



DATE: October 2017

OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE
Evidence-Based Practice Summary
Epidural Steroid Injections Medications and Dosages

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BACKGROUND

The underlying mechanism of action of epidurally administered steroid and local anesthetic injections is not well understood (Conn 2009). It is believed that the achieved neural blockade alters or interrupts nociceptive input, reflex mechanism of the afferent fibers, self-sustaining activity of the neurons, and the pattern of central neuronal activities (Boswell 2007; Manchikanti 2002). Few research studies have been conducted to determine the optimal dose and schedule for dexamethasone with epidural steroid injections. Additionally, there has been little research done to determine the type, dose and/or duration of local anesthetics to use with epidural steroid injections to improve clinical outcomes. This evidence brief was conducted to synthesize the literature available on the optimal dose and schedule for dexamethasone and the type, dose, duration of local anesthetics for use with epidural steroid injections.

ASK THE QUESTION

Question 1: In patients receiving epidural steroid injections, what is the minimum-effective dose of dexamethasone to relieve pain?

Question 2: In patients receiving epidural steroid injections, what local anesthetic (type, dose, duration) is associated with improved clinical outcomes and/or harms (ie weakness, cardiotoxicity, osteonecrosis, other)?

SEARCH FOR EVIDENCE

Databases included Ovid MEDLINE, MEDLINEinprocess, the Cochrane Central Register of Controlled Trials (CCRCT) & Cochrane Database of Systematic Reviews (CDSR).

1. exp Injections, Epidural/ (3431)



2. exp Analgesia, Epidural/ (7707)
3. (epidur* adj3 (inject* or infus* or administ* or analges* or (pain* adj3 relie*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (15176)
4. 1 or 2 or 3 (15788)
5. exp Steroids/ (832041)
6. 1 and 5 (773)
7. Dose-Response Relationship, Drug/ (391723)
8. (epidur* adj5 (steroid* or dexametha*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1170)
9. 7 and 8 (19)
10. exp Pain/ (364190)
11. exp pain management/ (27559)
12. exp pain measurement/ (77393)
13. 10 or 11 or 12 (400215)
14. 8 and 13 (751)
15. 6 or 9 or 14 (1162)
16. limit 15 to english language (1084)
17. limit 16 to (meta analysis or systematic reviews) (100)
18. limit 16 to (controlled clinical trial or guideline or randomized controlled trial) (197)
19. limit 16 to (comparative study or evaluation studies or validation studies) (130)
20. exp Epidemiologic Studies/ (2177321)
21. 16 and 20 (342)
22. 17 or 18 or 19 or 21 (549)
23. 16 not 22 (535)

Filters/limits included articles published in English in the last 15 years.

CRITICALLY ANALYZE THE EVIDENCE

Questions 1: In patients receiving epidural steroid injections, what is the minimum-effective dose of dexamethasone to relieve pain?



The literature search resulted in a number of studies including dexamethasone, although few studies were found analyzing the different doses between treatment groups and/or the most effective dose for relieving pain. One systematic review and two randomized-controlled studies (RCT) were found researching the most effective dose to relieve pain. One systematic review (De Oliveira 2011) was conducted to evaluate the dose-dependent analgesic effect of perioperative dexamethasone. In the meta-analysis that included 24 RCTs with approximately 2,500 patients, dexamethasone >0.1 mg/kg was found to reduce postoperative pain and opioid consumption. One RCT (Ahadian 2011) investigated the efficacy, dose-response profile, and safety of three doses of epidural dexamethasone. Subjects were randomized to receive transforaminal epidural dexamethasone 4mg, 8mg, or 12mg. The primary outcome for this measure was a reduction in radicular pain according to the visual analog scale from baseline. The study found there was no statistical difference between groups for either measure (all P values <0.05). The last RCT (Hong 2017) included investigated the effects and optimal dose of epidural dexamethasone on pain after major abdominal surgery. Patients were randomized to receive one of three treatment regimens: Dexamethasone 5mg (1mL) with normal saline (1mL) (Group D) or dexamethasone 10 mg (2mL) (Group E) or 2mL of normal saline (Group C) mixed with 8mL of 0.375% ropivacaine as a loading dose. The resting and effort visual analogue scale (VAS) was significantly lower in Group E compared to Group C at every time point through the study period. Only the resting VAS in Group D was lower at 2 hours and 6 hours after surgery.

In conclusion, there is moderate quality evidence for the use of dexamethasone to relieve pain. The studies demonstrated that dexamethasone was effective at reducing pain, but is it unclear the minimum-effective dosage to achieve the best outcomes. Overall, studies did not demonstrate a statistically significant reduction in pain between treatment groups receiving different doses.

Question 2: In patients receiving epidural steroid injections, what local anesthetic (type, dose, duration) is associated with improved clinical outcomes and/or harms (ie weakness, cardiotoxicity, osteonecrosis, other)?

There was limited literature found evaluating what local anesthetic (type, dose, duration) with epidural steroid injections is associated with improved clinical outcomes and/or harms. The majority of the research compared the effects of epidural steroid injections with or without local anesthetics. This brief includes studies that reported the type, dose or duration of local anesthetics used in treatment and includes ten studies: five systematic reviews, one RCT and four non-randomized studies.

One systematic review (Conn 2009) evaluated the effect of caudal epidural injections with or without steroids in managing various types of chronic low back and lower extremity pain. Eighteen RCTs and twenty observational studies were included in the systematic review using a variety of doses and durations of local anesthetics. One of the randomized trials evaluated spinal stenosis with or without steroids with local anesthetic (lidocaine 0.5%) showed positive results for short- and long-term relief. The included observational studies also showed positive short-term and long-term improvement. Another systematic review (Diwan 2012) evaluated the effect of cervical interlaminar epidural injections in managing various types of chronic neck and upper extremity pain. For cervical disc herniation, the review authors rated the evidence as “good” for cervical epidural with local anesthetics and steroids, whereas the rated with local anesthetic only as “fair”. For axial or



discogenic pain, the review authors rated evidence as “fair” for local anesthetic, with or without steroids. For spinal stenosis, the review authors rated the evidence as “fair” for local anesthetic, with or without steroids. And for postsurgery syndrome, the review authors rated the evidence as “fair” for local anesthetic, with or without steroids.

The systematic review conducted by Manchikanti assessed the efficacy of three categories of epidural injections for lumbar and spinal stenosis performed with saline with steroids, local anesthetic alone, or steroids with local anesthetic. The review found that adding bupivacaine to steroids showed very short-term (three-six weeks) effectiveness in three trials with 173 patients, whereas two trials with 142 patients reported a lack of effectiveness. There were seven trials assessing lidocaine as a sole agent or lidocaine with steroids and 3 trials assessing bupivacaine alone in comparison to bupivacaine with steroid. All three of the bupivacaine trials showed positive results with similar results with bupivacaine combined with steroid to avoid surgical interventions. Based on a qualitative synthesis of evidence of seven active-controlled trials comparing lidocaine to lidocaine with steroid, effectiveness was equal in both groups except in disc herniation where potential superiority was demonstrated. Six studies with 649 patients were utilized for pain improvement ratings, comparing lidocaine to lidocaine with steroid. They showed no difference in pain improvement between both groups at three or 12 months. Functional status was also assessed with inclusion of six studies at three months and seven studies at 12 months showing no difference in functional improvement between lidocaine alone or lidocaine with steroid at three or 12 months. This analysis showed the effectiveness of lidocaine and lidocaine with steroid for pain relief and functional status at three months and also 12 months with results slightly favoring local anesthetic alone.

Another systematic review (Liu 2015) investigated the effectiveness and safety of epidural steroid injections in patients with lumbar spinal stenosis (LSS). The epidural local anesthetic injection group in the analysis reported no significant difference for most common measures. The final systematic review (Meng 2015) included presented a current, comprehensive picture of epidural injections of anesthetic with steroids compared to those using local anesthetic alone. Thirteen RCTs involving 1,465 patients were include in the meta-analysis; Group 1 included patients administered with epidural injections of anesthetic with steroids and Group 2 included patients administered with local anesthetic alone. The overall number of injections per year was 3.2+/-1.3 and 3.4+/-1.2 with average total relief per year of 29.3+/-19.7 and 33.8+/-19.3 weeks in groups 1 and 2, respectively, and the opioid intakes decreased from baseline by 12.4 and 7.8 mg, respectively. However, there were no significant differences between the two groups in terms of the outcomes except in the total relief time.

