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

A Phase 3 Randomized, Double-blind, Placebo-controlled Trial, N01C3

Ravi D. Rao, MBBS[1]
Patrick J. Flynn, MD[2]
Jeff A. Sloan, PhD[3]
Gilbert Y. Wong, MD[4]
Paul Novotny, MS[3]
David B. Johnson, MD[5]
Howard M. Gross, MD[6]
Samer I. Renno, MD[7]
Mohammed Nashawaty, MD[2]
Charles L. Loprinzi, MD[1]

[1] Department of Medical Oncology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

[2] Department of Medical Oncology, Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, Minnesota.

[3] Department of Biostatistics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

[4] Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

[5] Department of Oncology, Wichita Community Clinical Oncology Program, Wichita, Kansas.

[6] Department of Hematology, Hematology & Oncology of Dayton Inc., Dayton, Ohio.

[7] Department of Hematology, Missouri Valley Cancer Consortium, Omaha, Nebraska.

BACKGROUND. Lamotrigine, an antiepileptic agent, has been reported as being effective in reducing symptoms of neuropathy associated with various etiologies. Based on such data, a multicenter double-blind, placebo-controlled, randomized trial was conducted to evaluate the effect of lamotrigine on pain and other neuropathic symptoms due to chemotherapy-induced peripheral neuropathy (CIPN).

METHODS. Patients with symptomatic CIPN with symptom scores of either 1) >3 on a 0-10 Numerical Rating Scale (NRS) or 2) >1 on the 0-3 the Eastern Cooperative Oncology Group (ECOG) neuropathy scale (ENS) were eligible (higher numbers corresponding to greater severity of symptoms in both scales). Patients were randomly assigned to receive lamotrigine (target dose of 300 mg/day) or placebo for 10 weeks. Endpoints were measured biweekly.

RESULTS. In all, 131 patients were enrolled. Both groups were well matched at baseline. Over the 10-week period of the trial, the average pain scores (NRS) for the lamotrigine and placebo arms declined in both arms, with no statistically significant difference noted between the changes in the 2 groups (0.3 and 0.5 unit reduction from baseline, respectively; $P = .56$). Similarly, decreases in the ENS with therapy were not statistically different (0.4 and 0.3, respectively; $P = .3$). Changes in other subjective symptom scales were also not found to be statistically different between the 2 groups. Toxicities were mild and similar in each group.

CONCLUSIONS. The results suggest that lamotrigine is not effective for relieving neuropathic symptoms in patients because of CIPN. ***Cancer* 2008;112:2802–8.**

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

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Additional participating institutions include: Michigan Cancer Consortium, Ann Arbor, MI 48106 (Philip J. Stella, MD); Atlanta Regional CCOP (Thomas E. Seay, MD, PhD); Carle Cancer Center CCOP, Urbana, IL (Kendrith M. Rowland, Jr, MD); Cedar Rapids Oncology Project CCOP, Cedar Rapids, IA (Martin Wiesenfeld, MD); Duluth CCOP, Duluth, MN (Daniel A. Nikcevich, MD); Geisinger Clinic & Medical Center CCOP, Danville, PA (Albert Bernath, MD); Medical College of Georgia, Augusta, GA (Anand P. Jillella, MD); Mobile Infirmary Medical Center, Mobile, AL (Paul Schwarzenberger, MD); Hawaii Minority-Based CCOP (William S. Loui, MD); Illinois Oncology Research Association CCOP, Peoria, IL (John W. Kugler, MD); Scottsdale CCOP, Scottsdale, AZ (Tom R. Fitch, MD); Siouxland Hematology-Oncology Associates, Sioux City, IA (Loren K. Tschetter, MD); and Toledo Community Hospital Oncology Program CCOP, Toledo, OH (Paul L. Schaefer, MD).

