

# Epidural Steroid Injections, Conservative Treatment, or Combination Treatment for Cervical Radicular Pain

## *A Multicenter, Randomized, Comparative-effectiveness Study*

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### ABSTRACT

**Background:** Cervical radicular pain is a major cause of disability. No studies have been published comparing different types of nonsurgical therapy.

**Methods:** A comparative-effectiveness study was performed in 169 patients with cervical radicular pain less than 4 yr in duration. Participants received nortriptyline and/or gabapentin plus physical therapies, up to three cervical epidural steroid injections (ESI) or combination treatment over 6 months. The primary outcome measure was average arm pain on a 0 to 10 scale at 1 month.

**Results:** One-month arm pain scores were 3.5 (95% CI, 2.8 to 4.2) in the combination group, 4.2 (CI, 2.8 to 4.2) in ESI patients, and 4.3 (CI, 2.8 to 4.2) in individuals treated conservatively ( $P = 0.26$ ). Combination group patients experienced a mean reduction of  $-3.1$  (95% CI,  $-3.8$  to  $-2.3$ ) in average arm pain at 1 month *versus*  $-1.8$  (CI,  $-2.5$  to  $-1.2$ ) in the conservative group and  $-2.0$  (CI,  $-2.7$  to  $-1.3$ ) in ESI patients ( $P = 0.035$ ). For neck pain, a mean reduction of  $-2.2$  (95% CI,  $-3.0$  to  $-1.5$ ) was noted in combination patients *versus*  $-1.2$  (CI,  $-1.9$  to  $-0.5$ ) in conservative group patients and  $-1.1$  (CI,  $-1.8$  to  $-0.4$ ) in those who received ESI;  $P = 0.064$ ). Three-month posttreatment, 56.9% of patients treated with combination therapy experienced a positive outcome *versus* 26.8% in the conservative group and 36.7% in ESI patients ( $P = 0.006$ ).

**Conclusions:** For the primary outcome measure, no significant differences were found between treatments, although combination therapy provided better improvement than stand-alone treatment on some measures. Whereas these results suggest an interdisciplinary approach to neck pain may improve outcomes, confirmatory studies are needed. (**ANESTHESIOLOGY 2014; 121:1045-55**)

**A**PPROXIMATELY two thirds of individuals will experience significant neck pain in their lifetime, with the annual prevalence rates ranging between 30 and 50%.<sup>1,2</sup> In large-scale studies, the annual incidence of cervical radiculopathy ranges between 1 and 3.5 per 1,000 person-years.<sup>3-5</sup>

The treatment of cervical radicular pain is challenging, with no reliably effective treatment. Epidural steroid injections (ESI) are the most commonly performed procedures in pain clinics throughout the United States,<sup>6</sup> yet systematic reviews evaluating their efficacy are mixed.<sup>7-13</sup> For cervical

#### What We Already Know about This Topic

- Both conservative treatment and epidural steroid injections may be beneficial in patients with cervical radicular pain, but we do not know which treatment(s) work best

#### What This Article Tells Us That Is New

- This randomized study suggests that conservative, epidural steroid, and combination treatment may all produce similar outcomes in terms of reduction in arm pain
- Combination treatment may offer some advantages for other outcomes such as neck and arm pain

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radiculopathy, two small controlled studies ( $n \leq 50$ ) have evaluated ESI,<sup>14,15</sup> with one demonstrating benefit.<sup>14</sup>

Conflicting results have also been observed for the treatment of radiculopathy with neuropathic pain medications, as well as physical therapy (PT). Although some small controlled studies have revealed modest improvements with pharmacotherapy,<sup>16,17</sup> others have found minimal benefit.<sup>18–20</sup> For PT, studies are similarly mixed.<sup>21–23</sup> These findings underscore the need for larger studies to determine which treatments work best.

Although some patients and those with serious neurological symptoms may benefit from surgery, most randomized studies evaluating surgery for neuropathic spinal pain have found minimal long-term benefit in most patients.<sup>24–28</sup> Consequently, identifying those aspects of nonsurgical care that afford the greatest improvement assumes increasing importance. This question is more critical when one considers the fact that cervical ESI may be associated with catastrophic consequences.<sup>29,30</sup> Yet, few randomized studies have compared ESI with other treatments. In a small trial performed in patients with lumbar spinal stenosis, Koc *et al.*<sup>31</sup> found ESI, and to a lesser extent PT, to be superior to a control group at 2 weeks, but no differences were observed thereafter. A similar study by Laiq *et al.*<sup>32</sup> noted better outcomes in patients treated with a single ESI compared with pharmacotherapy for only up to 1 month. Another study found a single caudal ESI to provide better pain relief through 3 months than nonsteroidal antiinflammatory drugs.<sup>33</sup> However, the medications prescribed in the latter two studies are not generally considered effective for radiculopathy or neuropathic pain.<sup>18,34–37</sup> To determine the relative effectiveness of nonsurgical treatments for cervical radicular pain, we conducted a randomized study comparing ESI to pharmacotherapy with gabapentin and/or nortriptyline along with PT, and the combination of the treatments. A secondary objective was to determine the factors associated with treatment outcome, which has never been prospectively done in this population.

## Materials and Methods

### Design Overview

A randomized, controlled, parallel group study was conducted in which subjects were allocated in a 1:1:1 ratio to receive cervical ESI, conservative care consisting of pharmacotherapy and PT, or a combination of the two treatments, for cervical radicular pain. Permission to conduct this multicenter study was granted by the internal review boards of Johns Hopkins (Baltimore, Maryland), Walter Reed (Bethesda, Maryland), Landstuhl Regional Medical Center (Landstuhl, Germany), San Antonio Military Medical Center (San Antonio, Texas), Case Western Reserve (Cleveland, Ohio), Penn State (Hershey, Pennsylvania), and the DC Veterans Administration Medical Center (Washington, D.C.), in addition to all participants who provided written, informed consent. All subjects were treated between June 2010 and August 2013.

