Epidural steroid injections compared with gabapentin for lumbosacral radicular pain: multicenter randomized double blind comparative efficacy study

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ABSTRACT

OBJECTIVE
To evaluate whether an epidural steroid injection or gabapentin is a better treatment for lumbosacral radiculopathy.

DESIGN
A multicenter randomized study 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 people with lumbosacral radicular pain secondary to herniated disc or spinal stenosis for less than four years in duration and in whom leg pain is as severe or more severe than back pain.

INTERVENTIONS
Participants received either epidural steroid injection plus placebo pills or sham injection plus gabapentin.

MAIN OUTCOME MEASURES
Average leg pain one and three months after the injection on a 0-10 numerical rating scale. A positive outcome was defined as a ≥2 point decrease in leg pain coupled with a positive global perceived effect. All patients had one month follow-up visits; patients whose condition improved remained blinded for their three month visit.

RESULTS
There were no significant differences for the primary outcome measure at one month (mean pain score 3.3 (SD 2.6) and mean change from baseline −2.2 (SD 2.4) in epidural steroid injection group versus 3.7 (SD 2.6) and −1.7 (SD 2.6) in gabapentin group; adjusted difference 0.4, 95% confidence interval −0.3 to 1.2; P=0.25) and three months (mean pain score 3.4 (SD 2.7) and mean change from baseline −2.0 (SD 2.6) versus 3.7 (SD 2.8) and −1.6 (SD 2.7), respectively; adjusted difference 0.3, −0.5 to 1.2; P=0.43). Among secondary outcomes, one month after treatment those who received epidural steroid injection had greater reductions in worst leg pain (−3.0, SD 2.8) than those treated with gabapentin (−2.0, SD 2.9; P=0.04) and were more likely to experience a positive successful outcome (66% v 46%; number needed to treat=5.0, 95% confidence interval 2.8 to 27.0; P=0.02). At three months, there were no significant differences between treatments.

CONCLUSIONS
Although epidural steroid injection might provide greater benefit than gabapentin for some outcome measures, the differences are modest and are transient for most people.

TRIAL REGISTRATION
ClinicalTrials.gov Identifier: NCT01495923.

Introduction

The physical, socioeconomic, and psychological impact of low back pain is enormous. Low back pain 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 bn a year in the United States (£67 bn, €93 bn), over half of which can be attributed to lost productivity.[3 4] Efforts to deal with the worldwide burden posed by low back pain have become an international priority.

The classification of back pain is perhaps the most important distinction for clinicians to make as it influences investigation and treatment decisions at all levels of care.[5] Since the development of validated instruments to categorize low back pain,[6 7] studies have determined that the proportion of chronic cases that are predominantly neuropathic (that is, 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 episodes,[13] lumbosacral radicular pain might be more responsive to procedural interventions than non-specific back pain.[12 14]

Epidural steroid injections are the most commonly performed procedure for pain relief in the world,[15] being more commonly used and more effective for radicular pain than mechanical spine pain.[12 16] Although mixed, most controlled studies have also

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WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

Gabapentin and epidural steroid injections are often used to treat lumbosacral radiculopathy and can provide benefit for a subset of patients, but we do not know which treatment works better

WHAT THIS STUDY ADDS

Both epidural steroid injections and gabapentin treatment resulted in significant improvements in pain scores and functional capacity

Although epidural steroid injections might be superior to gabapentin in some outcome measures, the differences are small and generally short lived

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found pharmacotherapy with gabapentinoids can be effective for lumbosacral radicular pain.[17-21]

Numerous controlled trials have been performed to evaluate epidural steroid injections and drug treatment in people with low back pain, 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 looked at epidural steroid injections compared with drug treatment. One study showed superiority for a single epidural steroid injection at one month but not later follow-up compared with tramadol and a muscle relaxant.[24] A second study showed that a single caudal epidural steroid injection provided better pain relief than non-steroidal anti-inflammatory drugs through three months.[25] Neither study evaluated first line adjuvant treatments (such as gabapentin) as a comparison group. A more recent three armed multicenter study was performed in 169 patients with cervical radiculopathy. Over six months participants received nortriptyline and/or gabapentin plus physical therapies, up to three cervical epidural steroid injections, or combination treatment in which they received both injections and conservative care. They found that the combination group experienced a higher success rate at three months but not six months.[26] Although these studies might simulate real life decisions facing clinicians, the fact that none were blinded precludes any conclusions regarding efficacy. We investigated a single epidural steroid injection compared with gabapentin in patients with lumbosacral radicular pain in a double blinded fashion.

