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A Multi-Center, Randomized, Double-Blind, Comparative-Efficacy Study Comparing Epidural Steroid Injections to Gabapentin for Sciatica

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Abstract

Objective: To evaluate whether an epidural steroid injection (ESI) or gabapentin is a better treatment for lumbosacral radiculopathy.

Design: A multicenter randomized study was conducted between 2011 and 2014. Computer-generated randomization was stratified by site. Patients and evaluating physicians were blinded to treatment outcomes.

Settings: Eight military, Veterans Administration and civilian hospitals.

Participants: 145 subjects with sciatica secondary to herniated disc or spinal stenosis < 4 years in duration, and leg ≥ back pain.

Interventions: Participants received either ESI + placebo pills or sham ESI + gabapentin.

Main outcome measures: Average leg pain 1 month after the injection. A positive outcome was defined as a ≥ 2-point decrease in leg pain coupled with a positive global perceived effect (GPE). All patients had 1-month follow-up visits; patients whose condition improved remained blinded for their 3-month visit.

Results: No significant differences were noted for the primary outcome measure (mean change from baseline -2.2 ± 2.4 in the ESI group vs. -1.7 ± 2.6 in the gabapentin group; adjusted difference [95% CI], 0.4 [-0.3 to 1.2]; p=0.252). Among secondary outcomes, 1-month after treatment those who received ESI had greater reductions in worst leg pain (-3.0 ± 2.8) than those treated with gabapentin (-2.0 ± 2.9; p=0.044) and were more likely to experience a positive successful outcome (65.8% vs. 45.8%; NNT=5.0; 95% CI, 2.8 to 27.0; p=0.016). At 3-months, no significant differences were noted between treatments.

Conclusions: Although ESI may provide greater benefit for some outcome measures than gabapentin, the differences are modest and for most people transient.

Trial registration: ClinicalTrials.gov Identifier: NCT01495923. Registered on 15 Dec 2011.

Introduction

The physical, socioeconomic and psychological impact of low back pain (LBP) is enormous. LBP has been the leading cause of years lost to disability over the past several decades,[1] with a lifetime prevalence that ranges between 50% and 90%.[2,3] The economic cost is estimated to exceed $100 billion per year in the U.S, over half of which can be attributed to lost productivity.[3,4] Efforts to address the worldwide burden posed by LBP amount to an international crisis.

The classification of back pain is perhaps the most important distinction for clinicians to make, as it informs work-up and treatment decisions at all levels of care.[5] Since the development of validated instruments to categorize LBP,[6,7] studies have determined that the proportion of chronic LBP cases that are predominantly neuropathic (i.e. sciatica; radicular pain from a herniated disc or neurogenic claudication from spinal stenosis) ranges between 17% and 55%,[7-11] with one review finding a median prevalence rate of 41%.[12] Whereas the presence of neuropathic symptoms portends a more negative prognosis for acute LBP episodes,[13] sciatica may be more responsive to procedural interventions than non-specific back pain.[12,14]

Epidural steroid injections (ESI) are the most commonly performed pain procedure in the world,[15] being more frequently utilized and effective for sciatica than mechanical spine pain.[12,16] Although mixed, most controlled studies have also found pharmacotherapy with gabapentinoids to be somewhat effective for sciatica.[17-21]

Numerous controlled trials have been performed evaluating ESI and medications in LBP, with review articles generally reporting modest effects.[12, 22] Yet, for clinicians the more relevant

question is not whether a real treatment is better than a sham treatment, but which treatment is more effective.[23]

Several small, randomized, open-label studies have compared ESI to medications. One study showed superiority for a single ESI at one month but not later follow-up compared to tramadol and a muscle relaxant.[24] A second demonstrated that a single caudal ESI provided better pain relief than non-steroidal anti-inflammatory drugs through 3 months.[25] However, neither study evaluated first-line adjuvants (e.g. gabapentin) as a comparison group. A more recent, 3-armed multi-center study performed in 169 patients with cervical radiculopathy compared a series of ESI, to gabapentin and/or nortriptyline plus physical therapy, to a combination group that received both injections and conservative care, and found that the combination group experienced a higher success rate at 3 but not 6 months.[26] Although these studies may simulate real-life decisions facing clinicians, the fact that none were blinded precludes any conclusions regarding efficacy. The purpose of our study is to compare a single ESI to gabapentin in patients with sciatica in a double-blinded fashion.

Methods

We performed a double-blind, randomized study comparing a single ESI to gabapentin. Approval to conduct this study was granted by the Internal Review Boards at all 8 participating institutions, and all subjects who provided informed consent. All participants were treated between December 15, 2011 and June 10, 2014.

Participants & Settings

The study sites consisted of 4 joint service military treatment facilities, 3 of which serve as teaching hospitals (Walter Reed, San Diego and San Antonio) and one of which is located in Europe; a VA hospital and 3 civilian teaching hospitals (Johns Hopkins, Case Western and Penn State). Inclusion criteria were age ≥ 18 years; average radicular leg pain score ≥ 4 on a 0- 10 numerical rating scale (NRS) scale over the preceding week, or ≥ 3/10 if greater if back pain is < 4/10; duration of current symptoms > 6 weeks and ≤ 4 years; and signs (e.g. straight leg raising test) and/ or symptoms (e.g. lower leg numbness) of lumbosacral radicular pain or neurogenic claudication with concordant magnetic resonance imaging (e.g. herniated disc or spinal stenosis, respectively). Patients were permitted to have multi-level symptoms. Exclusion criteria were neuropathic pain > 4 years in duration; previous failed trial with or adverse reaction to gabapentin or pregabalin; ESI within the past 3 years; cauda equina syndrome; previous spine surgery; pregnancy; allergic reaction to contrast dye; and serious medical (e.g. poorly controlled diabetes or unstable angina) or psychiatric condition (poorly controlled posttraumatic stress syndrome or depression) that might preclude an optimal response to treatment.

