The Oncologist®

Clinical Trial Results

Pregabalin for the Prevention of Oxaliplatin-Induced Painful Neuropathy: A Randomized, Double-Blind Trial

Daniel Ciampi de Andrade,[a,b] Manoel Jacobsen Teixeira,[a,c] Ricardo Galhardoni,[a,k] Karine S.L. Ferreira,[a,e] Paula Braz Mileno,[a,b] Nathalia Scisci,[a] Alexandra Zandonai,[a] William G.J. Teixeira,[e] Daniel F. Saragiotto,[e] Valquíria Silva,[a] Irina Raicher,[a,b] Rubens Gisbert Cury,[a,e] Ricardo Macarenco,[e] Carlos Otto Heise,[d] Mario Wilson Iervolino Brotto,[d] Alberto Andrade de Mello,[d] Marcelo Zini Megale,[d] Luiz Henrique Curti Dourado,[a] Luciana Mendes Bahia,[a,b] Antonia Lilian Rodrigues,[a] Daniella Parravano,[a] Julia Tizue Fukushima,[e] Jean-Pascal Lefaucheur,[f] Didier Bouhassira,[g] Evandro Sobroza,[e] Rachel P. Riechelmann,[e] Paulo M. Hoff,[e] and PreOx Workgroup (Fernanda Valério da Silva,[a] Thais Chile,[i] Camila S. Dale,[h] Daniela Nebuloni,[e] Luiz Senna,[e] Helena Brentani,[i] Rosana L. Pagano,[j] Ângela M. de Souza[b])

[a]Centro de Dor, Departamento de Neurologia, Universidade de Sao Paulo, Sao Paulo, Brazil; [b]Centro de Dor, Instituto do Cancer do Estado de São Paulo, São Paulo, Brazil; [c]Divisão de Neurocirurgia, Hospital das Clínicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil; [d]Departamento de Neurologia, Universidade de Sao Paulo, Brazil; [e]Instituto do Cancer do Estado de São Paulo, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil; [f]Clinical Neurophysiology Unit, Department of Physiology, Henri Mondor University Hospital, AP-HP, Créteil, France; [g]INSERM U-987, Centre d'Evaluation et de Traitement de la Douleur, Hôpital Ambroise Paré, Boulogne, France; [h]Departamento de Anatomia, Instituto de Ciências Biomedicas, Universidade de Sao Paulo, Brazil; [i]LIM 23, Instituto de Psiquiatria, Universidade de Sao Paulo, Brazil; [j]Laboratory of Neuromodulation and Experimental Pain, Hospital Sírio Libanês, Brazil; [k]Medical School of University of City of São Paulo (UNICID), São Paulo, Brazil

Trial Information

- **ClinicalTrials.gov Identifier**: NCT01450163
- **Sponsor(s)**: Pfizer, the Pain Center Department of Neurology (USP), and Fundação de Amparo a Pesquisa do Estado de Sao Paulo
- **Principal Investigators**: Daniel Ciampi de Andrade
- **IRB Approved**: Yes

Lessons Learned

- Pregabalin is a medication that can decrease neuronal hyperexcitability, relieve neuropathic pain, and reach stable plasma levels after a titration period of only a few days.
- Its use during oxaliplatin infusions was not able to decrease the incidence of chronic, oxalipaltin-related neuropathic pain, compared with placebo.

Abstract

Background. Patients with colorectal cancer (CRC) receiving oxaliplatin (OXA) develop acute and chronic painful oxaliplatin-induced peripheral neuropathy (OXAIPN). Acute and chronic OXA-related neuropathies have different pathophysiological bases, but both lead to a common phenomenon: central sensitization (CS) of nociceptive neuronal networks, leading to increased sensitivity (hyperlgesia, allodynia) in the somatosensory system, the common ground of chronic neuropathic pain. Because CS is related to increased risk of painful OXAIPN, we hypothesized that preemptive use of the anti-hyperalgesic drug pregabaline (known to decrease CS) during OXA infusions would decrease the incidence of chronic OXAIPN.

Methods. Pain-free, chemotherapy-naïve CRC patients receiving at least one cycle of modified-FLOX [5-FU(500 mg/m^2)+leucovorin(20 mg/m^2)/week for] 6 weeks+oxaliplatin(85 mg/m^2) at weeks 1-3-5 every 8 weeks] were randomized (1:1) into the study. Patients received either pregabalin or placebo for 3 days before and 3 days after each OXA infusion and were followed for up to 6 months. Clinical assessments were performed at baseline, at the end of chemotherapy, and after the follow-up period. The main outcome was average pain at the last visit assessed by the visual analogic scale (0–10) item of the Brief Pain Inventory (BPI). Secondary endpoints were presence of neuropathic pain according to the Douleur Neuropathique-4 (DN-4), pain dimensions (short- form McGill Pain Questionnaire [MPQ]), Neuropathic Pain Symptom Inventory (NPSI), and changes in nerve conduction studies (NCS) and side effect profile.

