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

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Abstract

Background: Despite common use, the benefit of adding steroids to local anaesthetics (SLA) for chronic non-cancer pain (CNCP) injections is uncertain. We performed a systematic review and meta-analysis of English-language RCTs to assess the benefit and safety of adding steroids to local anaesthetics (LA) for CNCP.

Methods: We searched MEDLINE, EMBASE, and CENTRAL databases from inception to May 2019. Trial selection and data extraction were performed in duplicate. Outcomes were guided by the Initiative in Methods, Measurements, and Pain Assessment in Clinical Trials (IMMPACT) statement with pain improvement as the primary outcome and pooled using random effects model and reported as relative risks (RR) or mean differences (MD) with 95% confidence intervals (CIs).

Results: Among 5097 abstracts, 73 trials were eligible. Although SLA increased the rate of success (42 trials, 3592 patients; RR=1.14; 95% CI, 1.03–1.25; number needed to treat [NNT], 13), the effect size decreased by nearly 50% (NNT, 22) with the removal of two intrathecal injection studies. The differences in pain scores with SLA were not clinically meaningful (54 trials, 4416 patients, MD=0.44 units; 95% CI, 0.24–0.65). No differences were observed in other outcomes or adverse events. No subgroup effects were detected based on clinical categories. Meta-regression showed no significant association with steroid dose or length of follow-up and pain relief.

Conclusions: Addition of cortico steroids to local anaesthetic has only small benefits and a potential for harm. Injection of local anaesthetic alone could be therapeutic, beyond being diagnostic. A shared decision based on patient preferences should be considered. If used, one must avoid high doses and series of steroid injections.

Clinical trial registration: PROSPERO #: CRD42015020614.

Keywords: chronic non-cancer pain; chronic pain; corticosteroids; local anaesthetic; meta-analysis; pain management; steroids; systematic review

Received: 17 December 2019; **Accepted:** 23 June 2020

Editor's key points

- Although the addition of steroids to local anaesthetic injections is used commonly for many chronic pain conditions, the biological rationale and clinical benefits of steroids are not clear.
- The authors performed a comprehensive systematic review and meta-analysis to assess the benefits and risks of combined corticosteroid and local anaesthetic injection.
- They found no meaningful improvement in pain scores or the duration of pain relief.
- Clinical decisions should consider the potential for harm with steroids and therapeutic benefit by local anaesthetic alone.

Chronic non-cancer pain (CNCP) is widely prevalent causing suffering, limitation of daily activities, and reduced quality of life (QoL). An estimated 100 million adults were affected by CNCP in the USA in 2012, with associated treatment costs ranging from $560 to $635 billion (US).[1] Most CNCP conditions are musculoskeletal, such as low back and neck pain, and joint pain.[2,3] Treatment options for these patients are associated with inconsistent results and, when effective, modest improvement in symptoms.[4]

Percutaneous injections are used to block or modify pain signals to decrease pain intensity and complement ongoing pharmacological and physical therapy. With these interventions two assumptions are made: the structure being targeted is involved in the pain pathway, and the injectate or intervention will have a biological effect on the target. Physicians who consider the need for a diagnostic block tend to confirm the involvement of the target structure by the response to a local anaesthetic (LA) injection; however, there are limited options to achieve a therapeutic response. Typically, they include steroid injections, radiofrequency treatments, chemical neurolysis in malignant pain, and spinal or peripheral stimulation techniques.[5] Injections of steroid mixed with LA (SLA) form the bulk of these injections,[6] such as epidural steroid injections (ESI),[7] soft tissue and intra-articular injections,[8–10] nerve blocks,[11] and even trigger point injections.[12] Although some consider LA to be placebo,[13–15] LAs are active agents as they block sensory signals from the region being injected. Up until the 1950s, the epidural injectate reported for sciatica consisted of LA and saline.[16–18] The scientific basis for adding steroids is not clear[19] and steroids, being anti-inflammatory, are not an appropriate rationale for most CNCP conditions (except in autoimmune conditions).[20] Although a mechanism-based approach is being advocated,[21] symptom-based paradigms have commonly informed treatment decisions in CNCP, and a positive treatment response with LA injections does not imply any precise disclosure of the underlying pathophysiology of pain.[5] Clinically, addition of steroid is expected to translate into either an increased success rate or prolonged duration of block.[6] However, such effects have also been shown with LA alone.[22,23] Steroid injections can have wide-ranging adverse effects, including hormonal changes, skin atrophy, osteoporosis, infection, and potentially devastating complications with neuraxial injections.[23–25] Most CNCP patients receive repeated and multiple injections from different physicians, leading to potentially accumulative steroidal side-effects.[24]

Despite the common use, existing reviews have several limitations; some have combined the use of LA with other biologically inactive controls,[26,27] and others have focused specifically on spinal or other targets for interventions.[18,28,29] Furthermore, many do not include a meta-analysis.[30,31] We have summarised the limitations in these reviews in our published protocol.[32] We undertook a systematic review and meta-analysis of RCTs of LA *vs* SLA that addresses these limitations.

