Double-blind, randomized, controlled, crossover trial of pregabalin for neurogenic claudication

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ABSTRACT

Objectives: To test the effects of pregabalin on the induction of neurogenic claudication.

Methods: This study was a randomized, double-blind, active placebo-controlled, 2-period, crossover trial. Twenty-nine subjects were randomized to receive pregabalin followed by active placebo (i.e., diphenhydramine) or active placebo followed by pregabalin. Each treatment period lasted 10 days, including a 2-step titration. Periods were separated by a 10-day washout period, including a 3-day taper phase after the first period. The primary outcome variable was the time to first moderate pain symptom (Numeric Rating Scale score ≥4) during a 15-minute treadmill test (T_{first}). Secondary outcome measures included pain intensity at rest, pain intensity at the end of the treadmill test, distance walked, and validated self-report measures of pain and functional limitation including the Roland-Morris Disability Questionnaire, modified Brief Pain Inventory–Short Form, Oswestry Disability Index, and Swiss Spinal Stenosis Questionnaire.

Results: No significant difference was found between pregabalin and active placebo for the time to first moderate pain symptom (difference in median T_{first} = −1.08 [95% confidence interval −2.25 to 0.08], p = 0.61). In addition, none of the secondary outcome measures of pain or functional limitation were significantly improved by pregabalin compared with active placebo.

Conclusions: Pregabalin was not more effective than active placebo in reducing painful symptoms or functional limitations in patients with neurogenic claudication associated with lumbar spinal stenosis.

Classification of evidence: This study provides Class I evidence that for patients with neurogenic claudication, compared with diphenhydramine, pregabalin does not increase the time to moderate pain during a treadmill test. ***Neurology*® 2015;84:265–272**

GLOSSARY

AE = adverse event; **CI** = confidence interval; **NRS** = Numeric Rating Scale.

Neurogenic claudication is the principal symptom associated with lumbar spinal stenosis for which patients seek treatment.[1] Neurogenic claudication has a distinct symptom pattern, most frequently presenting as pain in the buttocks or legs induced by walking or prolonged standing.[2] Lumbar spinal stenosis with neurogenic claudication is the leading indication for lumbar surgery for persons older than 60 years.[3,4] Elderly patients, especially those at risk of perioperative complications and those with moderate symptoms, often prefer to avoid surgery.[5] Furthermore, in a significant number of patients, neurogenic claudication is either not relieved by surgery or recurs within several years after surgery.[6] Although conservative symptom management may be a more appropriate treatment option for these patients, no such treatment for neurogenic claudication is supported by high-quality clinical evidence.[7]

Antiepileptic drugs, such as pregabalin (Lyrica; Pfizer, New York, NY), are efficacious for certain types of neuropathic pain,[8–10] and although very little evidence demonstrates their efficacy

in chronic low back pain syndromes, these drugs are often used to treat various forms of chronic low back pain. To our knowledge, no clinical trial has tested the effects of pregabalin on lumbar spinal stenosis with neurogenic claudication. In this clinical trial, we sought to understand whether the analgesic efficacy of pregabalin observed in other neuropathic conditions could be extrapolated to neurogenic claudication.

METHODS **Standard protocol approvals, registrations, and patient consents.** The University of Rochester Research Subjects Review Board approved this study, and written informed consent was obtained from all participants. This study was registered on clinicaltrials.gov (NCT00638443). A Data and Safety Monitoring Committee reviewed adverse events (AEs) monthly. The level of evidence is Class I.

Study design and intervention. This randomized, double-blind, active placebo-controlled, 2-period, crossover study was conducted at the Translational Pain Research Center at the University of Rochester between May 2008 and January 2010.

Each treatment period consisted of a 2-step titration and taper step, if needed. Pregabalin was started at 75 mg PO twice daily (active placebo, or diphenhydramine, 6.25 mg) and increased on day 4 to 150 mg PO twice daily (12.5 mg diphenhydramine) for 7 days. Pregabalin was decreased to 75 mg PO twice daily (6.25 mg diphenhydramine) on day 11 for 3 days of tapering (figure 1). If a subject could not tolerate 150 mg PO twice daily pregabalin (12.5 mg diphenhydramine), the subject was instructed to lower his or her dosage to 75 mg PO twice daily (6.25 mg diphenhydramine) for the remainder of the period, including the 3-day taper. Treatment periods were separated by a 7-day washout period in which the participant received no treatment. Assessments were made at baseline and on day 10 of each period (before starting the taper step).