Address for reprints: Charles L. Loprinzi, MD, Mayo Clinic, 200 First St., SW, Rochester, MN 55905; Fax: (507) 284-1803; E-mail: loprinzi.charles@mayo.edu

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Chemotherapy-induced peripheral neuropathy (CIPN) is a common toxicity of cancer therapy. CIPN frequently complicates the use of several classes of chemotherapeutic agents—taxanes (paclitaxel and docetaxel), platinum-based compounds (carboplatin, cisplatin, and oxaliplatin), and vinca alkaloids (vincristine and vinblastine). Because these drugs are frequently used to treat several prevalent cancers (eg, colon, lung, and breast), CIPN is relatively common. CIPN has been estimated to afflict 30% to 40% of patients treated with certain chemotherapeutic agents.[1–3] CIPN-related symptoms have negative effects on quality of life and functional capacity. In addition, the onset of CIPN often results in reduced doses of chemotherapy, or discontinuation of therapy altogether—likely impacting cancer-related outcomes in a negative way. Identifying effective therapies for CIPN remains an urgent unmet need for oncology patients.

Currently available therapy options for CIPN (eg, opioids or nonsteroidal antiinflammatory drugs [NSAIDs]) are suboptimal because they are only minimally effective in relieving symptoms (pain and discomfort) of CIPN and/or result in significant adverse events. Tricyclic antidepressants and antiepileptics (eg, gabapentin) are often utilized in clinical practice to treat CIPN; however, clinical trials evaluating the benefits of such therapies for therapy[4,5] or prophylaxis[6] of CIPN do not support such use.

Lamotrigine (Lamictal; GlaxoSmithKline, Philadelphia, PA) is an antiepileptic agent that is reported to inhibit the function of neuronal sodium channels in a concentration-dependent and voltage-dependent manner, decreasing the release of excitatory neurotransmitters, especially glutamate and aspartate.[7–9] Lamotrigine has been suggested as a potentially useful agent for treating pain in neuropathic syndromes, based on the observation that increased activity of sodium channels appears to be the basis for hyperalgesia (eg, as suggested by the benefit of sodium channel inhibitors such as lidocaine on raising the pain threshold). In normal volunteers lamotrigine has been demonstrated to raise the threshold to cold-induced pain compared with placebo.[10] At the time this study was designed, data were available to suggest a role for lamotrigine in the therapy of pain from a variety of etiologies, including painful diabetic neuropathy,[11] central poststroke pain,[12] human immunodeficiency virus (HIV)-associated neuropathy,[13] and trigeminal neuralgia.[14] In addition to these data, local anecdotal experience of using lamotrigine to treat patients with CIPN suggested that some patients appeared to benefit with such therapy, with a reduction in pain and other symptoms (such as numbness and tingling). Based on these preliminary data, a phase 3 randomized placebo-controlled study was conducted to evaluate the efficacy of lamotrigine in treating pain and other neuropathic symptoms resulting from chemotherapy exposure.

MATERIALS AND METHODS

The study was conducted after appropriate approval by the individual Institutional Review Boards in participating North Central Cancer Treatment Group (NCCTG) institutions. Written informed consent was obtained from all patients. The study drug and placebo were kindly supplied by the manufacturer (GlaxoSmithKline). No other associated funding for this study was provided by any private company.

Patient Characteristics

Adult patients with symptomatic CIPN, $\geq$1 month duration, because of neurotoxic chemotherapy (ie, taxanes [paclitaxel and docetaxel], platinum compounds [carboplatin, cisplatin, and oxaliplatin], and vinca alkaloids [vincristine and 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. To be eligible, patients had to report having 'average' daily pain severe enough to have either 1) a rating of $\geq$4 using the Numerical Rating Scale (NRS; 0 = no pain and 10 = worst pain possible), or 2) >1 using 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 $\leq$1.5 times the upper limit of normal and an estimated life expectancy of $\geq$6 months were required. Patients were ineligible if they had preexisting symptomatic neuropathy because of other causes (eg, radiation or malignant plexopathy, lumbar or cervical radiculopathy, vitamin B_{12} deficiency or diabetes), or if they were pregnant or lactating. Patients using the following agents at baseline were ineligible: antidepressants, opioids, adjuvant analgesic agents (eg, anticonvulsants, clonazepam, or mexelitine), topical analgesics, and amifostine (although therapy with any of these agents could be initiated after study entry, if necessary). The use of NSAIDs was permitted.