A prospective observational study (Cohen 2013) determined whether a standard, clinical local anesthetic injection can predict outcomes for epidural steroid injections (ESI). Patients received two injections of 1 mL of 1% lidocaine two weeks apart. A small but significant relationship was found between standardized subcutaneous pain score and reduction in leg ($r = -0.21$, 95% CI -0.38 to -0.04 ; $P = 0.03$) and back pain ($r = -0.022$, 95% CI -0.36 to -0.07 ; $P = 0.03$). One retrospective study (Delpont 2004) determined patient satisfaction, relief of pain, frequency of injections, change of function, and subsequent surgical rate in patients who received ESIs. The intervention included transforaminal or caudal fluoroscopically guided ESIs with 60 to 100mg of triamcinalone in combination with local anesthetic or normal saline. Patients who received two or more injections had better results ($P = .006$). Number of injections and amount of relief initially after injection was significant ($P = .007$).



One retrospective observational study (El- Yahchouchi 2014) assessed whether the immediate anesthetic response of pain relief (sensory blockade) or weakness (motor blockade) after lumbar transforaminal epidural steroid injection (TFESI) is associated with longer term effectiveness in pain relief and functional recovery. Patients were give 20 mg lidocaine (1 mL of 2% lidocaine). If there was no neurological change after one - two minutes, corticosteroid was injected betamethasone sodium phosphate/betamethasone acetate 12 mg in 2 mL; triamcinolone acetonide 80 mg in 2 mL; or preservative-free dexamethasone sodium phosphate 10 mg in 1 mL. The immediate pain response following TFESI was only weakly associated with successful response in pain or functional improvement at two-month follow-up (Spearman correlations, $P = 0.20, 0.21$, respectively). The pain score at two weeks was much more strongly associated with two-month response in both pain ($P = 0.59$) and function ($P = 0.51$). One RCT (Ghahreman 2010) was found comparing the outcomes of transforaminal injection of steroid and local anesthetic, local anesthetic alone, or normal saline, and intramuscular injection of steroid or normal saline. Patients were randomized to receive transforaminal injection of steroid and local anesthetic, local anesthetic alone, or normal saline, and intramuscular injection of steroid or normal saline. A significantly greater proportion of patients treated with transforaminal injection of steroid (54%) achieved relief of pain than did patients treated with transforaminal injection of local anesthetic (7%) or transforaminal injection of saline (19%), intramuscular steroids (21%), or intramuscular saline (13%). A cohort study (Wewalka 2012) was conducted to evaluate the efficacy of serial CT-guided transforaminal nerve root infiltrations with a supplement of tramadol for patients with persistent, radicular pain. 65 infiltrations were carried out with pain relief in more than 90% of the patients within 24 hours and an average pain reduction of 64%. Six months post-injection, 23 of 34 patients were available for follow-up (67.6%), and had a successful pain reduction of 84% on average.

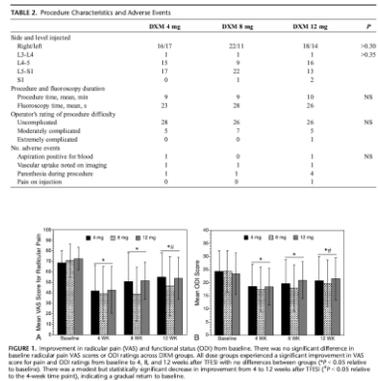
Overall, there is low quality of evidence for type, dose, or duration of local anesthetic with epidural steroid injections for improved outcomes. The studies included used a variety of doses and durations of local anesthetic, therefore we cannot conclude what type, dose, or duration is associated with improved clinical outcomes and/or harms.

Question 1 Primary Literature:

PICO Question: In patients receiving epidural steroid injections, what is the minimum-effective dose of dexamethasone to relieve pain?						<u>Lower Quality Rating if:</u>
Outcome: Reduce Pain						
<i>Author/Da te</i>	<i>Purpose of Study</i>	<i>Study Design & Methods</i>	<i>Sample</i>	<i>Outcomes</i>	<i>Design Limitations</i>	<input type="checkbox"/> Studies inconsistent (<i>wide variation of treatment effect across studies, populations, interventions, or outcomes varied</i>) <input type="checkbox"/> Studies are indirect
Total # of Studies: 3 # of Systematic Reviews: 1 # of RCTs: 2						
De Oliveira, G.S.J., et al., 2011, <i>Anesthesiology</i>	To perform a meta-analysis to evaluate the dose-dependent analgesic effect of	Systematic review with meta-analysis of RCTs	24 RCTs with 2,751 subjects were included	In a meta-analysis of approximately 2,500 patients, dexamethasone, > 0.1 mg/kg, reduced postoperative pain and opioid consumption.	Study Limitations = <input checked="" type="checkbox"/> None Systematic Review <input type="checkbox"/> Review did not address focused clinical question <input type="checkbox"/> Search was not detailed or exhaustive <input type="checkbox"/> Quality of the studies was	

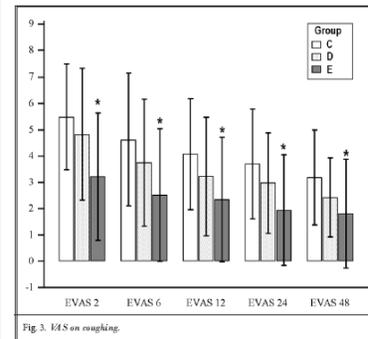
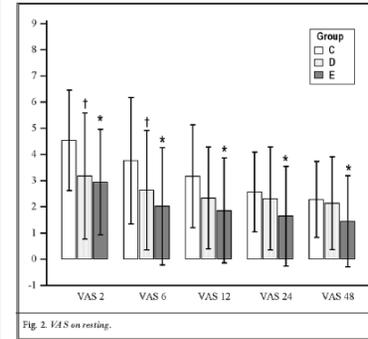


	perioperative dexamethasone				not appraised or studies were of low quality <input type="checkbox"/> Methods and/or results were inconsistent across studies	(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)
Ahadian, F.M., et al., 2011, <i>Regional Anesthesia & Pain Medicine</i>	To investigate the efficacy, dose-response profile, and safety of three doses of epidural dexamethasone	RCT; Subjects were randomized to receive transforaminal epidural dexamethasone 4 mg, 8mg, or 12mg. The primary outcome measure for this study was reduction in radicular pain according to the visual analog scale from baseline, with 30% reduction or higher considered clinically meaningful. Secondary measures included the Oswestry Low Back Disability Scale, and adverse events. Outcomes were assessed at 1, 4, 8, and 12 weeks after injection.	98 subjects; 4 mg (n = 33), 8 mg (n = 33), or 12 mg (n = 32)	Mean radicular pain according to the visual analog scale compared with baseline was reduced 41.7%, 33.5% and 26.6% AT 4, 8, and 12 weeks, respectively, after injection. Oswestry disability ratings declined from “moderate” at baseline to “minimal” at 4, 8, and 12 weeks after injection. There was no statistical difference between groups for either measure (all P values < 0.05, Bonferroni-corrected). Parallel effects were observed in “impression of change” and “satisfaction” measures. No serious adverse events were noted.	Study Limitations = <input checked="" type="checkbox"/> None RCTS <input type="checkbox"/> Lack of blinding <input type="checkbox"/> Lack of allocation concealment <input type="checkbox"/> Stopped early for benefit <input type="checkbox"/> Incorrect analysis of ITT <input type="checkbox"/> Selective reporting of measures (e.g., no effect outcome) <input type="checkbox"/> Large losses to F/U <input type="checkbox"/> Difference in important prognostic factors at baseline	<input type="checkbox"/> Studies are imprecise (When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain) <input type="checkbox"/> Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found) <u>Increase Quality Rating if:</u> <input type="checkbox"/> Large Effect <input type="checkbox"/> Dose-response gradient <input type="checkbox"/> Plausible confounders or other biases increase certainty of effect
Hong, J.M., et al., 2017, <i>Pain Physician</i>	To investigate the effects and optimal dose of epidural dexamethasone on pain after major abdominal surgery	RCT; Patients were assigned to receive one of three treatment regimens: Dexamethasone 5 mg (1 mL) with normal saline (1 mL) (Group D) or dexamethasone 10 mg (2 mL) (Group E) or 2 mL of normal saline (Group C) mixed with 8 mL of 0.375% ropivacaine as a loading dose.	120 ASA physical status I and II men, scheduled for gastrectomy, were enrolled; 40 in each group	The resting and effort VAS was significantly lower in Group E compared to Group C at every time point through the study period. On the contrary, only the resting VAS in Group D was lower at 2 hours and 6 hours after surgery. Total fentanyl consumption of Group E was significantly lower compared to other groups. There was no difference in adverse effect such as hypotension, bradycardia,	Study Limitations = <input type="checkbox"/> None RCTS <input checked="" type="checkbox"/> Lack of blinding <input type="checkbox"/> Lack of allocation concealment <input type="checkbox"/> Stopped early for benefit <input type="checkbox"/> Incorrect analysis of ITT <input type="checkbox"/> Selective reporting of measures (e.g., no effect outcome) <input type="checkbox"/> Large losses to F/U <input checked="" type="checkbox"/> Difference in important	<input type="checkbox"/> Quality (certainty) of evidence for studies as a whole: <input type="checkbox"/> High <input checked="" type="checkbox"/> Moderate <input type="checkbox"/> Low <input type="checkbox"/> Very Low



