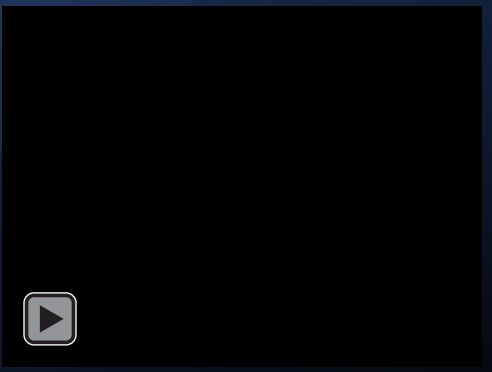
American Society of Interventional Pain Physicians ASIPP 24TH ANNUAL MEETING

Solutions in Epidural Injections: Do They Really Matter?



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BRIGHTER WORLD

- No conflicts of interests to declare

- I have funding from several academic organizations in support of my ongoing studies in acute and chronic pain management but none of them are relevant to this talk

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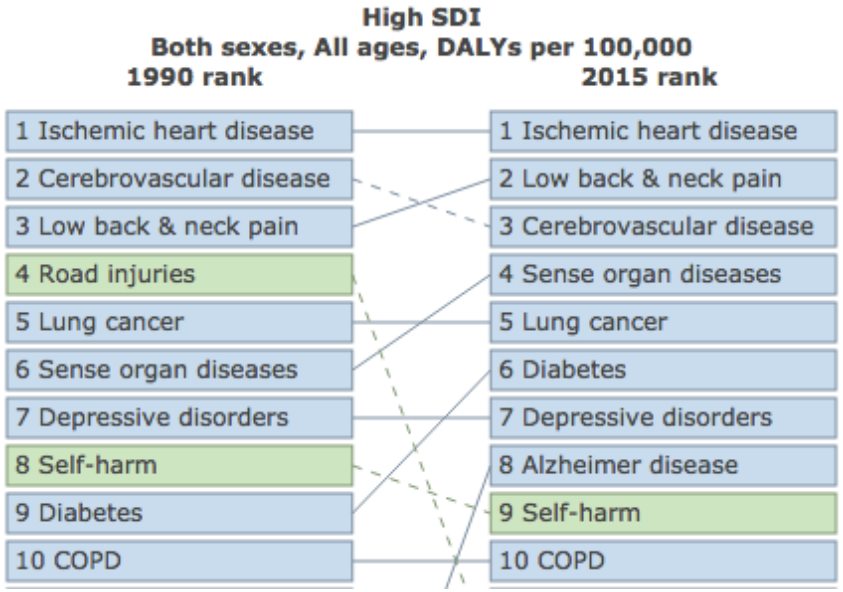
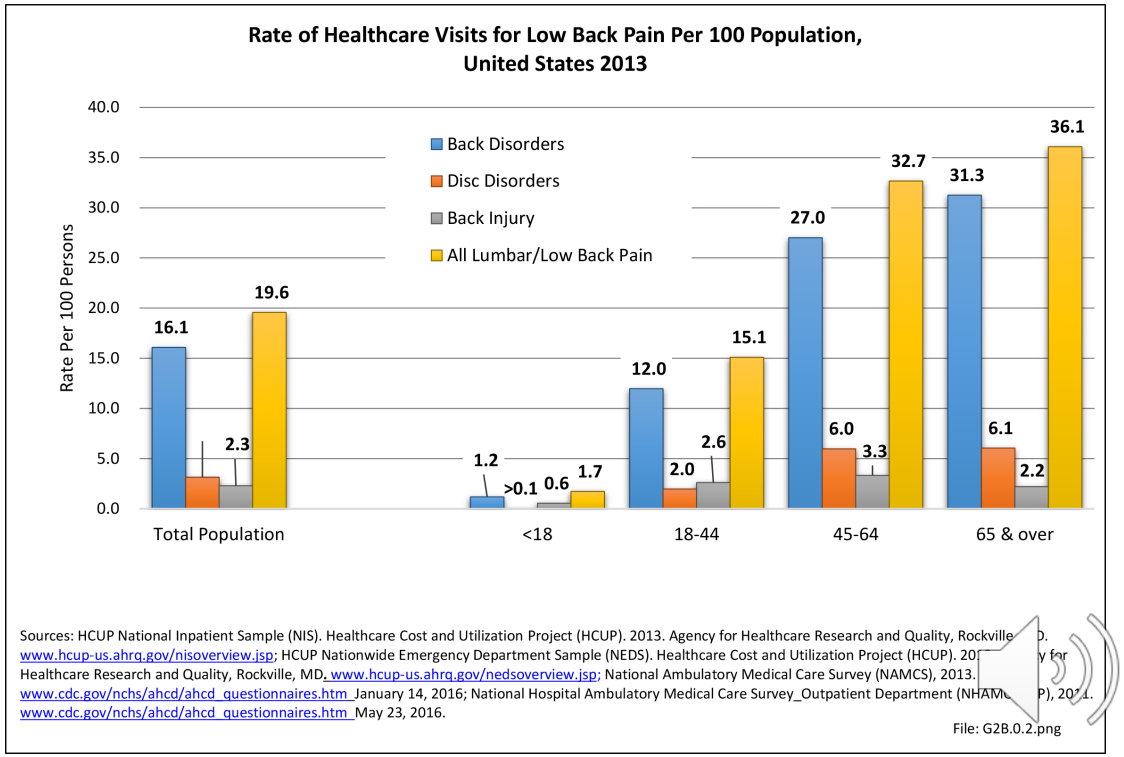
The vexed problems of chronic back and neck pain

- CLBP is the leading cause of years lived with disability
- Affects 70%-80% of the adult population at some point in life
- Among chronic conditions, chronic low back pain is the most prevalent condition contributing to need for rehabilitation
- Age dependent and in most the exact cause cannot be determined.



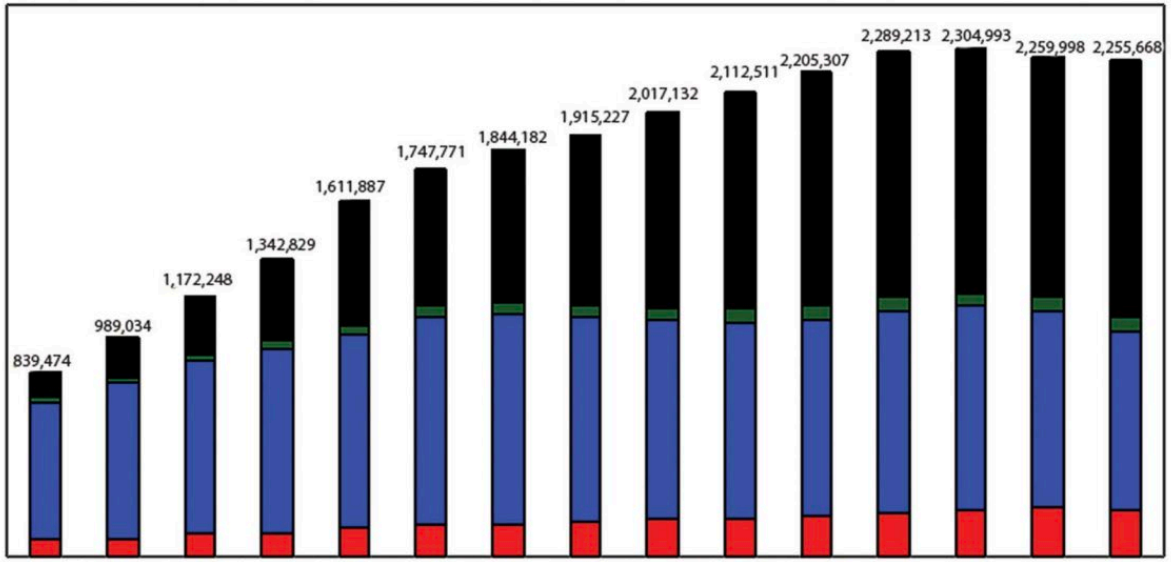


The State of US Health, 1990-2010: Burden of Diseases, Injuries, and Risk Factors. JAMA. 2013;310(6):591-606.

Cieza A, et al. Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2021 Dec 19;396(10267):2006-2017.

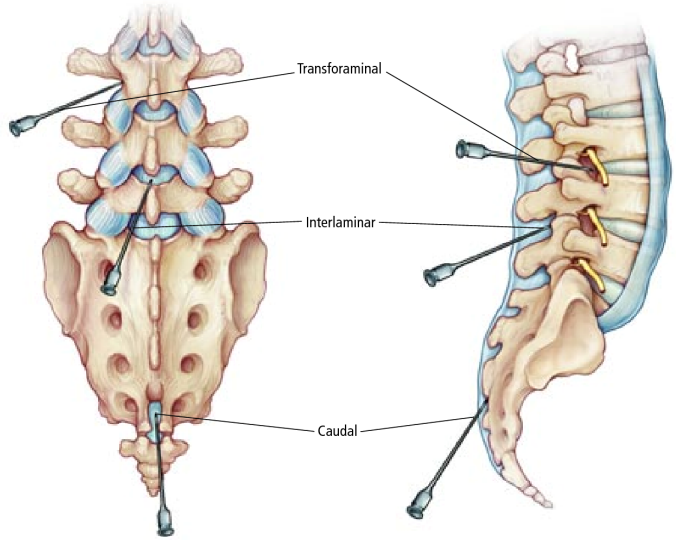
Epidural steroid injections are recognized treatments

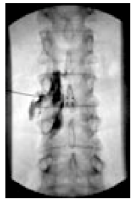
- Have been practiced for more than 80 years
- May not work in all patients-patient selection crucial
- Has gone through refinements in technique and safety
- Mostly safe when performed appropriately



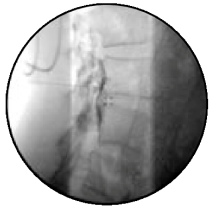
Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
C/T Interlaminar Epidurals (62310)	9.0%	8.5%	8.5%	8.2%	8.1%	8.1%	8.0%	8.2%	8.2%	8.3%	8.4%	8.7%	9.3%	9.6%	9.3%
L/S Interlaminar Epidurals (62311)	73.7%	71.1%	67.1%	62.5%	54.5%	54.1%	51.3%	48.4%	44.9%	42.0%	40.3%	39.9%	40.1%	39.9%	36.2%
C/T Transforaminal Epidurals (64479, 80)	2.7%	2.4%	2.5%	2.8%	2.7%	2.8%	2.9%	2.7%	2.8%	3.1%	3.2%	2.9%	2.5%	2.4%	2.6%
L/S Transforaminal Epidurals(64483, 84)	14.6%	18.1%	21.9%	26.6%	34.7%	35.0%	37.8%	40.8%	44.1%	46.6%	48.2%	48.5%	48.1%	48.1%	51.9%

Figure 1 Frequency of usage of epidural injections by procedures from 2000 to 2014, in Medicare recipients.





