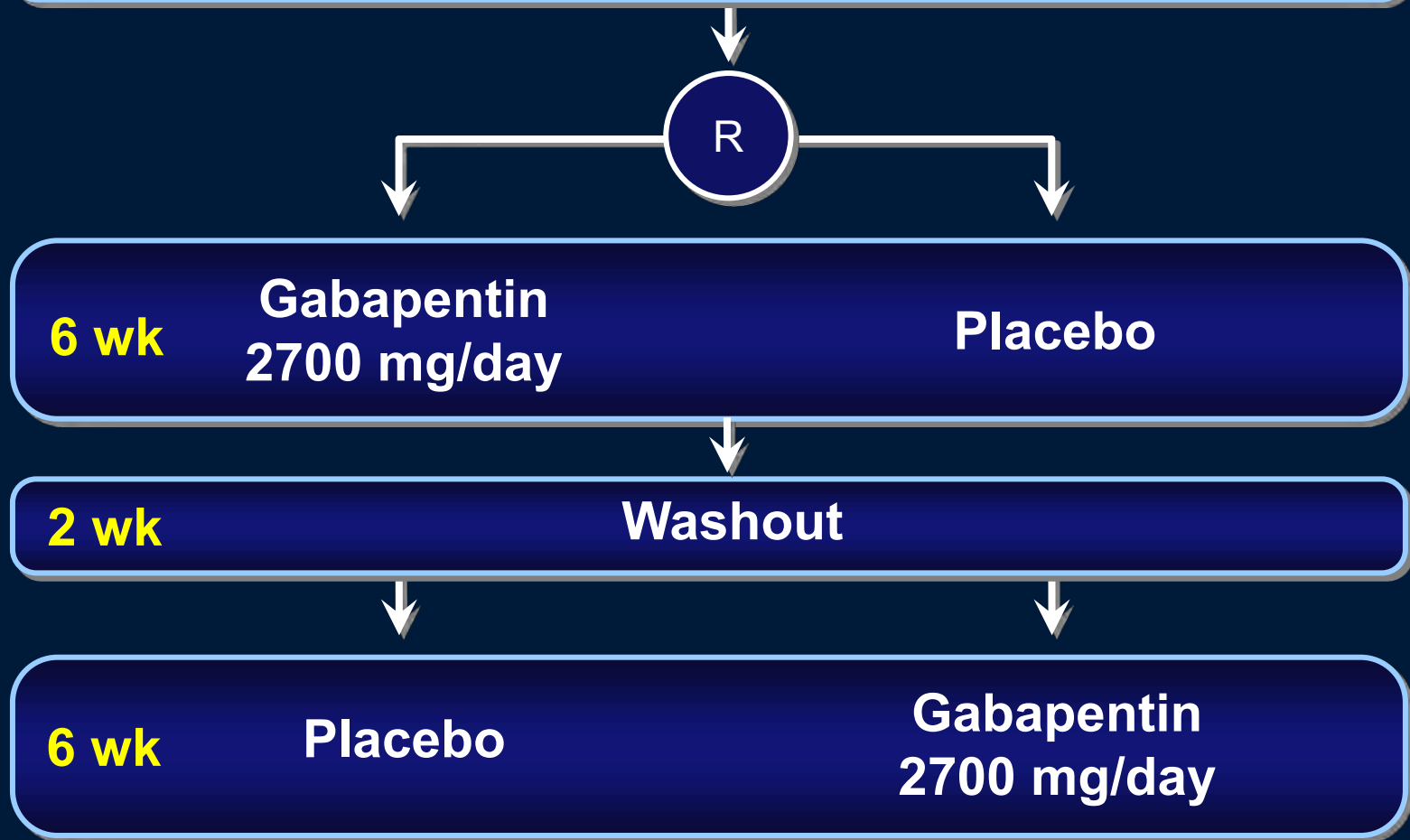
- 2012 - 2014, 5 Japanese manuscripts related to pregabalin therapy for CIPN, with English abstracts
 - 2 single case reports-positive
 - 13 cases, ?clinical experience?, with 8 'responding' pts (62%)
 - 27 oxaliplatin CIPN prospective trial, it seems
 - 27% 'responded'
 - 55 pts ?clinical experience?
 - 28 paclitaxel-29% 'responded'
 - 27 oxaliplatin—41% 'responded'

Efficacy of Gabapentin in the Management of Chemotherapy- Induced Peripheral Neuropathy: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Crossover Trial (N00C3)

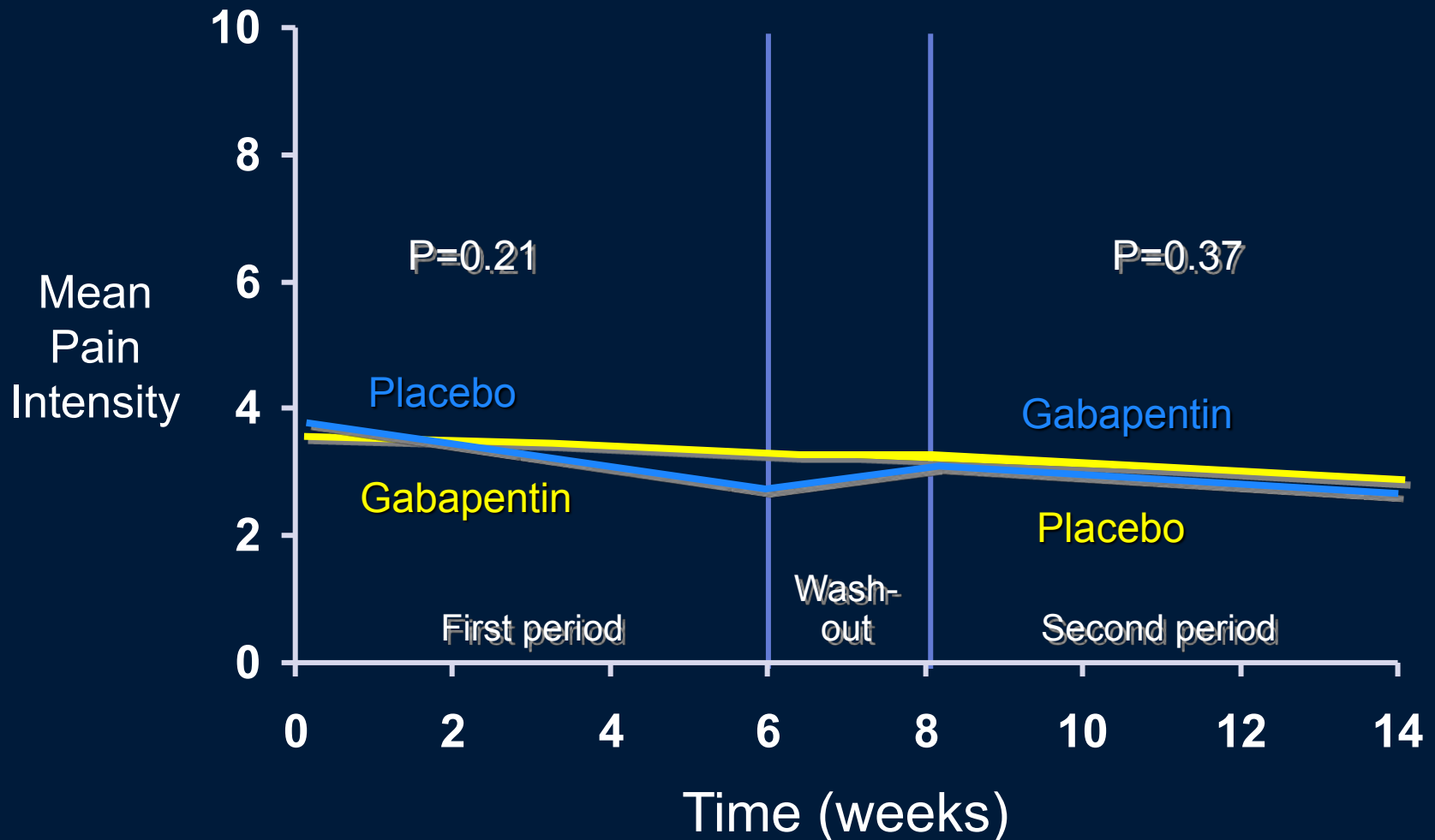
Rao R, Michalak J, Sloan J, Loprinzi C,
Soori G, Nikceovich D, Warner D,
Novotny P, Kutteh L, Wong G