PONV, pruritis, and urinary retention among groups.

prognostic factors at baseline



Question 1 Guideline Recommendations:

Three guidelines included recommendations on dosage of dexamethasone with epidural steroid injections for pain relieve outlined below:

In 2014, the **Alberta Provincial CNS Tumour Team** made the following recommendations for patients with high-grade glioma:

- Treatment with dexamethasone is recommended for symptom relief in adult patients with primary high-grade glioma and cerebral edema.



- After surgery, a maximum dose of 16 mg daily, administered in 4 equal doses, is recommended for symptomatic patients. This protocol should ideally be started by the neurosurgeon.
- A rapid dexamethasone tapering schedule should be considered where appropriate.
- Patients who have high-grade tumours, are symptomatic, or have poor life expectancy, can be maintained on a 0.5–1.0 mg dose of dexamethasone daily.
- Side effects with dexamethasone are common, and they increase in frequency and severity with increased dose and duration of therapy. Patients should be carefully monitored for endocrine, muscular, skeletal, gastrointestinal, psychiatric, and hematologic complications, and for infections and other general side effects.

In 2013, the **National Guideline Alliance (NGA) with the Institute for Clinical Systems Improvement (ICSI)** provided the following recommendations for the management of labor:

Pharmacologic Management of Preterm Labor

Tocolysis and Betamethasone

In most cases, management of preterm labor would include tocolysis for 48 hours and administration of two doses of betamethasone to accelerate fetal lung maturity.

The usual dosage regimen is betamethasone 12 mg intramuscularly (IM) STAT, then repeat in 24 hours.

An alternative medication is dexamethasone for a total of 24 mg (usual dosing regimen is 6 mg IM every 12 hours for four doses).

Treatment should be initiated in women with any symptoms or signs that might herald the onset of preterm delivery or a potential need for induced delivery, rather than waiting until the diagnosis or decision is certain. While a single complete course of antenatal corticosteroids provides significant multiple benefits to the preterm neonate, additional courses should not be used [*High Quality Evidence*].

Treatment should not be withheld because delivery appears to be imminent.

Antenatal corticosteroid therapy for fetal lung maturation reduces mortality, respiratory distress syndrome, and intraventricular hemorrhage in preterm infants. These benefits accrue to preterm neonates across a broad range of



gestational ages and are not limited by gender or race [Systematic Review]. The benefits of the administration of postnatal surfactant are enhanced by antenatal steroid therapy. No adverse consequences to a policy of administration of antenatal steroids to women in preterm labor have been identified [Guideline].

The beneficial effects of corticosteroids are greatest more than 24 hours after beginning treatment. However, treatment less than 24 hours in duration may improve outcome. Every effort should be made to treat women before spontaneous or elective preterm delivery.

In 2008, the **National Guideline Alliance (NGA)** made the following recommendations for patients with Metastatic spinal cord compression (MSCC):

Unless contraindicated (including a significant suspicion of lymphoma) offer all patients with MSCC a loading dose of at least 16 mg of dexamethasone as soon as possible after assessment, followed by a short course of 16 mg dexamethasone daily while treatment is being planned.

Continue dexamethasone 16 mg daily in patients awaiting surgery or radiotherapy for MSCC. After surgery or the start of radiotherapy the dose should be reduced gradually over 5 to 7 days and stopped. If neurological function deteriorates at any time the dose should be increased temporarily.

Reduce gradually and stop dexamethasone 16 mg daily in patients with MSCC who do not proceed to surgery or radiotherapy after planning. If neurological function deteriorates at any time the dose should be reconsidered.

Monitor blood glucose levels in all patients receiving corticosteroids.

Guideline Ratings

Guideline Issuer and Date	Alberta 2014	ICSI 2013	NGA 2008
1. Transparency	A	A	A
2. Conflict of interest	B	A	A
3. Development group	B	B	A



4. Systematic Review	A	A	A
5. Supporting evidence	B	A	A
6. Recommendations	B	B	B
7. External Review	NR	NR	NR
8. Currency and updates	B	B	B

See appendix B for full description of the Trustworthy Guideline grading system.

Question 2 Primary Literature:

<p>PICO Question: In patients receiving epidural steroid injections, what local anesthetic (type, dose, duration) is associated with improved clinical outcomes and/or harms (ie weakness, cardiotoxicity, osteonecrosis, other)?</p> <p>Outcome: Improved Clinical Outcomes and/or Harms</p>						<p>Lower Quality Rating if:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Studies inconsistent (<i>wide variation of treatment effect across studies, populations, interventions, or outcomes varied</i>) <input checked="" type="checkbox"/> Studies are indirect (<i>PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome</i>) <input type="checkbox"/> Studies are imprecise (<i>When studies include few patients and few events and thus have wide confidence intervals and the</i> 																							
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<p>Total # of Studies: 10 # of Systematic Reviews: 5 # of RCTs: 1 # of Non-Randomized Studies: 4</p>																													
<p>Conn, A., et al, 2009, <i>Pain Physician</i></p>	<p>To evaluate the effect of caudal epidural injections with or without steroids in managing various types of chronic low back and lower extremity pain emanating as a result of disc herniation or radiculitis, post-lumbar laminectomy syndrome, spinal stenosis, and chronic discogenic pain</p>	<p>Systematic Review</p>	<p>18 RCTs and 20 Observational Studies</p>	<p>The one randomized trial evaluating spinal stenosis with or without steroids with local anesthetic showed positive results for short- and long-term relief.</p> <p>Observational studies also showed positive short-term and long-term improvement.</p>	<p>Study Limitations =</p> <ul style="list-style-type: none"> <input type="checkbox"/> None <input checked="" type="checkbox"/> Systematic Review <input type="checkbox"/> Review did not address focused clinical question <input type="checkbox"/> Search was not detailed or exhaustive <input checked="" type="checkbox"/> Quality of the studies was not appraised or studies were of low quality <input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies 																								
<table border="1"> <thead> <tr> <th>Study/Methods</th> <th>Participants</th> <th>Intervention(s)</th> <th>Outcome(s)</th> <th>Result(s)</th> <th>Conclusion(s)</th> </tr> </thead> <tbody> <tr> <td>Meta-analysis of 10 RCTs (10)</td> <td>44 patients with chronic low back pain of discogenic origin, without disc herniation or radiculitis.</td> <td>Group 1: patients received caudal epidural injections with local anesthetic of lidocaine 0.5% preservative free, whereas Group 2: patients received caudal epidural injections with 0.5% lidocaine, 9 cc, mixed with 1 cc of steroid.</td> <td>Timing: 1 year, 4 years, and 11 years. Outcome: average pain, functional status, percentage of return, narcotic intake, and employment status.</td> <td>Significant pain relief (72% vs 61% of patients and functional status improvement) was demonstrated by a reduction of 0.9 in the VAS score in 65% of the patients. The overall average prevalence per year were 1.6 in Group 1 and 1.3 in Group 2 with an average cost estimate per year of \$23,100 vs \$25,800. Mean of Group 1 and Group 2 were 51 percent of 52 months.</td> <td>Positive short-term and long-term relief</td> </tr> <tr> <td>Meta-analysis of 2009 (16)</td> <td>79 patients (total) randomized to either phenol therapy, chymopapain, and nucleotome therapy or to receive the treatment per.</td> <td>Group 1: the treatment Group 2: local anesthetic and steroids (1 cc of 10 mg/ml, 10 cc of 1% methylprednisolone, and 1 cc of triamcinolone).</td> <td>Timing: 2 wks, 1 month, 3 months, 6 months, 1 year. Outcome: mean pain, functional status, percentage of return, narcotic intake, and employment status.</td> <td>Average pain, functional status, narcotic intake, functional status, return to work, and employment improved significantly in Group 1 and Group 2 at 2 wks, 1 month, 3 months, 6 months, and 1 year.</td> <td>Positive short-term and long-term relief</td> </tr> <tr> <td>Meta-analysis of 2002 (25)</td> <td>42 patients (total) randomized to either phenol therapy, chymopapain, and nucleotome therapy or to receive the treatment per.</td> <td>Control epidural injection: 2 wks of 10 mg/ml, 10 cc of 1% methylprednisolone, and 1 cc of triamcinolone.</td> <td>Timing: 1 year, 1 year, and 1 year. Outcome: average pain, functional status, percentage of return, narcotic intake, and employment status.</td> <td>40% of the pts in the surgery group had 40% of the pts in the positive therapeutic group were in successful category.</td> <td>Positive short-term and long-term relief data not available.</td> </tr> </tbody> </table>						Study/Methods	Participants	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s)	Meta-analysis of 10 RCTs (10)	44 patients with chronic low back pain of discogenic origin, without disc herniation or radiculitis.	Group 1: patients received caudal epidural injections with local anesthetic of lidocaine 0.5% preservative free, whereas Group 2: patients received caudal epidural injections with 0.5% lidocaine, 9 cc, mixed with 1 cc of steroid.	Timing: 1 year, 4 years, and 11 years. Outcome: average pain, functional status, percentage of return, narcotic intake, and employment status.	Significant pain relief (72% vs 61% of patients and functional status improvement) was demonstrated by a reduction of 0.9 in the VAS score in 65% of the patients. The overall average prevalence per year were 1.6 in Group 1 and 1.3 in Group 2 with an average cost estimate per year of \$23,100 vs \$25,800. Mean of Group 1 and Group 2 were 51 percent of 52 months.	Positive short-term and long-term relief	Meta-analysis of 2009 (16)	79 patients (total) randomized to either phenol therapy, chymopapain, and nucleotome therapy or to receive the treatment per.	Group 1: the treatment Group 2: local anesthetic and steroids (1 cc of 10 mg/ml, 10 cc of 1% methylprednisolone, and 1 cc of triamcinolone).	Timing: 2 wks, 1 month, 3 months, 6 months, 1 year. Outcome: mean pain, functional status, percentage of return, narcotic intake, and employment status.	Average pain, functional status, narcotic intake, functional status, return to work, and employment improved significantly in Group 1 and Group 2 at 2 wks, 1 month, 3 months, 6 months, and 1 year.	Positive short-term and long-term relief	Meta-analysis of 2002 (25)	42 patients (total) randomized to either phenol therapy, chymopapain, and nucleotome therapy or to receive the treatment per.	Control epidural injection: 2 wks of 10 mg/ml, 10 cc of 1% methylprednisolone, and 1 cc of triamcinolone.	Timing: 1 year, 1 year, and 1 year. Outcome: average pain, functional status, percentage of return, narcotic intake, and employment status.	40% of the pts in the surgery group had 40% of the pts in the positive therapeutic group were in successful category.	Positive short-term and long-term relief data not available.
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Study	Study Characteristics	Methodological Quality Scoring	Participants	Pain Relief		Results
				3 mos	12 mos	
Mitchell et al 2008 (7)	Rx, DR	7b	40	100% vs 65%	88% vs 65%	P
Chen et al 2008 (8)	O	5f	30	SI	SI	NA
Banno et al 2007 (10)	O	4f	34	65% vs 62%	54%	P