Study Design

The study employed a randomized double-blind placebo-controlled design. Eligible patients were randomly treated with lamotrigine (target dose of 300

mg, based on published data suggesting that this was an effective dose[13]) versus an identical-appearing placebo. Patients were started on a placebo or lamotrigine at a dose of 25 mg at bedtime for 2 weeks, then 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks, then 100 mg twice daily for 2 weeks, and then the dose was escalated to 150 mg twice daily, at which time therapy continued for 2 weeks. Dose escalation was continued per this schedule to allow each patient to reach his/her maximum tolerated dose. After a total of 10 weeks, of therapy from the time of drug initiation, patients were tapered off the drug/placebo over a 4-week period. If a patient wished to stop sooner for any reason before 10 weeks, they were encouraged to taper the drug over a 4-week period rather than discontinuing therapy abruptly.

Efficacy Assessment

The primary efficacy measure was patient-reported 'average' daily pain over a particular day, as measured using the NRS[15,16] and ENS.[17] These primary outcomes, as well as adverse events, were assessed weekly. Patients were also asked to assign a score for their 'worst' and 'least' pain experiences on the day of evaluation using the NRS. Because CIPN results in a spectrum of symptoms (several of which are related to, but are distinct from pain), several additional secondary measures were utilized to evaluate for 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)[18]; 2) the Short Form-McGill Pain Questionnaire (assesses different characteristics of neuropathic pain such as throbbing, gnawing, shooting, aching, and burning)[19]; 3) the Brief Pain Inventory-Short Form (BPI; assesses pain and its effects on functional abilities)[20]; 4) the Subjective Global Impression of Change (SGIC; a 7-point scale which rates the 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')[21]; 5) the Symptom Distress Scale (a 5-point scale which evaluates a range of symptoms commonly encountered by cancer patients)[22]; 6) the Profile of Mood States (POMS) Short Form (a 30-item scale to assess mood states)[23]; 7) a quality of life (QOL) Uniscale (a single-item measurement of global QOL on a numerical analog scale from 0 to 100)[24]; and 8) the Neuropathy Pain Scale (NPS)[25] (a 10-point scale that evaluates several specific pain qualities). These secondary measures and adverse events were assessed prospectively by biweekly phone calls and questionnaires. Toxicities were graded using the United States National Cancer Institute Common Toxicity Criteria (version 3).

Statistical Methods

This study was designed to have 60 patients in each arm to provide 80% power to detect differences in 'average' pain scores of 0.57 standard deviation for each coprimary endpoint (moderate effect size), with a 2-sided type I error rate of 2.5% to account for the presence of 2 primary endpoints via a Bonferroni correction. Patients were stratified by type of neurotoxic chemotherapeutic agents (vinca alkaloids vs taxanes vs platinum-based compounds vs combination of 2 or more of the previous agents); age; and whether the patient was enrolled during chemotherapy versus after completion of therapy. Methods used to analyze the data in the present study were similar to those used for previous NCCTG 2-treatment, placebo-controlled trials.[26–28] Analytical procedures used in these studies have been compiled into a specialized computer algorithm by the Mayo Clinic Cancer Center Statistics Unit for use in crossover studies.[29] These routines have recently been augmented by inclusion of a Bayesian modeling approach involving Markov Chain Monte Carlo procedures and Gibbs sampling.[30]

RESULTS

Between February 2004 and March 2005, 131 patients meeting the study entry criteria were registered. Of these, there were 4 cancellations and 2 patients were found to be ineligible. There were 125 eligible patients randomized to receive lamotrigine (n = 63) and placebo (n = 62). The CONSORT diagram[31] is depicted in Figure 1.

Patients in each arm were generally balanced with regard to demographic factors and chemotherapy drug(s) responsible for CIPN at baseline (Table 1). The proportion of patients actively receiving neurotoxic chemotherapy at the time of enrollment was 38% and 45% ($P = .47$) for the lamotrigine and placebo arms, respectively, with the others having completed chemotherapy at the time of enrollment. At the time of study entry, the scores for average pain using the NRS were 4.2 and 3.6 ($P = .22$), and symptoms using the ENS were 2.0 and 1.9 ($P = .31$) for the lamotrigine and placebo, respectively. Baseline symptoms were generally similar in severity when

