Critique author	Ed Whitney

Bibliographic Data	
Authors	Friedly JL, Comstock BA, et al.
Title	A randomized trial of epidural glucocorticoid injections for spinal stenosis.
PMID	24988555
Citation	New Engl J Med. 2014;371(1):11-21
Other information if relevant	The study protocol was registered at https://clinicaltrials.gov/ct2/show/NCT01238536

Methods	
Aim of study	To compare the effectiveness of epidural steroid injections (ESI) plus local anesthetic (LA) versus local anesthetic alone for patients with symptomatic lumbar spinal stenosis
Design	Randomized clinical trial

Participants	
Population from which participants are drawn	Patients with spinal stenosis who were referred to multiple specialty care centers in the United States for consideration of ESI as a treatment option
Setting (location and type of facility)	The principal investigator was at the University of Washington; the participating centers were distributed throughout the United States, mostly in departments of Physical Medicine and Rehabilitation, and the procedures were done by 26 board certified specialists in anesthesiology, physiatry, and radiology with expertise in epidural injections
Age	68
Sex	221 women, 179 men
Total number of participants for whom outcome data were reported	400

Inclusion criteria	- Pain in the low back, buttock, and/or lower extremity (pain NRS>=5) with standing, walking and/or spinal extension (buttock/leg>back pain). - Modified Roland-Morris score of at least 7. - Mild-severe lumbar central canal spinal stenosis identified by MRI or CT scan. - Lower extremity symptoms consistent with neurogenic claudication. - Ability to read English and complete the assessment instruments. - Age 50 or older
Exclusion criteria	- Cognitive impairment that renders the patient unable to give informed consent or provide accurate data. - Clinical co-morbidities that could interfere with the collection of data concerning pain and function. Known dx of fibromyalgia, chronic widespread pain, amputees, Parkinson's, head injury, dementia, stroke, other neurologic conditions - Severe vascular, pulmonary or coronary artery disease that limits ambulation including recent myocardial infarction (within 6 months). - Spinal instability requiring surgical fusion. - Severe osteoporosis as defined by multiple compression fractures or a fracture at the same level as the stenosis. - Metastatic cancer. - Excessive alcohol consumption or evidence of non-prescribed or illegal drug use. - Possible pregnancy or other reason that precludes the use of fluoroscopy. - Concordant pain with internal rotation of the hip (or known hip joint pathology). - Active local or systemic infection. - Abnormal coagulation. - Allergy to local anesthetic, steroid or contrast. - Previous lumbar spine surgery. - Epidural steroid injection within previous 6 months.
Other information if relevant	

Intervention Groups

Group 1	
Group name	LA + ESI
Number in group	200

Description of intervention	- All injections were placed one spinal level below the maximal canal stenosis for interlaminar injections and at the root level where symptoms were most pronounced for transforaminal injections, with the physician selecting the approach, which remained the same for each patient - The ESI+LA solution consisted of 1 to 3 ml of 0.25% to 1% lidocaine followed by the steroid which the physician ordinarily used in daily practice, either betamethasone, dexamethasone, or triamcinolone
Duration of treatment period	- 6 weeks was the point at which primary outcome data were collected, but interim outcome data were collected at 3 weeks - Data were collected by a research assistant unaware of the treatment group by telephone interview, in-person interview, or mailed questionnaires
Co-interventions if reported	
Additional information if relevant	

Group 2	
Group name	LA
Number in group	200
Description of intervention	- The procedure was identical to the ESI+LA group, except that the solution was an equivalent volume of 0.25% to 1% lidocaine
Duration of treatment period	- 6 weeks was the point at which primary outcome data were collected, but interim outcome data were collected at 3 weeks - Data were collected by a research assistant unaware of the treatment group by telephone interview, in-person interview, or mailed questionnaires
Co-interventions if reported	
Additional information if relevant	

Primary outcome	

Outcome name and criteria for definition	- Back-specific functional status as measured by the Roland-Morris Disability Questionnaire (RMDQ) at 6 weeks - The wording of the RMDQ was modified by the authors to incorporate leg pain into the questionnaire items - The standard RMDQ asks patients to rate their disability in terms of limitations imposed by their back, but the modified RMDQ asks them to rate their disability in terms of limitations posed by their back or leg problem - For example, "Because of my back, I use a handrail to get upstairs," was changed to "Because of my back or leg problem (sciatica), I use a handrail to get upstairs" - The 6 week RMDQ scores were adjusted for the baseline scores using analysis of covariance (ANCOVA)
Time points measured and/or reported	6 weeks
Differences between groups	- Both the ESI+LA group and the LA group had improvement on the RMDQ as compared to baseline (4.2 points and 3.1 points, respectively), but there was no significant difference in the RMDQ treatment effects between groups; the 95% confidence interval lay between 2.1 points in favor of ESI+LA to 0.1 points in favor of LA - Similarly, there were no significant between-group differences in the intensity of leg pain at 6 weeks - There were statistically equal proportions of patients in each group who had a 30% improvement in RMDQ (37.3% and 31.6% for the ESI+LA and LA groups respectively); the percentages of patients with 50% RMDQ improvement scores were 23.8% and 20.2%
Additional information if relevant	- A post-hoc (unplanned) analysis took into account the shorter duration of leg pain in the LA group at baseline, and this analysis showed a small statistical difference favoring ESI+LA in the 6 week RMDQ score but no difference in the leg pain score

