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Efficacy of gabapentin in treating chronic phantom limb and residual limb pain

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Abstract—Twenty-four adults with phantom limb pain (PLP) and/or residual limb pain (RLP) participated in a double-blind crossover trial. Participants were randomly assigned to receive gabapentin or placebo and later crossed over to the other treatment, with a 5-week washout interval in which they did not receive medication. Gabapentin was titrated from 300 mg to the maximum dose of 3,600 mg. Measures of pain intensity, pain interference, depression, life satisfaction, and functioning were collected throughout the study. Analyses revealed no significant group differences in pre- to posttreatment change scores on any of the outcome measures. More than half of the participants reported a meaningful decrease in pain during the gabapentin phase compared with about one-fifth who reported a meaningful decrease in pain during the placebo phase. In this trial, gabapentin did not substantially affect pain. More research on the efficacy of gabapentin to treat chronic PLP and RLP is needed.

Key words: amputation, chronic pain, gabapentin, limb loss, pain, pain treatment, phantom limb pain, randomized clinical trial, residual limb pain, treatment.

INTRODUCTION

Both phantom limb pain (PLP) and residual limb pain (RLP) are common chronic conditions in persons with amputation. A number of studies suggest that as many as 55 to 85 percent of persons who have had amputations will experience PLP at some point following the amputation [1–6]. Of persons with chronic PLP, as many as one-quarter are estimated to experience moderate to severe disability due to their PLP [2,7]. RLP is also quite common, affecting more than half of persons with amputation [2,6,8]. Unfortunately, although persons with limb loss

Abbreviations: ANOVA = analysis of variance, BPI = Brief Pain Inventory, CES-D = Center for Epidemiologic Studies Depression Scale, CHART = Craig Handicap Assessment and Reporting Technique, FIM = Functional Independence Measure, GABA = gamma-aminobutyric acid, NRS = numerical rating scale, PLP = phantom limb pain, RLP = residual limb pain, SF-MPQ = short-form McGill Pain Questionnaire, SWLS = Satisfaction with Life Scale, VAS = visual analog scale.

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report trying a number of pharmacological and nonpharmacological treatments to alleviate pain, the literature lacks controlled clinical trials of existing interventions [9].

Gabapentin, a drug originally developed as an antiepileptic medication, has become increasingly popular as a treatment for chronic PLP and RLP. Gabapentin is derived by addition of a cyclohexyl group to the backbone of gamma-aminobutyric acid (GABA). In brain membranes, gabapentin interacts with a high-affinity binding site, which is an auxiliary subunit of voltage-sensitive calcium channels. Human and rat brain nuclear magnetic resonance spectroscopies indicate that gabapentin increases GABA synthesis in vivo. In vitro, gabapentin increases nonsynaptic GABA responses from neuronal tissues and reduces the release of several monoamine neurotransmitters [10]. In rats, gabapentin increases the threshold for mechanical allodynia after spinal nerve ligation [11].

Several studies suggest that gabapentin effectively reduces pain associated with some chronic pain conditions in humans. These investigations include retrospective studies that suggest efficacy for sympathetically mediated pain syndromes [12], PLP [12], and cancer pain [13], as well as prospective studies for postherpetic neuralgia [14] and neuropathic pain secondary to multiple sclerosis [15]. For example, a prospective, double-blind, randomized study of pain due to diabetic neuropathy found a significantly greater reduction in daily pain in patients who received an 8-week trial of gabapentin (up to 3,600 mg/day) than in patients who received 8 weeks of placebo [16]. Quality of life (as measured by the 36-Item Short-Form Health Survey) and sleep were also significantly improved in the gabapentin-treated group compared with the placebo group. However, a study comparing gabapentin with amitriptyline showed little difference between the two for relief of pain associated with diabetic neuropathy, although relatively low doses of gabapentin (900 or 1,800 mg/day) were used [17].

