Efficacy of Gabapentin in the Management of Chemotherapy-induced Peripheral Neuropathy

A Phase 3 Randomized, Double-Blind, Placebo-controlled, Crossover Trial (N00C3)

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BACKGROUND. The antiepileptic agent, gabapentin, has been demonstrated to relieve symptoms of peripheral neuropathy due to various etiologies. On the basis of these data, a multicenter, double-blind, placebo-controlled, crossover, randomized trial was conducted to evaluate the effect of gabapentin on symptoms of chemotherapy-induced peripheral neuropathy (CIPN).

METHODS. Patients with symptomatic CIPN who complained of 'average' daily pain scores of either 1) $\geq$4 on a 0–10 numerical rating scale (NRS); or 2) $\geq$1 on the 0–3 Eastern Cooperative Oncology Group neuropathy scale (ENS) were eligible (higher numbers indicate greater severity of symptoms in both scales). Patients were randomized to receive gabapentin (target dose, 2700 mg) or placebo for 6 weeks. Crossover occurred after a 2-week washout period. CIPN-related symptoms were evaluated weekly by questionnaires. Statistical methods followed established methods for crossover designs, including Student *t* tests to compare average intrapatient differences between treatments and linear models to adjust for potential concomitant covariates.

RESULTS. There were 115 patients who were randomly assigned to the treatment or control arm. Both groups were well matched by symptoms at study entry. Changes in symptom severity were statistically similar between the 2 groups during the study. Adverse events were mild and similar in both groups.

CONCLUSIONS. This trial failed to demonstrate any benefit to using gabapentin to treat symptoms caused by CIPN. ***Cancer* 2007;110:2110–8.** © *2007 American Cancer Society.*

KEYWORDS: gabapentin, peripheral neuropathy, chemotherapy-induced peripheral neuropathy, taxanes, paclitaxel, cisplatin, carboplatin, vinca alkaloids, neurotoxicity, pain.

Peripheral neuropathy is a common complication of several classes of chemotherapeutic agents including taxanes (paclitaxel

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and docetaxel), platinum-based compounds (carboplatin, cisplatin, and oxaliplatin), and vinca alkaloids (vincristine and vinblastine). Because these agents are used to treat several prevalent cancers, chemotherapy-induced peripheral neuropathy (CIPN) is common in patients treated with chemotherapy.[1–3] CIPN is manifested by the development of paresthesias, dysesthesias, loss of joint and vibration sense, and loss of deep tendon reflexes. The onset of symptomatic CIPN usually leads to reductions in dose(s) and/or interruptions of therapy, which can negatively impact cancer-related outcomes.

There are few effective pharmacological options to treat symptoms due to CIPN. Analgesics (ie, opioids and nonsteroidal anti-inflammatory agents) are only modestly effective in treating symptoms from neuropathy. Tricyclic antidepressants (eg, nortriptyline and amitriptyline) have been suggested as therapeutic options for neuropathy; however, there are few data to support their use in CIPN. One randomized trial evaluated nortriptyline for therapy of CIPN symptoms; this agent was found to be ineffective.[4] The identification of alternate treatment strategies would be a welcome development for patients afflicted with CIPN.

Gabapentin, an antiepileptic drug that is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA), has been shown to be effective in treating symptoms from several neuropathic syndromes. Neuronal excitability that occurs after nerve injury is presumed to be mediated (at least in part) by up-regulation of the $\alpha 2\delta 1$ subunit of the voltage-dependent calcium channels in the dorsal nerve root ganglia.[5] Gabapentin inhibits the $\alpha 2\delta 1$ subunit, reducing calcium influx and neurotransmitter release from hyperexcited neurons, and thus provides the theoretical basis for reducing nociception in neuropathic syndromes in animal models.[5–7] Gabapentin use results in few adverse effects, which makes it an attractive adjunctive analgesic agent.