Correspondence: Daniel Ciampi de Andrade, M.D., Ph.D., Instituto de Cancer do Estado de São Paulo, University of São Paulo, rua dr eneas de carvalho aguiar, Sao Paulo 05410002, Brazil. Telephone: +55-11-97280-0027; e-mail: ciampi@usp.br Received April 27, 2017; accepted for publication May 14, 2017; published Online First on June 26, 2017. http://dx.doi.org/10.1634/theoncologist.2017-0235

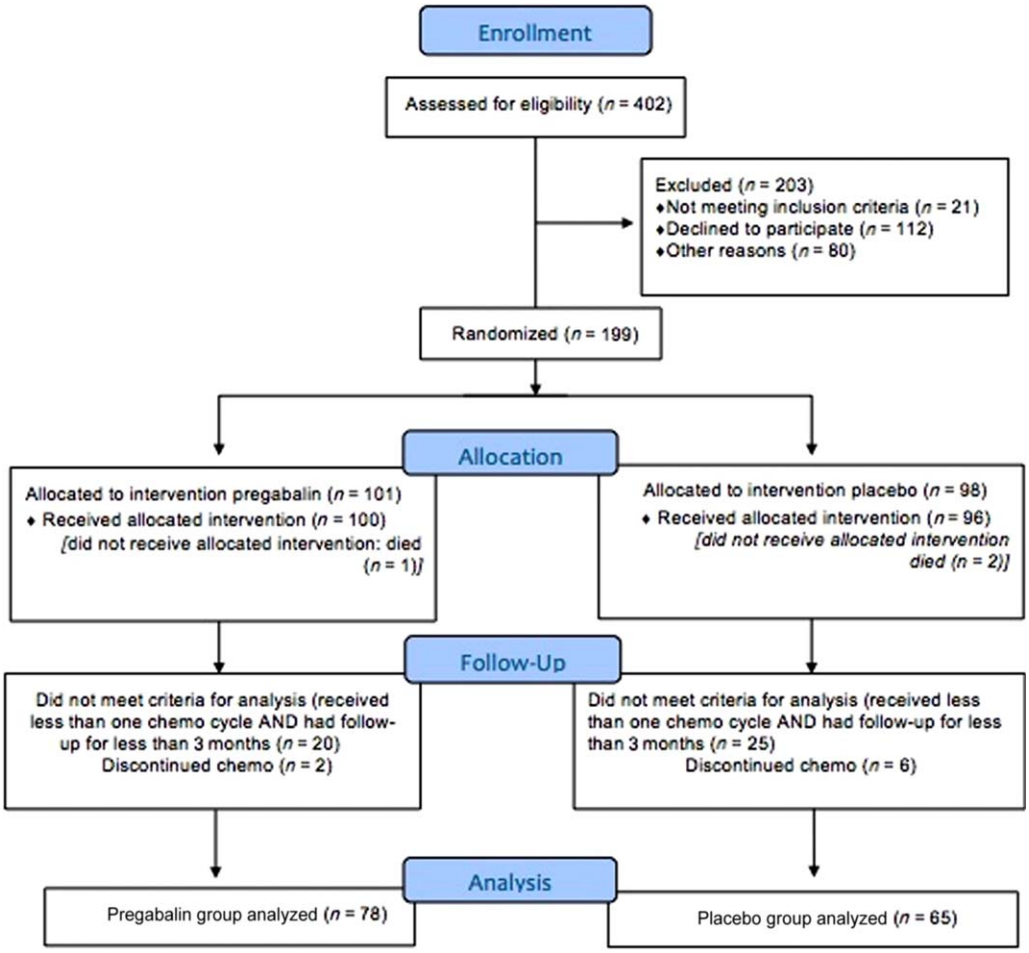

Figure 1. Consolidated Standards of Reporting Trials flowchart of screened and included patients.

Results. One hundred ninety-nine patients (57.0 ± 10.7 years old, 98 female, 101 male) were randomized. Data from 56 patients were not included in the analyses (as they did not receive at least one full cycle of modified FLOX). Data from 78 patients in the pregabalin group and 65 patients in the placebo group were retained for analyses. At the last visit, pain intensity in the pregabalin group was 1.03 (95% confidence interval [CI] = 0.79–1.26), and 0.85 (95% CI = 0.64–1.06) in the placebo group, which did not reach significance. Scores from the BPI, MPQ, DN-4, NPSI, and NCS and side-effect profiles and incidence of death did not differ between groups. Quality of life (QoL) score did not differ between groups (placebo = 76.9 ± 23.1, pregabalin group 79.4 ± 20.6). Mood scores were not significantly different between groups (placebo 9.7 [8.1–11.2]; pregabalin 6.8 [5.6–8.0]).