Patient population. Eligible subjects were older than 50 years with at least one level of radiographically confirmed lumbar spinal stenosis and symptoms of neurogenic claudication for ≥3 months (i.e., resting pain intensity ≤3/10 on the Numeric Rating Scale [NRS] [0 = no pain, 10 = worst pain imaginable] and inducible pain intensity ≥4/10 within 15 minutes of treadmill ambulation). Subjects were excluded if they had been previously exposed to pregabalin or if they had previous surgery for lumbar spinal stenosis within the past 2 years or received lumbar epidural steroid injection within the past 3 months. Other exclusion criteria included vascular disease (see reference 11 for diagnostic criteria), past or present movement disorder, any neurologic disease that might affect ambulation, cognitive impairment preventing full understanding of the study, moderate to severe arthritis of the knee or hip, serious concomitant medical illness, ongoing treatment with gabapentin, hypersensitivity or allergic reaction to diphenhydramine, and severe psychiatric disorder. Analgesic medications, other than gabapentin, were allowed at stable dosages started before or at baseline.

Randomization and blinding. A computer-generated randomization plan was used for assignment of subjects to 1 of 2 treatment sequences: pregabalin followed by active placebo or active placebo followed by pregabalin. The plan included blocking (block size = 4) to ensure balance between the sequences. The randomization was administered by a study pharmacist and no study personnel other than the programmer who generated the randomization plan and the study pharmacist, or study participants were aware of the treatment assignment. Blinding was maximized with the use of an active placebo, diphenhydramine, which has similar sedative properties to pregabalin and has been used previously as an active placebo in chronic pain trials without sacrificing assay sensitivity.[12–14] Pregabalin and diphenhydramine pills looked identical and were administered via identical titration and taper phases.

Outcome measures. The primary outcome measure was time to first reported pain of moderate intensity (i.e., T_{first} rating ≥4 on the NRS) during treadmill ambulation using a validated protocol.[11,15,16] In brief, subjects sat for 15 minutes before treadmill assessment or until their pain was ≤3, whichever came first. Subjects then walked on a 0° incline at 1.2 mph. They were instructed to walk with an upright posture and were not permitted to lean forward or hold onto the handrails. Subjects were asked to report their pain intensity on the NRS at 30-second intervals. The examination was stopped after 15 minutes or at the onset of severe symptoms (i.e., level of discomfort that would make subjects stop walking in everyday life).[11,15,16]

Secondary outcome measures assessed during the treadmill testing included pain at rest before starting the test, area under the pain intensity–time curve (pain assessed at 30-second intervals), pain intensity after 15 minutes of walking or upon stopping due to severe pain, whichever came first, time and distance walked on the treadmill, and time to return to baseline pain intensity after the treadmill ambulation assessment (recovery time). To compute the area under the pain intensity–time curve, the NRS score was assumed to increase linearly from the NRS score at the time the subject stopped walking due to severe pain to a value of 10 at the 15-minute time point. All pain intensity ratings were based on the 0 to 10 NRS. At each visit, the following patient-reported outcome measures were completed before treadmill testing: patient global assessment of low back pain, Roland-Morris Disability Questionnaire,[17] modified Brief Pain Inventory–Short Form,[18] Oswestry Disability Index,[19] and Swiss Spinal Stenosis Questionnaire.[20]

Safety assessment. AEs were assessed at each visit and during each phone call (days 4, 5, 11, 13, and 14 of each period) using the following open-ended question: "Have you experienced any changes since starting this study drug?"

