

Gabapentinoid use for CIPN: The Good And The Bad

Charles Loprinzi MD

Regis Professor of Breast Cancer Research

cloprinzi@mayo.edu

Potential COI

PledPharma AB re CIPN

I'd like some audience
input regarding
gabapentinoid use...

What was the first report
regarding the use of
gabapentin in clinical
practice?

The first known report:

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

Mitchell PL, et al: Addition of gabapentin to a modified FOLFOX regimen does not reduce oxaliplatin-induced neurotoxicity. *Clinical colorectal cancer* 6:146-51, 2006

Gabapentin use in clinical practice

- First known report regarding the use of gabapentin for chemotherapy-induced neuropathy:¹
 - With the initiation of neuropathy, gabapentin was given at a dose of 100 mg twice per day
 - Disappearance of neuropathy symptoms that continued even with the use of up to 14 total oxaliplatin doses
- Two sequential cohorts of patients who received similar oxaliplatin treatments for metastatic colorectal cancer²
 - 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

There are some limited reports
(Phase II and clinical practice
reviews) of gabapentinoid
efficacy, but remarkably few....

- 2009 manuscript
- Czech Republic
- Pregabalin in 30 children
- Open label trial design
- Pts had received a variety of neurotoxic drugs
- Pain score of at least 4/10

- Mean VAS score decreased by 59% during eight weeks of pregabalin treatment
- 86% of the eval. pts had long-lasting pain relief
- Question: Are unblinded data in children even more suspect to positive reports than might be seen in adults?

- In 2010, a report of 23 pts treated with pregabalin for oxaliplatin-induced neuropathy was published
- This appears to be a clinical practice experience, as opposed to a prospective clinical trial

- Authors felt that 40% of the patients responded to therapy
 - Judged by a neuropathy improvement of 1-2 grades
- Authors also noted that there were quite a few toxicities

- Between 2012 and 2014, five manuscripts written in Japanese, with English language abstracts, pertained to pregabalin therapy for chemotherapy-induced neuropathy
- All published in the same journal
- Same author groups in 2 sets of 2 publications
- I only reviewed the English language abstracts
- Nakashima T, et al.: Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 39:1443-5, 2012
- Nakashima T, et al: Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 39:809-12, 2012
- Nagahara H, et al: Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 40:1181-3, 2013
- Nihei S, et al: Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 40:1189-93, 2013
- Nihei S, et al: Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 41:1387-90, 2014

- First 2 were case reports that noted an improvement in chemotherapy neuropathy in single patients treated with pregabalin, both written by the same group of authors
- In 2013, another report noted that 13 patients, suffering from oxaliplatin-induced sensory neuropathy, were treated with pregabalin
 - It appears that this report is based on a review of clinical records, as opposed to the result of a prospective trial experience
 - The authors of this report felt that 8 of the 13 patients had neuropathy improvements that they attributed to pregabalin

- Another report in 2013, also appeared to be generated from a clinical practice review
- This report evaluated the use of pregabalin in 27 patients with oxaliplatin-induced neuropathy and 28 patients with paclitaxel-induced neuropathy
- They compared these patients to other patients who were treated with drugs other than gabapentinoids.
 - 41% of patients who had oxaliplatin-induced neuropathy and 29% of patients who had paclitaxel-induced neuropathy responded to therapy with pregabalin
 - Defined by a decrease of one grade of neuropathy
 - This was higher than what they observed in patients who received non-pregabalin drugs (10% and 12%, respectively)
 - From this, they concluded that pregabalin was efficacious

- Lastly, Nihei and colleagues described their use of pregabalin as the first line treatment for oxaliplatin-induced neuropathy
- This appears to be a prospective experience
- They felt that pregabalin was helpful in 33% of patients

What about randomized,
placebo-controlled trials?