Cancer 110; 2110: 2007

Chemotherapy-induced neuropathy



Mean Pain Intensity



A Reported Randomized, Double-blind, Placebo-controlled Trial

- Pregabalin for the prevention/treatment of CIPN
- Conducted in patients with advanced colorectal cancer receiving oxaliplatin-based chemotherapy

- Enrolled 64 patients
- Primary endpoint of this trial was the duration-adjusted average paresthesia change measured by a numerical rating scale
- Patients received flexible pregabalin dosing, from 150-600 mg/day versus placebos

- The trial was terminated early
- Interim analysis found that there was not sufficiently positive data to continue the trial, based on a 'conditional power to detect a difference in treatment groups'

ClinicalTrials.gov. prevention and treatment of chemotherapy-induced peripheral neuropathy in subjects with advanced colorectal cancer.

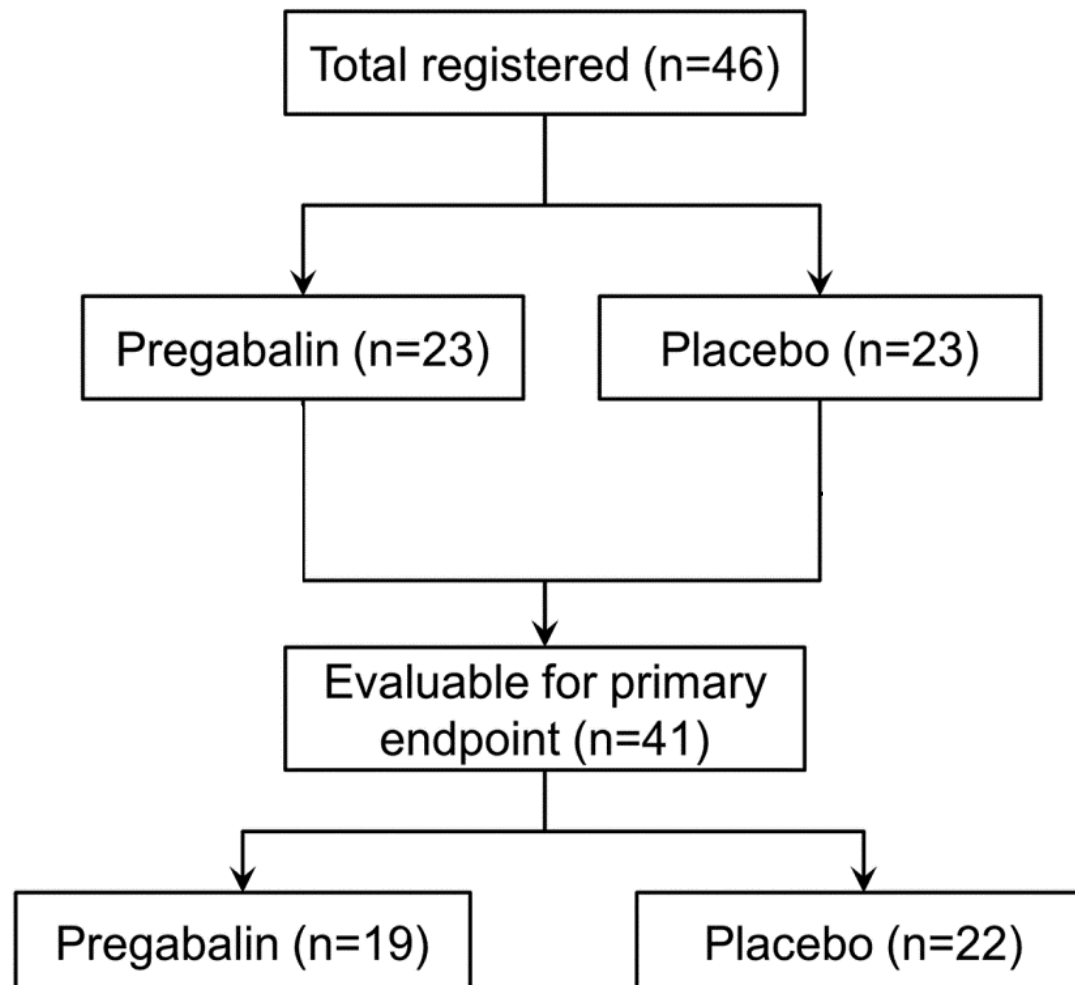
<https://Clinicaltrials.gov/ct2/show/NCT00380874>

(accessed 4014 dec 25)

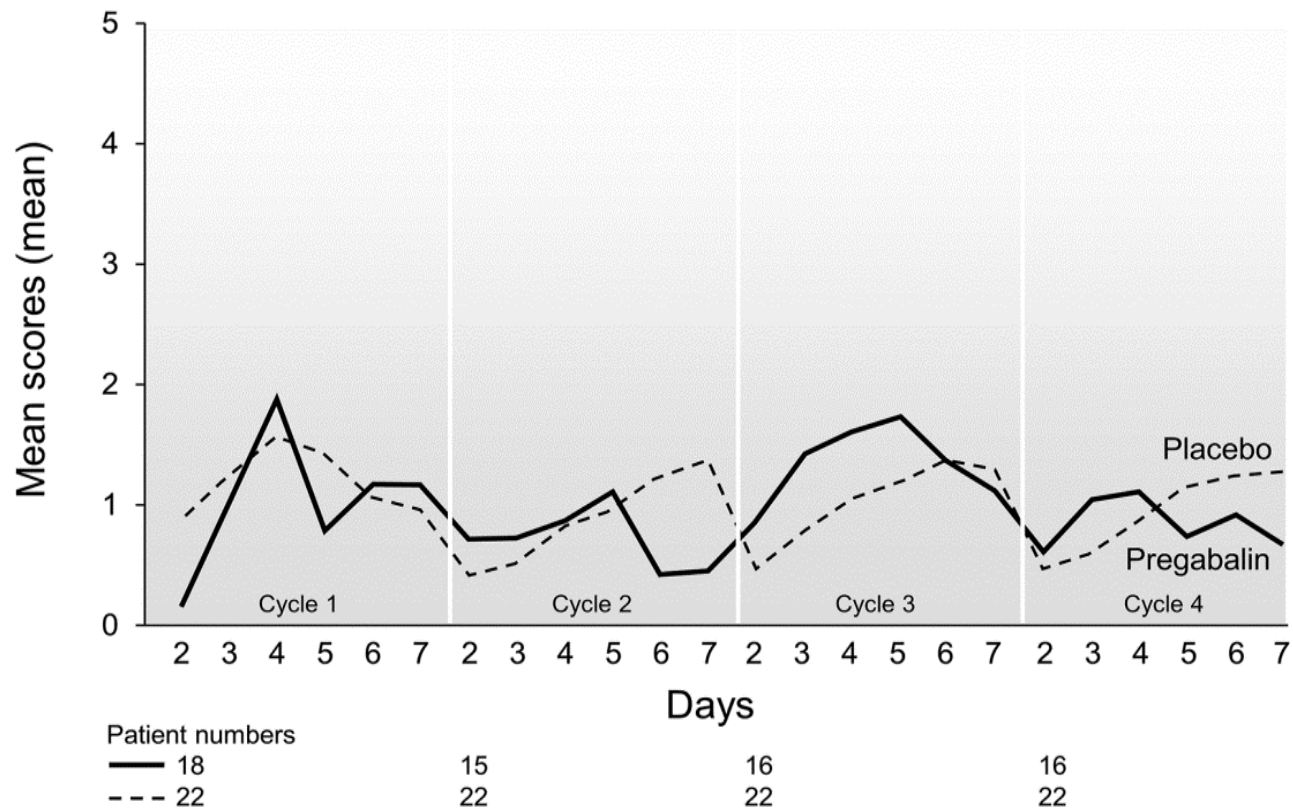
Can Pregabalin Prevent Paclitaxel-Associated Neuropathy?—A Pilot Trial