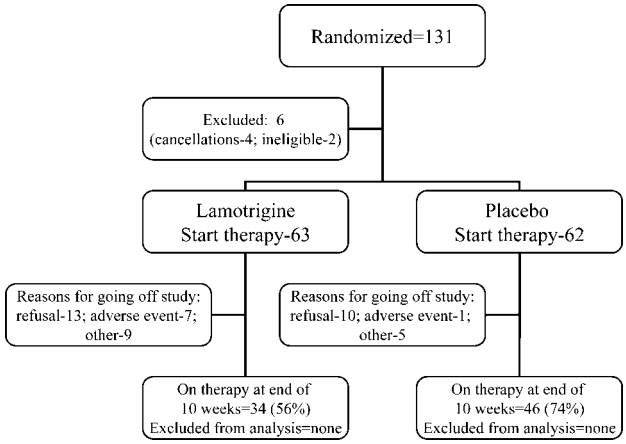

FIGURE 1. Consort statement.

measured using the other scales; however, a few minor differences were noted in a few of the secondary measures. For example, patients on lamotrigine had a higher score on the NPS sensitivity scale (mean, 3.5, 2.4; $P = .03$) and lower scores on the Symptom Distress Scale (SDS) insomnia scale (mean, 61, 71; $P = .05$) and SDS nausea frequency scale (mean, 88, 93.5; $P = .03$). There were no other significant differences in baseline characteristics by treatment arm.

At the end of the 10 weeks of therapy, symptom severity decreased, without significant differences between treatment groups. The mean score for average pain using the NRS decreased by 0.3 and 0.5 units ($P = .56$) (Fig. 2) and symptom severity measured by the ENS decreased by 0.4 and 0.3 units ($P = .36$) (Fig. 3) in the lamotrigine and placebo arms, respectively. Similarly, the changes in the worst and least pain scores by NRS (−0.2 and 0.1) and the WHO pain scales (−0.2 and −0.1) (Fig. 4) were similar between the lamotrigine and placebo arms, respectively. A few minor differences were noted between the 2 groups with regard to some of the secondary endpoints; for example, patients on the placebo arm more often reported a 10% improvement in SDS appearance (27% vs 10%, respectively; $P = .01$) and NPS hot pain (−0.3 vs 0.3, respectively, $P = .03$ at week 6). These findings likely are the artifacts of multiple testing, and do not appear to be clinically significant. No other differences were noted between the 2 groups using any of the other secondary endpoints (ie, SDS, McGill Pain Rating Index, BPI, QOL Uniscale, and SGI) at any point during therapy. These results are depicted in Table 2.

None of the subsets of patients, based on the stratification factors (eg, those patients still receiving chemotherapy vs those who had completed therapy), had a statistically significant different response to the study drug compared with placebo. Post hoc subset analyses did not reveal any significant differences in the outcomes between the 2 groups among patients with the highest symptom scores at baseline. At the end of the 10 weeks of therapy, 80 (65%) of those enrolled were receiving therapy; 34 (56%) and 46 (74%) of those randomized to lamotrigine and placebo, respectively.

TABLE 1
Baseline Characteristics

Characteristic	Lamotrigine (N = 63)	Placebo (N = 62)	Total (N = 125)	P
Mean age (range), y	62 (29-84)	59 (34-82)	61 (29-84)	.3
Gender				
Female	36 (57%)	38 (61%)	74 (59%)	.7
Male	27 (43%)	24 (39%)	51 (41%)	
Race				
Missing/refused	1	0	1	
Asian	1 (1.6%)	0 (0%)	1 (0.8%)	
Black	2 (3%)	5 (8%)	7 (6%)	.4
White	59 (94%)	57 (92%)	116 (93%)	
Chemotherapy				
Active	24 (38%)	28 (45%)	52 (42%)	.5
Discontinued or completed	39 (62%)	34 (55%)	73 (58%)	
Neurotoxic chemotherapy agents				
Vinca alkaloids	20 (32%)	24 (39%)	44 (35%)	
Taxanes	21 (33%)	13 (21%)	34 (27%)	.6
Platinum-based compounds	5 (8%)	4 (6%)	9 (7%)	
Combination	16 (25%)	19 (31%)	35 (28%)	

Adverse events occurred at relatively equivalent rates in both groups (Table 3). However, patients receiving lamotrigine were more likely to go off study because of refusals or adverse events than were patients on placebo (33% vs 18%, respectively, $P = .06$). The most common toxicities that were grade 2 or more in severity, as reported by those enrolled in the lamotrigine and placebo arms, were: ataxia (24%; 16%), rash (6%; 5%) constipation (0; 2%), arthralgia (2% each), dyspepsia (2; 0%), nausea and vomiting (0; 2%), pruritis (2%; 0), fatigue (2% each), and headache (0 and 4%), respectively. There was no statistically significant difference in the incidence of any of these individual toxic events between the 2 groups.