EA - randomized, O - observational, DR - double blind, NA - not available, SI - significant improvement vs. versus P - positive, N - negative

Characteristics of published studies of caudal epidural injections (including local anesthetic) in managing disc herniation and radiculitis

Study/Methods	Participants	Intervention(s)	Outcomes(s)	Results(s)	Conclusion(s) Short-term relief < 6 mos, Long-term relief > 6 mos
Mitchell et al 2008 (7) Randomized, double-blind experimental trial	40 patients were assigned to one of 2 groups: Group 1 patients received epidural steroid injections with no injection of local anesthetic (steroids); Group 2 patients received epidural steroid injections with 1 ml of 0.5% bupivacaine. Each patient was treated with 1 ml of steroid. Each patient was treated with 1 ml of 0.5% bupivacaine 5h or 1h after steroid injection. 10% of patients were lost to follow-up.	Group 1: caudal epidural steroid injections with no injection of local anesthetic (steroids); Group 2: caudal epidural steroid injections with 1 ml of 0.5% bupivacaine 5h or 1h after steroid injection. 10% of patients were lost to follow-up.	Assessments 3 mos, 6 mos, and 12 mos. Outcome: improvement in Oswestry scores of at least 50% was seen in 88% of the patients in Group 1 and 90% in Group 2.	The percentage of patients with significant pain relief at 3 mos or greater at 12 months was 79% in Group 1 and 79% in Group 2. Reduction of Oswestry scores of at least 50% was seen in 88% of the patients in Group 1 and 90% in Group 2.	Positive short-term and long-term relief
Chen et al 2008 (8) Prospective, unblinded, double-blind trial	40 patients with a 10-month history of sciatica to either lumbar epidural steroids and/or epidural injections with a steroid and/or local anesthetic and steroid treatment.	Corticosteroid injection with a total of 10 ml of bupivacaine 0.5% with 40 mg of triamcinolone. Epidural steroid injection with a steroid and/or local anesthetic and steroid treatment.	Assessments 6 mos, 12 mos, and 18 mos. Outcome: mean VAS 30, 30% and 30%.	Caudal group significant improvement was found for descriptive pain at 6 mos. Outcome: mean VAS 30, 30% and 30%.	Positive short-term relief; long-term relief not available
Bann et al 2007 (10) Randomized, double-blind trial	37 patients with low back pain and sciatica. Comparison between 2 groups.	Experiment 1: 20 ml, 0.5% bupivacaine and 10 mg of methylprednisolone (n=20). Control: 20 ml, normal saline (n=17). Frequency: 2 caudal injections, the first after admission to the trial and a second after 2 wks.	Timing: 2 wks, 1, 6, and 12 mos. Outcome: mean VAS 30, 30% and 30%.	Significantly better results with pain and QoL in experimental group vs control group. Mean VAS significantly better in long-term trial.	Positive short-term and long-term relief
Mathews et al 2007 (10) Experimental group, unblinded, double-blind trial	57 patients with sciatica with single root compression. Experimental group: methylprednisolone 10 mg, bupivacaine 0.5% (n=28). Control group: methylprednisolone 10 mg, normal saline (n=29). Frequency: 2 caudal injections, the first after admission to the trial and a second after 2 wks.	Experiment 1: 20 ml, 0.5% bupivacaine and 10 mg of methylprednisolone (n=28). Control: 20 ml, normal saline (n=29). Frequency: 2 caudal injections, the first after admission to the trial and a second after 2 wks.	Timing: 2 wks, 1, 6, and 12 mos. Outcome: mean VAS 30, 30% and 30%.	There was no significant difference between experimental and control groups with descriptive relief (57% vs 56%), after 3 mos, or experimental group pain-free than in control group.	Negative short-term and positive long-term relief
Diwan et al 2012 (10) Randomized, double-blind trial with crossover design	40 patients with low back pain and sciatica. 20 patients were operated on for herniated disc. 20 patients without previous back surgery were treated with 3 lumbar epidural injections.	20 patients without previous back surgery treated with 3 caudal epidural injections of bupivacaine 0.5% and 10 mg of methylprednisolone. 20 patients without previous back surgery were treated with 3 lumbar epidural injections of bupivacaine 0.5% and 10 mg of methylprednisolone.	Outcome: mean VAS 30, 30% and 30%.	14 of the 58 pts (24%) showing good clinical improvement or significant improvement in Oswestry scores. 12 of 49 pts (24%) who received bupivacaine followed by steroid response.	Positive short-term and long-term relief
Bann et al 2007 (10) Randomized, double-blind trial	37 patients with low back pain and sciatica. Comparison between 2 groups.	Caudal epidural injection with a total of 10 ml of bupivacaine 0.5% with 40 mg of triamcinolone. Epidural steroid injection with a steroid and/or local anesthetic and steroid treatment.	Timing: 2 wks, 1, 6, and 12 mos. Outcome: mean VAS 30, 30% and 30%.	54% of the pts reported a meaningful pain relief in experimental group compared to 30% of the pts in the placebo group.	Positive short-term relief; long-term relief not available

Diwan, S., et al., 2012, Pain Physician

To evaluate the effect of cervical interlaminar epidural injections in managing

Systematic review with meta-analysis

9 RCTs with 2 duplicate studies

For cervical disc herniation, the evidence is good for cervical epidural with local anesthetic and steroids; whereas, it is fair with local anesthetic only.