Gabapentin has been evaluated in numerous clinical trials for its benefits in relieving symptoms of neuropathy. These trials have demonstrated a benefit to using gabapentin to treat symptoms of neuropathy caused by a variety of etiologies, including diabetes,[8,9] postherpetic neuralgia,[10,11] tumor infiltration,[12,13] and postamputation phantom pain syndromes.[14] At the time this study was designed, preliminary data available from 1 trial (available in an abstract form) suggested that gabapentin was effective in reducing symptoms from oxaliplatin-induced neuropathy.[15] Based on these preliminary data, this prospective, randomized, double-blinded, placebo-controlled, crossover clinical trial was designed to test the hypothesis that gabapentin could improve pain and other neuropathy symptoms in patients with CIPN.

MATERIALS AND METHODS

This study was conducted after appropriate approval by individual institutional review boards of the treating sites of the North Central Cancer Treatment Group (NCCTG). Written informed consent was obtained from all patients.

Patient Characteristics

Adult patients with duration > 1 month symptomatic CIPN due to neurotoxic chemotherapy (ie, taxanes-paclitaxel or docetaxel; platinum compounds-carboplatin or cisplatin or oxaliplatin; vinca alkaloids-vincristine or vinblastine) were eligible. Patients who were currently receiving chemotherapy, as well as those who had completed therapy at the time of study entry, were eligible. Symptom severity for 'average' pain required for study entry were either 1) a rating of ≥ 4 on the Numerical Rating Scale (NRS; 0 = no pain and 10 = worst pain possible), or 2) a score ≥ 1 on the Eastern Cooperative Oncology Group neuropathy scale (ENS; 0 = none; 1 = mild paresthesias, loss of deep tendon reflexes; 2 = mild or moderate objective sensory loss, moderate paresthesias; 3 = severe objective sensory loss or paresthesias that interfere with function). Serum creatinine ≤ 1.5 times the upper limit of normal and an estimated life expectancy of ≥ 6 months were required. Patients who had pre-existing symptomatic neuropathy due to other causes (eg, radiation or malignant plexopathy, lumbar or cervical radiculopathy, vitamin B12 deficiency, or diabetes) or were pregnant or lactating were ineligible. Patients who were using the following agents at baseline were ineligible: antidepressants, opioids, adjuvant analgesic agents (eg, anticonvulsants, clonazepam, or mexiletine), topical analgesics, and amifostine (although therapy with any of these agents could be initiated after study entry if necessary). The use of nonsteroidal anti-inflammatory agents (NSAIDs) was permitted.

Study Design

This study used a double-blinded, placebo-controlled, crossover design consisting of two 6-week phases separated by a 2-week "washout" period. Eligible patients were randomly assigned to 1 of 2 arms, either gabapentin followed by placebo (hereby designated G/P) or the reverse order (designated P/G). Before their randomization, patients were strati-

fied by the type of neurotoxic chemotherapeutic agents used (vinca alkaloids vs taxanes vs platinum-based compounds vs combination, ie, 2 or more of the previously mentioned agents) and by whether they were enrolled during ongoing chemotherapy or had completed their therapy. The randomization was performed by using a dynamic allocation procedure that balanced marginal distributions of stratification factors between treatment groups.[16] Titration schedules and the duration of the washout period were designed based on the short half-life of gabapentin (5–7 hours). Doses of gabapentin (300 mg capsules) and identical placebo capsules were incrementally escalated over 3 weeks to a target dose of 9 capsules a day (ie, 2700 mg of gabapentin) regardless of efficacy noted at lower doses. This target dose was chosen on the basis of previous trials that had suggested efficacy and tolerability of comparable doses of gabapentin when used to treat symptomatic neuropathy.[8,11] If toxic events occurred, the dose was reduced to a previously well-tolerated dose level. After treatment with the maximal dose for 3 weeks, patients were weaned from the drug, after which they were crossed over to the opposite arm and treated in an identical manner.