Methods
Participants and settings
The study sites were four joint service military treatment facilities, three of which serve as teaching hospitals (Walter Reed, San Diego, and San Antonio) and one of which is located in Europe; a Veteran's Administration hospital; and three civilian teaching hospitals (Johns Hopkins, Case Western, and Penn State).

All participants were treated between 15 December 2011 and 10 June 2014. Inclusion criteria were age ≥17; an average score for radicular leg pain of ≥4 on a 0-10 numerical rating scale over the preceding week or 3/10 if the leg pain was as bad as or worse than back pain; current symptoms had lasted for more than six weeks and up to four years; and signs (such as straight leg raising test) and/or symptoms (such as lower leg pain) of lumbosacral radicular pain. All participants were also required to have findings of a herniated disc or spinal stenosis on magnetic resonance imaging, concordant with their presentation. Patients were permitted to have symptoms in more than one dermatome.

Exclusion criteria were neuropathic pain for more than four years in duration; previous failed trial with, or adverse reaction to, gabapentin or pregabalin; epidural steroid injections within the past three years; cauda equina syndrome; referrals for surgical evaluation; previous lumbar spine surgery; pregnancy; allergic reaction to contrast dye; known secondary gain (such as active litigation); active infection; and serious medical (such as poorly controlled diabetes, cirrhosis, recent myocardial infarction, congestive heart failure, or unstable angina) or psychiatric condition (such as dementia, poorly controlled post-traumatic stress syndrome as indicated by a score ≥44 on the post-traumatic stress disorder checklist,[27] substance abuse, somatization disorder, or depression as indicated by a Beck Depression score ≥21[28]) that might preclude an optimal response to treatment. Because our intention was to evaluate the relative effects of two commonly used treatments for radicular pain, we also excluded patients with neurogenic claudication from spinal stenosis who did not report lower leg pain (that is, those who had only weakness or paresthesias). Although heterogeneity is often desirable in comparative effectiveness trials, we performed briefings, debriefings, full time access to a senior investigator, and at one site practice enrollments to enhance selection consistency.

Randomization and interventions
We randomized 145 participants in a 1:1 ratio by computer generated randomization tables. An investigator physician enrolled participants, stratified by study site. Research nurses performed allocation in groups of 36 at Walter Reed and Johns Hopkins as these sites were expected to enroll more patients, and in groups of 18 at other sites, with treatment allocated with a sequentially numbered opaque sealed envelope before injection. Larger allocation blocks were used to promote allocation concealment with investigators. Participants at each site were suballocated separately on a 1:1 ratio based on the type of epidural steroid injection they received: those with unilateral pain received unilateral transforaminal epidural steroid injections, while those with bilateral pain underwent interlaminar epidural steroid injections. The patient, research nurse, and evaluating physician were blinded to assignment.

Epidural injections
A board certified pain medicine physician conducted or supervised all procedures using fluoroscopic guidance. 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 with image guidance in the anteroposterior and lateral views by using the loss of resistance technique. For transforaminal epidural steroid injections, a 22 gauge spinal needle was inserted coaxially 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 showed bilateral spread for all interlaminar injections and proximal epidural uptake for all transforaminal procedures. Once 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. Whereas some physicians routinely perform multilevel transforaminal injections, we limited our procedures to a single level to minimize risks because there are no controlled studies validating the use of more than one injection and because a well placed transforaminal epidural steroid injection generally spreads to multiple levels.[29 30]

Sham injections and maintenance of blinding
Participants were instructed ahead of time that they might or might not experience paresthesias during the procedure and were visually shielded from the image screen. The same technique (such as trajectory and use of multiplanar fluoroscopy) was used for injections except in sham injections 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 an additional 3 mL to simulate the injectate. A generic note was entered into the medical record without radiographs.