Randomization and Interventions

145 participants were randomized in a 1:1 ratio by computer-generated randomization tables. Enrollment was done by an investigator physician and stratified by study site. Allocation was performed by research nurses in groups of 36 at Walter Reed and Johns Hopkins as these sites were expected to enroll more patients, or 18 at other sites, with treatment divulged via a sequentially numbered opaque sealed envelope prior to injection. Larger allocation blocks were used to promote allocation concealment with investigators. Participants at each site were sub-allocated separately in a 1:1 ratio based on the type of ESI they received: those with unilateral pain received unilateral transforaminal ESI, while those with bilateral pain underwent interlaminar ESI. The patient, research nurse, and evaluating physician were blinded to assignment.

Epidural Injections

All procedures were conducted using fluoroscopic guidance by or under the supervision of a board-certified pain medicine physician. The segmental level at which the injection was administered was selected based on signs, symptoms and radiological findings. For interlaminar injections, a Tuohy needle was inserted in or near the midline and advanced into the epidural space using image guidance in the antero-posterior and lateral views using the loss of resistance technique. For transforaminal ESI, a 22-gauge spinal needle was inserted co-axially into the upper part of the targeted foramina with the imagine intensifier positioned in an oblique plane. Correct placement was confirmed with the injection of contrast, which revealed bilateral spread for all interlaminar injections and proximal epidural uptake for all transforaminal procedures. After the physician was satisfied with the pattern of contrast spread, a solution consisting of 60 mg of depomethylprednisolone + 1 mL of 0.25% bupivacaine was administered. For those who

received interlaminar injections, the injectate was diluted in normal saline to a volume of 4 mL; in the transforaminal subgroup, the total volume administered was 3 mL.

Sham Injections & Maintenance of Blinding

Subjects were instructed ahead of time that they may or may not experience paresthesias during the procedure and were visually shielded from the image screen. For all injections, the same technique (e.g. trajectory and use of multiplanar fluoroscopy) was used for sham injections except that the needle was positioned 1-2 cm proximal to the epidural space into the posterior ligaments. A small volume of saline was then injected in lieu of contrast, followed by 3 additional mL to simulate the injectate. A generic note was entered into the medical record without radiographs.

Pharmacotherapy

300 mg gabapentin and placebo capsules were over-capsulated by a central research pharmacy to appear identical. Prior to each shipment, the capsules were tested to ensure potency, or lack thereof for group 2. Titration schedules were prepared on a case-to-case basis in accordance with standard practice, but dosing targets generally ranged from 1800 mg/d to 3600 mg/d in TID regimens. Medications were generally up-titrated over a period of 15 to 24 days, with the only caveat being that a therapeutic dose range had to be obtained at least 5 days before follow-up.

Co-Interventions, Outcome Measures, Follow-up & Missing Data

No contact with the investigative team was permitted during the study. Tramadol and non-steroidal anti-inflammatory drugs could be prescribed on an "as needed" basis as rescue

medications (or opioids could be increased by < 20% for those on opioids), but no other co-interventions were permitted. Subjects were provided with instructions on how to taper their analgesic medications based on response. The first follow-up visit was performed 1-month after treatment initiation by an investigator blinded to treatment. The primary outcome measure was the average 0-10 numerical rating scale (NRS) leg pain score at 1-month, reflecting the average pain experienced during the week before follow-up. Pre-defined secondary outcome measures included worst leg pain over the past week, average and worst back pain, Oswestry disability index (ODI) score (version 2.0, MODEMS, Des Plaine, IL),[27] adverse effects and complications, reduction in analgesic medications (> 20% reduction in opioid use or complete cessation of non-opioid analgesics), and global perceived effect (GPE), which was defined as not requiring further non-rescue interventions along with an affirmative response to the following two questions:[28]

1. My pain has improved/ worsened/ stayed the same since my last visit;
2. I am satisfied/ not satisfied with the treatment I received and would/would not recommend it to others.

The Oswestry disability index is a 10-question survey used to assess function in people with low back and/ or leg pain, in which higher scores indicate greater levels of disability. The classification of spinal stenosis was made if the participant had moderate or severe canal stenosis (< 12 mm) not attributable to a herniated disc. Complications were assessed by fixed and open-ended questions asked 1-day after injections, and at all follow-up visits. In addition to individual variables, a positive composite outcome (i.e. successful procedure) was pre-designated to be a ≥ 2-point decrease in average leg pain coupled with a positive GPE.[29]

In those individuals who experienced a positive 1-month outcome, the final follow-up occurred at 3 months. For individuals with a positive outcome at 1-month, in addition to rescue

medications, the study medication could also be titrated upwards. For ethical reasons, those with a negative 1-month outcome exited the study 'per protocol' to receive non-study interventions, which is consistent with other randomized interventional studies.[26,28,30,31] Missing data points for pain scores, ODI and the composite outcome were imputed using the "last-observation-carried-forward" method, which may underestimate effect sizes when "dropouts" are due to lack of efficacy.[32]

Statistical Analysis

An intention-to-treat strategy was used for all analyses. Differences in treatment effects and 95% confidence intervals for pain and disability scores were calculated using analysis of covariance (ANCOVA) with adjustments for baseline values of outcome measures. An indicator of the treatment group was coded such that positive values favored the ESI group. No correction was pre-specified for multiple comparisons. Due to a difference in baseline gender distribution, post hoc analysis of outcomes was adjusted for gender. Logistic-regression models were used to compare the proportion of patients with adverse events in the first month and factors associated with binary outcomes in post-hoc analysis. Analysis of adverse event rates was conducted using Poisson regression models with robust standard errors. Effectiveness of blinding in each treatment group was evaluated using two indices. In the James blinding index[33] (range 0 to 1), 0 indicates total absence of blinding, 1 indicates complete blinding, and 0.5 indicates completely random blinding. In the Bang blinding index[34] (range -1 to 1), -1 indicates all patients guessed the incorrect treatment, 0 indicates all patients randomly guessed, and 1 indicates all patients guessed the correct treatment. Bonferroni-corrected significance thresholds were used for post-hoc subgroup analyses, with corrected P values calculated as 0.05 divided by the number of

comparisons being made. All other reported P values were based on two-sided tests, with < 0.05 considered statistically significant.