For any epidural injection, fluoroscopic guidance is recommended. Here, transforaminal epidural dye injection confirms proper placement.
Note, with correct placement, the spread of the dye to the epidural space and the recess and sleeve of the nerve route.



Manchikanti L, Pampati V, Hirsch JA. Retrospective cohort study of usage patterns of epidural injections for spinal pain in the US fee-for-service Medicare population from 2000 to 2014. BMJ Open. 2016 Dec 13;6(12):e013042.

Are We Overusing Interventional Treatments?

- As such we are over treating low back pain on a large scale
- Widening gap between utilization and societal benefit
- There is some evidence that interventional treatments are being overused
- Questions:
  - What injections? Why? How many? What is the benefit?

What about other non interventional treatments?

Although a similar trend and perception exists for procedures in other specialities, it is being particularly highlighted within interventional pain.

PAIN

Neuropathic pain clinical trials: factors associated with decreases in estimated drug efficacy

Nanna B. Finnerup[a,b,*], Simon Haroutounian[c], Ralf Baron[d], Robert H. Dworkin[e,f,g], Ian Gilron[h], Maija Haanpaa[i], Troels S. Jensen[a,b], Peter R. Kamerman[j,k], Ewan McNicol[l,m], Andrew Moore[n], Srinivasa N. Raja[o], Niels T. Andersen[p], Emily S. Sena[q], Blair H. Smith[r], Andrew S.C. Rice[s], Nadine Attal[t]

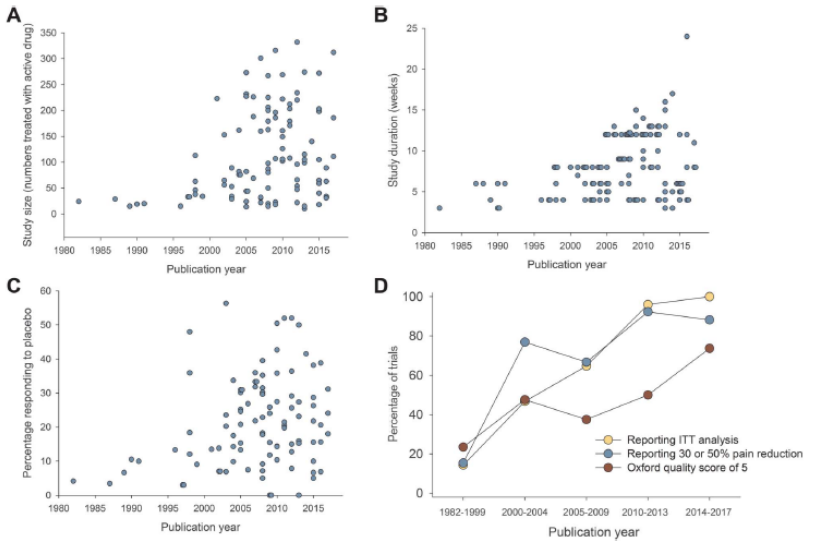


Figure 3. Relation between publication year and (A) study size (number of patients treated with active drug in individual studies), (B) study duration, (C) placebo response, and (D) percentage of studies reporting intention-to-treat (ITT) analysis, 30% or 50% pain reduction for outcome NNT calculation, and with a high-quality score (Oxford scale). Publication year for unpublished studies was arbitrarily set to 1 year after the results were posted. NNT, number needed to treat.

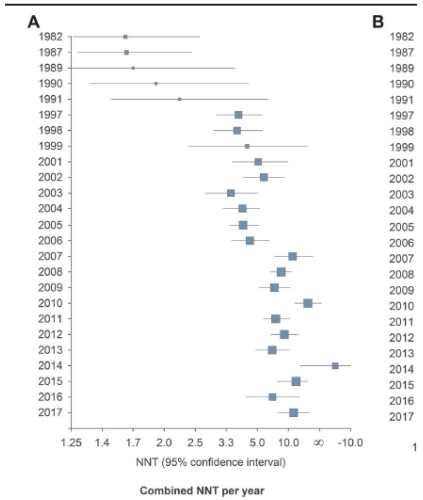


Figure 2. Change in study outcome over time. (A) Combined NNT (random effect) per year. (B dichotomous data for NNT calculation. NNT, number needed to treat.

Table 1| Success and failure of drug treatment for acute and chronic painful conditions

Drug and dose (mg)	% with outcome		Maximum possible success (100–placebo)	Success (active–placebo)	Failure (maximum–active)	Treatment specific effects (% of maximum)	
	Active	Placebo				Success	Failure
Acute pain (single dose postoperative)[w1]; outcome: ≥50% maximum pain relief over 6 hours							
Paracetamol 500+ibuprofen 200	74	10	90	64	26	71	29
Paracetamol 1000+oxycodone 10	68	13	87	55	32	63	37
Etoricoxib 120	64	11	89	53	36	60	40
Ibuprofen 400+codeine 25.6-60	64	18	82	46	36	56	44
Paracetamol 1000+codeine 60	53	7	93	46	47	49	51
Diclofenac 50	57	19	81	38	43	47	53
Ibuprofen 400	54	14	86	40	46	47	53
Naproxen 500/550	52	15	85	37	48	44	56
Paracetamol 1000	46	18	82	28	54	34	66
Aspirin 1000	43	16	84	27	57	32	68
Acute migraine headache (single dose)[w2-w5]; outcome: no worse than mild pain at 2 hours							
Zolmitriptan 10	68	34	66	34	32	52	48
Rizatriptan 2.5	61	29	71	32	39	45	55
Ibuprofen 400	57	25	75	32	43	43	57
Sumatriptan 100	61	32	68	29	39	43	57
Paracetamol 1000	56	36	64	20	44	31	69
Aspirin 1000	52	32	68	20	48	29	71
Osteoarthritis (12 weeks' treatment)[6 w6-w8]; outcome: ≥50% pain intensity reduction							
Tanezumab 10	51	31	69	20	49	29	71
Etoricoxib 60	44	23	77	21	56	27	73
Naproxen 1000	44	23	77	21	56	27	73
Celecoxib 200	39	22	78	17	61	22	78
Topical diclofenac 1.5%	60	50	50	10	40	20	80
Ibuprofen 2400	39	27	73	12	61	16	84
Duloxetine 60/100	40	30	70	10	60	14	86
Ankylosing spondylitis (6 weeks' treatment)[w9]; ≥50% reduction in BASDI							
Etoricoxib 120	50	14	86	36	50	42	58
Etoricoxib 90	46	14	86	32	54	37	63
Naproxen 1000	38	14	86	24	62	28	72
Chronic low back pain (12 weeks' treatment)[5 w6]; outcome ≥50% pain intensity reduction							
Etoricoxib 60	47	35	65	12	53	18	82
Etoricoxib 90	47	35	65	12	53	18	82
Duloxetine 60/100	39	30	70	9	61	13	87
Painful diabetic neuropathy (12 weeks' treatment)[w10-w12]; outcome ≥50% pain intensity reduction							
Duloxetine 60/100	48	26	74	22	52	30	70
Pregabalin 600*	46	30	70	16	54	23	77
Gabapentin ≥1200*	40	23	77	17	60	22	78
Lacosamide 400*	35	25	75	10	65	13	87
Pregabalin 300*	38	29	71	9	62	13	87
Postherpetic neuralgia (12 weeks' treatment) [w10 w11 w13]; outcome ≥50% pain intensity reduction or PGIC							
Pregabalin 600*	39	14	86	25	61	29	71
Topical capsaicin 8%	39	25	75	14	61	19	81
Pregabalin 300*	30	11	89	19	70	21	79

TEK IMAGE/SPL

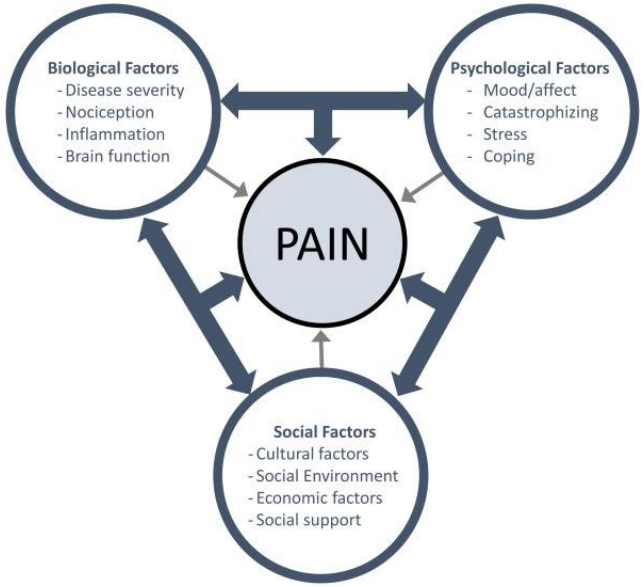
bmj.com ▶Research: Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain (*BMJ* 2008;336:199)

Expect analgesic failure; pursue analgesic success

Most analgesic drugs work well but in only a small percentage of people. We need to move away from a focus on average response and seek out what works for each patient, argue **Andrew Moore and colleagues**

Viewing our practice through our lens versus other lenses

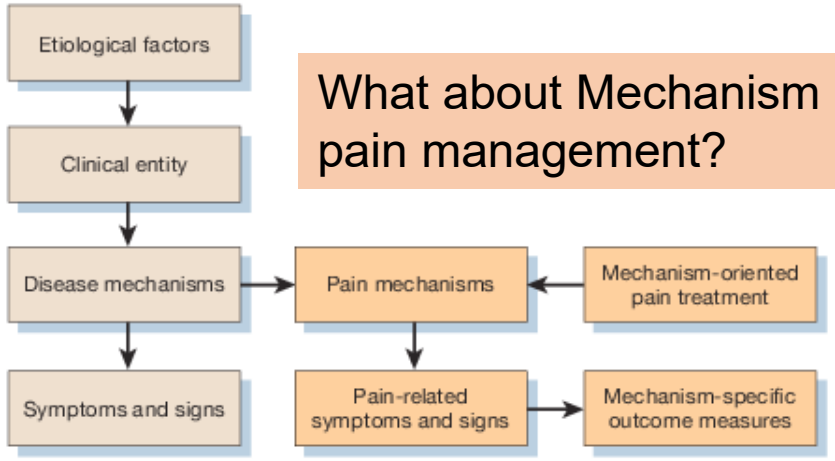
BioPsychoSocial Model of Chronic Pain



Are We Lemmings Going Off a Cliff? The Case Against the "Interventional" Pain Medicine Label

Interventional pain medicine: retreat from the biopsychosocial model of pain

Randy S Roth, PhD,[1,2] Michael E Geisser, PhD,[1] David A Williams, PhD[3,4]



What about Mechanism based pain management?

- Although PAIN is an experience, Biological factors underlie pain conditions.
- Pain interventions are mechanism based (assumed).