Pharmacotherapy
A central research pharmacy over-capsulated 300 mg gabapentin and placebo capsules to appear identical. Before 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/day to 3600 mg/day three times a day. Drugs 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 five days before follow-up.

Co-interventions, outcome measures, follow-up, and 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 up to 20% for those taking opioids), but no other co-interventions were permitted. Participants were provided with instructions on how to taper their analgesic drugs based on response. An investigator blinded to treatment carried out the first follow-up visit one month after the start of treatment. The primary outcome measure was the average leg pain score on a 0-10 numerical rating scale recorded at one and three months, reflecting the average pain experienced during the week before follow-up. Predefined secondary outcome measures included worst leg pain over the past week, average and worst back pain, score on the Oswestry disability index (version 2.0, MODEMS, Des Plaine, IL),[31] adverse effects and complications, reduction in analgesic drugs (>20% reduction in opioid use or complete cessation of non-opioid analgesics), and global perceived effect, which was defined as not requiring further non-rescue interventions along with

an affirmative response to the following two statements:[32] "My pain has improved/ worsened/stayed the same since my last visit" and "I am satisfied/not satisfied with the treatment I received and would/would not recommend it to others."

Because patients cannot accurately distinguish between neuropathic pain (which is more likely to respond to epidural steroid injection and gabapentin)[12 33] and mechanical pain, we separately recorded leg (neuropathic) and back (mechanical) pain scores as surrogates. Whereas a small percentage of cases of axial back pain might be neuropathic in nature,[34] and many forms of mechanical pain such as facet arthropathy and degenerative disc disease can radiate into the leg,[35] validated instruments have shown that leg pain emanating from the back is generally indicative of radicular pain.[7]

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. We assessed complications by asking fixed and open ended questions one day after injections and at all follow-up visits. In addition to individual variables, we predesignated a positive composite outcome (that is, successful procedure) to be a decrease of ≥2 points in average leg pain score coupled with a positive global perceived effect.[36]

In those individuals who experienced a positive outcome at one month, the final follow-up occurred at three months. In these individuals, in addition to rescue medications, the study drug could also be titrated upwards. For ethical reasons, those with a negative outcome at one month left the study "per protocol" to receive non-study interventions, which is consistent with other randomized interventional studies.[26 32 37 38] We imputed missing data points for pain scores, Oswestry disability index, and the composite outcome using the "last observation carried forward" method, which can underestimate effect sizes when "dropouts" occur because of lack of efficacy.[39]

Statistical analysis
We used an intention to treat strategy for all analyses. We calculated differences in treatment effects and 95% confidence intervals for pain and disability scores with analysis of covariance (ANCOVA) adjusting for baseline values of outcome measures. An indicator of the treatment group was coded such that positive values favored the epidural steroid injection group. No correction was prespecified for multiple comparisons. Because of a difference in sex distribution at baseline, we adjusted post hoc analysis of outcomes for sex. We used logistic regression models to compare the proportion of patients with adverse events in the first month and factors associated with binary outcomes in post hoc analysis. We used Poisson regression models with robust standard errors to analyze adverse event rates. Effectiveness of blinding in each treatment group was evaluated by using two indices. In the James blinding index[40] (range 0-1), 0 indicates total absence of blinding, 1 indicates

Table 1 | Baseline demographic and clinical characteristics of participants in study of epidural steroid injections compared with gabapentin for lumbosacral radicular pain. Figures are numbers of participants (percentage) unless stated otherwise