S. S. Shinde, D. Seisler, G. Soori, P. J. Atherton, D. R. Pachman, J. Lafky, K. J. Ruddy, C L. Loprinzi

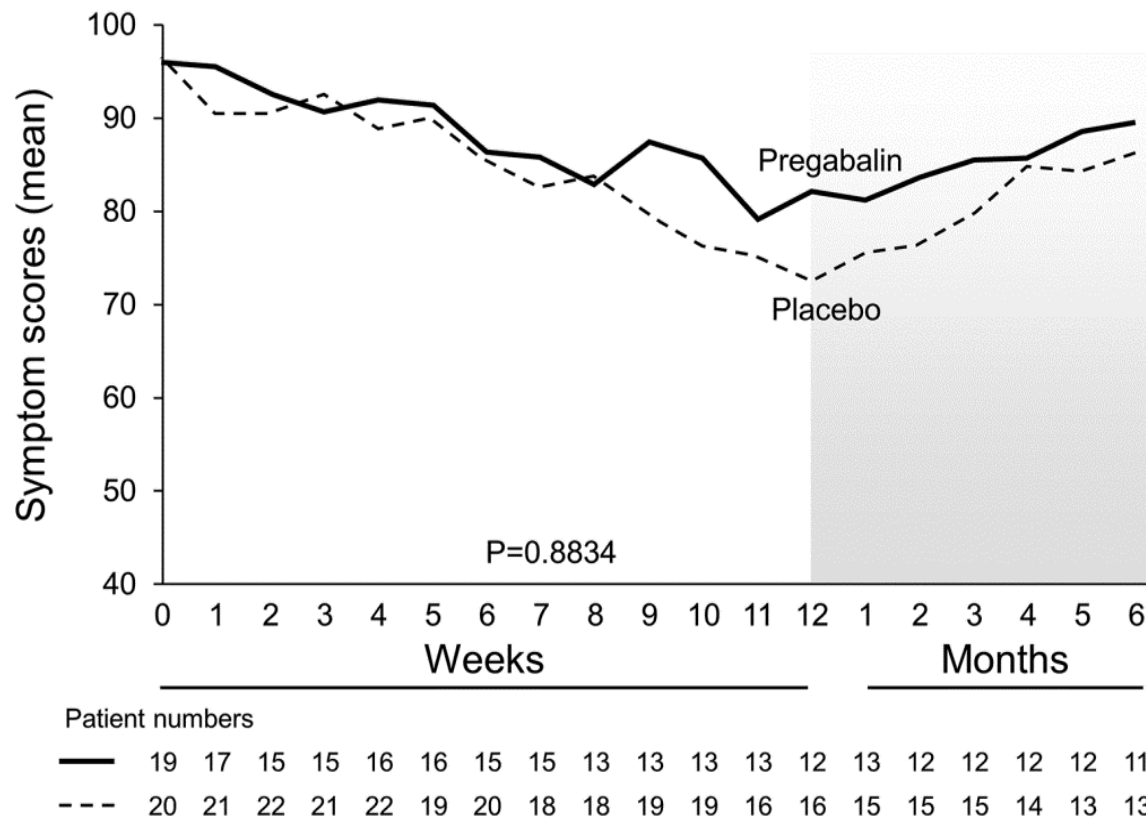
J Support Care in Cancer; on line ahead of publication



Average Aches and Pains in the last 24 Hours



EORTC QLQ – CIPN20: Sensory Subscale



Treatment agents endorsed

- Duloxetine
- Gabapentin
- **Topical BAK**
- Tricyclic antidepressants
- Acetyl-L-carnitine
- Lamotrigine

Treatment agents endorsed

- Duloxetine
- Gabapentin
- Topical BAK
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- Lamotrigine

Scrambler Therapy: A Potentially Effective Treatment Approach for CIPN

Scrambler Therapy

- Patient-specific *cutaneous* electro-stimulation similar to spinal cord stimulation, but non-invasive
- Creates "non pain" information in packets of rapidly varying impulses, given non-invasively using the patients own nerves
- US FDA sanctioned Feb 09



How did I get involved?

- Initial disbelief
- Promising pilot data
- We obtained a machine to test this product, in an investigative manner
- > 200 patients

Scrambler Therapy Results

- **15 trials/reports available**
 - **12 published manuscripts**
 - **2 published abstracts**
 - **1 Mayo study not yet published**

Scrambler Therapy Results

- **4 clinical practice experiences**
- **8 prospective-IRB approved**
- **1 randomized controlled trial**
- **2 randomized pt-blinded PC trials**

How does Scrambler therapy work?



First Trial

- 11 cancer patients with drug resistant visceral pain
 - 3 pancreas
 - 4 colon
 - 4 gastric