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Toward a Mechanism-Based Approach to Pain Diagnosis

Daniel Vardeh,* Richard J. Mannion,† and Clifford J. Woolf‡

Table 1. Pain States

Pain State	*Clinical Diagnostic Criteria*
Nociceptive	Evidence of noxious (mechanical) insult Symptoms: pain localized to area of stimulus/joint damage Signs: imaging—mechanical pathology/altered joint architecture such that normal movements will likely produce excessive forces sufficient to activate nociceptors
Inflammatory	Evidence of inflammation 1. Sterile 2. Infectious Symptoms: redness, warmth, swelling of affected area Signs: imaging (MRI, SPECT) signs of inflammatory changes, detection of pathogens/response to antibiotics
Neuropathic	Evidence of sensory nerve damage Symptoms: burning, tingling or shock-like, spontaneous pain; paresthesias or dysthesias Signs: decreased pinprick* or vibration sense, and straight leg raise,* mechanical and cold allodynia
Dysfunctional/centralized	Pain in the absence of detectable pathology No identifiable noxious stimulus, inflammation or neural damage; evidence of increased amplification or reduced inhibition.

Abbreviation: SPECT, single-photon emission computed tomography.
NOTE. The 4 categories of nociceptive, inflammatory, neuropathic, and dysfunctional/centralized pain, and their clinical presentation. Note that none of the diagnostic criteria are highly specific, and there is no gold standard for diagnosing these conditions. Pain states are not mutually exclusive, and coexistence of more than 1 is probably the rule rather than the exception.
*Most specific

Table 2. General Pain Mechanisms

			Nonspecific Treatment Examples			
General Pain Mechanism	*Clinical Diagnostic Criteria*	*Specific Treatment Examples*	*GABA-Pentinoid*	*AED*	*AD*	*Opioid*
Nociceptive transduction	Proportionate pain in response to identifiable noxious stimulus	Removing mechanical stimulus (eg, decompression of nerve)				X
Peripheral Sensitization	Primary hyperalgesia due to decreased transduction threshold of nociceptor terminal	Anti-inflammatory (eg, NSAID, coxibs); immunosuppressant		X	Possibly	X
Ectopic activity	Spontaneous pain in the absence of obvious trigger; relieved by local nerve block	Na_v channel blockers	X	X		X
Central sensitization	Secondary hyperalgesia; temporal summation; allodynia	NMDA antagonists (eg, ketamine)	X	Some (eg, VA, TPM)	X	X
Central disinhibition	Secondary hyperalgesia; allodynia	GABA-A subunit agonists; dual amine uptake inhibitors	X	See above	X	X

Abbreviations: AED, antiepileptic dugs; AD, antidepressants; NSAID, nonsteroidal anti-inflammatory drug; coxib, selective COX-2 inhibitor; VA, valproic acid; TPM, topiramate.
NOTE. More than 1 mechanisms may be at play in any given pain syndrome and no mechanism is specific to a particular pain state. It is currently impossible to distinguish clinically between central sensitization and disinhibition. Several of the proposed specific treatment examples are not in clinical use (eg, Nav-specific or GABA A receptor-specific antagonists). Note the low specificity of currently used medications for a single mechanism.

Pathologies that can lead to axial and extremity pain

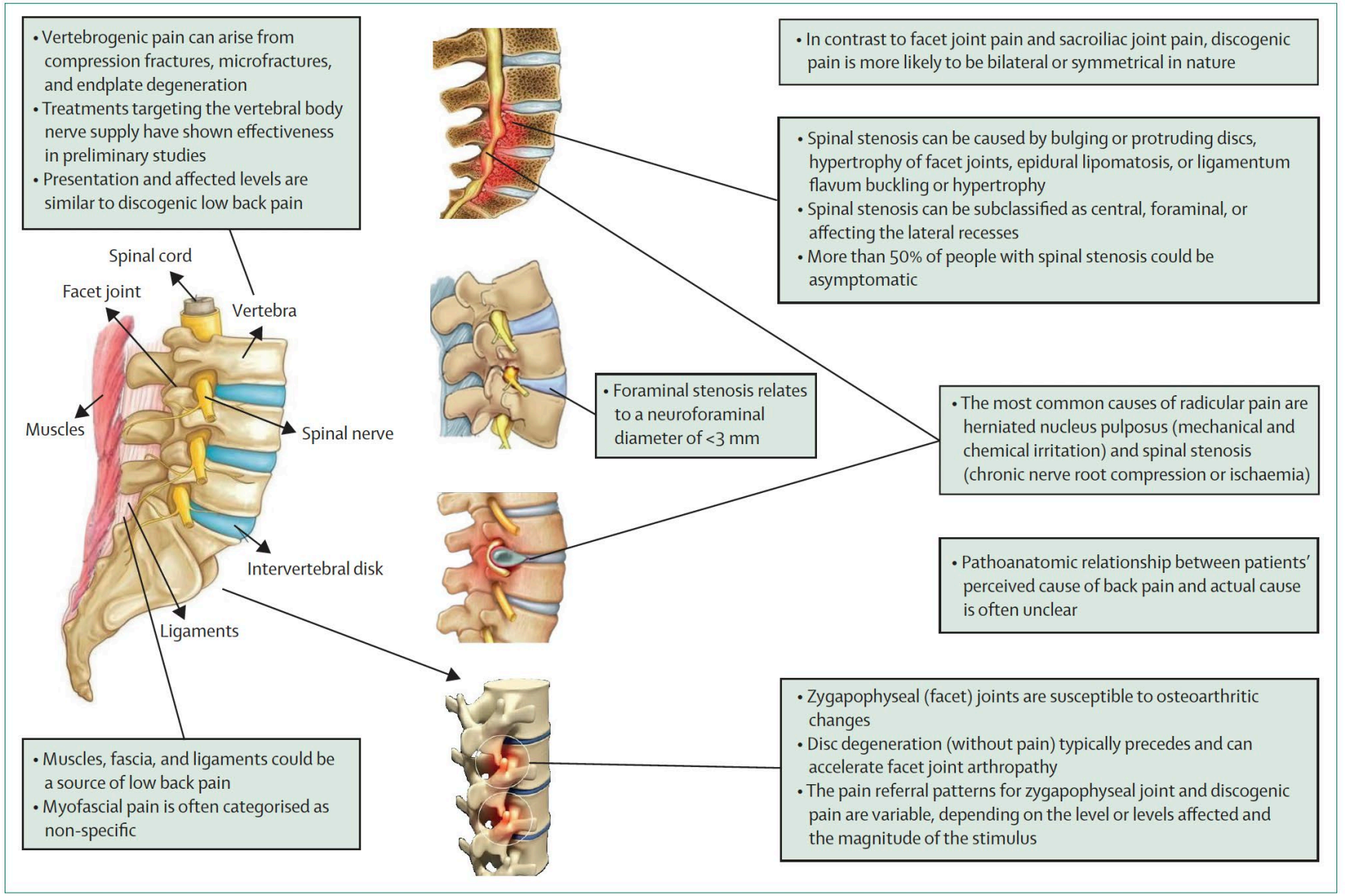


Figure 1: **Sagittal view of lumbar spine showing potential pain generators**

Identifying the Cause in a clinical context for ESI

Reliance on Symptom-based paradigms to indirectly inform Mechanisms

Nociceptive
- Inflammatory-Immune mechanisms

Neuropathic

Nociplastic
- Central sensitization

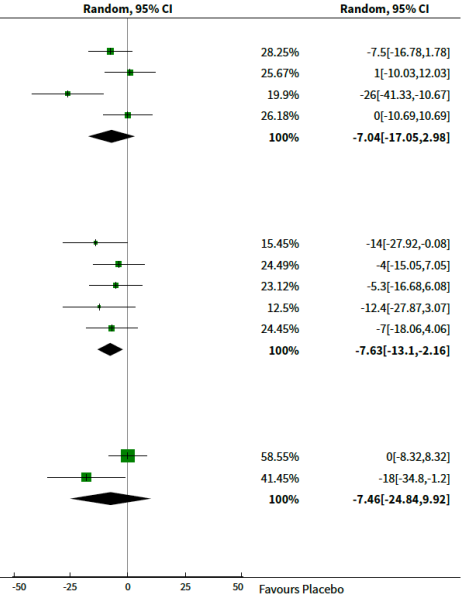
- Identifying the exact (predominant) CAUSE is not possible is many or most chronic pain patients
- Clinical features along with imaging findings and neuro-diagnostics as appropriate.

Clinical picture (category)
- Leg pain-radicular
- Leg pain>Back pain-not radicular
- Back pain>Leg pain or Mostly Back pain
  - Generally, most treatments fail because of non-specific nature

Structural (predominant) diagnosis
- Disc herniation
- Foraminal stenosis
- Epidural scarring with surgery
- Spinal stenosis

Analysis 2.2. Comparison 2 Epidural corticosteroid injections versus placebo - subgroup and sensitivity analyses, Outcome 2 Leg pain short-term - type of placebo.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.2.1 Epidural Anesthesic							
Tafazal 2009	65	-26.1 (26.6)	59	-18.6 (26.1)		28.25%	-7.5[-16.78,1.78]
Ng 2005	43	-21 (26.6)	43	-22 (25.6)		25.67%	1[-10.03,12.03]
Ghahreman 2010	28	41 (30)	27	67 (28)		19.9%	-26[-41.33,-10.67]
Iversen 2011	37	37.1 (24.2)	40	37.1 (23.6)		26.18%	0[-10.69,10.69]
Subtotal ***	**173**		**169**			**100%**	**-7.04[-17.05,2.98]**
Heterogeneity: Tau²=69.93; Chi²=9.39, df=3(P=0.02); I²=68.04%							
Test for overall effect: Z=1.38(P=0.17)							
2.2.2 Epidural Saline							
Ghahreman 2010	28	41 (30)	37	55 (26)		15.45%	-14[-27.92,-0.08]
Carette 1997	77	-26.5 (36)	79	-22.5 (34.4)		24.49%	-4[-15.05,7.05]
Iversen 2011	37	37.1 (24.2)	35	42.4 (25)		23.12%	-5.3[-16.68,6.08]
Cohen 2012	28	25.4 (31.5)	30	37.8 (28.4)		12.5%	-12.4[-27.87,3.07]
Karppinen 2001	80	36.9 (35.7)	80	43.9 (35.7)		24.45%	-7[-18.06,4.06]
Subtotal ***	**250**		**261**			**100%**	**-7.63[-13.1,-2.16]**
Heterogeneity: Tau²=0; Chi²=1.76, df=4(P=0.78); I²=0%							
Test for overall effect: Z=2.73(P=0.01)							
2.2.3 Interspinous							
Arden 2005	120	-15 (32)	108	-15 (32)		58.55%	0[-8.32,8.32]
Ghahreman 2010	28	41 (30)	28	59 (34)		41.45%	-18[-34.8,-1.2]
Subtotal ***	**148**		**136**			**100%**	**-7.46[-24.84,9.92]**
Heterogeneity: Tau²=116.28; Chi²=3.54, df=1(P=0.06); I²=71.78%							
Test for overall effect: Z=0.84(P=0.4)							
Test for subgroup differences: Chi²=0.01, df=1 (P=0.99), I²=0%							

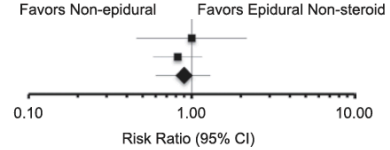


- Outcomes of Epidural Injections have been variable
- How do we explain such variability in Effect?
  - Success rate?
  - Duration?