Characteristic	Epidural steroid injection (n=73)	Gabapentin (n=72)
Mean (SD age (years)	43.8 (14.0)	41.7 (11.9)
Women*	25 (34)	13 (18)
Duration of pain:		
<3 months:	11 (15)	15 (21)
3-<months	26 (36)	27 (38)
1-3 years	27 (37)	23 (32)
>3 years	9 (12)	7 (10)
Treatment with opioids:		
None	54 (74)	55 (7)
<60 morphine equivalents/day	16 (22)	14 (19)
≥60 morphine equivalents/day	3 (4)	3 (4)
Mean (SD) oral morphine equivalents among opioid users (mg/day)	28.7 (34.8)	38.5 (53.0)
Diagnosis:		
Herniated nucleus pulposus	63 (85)	65 (90)
Spinal stenosis	10 (14)	7 (10)
Active duty military:		
Any	38 (52)	41 (57)
Enlisted	26 (36)	30 (42)
Officer	12 (16)	11 (15)
Inciting event:		
None	42 (58)	41 (60)
Motor vehicle crash	1 (1)	1 (1)
Fall	5 (7)	9 (13)
Lifting	13 (18)	6 (8)
Sports/training	8 (11)	13 (18)
Other†	4 (6)	2 (3)
Pain related to deployment	10 (14)	6 (8)
Current smoker‡	15 (21)	13 (18)
Obesity	13 (18)	19 (26)
Psychiatric comorbidity:		
None	56 (77)	49 (68)
Mood	9 (12)	12 (17)
Anxiety	7 (10)	6 (8)
Substance abuse	3 (4)	4 (6)
Post-traumatic stress disorder	1 (1)	4 (6)
Other§	1 (1)	3 (4)
Multiple diagnoses	4 (6)	6 (8)
Injection approach:		
Interlaminar	11 (15)	12 (17)
Transforaminal	62 (85)	60 (83)
Level of injection:		
L2-3	1 (1)	0
L3-4	1 (1)	2 (3)
L4-5	22 (30)	18 (25)
L5-S1	44 (60)	46 (64)
S1	5 (7)	6 (8)
Mean (SD) baseline pain scores¶:		
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)
Oswestry disability score	39.8 (15.3)	39.8 (14.7)

*Significant difference between two groups (P=0.027 by χ² test).
†Includes post-surgical, pregnancy, spinal tap, and work related.
‡Includes three participants who chew tobacco products.
§Includes attention deficit hyperactivity disorder and obsessive compulsive disorder.
¶Based on 0-10 numerical rating scale scores.

complete blinding, and 0.5 indicates completely random blinding. In the Bang blinding index[41] (range –1·1), –1 indicates that all patients guessed the incorrect treatment, 0 indicates all patients randomly guessed, and 1 indicates all patients guessed the correct treatment. We conducted subgroup analyses to ascertain which demographic and clinical variables were associated with outcome. Variables examined included etiology (such as stenosis v herniated disc), level of injection, pain duration ≥3 months, injection type (for instance, transforaminal epidural steroid injection for unilateral pain v interlaminar epidural steroid injection for bilateral pain), smoking status, military status, presence of psychiatric disease, obesity, age, sex, and gabapentin dose. We had intended to examine the effect of inciting events related to war, such as traumatic brain injury, but there were too few patients to render any analysis meaningful. We used Bonferroni-corrected significance thresholds 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 significant.

The study was powered to evaluate the effectiveness of epidural steroid injections compared with gabapentin. Assumptions include a difference of 1 point in pain scores between groups at one month, standard deviation of each group of 2 based on data from previous studies, a retention rate of 87%, and a two sided α level of 0.05. Although a 30% or 2 point decrease in pain has been shown to represent a clinically meaningful benefit to an individual patient, the same IMMPACT (Initiative on Methods, Measurement and Pain Assessment in Clinical Trials) guidelines note that smaller differences between groups can be considered to be clinically important in clinical trials.[36] We chose a 1 point difference in pain scores because it is consistent with US Food and Drug Administration requirements for approval of adjuvant analgesic drugs for low back pain and gabapentin for neuropathic pain.[42 43]

Patient involvement
Although non-scientists from the surrounding communities served on many of the approving review boards at participating institutions, patients did not participate in the design of this study. All participants will receive the results of the study and a copy of the final manuscript from their study team by email or post.