The study was powered to evaluate the effectiveness of ESI compared to gabapentin. Assumptions include a 1.0-point difference in pain scores between groups at 1 month, standard deviation of each group of 2.0 based on data from previous studies, a retention rate of 87%, and a two-sided alpha level of 0.05.

Results

348 potential participants were assessed, of whom 147 were eligible for inclusion and agreed to participate. 145 were assigned to receive either an ESI and sham-medication (n=73) or gabapentin and a sham injection (n=72). The two groups were similar with respect to baseline characteristics, except the ESI group had more females (Table 1, Figure 1).

Outcomes

At 1 month, both the ESI group and the gabapentin group experienced improvement in the average leg pain score (-2.2 points [SD 2.4] and -1.7 points [SD 2.6], respectively), but no significant between-group difference was observed (adjusted difference, 0.4 points; 95% confidence interval [CI], -0.3 to 1.2; P=0.252) (Table 2). Small between-group differences favoring ESI were present at 1 month for worst leg pain score (adjusted difference, 0.9 points; 95% CI, 0.0 to 1.9; P=0.044) and successful outcome (65.8% and 45.8%, P=0.016; NNT=5.0, 95% CI 2.8 to 27.0). For average and worst back pain at 1 month, moderate improvements were noted for the ESI (-1.5, SD 1.9) and gabapentin (-1.1, SD 2.3) groups, but the differences were not significant (adjusted difference, 0.3 points; 95% CI, -0.4 to 0.9; P=0.447). No significant

differences were observed for outcomes at 3 months or for patients proceeding to surgery within one year (12.5% and 14.5%, P=0.729).

Factors Associated with Outcome and Post Hoc Analyses

In subgroup analyses, military officers were more likely to experience a positive outcome than either enlisted personnel or non-service members (odds ratio 6.7, [95% CI, 1.8 to 24.6]; P=0.004). Performing an injection at S1 was associated with a greater reduction in leg pain than at other levels (-0.7; 95% CI, -0.1 to -1.2; P=0.022), but failed to reach significance when adjustments were made for multiple comparisons. No associations were found among the primary or composite outcome at 1 month based on etiology (e.g. stenosis vs. herniated disc), pain duration $\geq$ 3 months, injection type (i.e. transforaminal ESI for unilateral pain vs. interlaminar ESI for bilateral pain), smoking status, presence of psychiatric disease, obesity, age, gender, or dose of gabapentin. In post-hoc adjustments for gender, the between-group difference in worst leg pain reduction favoring ESI was no longer significant (0.3, [95% CI, -0.8 to 1.4], P=0.052).

Adverse Events

The proportion of patients reporting one or more adverse events from the injection was 8.2% in the ESI group and 9.7% in the gabapentin group (P=0.751). The proportion of patients reporting one or more adverse events from the medication was 41.7% in the ESI group and 51.4% in the gabapentin group (P=0.242; table 3).

Blinding

Blinding was assessed at 2 time points, immediately after the procedure to assess blinding for real ESI, and at the first follow-up to ensure blinding for real gabapentin. Immediately following the baseline procedure, patients were unaware of assigned treatments (James blinding index, 0.75; 95% CI, 0.69 to 0.80; P=1; Bing blinding index in ESI group, 0.07; 95% CI, -0.07 to 0.21; Bing blinding index in Gabapentin group, -0.24; 95% CI, -0.38 to -0.09), indicating successful blinding. At 1 month, the overall success of blinding was maintained (James blinding index, 0.56; 95% CI, 0.49 to 0.63; P=0.93), though there was a trend towards better insight into treatment assignment for the gabapentin group (Bing blinding index in ESI group, 0.08; 95% CI, -0.07 to 0.25; Bing blinding index in Gabapentin group, 0.19; 95% CI, 0.03 to 0.36).

Discussion

The main finding in this double-blind efficacy study is that although some small differences were noted in favor of ESI at 1-month, no statistically significant differences were noted for the primary outcome measure, and the differences observed mostly disappeared at 3-months. Although only a small percentage of our patients had spinal stenosis, our findings are consistent with a recent multi-center study that demonstrated modest, short-term benefit for ESI for this condition.[35] In this study, ESI were compared to epidural local anesthetic, which a systematic review showed was superior to soft-tissue control injections (i.e. not a placebo).[36] In our study, we elected to use a "true placebo" (intramuscular injection), which is more difficult to blind, but unlikely to provide benefit, and included patients with both spinal stenosis and herniated disc. Broad inclusion criteria enhance generalization and are consistent with guidelines on comparative-effectiveness research.[37]

Comparison to Other Studies and Explanation of Findings

Results of placebo-controlled studies evaluating gabapentinoids and other membrane stabilizers for radiculopathy are mixed, indicating a probable small effect size.[38] This suggests that differences between groups are unlikely to represent a large treatment effect. Although myriad reviews on ESI have yielded disparate conclusions, recent systematic and evidence-based reviews have indicated that any stand-alone treatment effect for ESI is likely to be modest and short-lived.[12,22]

In a recent open-label 3-arm comparative-effectiveness study pitting a series of ESI against conservative therapy consisting of pharmacotherapy (gabapentin and/or nortriptyline) and physical therapy and the combination of the two, it was found that combination treatment with ESI plus medication and physical therapy provided superior benefit to stand-alone treatment

on some outcome measures.[26] In some respects, the open-label format and inclusion of a multimodal treatment approach may better reflect "real-life" circumstances, though they preclude the evaluation of efficacy.