### Settings and Participants

The study centers included three academic civilian teaching facilities; two military treatment facilities that receive referrals from many smaller community hospitals (Walter Reed, San Antonio Military Medical Center); the largest American military medical center outside the United States (Landstuhl Regional Medical Center); and a veterans' administration hospital. Inclusion criteria were cervical radicular pain extending into the arm(s) based on history and physical; numerical rating scale arm pain score  $\geq 4/10$  or equivalent in intensity to neck pain; magnetic resonance imaging correlation of symptoms with pathology; and age  $\geq 18$  yr. Excluded from participation were patients with pain less than 1 month or more than 4 yr in duration; allergy to steroids or contrast; signs or symptoms of myelopathy; surgical referral for a diagnostic injection; previous spine surgery; previous trials with gabapentin or pregabalin and amitriptyline or nortriptyline; serious medical or psychiatric disorders that might preclude an optimal response to treatment; ongoing litigation; and previous cervical ESI.

### Randomization and Interventions

One hundred sixty-nine consecutive subjects were apportioned by computer-generated randomization tables into one of the three groups in equivalent allotments. A research nurse at each institution randomized participants in either groups of 24 (Johns Hopkins, Walter Reed, and Penn State) or 9, based on the anticipated enrollment. Patients in group I (conservative treatment) received either pharmacotherapy with gabapentin and/or nortriptyline, and PT, as indicated. The decision as to which medication(s) to prescribe and what dose to target was made on a case-to-case basis in accordance with standard practice. In general, medications were up-titrated over a period of 16 to 24 days, with the only caveat being that a therapeutic dose range had to be obtained at least 5 days before follow-up. PT was initiated within 1 week of enrollment and geared toward the alleviation of radicular symptoms. Treatments could include education, electrical stimulation, ultrasound, massage, and exercise. Individuals who already failed PT could opt out, pursue alternative treatments, or choose only parts of the PT regimen they had not tried.

Patients in group II (ESI) received at least one interlaminar ESI performed under the supervision of a pain management specialist. Under sterile conditions, the image intensifier was adjusted to maximize the opening between either the C6-7 or C7-T1 interspace. After the administration of superficial anesthesia, an epidural Tuohy needle was inserted into the epidural space using fluoroscopic guidance. In those participants with unilateral symptoms, the injection was done ipsilateral to midline, whereas a midline approach was employed for those with bilateral symptoms. Once the epidural space was identified using the loss-of-resistance technique, correct position was confirmed by the injection of contrast. After the attending physician was satisfied with

the contrast spread, a 3-ml solution containing 60 mg of depo-methylprednisolone and normal saline was administered. Repeat injections could be performed after the 1- and 3-month follow-ups at the discretion of the physician for those patients who experienced either a recurrence of their pain after resolution or only partial benefit.

Patients in the combination group received both ESI and pharmacotherapy with gabapentin and/or nortriptyline plus PT, in accordance with the guidelines outlined for the ESI and conservative groups.

### Follow-up and Data Collection

Baseline data were collected before the first injection. In addition to demographic data, clinical information included duration of pain, average and worst arm-and-neck pain scores on validated numerical rating scale pain scales over the past week, based on daily activity logs<sup>38</sup>; analgesic usage; duration of symptoms; neck disability index (NDI) score; and a host of clinical factors such as inciting event, obesity, smoking history, coexisting psychiatric morbidity garnered by self-report and medical records, and the presence of potential secondary gain issues. NDI is a validated measure of physical function in individuals with neck and/or arm pain scored on a 0 to 100% scale, with higher scores indicating greater limitations.<sup>39</sup> All patients enrolled in the study were allowed to continue their preenrollment analgesic regimen, but after treatment was initiated, patients were given instructions on how to decrease or stop analgesics medications, based on treatment response.

The first follow-up visit took place 1 month after the first injection or the initiation of medications by a disinterested investigator unaware of treatment allocation. The primary outcome measure was designated to be the average arm pain score over the past week at 1-month follow-up. In addition to baseline parameters, other information recorded were medication reduction, which was predefined as either a greater than 20% reduction in opioid consumption or complete cessation of a nonopioid analgesic<sup>40</sup>; medication and PT compliance, graded as either noncompliant (did not go to PT or took <50% of the prescribed medication for their target dose); partially compliant (*i.e.*, patient took between 50 and 80% of their prescribed medication); and fully compliant (*i.e.*, ≥80% of prescribed medication consumed, and ≥80% of PT sessions attended); adverse effects and complications (also recorded 1-day postinjection); global perceived effect; and a composite categorical outcome dichotomized into “success” or failure.” Global perceived effect was previously defined as a positive response to the following two questions<sup>40</sup>:

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

A composite categorical outcome was predetermined to be a two-point reduction or more in arm pain in conjunction

with a positive global perceived effect, obviating the need for further interventions. Causality for complications was determined *via* discussion by the investigators.