Conclusion. The preemptive use of pregabalin during OXA infusions was safe, but did not decrease the incidence of chronic pain related to OXAIPN. ***The Oncologist*** 2017;22:1154–e105

Discussion

The intensity of acute OXA-induced neuropathic phenomena may significantly increase the odds of developing chronic long-term neuropathy. The association between intense acute sensory symptoms and greater risk of developing chronic pain has been described in other settings and is probably related to the development of central neuronal plastic changes such as central sensitization after acute injury. Thus, it has been hypothesized that the modulation of neuronal firing related to acute pain by the use of pregabalin would decrease the likelihood of the development of neuropathic pain.

Based on this rationale, we tested the hypothesis that the preemptive use of pregabalin a few days before and after OXA would have a preventive effect on chronic OXAIPN and its most troublesome symptom: neuropathic pain. However, we found no effects of pregabalin in this scenario. It failed to impact both the acute and chronic pains seen after OXA. Pain-related effects, interference, and QoL were not influenced by the active treatment.

Trial Information	
Disease	CRC
Stage of Disease/Treatment	Prevention
Prior Therapy	None
Type of study - 1	Phase III
Type of study - 2	Randomized

Primary Endpoint	Pain intensity
Secondary Endpoint	Safety
Secondary Endpoint	QoL
Secondary Endpoint	Cummulative mFLOX dose
Secondary Endpoint	NPSI score
Secondary Endpoint	Presence of neuropathic pain
Secondary Endpoint	CTC-neuropathy

Additional Details of Endpoints or Study Design

Pain characterization: Pain intensity and interference with daily activities were assessed by the short-form of the Brief Pain Inventory (BPI), which evaluates current pain intensity as well as the worst, least, and average (study's main outcome) pain intensity (11-point scale) in the previous 24 hours. The BPI also assesses pain interference with daily activities (general activities, mood, walking, work, relationships with others, sleep, and enjoyment of life) in an 11-point scale from 0 (no pain/no interference) to 10 (as severe as possible) [28]. The McGill Pain Questionnaire (MPQ)-short form assesses different dimensions of pain (sensory, affective, and evaluative) [29, 30]. Assessments took place 1 week after each OXA infusion at planned visits and during the follow-up period by research nurses not implicated in OXA administration. The presence of neuropathic pain characteristics was assessed by the Douleur Neuropathique-4 (0–10, positive $\geq$4) [31]. Neuropathic Pain Symptom Inventory (0–100) was used for neuropathic pain profiling [32, 33].

Oxaliplatin-Related Neuropathy: The presence of neuropathy was assessed by the reduced version of the total neuropathy score (rTNS) [34] at baseline and at the last visit by blinded neurophysiologists with no other role in the study. The severity of oxaliplatin-induced neuropathy was assessed by the NCI-CTCv3 [34–36].

Concomitant Analgesic Medication Use: The number of psychotropic analgesics used during the trial was quantified in each visit by the BPI. The use of alpha-2-delta (pregabalin and gabapentin) ligands outside the protocol was not allowed during the study.

Quality of Life and Patient Report Outcomes: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core (EORTC-QLQ-C30v3)-items 29/30 were used to evaluate general health and quality of life (QoL). Depression and anxiety were assessed by the Hospital Anxiety and Depression Scale (HADS) [37], which provides anxiety (0–21) and depression (0–21) scores.

Safety: Safety was assessed by the presence and severity of adverse effects (AEs), discontinuation and death. CTCAE term (AE description) and grades were recorded according to the NCI-CTCAE-v3.0 [35].

Statistical Methods: Descriptive data analysis presented categorical variables as observed counts, and continuous variables as mean/median with the corresponding standard errors/range. The exploratory analysis evaluated distributions, frequencies, and percentages for each of the numeric and categorical variables. Categorical variables were evaluated for near-zero variation [38]. Extensive graphical displays were used for both univariate analysis and bivariate associations, accompanied by tests such as the maximal information coefficient [39] and non-negative matrix factorization algorithms [18] for numeric variables. Missing data were explored using a combination of graphical displays involving univariate, bivariate, and multivariate methods. Imputation was performed using a k-nearest neighbor's algorithm ($n = 5$) [40]. Balance at baseline was evaluated through one-way analysis of variance and chi-square tests. These tests were conducted with both the originally randomized sample as well as with those meeting the criteria for inclusion in the final analysis, based on time in the study and minimum time providing outcomes data. After balance evaluation, the modeling strategy employed a series of generalized estimating equation models to evaluate the association between all previously reported outcomes and the intervention versus placebo, accounting for all intermediate follow-up measurements. Of importance, confounding adjustment was applied to our analyses to account for bias resulting from imbalances generated through dropout rates and exclusion criteria.