A Direct comparison of epidural non-steroid to non-epidural injections

Study	Epidural Non-steroid Injection Events	Epidural Non-steroid Injection Total	Non-epidural Injection Events	Non-epidural Injection Total	Weight, %	Risk Ratio (95% CI)	Risk of Bias	Technical Quality Score
Ghahreman 2010[81]	11	64	10	58	41.9	1.00 (0.46, 2.17)	1	8
Klenerman 1984[83]	22	32	10	12	58.1	0.82 (0.58, 1.16)	0	4
Total (95% CI)	**33**	**96**	**20**	**70**	**100.0**	**0.90 (0.60, 1.33)**		

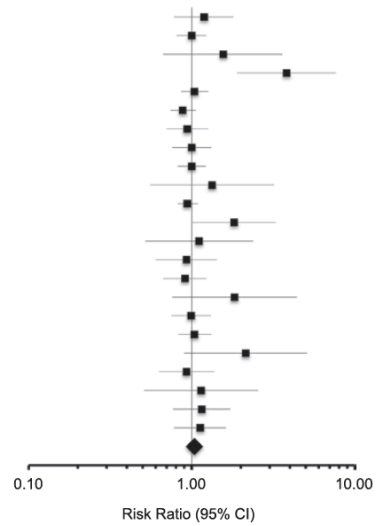
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



B Direct comparison of epidural steroid to epidural non-steroid injections

Study	Epidural Steroid Injection Events	Epidural Steroid Injection Total	Epidural Non-steroid Injection Events	Epidural Non-steroid Injection Total	Weight, %	Risk Ratio (95% CI)	Risk of Bias	Technical Quality Score
Cohen 2012[37]	32	54	15	30	3.2	1.19 (0.78, 1.80)	1	11
Manchikanti 2008[85]	34	42	34	42	8.0	1.00 (0.81, 1.23)	1	9
Cohen 2009[78]	14	18	3	6	0.9	1.56 (0.67, 3.59)	1	8
Ghahreman 2010[81]	15	28	9	64	1.3	3.81 (1.90, 7.65)	1	8
Manchikanti 2012[89]	48	60	46	60	8.8	1.04 (0.86, 1.26)	1	8
Manchikanti 2012[94]	45	60	51	60	9.1	0.88 (0.74, 1.06)	1	8
Manchikanti 2012[90]	31	50	33	50	5.4	0.94 (0.70, 1.26)	1	7
Manchikanti 2012[91]	23	30	23	30	5.7	1.00 (0.76, 1.32)	1	7
Manchikanti 2012[92]	26	30	26	30	8.4	1.00 (0.82, 1.22)	1	7
Snoek 1977[103]	9	27	6	24	0.9	1.33 (0.56, 3.20)	1	7
Manchikanti 2012[93]	50	60	53	60	10.7	0.94 (0.82, 1.09)	1	6
Nam & Park 2011[68]	13	17	8	19	1.8	1.82 (1.01, 3.27)	1	6
Cuckler 1985[79]	12	42	8	31	1.1	1.11 (0.52, 2.38)	1	5
Manchikanti 2008[86]	13	20	14	20	3.1	0.93 (0.60, 1.43)	1	5
Manchikanti 2012[88]	20	28	22	28	5.1	0.91 (0.67, 1.23)	1	5
Bush 1991[77]	8	12	4	11	0.9	1.83 (0.76, 4.41)	1	4
Kraemer 1997[84] (2)	19	24	20	25	5.6	0.99 (0.75, 1.31)	1	4
Manchikanti 2012[95]	48	70	46	70	7.2	1.04 (0.83, 1.32)	1	4
Breivik 1976[76]	9	16	5	19	0.9	2.14 (0.90, 5.09)	1	1
Rocco 1989[100]	12	15	6	7	3.5	0.93 (0.63, 1.38)	1	0
Anderberg 2007[52]	8	20	7	20	1.0	1.14 (0.51, 2.55)	0	4
Klenerman 1984[83]	15	19	11	16	3.4	1.15 (0.77, 1.72)	0	4
Beliveau 1971[75]	18	24	16	24	4.0	1.13 (0.78, 1.62)	0	1
Total (95% CI)	**522**	**766**	**466**	**746**	**100.0**	**1.04 (0.96, 1.13)**		

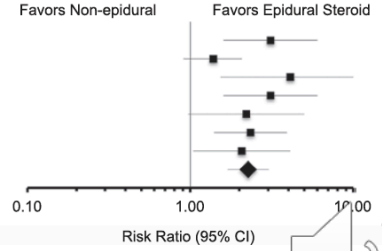
Heterogeneity: Tau² = 0.01; Chi² = 32.75, df = 22 (P = 0.07); I² = 33%
Test for overall effect: Z = 0.93 (P = 0.35)



C Direct comparison of epidural steroid to non-epidural injections

Study	Epidural Steroid Injection Events	Epidural Steroid Injection Total	Non-epidural Injection Events	Non-epidural Injection Total	Weight, %	Risk Ratio (95% CI)	Risk of Bias	Technical Quality Score
Ghahreman 2010[81]	15	28	10	58	13.6	3.11 (1.60, 6.02)	1	8
Price 2005[98]	40	113	27	105	24.2	1.38 (0.91, 2.07)	1	7
Dilke 1973[80]	16	35	4	36	7.2	4.11 (1.53, 11.09)	1	5
Mathews 1987[96]	15	28	10	58	13.6	3.11 (1.60, 6.02)	1	4
Hesla 1979[66]	12	15	4	11	9.8	2.20 (0.97, 5.00)	1	0
Kraemer 1997[84] (1)	53	87	12	46	18.9	2.34 (1.40, 3.91)	0	5
Stav 1993[104]	19	26	6	17	12.9	2.07 (1.04, 4.11)	0	3
Total (95% CI)	**170**	**332**	**73**	**331**	**100.0**	**2.26 (1.70, 3.02)**		

Heterogeneity: Tau² = 0.01; Chi² = 12.24, df = 6 (P = 0.06); I² = 51%
Test for overall effect: Z = 5.55 (P < 0.001)



ELSEVIER

CrossMark

The Spine Journal 14 (2014) 2500–2508

THE SPINE JOURNAL

Review Article

Predicting epidural steroid injections with laboratory markers and imaging techniques

Benoy V. Benny, MD[a], Monika Yogesh Patel, MD[b,*]

RESULTS: For patients with radicular pain, there is insufficient evidence to either support or refute the prognostic accuracy of spinal stenosis seen on imaging in determining epidural steroid outcomes (two Class IV studies). It is possible that low-grade nerve root compression as seen on lumbar magnetic resonance images does predict short-term reduction in pain after transforaminal ESI (Class II and III studies). For patients with lumbar radicular pain, there is both insufficient and conflicting evidence that either supports or refutes prognostic accuracy of high-sensitivity C-reactive protein in determining epidural steroid outcomes (two Class III studies). It is probable that interferon gamma (IFN-γ) more than 10 pg/mL from epidural lavage is predictive of short-term pain reduction after lumbar ESI (single Class I study). There is insufficient evidence that either supports or refutes prognostic accuracy of fibronectin-aggrecan complex from epidural lavage to determine epidural steroid outcome (single Class IV study).

ASIAN SPINE JOURNAL

Clinical Study

Asian Spine J 2021;15(6):753-760 • https://doi.org/10.31616/asj.2020.0295

Check for updates

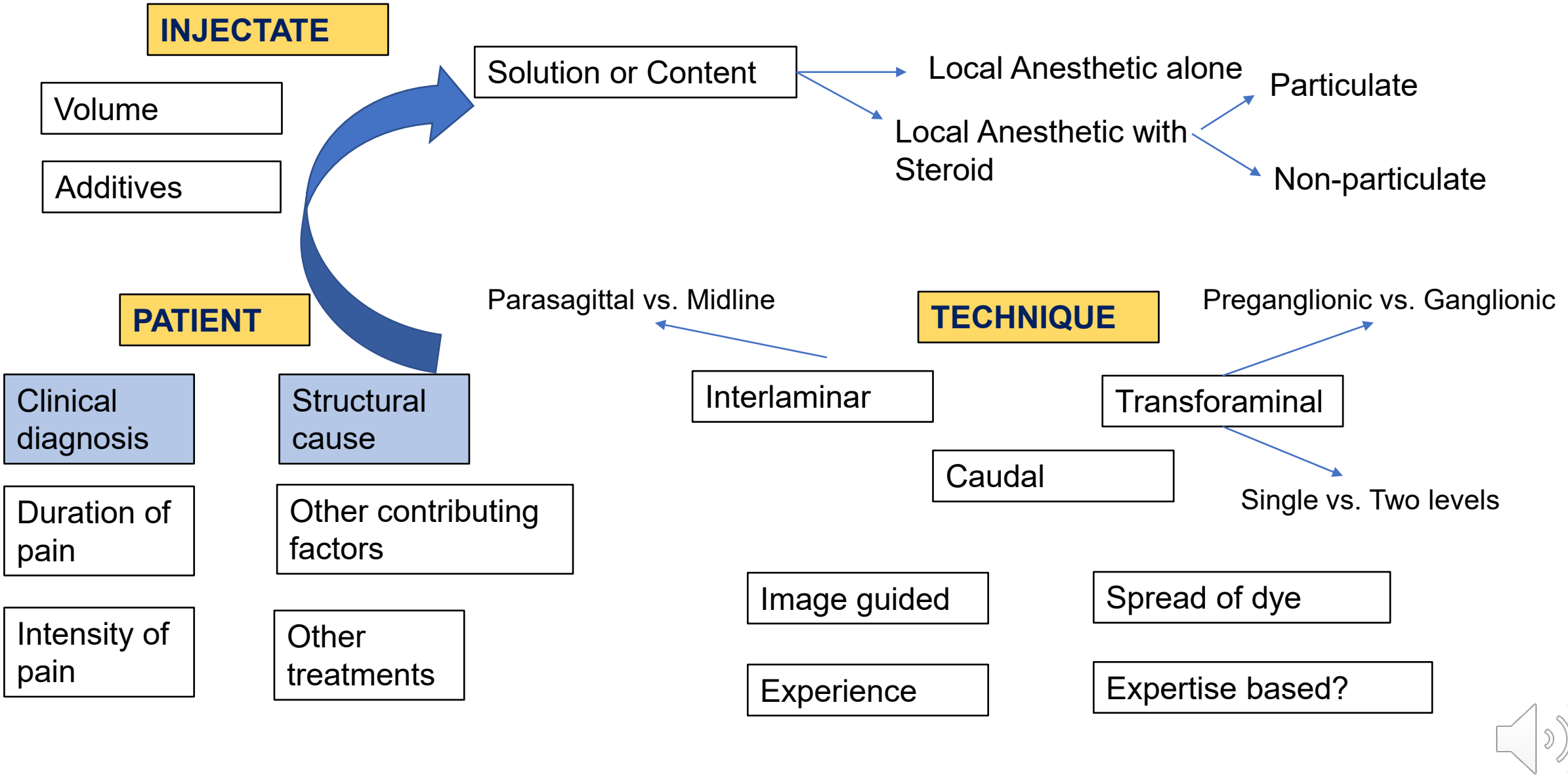
Can High-Sensitivity C-Reactive Protein Levels Predict Functional Outcome Following Epidural Steroid Injection in Patients with Lumbar Disc Disease?