To simulate clinical practice, those subjects with a negative categorical outcome at any follow-up exited the study per protocol to pursue different treatments. This was done for ethical reasons and is consistent with previous controlled and comparative-effectiveness trials.<sup>40–44</sup> For participants with a positive categorical outcome, the next follow-up visit was performed at 3 months. In those with near-complete pain relief, the 3-month follow-up visit took place without any intervening changes. In conservative group patients who obtained some relief but were satisfied with their treatment course, either medications could be titrated up over the next 2 months and/or the second medication added; in the ESI group participants with partial relief, a repeat ESI could be performed in the intervening time frame; and in individuals allocated to combination therapy, either another injection could be done and/or medications adjusted. In those individuals with a positive categorical outcome at 3 months, the final follow-up visit was conducted at 6 months, with the same treatment stipulations.

### Statistical Analysis

Before commencing the study, a power analysis determined that 51 patients were required in each group to have an 81% chance of detecting a 1.8-point difference in arm pain between treatment groups at 1-month follow-up, based on the following assumptions: a starting numerical rating scale pain score in each group of 6.0; an SD of change of 2.9; a range for pain fluctuation in response to treatment of eight points; and an  $\alpha$  level controlled at 0.017 using Bonferroni correction. To control for dropouts, we anticipated enrolling 168 participants.

Continuous variables are presented using means and SDs for normally distributed variables, and using medians and interquartile ranges for nonnormally distributed variables. Categorical variables are presented using frequencies and percentages. Analysis of covariance models were used to assess group differences for continuous outcome variables at 1 month, and logistic regression models were used to analyze secondary binary outcomes. Covariates for all models were chosen *a priori* based on suspected influence on treatment results and included sex, duration of symptoms, baseline NDI score, baseline opiate use, and type of hospital.

For 3- and 6-month analysis, the “last-observation-carried-forward” method was used in which the last observed data were imputed to 3- and 6-month time points in patients with a negative outcome (*i.e.*, those who failed treatment at 3 months and pursued other therapies had their 3-month data used at 6 months). This was determined *a priori* because it is the most conservative means to deal with nonresponders, and there is no pharmacological basis for patients who failed treatment at 1 month to obtain benefit at subsequent visits without additional interventions.<sup>10</sup> Dropouts were handled by omitting follow-up data from analysis.

Adjusting for multiple comparisons, a  $P$  value less than 0.05 was considered significant for the overall group differences effect, and  $P$  values less than 0.017 were considered statistically significant for between-group comparisons. Univariable logistic regression was utilized to identify variables associated with a positive treatment outcome at 3 months. A multivariable logistic regression model was then constructed using only  $P$  values less than 0.05 from the univariable model to determine their combined association with 3-month treatment outcomes. Data were analyzed using STATA 12.0 (StataCorp LP, College Station, TX).

## Results

Baseline demographic and clinical data are shown in table 1. The mean age of the participants was 47.8 yr (median, 47.0; 95% interquartile range, 40.0 to 55.0), and 50.9% were females. The mean duration of pain was 1.3 yr (median, 0.8; 95% CI, 0.25 to 2.0), with 37.4% receiving opioid therapy; 35.1% of subjects ( $n = 59$ ) were active duty military. Baseline arm-and-neck pain averaged 6.2 (1.9) and 5.8 (2.3), respectively. Preintervention average NDI score was 39.9 (SD, 16.9), indicating moderate-to-severe disability.

All seven study sites contributed patients with 69 recruited from military treatment facilities, 96 enrolled at a civilian institution, and 4 treated at a Veterans Administration hospital. Stratified by military status, service members were younger (mean age, 50.0 *vs.* 41.0 yr;  $P < 0.001$ ) and more likely to be male (62.7 *vs.* 41.3%;  $P = 0.008$ ). Service members were also less likely to use opioids at baseline (22.8 *vs.* 45.0%,  $P = 0.018$ ). When broken down by institution type, unadjusted categorical outcomes were significantly better at 1 month (64.7 *vs.* 47.4%,  $P = 0.028$ ), 3 months (54.4 *vs.* 33.7%,  $P = 0.008$ ), and 6 months (45.6 *vs.* 28.4%,  $P = 0.024$ ) in military *versus* civilian hospitals. However, these were not significantly different after multivariate adjustment ( $P = 0.272$ ,  $P = 0.196$ , and  $P = 0.170$  for 1, 3, and 6 months, respectively).

Among participants in the ESI and combination groups, the mean number of ESI was 1.3 (SD, 0.6; median, 1; interquartile range, 1 to 2). In the conservative group, 25 (42.4%) of participants received nortriptyline, 14 (23.7%) received gabapentin, and 20 (33.9%) received both medications. In the combination group, these proportions were 41.8, 41.8, and 16.4%, respectively (average dosages of gabapentin and nortriptyline 1,500.0, SD 778.5 and 50.3, SD 25.0, respectively). In those individuals prescribed adjuvants, 60.9% of subjects were fully compliant with their medication regimens, 7.6% were partially compliant, and 31.5% were noncompliant or discontinued their medications secondary to adverse effects. For conservative and combination group participants, 37.4% did not attend PT, a slight majority (51.4%) because they had already completed a course, 46.5% were fully compliant with their regimen, and 16.2% were partially compliant. Fourteen patients in

the conservative and combination groups underwent acupuncture as part of their conservative care, two received chiropractic treatment, and one engaged in therapeutic yoga.

### Dropouts

Seventeen people dropped-out of the study, four in the conservative group, eight in the ESI group, and five in the combination group. In two conservative group dropouts, participants exited despite a positive outcome at 1 and 3 months for treatment of refractory neck pain by surgery and radiofrequency denervation, respectively. Three combination group dropouts and one ESI group dropout did not complete any follow-ups.