Results were reported as predicted means for numeric outcomes (significance was present when 95% CI values from each variable did not intersect between groups) and odds ratios for Boolean (yes/no) outcomes with 95% CI. Per protocol, our main results concerned participants who provided outcome data beyond visit eight (i.e., patients who receive at least 2 months of chemotherapy and were followed for at least 3 months, thus staying in the protocol for at least 5 months). However, the analyses also followed an intention-to-treat protocol by performing a sensitivity analysis where all subjects were included regardless of their follow-up time or therapy. A single post-hoc analysis was reported as per our protocol, stratifying outcomes by the presence of metastasis at baseline. All analyses were performed using the R-statistical language. A sample of 154 patients randomly assigned to the treatment or placebo group (77 for each arm) was required for 90% power and type-I error = 0.05. Taking into account the prevalence of acute OXAIPN and 30% losses due to deaths/dropouts during the follow-up, we estimated 100 participants per group would be appropriate.

Investigator's Analysis	Level of activity did not meet planned endpoint

Drug Information for Phase III Pregabalin

Drug 1	
Generic/Working name	Pregabalin
Trade name	Lyrica
Company name	Pfizer
Drug type	Other
Drug class	Other
Dose	150–600 mg p.o. q.d. milligrams (mg) per flat dose
Route	Oral (p.o.)

Schedule of administration

This was a double-blind, placebo-controlled randomized trial. Patients referred to our institution's outpatient clinic were screened for participation and were randomized in blocks of twenty to receive either placebo or pregabalin (1:1). Oral medication (pregabalin or placebo) was taken in an outpatient setting intermittently in flexible daily doses of 150–600 mg in a time period extending from 3 days before to 3 days after each OXA infusion (i.e., weeks 1-3-5 in each of the three cycles). During the 4 days preceding the very first infusion of OXA in the study, the dose of pregabalin or placebo was progressively titrated from 75 mg b.i.d. up to 300 mg b.i.d. Titration was monitored by programmed phone calls from study nurses blinded to the treatment arm, who coached patients to take medications and adjust the daily dose of medication according to each individual's tolerance and side effects profile, according to a standardized protocol. Thus, patients had medication titrated up to their highest tolerable dosage before the first Oxa infusion (150 mg increase/day), and from this point onward, this individualized dosage was used in a fixed-dose regimen (starting at the top dose from beginning) 3 days before and 3 days after each of the following Oxa infusions throughout the study. Patients were considered noncompliant to the protocol when presenting more than three absences in protocol visits or in case of failure to take more than 50% of the expected study medication dose before more than two treatment infusions of OXA. Compliance was assessed by counting empty blisters. Allocation concealment was assured by the use of opaque envelopes labeled with a code designating the study protocol number of each participant and the study group.

Drug Information For Phase III Placebo

Drug 1	
Generic/Working name	Placebo
Trade name	Placebo
Drug type	Other
Drug class	Other
Dose	150–600 milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of administration	
(a) Chemo regimen: patients were scheduled to receive modified-FLOX (5-FU bolus 500 mg/m^2 + bolus of leucovorin 200 mg/m^2/week for 6 weeks + OXA 85 mg/m^2 in 2 hour-infusions at weeks 1–3-5 every 8 weeks)	
(b) Intervention: pregabalin: daily, 3 days before and 3 days after OXA infusion; placebo provided in a blister pack identical to that for the pregabalin in the same dose regimen	
Drug 2	
Generic/Working name	Placebo
Trade name	Placebo
Company name	
Drug type	Other
Drug class	Other
Dose	150 milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of administration	Similar to pregabalin

Patient Characteristics for Phase III Pregabalin

Number of patients, male	99
Number of patients, female	100
Stage	
Eligible patients were chemotherapy-naïve adults with histologically confirmed CRC (stage III/IV) with a Karnofsky Performance Status $\geq$50, scheduled to receive at least one complete cycle (e.g., three oxapliplatin infusions) of modified-FLOX. Exclusion criteria were known central nervous system (CNS) metastasis, uncontrolled concurrent systemic illness, symptoms of peripheral neuropathy (NCI-CTCAE-v3.0-grade $\geq$1), presence of possible neuropathic pain (Douleur Neuropathique questionnaire $\geq$4), or positive plasma ß-hCG. The protocol was approved by our institution's Ethics Review Board (007/11) and registered as NCT0145016. All patients gave written informed consent to participate in the study protocol.	
Of 199 subjects undergoing randomization, 143 were included in analyses (Fig. 1). Additional information on the balance between arms for the entire patient sample is available in supplemental online Table 1. 90.5% of patients in the pregabalin arm and 91.3% of patients in the placebo arm received at least three complete cycles of modified-FLOX (9-OXA infusions).	
Fifty-six patients were not included in the analyses (pregabalin group: one died before chemo, 20 received less than one chemo cycle and had follow-up for less than 3 months, two discontinued chemo; placebo group: two died before chemo started, 25 received less than one chemo cycle and had follow-up for less than 3 months, six discontinued chemo).	
Age	Median (range): 57.13 $\pm$ 10.51
Number of prior systemic therapies	Median (range): none
Cancer types or histologic subtypes	CRC: 199