Although gabapentin is commonly prescribed for chronic PLP and RLP, only one published randomized clinical trial of its efficacy was identified [18]. In the study, 19 multidisciplinary pain clinic patients with PLP were entered into a randomized, double-blind, placebo-controlled, crossover trial comparing gabapentin with an inert placebo. Each treatment phase was 6 weeks long with a 1-week washout period in between. During the active medication phase, gabapentin was titrated in increments of 300 mg to either the maximum tolerated dose or 2,400 mg. For the 14 participants who completed both phases of the study, both gabapentin and placebo treatments resulted in reduced pain intensity scores, as measured by a 100 mm visual analog scale (VAS). Analyses revealed that PLP intensity change scores were significantly greater for gabapentin as compared with placebo; however, the two treatment groups did not significantly differ on measures of sleep interference, mood, or activities of daily living. The authors reported that gabapentin was generally well tolerated, with few side effects. This study did not examine RLP; thus whether gabapentin effectively relieves this type of pain is unknown.

Given the potential for gabapentin to relieve PLP and RLP, as well as the fact that it is already commonly prescribed for these conditions, we performed a double-blind, randomized, placebo-controlled, crossover trial to test its efficacy in persons with chronic PLP and RLP. The primary study hypothesis was that gabapentin would be superior to placebo in reducing PLP and RLP intensity. A secondary hypothesis was that gabapentin would be superior to placebo in increasing activity levels and participation and in reducing distress and use of pain-related medical services in persons with PLP and RLP.

METHODS

Participants

We solicited participants from several sources. Notices of the study were placed in area clinics and prosthetists' offices serving patients with amputation. Potential study participants were asked to contact the investigators to learn more about the study. Patients being seen for amputation-related clinical care at Good Samaritan Hospital in Puyallup, Washington, were also approached about possible study participation. Survey respondents from a previous study of patients treated for amputation at Harborview Medical Center (a regional trauma center) or Department of Veterans Affairs Puget Sound Health Care System who indicated interest in future research participation were called on the telephone and asked if they might be interested in participating [2].

Study inclusion criteria were as follows:

1. Lower-limb amputation at least 6 months prior.
2. Average pain rating in the last month of at least 3 on a 0 to 10 numerical rating scale (NRS) in either the phantom or residual limb.
3. Agreement with medication schedules and protocols.
4. Ability to read and speak English.

Individuals were excluded if they were younger than 18 years; taking other antiepileptic medication or cimetidine (Tagamet); consuming more than two alcoholic drinks per day; if female, pregnant or breast-feeding a baby; found to have a high serum creatinine clearance level or low estimated creatinine clearance in a screening serum creatinine; or found to have a history of kidney disease. The University of Washington Human Subjects Review Committee approved the study, and each subject gave informed written consent.

Among 78 individuals screened for potential participation, 25 were ineligible. The most common reasons for ineligibility were not enough pain (less than 3 on the 0 to 10 NRS, sporadic pain) and abnormal serum creatinine levels. Twenty-nine participants declined to participate. The most common reasons for declining were not wanting to take the study medication and prior negative experience with gabapentin. A total of 24 persons (45% of those eligible) enrolled in the study.

Measures

Primary Outcome

Participants rated PLP, defined as painful sensations in the part of the limb that had been amputated, and RLP, defined as pain in the residual limb (also known as the stump), using a 0 (no pain) to 10 (pain as bad as it could be) NRS. During both phases, participants were called three times during pretreatment and the last week of treatment and asked to use the NRS to rate their average and worst PLP and RLP in the previous 24 hours. These three ratings were then averaged to produce composite scores of average and worst PLP and RLP pain within each 7-day assessment window.

Secondary Outcomes

Following each phase, participants were asked to rate the meaningfulness of change in pain from pre- to post-treatment using the following 5-point categorical scale:

1. "My pain decreased to a meaningful extent."
2. "There was some decrease in my pain but not enough to be meaningful."
3. "There was no change in my pain."
4. "There was some increase in my pain but not enough to be meaningful."
5. "My pain increased to a meaningful extent."