There are several possible explanations for our findings. The first is that both treatments are equally effective, but the effects dissipate over time. Unlike studies for ESI which frequently follow patients for up to one year,[39-44] few studies have examined the long-term effectiveness of gabapentin, but those that have indicate that the beneficial effects for neuropathic pain are most pronounced early on during treatment.[45,46] A second hypothesis is that neither treatment is effective, and the benefits observed were due to a placebo response or the natural course of the disease. However those with chronic radiculopathy are less likely to spontaneously improve or respond to treatment than those with shorter duration of symptoms.[47] A third possibility is that ESI are superior to gabapentin, but the relatively small sample size, allowing only one ESI, treatment blinding, and our failure to reinforce the short-term benefit with physical therapy rendered 3-month differences indistinguishable. In a comparative-effectiveness study that compared a series of ESI to neuropathic adjuvants plus physical therapy to combination therapy for cervical radiculopathy, the combination group fared better than both stand-alone treatments.[26]

Limitations

There are several limitations to our study, including the primary outcome being measured at 1-month (which was necessary because we allowed those with an unsuccessful outcome to seek other treatments), and the lack of a true placebo group, which renders the assay sensitivity questionable. Without a true placebo group, one cannot assess the true efficacy of the 2 treatments. A third limitation is that we did not permit repeat ESI or allow combination drug treatment. Studies have demonstrated there is little basis for a rote "series" of ESI, though some

may benefit from repeat injections, which are often performed in clinical practice.[12,26,28,35,44,48,49] Similarly, randomized studies have shown that combination therapy with drugs that include gabapentinoids may provide superior relief for neuropathic and LBP compared to single agent treatment.[50] A fourth limitation inherent in our design is that blinding subjects may have altered our findings. "Blinding" is not a tenet of comparative-effectiveness research, which seeks to determine the best treatment in "real-world" conditions. The placebo effect is especially powerful for subjective measures such as pain, and stronger for procedures than pills, which may have mitigated any "real-world" differences between treatments.[51,52] A final limitation is our broad inclusion criteria which included patients on opioids, and those with herniated disc and spinal stenosis. These conditions are characterized by slightly different pathophysiological mechanism and may have different natural outcomes. A larger study would be needed to determine whether certain patients (e.g. herniated disc vs. spinal stenosis) or treatments (transforaminal vs. interlaminar ESI) experienced better outcomes than others. In practice, patients generally receive ESI and/or adjuvants regardless of the etiology of their neuropathic pain. In clinical trials, most ESI [12,24-26,28,39,41,43] and all gabapentinoid studies [17-21] included both etiologies, with a majority of studies finding no difference in ESI[12] or gabapentinoid (personal communication from Ralf Baron 10-9-2014)[20,21] outcomes between stenosis and disc herniation.

Generalizability

These results are readily generalizable to primary care settings, pain physicians, and surgeons, where practitioners are often faced with the question about the best non-operative way to manage sciatica. Future studies might include both placebo and combination groups, allow for multiple injections and medications, and require physical therapy in an effort to determine whether any benefit that is observed could be prolonged. However, the logistical and ethical

obstacles in designing such studies (e.g. blinding multiple medications or performing multiple sham injections in patients who fail to respond to the first one) will make them difficult to execute.

Conclusions

Gabapentin and ESI both resulted in modest improvements in pain and function which persisted through 3 months. Although some differences favored ESI at 1-month, these tended to be small and transient. The similar outcomes between treatment groups on most measures suggest that a trial with neuropathic medications is a reasonable first-line treatment option before attempting an ESI.

References

1. US Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA* 2013; 310: 591-608.
2. Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, et al. A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012; 64: 2028-37.
3. Juniper M, Le T, Mladsi D. The epidemiology, economic burden, and pharmacological treatment of chronic low back pain in France, Germany, Italy, Spain and the UK: a literature-based review. *Expert Opin Pharmacother* 2009; 10: 2581-92.
4. Crow W, Willis D. Estimating cost of care for patients with acute low back pain: a retrospective review of patient records. *J Am Osteopath Assoc* 2009; 109: 229-33.
5. Cohen SP, Mao J. Mechanisms of neuropathic pain and their clinical implications. *BMJ* 2014; 348: f7656.
6. Bennett M. The LANSS pain scale: the Leeds Assessment of Neuropathic Symptoms and Signs. *Pain* 2001; 92: 147–57.
7. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006; 22: 1911-20.
8. El Sissi W, Arnaout A, Chaarani M, Fouad M, El Assuity W, Zalzala M, et al. Prevalence of neuropathic pain among patients with chronic low-back pain in the Arabian Gulf Region assessed using the Leeds assessment of neuropathic symptoms and signs pain scale. *J Int Med Res* 2010; 38: 2135-45.

9. Beith I, Kemp A, Kenyon J, Prout M, Chestnut TJ. Identifying neuropathic back and leg pain: a cross-sectional study. *Pain* 2011; 152: 1511-6.

10. Kaki A, El-Yaski A, Youseif E. Identifying neuropathic pain among patients with chronic low-back pain: use of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale. *Reg Anesth Pain Med* 2005; 30: 422-8.

11. Hassan A, Saleh H, Baroudy Y, Abdul-Rahman KI, Najjar MW, Kazi MS, et al. Prevalence of neuropathic pain among patients suffering from chronic low back pain in Saudi Arabia. *Saudi Med J* 2004; 25: 1986-90.

12. Cohen SP, Jamison D, Bicket M, Wilkinson I, Rathmell JN. Epidural steroids: A comprehensive, evidence-based review. *Reg Anesth Pain Med* 2013; 38: 175-200.

13. Hill JC, Konstantinou K, Egbewale BE, Dunn KM, Lewis M, van der Windt D. Clinical outcomes among low back pain consulters with referred leg pain in primary care. *Spine (Phila Pa 1976)* 2011; 36: 2168-75.

14. Jacobs WC, Rubinstein SM, Koes B, van Tulder MW, Peul WC. Evidence for surgery in degenerative lumbar spine disorders. *Best Pract Res Clin Rheumatol* 2013; 27: 673-84.