Primary Assessment Method for Phase III Pregabalin	
Assessment	
Number of patients screened	402
Number of patients enrolled	199
Number of patients evaluable for toxicity	199
Number of patients evaluated for efficacy	143
Evaluation method	Clinical (questionnaire and scales)
(Median) duration assessments response duration	12 months
(Median) duration assessments duration of treatment	6 months

Adverse Events: Phase III Pregabalin							
	All Dose Levels, All Cycles						
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Peripheral sensory neuropathy	86%	8%	6%	0%	0%	0%	14%

Abbreviations: NC/NA, no change from baseline/no adverse event.
Safety was assessed by the presence and severity of AEs, discontinuation, and death. CTCAE term (AE description) and grades were recorded according to the NCI-CTCAE-v3.0.(17)
At the last visit, AEs were present in 31% (CTC-grade 1 = 54%) of patients in the pregabalin arm and in 33% of patients (CTC-grade 1 = 50%) in the placebo arm. Twenty-six patients died in the pregabalin arm and 25 patients died in the placebo arm during the study, none related to the trial.

Assessment, Analysis, and Discussion	
Completion	Study completed
Pharmacokinetics/Pharmacodynamics	Not collected
Investigator's Assessment	Level of activity did not meet planned endpoint

The intensity of acute OXA-induced neuropathic phenomena may significantly increase the odds of developing chronic long-term neuropathy [1, 2]. The association between intense acute sensory symptoms and greater risk of developing chronic pain has been described in other settings [3, 4] and is probably related to the development of central neuronal plastic changes such as central sensitization after acute injury. Central sensitization occurs in central relay centers, such as the spinal cord, and comprises a series of neuronal processes leading to sensory gain in the nervous system [5]. In fact, it has been shown that OXA triggers activation of glutamate-NMDA receptors in the spinal cord, a major step in central sensitization to painful stimuli [6]. Thus, it has been hypothesized that the modulation of the neuronal firing related to acute pain by the use of pregabalin would decrease the likelihood of the development of neuropathic pain. This strategy has been tested in several models of postoperative pain, in which gabapentinoids were administered perioperatively with the aim of decreasing the incidence of long-term chronic pain, yielding promising results [7]. Also, it has been shown that a single 300-mg dose of oral pregabalin was sufficient to reach significant concentrations in the cerebral spinal fluid [8], and the use of gabapentinoids before and a few days after surgery not only significantly decreased perioperative pain [9] but also seemed to reduce chronic post-surgical pain.

Based on this rationale, we tested the hypothesis that the preemptive use of pregabalin a few days before and after OXA would have a preventive effect on chronic OXAIPN and its most troublesome symptom: neuropathic pain. However, we found no effects of pregabalin in this scenario. It failed to impact both the acute and chronic pains seen after OXA. Pain-related effects, interference, and quality of life were not influenced by the active treatment.

Previous studies have tried to prevent [10, 11] or treat [12] OXA-induced neuropathy with limited or no success. While some studies have tested a prophylactic approach to OXA-induced neuropathy by administering drugs before chemotherapy was started [10, 11, 13–15], others have focused on patients already with OXAIPN [12, 16, 17] and already presenting with neuropathic symptoms [18], thus performing a formal treatment trial rather than a preemptive or prophylactic approach. The bulk of evidence is negative for both scenarios [12, 14, 19, 20], with rare exceptions [17, 21]. Importantly, the large majority of studies have not used validated pain measurement tools [10, 11, 13, 14, 16, 19, 22, 23], while most have used the common terminology criteria (CTC) adverse events grading system as the primary outcome measurement. While this choice is sound and supported by robust evidence [24], it must be kept in mind that most patients with OXAIPN have small-fiber-predominant polyneuropathy [1], which has as its

main symptom neuropathic pain. However, pain itself (i.e., visual analog scale (VAS), BPI) or neuropathic pain symptoms (i.e., NPSI) have rarely been used as a primary outcome in studies on OXAIPN, and only a few have used validated pain scales or questionnaires at all [12, 20, 21, 25]. Also, neuropathic symptoms have only rarely been evaluated [17, 26]. In fact, "pain" is not mentioned in the CTC grading system for "neuropathy", which is centered on the functional impairment due to paresthesia. It is also noteworthy that no larger trial published so far used formal neuropathic pain criteria or grading system [27] among its endpoints, or one of the many published screening tools for neuropathic pain.

Even though the results of our study are in line with the previous literature, the study has limitations. For instance, the incidence of chronic neuropathic pain was only mild in our sample, maybe due to the inclusion of patients with metastatic disease, who may receive fewer cycles of Oxa. The current management of acute OXA-induced dysesthesias by reduction of OXA dosage in subsequent chemotherapy sessions may have also played a role in the reduction of chronic OXAINP in our sample. Also, the placebo group receive significantly more medication than the pregabalin arm. However, the net difference between groups was equivalent to approximately one pill of medication (75 mg). Because the average participant took 5 to 6 pills daily and all participants were pregabalin-naû£ve, we believe this may not have played a major role in our results.