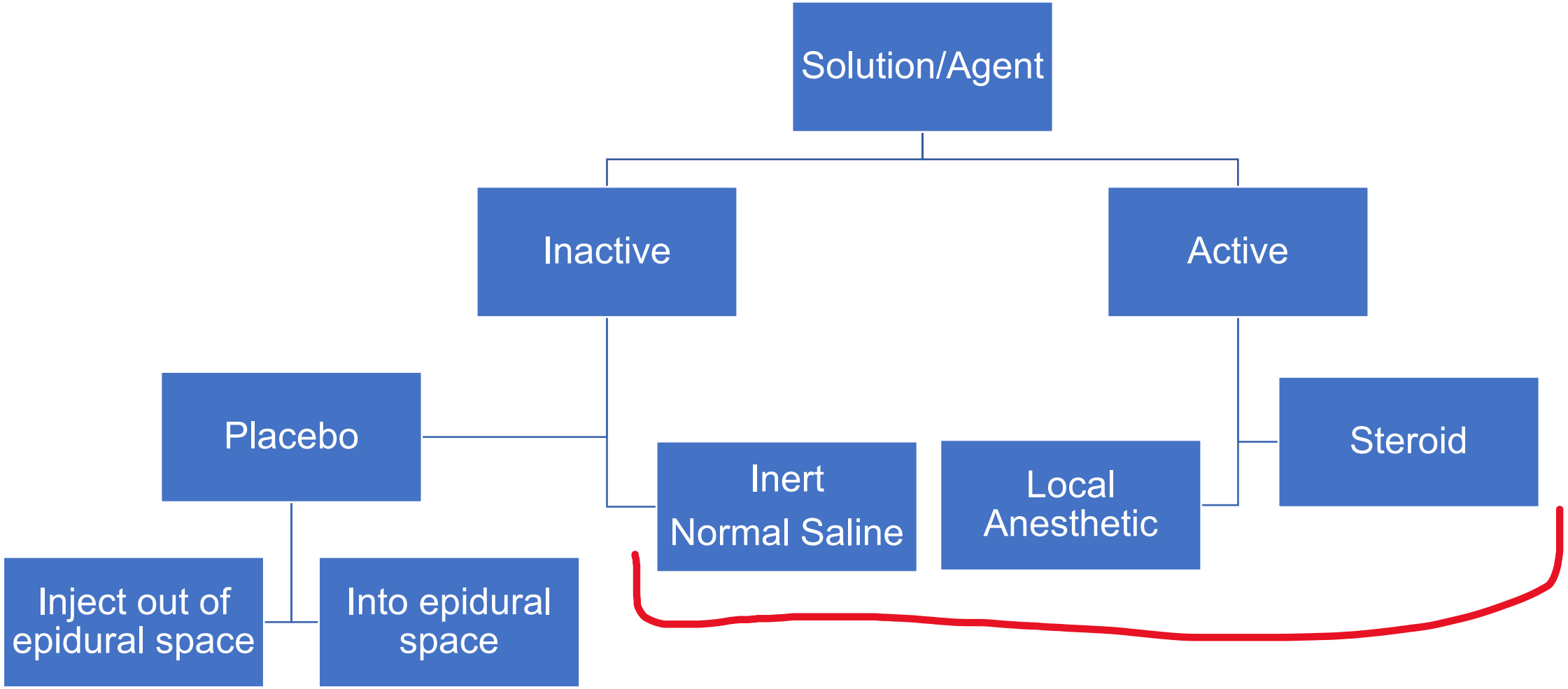
Rajesh Gopireddy[1], Karthick Rangasamy[1], Vijay G. Goni[1], Pulak Vatsya[2], Prateek Behera[3], Yatindra K. Batra[4], Chetana Vaishnavi[5]

Results: Out of 77 patients, 52 had acute and 25 had chronic low back pain. Thirty-six patients with acute pain obtained significant improvement, while 16 had an insignificant response to the ESI. None of the chronic cases had a significant response. The mean baseline hs-CRP (mg/L) among the study group (29.83±10.43) was significantly higher than for the controls (10.26±2.783). The baseline hs-CRP among acute cases, where post ESI MODY score at 2 months had significant reduction, was 32.19±5.126, and those with insignificant reduction was 18.13±7.949 (p<0.001).

Conclusions: Baseline hs-CRP levels can be used to prognosticate the outcome following ESI in patients with acute lumbar disc disease, with radicular pain refractory to physiotherapy and analgesics.

Variable outcomes and Possible determinants of success in epidural injections



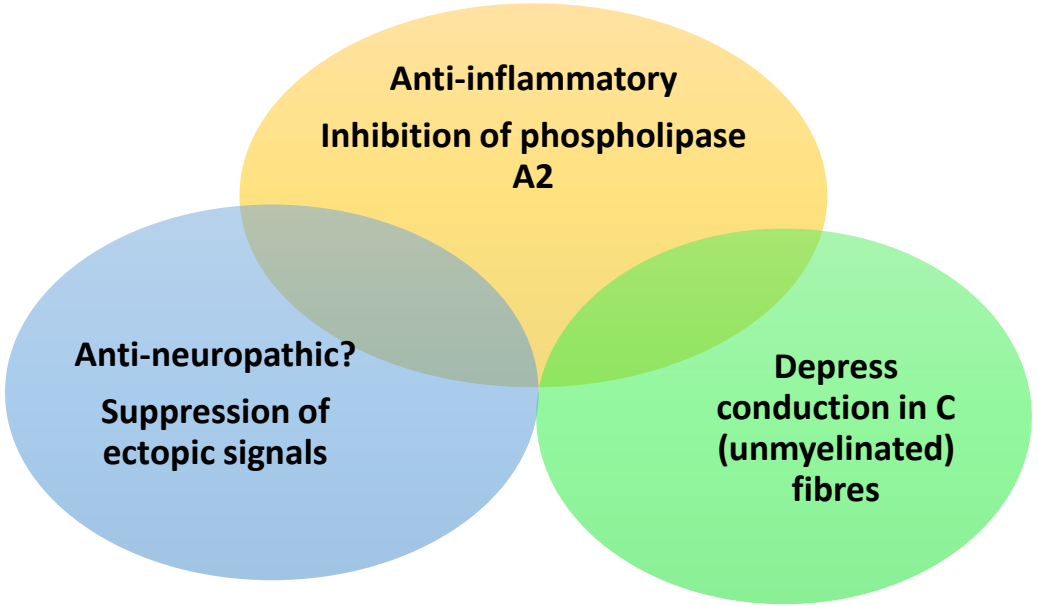


ACTIVE AGENT:

1. Biological validity (effect) and
2. Clinical response (response)

Postulated Mechanisms of Epidural Injections

- Anti-inflammatory
- Immune
- LA effects on neural blockade and decreased neural sensitization
- Washout effect and osmotic dilution
- Hydrostatic effect-breakdown of fibrosis or neural compression



WHAT DO STEROIDS OFFER AS OUTCOMES?

- Increased success
- Prolonged duration
- Better pain relief
- Side effects?

Evans W. Intrasacral epidural injection in the treatment of sciatica. The Lancet. 1930;216(5597):1225–9.

production of new drugs and for their experimental and clinical trial. We in this country prefer not to be regimented in that way. Our genius appears to run more in the direction of individualistic effort. Yet it might be possible for the members of the different departments of our medical school to coöperate in work which may not only advance the reputation of this ancient university, but also help in the solution of the fundamental medical problem, the prevention and cure of disease.

INTRASACRAL EPIDURAL INJECTION IN THE TREATMENT OF SCIATICA.

By William Evans, M.D., M.R.C.P. Lond.,
medical first assistant and registrar, london hospital.

Although it is the purpose of this paper to describe the results obtained in the treatment of sciatica by intrasacral epidural injection, it is necessary at the outset to examine briefly the theories that have been advanced by different writers to explain the nature and mechanism of production of sciatic pain. This preliminary review is introduced in order to emphasise the difficulty experienced in allocating the series of cases discussed in this paper to any group or subdivision other than that of *primary* or *idiopathic* sciatica, and also to determine how far one is able to regard the response to this form of treatment as throwing some light on the ætiology of sciatica.

and that the remaining 15 were examples of sciatic neuritis.

In the experience of these writers, therefore, secondary or symptomatic sciatica occurs with greater frequency than the primary or idiopathic form. The results obtained from the present investigation do not lend support to this view, but indicate that when a careful survey has been made of the history of the illness, the clinical examination of the patient, and the radiological investigation of the lumbosacral region, and when hypothesis and mere speculation as to the probable cause of the neuralgia have been excluded, the majority of cases are instances of primary or idiopathic sciatica. The fact that the true nature of the lesion in these cases has remained obscure or cryptic warrants their inclusion in this group.

The Cases and their Treatment.

In accordance with the definition outlined in the previous paragraph, the 40 cases discussed here have been regarded as instances of primary or idiopathic sciatica. There were 21 males and 19 females. The age varied from 20 to 66, the average age being 40 years. The sciatic pain in all cases had been sudden in its onset, and had continued without intermission for periods varying from 5 days to 18 months; the average duration of symptoms was five and a half months. In all the 40 cases the neuralgia was confined to one side, and occurred in the right limb in 25 and in the left in 15. The pain, which was most severe in the thigh, radiated in the distribution of the sciatic nerve. There was no history of strain or injury, and no clinical evidence of disease in the lumbosacral part of the spine, and radiological examination in 15 cases failed to reveal any pathological changes in

Mixter WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. N Engl J Med 1934; 211: 210 – 5

Hench PS, Kendall EC, Slocumb CH. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis. Proc Staff Meetings Mayo Clin 1949; 24: 181 – 97

Lindahl O, Rexed B. Histological changes in spinal nerve roots of operated cases of sciatica. Acta Orthop Scand 1951; 20: 215 – 25

Lievre JA, Bloch-Michel H, Pean G. L' hydrocortisone en injection locale. Revue du Rhumatisme et des Maladies Osteo-articulares 1953; 20: 310 – 1 67

'The history of sciatica is, it must be confessed, the record of pathological ignorance and therapeutic failure'. Fuller. Rheumatism, Rheumatic Gout and Sciatica (1852).

Can Local Anesthetic solutions be used for therapy?