Sample size calculation. Data from a surgical study using treadmill testing in 50 subjects with severe lumbar spinal stenosis[11] suggested that the mean ± SD of the time to first pain symptom (T_{first}) while taking placebo treatment was approximately 2.0 ± 3.0 minutes. This study provided no information on the variability of the within-subject differences; therefore, we conservatively assumed that the variability of the within-subject difference in T_{first} was the same as the variability of the T_{first} at one time point. A sample size of 26 subjects was required to provide 90% power to detect a mean difference of 2 minutes between groups, using a 2-tailed paired t test and a 5% significance level.

Statistical analysis. The prespecified primary analysis compared the distribution of walking-induced time to first pain of moderate intensity (T_{first} of ≥4 on the NRS) between pregabalin and active placebo periods using an extension of the generalized Wilcoxon test for right-censored data.[21] The level of evidence for this analysis is Class I. The treatment effect was estimated using contrasts among the median T_{first} values
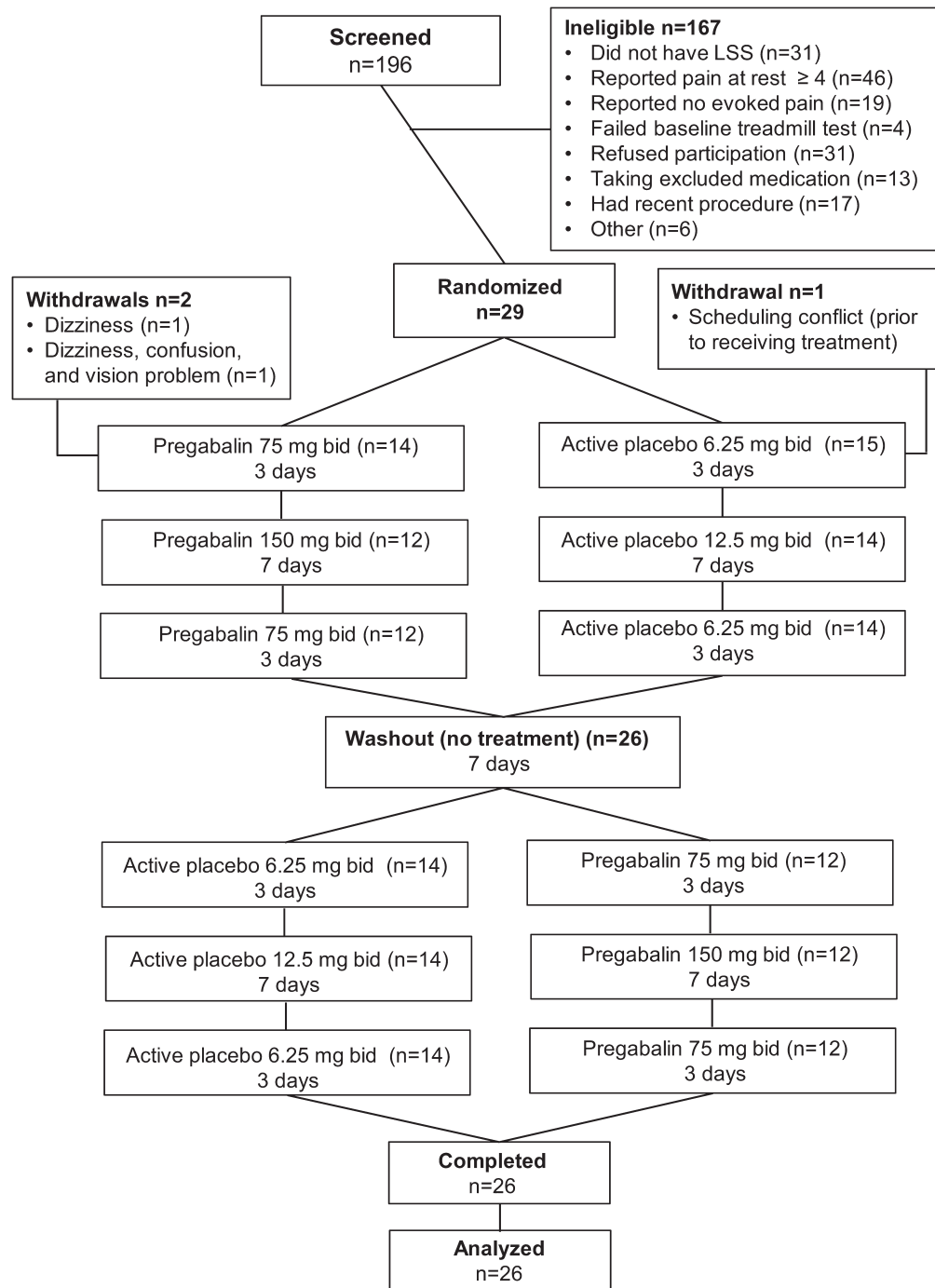
Bid = twice a day; LSS = lumbar spinal stenosis.