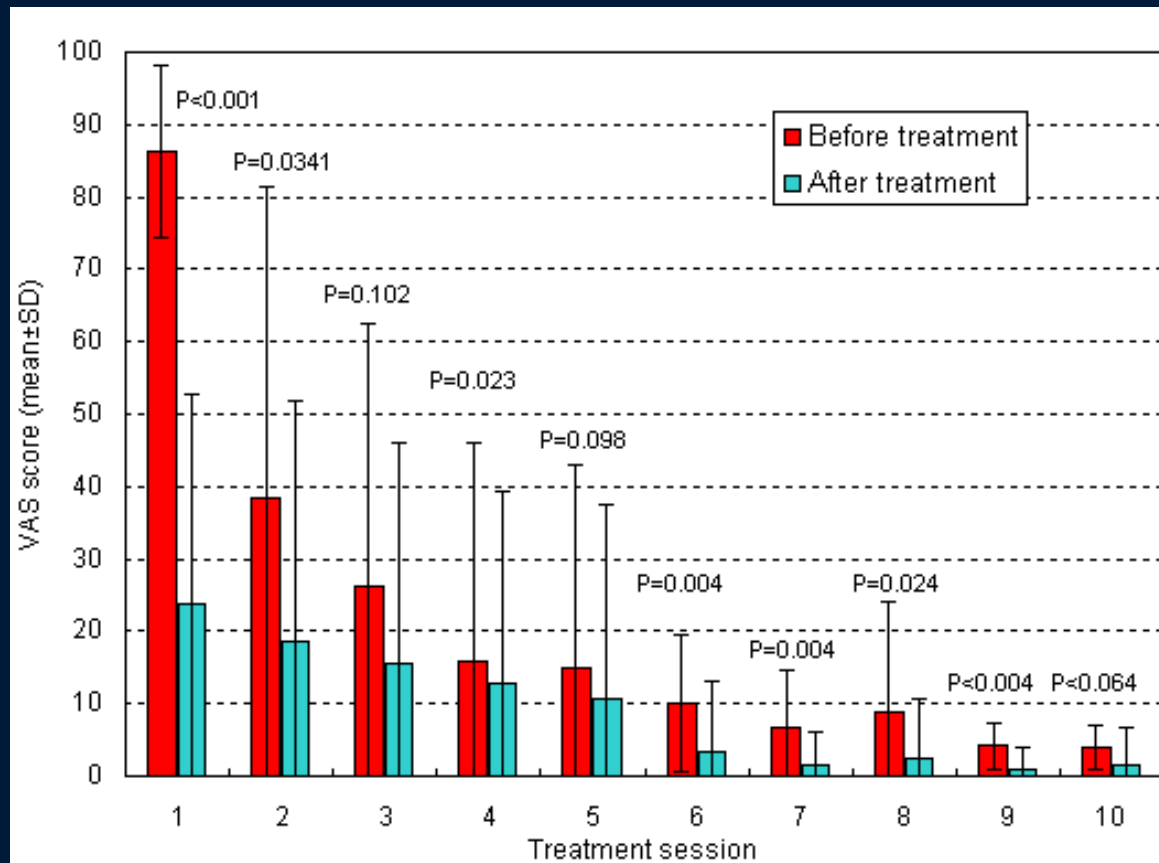
Marineo G: Untreatable pain resulting from abdominal cancer: new hope from biophysics? Jop 4:1-10, 2003

First Trial

- Pain was quickly and markedly reduced
- 9 of 11 *stopped* pain drugs in the first 5 applications
- No side effects
- Pain reductions continued until death
- Recurrent pain, months later, successfully retreated.

Marineo G: Untreatable pain resulting from abdominal cancer: new hope from biophysics? Jop 4:1-10, 2003

First Trial



Marineo G: Untreatable pain resulting from abdominal cancer: new hope from biophysics? Jop 4:1-10, 2003

Second Trial

- 226 patients with neuropathic pain
 - Prospective study, details sketchy
 - Failed back surgery, brachial plexus neuropathy, and others
 - 80% of patients responded with > 50% pain relief,
 - 10% responded with pain relief from 25% to 49%
 - 10% had no response.
 - No toxicities were noted

**Sabato, Marineo G, Gatti A: Calmare therapy.
Minerva Anestesiol 71:479-82, 2005**

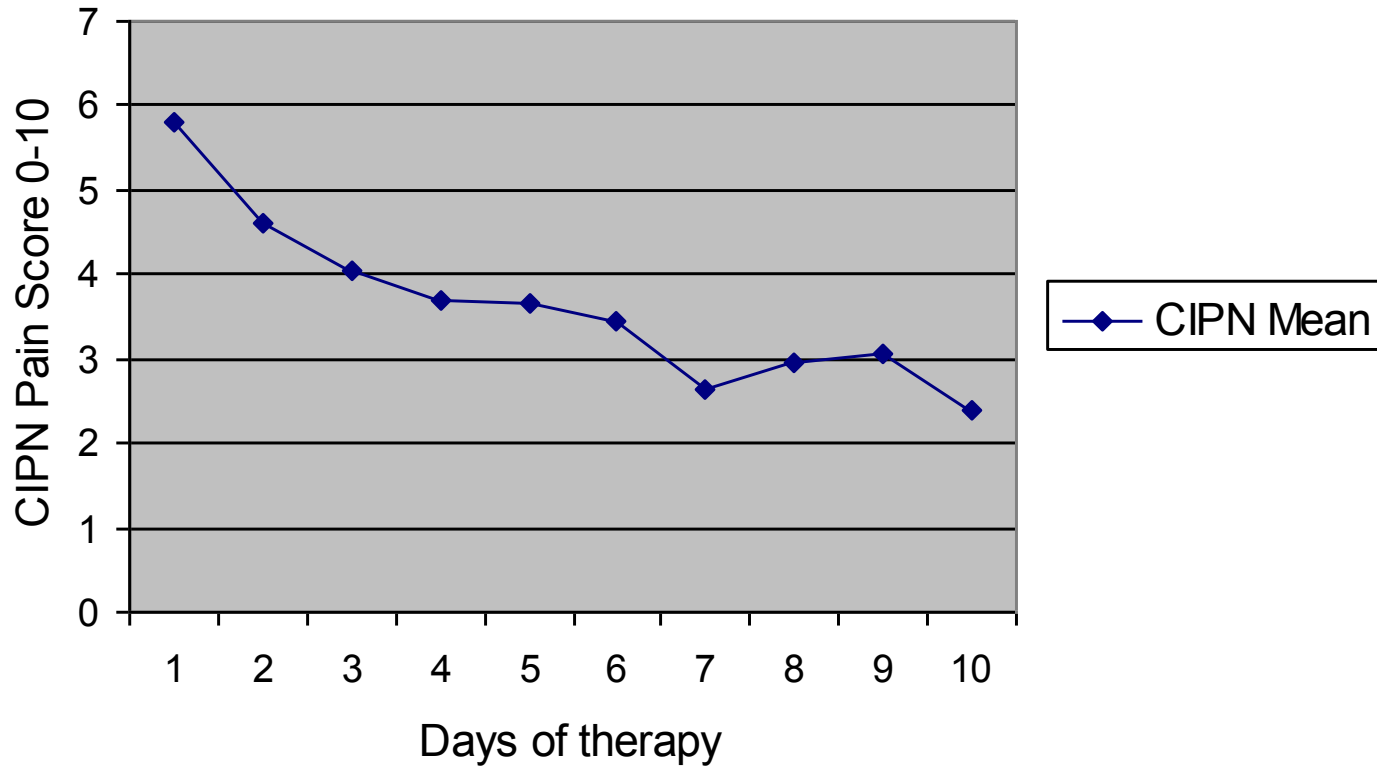
Pilot trial of a Patient-specific Cutaneous Electro-stimulation Device (MC5-A Calmare®) for Chemotherapy Induced Peripheral Neuropathy