Secondary outcomes	
Outcome name and criteria for definition	- Cortisol suppression - Morning serum cortisol levels, drawn before 9 AM
Time points measured	3 and 6 weeks

Differences between groups	- In the LA group, only 1 of 151 patients had a morning cortisol less than 3 mcg/dl at 3 weeks, compared to 16 of 163 patients in the ESI+LA group - At 6 weeks, no patient in the LA group had an AM cortisol less than 3 mcg/dl, and 5 of 152 patients in the ESI+LA group had AM cortisol less than 3 mcg/dl
Additional information if relevant	- The Swiss Spinal Stenosis Questionnaire has a patient satisfaction with treatment item, and this was greater for ESI+LA (67% satisfied) than for the LA group (54% satisfied); the other SSSQ items did not differ between groups

Conclusions	
Key conclusions of study authors	- The authors observed no significant differences at 6 weeks between LA and ESI+LA with respect to pain-related functional disability; at 3 weeks, the ESI+LA had a small and clinically unimportant advantage over LA with respect to disability - There is an effect of ESI on hypothalamic-pituitary-adrenal axis function, evidenced by measureable differences in AM cortisol suppression between the two groups - Epidural injection of glucocorticoid plus local anesthetic offers minimal to no benefit compared to injection of local anesthetic alone at 6 weeks following the procedure

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments
Random sequence generation *(selection bias)*	Low	
Allocation concealment *(selection bias)*	Low	The randomization allocation was revealed at the time of the procedure through a password-protected website which was accessed by an assistant who was otherwise not involved in the data collection

Blinding of participants and personnel *(performance bias)*	Low	The physicians who performed the injections were given one of two opaque prefilled syringes at the time of the procedure, and the selection of the syringe was done by the assistant as described above
Blinding of outcome assessment *(detection bias)*	Low	The interviewers who collected the outcome data were not aware of treatment assignment
Incomplete outcome data *(attrition bias)*	Low	
Selective outcome reporting? *(reporting bias)*	Low	The published report and the registered protocol are concordant
Other bias		

Sponsorship if reported		
Study funding sources if reported	Agency for Healthcare Research and Quality (AHRQ)	
Possible conflicts of interest for study authors	No direct conflicts of interest reported, but various authors have received consulting fees and grant supports from companies such as Cytonics and Seikagaku	
Notes:		

Comments by DOWC staff

- Overall a high quality clinical trial which conforms to the highest standards of conduct and reporting established by international standards
- One point was not clarified; the research assistants could collect followup data by phone interview, in-person interview, or mailed questionnaires, but the numbers of patients assessed by each method is not reported; if there were differences in outcome data collected by the three different methods, that should have been reported
- The primary outcome, the RMDQ, has 24 items relating to back disability, all of which are equally weighted
- However, in the setting of spinal stenosis, not all 24 items are equally relevant or sensitive to changes in stenosis-related functional difficulties
- For example, an item like "my appetite is not very good because of my back problems or leg pain" is weighted equally with an item like ""I am not doing any of the jobs I usually do around the house"
- For this reason, there was some concern that the RMDQ could fail to capture some variables, such as balance and weakness, which are common limitations of spinal stenosis, and this could be an important limitation to the conclusions of the study
- Accordingly, the authors (Makris 2017) reanalyzed the trial data using patient priority weighting, assigning weights to the RMDQ items which reflect their differential relevance to spinal stenosis patient-important outcomes, so that an item like having to hold onto something to get out of an easy chair carries 8.2 points while an item relating to appetite carries only 3.7 points
- The authors hypothesized that the re-analysis would change the primary outcome data and would affect the conclusion of the original study
- When this re-analysis was done, however, the conclusions of the original study were unchanged; the authors again concluded that there were no clinically important differences between ESI and lidocaine injection

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☒ High quality ☐ Adequate ☐ Inadequate	A high quality, large-sample randomized trial supporting good evidence that there are no significant differences between epidural injections with corticosteroid plus local anesthetic versus local anesthetic alone in patients with symptomatic spinal stenosis; however, there are measureable differences with respect to morning cortisol levels at 3 and 6 weeks after the injection, suggesting that the corticosteroid injection is capable of inducing suppression of the hypothalamic-pituitary-adrenal axis
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
- Makris UE, Edwards TC, et al. Patient Priority Weighting of the Roland Morris Disability Questionnaire Does Not Change Results . Spine of the Lumbar Epidural Steroid Injections for Spinal Stenosis Trial. Spine 2017;42:(1):42-48.