Results
We assessed 348 potential participants, of whom 147 were eligible for inclusion and agreed to participate. Of these, 145 were assigned to receive either an epidural steroid injections and sham drug (n=73) or gabapentin and a sham injection (n=72). The two groups were similar with respect to baseline characteristics, except that the epidural steroid injection group contained more women (table 1, figure).

Outcomes
At one month, both the epidural steroid injection group and the gabapentin group experienced improvement in
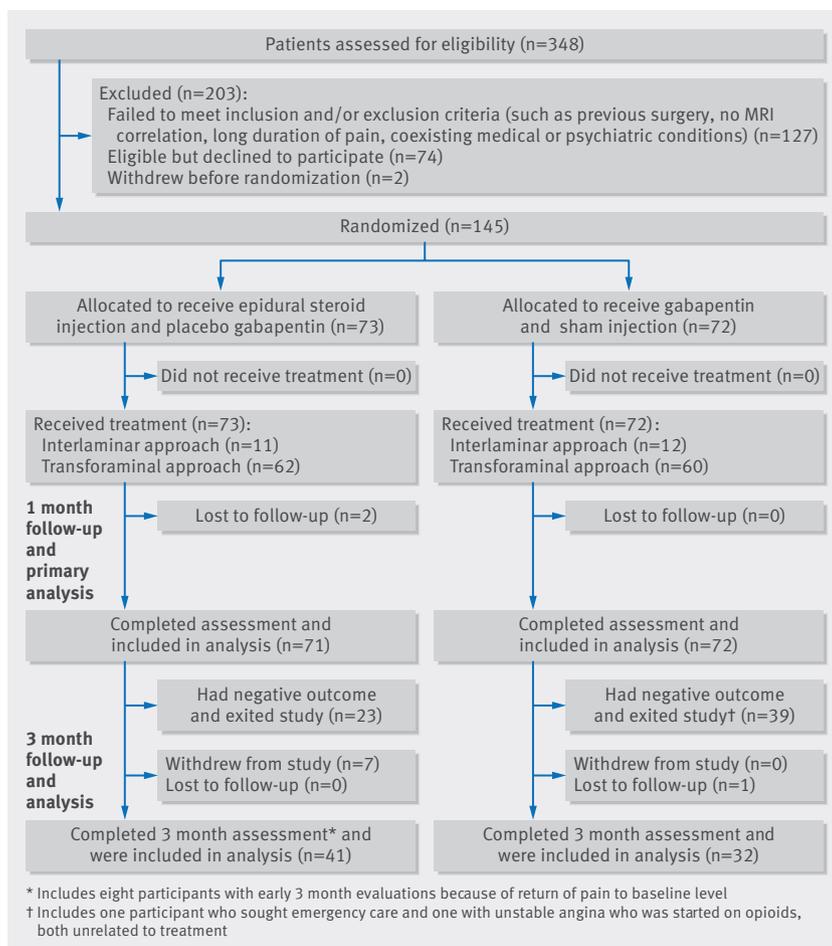
Flow of progress of participants through clinical trial of epidural steroid injections and gabapentin in people with lumbosacral radicular pain

the average leg pain score (mean 3.3 points (SD 2.6) and mean change from baseline −2.2 points (SD 2.4) in epidural steroid injection group versus 3.7 points (SD 2.6) and −1.7 points (SD 2.6) in gabapentin group), but no significant difference between groups was observed (adjusted difference 0.4 points, 95% confidence interval −0.3 to 1.2; P=0.25) (table 2). At three months, improvements in average leg pain score persisted (mean 3.4 points (SD 2.7) and −2.0 points (SD 2.6) versus mean 3.7 points (SD 2.8) and −1.6 points (SD 2.7), respectively), but again with no significant difference between groups (0.3 points, −0.5 to 1.2; P=0.43).