**Thomas J. Smith MD, Patrick J. Coyne RN MSN, Patricia
Dodson BSN MA, , Gwendolyn Parker RN MSN, V.
Ramakrishnan, PhD**

Massey Cancer Center of Virginia Commonwealth University

Smith et al, J Pain Symptom Manage 40:883-91, 2010

Third Trial



Unadjusted CIPN "pain now" scores

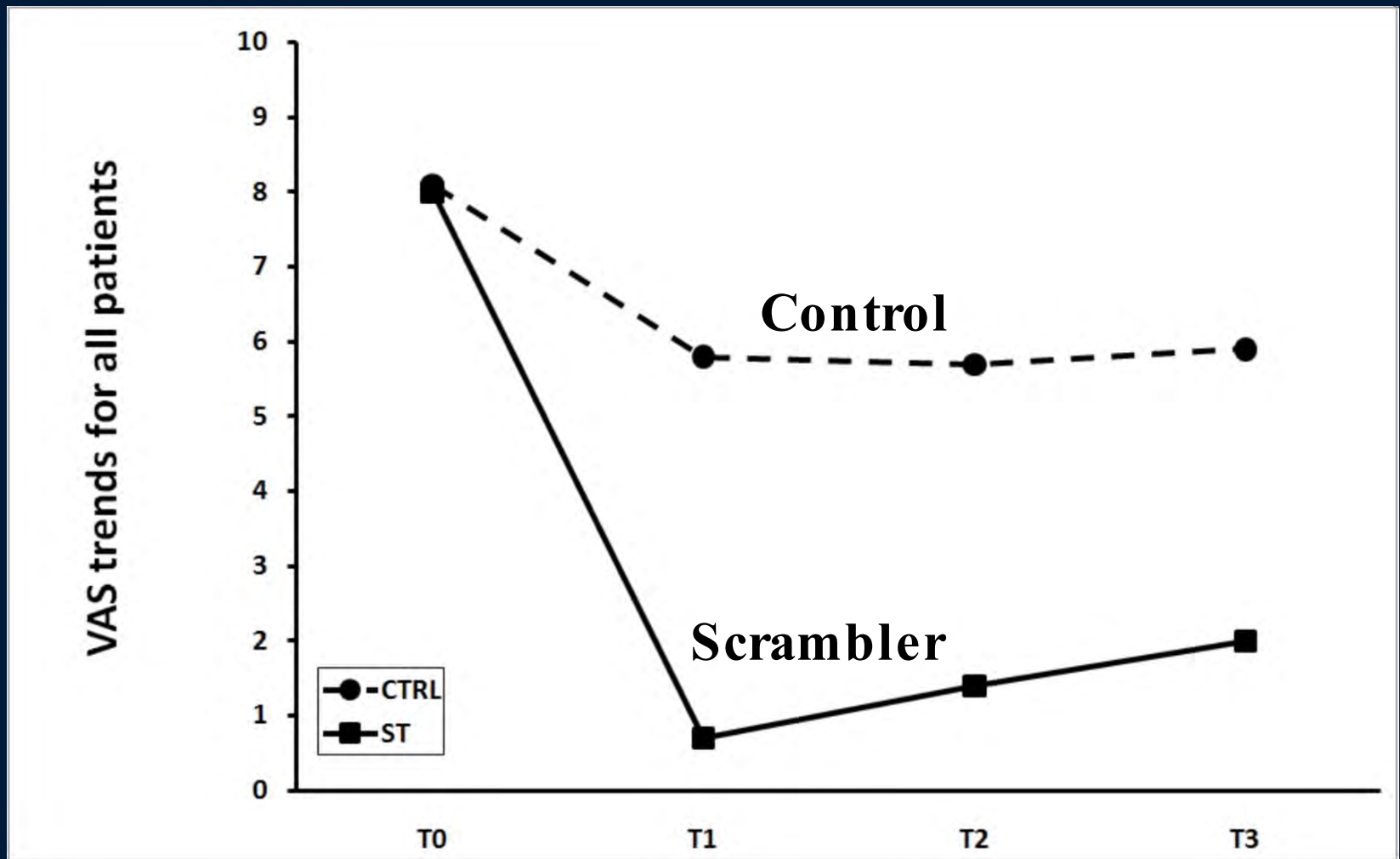
Smith et al, J Pain Symptom Manage 40:883-91, 2010

Fifth Trial

- 52 patients with chronic neuropathic pain
- Randomized to Scrambler vs standard pharmacology guidelines
- Post surgical, post herpetic, or spinal cord stenosis
- Mean pain scores of 8.1, despite medical therapy

Marineo G et al, *J Pain Symptom Manage.* 2012 43(1):87-95

Fifth Trial



Marineo G et al, *J Pain Symptom Manage*. 2012 43(1):87-95

Eleventh Trial/Report

- DB, PC, R trial
- 14 pts with CIPN
- Little experience
- No differences between arms; no placebo effect
- Sham procedure looked viable
- ASCO abstract; no manuscript

Campbell, et al; J Clin Oncol 31, 2013 (suppl; abstr 9635)

Twelfth Trial/Report

Scrambler Therapy for the Treatment of Neuropathy and Pain: An Open Access Trial

Eligibility

- Pts had pain or CIPN symptoms of ≥ 1 month duration with tingling and/or pain $\geq 4/10$ during the prior week

Treatment

- Patients were treated with Scrambler therapy to the affected area(s) for up to 10 daily 30 minute sessions

Initial CIPN Patient Cohort

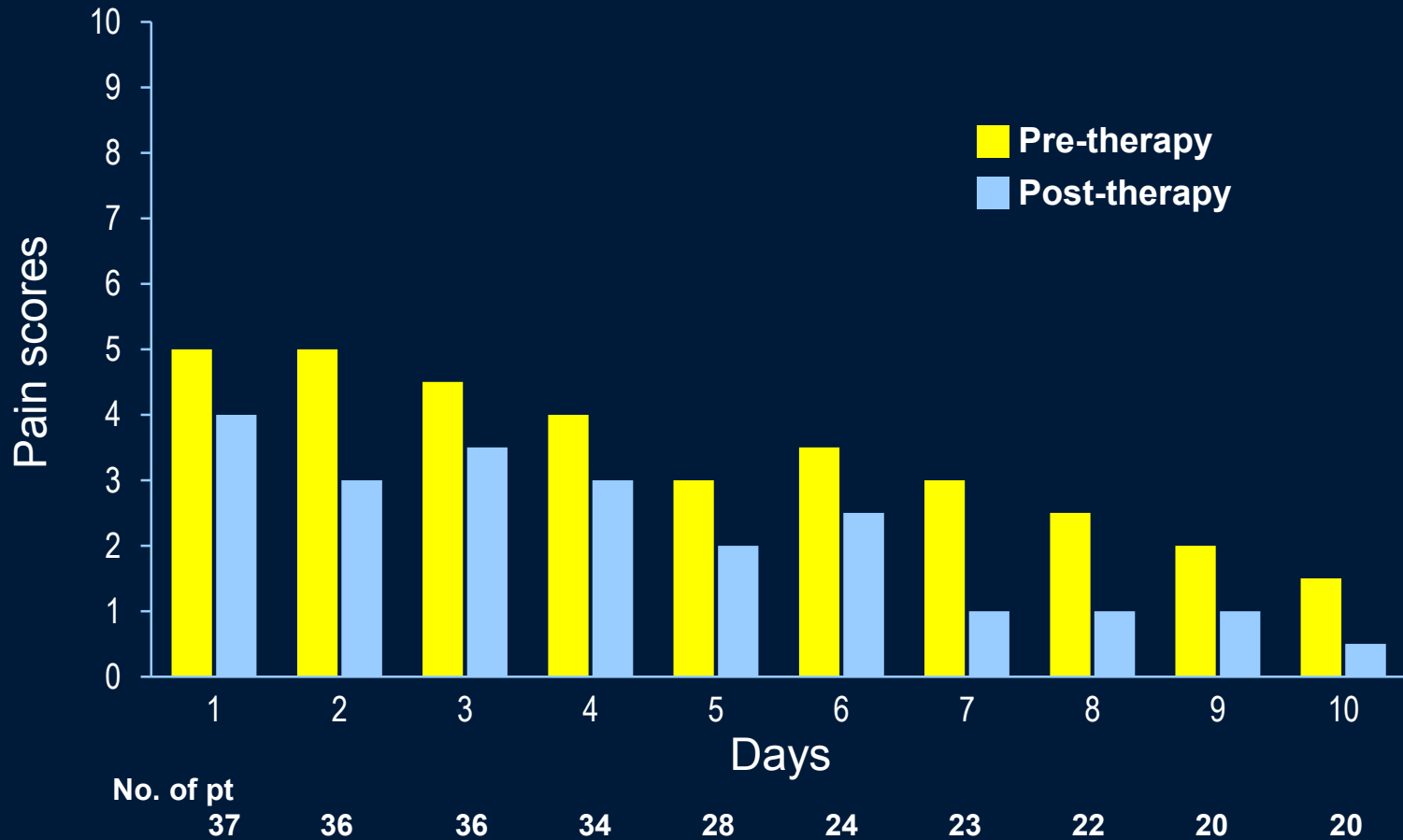
Pachman et al; Sup Care in Cancer, 2014

Patients

- First 37 patients enrolled on study
 - 25 were treated primarily on their lower extremities
 - 12 were treated primarily on their upper extremities.