DISCUSSION

Chemotherapy-induced neuropathy is a common and often debilitating toxicity induced by exposure to several commonly used chemotherapeutic agents. Whereas much clinical research has focused on developing therapies for neuropathy from several different etiologies, to our knowledge very little of this

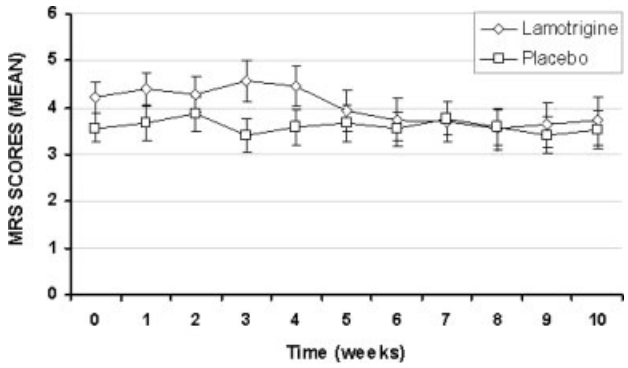

FIGURE 2. Numerical rating scale (NRS) scores for 'average' pain over the duration of the study in both arms. Error bars represent the standard error of the mean.

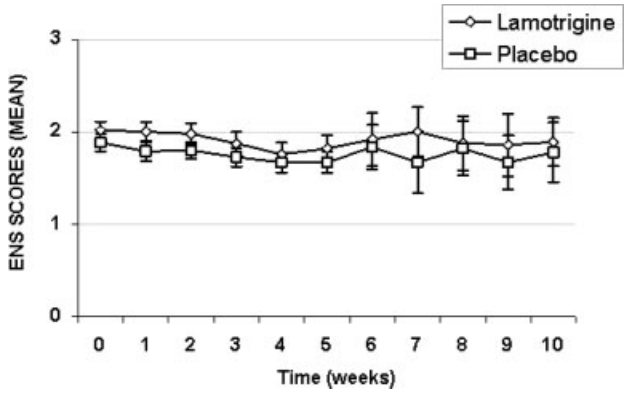

FIGURE 3. Symptoms evaluated by the Eastern Cooperative Oncology Group (ECOG) neuropathy scale (ENS) over the duration of the study therapy. Error bars represent the standard error of the mean.

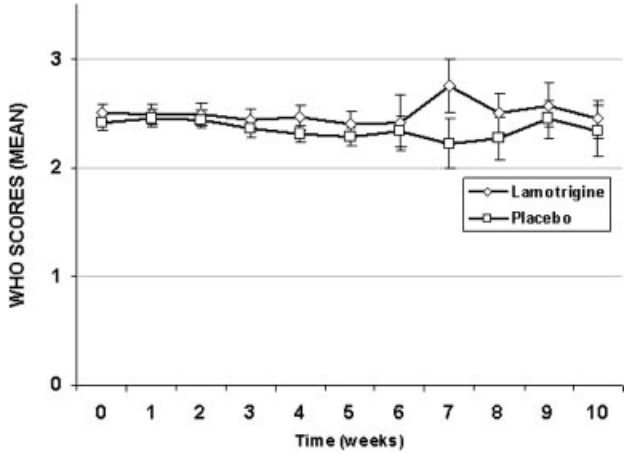

FIGURE 4. Symptoms as evaluated by the World Health Organization (WHO) score over the duration of the study in both arms. Error bars represent the standard error of the mean.