### Differences between Groups at 1 Month

With regard to the primary outcome measure, the mean adjusted 1-month arm pain scores were 3.5 (95% CI, 2.8 to 4.2) in the combination group, 4.3 (95% CI, 3.6 to 5.0) in the conservative group, and 4.2 (95% CI, 3.5 to 4.9) in the ESI group ( $P = 0.26$ ). For neck pain, adjusted means were 3.5 (95% CI, 2.8 to 4.3) in the combination group, 4.7 in the conservative group (95% CI, 4.1 to 5.4), and 4.6 in the ESI (95% CI, 3.9 to 5.3) group ( $P = 0.047$ ). With respect to reduction in arm pain, the average decrease in those participants who received combination therapy was -3.1 (95% CI, -3.8 to -2.3) *versus* -1.8 (95% CI, -2.5 to -1.2) in those treated conservatively and -2.0 (-2.7 to -1.3) in individuals who received ESI ( $P = 0.035$ ). Mean reduction in NDI scores in the combination, conservative, and ESI groups were -11.8 (95% CI, -15.5 to -8.2), -8.2 (95% CI, -11.6 to -4.9), and -6.8 (95% CI, -10.3 to -3.4), respectively. In pairwise comparisons between the ESI and conservative groups, no significant differences were observed on any outcome measure.

### Within-group Changes at 1 Month

For arm pain, all groups experienced significant reductions, with the greatest difference observed in the combination group (mean change from baseline -3.09; 95% CI, -3.82 to -2.35). Reductions in neck pain were less pronounced across all groups, but were again largest in the combination group (mean change from baseline, -2.23; 95% CI, -2.98 to -1.48). In general, improvements in functional capacity mirrored the same pattern noted for arm and neck pain. For secondary outcome measures, the largest improvements favored the combination group but were less pronounced (table 2).

### Three- and Six-month Outcomes

Three- and 6-month treatment outcomes are shown in tables 3–5 (see fig. 1 for number of patients analyzed). At each time point, those who received combination treatment were more likely to experience a positive categorical outcome than those in the other two groups, although the difference reached statistical significance only at 3 months (56.9%

**Table 1.** Baseline Demographic and Clinical Characteristics

Characteristic*	Conservative Treatment (n = 59)	Epidural Steroid Injection (n = 55)	Combination Therapy (n = 55)	P Value†
Age (median, IQR)	45.0 (41.0–54.0)	44.0 (39.0–51.0)	49.0 (41.0–59.0)	0.10
Sex (n, %)	33 (55.9)	28 (50.9)	25 (45.5)	0.54
Female				
Duration of pain in years (median, IQR)	1.0 (0.5–2.0)	0.8 (0.3–2.0)	0.7 (0.3–2.5)	0.61
Opioid therapy (n, %)	18 (31.0)	20 (37.0)	24 (44.4)	0.42
Active duty military (n, %)	23 (39.7)	19 (34.5)	17 (30.9)	0.62
Smoking (n, %)	13 (23.6)	9 (16.4)	13 (23.6)	0.61
Disability/worker's compensation/medical board	16 (27.1)	10 (18.2)	14 (25.9)	0.48
Obesity (n, %)	21 (35.6)	14 (25.5)	12 (21.8)	0.23
Site				
Military treatment facility	24 (40.7)	23 (41.8)	21 (38.2)	0.92
Civilian hospital	35 (59.3)	32 (58.2)	34 (61.8)	
Psychiatric comorbidity				0.54†
None	35 (59.3)	38 (69.1)	36 (65.5)	
Mood disorder	15 (25.4)	12 (21.8)	15 (27.3)	
Anxiety disorder	10 (16.7)	8 (14.6)	6 (10.9)	
Substance abuse disorder	5 (8.5)	5 (9.1)	0	
Psychosis	0	0	1 (1.8)	
Other‡	3 (5.1)	2 (3.6)	1 (1.8)	
Multiple diagnoses	7 (11.9)	8 (14.6)	5 (9.1)	
Inciting event				0.021†
None	28 (47.5)	39 (70.9)	37 (67.3)	
Motor vehicle accident	7 (11.9)	6 (10.9)	6 (10.9)	
Fall	5 (8.5)	2 (3.6)	2 (3.6)	
Training/sports	9 (15.3)	7 (12.7)	5 (9.1)	
Lifting	6 (10.2)	3 (5.5)	4 (7.3)	
Other§	4 (6.8)	1 (1.8)	2 (3.6)	
Multiple	1 (1.7)	2 (3.6)	1 (1.8)	
Baseline arm pain (mean, SD)	6.1 (2.2)	6.2 (1.7)	6.4 (1.9)	0.76
Baseline neck pain (mean, SD)	5.9 (2.1)	5.8 (2.3)	5.6 (2.4)	0.81
Baseline NDI (median, IQR)	34.0 (28.0–52.0)	38.0 (30.0–50.0)	38.0 (28.0–48.0)	0.60

\* Mean and SD used for continuous variables with a normal distribution and median and IQR for continuous variables not normally distributed. No variable differed significantly between treatment groups. † P values generated by comparing binary categorization of variable in question (none vs. any psychiatric comorbidity or any inciting event). ‡ Includes obsessive-compulsive disorder, posttraumatic stress disorder, and attention deficit hyperactivity disorder. § Includes childbirth, positioning during flight, work injury, body armor injury during combat, and assault.

IQR = interquartile range; NDI = neck disability index.

[29/51] in the combination group *vs.* 26.8% [15/56] and 36.7% [18/49] in the conservative and ESI groups, respectively;  $P = 0.006$ ). Using last-observation-carried-forward analysis, continuous parameters did not reach statistical significance ( $P < 0.017$ ) when adjustments were made for multiple comparisons (table 5).