Pachman et al; Sup Care in Cancer, 2014

Current Pain



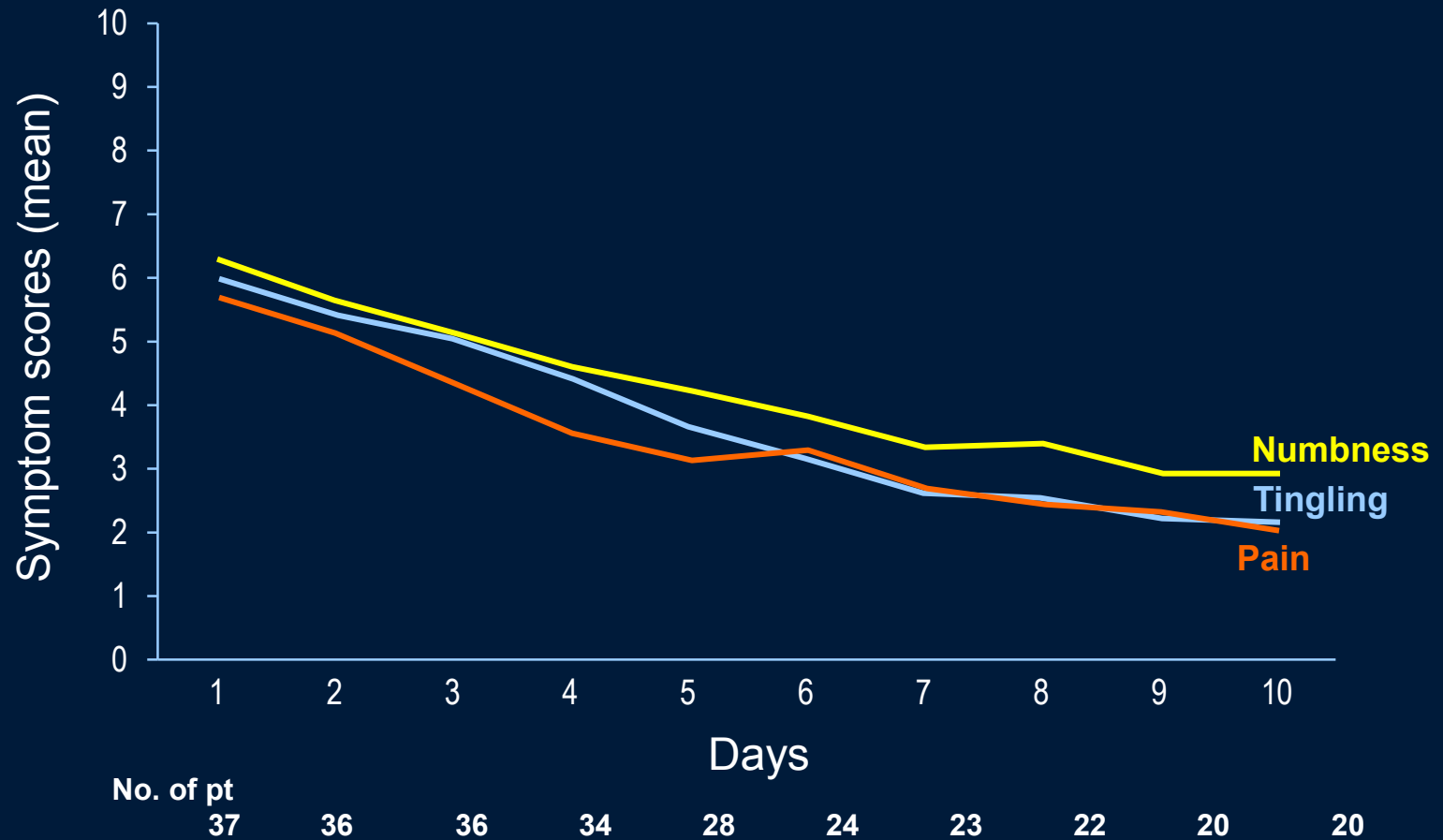
Pachman et al; Sup Care in Cancer, 2014

Effect of Scrambler Therapy on **Average** CIPN Scores

Symptom	Mean baseline score	Mean final score	Average drop in symptom score (%)	P
Pain	5.7	2.6	53	<0.0001
Tingling	6.0	3.3	44	0.0001
Numbness	6.3	4.0	37	0.0002