Similarly, to assess overall benefit from the study medication, participants were asked after each treatment phase and before unblinding to choose one of the following descriptors:

1. "The benefits far outweighed the negative side effects."
2. "The benefits somewhat outweighed the negative side effects."
3. "There were no benefits or side effects, or there were very mild benefits and side effects."
4. "Although there were both benefits and side effects, they were about equal."
5. "The negative side effects somewhat outweighed the benefits."
6. "The negative side effects far outweighed the benefits."

Participants were also asked after each treatment phase to guess which medication they had just received and on what they had based their guess (i.e., based on pain relief, side effects, or other reasons).

Pain interference was assessed with a modified version of the pain interference scale of the Brief Pain Inventory (BPI) [19], which asks respondents to rate the degree to which pain has interfered during the past week with seven daily activities, including general activity, mood, walking, normal work, relations with other people, sleep, and enjoyment of life. The walking item was changed to "mobility (ability to get around)" to be relevant to participants who were unable to walk, and three items pertaining to self-care, recreational activities, and social activities were added to gain a more thorough perspective of pain interference. The pain interference scale of the BPI has demonstrated its validity through strong associations with pain intensity across diverse pain conditions [19].

The short-form McGill Pain Questionnaire (SF-MPQ) consists of 15 pain descriptors that respondents rate on a scale from 0 (none) to 3 (severe) [20]. The SF-MPQ total score correlates highly with the original MPQ total score and is sensitive to the effects of treatments for pain [20].

Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item scale assessing how often participants have felt various depressive symptoms during the past week [21]. The CES-D has been shown to be a reliable and valid measure of depressive symptoms [21]. In addition, the CES-D has been shown to be a valid measure of depression among patients with chronic pain [22].

The Functional Independence Measure (FIM) is an 18-item measure that was developed by the American Congress of Rehabilitation Medicine and the American Academy of Physical Medicine and Rehabilitation Task Force to Develop a National Uniform Data System for Medical Rehabilitation. The FIM rates the severity of patient disability and assesses outcomes of medical rehabilitation [23]. The FIM assesses independent functioning in self-care, sphincter control, mobility, transfers, locomotion, communication, and social cognition. An interview version of the FIM [24] was used in this study.

The Satisfaction with Life Scale (SWLS) is a 5-item scale that measures global life satisfaction [25]. Diener et al. demonstrated that the SWLS assesses a single factor and has excellent test-retest stability and internal consistency [25].

To assess disability, we used an interview version of the Craig Handicap Assessment and Reporting Technique (CHART) [26]. The CHART is a 27-item measure that assesses six dimensions: orientation, physical independence, mobility, occupation, social integration, and economic self-sufficiency. Respondents indicate the time spent in various activities, as well as their level of independence when performing these activities. Test-retest stability of the interview responses to the CHART is excellent [26].

Finally, participants were asked to indicate the temporal pattern of any PLP before and after each treatment phase by rating their PLP as—

1. "Constant with little or no variation."
2. "Constant with variations in intensity."
3. "Some pain-free periods."

Based on their response to this question, participants were classified into three groups: those who reported a change from constant pain at pretreatment to intermittent pain at posttreatment (improved), those who reported a change from intermittent pain at pretreatment to constant pain at posttreatment (worse), and those who reported the same pattern of PLP from pre- to posttreatment (no change). This process variable helped us understand the impact of gabapentin on the meaningfulness ratings (see analyses that follow).

Study Design and Procedures

The study was a double-blind, randomized, placebo-controlled, crossover trial of gabapentin for the treatment of pain in persons with amputations. All participants received 6 weeks of therapy with gabapentin and 6 weeks of therapy with placebo (lactose) in random order. After being screened and enrolled in the study, participants underwent a full medical history and physical examination. Telephone interviews were conducted during the pretreatment week prior to both phases of treatment. During the interviews, participants were asked to complete the primary and secondary outcome measures described in the methods section. Participants were then randomly assigned to receive either gabapentin (n = 11) or placebo (n = 13) during the first phase of treatment. The study pharmacist conducted the randomization technique using computer-generated random numbers. The Harborview Medical Center pharmacy compounded gabapentin and placebo capsules that were identical in appearance so that study investigators and participants could not determine study assignment by the capsules.