- LA solutions have been historically used as treatment for sciatica
- LA are used for diagnostic injections as they block nerves
- There is biological plausibility that LA solutions can lead to long term pain relief

ripheral stimuli in lower back pain patients.[58,61] How then can the temporary numbing of a localized peripheral site, with or without the addition of steroids, result in long-lasting and profound changes in pain perception? One possibility is that a stable "pathological pain network" is established in the CNS of chronic pain patients and this is dependent on continuous input from peripheral sites to maintain it; when this generator is temporarily removed, the system reverts to lower amplification levels.[63] Alternatively,

Pain, 51 (1992) 175–194

PAIN 02136

Painful neuropathy: altered central processing maintained dynamically by peripheral input

Richard H. Gracely, Sue A. Lynch * and Gary J. Bennett

Neurobiology and Anesthesiology Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, MD 20892 (USA)

(Received 3 December 1991, revision received and accepted 28 May 1992)

Summary We performed sensory assessments before and during diagnostic tourniquet-cuff and local anesthetic blocks in 4 patients diagnosed with reflex sympathetic dystrophy (RSD). All patients complained of mechano-allodynia; lightly touching the skin evoked an intense pain sensation. At detection levels, electrical stimuli were perceived as painful, suggesting that the mechano-allodynia was mediated by Aβ low-threshold mechanoreceptor afferents. Aβ-mediated allodynia was further supported by reaction time latencies to painful electrical stimuli at threshold for A-fiber activation and, in 1 patient, by differential cuff blocks which abolished Aβ function and allodynia while thermal sensation (warm and cold) were preserved. Local anesthetic block of painful foci associated with previous trauma abolished mechano-allodynia, cold allodynia, and spontaneous pain in all patients

Vardeh D, Mannion RJ, Woolf CJ. Toward a Mechanism-Based Approach to Pain Diagnosis. J Pain. 2016 Sep;17(9 Suppl):T50-69.

SPINE Volume 23, Number 22, pp 2383–2390

Effects of Lidocaine on Nucleus Pulposus–Induced Nerve Root Injury

A Neurophysiologic and Histologic Study of the Pig Cauda Equina

Shoji Yabuki, MD, PhD,*† Yoshiharu Kawaguchi, MD,*‡
Claes Nordborg, MD, PhD,§ Shinichi Kikuchi, MD, PhD,†
Björn Rydevik, MD, PhD,* and Kjell Olmarker, MD, PhD*

Study Design. Application of autologous nucleus pulposus on nerve roots and treatment with local application of lidocaine in the pig.

Objectives. Studies of the effects of lidocaine on nucleus pulposus–exposed nerve roots.

Summary of Background Data. Nerve root infiltration may improve radicular symptoms beyond the pharmacologic duration of local anesthetics, but the mechanisms for this effect are not known.

Methods. Nucleus pulposus was harvested from a lumbar disc and placed onto the sacrococcygeal cauda equina in pigs. In Series 1, early lidocaine treatment of nucleus pulposus–induced nerve root injury, pigs received 2% lidocaine (n = 5) or saline (n = 5) before and after surgery. Nerve conduction velocity and histologic appearance were studied after 3 days. In Series 2, delayed lidocaine treatment of nucleus pulposus–induced nerve root injury, after 7 days 2% lidocaine was administered epidurally to nucleus pulposus–exposed (n = 4) and –nonexposed (n = 4) nerve roots. Nerve conduction velocity, muscle action potentials, and histologic appearance were assessed.

Results. In Series 1, early treatment with lidocaine limited the reduction in nerve conduction velocity. The epidural inflammation was less in lidocaine treated animals. In Series 2, nerve conduction velocity was lower in nucleus pulposus–exposed animals than in nonexposed animals. The initial reduction of nerve conduction velocity and muscle action potential was similar between the groups, but the recovery of muscle action potential was slower and less complete in nucleus pulposus–exposed nerve roots. There was minimal histologic nerve injury in both series and in both protocols.

Conclusions. Early treatment with lidocaine may reduce nucleus pulposus–induced nerve root injury. Lidocaine induced a delayed recovery in nerve roots exposed to nucleus pulposus. Further studies are needed to clarify the therapeutic effects of nerve root infiltration and the pathophysiology of nucleus pulposus–induced nerve root injury. [Key words: lidocaine, nerve root infiltration, nerve roots, nucleus pulposus, radiculopathy, sciatica] **Spine 1998;23:2383–2390**

Nerve root infiltration (NRI) has been used to improve radicular symptoms beyond the duration of the effects of local anesthetics. For example, NRI has been used as a nonsurgical treatment for lumbar radiculopathy.[7,10] It has been suggested that this effect is related to an increase in the intraradicular blood flow[27] or is a reaction to breaking up the "vicious circle" of pain,[7] but the exact mode of action of NRI is still unknown. The purpose of this study was to examine the effects of lidocaine in a recently developed model for inducing nerve root irritation using autologous epidural application of nucleus pulposus (NP) on the cauda equina in pigs[17] and at-

BJA

British Journal of Anaesthesia, 125 (5): 779–801 (2020)

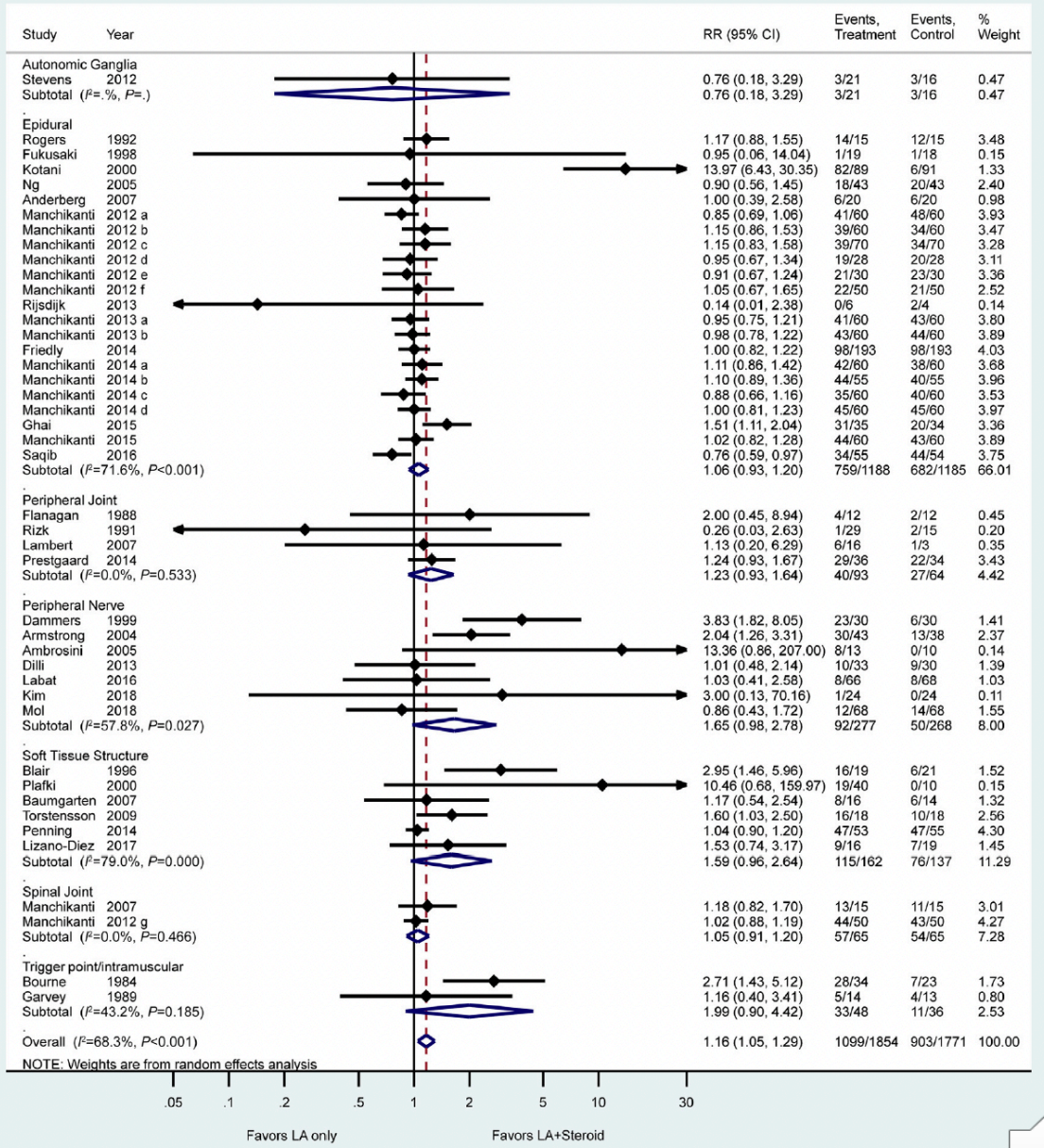
doi: 10.1016/j.bja.2020.06.062
Advance Access Publication Date: 12 August 2020
Review Article

REGIONAL ANAESTHESIA

Addition of corticosteroids to local anaesthetics for chronic non-cancer pain injections: a systematic review and meta-analysis of randomised controlled trials

Harsha Shanthanna[1,2,*], Jason Busse[1,2], Li Wang[1,2], Alka Kaushal[3], Prathiba Harsha[1], Erica A. Suzumura[4], Varun Bhardwaj[1], Edward Zhou[1], Rachel Couban[2], James Paul[1], Mohit Bhandari[5] and Lehana Thabane[6]

- Addition of steroids resulted in a small increase in success rate, 42 trials, 3592 patients, RR=1.14 [95% CI, 1.03-1.25], NNT: 22
- The differences in pain scores were not clinically meaningful; 54 trials, 4416 patients, MD=0.44 units [95% CI, 0.24-0.65].
- No subgroup effects based on clinical categories
- Value of adding steroids to chronic pain interventions is questionable



Meta-Analysis > Pain Physician. 2020 Aug;23(4S):S239-S270.

Lack of Superiority of Epidural Injections with Lidocaine with Steroids Compared to Without Steroids in Spinal Pain: A Systematic Review and Meta-Analysis

Nebojsa Nick Knezevic [1], Laxmaiah Manchikanti [2], Ivan Urits [3], Vwaire Orhurhu [3], Brahma Prasad Vangala [4], Rachana Vanaparthy [5], Mahendra R Sanapati [6], Shalini Shah [7], Amol Soin [8], Amit Mahajan [9], Sairam Atluri [10], Alan D Kaye [11], Joshua A Hirsch [12]

Affiliations + expand

PMID: 32942786

15 RCTs

The results showed Level II, moderate evidence, for short-term and long-term improvement in pain and function with epidural injections of LA with or without steroids in managing spinal pain of any origin

Meta-Analysis > Pain Physician. 2018 Sep;21(5):449-468.

Comparison of Clinical Efficacy of Epidural Injection With or Without Steroid in Lumbosacral Disc Herniation: A Systematic Review and Meta-analysis

Jung Hwan Lee [1], Dong Hwan Kim [2], Du Hwan Kim [3], Kyoung-Ho Shin [4], Sung Jin Park [5], Goo Joo Lee [6], Chang-Hyung Lee [7], Hee Seung Yang [8]

Affiliations + expand

PMID: 30282390

14 RCTs,
No significant differences in clinical efficacy were found between steroid and control such as saline or LA in 8 studies. The other 6 studies showed better outcomes with steroid.