obtained from each treatment-period combination, and an associated 95% confidence interval (CI) was obtained from the bootstrap distribution of these treatment effect estimates based on 100,000 bootstrap replications.[21] The effect of pregabalin on the continuous secondary outcome variables was assessed using a mixed-effects analysis of variance model applied to the outcomes obtained at the end of each treatment period, with fixed effects for treatment and period and a random effect for subject.[22] Estimated treatment effects and their associated 95% CIs were obtained from this model. All statistical tests were 2-tailed and performed using a 5% level of significance.

RESULTS **Participants.** A total of 196 subjects were screened for the study; 167 subjects failed prescreening (figure 1). Thirty-three subjects signed consent; 4 subjects failed the treadmill walking test because their pain was not evoked when walking. Twenty-nine subjects were randomized. Three subjects provided no postbaseline data and were not included in the analyses. One subject assigned to receive active placebo first withdrew because of a scheduling conflict before taking any study medication. Two

subjects assigned to receive pregabalin first withdrew in the first period because of AEs. The remaining 26 subjects completed the study (figure 1). The majority of participants were male (73%) and white (96%). Most participants (89%) had neurogenic claudication symptoms for >12 months (table 1). Baseline characteristics are summarized separately for each sequence group and combined in table 1. No apparent clinically meaningful differences between sequence groups were observed (table 1).

Five subjects tapered down to the lower dosage of study drug before the scheduled taper phase (4 during the pregabalin period and one during the placebo period). Two subjects withdrew from the study after tapering to a lower dosage of pregabalin, leaving 3 subjects who completed the study on a reduced dosage of pregabalin and one on a lower dosage of placebo.

Efficacy. No significant difference was found between pregabalin and active placebo in the distribution of time to first moderate pain (difference in median $T_{first} = -1.08$ [95% CI -2.25 to 0.08], $p = 0.61$) (figure 2). No significant differences were detected between pregabalin and active placebo regarding any of the other treadmill test outcomes or patient-reported outcome measures of pain or functional disability with the exception of the

Table 1	Baseline characteristics of trial participants		
Variable	Pregabalin/ diphenhydramine (n = 14)	Diphenhydramine/ pregabalin (n = 15)	Total (n = 29)
Age, y, mean (SD)	71.1 (7.9)	69 (8.7)	70.1 (8.3)
Male sex, n (%)	10 (71)	10 (67)	20 (69)
White, n (%)	14 (100)	14 (93)	28 (97)
Duration of symptoms, n (%)			
3-6 mo	2 (15)	1 (7)	3 (11)
>12 mo	11 (84)	14 (93)	25 (89)
Time to pain onset after standing, n (%)			
1-3 min	7 (50)	6 (40)	13 (45)
3-5 min	3 (21)	8 (53)	11 (38)
5-10 min	4 (28)	0 (0)	4 (14)
>15 min	0 (0)	1 (7)	1 (3)
Body mass index, kg/m², mean (SD)	30.7 (4.4)	33.5 (5.4)	32.1 (5.1)
Treadmill testing, mean (SD)			
Time to NRS score ≥4, min	3.1 (2.5)	2.0 (1.7)	2.5 (2.1)
Pain at rest, NRS	1.5 (1.1)	1.5 (1.4)	1.5 (1.2)
Final pain rating, NRS	7.7 (1.4)	7.1 (1.3)	7.7 (1.3)
Area under pain intensity-time curve	96.7 (26.0)	109.1 (18.0)	103.1 (22.7)
Time walked, min	8.7 (5.0)	6.0 (3.0)	7.3 (4.2)
Distance walked, m	279.7 (161.4)	192.9 (96.3)	234.8 (136.7)
Recovery time, min	3.0 (3.1)	2.7 (2.0)	2.8 (2.5)
Patient global assessment of pain, mean (SD)	2.8 (1.0)	2.9 (1.1)	2.9 (1.0)
Roland-Morris Disability Questionnaire, mean (SD)	12.9 (3.7)	13.8 (4.6)	13.3 (4.1)
Modified BPI-SF, mean (SD)			
Interference score	4.6 (1.8)	4.8 (1.5)	4.6 (1.7)
Pain intensity score	4.6 (1.4)	4.6 (1.9)	4.7 (1.6)
Oswestry Disability Index, mean (SD)	36.4 (9.3)	39.0 (11.0)	37.7 (10.1)
Swiss Spinal Stenosis Questionnaire, mean (SD)			
Symptom severity, mean (SD)	2.9 (0.5)	3.2 (0.4)	3.1 (0.5)
Physical function, mean (SD)	2.3 (0.3)	2.5 (0.5)	2.4 (0.4)