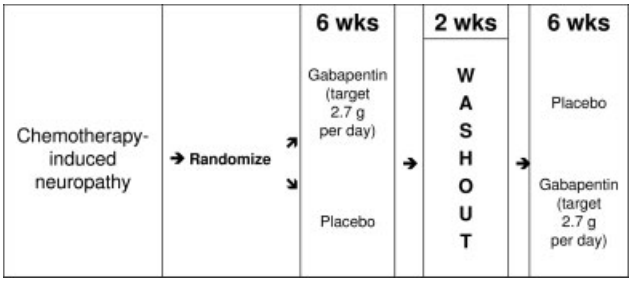

FIGURE 1. Study schema.

Assessment Tools

The primary efficacy measure was the patient-reported 'average' pain over a particular day, as measured by using the NRS[17,18] and ENS.[19] These primary outcomes as well as adverse events were assessed weekly. Patients were asked to assign a score on each scale for their 'worst' and 'least' pain experiences on the day of evaluation. Because CIPN results in a spectrum of symptoms (several of which are related to, but are distinct from, pain), several additional secondary measures were used to evaluate changes in these symptoms. These secondary efficacy measures included 1) the World Health Organization (WHO) classification scale for neuropathy-related symptoms (0–4; 0 = none; 1 = paresthesias and/or decreased tendon reflexes; 2 = severe paresthesias and/or mild weakness; 3 = intolerable paresthesias and/or marked motor loss; 4 = paralysis)[20]; 2) the Short Form–McGill Pain Questionnaire (assesses different characteristics of neuropathic pain such as throbbing, gnawing, shooting, aching, and burning)[21]; 3) the Brief Pain Inventory–Short Form (BPI; assesses pain and its effects on ability to function)[22]; 4) the Subjective Global Impression of Change (SGI; a 7-point scale that rates change in overall status of symptoms since the beginning of the study with choices of 'much improved', 'moderately improved', 'minimally improved', 'no change', 'minimally worse', 'moderately worse', or 'much worse')[23]; 5) the Symptom Distress Scale (a 5-point scale that evaluates a range of symptoms commonly encountered by cancer patients)[24]; 6) the Profile of Mood States (POMS) Short Form (a 30-item scale to assess mood states)[25]; and 7) a quality-of-life (QOL) Uniscale (a single-item measurement of global QOL on a numeric analog scale from 0 to 100).[26] These secondary measures were evaluated at baseline and at the end of 6, 8, and 14 weeks. Compliance and adverse events were assessed by weekly phone calls by a member of the research team. All administered ancillary treatments were recorded weekly.

Statistical Considerations

This study was designed to have 50 patients in each arm to provide 80% power to detect differences in 'average' pain scores of 0.63 standard deviations via a standard 2-sample Student *t* test, by using a 2-sided type I error rate of 2.5% to account for the presence of 2 primary endpoints via a Bonferroni correction. Decisions pertinent to efficacy were made on the basis of these statistical comparisons for the first 6-week phase of the study; additional comparisons were made after taking into consideration results of the crossover phase. Analytical procedures compiled into a specialized computer algorithm by the Mayo Clinic Cancer Center Statistics Unit for use in crossover studies were used.[27] The scores for 'average' pain for each of the primary endpoint variables were calculated for each treatment period for input into a classic crossover "sums and differences" analysis.[28] Two-sample Student *t* tests and/or Wilcoxon rank-sum tests were employed, depending upon the measurement level and normality of data. Wilcoxon and Fisher exact tests were used to test the equality of pain distributions across the 2 study groups. All treatment comparisons used 2-sided testing and a 5% type I error rate, unless otherwise specified. Analyses for secondary endpoints were identical to those of the primary endpoint by crossover trial analytical methodology. Missing data were handled in a