For axial or discogenic pain, the evidence is fair for local anesthetic, with

Study Limitations =

- None
- Systematic Review**
- Review did not address focused clinical question
- Search was not detailed or exhaustive
- Quality of the studies was

results are uncertain)

Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)

Increase Quality Rating if:

- Large Effect
- Dose-response gradient
- Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:

- High
- Moderate
- Low
- Very Low



	<p>various types of chronic neck and upper extremity pain emanating as a result of cervical spine pathology</p>		<p>39 trials; 11 studies</p>	<p>or without steroids.</p> <p>For spinal stenosis, the evidence is fair for local anesthetic, with or without steroids.</p> <p>For postsurgery syndrome, the evidence is fair for local anesthetic, with or without steroids.</p>	<p>not appraised or studies were of low quality</p> <p><input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies</p>	
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Table 2. Assessment of methodological quality of cervical/neck/upper extremity pain studies for radicular pain.

Study ID	Blinded to Allocation Sequence	Blinded to Treatment	Blinded to Outcome	Number of Patients	Number of Events	Relative Risk	95% CI	Comments
Manchikanti et al. (2011)	Y	Y	Y	100	100	1.0	0.5-1.8	Blinded to allocation sequence, treatment, and outcome. Relative risk of 1.0 indicates no effect. 95% CI of 0.5-1.8 indicates no effect.
Manchikanti et al. (2012)	Y	Y	Y	100	100	1.0	0.5-1.8	Blinded to allocation sequence, treatment, and outcome. Relative risk of 1.0 indicates no effect. 95% CI of 0.5-1.8 indicates no effect.
Manchikanti et al. (2013)	Y	Y	Y	100	100	1.0	0.5-1.8	Blinded to allocation sequence, treatment, and outcome. Relative risk of 1.0 indicates no effect. 95% CI of 0.5-1.8 indicates no effect.
Manchikanti et al. (2014)	Y	Y	Y	100	100	1.0	0.5-1.8	Blinded to allocation sequence, treatment, and outcome. Relative risk of 1.0 indicates no effect. 95% CI of 0.5-1.8 indicates no effect.
Manchikanti et al. (2015)	Y	Y	Y	100	100	1.0	0.5-1.8	Blinded to allocation sequence, treatment, and outcome. Relative risk of 1.0 indicates no effect. 95% CI of 0.5-1.8 indicates no effect.



<p>et al, 2016, <i>Pain Physician</i></p>	<p>efficacy of 3 categories of epidural injections for lumbar and spinal stenosis: performed with saline with steroids, local anesthetic alone, or steroids with local anesthetic and separate facts from opinions</p>	<p>analysis</p>	<p>assessing caudal epidural injections, 16 studies assessed interlaminar epidural injections, and 18 studies assessed transforaminal epidural injections.</p>	<p>showed a lack of effectiveness in 3 trials with 131 patients and short-term (3 months) effectiveness in one trial with 50 patients. Adding bupivacaine to steroids showed very short-term (3-6 weeks) effectiveness in 3 trials with 173 patients, whereas 2 trials with 142 patients reported a lack of effectiveness. There were no placebo-controlled trials available with lidocaine, and one trial, with the addition of mepivacaine, showed a lack of effectiveness. Meta-analysis shows results of pain relief and functional status improvement of placebo-controlled trials of epidural steroids with saline or bupivacaine with follow-up data of 3 months and 6 months. Among the 9 placebo-controlled trials, 3 trials were excluded. Among 5 studies with a total of 763 patients, steroid was mixed with saline in 2 studies with 232 patients and with bupivacaine in 3 studies with 531 patients. There was no difference between placebo- and steroid-treated groups with either steroid mixed with saline or steroid mixed with bupivacaine.</p> <p>A. Short term follow-up with minimum 3 months of pain relief.</p> <table border="1"> <thead> <tr> <th rowspan="2">Study</th> <th colspan="2">Steroid with Sodium Chloride Solution or Bupivacaine</th> <th colspan="2">Placebo</th> <th rowspan="2">Weight</th> <th rowspan="2">Std. Mean Difference, 95% CI</th> </tr> <tr> <th>Mean</th> <th>SD</th> <th>Mean</th> <th>SD</th> </tr> </thead> <tbody> <tr> <td>Inversen et al., 2011 (47)</td> <td>0</td> <td>12</td> <td>27</td> <td>14</td> <td>39</td> <td>16.40%</td> </tr> <tr> <td>Anders et al., 2005 (59)</td> <td>4.9</td> <td>5</td> <td>200</td> <td>4.3</td> <td>5</td> <td>49.30%</td> </tr> <tr> <td>Kapponen et al., 2001 (78)</td> <td>2.3</td> <td>5</td> <td>78</td> <td>2</td> <td>5</td> <td>34.30%</td> </tr> <tr> <td>Total (95% CI)</td> <td></td> <td></td> <td>232</td> <td></td> <td>227</td> <td>100.00%</td> </tr> </tbody> </table> <p>Heterogeneity: $\chi^2 = 0.75$, $df = 2$ ($P = 0.69$); $I^2 = 0\%$ Test for overall effect: $Z = 0.58$ ($P = 0.56$)</p> <p>IV, Random, 95% CI</p> <p>Only 3 studies with 462 patients utilizing a mixture of bupivacaine with</p>	Study	Steroid with Sodium Chloride Solution or Bupivacaine		Placebo		Weight	Std. Mean Difference, 95% CI	Mean	SD	Mean	SD	Inversen et al., 2011 (47)	0	12	27	14	39	16.40%	Anders et al., 2005 (59)	4.9	5	200	4.3	5	49.30%	Kapponen et al., 2001 (78)	2.3	5	78	2	5	34.30%	Total (95% CI)			232		227	100.00%	<p><input type="checkbox"/> None Systematic Review <input type="checkbox"/> Review did not address focused clinical question <input type="checkbox"/> Search was not detailed or exhaustive <input checked="" type="checkbox"/> Quality of the studies was not appraised or studies were of low quality <input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies</p>	
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steroids met inclusion criteria and provided data for meta-analysis with 6 month follow-up. They showed no difference between placebo and steroid with bupivacaine treated groups of patients.

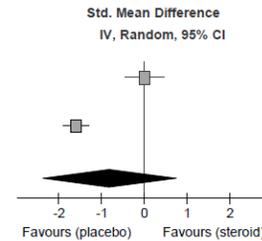
Functional improvement resulted in no difference between placebo and steroid solutions mixed with saline or bupivacaine.

Multiple active-controlled trials assessed the role of local anesthetic alone compared to local anesthetic with steroids.

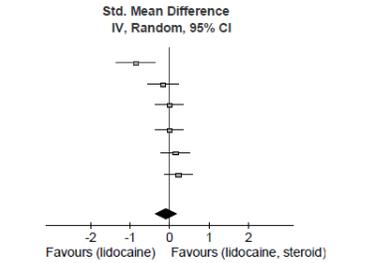
A. Long term follow-up of 3 months of functional status.