In conclusion, the use of pregabalin failed to decrease acute or chronic OXA-related pain despite being safe and relatively well tolerated.

Acknowledgments

The authors thank the patients, who have endured the clinical and neurophysiological assessments during this trial in the hope that a more reliable symptomatic control could be achieved for those affected by OXAIPN and neuropathic pain. This research was partially funded by an investigator-initiated research grant from Pfizer (WS55072), the Pain Center Department of Neurology (USP), and Fundação de Amparo a Pesquisa do Estado de Sao Paulo.

Disclosures

Didier Bouhassira: Pfizer, Grunenthal, TEVA (C/A); **Karine S.L. Ferreira:** Johnson & Johnson (E); The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Attal N, Bouhassira D, Gautron M et al. Thermal hyperalgesia as a marker of oxaliplatin neurotoxicity: A prospective quantified sensory assessment study. Pain 2009;144:245–252.

2. Ventzel L, Jensen AB, Jensen AR et al. Chemotherapy-induced pain and neuropathy: A prospective study in patients treated with adjuvant oxaliplatin or docetaxel. Pain 2016;157:560–568.

3. Nikolajsen L, Ilkjaer S, Krøner K et al. The influence of preamputation pain on postamputation stump and phantom pain. Pain 1997;72:393–405.

4. Zeilig G, Enosh S, Rubin-Asher D et al. The nature and course of sensory changes following spinal cord injury: Predictive properties and implications on the mechanism of central pain. Brain 2012;135:418–430.

5. Hansen N, Obermann M, Uçeyler N et al. [Clinical application of pain-related evoked potentials]. Schmerz 2012;26:8–15.

6. Mihara Y, Egashira N, Sada H et al. Involvement of spinal NR2B-containing NMDA receptors in oxaliplatin-induced mechanical allodynia in rats. Mol Pain 2011;7:8.

7. Schmidt PC, Ruchelli G, Mackey SC et al. Perioperative gabapentinoids: Choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology 2013;119:1215–1221.

8. Buvanendran A, Kroin JS, Kari M et al. Can a single dose of 300 mg of pregabalin reach acute antihyperalgesic levels in the central nervous system? Reg Anesth Pain Med 2010;35:535–538.

9. Buvanendran A, Kroin JS, Della Valle CJ et al. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: A prospective, randomized, controlled trial. Anesth Analg 2010;110:199–207.

10. Cascinu S, Catalano V, Cordella L et al. Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: A randomized, double-blind, placebo-controlled trial. J Clin Oncol 2002;20:3478–3483.

11. Gamelin L, Boisdron-Celle M, Delva R et al. Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: A retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer. Clin Cancer Res 2004;10:4055–4061.

12. Nagashima M, Ooshiro M, Moriyama A et al. Efficacy and tolerability of controlled-release oxycodone for oxaliplatin-induced peripheral neuropathy and the extension of FOLFOX therapy in advanced colorectal cancer patients. Support Care Cancer 2014;22:1579–1584.

13. Argyriou AA, Chroni E, Polychronopoulos P et al. Efficacy of oxcarbazepine for prophylaxis against cumulative oxaliplatin-induced neuropathy. Neurology 2006;67:2253–2255.

14. Kautio AL, Haanpää M, Leminen A et al. Amitriptyline in the prevention of chemotherapy-induced neuropathic symptoms. Anticancer Res 2009;29:2601–2606.

15. Grothey A, Nikcevich DA, Sloan JA et al. Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7. J Clin Oncol 2011;29:421–427.

16. Penz M, Kornek GV, Raderer M et al. Subcutaneous administration of amifostine: A promising therapeutic option in patients with oxaliplatin-related peripheral sensitive neuropathy. Ann Oncol 2001;12:421–422.

17. Durand JP, Deplanque G, Montheil V et al. 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. Ann Oncol 2012;23:200–205.

18. Paatero P, Tapper U. Positive matrix factorization: A non-negative factor model with optimal utilization of error estimates of data values. Environmetrics 1994;5:111–126.

19. Loprinzi CL, Qin R, Dakhil SR et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). J Clin Oncol 2014;32:997–1005.

20. Rao RD, Michalak JC, Sloan JA et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: A phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer 2007;110:2110–2118.

21. Smith EM, Pang H, Cirrincione C et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. JAMA 2013;309:1359–1367.

22. Kono T, Hata T, Morita S et al. Goshajinkigan oxaliplatin neurotoxicity evaluation (GONE): A phase 2, multicenter, randomized, double-blind, placebo-controlled trial of goshajinkigan to prevent oxaliplatin-induced neuropathy. Cancer Chemother Pharmacol 2013;72:1283–1290.

23. Afonseca SO, Cruz FM, Cubero Dde I et al. Vitamin E for prevention of oxaliplatin-induced peripheral neuropathy: A pilot randomized clinical trial. Sao Paulo Med J 2013;131:35–38.