### Factors Associated with Treatment Outcome

The factors associated with 3-month treatment outcome are presented in table 6. This time point was selected *a priori* because it is the reference standard used by the U.S. Food and Drug Administration to determine analgesic drug efficacy and is the treatment period required by major insurance companies for conservative treatment (*e.g.*, PT) to be considered a failure. As part of a sensitivity analysis, these data are presented as unadjusted means. In univariable analysis, female sex, active smoking, and higher baseline NDI score were associated with a negative categorical outcome at

3 months, whereas combination treatment and treatment at a military hospital were predictive of a positive outcome. In multivariable analysis, only treatment group (odds ratio, 3.47; 95% CI, 1.44 to 8.35;  $P = 0.005$ ) and baseline disability (odds ratio, 0.98; 95% CI, 0.95 to 1.00;  $P = 0.046$ ) were associated with outcome. The area under a constructed receiver operating characteristic curve was 0.73, suggesting the logistic regression model has reasonably good discriminative power.

### Complications and Adverse Effects

Adverse effects associated with pharmacotherapy are shown in table 7. Overall, 75% of individuals experienced an adverse effect with nortriptyline, 45.4% with gabapentin, and 64.3% with combination medical management. All were considered nonserious. Among the 147 ESI, there were 10 complications in eight patients. These included two headaches, one wet-tap not associated with neurological sequelae,

**Table 2.** Between and within-group Differences Stratified by Study Group 1 Month after Treatment

Variable	Adjusted Mean (95% CI)*			P Value	Between-group Difference (95% CI)		
	Conservative (n = 59)	ESI (n = 55)	Combination (n = 55)		Conservative vs. ESI	Conservative vs. Combination	ESI vs. Combination
NRS arm pain @ 1 month	4.3 (3.6–5.0)	4.2 (3.5–4.9)	3.5 (2.8–4.2)	0.26	0.2 (–0.8 to 1.1), P = 0.70	–0.8 (–1.9 to 0.3), P = 0.16	–0.6 (–1.6 to 0.4), P = 0.23
Change from baseline (95% CI)	–1.8 (–2.5 to –1.2)	–2.0 (–2.7 to –1.3)	–3.1 (–3.8 to –2.3)	0.035	0.2 (–0.7 to 1.1), P = 0.722	–1.2 (–2.3 to –0.1), P = 0.027	–1.1 (–2.2 to 0), P = 0.045
NRS neck pain @ 1 month	4.7 (4.1–5.4)	4.6 (3.9–5.3)	3.5 (2.8–4.3)	0.047	0.2 (–0.8 to 1.1), P = 0.75	–1.2 (–2.3 to –0.2), P = 0.025	–1.0 (–2.2 to 0.1), P = 0.07
Change from baseline (95% CI)	–1.2 (–1.9 to –0.5)	–1.1 (–1.8 to –0.4)	–2.2 (–3.0 to –1.5)	0.06	–0.1 (–1.0 to 0.8), P = 0.89	–1.1 (–2.2 to 0), P = 0.056	–1.1 (–2.2 to 0), P = 0.054
NDI @ 1 month	32.0 (28.7–35.4)	33.4 (29.8–36.9)	28.4 (24.8–32.1)	0.15	–1.2 (–6.1 to 3.6), P = 0.61	–3.6 (–8.3 to 1.1), P = 0.13	–5.5 (–11.0 to 0.1), P = 0.055
Change from baseline (95% CI)	–8.2 (–11.6 to –4.9)	–6.8 (–10.3 to –3.4)	–11.8 (–15.5 to –8.2)	0.15	–1.2 (–6.1 to 3.6), P = 0.61	–3.6 (–8.3 to 1.1), P = 0.13	–5.5 (–11.0 to 0.1), P = 0.055
Secondary Binary Variable	Conservative (n = 59)	ESI (n = 55)	Combination (n = 55)	P Value	Conservative vs. ESI OR (95% CI, P Value)	Conservative vs. Combination OR (95% CI, P Value)	ESI vs. Combination OR (95% CI, P Value)
Medication reduction (n, %) <sup>†</sup>	16 (35.6)	15 (34.9)	23 (54.8)	0.09	1.0 (0.4–2.7), P = 0.97	1.9 (0.7–4.9), P = 0.18	2.3 (0.9–5.8), P = 0.08
Positive global perceived effect (n, %)	35 (60.3)	33 (61.1)	37 (72.6)	0.23	1.0 (0.4–2.2), P = 0.98	1.8 (0.7–4.3), P = 0.21	1.8 (0.7–4.5), P = 0.19
Positive categorical outcome (n, %) <sup>‡</sup>	30 (51.7)	29 (53.7)	33 (64.7)	0.28	1.0 (0.5–2.1), P = 0.94	1.7 (0.7–3.9), P = 0.20	1.6 (0.7–3.6), P = 0.29
Proceeded to surgery (n, %) <sup>§</sup>	4 (6.8)	3 (5.5)	3 (5.5)	0.37	2.1 (0.4–12.8), P = 0.41	0.4 (0.1–2.5), P = 0.33	0.8 (0.1–6.6), P = 0.82

\* Means adjusted for sex, duration of symptoms, baseline NDI, opiate use, and type of hospital. † Defined as  $\geq 20\%$  decrease in opioid use or cessation or nonopioid analgesic. ‡ Defined as  $\geq 50\%$  decrease in arm pain coupled with a positive global perceived effect. § Within 1 yr of treatment.

ESI = epidural steroid injection; NDI = neck disability index score; NRS = 0–10 numerical rating pain scale; OR = odds ratio.