Study	Steroid with Sodium Chloride Solution or Bupivacaine			Placebo			Weight	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Iversen et al. 2011 (47)	1.9	0.2	39	1.5	4.2	37	49.40%	0.00 (-0.45, 0.45)
Arden et al. 2005 (59)	31	5	108	39	5	120	50.60%	-1.59 (-1.89, -1.30)
Total (95% CI)			147			157	100.00%	-0.81 (-1.2, -0.76)

Heterogeneity: Chi² = 24.24, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.01 (P = 0.31)



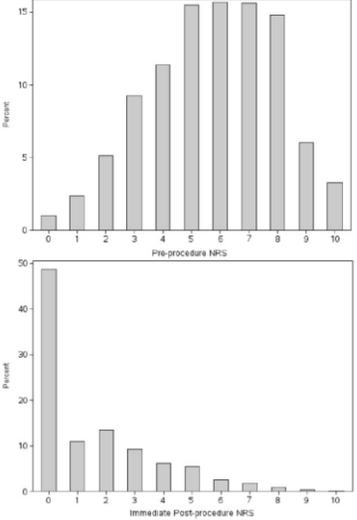
There were 7 trials assessing lidocaine as a sole agent or lidocaine with steroids and 3 trials assessing bupivacaine alone in comparison to bupivacaine with steroid. All 3 of the bupivacaine trials showed positive results with similar results with bupivacaine combined with steroid to avoid surgical interventions. Based on a qualitative synthesis of evidence of 7 active-controlled trials comparing lidocaine to lidocaine with steroid, effectiveness was equal in both groups except in disc herniation where potential superiority was demonstrated. 6 studies with 649 patients were utilized

				<p>for pain improvement ratings, comparing lidocaine to lidocaine with steroid. They showed no difference in pain improvement between both groups at 3 or 12 months</p> <p>Functional status was also assessed with inclusion of 6 studies at 3 months and 7 studies at 12 months showing no difference in functional improvement between lidocaine alone or lidocaine with steroid at 3 or 12 months. This analysis showed the effectiveness of lidocaine and lidocaine with steroid for pain relief and functional status at 3 months and also 12 months with results slightly favoring local anesthetic alone.</p> <table border="1" data-bbox="1052 634 1419 784"> <thead> <tr> <th rowspan="2">Study</th> <th colspan="3">Lidocaine steroid with Sodium Chloride Solution or Bupivacaine</th> <th colspan="3">Lidocaine only</th> <th rowspan="2">Weight</th> <th rowspan="2">Std. Mean Difference</th> </tr> <tr> <th>Mean</th> <th>SD</th> <th>Total</th> <th>Mean</th> <th>SD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>Marchkanti et al. 2012 (48)</td> <td>4.4</td> <td>1.7</td> <td>60</td> <td>4</td> <td>1.8</td> <td>60</td> <td>17.50%</td> <td>0.23 (-0.13, 0.59)</td> </tr> <tr> <td>Marchkanti et al. 2012 (53)</td> <td>3.5</td> <td>1.5</td> <td>50</td> <td>3.8</td> <td>1.8</td> <td>50</td> <td>16.40%</td> <td>-0.10 (-0.55, 0.23)</td> </tr> <tr> <td>Marchkanti et al. 2014 (60)</td> <td>4.5</td> <td>1</td> <td>60</td> <td>4.3</td> <td>1.6</td> <td>60</td> <td>17.50%</td> <td>0.15 (-0.21, 0.51)</td> </tr> <tr> <td>Gilani et al. 2015 (62)</td> <td>1.5</td> <td>1.4</td> <td>75</td> <td>4.8</td> <td>1.4</td> <td>75</td> <td>18.50%</td> <td>-0.86 (-1.35, -0.38)</td> </tr> <tr> <td>Marchkanti et al. 2015 (70)</td> <td>4.3</td> <td>1.5</td> <td>60</td> <td>4.3</td> <td>1.3</td> <td>60</td> <td>17.50%</td> <td>0.00 (-0.36, 0.36)</td> </tr> <tr> <td>Marchkanti et al. 2014 (74)</td> <td>4.2</td> <td>1.5</td> <td>60</td> <td>4.2</td> <td>1.8</td> <td>60</td> <td>17.50%</td> <td>0.00 (-0.36, 0.36)</td> </tr> <tr> <td>Total (95% CI)</td> <td></td> <td></td> <td>325</td> <td></td> <td></td> <td>324</td> <td>100.00%</td> <td>-0.08 (-0.34, 0.19)</td> </tr> </tbody> </table> <p>Heterogeneity: $Chi^2 = 14.12$, $df = 5$ ($P = 0.01$); $I^2 = 65%$ Test for overall effect: $Z = 0.37$ ($P = 0.37$)</p> 	Study	Lidocaine steroid with Sodium Chloride Solution or Bupivacaine			Lidocaine only			Weight	Std. Mean Difference	Mean	SD	Total	Mean	SD	Total	Marchkanti et al. 2012 (48)	4.4	1.7	60	4	1.8	60	17.50%	0.23 (-0.13, 0.59)	Marchkanti et al. 2012 (53)	3.5	1.5	50	3.8	1.8	50	16.40%	-0.10 (-0.55, 0.23)	Marchkanti et al. 2014 (60)	4.5	1	60	4.3	1.6	60	17.50%	0.15 (-0.21, 0.51)	Gilani et al. 2015 (62)	1.5	1.4	75	4.8	1.4	75	18.50%	-0.86 (-1.35, -0.38)	Marchkanti et al. 2015 (70)	4.3	1.5	60	4.3	1.3	60	17.50%	0.00 (-0.36, 0.36)	Marchkanti et al. 2014 (74)	4.2	1.5	60	4.2	1.8	60	17.50%	0.00 (-0.36, 0.36)	Total (95% CI)			325			324	100.00%	-0.08 (-0.34, 0.19)	
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<p>Liu, K., et al., 2015, <i>Drug design, development & therapy</i></p>	<p>To investigate the effectiveness and safety of epidural steroid injections in patients with lumbar spinal stenosis (LSS).</p>	<p>Systematic review with meta-analysis</p>	<p>10 studies with 1,010 participants</p>	<p>With respect to the epidural local anesthetic injection group, there was no significant difference for most outcome measures, such as the Brief Pain Inventory (BPI) Interference Scale (3 weeks, 6 weeks); SSSQ Physical Function Subscales (3 weeks, 6 weeks); Eight-question version of the Patient Health Questionnaire (PHQ-8) (3 weeks, 6 weeks); Generalized Anxiety Disorder 7 (GAD-7) scale (3 weeks, 6 weeks); Oswestry Disability Index (ODI) score (6 weeks, 3 months,</p>	<p>Study Limitations =</p> <ul style="list-style-type: none"> <input type="checkbox"/> None <input type="checkbox"/> Systematic Review <input type="checkbox"/> Review did not address focused clinical question <input type="checkbox"/> Search was not detailed or exhaustive <input checked="" type="checkbox"/> Quality of the studies was not appraised or studies were of low quality <input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies 																																																																														



		<p>wheel. Numerical rating scale pain scores were correlated with leg and back pain relief, and functional improvement, through 3-month follow-up</p>		<p>2.7 for leg, $P < 0.01$; mean 3.7, SD 2.6 vs 5.0, SD 3.0 for back, $P = 0.02$) and 3-month (mean 3.8, SD 2.7 vs 5.2, SD 3.1 for leg, $P = 0.01$; mean 4.0, SD 2.6 vs 4.9, SD 3.1 for back; $P = 0.14$) follow-up.</p>	
<p>Delpont, E.G., et al., 2004, <i>Archives of Physical Medicine & Rehabilitation</i></p>	<p>To determine patient satisfaction, relief of pain, frequency of injections, change of function, and subsequent surgical rate in patients who received epidural steroid injections (ESIs) for the diagnosis of lumbar spinal stenosis (LSS)</p>	<p>Retrospective Study; Transforaminal or caudal fluoroscopically guided ESIs with 60 to 100mg of triamcinalone in combination with local anesthetic or normal saline. Main outcome measures Duration and amount of pain relief, change in functional status, patient satisfaction, and surgical rate, assessed by a 5-item questionnaire.</p>	<p>140 patients at or over the age of 55 years diagnosed with LSS who received ESI(s).</p>	<p>32% reported more than 2 months of pain relief, 39% reported less than 2 months of pain relief, and 29% reported no relief from the injection(s). Twenty percent subsequently had surgery. Fifty-three percent reported improvement in their functional abilities. Seventy-four percent were at least somewhat satisfied with ESI as a form of treatment.</p> <p>Patients who underwent subsequent surgery were less likely to have had relief with epidurals ($P < .001$).</p> <p>Patients who received 2 or more injections had better results ($P = .006$). Number of injections and amount of relief initially after injection was significant ($P = .007$).</p>	<p>Study Limitations =</p> <ul style="list-style-type: none"> <input type="checkbox"/> None Non-Randomized Studies <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input checked="" type="checkbox"/> Failure to adequately control confounding <input checked="" type="checkbox"/> Incomplete or inadequately short follow-up <input checked="" type="checkbox"/> Differences in important prognostic factors at baseline
<p>El-Yahouchi, C., et al., 2014, <i>Pain Medicine</i></p>	<p>To assess whether the immediate anesthetic response of pain relief (sensory blockade) or weakness (motor</p>	<p>Retrospective Observational Study; 20 mg lidocaine (1 mL of 2% lidocaine) test dose was injected. If there was no neurological change over the next 1–2 minutes, corticosteroid was injected (betamethasone sodium phosphate/ betamethasone acetate [Celestone] 12 mg in 2 mL, American Regent, Inc., Shirley, NY, USA; triamcinolone</p>	<p>3,645 lumbar TFESIs performed on 2,634 subjects</p>	<p>The mean (standard deviation) NRS and R-M scores prior to the 2174 procedures in the cohort were 5.8 (2.2) and 12.5 (5.2), respectively. Local anesthetic blockade, an NRS pain score of 2 or less immediately following the TFESI, was achieved in 73.3% of procedures. The categorical pain relief and functional recovery outcomes at 2 weeks and 2 months, including stratification by steroid type, have been previously</p>	<p>Study Limitations =</p> <ul style="list-style-type: none"> <input type="checkbox"/> None Non-Randomized Studies <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or