**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, Nikcevich D, Warner D,
Novotny P, Kutteh L, Wong G

Cancer 110; 2110: 2007

Chemotherapy-induced neuropathy



6 wk

**Gabapentin
2700 mg/day**

Placebo

2 wk

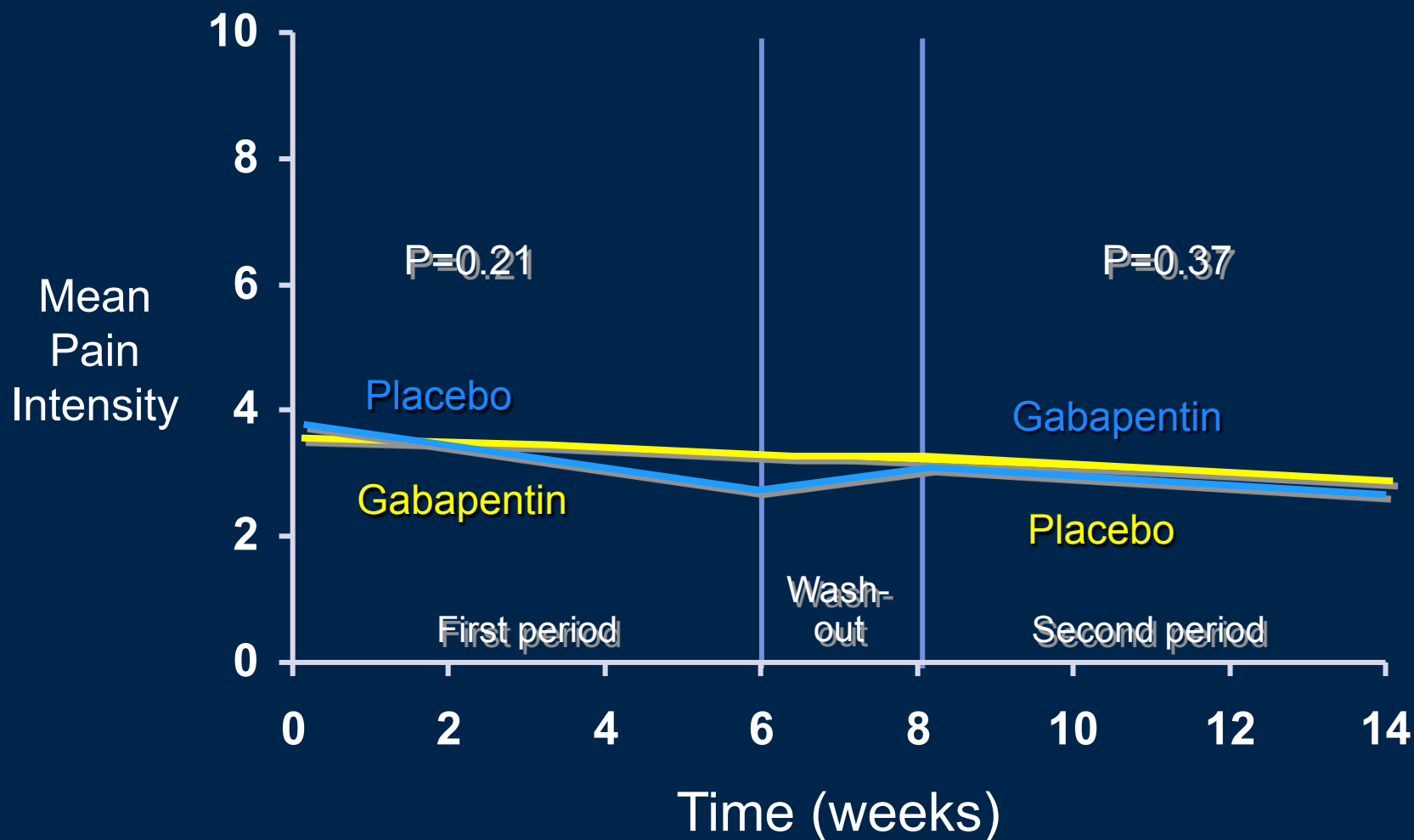
Washout

6 wk

Placebo

**Gabapentin
2700 mg/day**

Mean Pain Intensity



Phase 3 clinical trial of gabapentin for the treatment of CIPN

- Patients with CIPN randomized to receive:
 - Gabapentin 2700 mg/day for 6 weeks followed by placebo for 6 weeks after 2-week washout
 - Placebo followed by gabapentin
- No significant difference between treatment groups on mean pain intensity score