**Table 3.** Successful Treatment Outcome Stratified by Treatment Group

Positive Outcome* <sup>†</sup>	Conservative <sup>‡</sup>	Epidural Steroids	Combination <sup>‡</sup>	P Value <sup>§</sup>
1 month (n, %)	30/58 (51.7)	29/54 (53.7)	33/51 (64.7)	0.35
3 months (n, %)	15/56 (26.8)	18/49 (36.7)	29/51 (56.9)	0.006
6 months (n, %)	13/55 (23.6)	12/47 (25.5)	22/50 (44.0)	0.06

\* Lost-to-follow-up patients excluded from analysis. † A positive outcome defined as two-point decrease or more in arm pain, coupled with a positive global perceived effect without additional procedural interventions. ‡ In the 14 individuals in the conservative and combination groups who received complementary and alternative medicine treatment, 9 (64.2%) and 6 (42.9%) experienced a positive outcome at 3 and 6 months, respectively. § Fisher exact test used.

one case of prolonged postprocedure pain requiring a prescription, two cases of temporary (<2 weeks) worsening neurological symptoms not accompanied by magnetic resonance imaging progression, one rash, two vasovagal episodes, and one case of tachycardia (>120 beats/min) in the postanesthesia recovery area that resolved with assurance.

## Discussion

This is the largest comparative-effectiveness study comparing pharmacotherapy to injection therapy for radicular pain, the

only one to include a combination group, and the first to evaluate treatment in patients with neck pain. The main finding is that although the combination group experienced superior results for some outcome measures compared with stand-alone therapies, most differences generally fell shy of statistical significance, including for the primary outcome measure.

Although neither monotherapy group fared well, the conservative group experienced particularly poor outcomes. This latter finding is not surprising, as the most robust studies evaluating gabapentinoids and antidepressants for

**Table 4.** Successful Treatment Outcome Stratified by Treatment Group and Compliance Status

Positive Outcome*†	Conservative Noncompliant (n = 42)	Conservative Compliant (n = 16)	Combination Noncompliant (n = 36)	Combination Compliant (n = 15)	P Value‡
1 month (n, %)	23/42 (54.8)	7/16 (43.8)	19/36 (52.8)	14/15 (93.3)	0.014
3 months (n, %)	11/40 (27.5)	4/16 (25.0)	17/36 (47.2)	12/15 (80.0)	0.002
6 months (n, %)	10/39 (25.6)	3/16 (18.8)	13/35 (37.1)	9/15 (60.0)	0.06

\* A positive outcome defined as two-point decrease or greater in arm pain, coupled with a positive global perceived effect without additional procedural interventions. † Lost-to-follow-up patients excluded from analysis. ‡ Fisher exact test used.

**Table 5.** “Last-observed-carried-forward” Outcomes Broken Down by Treatment Group

Outcome Variable	Follow-up	Conservative†	Epidural Steroids‡	Combination§	P Value
NRS arm pain score (mean, SD)*	1 month	4.30 (0.35)	4.22 (0.37)	3.41 (0.38)	0.10
	3 months	3.29 (0.51)	2.96 (0.56)	2.30 (0.47)	0.33
	6 months	1.16 (0.50)	2.38 (0.48)	2.02 (0.37)	0.20
NRS neck pain score (mean, SD)*	1 month	4.72 (0.35)	4.66 (0.37)	3.48 (0.38)	0.031
	3 months	3.98 (0.49)	3.04 (0.51)	2.83 (0.45)	0.20
	6 months	1.80 (0.61)	3.32 (0.54)	2.83 (0.43)	0.18
Neck disability score (mean, SD)*	1 month	31.81 (2.31)	34.61 (2.39)	27.57 (2.46)	0.12
	3 months	14.10 (2.73)	15.82 (2.85)	18.10 (2.96)	0.61
	6 months	5.37 (2.43)	11.02 (2.43)	15.03 (2.49)	0.023

\* Unadjusted means and regressions; imputed data from 1 and 3 months carried over to subsequent time points for treatment failures. Total numbers analyzed: † Conservative: 1 month (n = 58), 3 months (n = 56), 6 months (n = 55). ‡ Epidural steroid injection: 1 month (n = 54), 3 months (n = 49), 6 months (n = 47). § Combination: 1 month (n = 51), 3 months (n = 51), 6 months (n = 50).