	<p>blockade) after lumbar transforaminal epidural steroid injection (TFESI) is associated with longer term effectiveness in pain relief and functional recovery</p>	<p>acetoneide [Kenalog], 80 mg in 2 mL, Bristol-Myers Squibb, New York, NY, USA; or preservative-free dexamethasone sodium phosphate, 10 mg in 1 mL, APP Pharmaceuticals, LLC, Lake Zurich, IL, USA). The patient was taken to a recovery area and re-evaluated by the treating physician in 10–15 minutes. A post-procedure pain score (NRS, 0–10) was recorded, typically with the patient ambulating or performing maneuvers or adopting postures that would typically provoke the index pain. Subjects completed a pain numerical rating scale (NRS, 0–10) and Roland–Morris disability questionnaire (R-M) prior to and immediately after TFESI (NRS) and at 2 weeks and 2 months follow-up. Successful pain relief was $\geq 50\%$ NRS reduction; functional success was $\geq 40\%$ R-M reduction. Post-procedure motor weakness was recorded.</p>		<p>reported.</p>  <p>The immediate pain response following TFESI was only weakly associated with successful response in pain or functional improvement at 2 months follow-up (Spearman correlations, $P = 0.20, 0.21$, respectively). The pain score at 2 weeks was much more strongly associated with 2 month response in both pain ($P = 0.59$) and function ($\rho = 0.51$).</p>	<p>inadequately short follow-up <input type="checkbox"/> Differences in important prognostic factors at baseline</p>	
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<p>Ghahreman, A., et al., 2010, <i>Pain Medicine</i></p>	<p>To compare the outcomes of transforaminal injection of steroid and local anesthetic, local anesthetic alone, or normal saline, and intramuscular injection of steroid or normal saline</p>	<p>RCT; Patients were randomized to receive transforaminal injection of steroid and local anesthetic, local anesthetic alone, or normal saline, and intramuscular injection of steroid or normal saline. The primary outcome measure was the proportion of patients who achieved complete relief of pain, or at least 50% relief, at 1 month after treatment. Secondary outcome measures were function, disability, patient-specified functional outcomes, use of other health care, and duration of relief beyond 1 month.</p>	<p>130 patients</p>	<p>A significantly greater proportion of patients treated with transforaminal injection of steroid (54%) achieved relief of pain than did patients treated with transforaminal injection of local anesthetic (7%) or transforaminal injection of saline (19%), intramuscular steroids (21%), or intramuscular saline (13%). Relief of pain was corroborated by significant improvements in function and disability, and reductions in use of other health care.</p>	<p>Study Limitations = <input type="checkbox"/> None RCTS <input checked="" type="checkbox"/> Lack of blinding <input checked="" type="checkbox"/> Lack of allocation concealment <input type="checkbox"/> Stopped early for benefit <input checked="" type="checkbox"/> Incorrect analysis of ITT <input type="checkbox"/> Selective reporting of measures (e.g., no effect outcome) <input checked="" type="checkbox"/> Large losses to F/U <input type="checkbox"/> Difference in important prognostic factors at baseline</p>
<p>Wewalka, M., et al., 2012, <i>Pain Physician</i></p>	<p>To evaluate the efficacy of serial CT-guided transforaminal nerve root infiltrations with a supplement of tramadol for patients with persistent, radicular pain.</p>	<p>Cohort Study; Patients who had radicular leg pain for over 9 weeks received up to 3 CT-guided transforaminal nerve root infiltrations at intervals of 2 weeks as long as their level of pain was over 3 on a numerical rating scale from 0 to 10. 50 mg of Tramadol were added to a combination of local anesthetic (Ropivacain, 2 mg) and corticosteroid (Triamcinolon, 40 mg). Evaluations were carried out 24 hours after the Infiltration as well as 2 weeks, 3 and 6 months after the treatment series. The intensity of their radicular pain was measured by a numerical rating scale (NRS). Pain reduction of at least 50% was defined as successful outcome</p>	<p>37 patients</p>	<p>65 infiltrations were carried out with pain relief in more than 90% of the patients within 24 hours and an average pain reduction of 64%. Six months post-injection 23 of 34 patients available for follow-up (67.6%) had a successful pain reduction of 84% on average. No adverse effects ascribable to the use of tramadol were noted.</p>	<p>Study Limitations = <input checked="" type="checkbox"/> None Non-Randomized Studies <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input type="checkbox"/> Differences in important prognostic factors at baseline</p>



Question 2 Guideline Recommendations:

Two guidelines included recommendations on what local anesthetic (type, dose, and duration) is associated with improved clinical outcomes and/or harms below:

In 2014, the **American Association of Neurological Surgeons/Congress of Neurological Surgeons Lumbar Trigger Point Injections** released the following guideline update with the following recommendation:

Grade B

Trigger point injections (TPIs) performed as dry needling, with anesthetics alone or with steroids, are not recommended in patients with chronic low-back pain without radiculopathy from degenerative disease of the lumbar spine because a long-lasting benefit has not been demonstrated (Level II evidence)

In 2013, the **American Society of Interventional Pain Physicians** provided the following recommendations:

Management of Low Back Pain

Diagnostic Selective Nerve Root Blocks

- The evidence for accuracy of diagnostic selective nerve root blocks is limited in the lumbar spine in patients with an equivocal diagnosis and involvement of multiple levels.
- Diagnostic selective nerve root blocks are recommended in the lumbar spine in select patients with an equivocal diagnosis and involvement of multiple levels.

Lumbar Discography

- The evidence for diagnostic accuracy for lumbar provocation discography is fair and the evidence for lumbar functional anesthetic discography is limited.
- Lumbar provocation discography is recommended with appropriate indications in patients with low back pain to prove a diagnostic hypothesis of discogenic pain specifically after exclusion of other sources of lumbar pain.

Diagnostic Lumbar Facet Joint Nerve Blocks

- The evidence for diagnostic lumbar facet joint nerve blocks is good with 75% to 100% pain relief as the criterion standard with controlled local anesthetic or placebo blocks.
- Diagnostic lumbar facet joint nerve blocks are recommended in patients with suspected facet joint pain.



Diagnostic Sacroiliac Joint Blocks

- The evidence for diagnostic intraarticular sacroiliac joint injections is good with 75% to 100% pain relief as the criterion standard with controlled local anesthetic or placebo blocks, and fair due to the limitation of the number of studies with 50% to 74% relief with a dual block.
- Controlled sacroiliac joint blocks with placebo or controlled comparative local anesthetic blocks are recommended when indications are satisfied with suspicion of sacroiliac joint pain.

Therapeutic Epidural Injections

- The evidence for caudal epidural, interlaminar epidural, and transforaminal epidural injections is good in managing disc herniation or radiculitis; fair for axial or discogenic pain without disc herniation, radiculitis or facet joint pain with caudal and lumbar interlaminar epidural injections, and limited with transforaminal epidural injections; fair for spinal stenosis with caudal, interlaminar, and transforaminal epidural injections; and fair for post surgery syndrome with caudal epidural injections and limited with transforaminal epidural injections.
- The recommendation for epidural injections for disc herniation is that one of the 3 approaches may be used; for spinal stenosis any of the 3 approaches are recommended; whereas for axial or discogenic pain, either lumbar interlaminar or caudal epidural injections are recommended. However for transforaminal the evidence is limited for axial or discogenic pain and post surgery syndrome.

Therapeutic Lumbar Facet Joint Interventions

- The evidence for lumbar conventional radiofrequency neurotomy is good, limited for pulsed radiofrequency neurotomy, fair to good for lumbar facet joint nerve blocks, and limited for intraarticular injections.
- Among the therapeutic facet joint interventions either conventional radiofrequency neurotomy or therapeutic facet joint nerve blocks are recommended after the appropriate diagnosis with controlled diagnostic lumbar facet joint blocks.