The research study nurse contacted each participant to assess pain intensity and side effects. If a participant continued to report pain with few or no side effects, the dose was titrated to the next standardized level. Dose increases followed a standardized titration schedule (300 mg increases every 2 to 3 days) unless the pain intensity rating was 0 or uncomfortable side effects were reported. In the case of side effects, doses were either decreased or maintained at the same level, depending on the severity of the side effects. Participants receiving gabapentin were titrated from an initial dose of 300 mg on day 1 to the maximum tolerated dose or 3,600 mg maximum, taken in three divided doses. Seventy-nine percent (19) achieved the maximum dose of 3,600 mg (82% during Phase 1 and 77% during Phase 2). Identical dosing procedures were used for the placebo phase of treatment; that is, the number of placebo capsules taken was titrated so that it matched the standardized titration schedule of the gabapentin phase. Similarly, if participants reported side effects or a pain intensity of 0 during the placebo phase, the number of capsules was either decreased or maintained at the same level. Phase 1 posttreatment telephone interviews were completed during week 6 in which participants again completed all primary and secondary outcome measures. Participants in both groups were gradually titrated off of the medication during week 7. After a washout period of 5 weeks, Phase 2 of the study was conducted following the same procedures as Phase 1: pre- and posttreatment telephone interviews (during weeks 12 and 18, respectively), weekly contact with the research study nurse, and 6 weeks (weeks 13–18) of whichever study medication was not received during Phase 1, following the same titration schedule.

At the end of Phase 2 of treatment, a study investigator who was not involved in data collection or analyses unblinded the participants.

Overview of Data Analyses

We examined the significance of changes in pain intensity during the gabapentin phase compared with the placebo phase by first calculating change scores (posttreatment minus pretreatment) for each participant during each phase. We then calculated change scores for average and worst PLP intensity and average and worst RLP intensity. For each of the four measures of pain intensity, we used a paired samples *t*-test to compare each participant's change score while receiving gabapentin with his or her change score while receiving placebo. We used the same procedures to test the significance of changes in pain interference (BPI), pain sensations (SF-MPQ), depressive symptoms (CES-D), satisfaction with life (SWLS), and functional ability (FIM, CHART).

In addition, we tested for possible order effects by performing four two-way analyses of variance (ANOVAs), with treatment order (first vs second phase) and drug (gabapentin vs placebo) as the independent variables and pain intensity change score (examined separately for average and worst PLP and average and worst RLP) as the dependent variable. In this way, we were also able to test for interactions between treatment order and drug for each of the four pain intensity change scores. Because amputation-related pain is often intermittent, we believed that constancy of pain (constant vs intermittent) was another potentially important outcome. We hypothesized that gabapentin would change the pattern of pain such that pain episodes would be experienced less often. Therefore, we conducted Pearson's chi-square analyses to examine any differences in the proportions of participants who reported constant versus intermittent pain at pre- and posttreatment. We conducted exploratory analyses, described in more detail in the results section, to further investigate several interesting findings that emerged regarding reported meaningfulness of changes in pain and reported benefits of the drug.

RESULTS

Participant Characteristics

Table 1 presents sociodemographic and amputation characteristics for the 24 participants. The majority of participants (n = 21) had lower-limb amputations. **Table 2** presents characteristics of the participants' PLP and RLP at enrollment.