15. Manchikanti L, Falco FJ, Singh V, Pampati V, Parr AT, Benyamin RM, et al. Utilization of interventional techniques in managing chronic pain in the Medicare population: analysis of growth patterns from 2000 to 2011. *Pain Physician* 2012; 15: E969-82.

16. Hopwood M, Abram S. Factors associated with failure of lumbar steroids. *Reg Anes* 1993; 18: 238-43.

17. McCleane GJ. Does gabapentin have an analgesic effect on background, movement and referred pain? A randomized, double-blind, placebo controlled study. *Pain Clinic* 2001; 13: 103-7.

18. Yildirim K, Sisecioglu M, Karatay S, Erdal A, Levent A, Ugur M, Senel K. The effectiveness of gabapentin in patients with chronic radiculopathy. *Pain Clinic* 2003; 15: 213-8.

19. Romano CL, Romanò D, Bonora C, Mineo G.. Pregabalin, celecoxib, and their combination for treatment of chronic low-back pain. *J Orthopaed Traumatol* 2009;10(4): 185-91.

20. Baron R, Martin-Mola E, Müller M, Dubois C, Falke D, Steigerwald I. Effectiveness and safety of tapentadol prolonged release (PR) versus a combination of tapentadol PR and pregabalin for the management of severe, chronic low back pain with a neuropathic component: A randomized, double-blind, phase 3b study. *Pain Pract* 2014 Apr 17. doi: 10.1111/papr.12200. [Epub ahead of print].

21. Baron R, Freynhagen R, Tölle TR, Cloutier C, Leon T, Murphy TK, Phillips K; A0081007 Investigators. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. *Pain* 2010; 150: 420-7.

22. Pinto RZ, Maher CG, Ferreira ML, Hancock M, Oliveira VC, McLachlan AJ, et al. Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis. *Ann Intern Med* 2012; 157: 865-77.

23. Brouwers MC, Thabane L, Moher D, Straus SE. Comparative effectiveness research paradigm: implications for systematic reviews and clinical practice guidelines. *J Clin Oncol* 2012; 30: 4202-7.

24. Laiq N, Khan MN, Iqbal MJ, Khan S. Comparison of epidural steroid injections with conservative management in patients with lumbar radiculopathy. *J Coll Physicians Surg Pak* 2009; 19: 539-43.

25. Dincer U, Kiralp MZ, Cakar E, Yasar E, Dursan H. Caudal epidural injection versus non-steroidal anti-inflammatory drugs in the treatment of low back pain accompanied with radicular pain. *Joint Bone Spine* 2007; 74: 467-71.

26. Cohen SP, Hayek S, Semenov Y, Pasquina PF, White RL, Veizi E, et al. Epidural steroid injections, conservative treatment or combination treatment for cervical radiculopathy: A multi-center, randomized, comparative-effectiveness study. *Anesthesiology* 2014; 121: 1045-55.

27. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. *Physiotherapy* 1980; 66: 271-3.

28. Cohen SP, White RL, Kurihara C, Larkin TM, Chang A, Griffith SR, et al. Epidural steroids, etanercept, or saline in subacute sciatica: A multicenter randomized trial. *Ann Intern Med* 2012; 156: 551-9.

29. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008; 9: 105-21.

30. Ackerman WE 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg* 2007; 104: 1217-22.

31. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med* 2010; 11: 1149-68.

32. Lane P. Handling drop-out in longitudinal clinical trials: a comparison of the LOCF and MMRM approaches. *Pharm Stat* 2008; 7: 93-106.

33. James KE, Bloch DA, Lee KK, Kraemer HC, Fuller RK. An index for assessing blindness in a multicentre clinical trial: Disulfiram for alcohol cessation – a VA cooperative study. *Stat Med* 1996; 15: 1421-34.

34. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004; 25: 143-56.

35. Friedly JL, Comstock BA, Turner JA, Heagerty PJ, Deyo RA, Sullivan SD, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med* 2014; 371: 11-21.

36. Bicket M, Gupta A, Brown C, Cohen SP. Epidural injections for spinal pain: A systematic review and meta-analysis evaluating the "control" injections in randomized controlled trials. *Anesthesiology* 2013; 119: 907-31.

37. Brouwers MC, Thabane L, Moher D, Straus SE. Comparative effectiveness research paradigm: Implications for systematic reviews and clinical practice guidelines. *J Clin Oncol* 2012; 30: 4202-7.

38. Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M, Oliveira VC, et al. Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis. *BMJ* 2012; 344: e497.

39. Iversen T, Solberg TK, Romner B, Wilsgaard T, Twisk J, Anke A, et al. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: Multicentre, blinded, randomised controlled trial. *BMJ* 2011; 343: d5278.

40. Arden NK, Price C, Reading I, Stubbing J, Hazelgrove J, Dunne C, et al; WEST Study Group. A multicentre randomized controlled trial of epidural corticosteroid injections for sciatica: The WEST study. *Rheumatology (Oxford)* 2005; 44: 1399-406.

41. Karppinen J, Malmivaara A, Kurunlahti M, Kyllönen E, Pienimäki T, Nieminen P, et al. Periradicular infiltration for sciatica: A randomized controlled trial. *Spine (Phila Pa 1976)* 2001; 26: 1059-67.

42. Sayegh FE, Kenanidis EI, Papavasiliou KA, Potoupnis ME, Kirkos JM, Kapetanos GA. Efficacy of steroid and nonsteroid caudal epidural injections for low back pain and sciatica: A prospective, randomized, double-blind clinical trial. *Spine (Phila Pa 1976)* 2009; 34: 1441-7.

43. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: A prospective randomized study. *Spine (Phila Pa 1976)* 2002; 27: 11-6.

44. Riew KD, Park JB, Cho YS, Gilula L, Patel A, Lenke LG, Bridwell KH. Nerve root blocks in the treatment of lumbar radicular pain. A minimum five-year follow-up. *J Bone Joint Surg Am* 2006; 88: 1722-5.