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

More Data

- Enrolled 64 patients
- Patients received flexible pregabalin dosing, from 150-600 mg/day versus placebos

More Data

The trial was terminated early as an interim analysis found that there was not sufficiently positive data to continue the trial

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

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

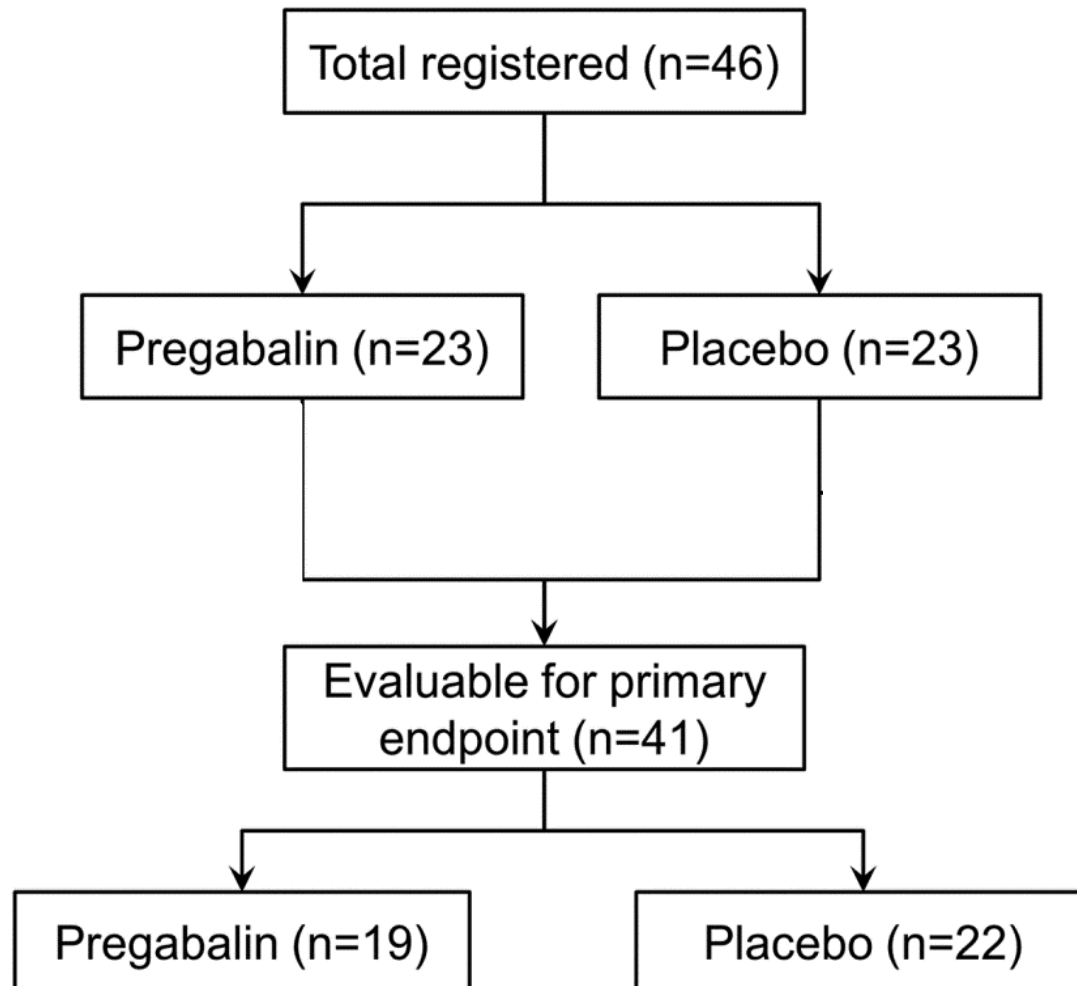
(accessed 4014 dec 25)