For secondary outcome measures, there were small differences between groups favoring epidural steroid injections at one month for worst leg pain score (adjusted difference 0.9 points, 95% confidence interval 0.0 to 1.9; P=0.04 (table 2)) and successful outcome (66% and 46%, P=0.02 (table 3); number needed to treat 5.0, 95% confidence interval 2.8 to 27.0). For average back pain at one month, there was a moderate improvement for the epidural steroid injections group (−1.5, SD 1.9) and a mild improvement for the gabapentin group (−1.1, SD 2.3), but the differences were not significant (adjusted difference 0.3 points, −0.4 to 0.9; P=0.45) (table 2). No significant differences were observed for outcomes at three months or for patients proceeding to surgery within one year of enrollment (9 (13%) in epidural steroid injection group v 10 (15%) in gabapentin group; P=0.73) (table 3).

Factors associated with outcome and post hoc analyses

In subgroup analyses, military officers were more likely to experience a positive outcome than either enlisted

Table 2 | Outcomes related to pain and disability in people with lumbosacral radicular pain according to treatment with epidural steroid injections or gabapentin*

	Epidural steroid injection			Gabapentin			Treatment comparison	
	No of patients	Overall mean (SD)	Mean change from baseline	No of patients	Overall mean (SD)	Mean change from baseline	Adjusted difference (95% CI)†	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)	0.25
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)	0.43
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)	0.04
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)	0.54
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)	0.45
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)	0.85
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)	0.38
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)	0.91
Oswestry disability score‡:								
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)	0.18
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)	0.12

*Data for missing 1 month and 3 months outcomes including pain scores, Oswestry disability scores 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.
†Differences for pain and Oswestry disability scores adjusted for baseline values. Negative coefficients favor gabapentin group. Positive coefficients favor epidural steroid injection group.
‡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]

Table 3 | Further outcomes in people with lumbosacral radicular pain according to treatment with epidural steroid injections or gabapentin

	Epidural steroid injection		Gabapentin		
	No of patients	No (%)	No of patients	No (%)	P value for comparison
Reduction in drug treatment*:					
4 weeks	67	40 (60)	65	32 (49)	0.23
12 weeks	40	23 (58)	30	14 (47)	0.37
Global perceived effect (positive)†:					
1 month	73	49 (67)	72	41 (57)	0.21
3 months	73	33 (45)	72	24 (33)	0.14
Composite outcome (positive)†‡:					
1 month	73	48 (66)	72	33 (46)	0.02
3 months	73	27 (37)	72	21 (29)	0.32
Proceeded to surgery within year of enrollment	72	9 (13)	69	10 (14)	0.73

*Reduction in analgesics corresponds to >20% reduction in opioid use or complete cessation of non-opioid analgesics. Patients who were not on pain drugs were excluded from this analysis.
†Missing data for 1 month and 3 months imputed by last observed outcome carried forward.
‡>2 point decrease in average leg pain coupled with positive global perceived effect without additional procedural or non-rescue pharmacological interventions.

personnel or non-service members at one month (odds ratio 6.7, 95% confidence interval 1.8 to 24.6; P=0.004). Injection at S1 was associated with a greater reduction in leg pain than at other levels (−0.7, −0.1 to −1.2; P=0.02) but failed to reach significance when we adjusted for multiple comparisons. We found no associations among the primary or composite outcomes at one month based on etiology (such as stenosis v herniated disc), pain duration ≥3 months, injection type (transforaminal epidural steroid injections for unilateral pain v interlaminar epidural steroid injections for bilateral pain), smoking status, presence of psychiatric disease, obesity, age, sex, or dose of gabapentin. In post hoc adjustments for sex, the difference between groups in reduction of worst leg pain favoring epidural steroid injections was no longer significant (0.3, −0.8 to 1.4; P=0.05).

Adverse events
The proportion of patients reporting one or more adverse events from the injection was 8% (n=6) in the epidural steroid injection group and 10% (n=7) in the gabapentin group (P=0.75). The proportion of patients reporting one or more adverse events from drug treatment was 42% (n=30) in the epidural steroid injection group and 51% (n=37) in the gabapentin group (P=0.24; table 4).