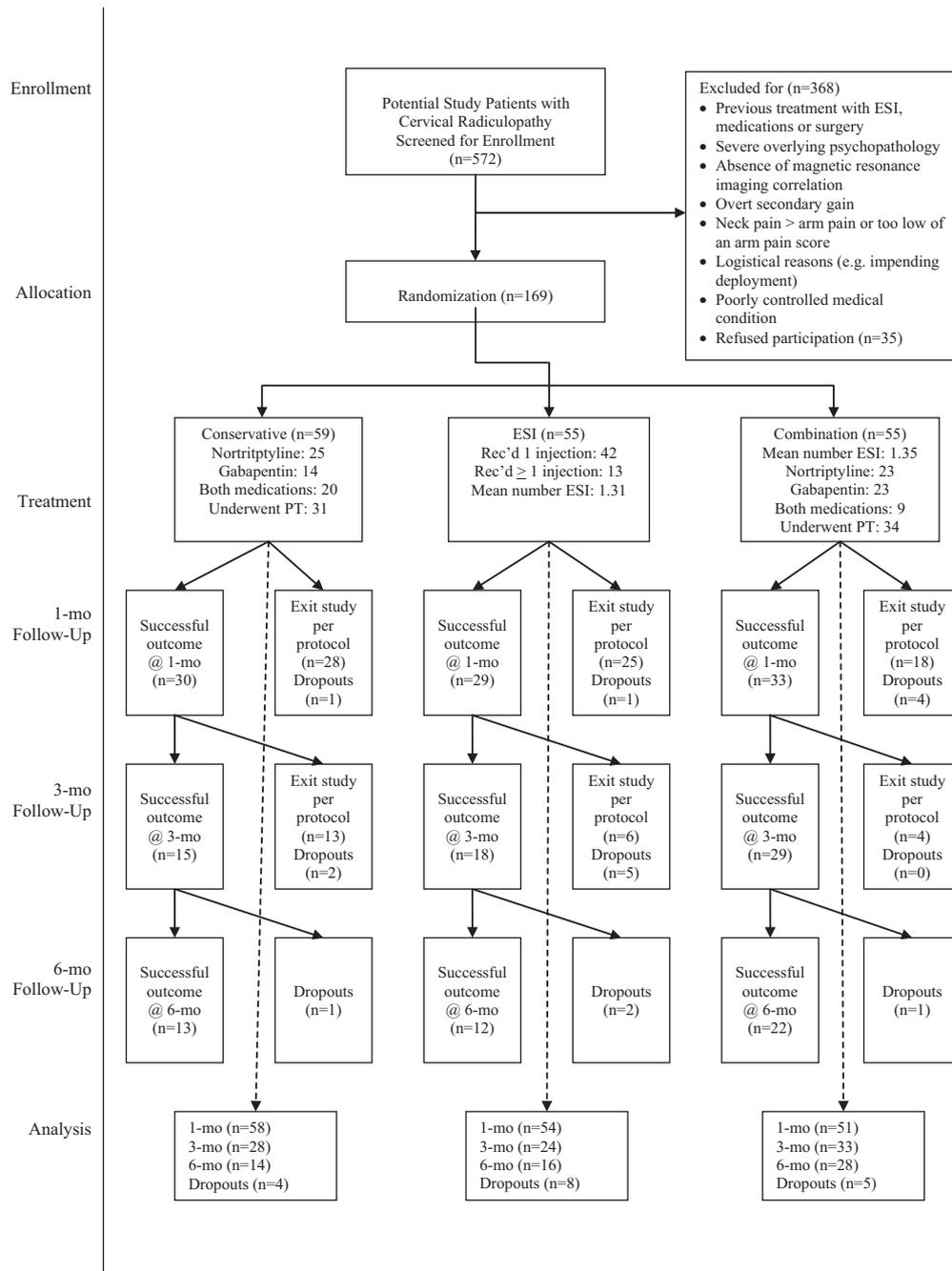
NRS = 0–10 numerical rating scale.

radiculopathy failed to demonstrate efficacy.<sup>18–20</sup> This is in contrast to multiple open-label studies that have reported benefit for pharmacotherapy,<sup>45–47</sup> including one that enrolled patients with cervical radiculopathy.<sup>47</sup> Although one might speculate that PT would increase the success rate of the conservative group, the evidence supporting this is mixed, and based on unblinded studies.<sup>21–23,31</sup> Many patients in our study had already failed PT and elected not to pursue a second course. Because we used the most conservative means (last observation carried forward) to address the missing data in nonresponders who exited the study to receive alternative treatments, our results may have underestimated the effectiveness of all treatment groups, particularly in those patients who may have positively responded to higher doses of medications or multiple injections. For example, in a comprehensive review on transforaminal ESI by MacVicar *et al.*,<sup>48</sup> the authors determined that 6% of individuals will require more than one injection to obtain a successful outcome.

There are several possible explanations for our findings. The first is that no real difference exists between the treatment groups. A second hypothesis, and in our opinion the more likely one given that nearly all findings favored the treatment group that was expected to fare better, is that combination treatment provides superior results to stand-alone treatment, but that the effect size is more modest than what we anticipated. If the latter is true, then the operable question becomes “why did the combination group experience better results?” One plausible reason is that the effects of pharmacotherapy, PT, and ESI may complement or enhance each other. For example, although steroids may work better

for individuals with an ongoing inflammatory process, and PT when deconditioning plays a role, patients whose pain stems from ectopic discharges from chronically-injured nerve roots and/or central sensitization may respond better to pharmacotherapy.<sup>13,49,50</sup> A second explanation is that subjects allocated to the combination group experienced greater benefit because of a larger placebo effect. In essence, subjects in group 3 may have experienced magnified expectations because they were the “lucky ones” slated to receive all treatments. Inappropriate or absence of blinding has been shown in systematic reviews to increase the reported benefit by as much as 30% for some treatments.<sup>51,52</sup> The placebo effect is especially powerful for subjective outcomes such as pain, and may be influenced by provider and patient expectations, and the number and type of encounters, which could have mitigated the effect in group 2.<sup>53–55</sup> A third explanation is that ESI provide significant short-term pain relief that allows optimal participation in PT, which provides long-term benefit. This principle forms a cornerstone of treatment for other neuropathic pain conditions.<sup>56</sup>

Our results are in contrast to those of other investigators who did not even find a trend toward long-term benefit with ESI compared with conservative treatment.<sup>31,32</sup> However, unlike those studies which limited injections to one procedure, and utilized medications that are not very effective for neuropathic pain, we allowed for multiple injections based on clinical response, and for combination therapy with first-line medications titrated to effect. Because the beneficial effects of ESI tend to be short-lived, in practice ESI are often administered on an “as needed”