24. Hershman DL, Lacchetti C, Dworkin RH et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32:1941–1967.

25. Guo X, Gao G, Wang X et al. Effects of bilateral deep brain stimulation of the subthalamic nucleus on olfactory function in Parkinson's disease patients. Stereotact Funct Neurosurg 2008;86:237–244.

26. Kus T, Aktas G, Alpak G et al. Efficacy of venlafaxine for the relief of taxane and oxaliplatin-induced acute neurotoxicity: A single-center retrospective case-control study. Support Care Cancer 2016;24:2085–2091.

27. Treede RD, Jensen TS, Campbell JN et al. Neuropathic pain: Redefinition and a grading system for

clinical and research purposes. Neurology 2008;70: 1630–1635.

28. Cleeland CS, Ryan KM. Pain assessment: Global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–138.

29. Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods. Pain 1975;1: 277–299.

30. Ferreira KA, de Andrade DC, Teixeira MJ. Development and validation of a Brazilian version of the short-form McGill pain questionnaire (SF-MPQ). Pain Manag Nurs 2013;14:210–219.

31. Santos JG, Brito JO, de Andrade DC et al. Translation to Portuguese and validation of the Douleur Neuropathique 4 questionnaire. J Pain 2010;11:484–490.

32. de Andrade DC, Ferreira KA, Nishimura CM et al. Psychometric validation of the Portuguese version of the Neuropathic Pain Symptoms Inventory. Health Qual Life Outcomes. 2011;9:107.

33. Bouhassira D, Attal N, Fermanian J et al. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 2004;108:248–257.

34. Cavaletti G, Frigeni B, Lanzani F et al. The Total Neuropathy Score as an assessment tool for grading the course of chemotherapy-induced peripheral neurotoxicity: Comparison with the National Cancer Institute-Common Toxicity Scale. J Peripher Nerv Syst 2007;12:210–215.

35. National Cancer Institute: Common Terminology Criteria for Adverse Events, 2003. Available at http://ctep.cancer.gov. Accessed June 9, 2017.

36. Cavaletti G, Bogliun G, Marzorati L et al. Grading of chemotherapy-induced peripheral neurotoxicity using the Total Neuropathy Scale. Neurology 2003;61:1297–1300.

37. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67: 361–370.

38. Kuhn M, Johnson K. Applied predictive modeling. Berlin, Germany: Springer, 2013.

39. Reshef DN, Reshef YA, Finucane HK et al. Detecting novel associations in large data sets. Science 2011;334:1518–1524.

40. Prantner B, Visualization of imputed values using the R-package VIM, 2011. Available at https://cran.r-project.org/web/packages/VIMGUI/vignettes/VIM-Imputation.pdf. Accessed June 9, 2017.

Figures and Tables

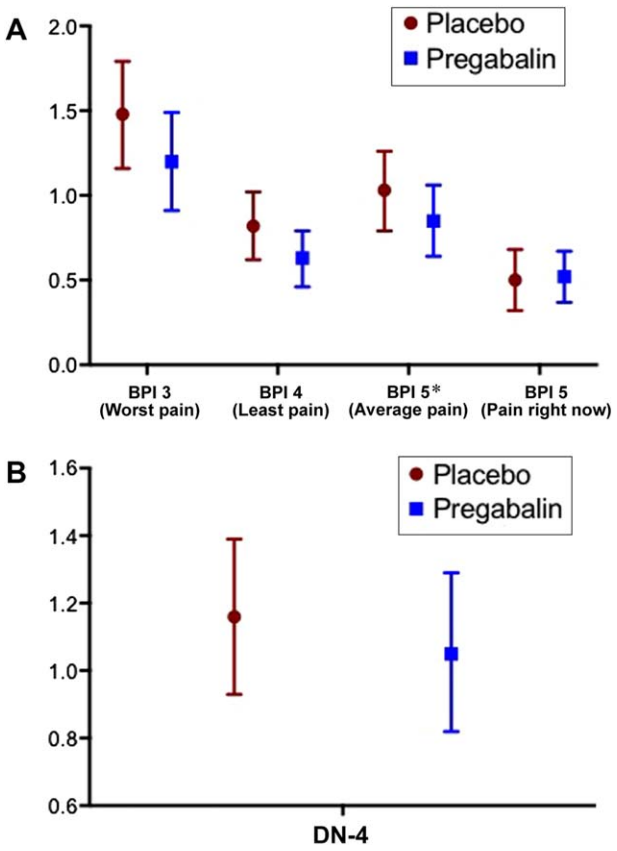

Figure 2. Effects of study medications on pain intensity. **(A)**: Brief Pain Inventory pain intensity scores (0–10). **(B)**: Neuropathic pain symptoms (Douleur Neuropatique-4). Statistical significance is considered when confidence intervals from both groups do not intersect.

*Main outcome.

Abbreviations: BPI, brief pain inventory; DN-4, Douleur Neuropatique-4.