TABLE 2
Outcome Analysis Results for the Symptom Scores in Both Groups

		Baseline	*P**	Change at the end of study (10 weeks)	*P**
No. in each group	Lamotrigine	63		34	
	Placebo	62		46	
Mean NRS–"average" pain†	Lamotrigine	4.1	.6	−0.3	.5
	Placebo	3.7		−0.5	
Mean NRS–"worst" pain†	Lamotrigine	5.0	.3	−0.2	.5
	Placebo	4.5		−0.8	
Mean ENS†	Lamotrigine	2	.3	−0.4	.4
	Placebo	1.9		−0.3	
Adverse event (grade ≥2)	Lamotrigine	NA		26	NS
	Placebo	NA		28	
Mean total SDS score	Lamotrigine	74.9	.84	4.4	1.0
	Placebo	75.4		4.0	
BPI "average" score†	Lamotrigine	3.8	.98	−0.1	.2
	Placebo	3.8		−0.8	
McGill Pain Rating Index†	Lamotrigine	38.3	.2	−12.3	.3
	Placebo	32.5		−4.0	
QOL uniscale‡	Lamotrigine	64.1	.9	−4.3	.3
	Placebo	64.6		0.3	
Subject Global Impression of Change, no. of patients who noted an improvement‡	Lamotrigine	—	—	6	.4
	Placebo	—		8	

NRS indicates numerical rating scale; ENS, Eastern Cooperative Oncology Group neuropathy scale; NA, not available; NS, not significant; SDS, Symptom Distress Scale; BPI, Brief Pain Inventory; QOL, quality of life.

* *P* values correlate with comparisons between the 2 groups at the corresponding timepoint.

† Higher scores indicate greater severity of symptoms.

‡ Higher scores indicate lesser severity of symptoms.

effort has focused on patients suffering from peripheral neuropathy caused by chemotherapeutic agents. To our knowledge to date, no single therapeutic modality has been demonstrated to have a benefit when used to treat and/or prevent CIPN. Identifying an active and well-tolerated agent to treat CIPN is thus an unmet need for oncology patients. The identification of such an agent should have a significant positive impact in the management of patients with CIPN and on the applicability of chemotherapy in general.

A main strength of this study is the inclusion of a placebo control arm for an adequate comparison of drug effect. In the absence of such controlled comparisons, natural temporal improvement of symptoms may have been falsely attributed to drug effect(s). The relatively high proportion of patients who failed to complete therapy may be noted as a limitation. Although one would have liked to have seen all of the entered patients complete the entire planned study program, extensive experience has repeatedly demonstrated that this is not clinical reality for symptom control studies in oncology. In this

TABLE 3
Adverse Events Attributed to Therapy*

Adverse event attributed to drug	Lamotrigine	Placebo	*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%)	

* Symptom severity was measured using the National Cancer Institute's Common Toxicity Criteria (v. 3.0).

regard, the experience in this study is comparable to another recently completed study in which gabapentin was tested for its effects on CIPN symptoms.[5] In many aspects, this experience is not unlike regular clinical practice when instituting a potentially effective (or ineffective) treatment for management of a symptom, wherein patients who perceive a lack of benefit choose to stop therapy.

The dose chosen to be tested in this study (300 mg per day) was selected based on efficacy data from a previous study.[13] Subsequent studies have used a slightly higher dose (400 mg daily) as possibly being more efficacious. However, a subsequent randomized controlled trial that tested this higher dose in HIV neuropathy patients was negative.[32] Moreover, the high rate of discontinuation of therapy in this study (higher in the lamotrigine arm when compared with placebo) would indicate that a higher dose would be less well tolerated. Therefore, it appears unlikely that the lack of efficacy noted in this study can be attributed to suboptimal dosing.

The suggested benefit of lamotrigine in treating neuropathic symptoms is based on preclinical studies that suggest that sodium channel inhibitors reduce signaling caused by neuronal damage.[7–9,33–37] In addition, there are some clinical data (mostly from small uncontrolled clinical trials) suggesting a benefit to using lamotrigine for treating pain in normal volunteers or in patients with a variety of neuropathic syndromes.[10,12–14,38–46] Conversely, several other studies have noted either a lack of benefit or an inconsistent benefit[47–49] when lamotrigine was tested for its benefit in neuropathy, a meta-analysis of all the placebo-controlled studies published concluding that there were no data to support the utility of lamotrigine as a therapy for pain syndromes.[50] This current trial adds to this literature, with evidence supporting the lack of efficacy of lamotrigine when used to treat CIPN-related symptoms.

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