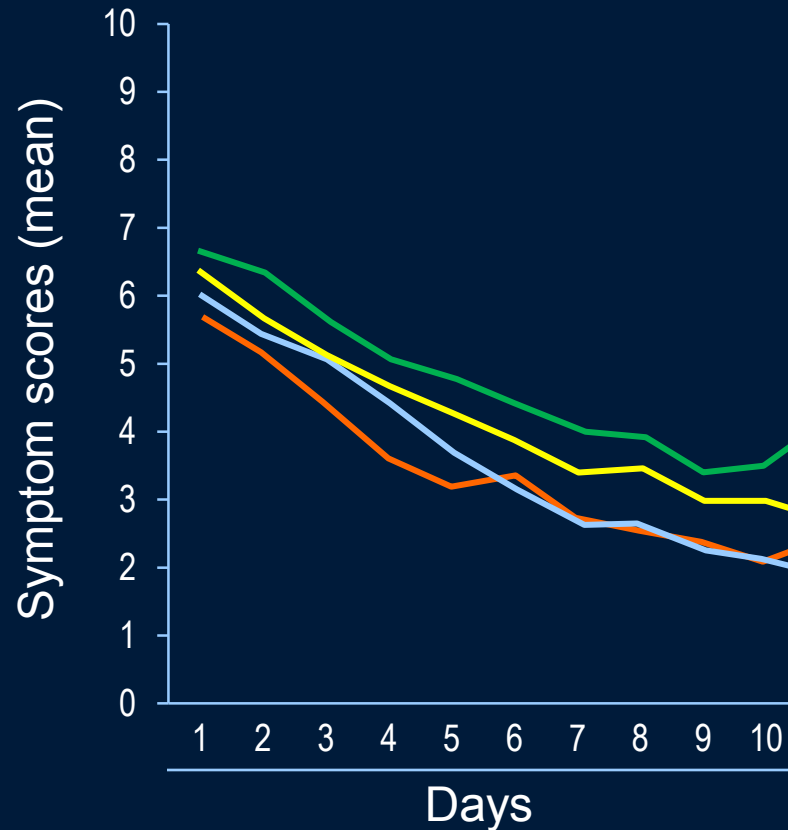
Pachman et al; Sup Care in Cancer, 2014

Mean Symptom Severity in the Past 24 Hours



Pachman et al; Sup Care in Cancer, 2014

Mean Symptom Severity



Patient numbers

37 36 36 34 28 24 23 22 20 20

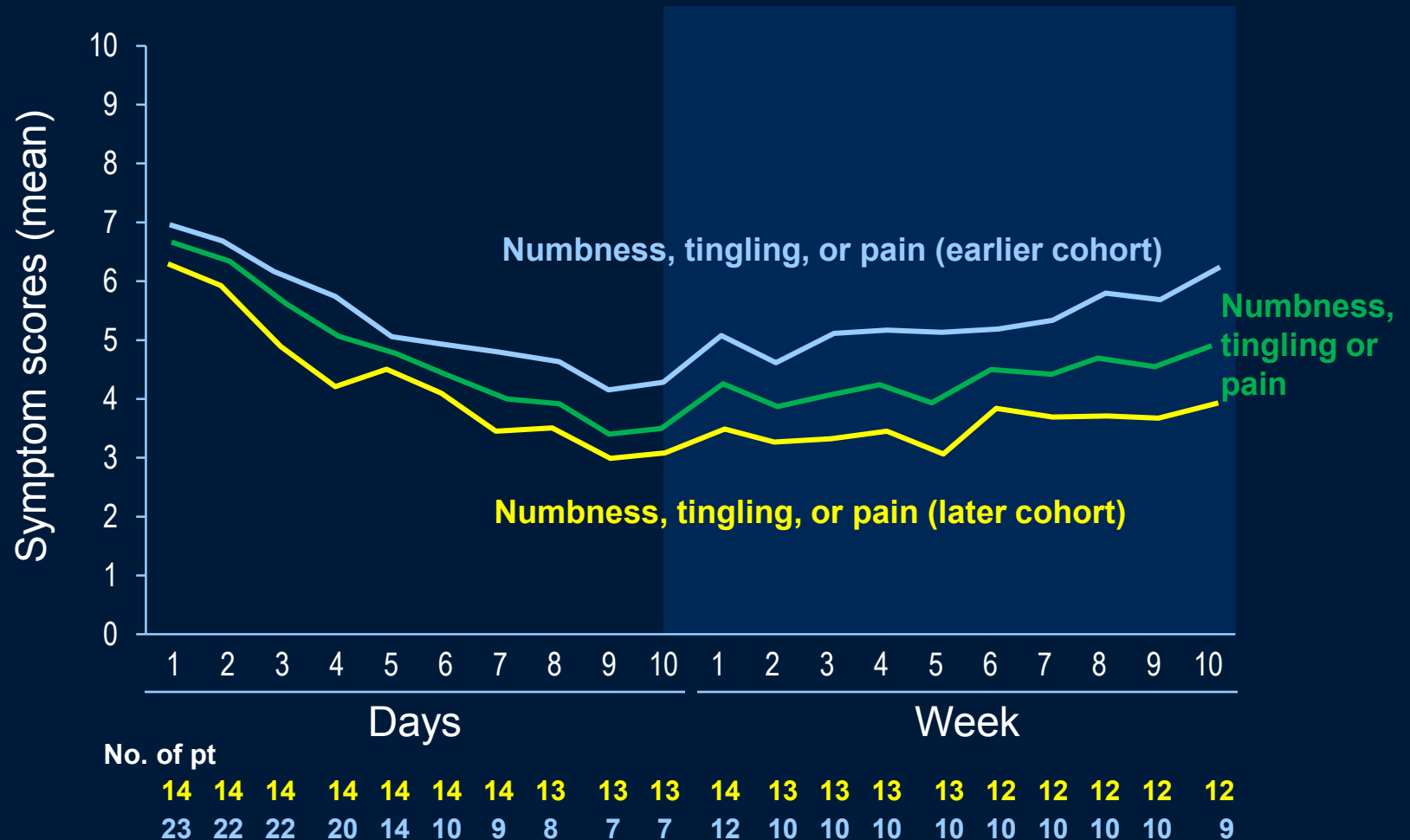
37 36 36 34 28 21 23 22 20 20

37 36 36 34 28 24 23 22 20 20

37 36 36 34 28 24 23 22 20 20

Pachman et al; Sup Care in Cancer, 2014

Average Numbness, Tingling, or Pain



Pachman et al; Sup Care in Cancer, 2014

Average Numbness, Tingling, or Pain by Date Registered

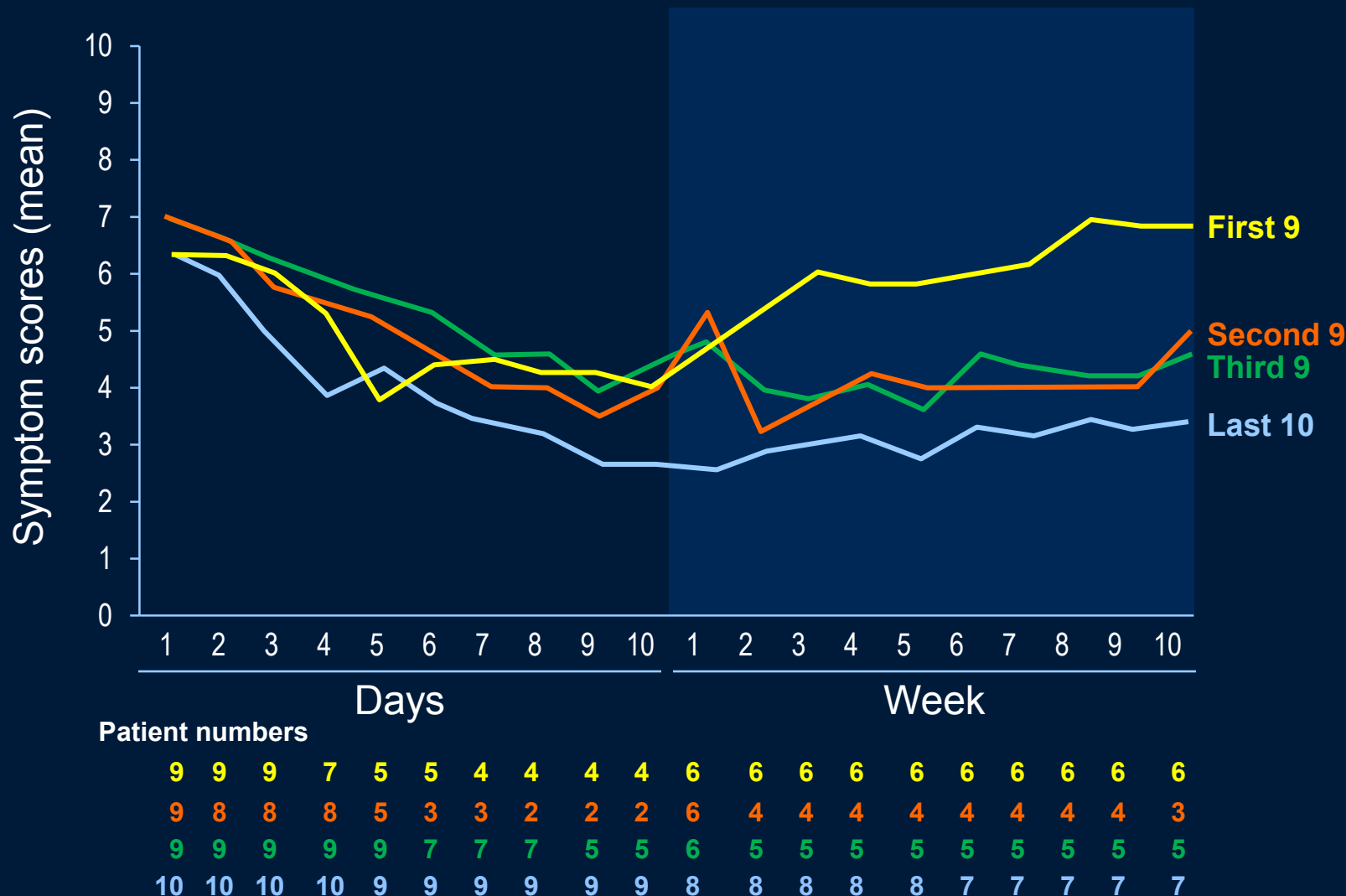


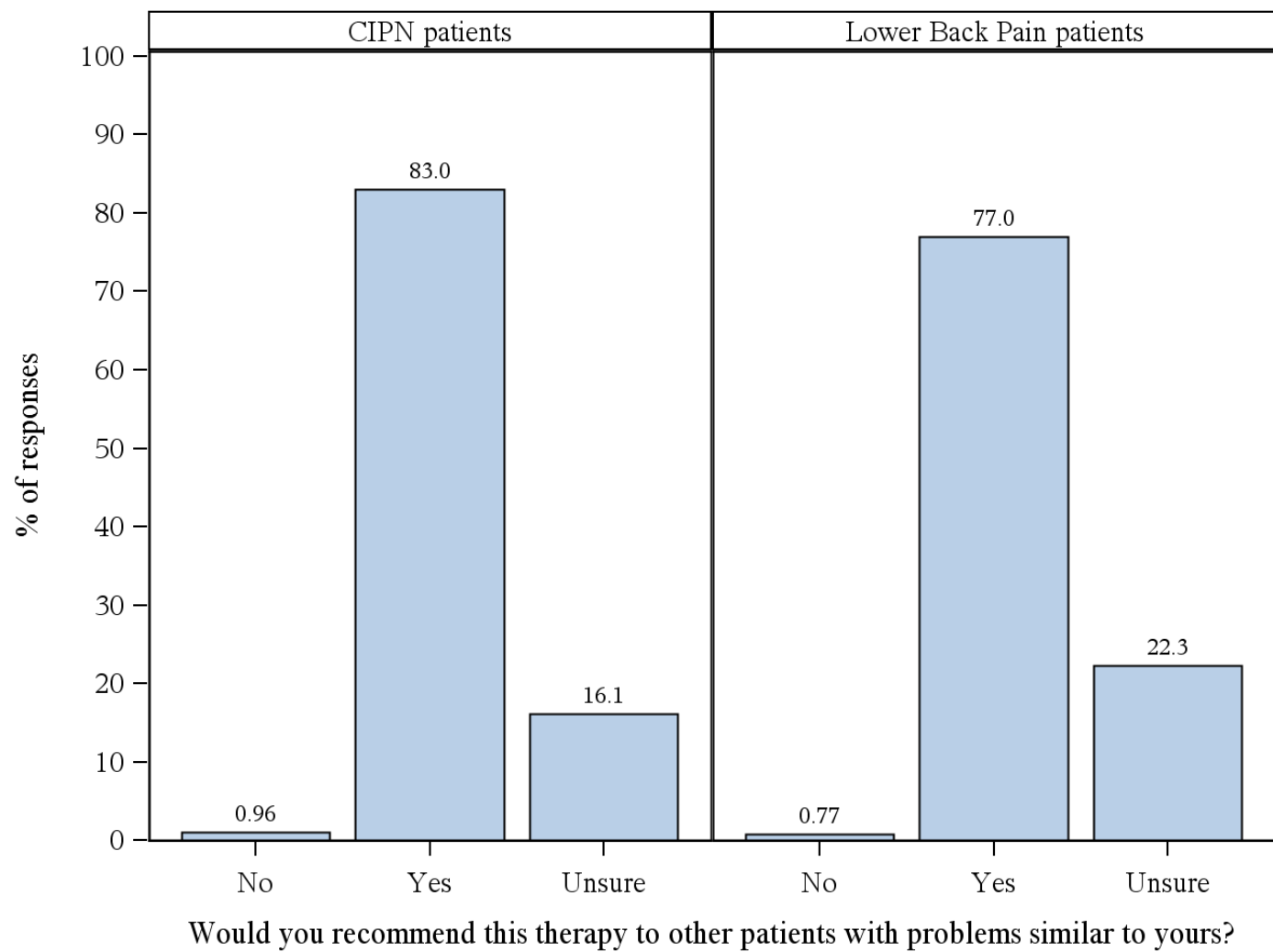
Table of Individual Patient Scores over Treatment Days (Average Pain in the Past 24 Hours) – Lower Extremities

[illegible]

Table of Individual Patient Scores over Treatment Days (Average Pain in the Past 24 Hours) – Upper Extremities

	Treatment Day										
	1	2	3	4	5	6	7	8	9	10	
Study ID	Upper Extremities										Change (%)
26	2	2	1	0	0	3	0	0	0	0	-100%
27	9	6	5	2	1	0	1	1+	1+	1+	-88.9%
28	8	1	0	1	1	1+	1+	1+	1+	1+	-87.5%
29	5	6	4	2	2+	2+	2+	2+	2+	2+	-60.0%
30	8	6	6	5	5	5	5	5	4	4	-50.0%
31	9	6	5	6	5	7	5	5	5	5	-44.4%
32	3	3	3	3	3	2	3	2	2	2	-33.3%
33	9	10	7	7	6	6+	6+	6+	6+	6+	-33.3%
34	3	3	2	2+	2+	2+	2+	2+	2+	2+	-33.3%
35	6	6	3	5	4	4*	4*	4*	4*	4*	-33.3%
36	9	9	8	8+	8+	8+	8+	8+	8+	8+	-11.1%
37	8	8+	8+	8+	8+	8+	8+	8+	8+	8+	0.0%
Average Pain	5.7	5.2	4.5	3.8	3.4	3.5	3.0	2.8	2.8	2.6	-53.8%
(SD)	2.6	2.5	2.6	2.5	2.4	2.4	2.4	2.4	2.4	2.4	(7.4%)

Pachman et al; Sup Care in Cancer, 2014



Fifteenth Trial/Report

- DB, randomized, controlled trial
- 30 pts with LBP
- Significant decreases in:
 - Worst BPI pain and interference scores