Abbreviations: BPI-SF = Brief Pain Inventory–Short Form; NRS = Numeric Rating Scale.

Figure 2 Distribution of time to walking-induced moderate pain severity (≥4 on 0-10 NRS) by treatment condition
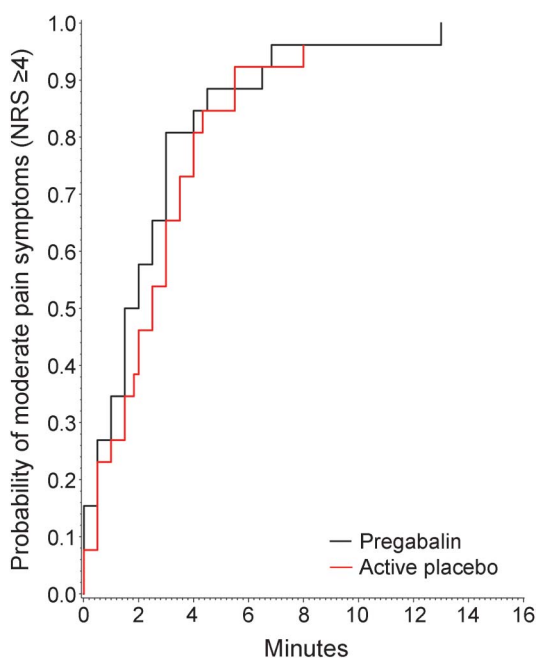
NRS = Numeric Rating Scale.

Roland-Morris Disability Questionnaire, which favored placebo (table 2).

Safety. Nineteen of 28 subjects (64.3%) treated with pregabalin experienced AEs; 9 of the 26 subjects

(34.6%) treated with active placebo experienced AEs. The AEs occurring in each treatment condition can be found in table 3; dizziness was the most common AE during pregabalin treatment. No deaths or serious AEs were reported. Two subjects discontinued participation because of AEs while treated with pregabalin; one experienced dizziness and the other dizziness, confusion, and vision changes. No subjects discontinued participation because of AEs during the active placebo period.

DISCUSSION Although this study had sufficient power to detect a relatively small difference (i.e., 2 minutes) in time to onset of clinically significant pain (≥4 NRS), no effect of pregabalin was detected on this primary outcome variable. Furthermore, the upper limit of the CI was 0.08, suggesting that a benefit of pregabalin that is more than 0.08 minutes of increased low-pain walking time can be ruled out with 95% confidence. Walking tolerance tests are frequently used to assess treatment response after surgery in subjects with neurogenic claudication.[11,15,23] Formal treadmill testing has several advantages. It is a validated,[16,23] direct assessment of physical function that eliminates recall bias associated with most patient-reported outcome measures for pain symptoms. Furthermore, it is highly clinically relevant because it mimics the disabling symptoms for which subjects most often seek medical attention. Finally, it is generally safe and easy to administer.[11,16] Pregabalin also did not improve pain interference or physical function, or lessen