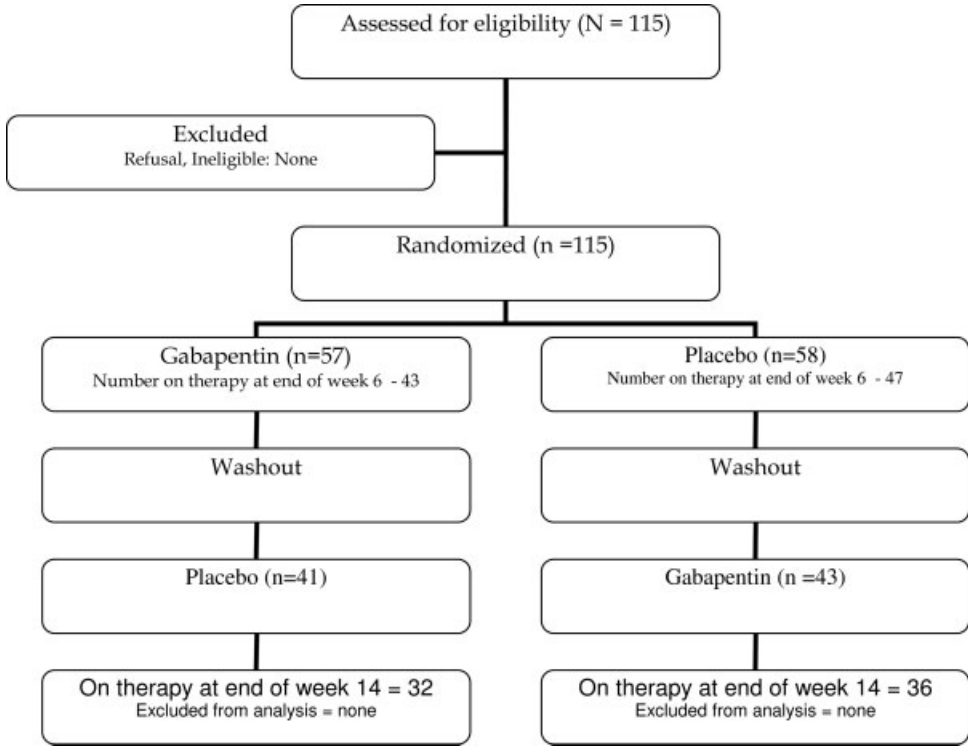

FIGURE 2. Consort diagram.

number of ways to assess the robustness of results obtained, relative to missing data.[29] Results were consistent regardless of the analytical method used for handling missing data. Results that used all available data without imputation are presented here.

RESULTS

Between March 2002 and December 2003, 115 patients that had met study-entry criteria were randomized. The accrual exceeded the target by 15, as these patients had already initiated the process of registering for this trial at the time the study formally closed. The schema is depicted in Figure 1, and a Consort (Consolidated Standard for Reporting Clinical Trials) diagram is presented in Figure 2. A total of 57 and 58 patients were enrolled into the G/P arm and the P/G arm, respectively. Patients in each arm were well balanced by demographic factors, chemotherapy drugs responsible for CIPN, and severity of outcome measures (Table 1). The NRS scores for 'average' daily pain at baseline were 4.3 and 3.6 ($P = .06$) in the G/P and P/G arms, respectively. Patients were eligible to enroll when they met symptom severity criteria for either the ESN or the NRS (but did not need to fulfill both criteria), hence a few

TABLE 1
Baseline Characteristics

	G/P N = 57 No. (%)	P/G N = 58 No. (%)	Total N = 115 No. (%)	*P*
Age, y				.5
Mean [range]	59 [28–84]	60 [25–80]	59 [25–84]	
Sex				1.0
Women	42 (74)	42 (72)	84 (73)	
Men	15 (26)	16 (28)	31 (27)	
Race				.5
Missing	2	1	3	
Asian	1 (2)	0	1 (1)	
Black	3 (6)	2 (4)	5 (5)	
White	51 (93)	55 (97)	106 (95)	
Chemotherapy				.6
Active	27 (47)	31 (53)	58 (50)	
Discontinued or completed	30 (53)	27 (47)	57 (50)	
Neurotoxic chemo agents				.1
Vinca alkaloids	9 (16)	2 (3)	11 (10)	
Taxanes	23 (40)	27 (47)	50 (44)	
Platinum-based compounds	12 (21)	11 (19)	23 (20)	
Combination	13 (23)	18 (31)	31 (27)	

G/P indicates the group that received gabapentin in the first 6-week period and placebo in the second 6-week period; P/G, the group that received therapy in the reverse order.