Steroid showed significantly better pain control than control at 1 month, 3 months, and 6 months, but the effects decreased after 1 month.

SPINE Volume 30, Number 8, pp 857–862

The Efficacy of Corticosteroids in Periradicular Infiltration for Chronic Radicular Pain

A Randomized, Double-Blind, Controlled Trial

Leslie Ng, MRCS, Neeraj Chaudhary, MRCS, and Philip Sell, FRCS, MRCS

- Radicular pain due to disc or foraminal stenosis
- 43 patients in the bupivacaine and methylprednisolone group and 43 patients in the bupivacaine only group
- No statistically significant difference in the outcome measures between the groups at 3 months (ODI [P=0.68], change in visual analogue score [back pain, P=0.68; leg pain, P= 0.94], change in walking distance [P=0.7]).
- Duration of symptoms significant negative association with the change in ODI (P=0.03).

Randomized Controlled Trial > Pain Med. 2010 Aug;11(8):1149-68.
doi: 10.1111/j.1526-4637.2010.00908.x.

The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain

Ali Ghahreman [1], Richard Ferch, Nikolai Bogduk

Affiliations + expand

PMID: 20704666 DOI: 10.1111/j.1526-4637.2010.00908.x

- 5 groups for categorical outcomes
- Patients of only radicular pain due to disc pathology
- Can we ignore the differences in acute and chronic pain patients?
- Sample size analysis?
- Intramuscular normal saline was better than epidural LA?

Feature	TFST	TFNS	TFLA	IMST	IMNS	*P*
Male	17	19	17	15	21	
Female	11	18	10	13	9	0.567
Age						
Median	49	44	43	49	46	
IQR	39–61	33–54	35–66	38–62	37–64	
Acute	19	21	13	12	15	
Chronic	9	16	14	16	15	0.379
Duration (weeks)						

	Original Treatment				
Outcome	IMNS (n = 30)	IMST (n = 28)	TFLA (n = 27)	TFNS (n = 37)	TFST (n = 28)
Relief	4	6	2	7	15
No relief	26	22	25	30	13
No rescue	2	1	2	4	3
Surgery	2	3	5	3	6
Rescue with TFST	22	18	18	23	4
Relief after rescue (proportion of rescue)	8 (0.36)	8 (0.44)	6 (0.33)	7 (0.30)	2 (0.50)
95% confidence intervals	0.16–0.56	0.21–0.67	0.11–0.55	0.11–0.49	0.01–0.99
No relief					
Surgery	7	5	5	6	0
No surgery	2	1	0	1	1
Withdrew	1	1	0	0	0
Died	0	1	0	1	0
Lost to follow-up	4	2	7	8	1
Surgery after initial relief lapsed	0	0	0	0	4

Patients who were lost to follow-up were on record as not having had surgery.

ter Meulen et al. BMC Musculoskeletal Disorders (2017) 18:215
DOI 10.1186/s12891-017-1571-8

BMC Musculoskeletal Disorders

STUDY PROTOCOL Open Access

Treatment of acute sciatica with transforaminal epidural corticosteroids and local anesthetic: design of a randomized controlled trial

Bastiaan C. ter Meulen[1*], Esther T. Maas[2], Amrita Vyas[3], Marinus van der Vegt[4], Koo de Priester[5], Michiel R. de Boer[2], Maurits W. van Tulder[2,6], Henry C. Weinstein[1] and Raymond W. J. G. Ostelo[2,6]

264 patients with acute sciatica (<8 weeks)
Randomized to 3 groups

- Control (oral meds)
- LA
- LA + Steroid

Three primary outcomes

- Pain score
- Functions
- Global perceived effect

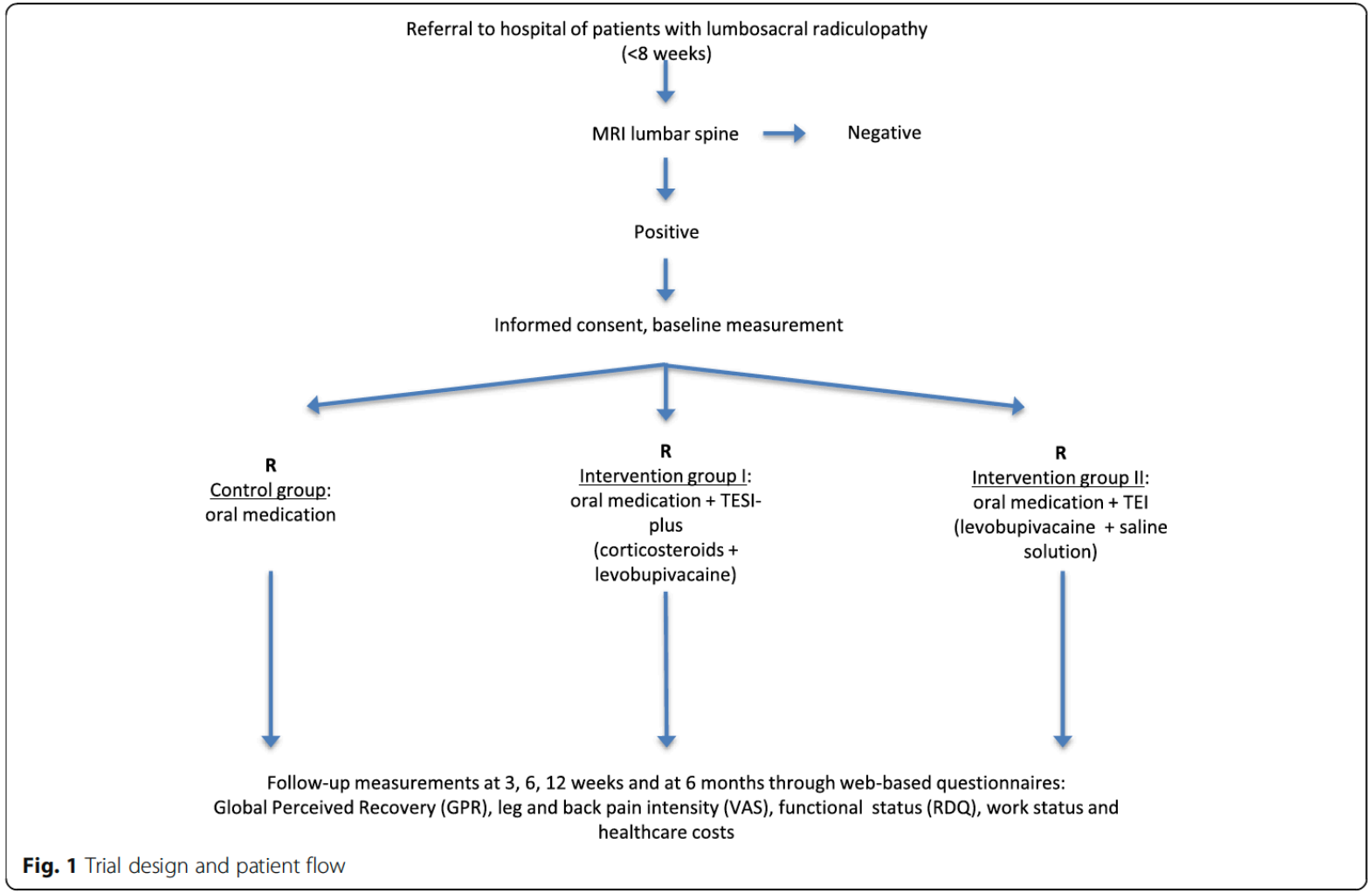


Fig. 1 Trial design and patient flow

Lumbar Spinal Stenosis: does anything work?

Review > Drug Des Devel Ther. 2015 Aug 13;9:4657-67. doi: 10.2147/DDDT.S85524. eCollection 2015.

Epidural injections with or without steroids in managing chronic low back pain secondary to lumbar spinal stenosis: a meta-analysis of 13 randomized controlled trials

Hai Meng [1], Qi Fei [1], Bingqiang Wang [1], Yong Yang [1], Dong Li [1], Jinjun Li [1], Nan Su [1]

- **Results:** 13 RCTs, involving 1,465 patients.
- Significant pain relief (>50%) was demonstrated in 53.7% of patients administered with LA with steroids and in 56.4% of those administered with LA alone.

Randomized Controlled Trial > N Engl J Med. 2014 Jul 3;371(1):11-21. doi: 10.1056/NEJMoa1313265.

A randomized trial of epidural glucocorticoid injections for spinal stenosis

Janna L Friedly [1], Bryan A Comstock, Judith A Turner, Patrick J Heagerty, Richard A Deyo, Sean D Sullivan, Zoya Bauer, Brian W Bresnahan, Andrew L Avins, Srdjan S Nedeljkovic

- No significant differences in the proportions of patients in the LA plus steroid group and the LA alone group in
- > 30% improvement in the RMDQ score (37.3% and 31.6%, P=0.24),
- 50% improvement in the RMDQ score (23.8% and 20.2%, P=0.39),
- 30% improvement in the rating of leg pain at 6 weeks (49.2% and 49.7%, P = 0.88),
- 50% improvement in the rating of leg pain at 6 weeks (38.3% and 38.3%, P = 0.97).

Lumbar Spinal Stenosis Severity by CT or MRI Does Not Predict Response to Epidural Corticosteroid versus Lidocaine Injections

F.A. Perez, S. Quinet, J.G. Jarvik, Q.T. Nguyen, E. Aghayev, D. Jitjai, W.D. Hwang, E.R. Jarvik, S.S. Nedeljkovic, A.L. Avins, J.M. Schwalb, F.E. Diehn, C.J. Standaert, D.R. Nerenz, T. Annaswamy, Z. Bauer, D. Haynor, P.J. Heagerty, and J.L. Friedly

RMDQ: Roland Morris Disability Questionnaire

Side effects of epidural glucocorticoids

- Systemic
- Local
- Spinal infarction
- Contamination and Meningitis

Table 2 Systemic and local side effects of steroids

Endocrine	Adrenal suppression, hypercortisolism, cushingoid syndrome, hyperglycemia, precipitation of diabetes mellitus, immunosuppression, hypokalemia, amenorrhea, menstrual disturbances, growth retardation
Metabolic	Hyperglycemia, glucosuria, redistribution of fat, negative nitrogen balance, sodium and water retention
Cardiac	Hypertension, fluid retention, CHF, DVT
Musculoskeletal	Osteopenia/osteoporosis, avascular necrosis of bone, pathologic fracture, muscle wasting and atrophy, muscle and joint pain
Psychological	Mood swings, insomnia, psychosis, anxiety, euphoria, depression
Gastrointestinal	Ulcerative esophagitis, hyperacidity, peptic ulceration, gastric hemorrhage, diarrhea, constipation
Ocular	Retinal hemorrhage, posterior subscapular cataracts, increased intraocular pressure, exophthalmos, glaucoma, damage to optic nerve, secondary fungal and viral infection
Dermatologic	Facial flushing, impaired wound healing, hirsutism, petechiae, ecchymosis, hives, dermatitis, hyperpigmentation, hypopigmentation, cutaneous atrophy, sterile abscess
Nervous System	Headache, vertigo, insomnia, restlessness, increased motor activity, ischemic neuropathy, seizures
Other	Epidural lipomatosis, fever