Table 2 Treatment effects on secondary outcome variables

Variable	Pregabalin, mean (SE)	Active placebo, mean (SE)	Treatment effect (95% CI)	p Value
Treadmill testing				
Pain at rest, NRS	1.82 (0.35)	1.53 (0.35)	0.29 (−0.41, 0.98)	0.40
Final pain rating, NRS	7.22 (0.36)	6.97 (0.36)	0.25 (−0.44, 0.94)	0.46
AUC	100.59 (5.15)	95.26 (5.15)	5.33 (−5.85, 16.50)	0.34
Distance walked, m	237.49 (27.47)	261.55 (27.47)	−24.06 (−75.63, 27.52)	0.35
Recovery time, min	2.36 (0.43)	3.15 (0.43)	−0.79 (−1.86, 0.28)	0.14
Patient global assessment of pain	2.75 (0.19)	2.83 (0.19)	−0.08 (−0.45, 0.29)	0.67
Roland-Morris Disability Questionnaire	12.98 (0.92)	11.48 (0.92)	1.50 (0.38, 2.62)	0.01
Modified BPI-SF				
Interference score	3.70 (0.42)	3.58 (0.42)	0.12 (−0.48, 0.72)	0.68
Pain intensity score	4.35 (0.37)	4.49 (0.37)	−0.14 (−0.84, 0.56)	0.68
Oswestry Disability Index	37.77 (2.76)	36.49 (2.76)	1.29 (−1.57, 4.14)	0.36
Swiss Spinal Stenosis Questionnaire				
Symptom severity	3.09 (0.12)	2.94 (0.12)	0.15 (−0.01, 0.31)	0.07
Physical function	2.40 (0.09)	2.45 (0.09)	−0.05 (−0.22, 0.13)	0.57

Abbreviations: AUC = area under the pain intensity–time curve; BPI-SF = Brief Pain Inventory–Short Form; CI = confidence interval; NRS = Numeric Rating Scale; SE = standard error.
Means, SEs, and treatment effects are derived from a mixed-effects analysis of variance model; see text for details.

Table 3	Adverse events	
Adverse event	Pregabalin (n = 28)	Active placebo (n = 26)
Dizziness	12 (42.9)	1 (3.8)
Confusion	2 (7.1)	0 (0.0)
Constipation	1 (3.6)	0 (0.0)
Diarrhea	3 (10.7)	2 (7.7)
Somnolence	5 (17.9)	2 (7.7)
Dry mouth	4 (14.3)	0 (0.0)
Nausea	3 (10.7)	4 (15.4)
Peripheral edema	5 (17.9)	2 (7.7)
Vision changes	2 (7.1)	0 (0.0)
Headache	0 (0.0)	1 (3.8)
Frequent urination	0 (0.0)	1 (3.8)

Data are n (%). Denominators are the numbers of trial participants who were exposed to the intervention (pregabalin or active placebo).

disability as measured by well-validated patient-reported outcomes, including one developed and validated specifically for lumbar spinal stenosis–associated symptoms.[17–20,23,24]

Despite the prevalent use of oral pain medications for the treatment of patients diagnosed with lumbar spinal stenosis, very few high-quality studies have investigated their efficacy.[7] Furthermore, only one published unblinded randomized controlled trial supports the use of an antiepileptic drug, gabapentin, when combined with standard treatment (i.e., a combination of exercise, nonsteroidal anti-inflammatory drugs, and bracing) for neurogenic claudication associated with lumbar spinal stenosis.[25] In that open-label study, gabapentin treatment increased walking distance and decreased movement-induced pain intensity of the low back and leg compared with standard treatment alone.[25] Consistent with our results, a recent enriched enrollment randomized withdrawal study of pregabalin for neuropathic pain associated with chronic lumbosacral radiculopathy failed to show a significant effect of pregabalin on time to loss of response (i.e., >1-point increase in pain, discontinuation from the study, or use of rescue medication).[26] Another study demonstrated that tapentadol alone was not inferior to tapentadol plus pregabalin for treating chronic low back pain with a neuropathic component.[27] A recently published study in 400 subjects demonstrated that epidural injection of glucocorticoid plus lidocaine was no more effective than lidocaine alone after 6 weeks, revealing that another conservative treatment frequently used in clinical practice may have minimal efficacy.[28] One explanation for the multiple negative trials of oral and interventional analgesic approaches for the treatment of painful symptoms of lumbar stenosis is the use of anatomical findings, which often lack sensitivity and specificity for the experience of pain, to define the study population.[29] Rigorous studies of other nonsurgical therapies, such as intranasal calcitonin, did not demonstrate superiority of experimental treatment.[7]