TABLE 2
Outcome Analysis Results for the Crossover Design

	Baseline	P^*	End of 6 Wks	P^*	End of 14 Wks	P^*
No. in each group		—		—		—
G/P	57		38		32	
P/G	58		39		36	
ENS 'average' pain†		.7		.3		.7
G/P	1.9		1.7		1.5	
P/G	2.0		1.8		1.5	
NRS 'average' pain†		.06		.8		.2
G/P	4.3		3.3		3.1	
P/G	3.6		3.0		2.5	
NRS 'worst' pain†		.5		.8		.05
G/P	5.0		4.4		4.2	
P/G	4.7		4.0		3.2	
Opioids used (initiation of opioid therapy was permitted after enrollment)‡		—		.8		1.0
G/P	—		8 (14%)		5 (9%)	
P/G	—		7 (12%)		7 (12%)	
Nonopioid analgesics used‡		.8		.09		.4
G/P	33%		19 (33%)		13 (23%)	
P/G	36%		29 (50%)		18 (31%)	
Adverse event, grade ≥2		—		.2		.7
G/P	N/A		44		29	
P/G	N/A		50		31	
Total SDS score, mean†		.7		.6		.9
G/P	75.0		78.7		83.0	
P/G	73.0		77.5		76.8	
BPI 'average' score†		.6		.2		.6
G/P	3.9		2.8		2.8	
P/G	3.7		3.3		3.0	
McGill pain rating index†		.2		.03		.97
G/P	29.6		17.6		15.1	
P/G	23.4		19.9		24.0	
QOL uniscale§		.7		.8		.7
G/P	65.1		67.6		67.0	
P/G	67.0		64.9		62.4	
Subject global impression of change§		—		.7		.3
G/P	—		0.3		0.5	
P/G	—		0.2		0.1	
WHO neuropathy score†		.9		.7		.3
G/P	1.5		1.5		1.4	
P/G	1.5		1.4		1.3	

* *P* values relate to comparisons between the 2 groups at the corresponding time point.

† Higher scores correspond to greater severity of symptoms.

‡ Use of specified therapy reported at any point during the specified phase of therapy.

§ Higher scores denote improvement or fewer symptoms.

G/P indicates the group that received gabapentin in the first 6-week period and gabapentin in the second 6-week period; P/G, the group that received therapy in the reverse order; BPI, Brief Pain Inventory; ENS, Eastern Cooperative Oncology Group Neuropathy Scale; QOL, Quality of life; NRS, Numeric rating scale; SDS, Symptom Distress Scale; WHO, World Health Organization.

patients were enrolled with NRS scores of < 4 and ESN scores of < 1. Corresponding scores for 'average' pain were statistically similar at the end of the first phase (3.3 and 3.1; $P = .8$) and second phase (3.1 and 2.5; $P = .2$) of therapy. The corresponding ENS scores for 'average' pain at study entry (1.9 and 2.0; $P = .7$), at the end of the first phase (1.7 and 1.8; $P = .3$), and at the end of the second phase (1.5 and 1.5; $P = .7$) were similar. The NRS scores for the 'worst' pain at the end of the second phase of therapy in the P/G and G/P arms were 3.2 and 4.2 ($P = .05$), and the McGill Pain Rating Index score at 6 weeks was lower (ie, better) in the gabapentin-treated group (17.6 vs 19.9; $P = .03$). There were no significant differences in secondary endpoints, ie, the SDS, McGill Pain Rating Index, BPI, QOL Uniscale, and the SGI at any point during therapy. No subset of patients, on the basis of stratification factors