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

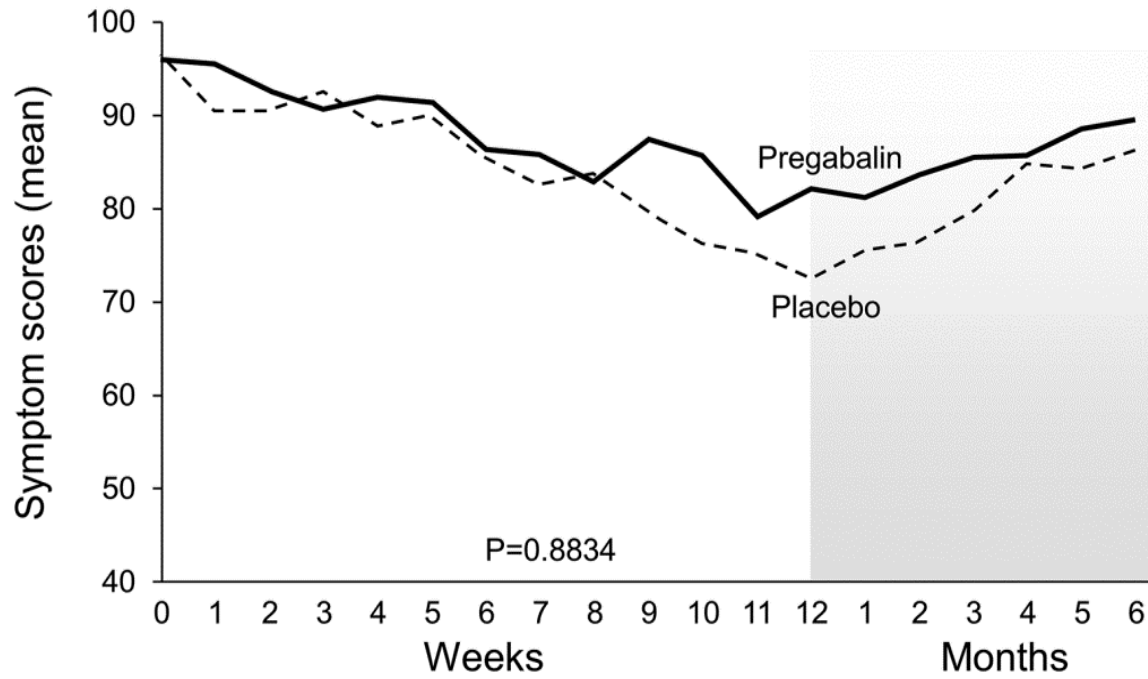
S. S. Shinde, D. Seisler, G. Soori, P. J. Atherton, D. R. Pachman, J. Lafky, K. J. Ruddy, C L. Loprinzi

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Support Care in Cancer 2016; 24: 547-553



EORTC QLQ – CIPN20: Sensory Subscale



Patient numbers

—	19	17	15	15	16	16	15	15	13	13	13	13	12	13	12	12	12	12	11
- - -	20	21	22	21	22	19	20	18	18	19	19	16	16	15	15	15	14	13	13

Large Medical Center Survey: Circa 2015

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%

Conclusions

Why might one use gabapentinoids for CIPN:

- CIPN is a big problem
- Limited other effective agents
- ASCO guidelines tepidly endorse
- Some pts claim benefit
- Such work for other pains/neuropathies
- Provides hope/placebo effect
- Could be used for a limited trial

Why might one choose not to use gabapentinoids for CIPN:

- The bulk of data support that they do not work for CIPN
- Toxicities/cost
- Duloxetine works better
- Withdrawal effects

If used, how to do:

- Pilot period trial
- Discontinue if not effective
- Beware of withdrawal

Personal Conclusions Regarding Gabapentinoid use for CIPN

- I do not think that it works very well
- Toxicity is a problem
- I have not been using it

Thanks for your
attention!!