At the end of each phase, participants were asked to guess which medication they had been receiving. Of the 21 participants who answered this question after the gabapentin phase, 15 (62.3%) correctly guessed gabapentin, while 6 (25.0%) incorrectly guessed placebo. Of the 15 participants who guessed accurately, 7 based their guess on pain relief, 3 on side effects, 4 on both pain relief and side effects, and 1 on other reasons. Of the 6 who guessed incorrectly, 2 based their guess on pain relief, 2 on side effects, and 2 on both pain relief and side effects. Of the 20 participants who answered this question after the placebo phase, 12 (50.0%) correctly guessed placebo, while 8 (33.3%) incorrectly guessed gabapentin. Of the 12 participants who guessed accurately, 4 based their guess on pain relief, 0 on side effects, 5 on both pain relief and side effects, and 3 on other reasons. Among the 8 who guessed incorrectly, 2 based their guess on pain relief, 3 on side effects, 2 on both pain relief and side effects, and 1 on other reasons (i.e., "random guess"). The proportions of participants who guessed correctly in the gabapentin phase compared with the placebo phase were not significantly different (χ^2 = 0.60, p = 0.44).

Of the participants who reported that their pain decreased to a meaningful extent during the gabapentin phase, eight correctly guessed gabapentin, three incorrectly guessed placebo, and two did not answer the question. Of the participants who reported a meaningful pain decrease during the placebo phase, only one correctly guessed placebo, three incorrectly guessed gabapentin, and one did not answer the question. These analyses support the conclusion that participants could not easily identify whether they were receiving gabapentin or placebo and therefore the blinding process was successful.

Pain Intensity

As shown in **Table 3**, no significant differences in pre- to posttreatment pain intensity change scores while receiving gabapentin versus placebo were found for any of the four types of pain intensity (average and worst PLP and average and worst RLP). Effect sizes for these analyses ranged from 0.31 to 0.36, values usually interpreted as small [27]. In addition, **Table 4** shows that no significant differences were found for change scores in pain sensations (SF-MPQ), depressive symptoms (CES-D), or pain interference (BPI). Satisfaction with life (SWLS) and

Table 1.
Sociodemographic and amputation characteristics of study participants (N = 24).

Characteristic	Value
Age (yr)	
Mean ± SD	52.1 ± 15.5
Range	25–76
Sex, %	
Male	75.0
Female	25.0
Ethnic Group, % (*n*)	
Caucasian	70.8 (17)
African American	12.5 (3)
Native American	8.3 (2)
Other	8.3 (2)
Marital Status, % (*n*)	
Married	41.7 (10)
Separated/divorced	33.4 (8)
Living with partner	8.3 (2)
Never married	8.3 (2)
Widowed	8.3 (2)
Education, % (*n*)	
Eleventh grade or below	4.2 (1)
High school graduate	16.7 (4)
Vocational/technical/some college	50.0 (12)
College graduate	25.0 (6)
Graduate/professional school	4.2 (1)
Employment Status, % (*n*)*	
Employed full time	25.0 (6)
Employed part time	12.5 (3)
Retired	41.7 (10)
Unemployed due to disability	25.0 (6)
Unemployed other	4.2 (1)
Level of Amputation, % (*n*)	
Transfemoral	33.4 (8)
Transtibial	41.7 (10)
Total knee	4.2 (1)
Hip	4.2 (1)
Toes	4.2 (1)
Hand	4.2 (1)
Transhumeral	4.2 (1)
Shoulder	4.2 (1)
Cause of Amputation, % (*n*)*	
Tumor	8.3 (2)
Diabetes	8.3 (2)
Vascular disease	8.3 (2)
Injury	54.2 (13)
Infection	25.0 (6)
Gangrene	12.5 (3)
Other	12.5 (3)

*Sum is > 100% because participants could give more than one response.
SD = standard deviation.

Table 2.
Pain and sensation characteristics at enrollment.