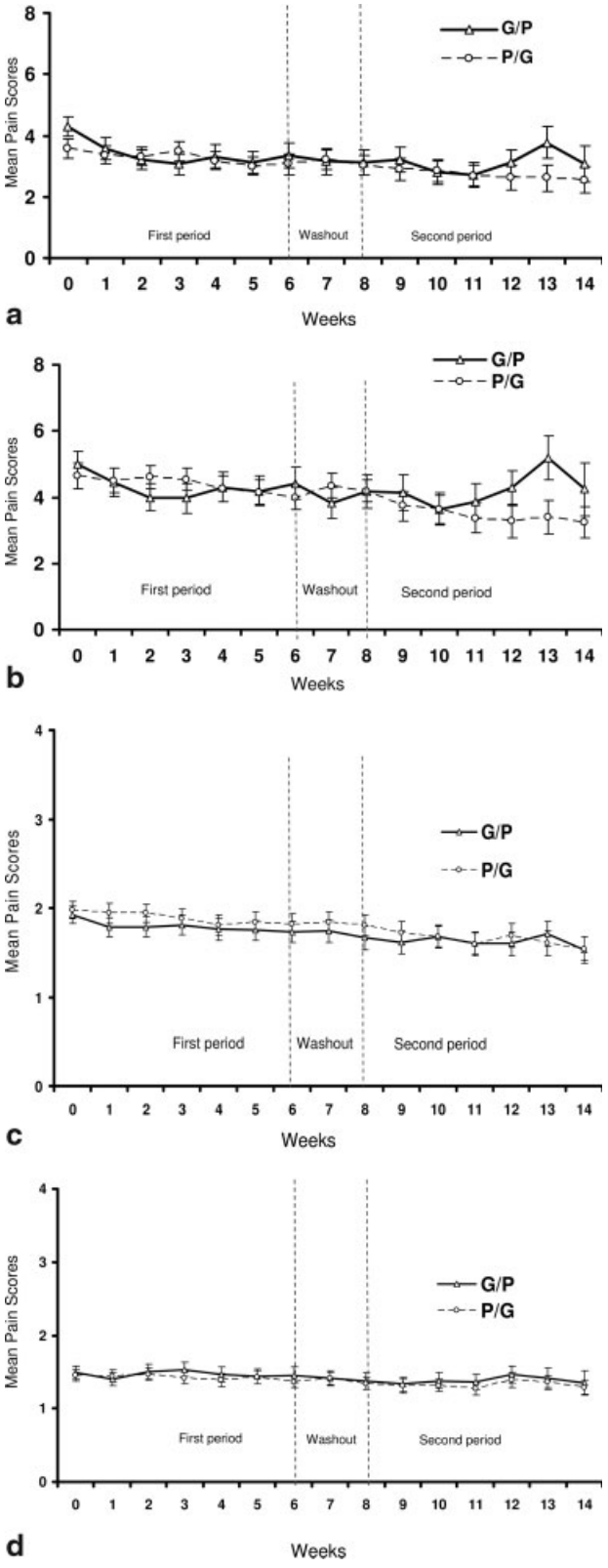

FIGURE 3. Changes in (a) NRS 'average' pain score; (b) NRS 'worst' pain score; (c) ENS 'average' pain score; and (d) the WHO neuropathy scale. Error bars represent standard errors of the mean (SEM).

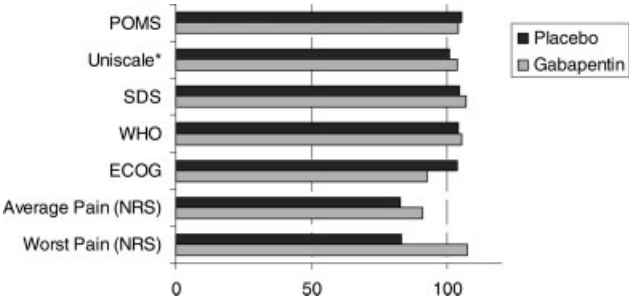

FIGURE 4. Mean value at the end of the first 6-week phase (expressed as a percentage of baseline score). *Higher score represents less severe symptoms. (For all other measures, lower scores denote less severe symptoms.) Changes in symptom severity scores for each arm in the first 6-week phase. The changes are expressed as a percentage of the baseline value for each corresponding scale.

ECOG indicates Eastern Cooperative Oncology Group Neuropathy Scale; Uniscale, Uniscale Quality of Life Scale; NRS, Numeric Rating Scale; SDS, Symptom Distress Scale; WHO, World Health Organization; POMS, Profile of Mood States.