45. Johnson P, Becker L, Halpern R, Sweeney M. Real-world treatment of post-herpetic neuralgia with gabapentin or pregabalin. *Clin Drug Investig* 2013; 33: 35-44.

46. Liedgens H, Hertel N, Gabriel A, Nuijten M, Dakin H, Mitchell S, Nautrup BP. Cost-effectiveness analysis of a lidocaine 5% medicated plaster compared with gabapentin and

pregabalin for treating postherpetic neuralgia: a German perspective. *Clin Drug Investig* 2008; 28: 583-601.

47. Haugen AJ, Brox JI, Grøvle L, Keller A, Natvig B, Soldal D, Grotle M. Prognostic factors for non-success in patients with sciatica and disc herniation. *BMC Musculoskelet Disord* 2012; 13: 183.
48. Novak S, Nemeth WC. Novak S, Nemeth WC. The basis for recommending repeating epidural steroid injections for radicular low back pain: a literature review. *Arch Phys Med Rehabil* 2008; 89: 543-52.
49. Carette S, Leclaire R, Marcoux S, Grondin C, Gagnon J, Allard Y, Latulippe M. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *N Engl J Med* 1997; 336: 1634-40.
50. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev* 2012; 7: CD008943.
51. Kaptchuk TJ, Stason WB, Davis RB, Legedza AR, Schnyer RN, Kerr CE, et al. Sham device v inert pill: Randomized controlled trial of two placebo treatments. *BMJ* 2006; 332: 391-7.
52. Koshi EB, Short CA. Placebo theory and its implications for research and clinical practice: A review of the recent literature. *Pain Pract* 2007; 7: 4-20.

Table 1. Baseline demographic and clinical characteristics of study subjects[1]

Characteristic	Epidural Steroid Injection Group (n = 73)	Gabapentin Group (n = 72)
Age – years	43.8 ± 14.0	41.7 ± 11.9
Female sex – no. (%)[2]	25 (34.2)	13 (18.1)
Duration of pain - no. (%)		
< 3 months	11 (15.1)	15 (20.8)
3 to < 12 months	26 (35.6)	27 (37.5)
1 to 3 years	27 (37.0)	23 (31.9)
> 3 years	9 (12.3)	7 (9.7)
Opioid therapy – no. (%)		
No opioids	54 (74.0)	55 (76.4)
< 60 morphine equivalents/day	16 (21.9)	14 (19.4)
>= 60 morphine equivalents/day	3 (4.1)	3 (4.2)
Average morphine equivalents among opioid users	28.7 (34.8)	38.5 (53.0)
Diagnosis – no. (%)		
Herniated nucleus pulposus	63 (84.9)	65 (90.3)
Spinal stenosis	10 (13.7)	7 (9.7)
Active duty military - no. (%)	38 (52.0)	41 (56.9)
Enlisted	26 (35.6)	30 (41.7)
Officer	12 (16.4)	11 (15.3)
Inciting event – no. (%)		
None	42 (57.5)	41 (56.9)
Motor Vehicle Accident	1 (1.4)	1 (1.4)
Fall	5 (6.9)	9 (12.5)
Lifting	13 (17.8)	6 (8.3)
Sports/Training	8 (11.0)	13 (18.1)
Other[3]	4 (5.5)	2 (2.8)
Pain related to deployment – no. (%)	10 (13.7)	6 (8.3)
Current smoker – no. (%)[4]	15 (20.6)	13 (18.1)
Obesity – no. (%)	13 (17.8)	19 (26.4)
Psychiatric comorbidity – no. (%)		
None	56 (76.7)	49 (68.1)
Mood	9 (12.3)	12 (16.7)
Anxiety	7 (9.6)	6 (8.3)
Substance abuse	3 (4.1)	4 (5.6)
Posttraumatic stress disorder	1 (1.4)	4 (5.6)
Other[5]	1 (1.4)	3 (4.2)
Multiple diagnoses	4 (5.5)	6 (8.3)
Injection approach – no. (%)		
Interlaminar	11 (15.1)	12 (16.7)
Transforaminal	62 (84.9)	60 (83.3)
Level of injection – no. (%)		
L2-3	1 (1.4)	0 (0)

L3-4	1 (1.4)	2 (2.8)
L4-5	22 (30.1)	18 (25.0)
L5-S1	44 (60.3)	46 (63.9)
S1	5 (6.9)	6 (8.3)
Baseline pain scores[6]		
Average Leg Pain	5.4 ± 2.1	5.4 ± 1.9
Worst Leg Pain	7.9 ± 1.7	7.8 ± 2.0
Average Back Pain	5.0 ± 2.6	4.7 ± 2.4
Worst Back Pain	7.0 ± 2.6	7.0 ± 2.9
Baseline Oswestry Disability Score	39.8 ± 15.3	39.8 ± 14.7

1. Plus–minus values are means ± SD.
2. The difference between the two groups was significant (P = 0.027 by the chi-squared test).
3. Other inciting events include post-surgical, pregnancy, spinal tap and work-related.
4. Smoking includes 3 participants who chew tobacco products.
5. Other psychiatric comorbidities include attention deficit hyperactivity disorder and obsessive-compulsive disorder.
6. Based on 0-10 numerical rating scale scores

Table 2. Outcomes according to treatment group.[1]