The lack of efficacy of this drug in syndromes localizing to the cauda equina and lumbar radicular syndromes may be explained by a relative importance of inflammatory and vascular pathophysiology in neuropathic pain induced by mechanical compression.[30] Consistently, pregabalin relieves pain from diabetic neuropathy and postherpetic neuralgia,[8–10,31] neither of which include abnormal mechanical compression of neural or perineural (e.g., microvasculature) structures.

A recent Cochrane review of evidence for conservative treatments of lumbar spinal stenosis with neurogenic claudication concluded that because of lack of quality evidence, no conservative treatments could be recommended.[7] A recent systematic review investigating clinical trials that compared surgical procedures with conservative treatment for lumbar spinal stenosis found that in all 5 high-quality trials, the surgical intervention performed better than conservative interventions.[32] These studies all lacked a standardized protocol for nonsurgical treatment and only included participants in whom conservative treatments had failed for 3 to 6 months. One nonresective surgical option included in the systematic review was the minimally invasive surgical implantation of a decompression device (i.e., X Stop) in the interspinous process for patients with lumbar spinal stenosis with neurogenic claudication. Severity of neurogenic claudication was the primary outcome variable in the X Stop study,[33] which was used as the basis for approval by the US Food and Drug Administration, demonstrating that severity of neurogenic claudication is recognized by regulatory agencies as an important primary outcome variable.

The dosage and timing of pregabalin treatment could be a limitation in this study. Up to 300 mg of pregabalin was administered for 10 days. It is possible that the treatment duration was too short to reach the maximum analgesic effect. In trials of pregabalin in diabetic peripheral neuropathy and postherpetic neuralgia, however, significant treatment effects were detected as early as 1 week after treatment initiation.[8–10,31,34] It is also possible that the daily dosage of pregabalin was too low. However, multiple studies have demonstrated efficacy of pregabalin for neuropathic pain at 300 mg/d[8,10,31,34] and higher dosages may be associated with more adverse effects.

This randomized, double-blind, placebo-controlled, crossover trial failed to demonstrate efficacy of pregabalin regarding the primary outcome variable of time to onset of moderate-intensity pain and all secondary outcome variables, including functional limitations. The enormous

costs and side-effect burden of treatments for chronic low back pain syndromes require that the most common treatments provide greater relief than placebo.[4,35] Treadmill testing was shown to be a feasible, well-tolerated, and safe method for identifying patients with neurogenic claudication and testing oral analgesics for a chronic low back pain syndrome associated with neurogenic claudication. Future clinical trials using treadmill testing to match a therapeutic intervention with the target symptom of neurogenic claudication may increase the feasibility of detecting true treatment effects. The number of patients with lumbar spinal stenosis who experience neurogenic claudication will likely increase substantially in the future.[3] High-quality, randomized controlled trials are needed to evaluate conservative management, including both pharmacologic and non-pharmacologic interventions.[7]

AUTHOR CONTRIBUTIONS

J.D. Markman, M.P. McDermott, L.S. Simon, W.H. Pilcher, and R.H. Dworkin designed the trial. J.D. Markman, M.E. Frazer, and S.A. Rast conducted the trial. A.K. Chowdhry and M.P. McDermott performed the statistical analyses. J.S. Gewandter, M.E. Frazer, K. Czerniecka, and John D. Markman interpreted the data and wrote the manuscript. All authors critically revised and approved the final manuscript.

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DISCLOSURE

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