Safety of Epidural Steroid Injections for Lumbosacral Radicular Pain

Unmet Medical Need

Steven P. Cohen, MD, Emileigh Greuber, PhD,† Kip Vought, BSc,† and Dmitri Lissin, MD†*

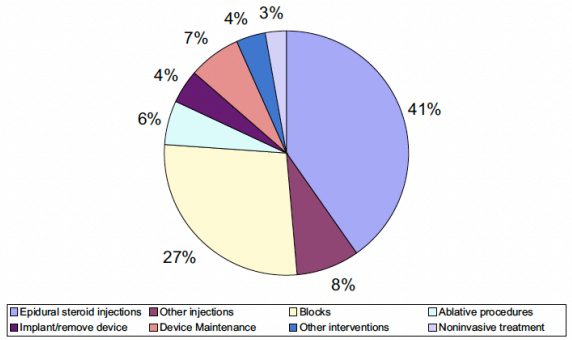
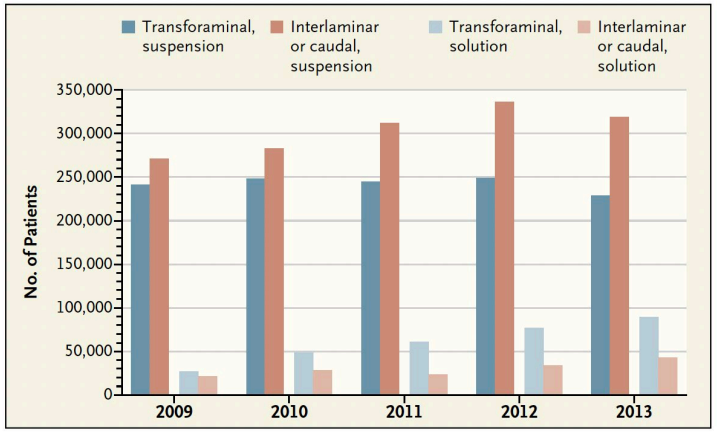


Figure 1 Distribution of Chronic Pain Management Claims based on events occurring between 1970 and 1999 and collected through December of 2000 by Closed Claims Project.



Estimated Numbers of Patients under 65 Years of Age in the Commercially Insured U.S. Population Who Received an Epidural Glucocorticoid Injection (EGI), According to Method of Administration and Type of Formulation, 2009–2013.

Data are from IMS Lifelink Health Plan Claims Database, November 2014.

Review > Microbiol Spectr. 2016 Apr;4(2). doi: 10.1128/microbiolspec.EI10-0005-2015.

Fungal Infections Associated with Contaminated Steroid Injections

Carol A Kauffman [1], Anurag N Malani [2]

Affiliations + expand

PMID: 27227303 DOI: 10.1128/microbiolspec.EI10-0005-2015

Free article

Abstract

In mid-September 2012, the largest healthcare-associated outbreak in U.S. history began. Before it was over, 751 patients were reported with fungal meningitis, stroke, spinal or paraspinal infection, or peripheral osteoarticular infection, and 64 (8.5%) died. Most patients had undergone epidural injection, and a few osteoarticular injection, of methylprednisolone acetate that had been manufactured at the New England Compounding Center (NECC). The offending pathogen in most

Serious Neurologic Events after Epidural Glucocorticoid Injection — The FDA's Risk Assessment

Judith A. Racoosin, M.D., M.P.H, Sally M. Seymour, M.D., Laurelle Cascio, Pharm.D., and Rajdeep Gill, Pharm.D.

At times, the Food and Drug Administration (FDA) must grapple with safety concerns related to off-label uses of FDA-approved medications. Over the past several years, we have sought to understand the risk of serious neurologic events that occur after the epidural injection of glucocorticoids (corticosteroids) — a procedure that is commonly performed in the United States in an effort to manage radicular neck and back pain. The FDA has not approved any injectable glucocorticoid product for epidural administration, so any such use is considered off-label — part of the practice of medicine and not regulated by the FDA.

In 2009, the FDA began evaluating serious neurologic events associated with epidural glucocorticoid injections. Between 1997 and 2014, a total of 90 serious and sometimes fatal neurologic events were reported to the FDA Adverse Event Reporting System (FAERS), including cases of paraplegia, quadriplegia, spinal cord infarction, and stroke. (Compounded glucocorticoids used in epidural injections have been associated with fungal meningitis, but cases involving contaminated products were not included in the se

Summarizing the evidence so far…

- LA solution cannot be considered a placebo
- Additional benefits of steroids over LA may be observed in patients of with radicular pain of short duration, predominantly due to disc pathology
  - It is unlikely that steroids have any benefit compared to LA beyond 6 weeks
- In patients of spinal stenosis or patients with mixed pathology, LA alone could provide equivalent effect as LA with steroids
- Clinical decision making needs to take into account potential side effects of steroids
- Frequency of epidural injections:
  - to consider steroids effects as well as overall risks and benefits in individual patients

Future: Establishing better evidence but How?

Measuring pain and success

- Pain scores are a poor way of assessing the impact and severity of pain
- We also do not agree on what we can call a success (how much and how long).

Establishing aspects of interventional therapies

- Determinants and Fidelity (Injection/Drug/Image guidance/Person delivering)
- Fidelity: refers to the degree to which an intervention is delivered as intended

Average effect versus Individual effect

- Responder analysis; Number Needed to Treat (NNT)

Appropriate EBM tools-going beyond traditional RCTs

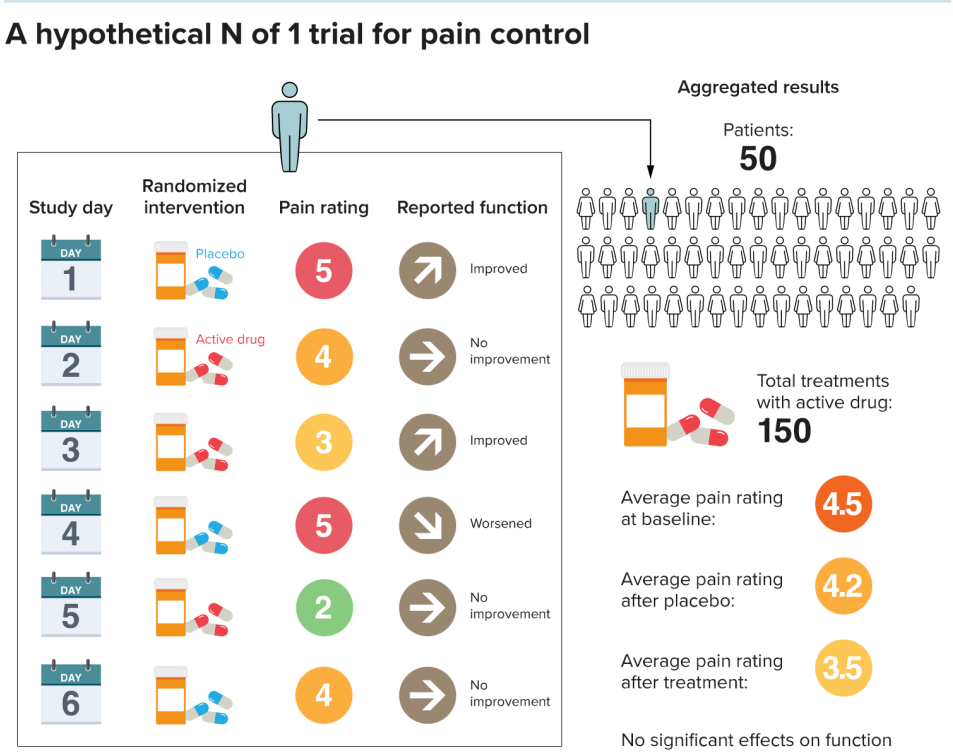
- N of 1 trials
- Randomized withdrawal designs
- Adaptive studies

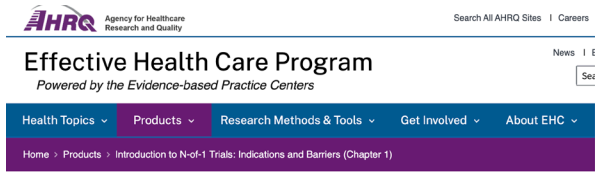
EBM for Interventional Pain: going beyond traditional RCTs

- RCTs are not the only way to establish evidence.
- RCTs rarely represent the clinical population we treat
- The conflict between Exploratory Vs. Pragmatic trials: establishing efficacy Vs applicability
- Challenges with Placebo control, Blinding
- RCTs are very costly
  - *a double-blind, placebo-controlled trial of radiofrequency neurotomy for neck pain cost some $500,000.*
  - *The costs of a placebo-controlled trial of intradiscal electrothermal therapy were estimated at over $1,000,000.*
- Rare beneficial or harmful events may be missed in a RCT
- Small RCTs can be misleading with its results

Bogduk N, Fraifeld EM. Proof or consequences: who shall pay for the evidence in pain medicine? Pain Med. 2010 Jan;11(1):1-2
Loeser JD. Evidence-based medicine and neuromodulation. Neuromodulation. 2008 Jul;11(3):151-5
Merrill DG. Hoffman's glasses: evidence-based medicine and the search for quality in the literature of interventional pain medicine. Reg Anesth Pain Med. 2003 Nov-Dec;28(6):547

- Individual study results may not be generalizable to population level
- Personalized treatment based on clinical response





Introduction to N-of-1 Trials: Indications and Barriers (Chapter 1)

PAIN MEDICINE
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NEUROPATHIC PAIN SECTION

Original Research Articles

N-of-1 Randomized Trials to Assess the Efficacy of Gabapentin for Chronic Neuropathic Pain

- 55 patients with chronic neuropathic pain
  Went through 3 cycles of Gabapentin vs. Placebo
- Individually, each patient was assessed
- Group outcomes meta-analyzed using Bayesian analysis
- Definite response to Gabapentin in 15% and Partial response in 15%
- Another 69% non responders

Promoting Therapies Based on Efficacy and Value

A therapy should satisfy three criteria, there should be convincing evidence that:

(1), compared with no treatment, the **treatment is effective in improving health outcomes**;

(2) compared with no treatment, its **beneficial effects on health outcomes should outweigh any harmful effects** on health outcomes; and

(3) compared with the next best alternative treatment, the **treatment should represent a good use of resources**.

- *Need for societies to come together to be able to agree and disagree on techniques and methods.*
- *We need to better engage our patients in our efforts*.

Eddy DM. Clinical decision making: from theory to practice. Principles for making difficult decisions in difficult times. JAMA. 1994 Jun 8;271(22):1792-8.

Thanks