(listed in the study-design section), had a statistically different response to the study drug when compared with placebo. Likewise, the subset of patients who had higher (ie, more severe) pain scores at baseline did not appear to have a preferential benefit with gabapentin therapy, when compared with those with lower baseline pain scores. These results are depicted in Table 2 and Figure 3. The changes in the symptom scores in the first 6-week period (expressed as a percentage of baseline) are depicted in Figure 4.

Therapy for the 14-week duration of the trial was administered to 61% and 60% of patients enrolled in the G/P and P/G arms, respectively. In patients who discontinued therapy, the reasons for stopping therapy were given as 'refusal' (presumably because of perceived lack of activity) in 20% and in 29% of those who received gabapentin and placebo, respectively, at the time of discontinuation. Other reasons for stopping therapy were disease progression, death (due to the cancer), and decision to switch to alternative therapies. Regarding reasons given to study personnel for stopping therapy, there were no statistically significant differences between patients on placebo or patients on gabapentin. All available data from patients who stopped therapy were included in analyses.

Overall, CIPN scores improved for all patients during the trial, compared with their scores at baseline (irrespective of treatment assigned). The NRS score for 'average' pain improved by 0.12 unit per week in all enrolled patients ($P = .03$; for comparisons from baseline to study end). These improvements in NRS scores were most pronounced in those

with moderate to severe symptoms (ie, baseline NRS score for 'average' pain of $\geq$4); in this subset, scores for 'average' pain improved by 1 unit every 4 weeks. Statistically significant improvements in scores upon serial follow-up were likewise noted in the subset of patients who were actively receiving chemotherapy at study entry – the NRS 'average' pain score improved by 0.19 unit per week ($P = .02$; for comparisons from baseline to study end). Similarly, the subgroup that was no longer receiving chemotherapy at study entry (when compared with patients who were actively receiving chemotherapy at study entry) reported greater improvements (when compared with baseline) in the SDS scores ($P = .01$), QOL Uniscale ($P = .04$), POMS scores ($P = .003$), and McGill Pain Rating Index ($P = .001$). There was no evidence for a crossover effect.

Adverse events occurred at relatively equivalent rates in both groups. There were no differences in the incidence of fatigue or somnolence reported by patients who were being treated with gabapentin and placebo. The maximal tolerated dose achieved was identical in both groups (median, 2700 mg per day; or placebo equivalent). Data on adverse events are presented in Table 3.

TABLE 3
Adverse Events Attributed to Therapy

	Maximum adverse event attributed to medication		
Adverse event attributed to drug	Gabapentin n = 91 No. (%)	Placebo n = 89 No. (%)	*P*
Dehydration			.3
Grade 3	0	1 (1)	
Diarrhea			.7
Grade 2	3 (3)	1 (1)	
Dizziness			.1
Grade 2	6 (7)	3 (3)	
Grade 3	2 (2)	1 (1)	
Dyspepsia			.1
Grade 2	0	3 (3)	
Fatigue			.6
Grade 2	4 (4)	5 (6)	
Grade 3	1 (1)	2 (2)	
Flatulence			.2
Grade 2	0	2 (2)	
Grade 3	1 (1)	0	
Nausea			.3
Grade 2	2 (2)	5 (6)	
Rash			.1
Grade 2	1 (1)	0	
Grade 3	2 (2)	0	
Myalgia			.6
Grade 2	2 (2)	2 (2)	
Vomiting			.6
Grade 2	2 (2)	3 (3)	

DISCUSSION

The currently available options to treat CIPN are clearly inadequate. Given the relatively high incidence of CIPN, this represents an urgent unmet medical need. The development of a well-tolerated nonopioid oral agent for effective therapy of CIPN is a priority for oncology patients. Gabapentin is known to have efficacy in treating several neuropathic pain syndromes and is currently licensed in several countries for such indications. Despite preliminary data suggesting that gabapentin may be effective in treating pain from CIPN,[8,10,12,14] the current study failed to demonstrate any benefit to using gabapentin for this indication.