Table 1. Baseline characteristics in both study groups

Variables	Total (143)	Placebo (65)	Pregabalin (78)	*p* value
Age	57.13 ± 10.51	55.86 ± 10.21	58.19 ± 10.71	.186
Female gender	70	39	31	.025
Education				.240
- Illiterate	9	6	3	
- Elementary school	68	35	33	
- Middle school	48	18	30	
- High school	14	4	10	
- University	4	2	2	
Religion				.358
- Catholic	81	38	43	
- Gospel	46	23	23	
- Spiritism	5	1	4	
- Other	11	3	8	
Income (in Brazilian *reais*)	2,121 ± 1,903	2,247 ± 2,285	2,016 ± 1,523	.492
Cancer type				.489
- Colon	86	37	49	
- Rectum	49	23	26	
- Unspecified	8	5	3	
rTNS	1.07 ± 1.93	1.37 ± 2.36	0.81 ± 1.43	.116
Hospital anxiety scale	4.97 ± 4.08	5.57 ± 4.03	4.46 ± 4.07	.106
Hospital depression scale	3.96 ± 4.13	4.75 ± 4.44	3.29 ± 3.74	.038
HADS total score	8.92 ± 7.42	10.32 ± 7.58	7.76 ± 7.12	.04
Presence of pain (VAS >0)	0	0	0	1.00

For all these scores/questionnaires (VAS, HADS, rTNS), higher values indicate more pain/more intense mood symptoms/more signs of neuropathy.
The values are presented as mean ± SD or *n*. Statistical significance was set at $p < .05$.
Abbreviations: HADS, hospital anxiety and depression scale; rTNS, total neuropathy score-reduced; SD, standard deviation; VAS, visual analog scale.

Table 2. Study outcomes taking into account all measurements over the entire trial period

Variables	Placebo	Pregabalin
BPI item 5 ("average pain")[a]	1.03 (0.79–1.26)	0.85 (0.64–1.06)
BPI item 3 ("worst pain")	1.48 (1.16–1.79)	1.2 (0.91–1.49)
BPI item 4 ("least pain")	0.82 (0.62–1.02)	0.63 (0.46–0.79)
BPI item 6 ("pain right now")	0.50 (0.32–0.68)	0.52 (0.37–0.67)
BPI interference score	3.63 (2.45–4.80)	3.02 (1.91–4.13)
NPSI score	13.78 (11.79–15.77)	10.7 (8.74–12.66)
DN-4 score	1.16 (0.93–1.39)	1.05 (0.82–1.29)
rTNS score	2.81 (2.12–3.51)	2.72 (2.12–3.32)
Hospital anxiety scale	4.98 (4.22–5.74)	3.78 (3.13–4.43)
Hospital depression scale	4.76 (3.86–5.67)	3.08 (2.46–3.7)
HADS total score	9.7 (8.16–11.24)	6.86 (5.67–8.05)

The values were presented as predicted means from generalized estimating equations (95% CI). Statistical significance is considered when CI from both groups do not intersect.
For all these scores/questionnaires (BPI, DN4, HADS, rTNS), higher values indicate more pain/more intense mood symptoms/more signs of neuropathy.
[a]Main outcome.
Abbreviations: BPI, brief pain inventory; CI, confidence interval; DN-4, Douleur Neuropathique-4; HADS, hospital anxiety and depression scale; NPSI, neuropathic pain symptom inventory; rTNS, total neuropathy score-reduced.

Table 3. Pain outcomes comparison between interventions considering the dichotomous variables

Variables	Odds ratio (95% CI; placebo group as reference)
DN-4 1a (burning)	1.08 (0.68–1.71)
DN-4 1b (painful cold)	0.84 (0.57–1.22)
DN-4 1c (electric shocks)	0.79 (0.54–1.16)
DN-4 2a (tingling)	0.83 (0.57–1.22)
DN-4 2b (pins and needles)	0.86 (0.54–1.37)
DN-4 2c (numbness)	0.87 (0.6–1.26)
DN-4 2d (itching)	0.81 (0.4–1.63)
DN-4 3a (hypoesthesia to touch)	1.1 (0.64–1.89)
DN-4 3b (hypoesthesia to prick)	0.97 (0.55–1.71)
DN-4 4 (brushing)	1.49 (0.71–3.12)
CTC neuropathy score	0.97 (0.7–1.35)
Presence of pain (VAS >0)	0.93 (0.64–1.35)
Superficial spontaneous pain	0.82 (0.5–1.34)
Deep spontaneous pain	0.81 (0.42–1.56)
Paroxysmal pain	0.57 (0.34–0.95)
Evoked pain	0.85 (0.56–1.28)
Paresthesia or dysesthesia	0.67 (0.44–1.02)

For all these scores/questionnaires, higher values indicate more severe symptoms.
Abbreviations: CI, confidence interval; CTC, common toxicity criteria; DN-4, Douleur Neuropathique-4; VAS, visual analog scale.