**Fig. 1.** Consort flowchart demonstrating the progression of study subjects and data for analysis at various time points. ESI = epidural steroid injection; PT = physical therapy.

basis,<sup>13,57–59</sup> and combination therapy with nortriptyline and gabapentin has been shown in clinical trials to provide greater benefit than either drug alone.<sup>60,61</sup> The observation that the combination group may possibly have fared better than the ESI-only group is consistent with open-label studies demonstrating some benefit for pharmacotherapy.<sup>45–47</sup>

The results of our study are readily generalizable to a primary care setting, where healthcare practitioners often face the decision to treat patients conservatively, refer them for interventions, or do both. On the basis of these findings and the risks associated with cervical ESI, one might reasonably

conclude that ESI should not be a first-line, stand-alone treatment for cervical radiculopathy.<sup>29,30</sup> Although the open-label comparator design and broad inclusion criteria reflect the clinical context in which frontline physicians provide treatment in accordance with comparative-effectiveness research principles,<sup>62</sup> the heterogeneity of subjects limits the conclusions one can draw regarding “efficacy.”

There are several limitations to our study. First, this study was open-label and the treatment regimens were nonstandardized, which enables us to draw robust conclusions on comparative-effectiveness, but precludes inferences regarding

**Table 6.** Factors Associated with 3-month Treatment Outcome\*

Variable	Univariable Analysis OR (95% CI)	P Value	Multivariable Analysis OR (95% CI)†	P Value
Study group				
ESI	1.59 (0.69–3.64)	0.28	0.61 (0.26–1.48)	0.28
Conservative	Reference		Reference	
Combination	3.60 (1.60–8.10)	0.002	2.57 (1.10–6.10)	0.031
Age	1.00 (0.97–1.03)	0.87		
Female	0.53 (0.28–1.02)	0.06		
Duration	1.02 (0.77–1.34)	0.91		
Baseline NDI	0.96 (0.94–0.99)	0.002	0.97 (0.95–0.99)	0.018
Military hospital	2.47 (1.28–4.77)	0.007	1.79 (0.85–3.77)	0.12
Obesity	0.62 (0.30–1.30)	0.21		
Smoking	0.41 (0.17–0.98)	0.044	0.46 (0.18–1.20)	0.11
Psychiatric illness	0.63 (0.32–1.25)	0.19		
Inciting event	1.45 (0.74–2.82)	0.28		

\* Categorical variables definition: female sex, military hospital, obesity, smoking, presence of psychiatric illness, and presence of an inciting event (1 = yes, 0 = no). Based on 156 observations. † Only statistically significant variables from univariable regression (e.g., study group, baseline NDI, type of hospital, and smoking) were included in multivariable logistic regression.

ESI = epidural steroid injection; NDI = neck disability index; OR = odds ratio.

**Table 7.** Adverse Effects Stratified by Medication Type

Adverse Event (n, %)	Nortriptyline Only (n = 48)	Gabapentin Only (n = 37)	Nortriptyline + Gabapentin (n = 29)
None	10 (20.8)	26 (70.3)	12 (41.4)
Sleepiness, fatigue	14 (29.2)	8 (21.6)	9 (31.0)
Cognitive	6 (12.5)	5 (13.5)	4 (13.8)
Weight gain	2 (4.2)	0	0
Dry mouth	9 (18.8)	0	5 (17.2)
Gastrointestinal	1 (2.1)	2 (5.4)	2 (6.9)
Bowel/bladder	2 (4.2)	0	1 (3.5)
Other*	5 (10.4)	4 (10.8)	5 (17.2)
Multiple	8 (16.7)	7 (18.9)	8 (27.6)

\* Includes nightmares, hair loss, tremors, rash, headache, visual changes, wheezing, paresthesias, cramping, and decreased libido.

efficacy. Along these lines, the PT program was unstructured, with many subjects either having already failed treatment or who were noncompliant with their regimen. Second, because patients in groups 2 and 3 were allowed to receive multiple therapies, we cannot determine whether or not these treatments provide stand-alone benefit, or reinforce benefits effected by other means (*i.e.*, PT). Third, we did not subcategorize the different etiologies of radicular pain, as there is mixed evidence that some may respond more favorably to injections than others.<sup>13,63</sup> Fourth, we did not evaluate return-to-work, which is not considered a core outcome domain as the likelihood of a person out of work for any extended period of time because of pain returning to work is very low.<sup>64</sup> Fifth, our study contained a large percentage of active and retired military personnel, who may have different stressors and motivations than their civilian counterparts, which could affect generalizability. Our modest effect sizes also indicate that future studies should contain larger sample sizes, especially when different treatments are being compared.

In conclusion, for the primary outcome measure, we found no statistical differences between the three treatment groups.

With respect to the categorical outcome measure, a higher proportion of participants receiving combination treatment obtained a positive outcome at 3 months than those in the other groups. Our mixed results suggest that combination therapy may provide better and more prolonged benefit in some individuals than either conservative or interventional treatments in isolation, although the effect size was smaller than expected. Future studies of larger size should seek to confirm or refute our findings in other settings (*i.e.*, sciatica), establish efficacy in a controlled trial, identify a phenotype of those patients likely to respond to each type of treatment, and determine reason(s) for the possible increased effectiveness of combination treatment in certain individuals.

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## Competing Interests

Dr. Cohen took on a consulting role in 2014 in the design of a clinical trial for a new steroid preparation for Semnur Pharmaceuticals, Mountain View, California, a company working with the Food and Drug Administration to get approval for the first epidurally administered steroid solution. He also serves on the Advisory Board of Kimberly Clark, Roswell, Georgia. The other authors declare no competing interests.

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