Blinding
We assessed blinding at two time points: immediately after the procedure to assess blinding for real epidural steroid injections and at the first follow-up to ensure blinding for real gabapentin. Immediately after the baseline procedure, patients were unaware of assigned treatments (James blinding index 0.75, 95% confidence interval 0.69 to 0.80; P=1.0; Bing blinding index 0.07 (−0.07 to 0.21) in the epidural steroid injections group and −0.24 (−0.38 to −0.09) in gabapentin group),

indicating successful blinding. At one month, the overall success of blinding was maintained (James blinding index 0.56, 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 0.08 (−0.07 to 0.25) in epidural steroid injection group and 0.19 (0.03 to 0.36) in gabapentin group).

Discussion
Principal findings and study rationale
In people with lumbosacral radicular pain randomized to epidural steroid injections or gabapentin, we found that although there were some small differences in favor of the injections at one month, there were no significant differences for our primary outcome measure (average leg pain one and three months), and the differences observed mostly disappeared at three months. Although only a small percentage of our patients had spinal stenosis, our findings are consistent with a recent multicenter study that found modest short term benefit for epidural steroid injections for this condition.[44] In our study we compared epidural steroid injections with epidural local anesthetic, which a systematic review showed was superior to soft tissue control injections (that is, not a placebo).[45] 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.[46 47]

The rationale for this comparative efficacy study is that there are well over 50 published clinical trials epidural steroid injections or adjuvants compared with placebo for radiculopathy, but none that compared one treatment with another. In accordance with the US Department of Health and Human Services recommendation to increase and improve comparative effectiveness research,[46] we decided to compare two of the most common treatments for lumbosacral radicular pain in a double blind fashion.[46]

Comparison with other studies
Results of placebo controlled studies evaluating gabapentinoids and other membrane stabilizers for radiculopathy are mixed, indicating a probable small effect size.[48] This suggests that differences between groups are unlikely to represent a large treatment effect. Although myriad reviews on epidural steroid injections have yielded disparate conclusions, recent systematic and evidence based reviews have indicated that any stand alone treatment effect for epidural steroid injections is likely to be modest and short lived.[12 22]

In a recent open label three arm comparative effectiveness study pitting a series of epidural steroid injections 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 epidural steroid injections plus drugs and physical therapy provided superior benefit to stand alone treatment on some

Table 4 | Adverse events in people with lumbosacral radicular pain according to treatment with epidural steroid injections or gabapentin. *Figures are numbers (percentage) of participants unless stated otherwise

Adverse event	Epidural steroid injection group (n=73)	Gabapentin group (n=72)	P value
Related to injection			
Injection received	Epidural steroid injections	Sham injection	—
≥1 event*	6 (8)	7 (10)	0.75
Total adverse events (event rate)†	6 (0.08)	9 (0.13)	0.42
Reported symptoms or events:			
Excessive pain	2‡	4‡	—
Fever, infection, or both	2	0	—
Falls	1‡	0	—
Vasovagal	0	2‡	—
Other§	1	3	—
Related to drug treatment			
Treatment received	Sham pills	Gabapentin pills	—
Mean (SD) dose (mg)	2132.9 (609.4)	2095.8 (678.3)	0.73
Compliance¶:			
None	6 (8)	8 (11)	0.68
Partial (50-89%)	11 (15)	8 (11)	
Full (>90%)	55 (76)	56 (78)	
≥1 event*¶	30 (42)	37 (51)	0.24
Total adverse events (event rate)*¶	45 (0.63)	50 (0.69)	0.61
Reported symptoms or events¶:			
Sedation/fatigue	8 (11)	13 (18)‡	—
Cognitive	5 (7)	7 (10)‡	—
Weight gain	4 (6)	7 (10)‡	—
Headache	4 (6)	1 (1)	—
Gastrointestinal	13 (18)	8 (11)‡	—
Swelling	0 (0)	3 (4)‡	—
Other**	11 (15)	11 (15)‡	—