Limb Pain	Value
Phantom Limb Pain (PLP)	
Participants with PLP (%)	87.5
Constant PLP, little variation	8.3
Constant PLP, with variation	29.2
Some pain-free periods	58.3
PLP rating (mean ± SD)	4.38 ± 2.57
Frequency of Intermittent PLP	
Hourly	16.7
Daily	29.2
Weekly	8.3
Duration of PLP Episodes (min)	
Median	45.00
Range	1–840
Location of PLP (%)*	
Calf	29.2
Ankle	41.7
Foot	75.0
Toes	50.0
Residual Limb Pain (RLP)	
Participants with RLP (%)	83.3
RLP rating (mean ± SD)	3.96 ± 2.73
Nonpainful Limb Sensations (NPLS)	
Participants with NPLS (%)	50.0
Location of NPLS (%)*	
Calf	20.8
Ankle	20.8
Foot	33.3
Toes	33.3

*Sum is > 100% because participants could give more than one response.
SD = standard deviation.

functional ability (FIM, CHART) change scores were also not significant (not shown). Results of two-way ANOVAs with drug (gabapentin vs placebo) and treatment order (first vs second phase) as the independent variables and pain intensity change scores as the dependent variable were not significant for average and worst PLP and RLP. We ruled out order effects because neither a main effect for treatment order nor a significant interaction between drug and order was found.

Meaningfulness of Change in Pain

As described earlier, participants were asked at the end of each phase to rate the meaningfulness of any PLP or RLP change on a scale from 1 (My pain decreased to a

Table 3.
Pre- and posttreatment pain intensity and change scores.

Measure	Gabapentin Phase (Mean ± SD)			Placebo Phase (Mean ± SD)			Gabapentin vs Placebo	
	Pre	Post	Pre – Post	Pre	Post	Pre – Post	*t* *	ES
Average PLP	4.38 ± 2.57	3.43 ± 2.45	0.94 ± 1.98	4.09 ± 2.44	3.60 ± 2.67	0.49 ± 2.20	0.70	0.31
Worst PLP	5.91 ± 3.15	4.65 ± 3.05	1.15 ± 2.41	5.59 ± 2.98	4.82 ± 3.22	0.58 ± 2.86	–0.64	0.35
Average RLP	3.63 ± 2.75	2.26 ± 1.94	1.22 ± 2.56	3.21 ± 2.43	2.79 ± 2.28	0.74 ± 1.94	0.81	0.36
Worst RLP	4.71 ± 3.26	3.35 ± 2.93	1.22 ± 3.32	4.71 ± 3.00	4.21 ± 3.23	0.65 ± 3.05	0.76	0.32

**t*-scores are not significant.
ES = effect size, PLP = phantom limb pain, RLP = residual limb pain, SD = standard deviation.

Table 4.
Pre- and posttreatment secondary outcome measure scores (pain sensations [SF-MPQ], depression [CES-D], pain interference [BPI]) and change scores.

Measure	Gabapentin Phase (Mean ± SD)			Placebo Phase (Mean ± SD)			*t* *
	Pre	Post	Pre – Post	Pre	Post	Pre – Post	
SF-MPQ Sensory	11.74 ± 7.87	10.71 ± 6.84	1.25 ± 6.80	12.52 ± 7.87	10.35 ± 8.78	2.17 ± 7.52	–1.08
SF-MPQ Affective	3.17 ± 2.81	3.15 ± 3.45	0.21 ± 2.20	3.61 ± 3.35	2.91 ± 3.42	0.70 ± 2.55	–1.65
CES-D	17.50 ± 10.71	13.74 ± 10.17	4.22 ± 9.20	18.58 ± 12.67	14.81 ± 9.82	3.78 ± 10.13	–0.11
BPI	30.51 ± 22.03	23.61 ± 19.40	6.05 ± 29.90	33.36 ± 25.19	25.38 ± 19.29	7.98 ± 24.19	–0.51

**t*-scores are not significant.
BPI = Brief Pain Inventory, CES-D = Center for Epidemiologic Studies Depression Scale, SF-MPQ = short-form McGill Pain Questionnaire, SD = standard deviation.

meaningful extent) to 5 (My pain increased to a meaningful extent). More than half of the participants reported a meaningful decrease in pain during the gabapentin phase compared with about one-fifth who reported a meaningful decrease in pain during the placebo phase (**Table 5**). A Pearson's chi-square analysis revealed that significantly more participants reported a meaningful pain decrease during the gabapentin phase ($\chi^2 = 5.69$, $p < 0.05$).