 - Pain sensitivity
 - mRNA expression of 17 pain genes

Starkweather et al. Res Nur Health 2015 38(1):29-38

There is 'no proof' that Scrambler works

- All of the reports have weaknesses
- No large placebo-controlled trials-ideally should be 2
- Potential COI
 - Some reports (4) involve inventor
- Multiple prior claims of therapies that have not been able to withstand the test of time/investigation

Why do 'I believe that it works'?

- Independent investigators have replicated findings reported by Marineo
- 2 positive randomized controlled trials
- Multiple positive reports (>700 patients) from multiple investigators
- All reports, save one small abstract, were considered to be positive, by the authors
- I've seen too many anecdotes to believe it doesn't work

Conclusions-ASCO Guidelines

- Duloxetine does work a little bit and is the best demonstrated treatment-**I recommend/use**
- Gabapentin is commonly used for lots of neuropathies, but data are lacking for CIPN-**I do not use, many do**
- Tricyclic antidepressants are used for neuropathies but limited data for CIPN- **I do not use, some do**
- Topical baclofen/amitriptyline/ketamine-**The jury is still out**

Conclusions-Scrambler

There is no proof that Scrambler therapy provides remarkable benefit

- Scientific hat

I believe that Scrambler therapy provides remarkable benefit

- Clinical and scientific hats

Scrambler therapy should be clinically available at Mayo

- Clinical hat



Australia

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ANNUAL MEETING ON
SUPPORTIVE CARE IN CANCER

Adelaide, Australia | 23-25 June, 2016



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Thanks for your
attention!!