	Epidural Steroid Injection Group			Gabapentin Group			Treatment Comparison	
	No. of Patients	Overall Mean	Mean Change from Baseline	No. of Patients	Overall Mean	Mean Change from Baseline	Adjusted Difference (95% CI)[2]	P Value
Average Leg Pain								
Baseline	73	5.4 ± 2.1	-	72	5.4 ± 1.9	-	-	-
1-month	73	3.3 ± 2.6	-2.2 ± 2.4	72	3.7 ± 2.6	-1.7 ± 2.6	0.4 (-0.3 to 1.2)	0.252
3-months	73	3.4 ± 2.7	-2.0 ± 2.6	72	3.7 ± 2.8	-1.6 ± 2.7	0.3 (-0.5 to 1.2)	0.426
Worst Leg Pain								
Baseline	73	7.9 ± 1.7	-	72	7.8 ± 2.0	-	-	-
1-month	73	4.9 ± 3.1	-3.0 ± 2.8	72	5.8 ± 3.0	-2.0 ± 2.9	0.9 (0.0 to 1.9)	0.044
3-months	73	5.2 ± 3.4	-2.7 ± 3.2	72	5.5 ± 3.4	-2.3 ±3.5	0.3 (-0.7 to 1.4)	0.541
Average Back Pain								
Baseline	73	5.0 ± 2.6	-	72	4.7 ± 2.4	-	-	-
1-month	73	3.5 ± 2.6	-1.5 ± 1.9	72	3.6 ± 2.6	-1.1 ± 2.3	0.3 (-0.4 to 0.9)	0.447
3-months	73	3.9 ± 2.7	-1.1 ± 2.4	72	3.7 ± 2.5	-1.0 ± 2.4	-0.1 (-0.8 to 0.6)	0.847
Worst Back Pain								
Baseline	73	7.0 ± 2.6	-	72	7.0 ± 2.9	-	-	-
1-month	73	5.1 ± 2.9	-1.9 ± 2.4	72	5.4 ± 3.2	-1.6 ± 2.6	0.3 (-0.4 to 1.1)	0.378
3-months	72	5.6 ± 3.2	-1.4 ± 2.9	72	5.6 ± 3.1	-1.4 ± 2.8	0.0 (-0.8 to 0.9)	0.914
Oswestry Disability Score[3]								
Baseline	73	39.8 ± 15.3	-	72	39.8 ± 14.7	-	-	-
1-month	73	32.6 ± 18.3	-7.3 ± 12.5	72	29.6 ± 16.0	-10.2 ± 14.5	-2.9 (-7.2 to 1.3)	0.176
3-months	73	33.6 ± 19.4	-6.2 ± 15.8	72	29.6 ± 16.3	-10.2 ± 16.7	-3.9 (-9.0 to 1.1)	0.122
Medication Reduction – no. (%)[4]								
4 weeks	67	40 (59.7)	-	65	32 (49.2)	-	-	0.227

12 weeks	40	23 (57.5)	-	30	14 (46.7)	-	-	0.369
Global Perceived Effect (positive) – no. (%)								
1-month	73	49 (67.1)	-	72	41 (56.9)	-	-	0.207
3-months	73	33 (45.2)	-	72	24 (33.3)	-	-	0.143
Composite Outcome (positive) - no. (%)[5]								
1-month	73	48 (65.8)	-	72	33 (45.8)	-	-	0.016
3-months	73	27 (37.0)	-	72	21 (29.2)	-	-	0.317
Proceeded to Surgery – no. (%)								
Within 1-year of enrollment	72	9 (12.5)	-	69	10 (14.5)	-	-	0.729

1. Plus-minus values are means ± SD. CI denotes confidence interval. Data for missing 1 month and 3 months outcomes including pain scores, Oswestry disability scores, global perceived effect and composite outcome were imputed by last observed outcome carried forward. Numerical rating scores for pain are based on 0-10 numerical rating scales, with 0 indicating no pain and 10 indicating severe pain.
2. Differences for pain and Oswestry disability scores were adjusted for baseline outcome values. Negative coefficients favor the gabapentin group. Positive coefficients favor the epidural steroid injection group.
3. The Oswestry disability index is a 10-question survey used to assess function in people with low back and/ or leg pain, in which higher scores indicate greater levels of disability. [26]
4. Reduction in analgesic medications corresponds to > 20% reduction in opioid use or complete cessation of non-opioid analgesic. Patients who were not on pain medications were excluded from this analysis.
5. Defined as ≥ 2-point decrease in average leg pain coupled with a positive global perceived effect without additional procedural or non-rescue pharmacological interventions.

Table 3. Adverse Events [1]

Adverse Event	Epidural Steroid Injection Group (n = 73)	Gabapentin Group (n = 72)	P-Value
Injection	**Epidural Steroid Injections**	**Sham Injection**	
≥1 event – no. of patients (%)[2]	6 (8.2)	7 (9.7)	0.751
Total adverse events – no. of events (event rate)[3]	6 (0.08)	9 (0.13)	0.422
Reported symptoms or events – no. (%)			
Excessive pain	2[7]	4[7]	
Fever, infection, or both	2	0	
Falls	1[7]	0	
Vasovagal	0	2[7]	
Other[4]	1	3	
Medication	**Sham Pills**	**Gabapentin Pills**	
Dose (mg)	2132.9 ± 609.4	2095.8 ± 678.3	0.730
Compliance - no. (%)[5]			
None	6 (8.3)	8 (11.1)	0.681
Partial (50-89%)	11 (15.3)	8 (11.1)	
Full (>90%)	55 (76.4)	56 (77.8)	
≥1 event – no. of patients (%)[2,5]	30 (41.7)	37 (51.4)	0.242
Total adverse events – no. of events (event rate)[3,5]	45 (0.63)	50 (0.69)	0.609
Reported symptoms or events – no. (%)[5]			
Sedation/ Fatigue	8 (11.1)	13 (18.1)[7]	
Cognitive	5 (6.9)	7 (9.7)[7]	
Weight gain	4 (5.6)	7 (9.7)[7]	
Headache	4 (5.6)	1 (1.4)	
Gastrointestinal	13 (18.1)	8 (11.1)[7]	
Swelling	0 (0)	3 (4.2)[7]	
Other[6]	11 (15.3)	11 (15.3)[7]	

1. Plus–minus values are means ± SD.
2. Statistical significance was assessed using logistic regression model adjusted for treatment group assignment.
3. Statistical significance was assessed using a Poisson regression model with robust standard errors adjusted for treatment group assignment.