To investigate this finding further, we performed a two-way analysis of covariance with drug (gabapentin vs placebo) and treatment order (first vs second phase) as the independent variables and meaningfulness of change score as the dependent variable, while controlling for type of PLP (constant vs intermittent) at posttreatment. The covariate, type of PLP, was significant ($F_{1, 46} = 5.70$, $p < 0.05$); specifically, participants with intermittent pain rated their pain decrease as significantly more meaningful (mean = 1.82) compared with participants with constant pain (mean = 3.00). Even after controlling for type of PLP, we still found a significant treatment effect on meaningfulness ($F_{1, 46} = 4.71$, $p < 0.05$) such that participants during the gabapentin phase rated their pain decrease as significantly more meaningful (mean = 1.69) compared with participants during the placebo phase (mean = 2.35). We found no main effect for treatment order and no significant interaction between drug and treatment order.

Reported Drug Benefits

Participants also rated the overall benefit from the drug at the end of each treatment phase. Similar to the meaningfulness question, more than half of the participants of the gabapentin phase reported that the benefits of the drug outweighed the side effects compared with one-third of the placebo participants who reported this level of benefit. Pearson's chi-square analysis of this difference, however, was not statistically significant (**Table 5**). Of participants in the gabapentin phase, approximately 17 percent reported that the side effects outweighed the benefits of the drug compared with approximately 8 percent of participants in the placebo phase, but again, the chi-square analysis was not significant.

Intermittent Versus Constant

Table 6 reports the number and percentage of participants reporting intermittent versus constant pain during each phase. Regarding changes in the temporal pattern of PLP, 6 participants improved (i.e., reported a change from constant to intermittent pain), 16 had no change, and 0 got worse (i.e., reported a change from intermittent to constant

Table 5.
Participant (%) reports of pain decrease and overall treatment benefit.

Participant Response	Gabapentin Phase	Placebo Phase	χ^2
Meaningful Pain Decrease	54.2	20.8	5.69*
Treatment Benefits Outweighed Side Effects	54.2	33.3	2.56
Treatment Side Effects Outweighed Benefits	16.8	8.4	0.40

*$p < 0.05$.

Table 6.
Number and percentage (%) of participants reporting constant vs intermittent phantom limb pain pre- and posttreatment.*

Pain	Gabapentin Phase		Placebo Phase	
	Pre	Post	Pre	Post
Constant	8 (36)	2 (9)	6 (27)	5 (23)
Intermittent	14 (64)	20 (91)	16 (73)	17 (77)

*Only 22 participants were included due to missing data.

pain) during the gabapentin phase. In the placebo phase, 2 participants improved, 19 had no change, and 1 got worse. We conducted a chi-square analysis of the proportions of participants in each of these three groups during the gabapentin phase compared with the placebo phase. Although more participants in the gabapentin phase appeared to move from constant to intermittent pain, a comparison of the proportion of participants in each phase was not statistically significant ($\chi^2 = 3.26$, $p = 0.20$).