Therapeutic Sacroiliac Joint Interventions

- The evidence for sacroiliac cooled radiofrequency neurotomy is fair; limited for intraarticular steroid injections; limited for periarticular injections with steroids or botulinum toxin; and limited for both pulsed radiofrequency and conventional radiofrequency neurotomy.
- Due to emerging evidence for intraarticular injections, they are recommended in select cases with or without periarticular injections. Cooled radiofrequency neurotomy is recommended after appropriate diagnosis confirmed by diagnostic sacroiliac joint injections.



Percutaneous Adhesiolysis

- The evidence for lumbar epidural adhesiolysis in managing chronic low back and leg pain secondary to post lumbar surgery syndrome is fair to good and spinal stenosis is fair.
- Percutaneous adhesiolysis is recommended after failure of conservative management and fluoroscopically directed epidural injections.

Thermal Annular Procedures

- The evidence for intradiscal electrothermal therapy (IDET) and biaculoplasty is limited to fair and is limited for discTRODE.
- IDET and biaculoplasty may be performed in a select group of patients with discogenic pain nonresponsive to conservative modalities including epidural injections.

Percutaneous Disc Decompression

- The evidence for various modes of percutaneous disc decompression is limited to fair for nucleoplasty, and limited for automated percutaneous lumbar discectomy (APLD), percutaneous lumbar disc decompression, and decompressor.
- The Centers for Medicare and Medicaid Services (CMS) has issued a noncoverage decision for nucleoplasty.
- APLD and percutaneous lumbar disc decompression and nucleoplasty are recommended in select cases.

Management of Neck Pain

Cervical Provocation Discography

- The evidence for the diagnostic accuracy of cervical discography is limited.
- Cervical discography is indicated to test the diagnostic hypothesis of discogenic pain of the cervical spine in individuals who have been properly selected and screened to eliminate other sources of cervical pain.

Diagnostic Cervical Facet Joint Nerve Blocks

- The evidence for diagnostic cervical facet joint nerve blocks is good with a criterion standard of 75% or greater relief with placebo or local anesthetic controlled diagnostic blocks.
- Diagnostic cervical facet joint nerve blocks are recommended for the diagnosis of cervical facet joint pain.

Therapeutic Cervical Interlaminar Epidural Injections

- The evidence is good for cervical disc herniation or radiculitis; whereas it is fair for axial or discogenic pain, pain of spinal stenosis, and pain of post cervical surgery syndrome.



- Cervical interlaminar epidural injections are recommended for patients with chronic neck and upper extremity pain secondary to disc herniation, spinal stenosis, and post cervical surgery syndrome.

Therapeutic Cervical Facet Joint Interventions

- The evidence is fair for cervical radiofrequency neurotomy and cervical medial branch blocks, and limited for cervical intraarticular injections.
- Conventional radiofrequency neurotomy or therapeutic facet joint nerve blocks are recommended in managing chronic neck pain after the appropriate diagnosis from controlled diagnostic blocks.

Management of Thoracic Pain

Thoracic Provocation Discography

- The evidence for thoracic discography is limited.
- Thoracic discography is recommended to decide if an intervertebral disc is painful or not in rare circumstances.

Diagnostic Thoracic Facet or Zygapophyseal Joint Nerve Blocks

- The evidence for diagnostic accuracy of thoracic facet joint nerve blocks is good with a criterion standard of at least 75% pain relief with placebo or local anesthetic controlled diagnostic blocks.
- The diagnostic thoracic facet or zygapophyseal joint nerve blocks are recommended in the diagnosis of chronic thoracic pain.

Thoracic Epidural Injections

- The evidence for thoracic epidural injection in treating chronic thoracic pain is fair.
- Thoracic epidural injections are recommended for thoracic discogenic, disc-related, post surgery syndrome, or spinal stenosis pain.

Therapeutic Thoracic Facet or Zygapophyseal Joint Nerve Blocks

- The evidence is fair for therapeutic thoracic facet or zygapophyseal joint nerve blocks, limited for radiofrequency neurotomy, and none for thoracic intraarticular injections.
- Therapeutic thoracic facet or zygapophyseal joint nerve blocks are recommended.
- However, radiofrequency neurotomy and conventional radiofrequency neurotomy may be performed based on emerging evidence.



Implantables

Spinal Cord Stimulation (SCS)

- The evidence for SCS is fair in managing patients with failed back surgery syndrome (FBBS).
- SCS is indicated in chronic low back pain with lower extremity pain secondary to FBBS, after exhausting multiple conservative and interventional modalities.

Implantable Intrathecal Drug Administration Systems

- The evidence for intrathecal infusion systems is limited in managing chronic noncancer pain.
- The recommendations for intrathecal infusion pumps include recalcitrant chronic noncancer pain.

Antithrombotic and Antiplatelet Therapy

- Nonsteroidal anti-inflammatory agents (NSAIDs) including low dose aspirin do not increase the risk of spinal epidural hematoma and are not a contraindication for interventional techniques.
- However, high dose aspirin and combination of multiple drugs should be taken into consideration and may or may not be discontinued based on clinical judgment of individual risk and benefits assessment. In this regard, the simultaneous use of multiple agents that possess anticoagulant properties (e.g., NSAIDs or aspirin along with selective serotonin re-uptake inhibitors [SSRIs], fish oil, etc.) will increase the risk of morbidity and/or mortality.
- Phosphodiesterase inhibitors including dipyridamole (Persantine), Aggrenox (dipyridamole plus aspirin), and cilostazol (Pletal) do not appear to increase the risk of spinal epidural hematoma and are not a contraindication for interventional techniques (evidence – fair). They may or may not be discontinued prior to interventional techniques (evidence – good).
- Platelet aggregation inhibitors including ticlopidine (Ticlid), clopidogrel (Plavix), and prasugrel (Effient) may be continued or discontinued prior to interventional techniques (evidence – fair).
- Based on patient factors and managing cardiologist's opinion, if a decision is made to discontinue, the current recommendations are that they may be discontinued for 7 days with clopidogrel and prasugrel and/or 10 to 15 days with ticlopidine (evidence – fair).
- There is also emerging evidence that discontinuation of 3 days may be effective (evidence – limited).
- If a clinician chooses to discontinue, they may be discontinued for 7 days (evidence – limited).
- Warfarin may be continued or discontinued based on international normalized ratio (INR) achieved during therapy (evidence – good).



- For high risk interventional techniques including interlaminar epidural injections, percutaneous adhesiolysis, disc decompression, sympathetic blocks, and placement of implantables, warfarin must be discontinued for an appropriate period of time and INR of 1.4 or less must be achieved (evidence – good).
- For intermediate risk procedures such as caudal epidural injection, paravertebral interventional techniques, and peripheral joint injections, warfarin must be continued for an appropriate period of time and an INR of 2 or less may be considered (evidence – limited).
- Unfractionated heparin or low-molecular-weight heparin (LMWH) may be discontinued approximately 12 hours prior to providing interventional techniques (evidence - limited).
- Dabigatran (Pradaxa) may be stopped 2 to 4 days for major interventional techniques with high risk of bleeding in patients with creatinine clearance greater than 50 mL per minute. For low risk or paravertebral interventional techniques and caudal, it may be stopped for one day in patients with normal renal function. May be stopped at least 4 to 5 days for those with creatinine less than 50 mL per minute (evidence – limited).
- Rivaroxaban (Xarelto) may be stopped for one day or longer (evidence – limited).

Guideline Ratings

Guideline Issuer and Date	AANS 2014	ASIPP 2013
1. Transparency	B	B
2. Conflict of interest	NR	B
3. Development group	B	B
4. Systematic Review	B	B
5. Supporting evidence	A	B
6. Recommendations	A	B
7. External Review	NR	NR
8. Currency and updates	B	B

See appendix B for full description of the Trustworthy Guideline grading system.

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Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial—high

Observational study—low

Any other evidence—very low

Criteria for increasing or decreasing level

Reductions

Study quality has serious (–1) or very serious (–2) problems

Important inconsistency in evidence (–1)

Directness is somewhat (–1) or seriously (–2) uncertain

Sparse or imprecise data (–1)

Reporting bias highly probable (–1)

Increases

Evidence of association† strong (+1) or very strong (+2)

†Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.



Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania’s Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine’s “Standards for Developing Trustworthy Clinical Practice Guidelines” (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:
Who wrote the initial draft
How the committee voted on or otherwise approved recommendations
Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything,



this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:
 Describe itself as systematic or report search strategies using multiple databases
 Define the scope of the review (including key questions and the applicable population)
 Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.



To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers’ stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst’s discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.