4. Other adverse events for epidural steroid injection group include 'low cortisol noted on labs 3 weeks after injection in a patient also on oral steroids with no symptoms'. Other adverse events for gabapentin group (sham injection) include bruising, temporary inability to lift legs, and 'GI bleed after 3 days in a patient on low molecular weight heparin'. None were deemed related to treatment.
5. Data were missing for one patient in the epidural steroid injection group.
6. For medication, other adverse events for epidural steroid injection group (placebo pills) include ataxia, balance problems, depression, emotionality, kidney stones, muscle twitching, hot flashes, restlessness, rhinorrhea with congestion, sexual, vivid dreams, and one without description. Other adverse events for gabapentin group include blackout,[7] depression requiring hospitalization, dizziness (2),[7] dry mouth (2),[7] leg spasms, mood changes, rhinorrhea with flu-like symptoms, and one with no description.
7. Deemed related or possibly related to treatment.

Figure Legend

Figure 1. CONSORT flow diagram demonstrating progress of participants through the clinical trial.

What is already known about this topic: Both gabapentin and epidural steroid injections are frequently used to treat lumbosacral radiculopathy and may provide benefit for a subset of patients, but we do not know which treatment works better.

What this study adds: Although epidural steroid injections may be superior to gabapentin in some outcome measures, the differences are small and short-lived.

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Data sharing statement: Statistical code, and limited, anonymized dataset will be available pending permission from the U.S. Army by contacting the corresponding author at scohen40@jhmi.edu

Author Contributions:

SPC: Designed study, wrote protocol, served as overall PI, performed treatments, wrote and reviewed manuscript

SH, YV, RLW, KBG, ZZ: Site PI, performed treatments, reviewed manuscript

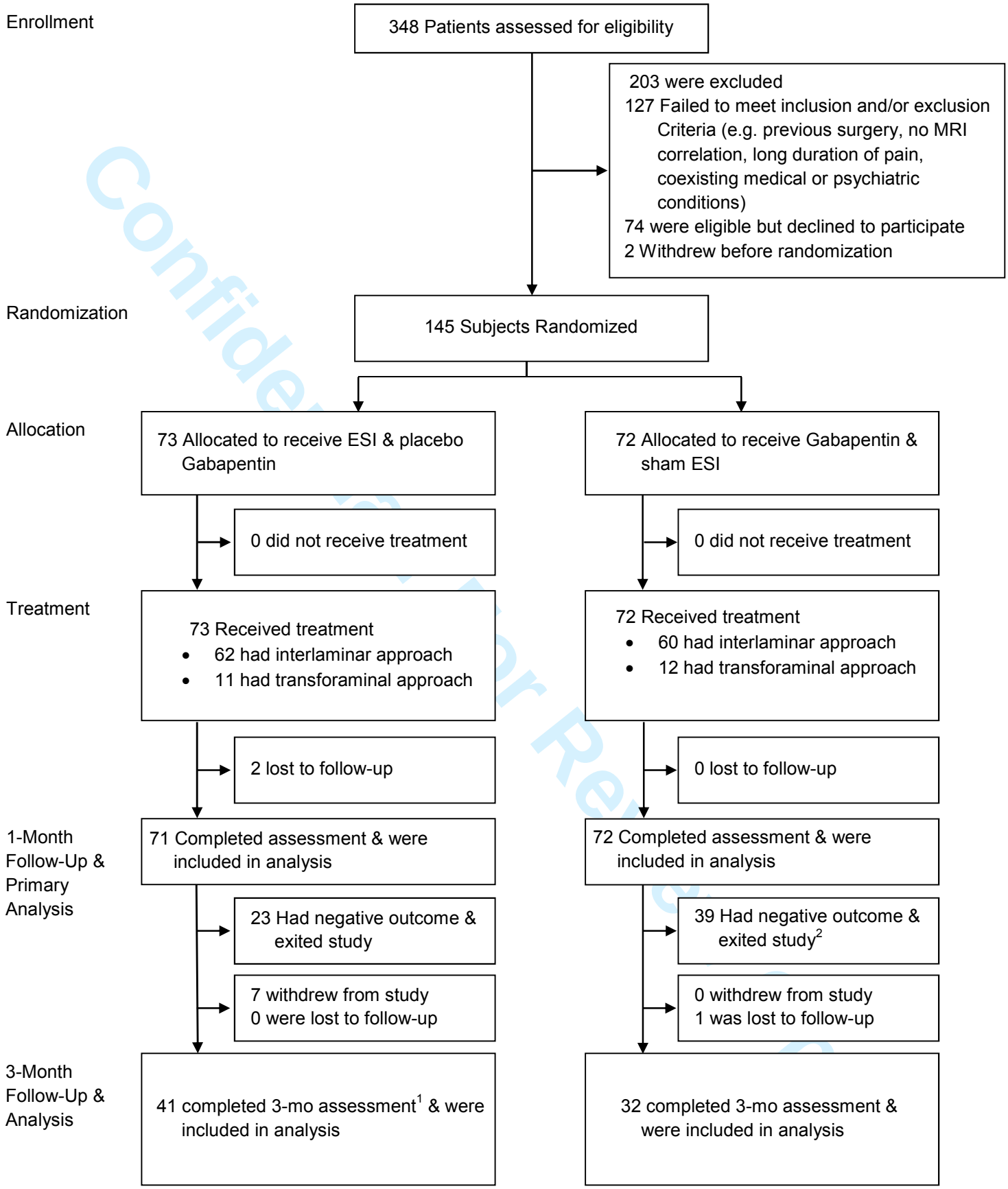
SRG, VG, EV: Assisted with protocol adaptation for individual sites, performed treatments, reviewed manuscript

MAW, CK: Research nurses (CK was Chief research nurse), collected data, assisted with protocol adaptations and submissions

MCB: Helped write manuscript, statistical analysis

PFP: Helped design study, funding source, critical review of manuscript

SPC and PFP are guarantors



1. This total includes 8 participants with early 3-month evaluations because of return of pain to baseline.
2. This includes 1 participant who sought emergency care and 1 patient with unstable angina who was started on opioids, both unrelated to treatment.