DISCUSSION

In contrast to previous studies on the use of gabapentin for neuropathic pain, this study did not find significant differences between gabapentin and placebo on measures of pain intensity. Specifically, pre- to posttreatment change scores for gabapentin versus placebo were not significantly different for any of the four types of pain intensity (average and worst PLP and average and worst RLP). This contrasts with Bone et al.'s study in which PLP pain intensity ratings significantly decreased during the gabapentin phase as compared with the placebo phase [18]. Several important differences between the present study and Bone et al. may account for this discrepant finding. We recruited the present study sample from a wide range of resources, including the community. In contrast, Bone et al.'s participants were persons attending a multidisciplinary pain clinic and thus may have had more room for improvement with gabapentin treatment. In addition, their inclusion criteria required pain intensity ratings of at least 40 on a 100 mm VAS, whereas ours required a 3 or greater on the 0 to 10 NRS. Given the sample sources, the Bone et al. sample not surprisingly had a baseline pain rating (VAS of 67 in placebo first phase, 61 in gabapentin first phase) that was 18 to 35 percent higher than our sample (4.36 in placebo first phase, 5.00 in gabapentin first phase, 4.65 for whole sample). In addition, Bone et al. only studied PLP, whereas we included participants with either PLP or RLP. Gabapentin is possibly more effective in patients reporting greater pretreatment pain intensities (moderate to severe) or in patients specifically with PLP than in patients with RLP or patients who experience only mild pain. Future research must examine the differential effects of different pain severities and pain locations, but our current sample size and design precluded such analyses.

One notable finding is that the pain intensity change scores, the primary outcome variable, varied widely within groups during each phase, as one can see when comparing the mean change scores with their standard deviations (**Table 3**). Why the pain intensity change scores varied so greatly is not clear; however, between-group (or in this case, between-phase) differences are certainly more difficult to detect and effect size is smaller when score variance is high within groups. It may indeed be necessary to conduct a larger trial with more power to detect moderate but still potentially meaningful differences or to identify subgroups of responders.

Interestingly, although we did not find significant differences on the primary outcome measure, exploratory analysis of the secondary measures did demonstrate a significantly greater proportion of participants reporting a meaningful decrease in pain during the gabapentin phase compared with the placebo phase. Participants with intermittent pain rated their pain decrease as significantly more meaningful compared with participants with constant pain, and when we controlled for type of PLP (constant vs intermittent), a significant treatment effect on meaningfulness was still observed. This finding is particularly interesting given that participants did not more accurately guess that they were receiving gabapentin than placebo. Thus, a placebo effect alone does not seem to account for these differences. Several explanations may account for this interesting but very exploratory finding. One possibility is that

the meaningfulness measure was more sensitive to changes in pain than the pain intensity measure used as the primary outcome in this study. In the pain field, the limitations of the 0 to 10 NRS as the only primary outcome measure in trials have been acknowledged [28]. Recently, a consensus panel recommended that participant ratings of global improvement and satisfaction with pain treatment be included as core outcomes in randomized clinical trials of pain treatments [28]. Such measures aggregate multiple aspects of the pain experience, including pain relief, side effects, changes in functioning, and convenience of treatment use, into a single measure. This explanation, while intriguing, is only hypothetical and in need of further study. Future studies of gabapentin should include participant ratings of global improvement and satisfaction with treatment as core outcomes. Another plausible explanation for the differences in meaningfulness of change is that, given the multiple analyses conducted, the finding was simply due to chance and not to an effect of gabapentin.

Several limitations of this trial must be considered in the interpretation of its results. First, the sample size of this study was relatively small and therefore the study was underpowered. Given the increasing popularity of gabapentin treatment for PLP during the study period (1999–2003), we had growing difficulty finding potential participants who had never taken gabapentin. As mentioned earlier, a larger sample size might have increased our power to detect possible significant differences. Another issue to consider is that the participants in the present study may have had different mechanisms underlying their pain; for example, pain from nerve damage directly related to amputation versus pain from muscle cramping in the residual limb. Gabapentin is possibly more effective for one type of pain problem than for others, and these effects may have been washed out in the current sample.

CONCLUSIONS

Despite certain limitations, the current study is the largest reported trial studying gabapentin for chronic PLP and is the only study that has included persons with RLP. The findings suggest that, on average, gabapentin does not provide strong pain relief for these chronic pain conditions. However, the fact that participants reported greater “meaningfulness” of pain relief after receiving gabapentin supports the need for further study of gabapentin in PLP and RLP treatment. Further investigation is warranted to better elucidate the efficacy of gabapentin beyond any placebo effects and to determine if subgroups of persons with amputation respond to its use.

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