In the current study, the 2 randomized study groups were well balanced at study entry. The primary study endpoint and virtually all other secondary endpoints were similar in both groups throughout the duration of the study. The exceptions were the McGill Pain Rating Index score at 6 weeks (worse in the P/G cohort) and the NRS score for 'worst pain' at 14 weeks (worse in the G/P cohort), as listed in Table 2. Given their concordance among all other primary and secondary endpoints, these findings are likely explainable by multiple testing. Conclusions from the current trial are similar to those reported in another recent study, where patients who received oxaliplatin-based chemotherapy for metastatic colon cancer were treated concurrently with gabapentin with the aim of preventing neuropathy,[30] with comparisons made with a similar cohort who received identical chemotherapy. Incidence and severity of neuropathy were found to be similar in both cohorts, thus suggesting a lack of benefit of gabapentin use in this setting.[30]

Gabapentin was remarkably well tolerated in this patient population. A higher incidence of fatigue had been expected in this study with gabapentin use, on the basis of previously published reports that evaluated gabapentin for different indications.[31–33] It is noteworthy that such toxicity was also not prominent in other peripheral neuropathy trials where gabapentin was evaluated.[8,34] Similarly, a high incidence of somnolence was expected with gabapentin, given reports in available literature[10]; however, the incidence of somnolence reported by those treated with placebo and gabapentin in the current study was similar.

Data from the current trial are discordant from animal models that suggest that gabapentin increases the pain threshold in neuropathy-induced by chemotherapy.[35] Data from some animal experi-

ments suggest that up-regulation of the α2δ1 subunit of the voltage-dependent calcium channels in dorsal nerve root ganglia (the presumed basis for neuronal hyperexcitability after nerve injury) does not occur in the case of nerve injury induced by chemotherapy exposure (in contrast to nerve injury caused by other etiologies).[36] Because binding of gabapentin to the α2δ1 subunit is the presumed basis for gabapentin's antinociceptive effects,[5,36] these observations may explain the lack of efficacy of gabapentin when used to treat (or prevent) CIPN. Furthermore, unlike results of these animal experiments, patients with CIPN develop loss of sensation to light touch, pin prick, and temperature sensation (that is not hypersensitive)[37] rather than mechanical allodynia or thermal hyperalgesia. Due to these differences, results of these experimental studies in animal models may not be directly applicable to CIPN therapy in oncology patients. A different, and yet undefined, molecular and neurophysiological mechanism may be responsible for the allodynia caused by CIPN. Hopefully, future research will elucidate the neurobiological basis for CIPN and help identify agents that may be active in treating them.

In the context of current trial results, it is worth noting that gabapentin has been demonstrated to be effective in relieving cancer pain, if the pain is caused by direct malignant nerve infiltration or compression. In a recently reported study, patients were enrolled when they had pain due to cancer plexopathy, when they were not actively receiving anticancer therapies, and when they were already on concurrent therapy with opioids. Compared with those treated with placebo, patients randomized to gabapentin treatment reported a clinically relevant reduction in neuropathic pain in this study.[13]

Patients being treated with opioids at baseline were ineligible to participate in this trial (although administration of opioids was allowed during the study). This stipulation might have resulted in the exclusion of patients with severe pain as the predominant manifestation of CIPN. It can be argued that this particular subset, ie, those with greater severity of pain, might have benefited from gabapentin therapy. This is a conjecture at this time; however, a post hoc subset analysis of patients with the highest pain scores did not indicate any differential benefit to this group with gabapentin treatment when compared with those treated with placebo.

In summary, findings of the current study suggest a lack of benefit to gabapentin use to treat CIPN-related symptoms. Analysis of pain scores measured serially in this trial reveals a statistically significant (and gradual) decline in the severity of CIPN-related pain in all patients, irrespective of therapy received. Conceivably, such spontaneous improvements in CIPN symptoms upon serial evaluation might have been incorrectly attributed to a treatment effect in previously conducted uncontrolled studies.

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