*Significance assessed with logistic regression model adjusted for treatment group assignment.
†Significance assessed with Poisson regression model with robust standard errors adjusted for treatment group assignment.
‡Deemed related to or possibly related to treatment.
§Other adverse events for epidural steroid injection group include "low cortisol noted on lab tests three weeks after injection in patient also receiving oral steroids with no symptoms." Other adverse events for gabapentin group (sham injection) include bruising, temporary inability to lift legs, and "GI bleed after three days in patient receiving low molecular weight heparin." None deemed related to treatment.
¶Data missing for one patient in epidural steroid injection group.
**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, ‡ depression requiring admission to hospital, dizziness (2), ‡dry mouth (2), ‡leg spasms, mood changes, rhinorrhea with flu-like symptoms, and one without description.

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

Explanation of findings

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 of epidural steroid injections that often follow patients for up to one year,[49-54] 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.[55] [56] A second hypothesis is that neither treatment is effective, and the benefits observed were caused by a placebo response or the natural course of the disease. Those with chronic radiculopathy, however, are less

likely than those with shorter duration of symptoms to spontaneously improve or respond to treatment.[57] A third possibility is that epidural steroid injections are superior to gabapentin, but the relatively small sample size, the use of only one injection, treatment blinding, and our failure to reinforce the short term benefit with physical therapy rendered three month differences indistinguishable. In their effectiveness study that compared a series of epidural steroid injections, neuropathic adjuvants plus physical therapy, and combination therapy for cervical radiculopathy, Cohen and colleagues reported that the better outcomes in the combination group might have been attributable to the ability of physical therapy to reinforce the short term gains afforded by procedures.[26]

Strengths and limitations

The main strength of our study is that we compared two of the most commonly used treatments for lumbosacral radiculopathy pain in a double blind fashion at institutions that reflect the gamut of settings in which patients might seek treatment. There are several limitations to our study, including the primary outcome being measured at one 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 two treatments. A third limitation is that we did not permit repeat epidural steroid injections or allow combination drug treatment. Studies have shown there is little basis for a rote "series" of epidural steroid injections, though some might benefit from repeat injections, which are often performed in clinical practice.[12 26 32 44 54 58 59] Similarly, randomized studies have shown that combination treatment with drugs that include gabapentinoids could provide superior relief for neuropathic and low back pain compared with treatment with a single agent.[60] A fourth limitation inherent in our design is that blinding of participants might 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 for pills, which might have mitigated any "real world" differences between treatments.[61 62] A final limitation is our broad inclusion criteria, which included patients taking opioids and those with herniated disc and spinal stenosis. These conditions are characterized by slightly different pathophysiological mechanisms and might have different natural outcomes. A larger study would be needed to determine whether certain patients (such as those with herniated disc versus spinal stenosis) or treatments (transforaminal versus interlaminar epidural steroid injections) experience better outcomes than others. In practice, patients generally receive epidural steroid injections and/or adjuvants regardless of the etiology of their neuropathic pain. In clinical trials, most epidural steroid injection

studies[12 24–26 32 49 51 53] and all gabapentinoid studies[17-21] included both etiologies, with most studies finding no difference in outcomes with epidural steroid injection[12] or gabapentinoid (R Baron, personal communication, 2014)[20 21] between people with stenosis and disc herniation.

Generalizability

These results are readily generalizable to primary care settings, pain clinics, and spine surgery centers, where practitioners are often faced with the question about the best non-operative way to manage lumbosacral radicular pain. Future studies might include both placebo and combination groups (for example, factorial design), allow for multiple injections and drugs, and require physical therapy in an effort to determine whether any observed benefit could be prolonged. The logistical and ethical obstacles in designing such studies (such as blinding multiple drugs or performing multiple sham injections in patients who fail to respond to the first one), however, will make them difficult to execute.

Conclusions and policy implications

Gabapentin and epidural steroid injections used to treat lumbosacral radicular pain both resulted in modest improvements in pain and function, which persisted through three months. Although some differences favored epidural steroid injections, these tended to be small and transient. The similar outcomes between treatment groups on most measures suggest that a trial with neuropathic drugs might be a reasonable first line treatment option.

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