Methods

We registered our review with PROSPERO (CRD42015020614)[33] and published our protocol.[32]

Objectives

The primary objective of this systematic review and meta-analysis was to evaluate the effect of injections using SLA *vs* LA for pain relief among adults with CNCP. The secondary objectives were to compare effectiveness on physical functioning, emotional functioning, global impact and satisfaction, adverse effects and participant disposition, as noted in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) statement[34]; to compare the duration of pain relief; and to assess the effect of multiple injections and steroid dose on pain.

Study eligibility

Trials published in English with adult (≥18 yr of age) patients having CNCP were included if they randomised patients to receive SLA or LA (with or without saline), administered as a percutaneous injection. Our operational definition for CNCP was the presence of pain lasting longer than 3 months, which is usually considered as the expected period of healing, in the absence of neoplastic origin.[4] Studies were excluded if included patients had a known inflammatory cause of pain such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, or gouty arthritis, and pain of generalised nature such as fibromyalgia. If a trial involved a mix of patients, we included the study only if they reported outcomes separately for our study population of interest, or if at least 90% of the trial patients were >18 yr old with CNCP. We excluded crossover and *N*-of-1 trials, and non-therapeutic trials. Crossover studies may not be suitable because some conditions can improve over time; a suitable washout period cannot be clearly estimated for interventions which lead to unexpectedly prolonged relief; and many crossover studies do not provide appropriate paired analysis required for meta-analysis.[35] We also excluded trials involving injections with additional agents (e.g. hyaluronidase, dextrose, plasma), or if injections involved a co-interventional procedure (e.g. radiofrequency treatment, epidurolysis).

Information sources and search strategy

We searched MEDLINE, EMBASE, and CENTRAL from their inception until May 7, 2019, without any limits for language. We complemented our search by reviewing bibliographies of relevant reviews published in anaesthesia and pain journals (Appendix S1) over the past 5 yr on the topic of steroid

injections for CNCP, and by searching the WHO clinical trial registry (http://apps.who.int/trialsearch/) and the clinical trial registry (https://clinicaltrials.gov/), to look for any registered studies fulfilling our eligibility criteria and crosscheck for published results. The search was performed using a sensitive strategy, prepared by an experienced librarian (RC) for each specific database, based in part on a comprehensive list of CNCP indications for which LA and SLA injections are commonly used. The search terms included possible indications, along with terms identifying corticosteroids, and LAs. Details of search strategy are provided in Appendix S1.

Study selection

Using an online software tool specially optimised to conduct systematic reviews (DistillerSR – http://systematic-review.net/), studies were selected using a two-stage (abstract and full text) process by paired reviewers working independently and in duplicate. Non-English publications were excluded at the full-text level. A calibration exercise was performed between each reviewer pair and disagreement was resolved by consensus or by discussion with a third reviewer (HS). A quadratic kappa statistic was calculated as a measure of inter-observer agreement for full-text screening, independent of chance regarding study eligibility and interpreted as almost perfect agreement (0.81–0.99); substantial agreement (0.61–0.80); moderate agreement (0.41–0.60); fair agreement (0.21–0.40); slight agreement (0.01–0.20); and ≤0 as less than chance agreement.[36]

Data extraction

Multiple teams of paired reviewers extracted data using standardised data extraction forms, independently and in duplicate. A detailed instruction manual was provided along with each relevant form. Extracted items included study characteristics, risk of bias items, demographic information, participant flow through the study, and outcomes for the six core domains recommended by the 2005 IMMPACT statement.[34]

Outcome measures and data synthesis

Relief of pain was considered the primary outcome, and other core IMMPACT outcomes as secondary outcomes (including physical function improvement, global improvement, QoL and adverse events). Continuous and categorical outcome measures were separately extracted, analysed, and reported. Pooling was done if there were two or more studies that contributed to a particular outcome domain. For the primary outcome of pain relief, we considered the outcomes reported closest to 4 weeks as indicative of treatment effectiveness. Based on the most common range of duration of follow-ups observed in included studies, we decided to separately pool studies reporting their first pain relief outcome between 2–6 weeks and 2–4 months. Hence, all studies were included either in the first or second, or both groups if outcomes were reported during both durations. Binary outcome of 'success' was considered based on dichotomous study reporting. If studies used categorical reporting such as mild, moderate, and severe, patients were dichotomised to 'successful' or 'failure' categories based on their change from higher to lower category, such as from severe to moderate or mild. This was based on the assumption that any change from a higher ordinal category to a lower category is considered successful and mild-to-moderate pain represents an acceptable state of pain compared with severe pain.[37,38] We converted all continuous measures to a common scale: (1) pain scores to 0–10 numerical rating scale (NRS); (2) functional improvement to a percentage scale of Oswestry Disability Index (ODI) (0%, no disability; 100%, complete disability)[39]; and (3) improvement in QoL to a 0–100 scale (0, worst; 100, best). We performed all statistical analyses using Stata statistical software version 15.1 (StataCorp, College Station, TX, USA). All comparisons were two-tailed using a threshold $P \leq 0.05$. We performed random-effects models using the DerSimonian–Laird method for all meta-analyses. If there were more than one treatment group (two different steroids or doses of steroids), they were combined into one group before pooling.[35] As the primary objective of this review was to establish if addition of any steroid to LA would improve the response (pain relief), this is appropriate. Although there may be differences in responses between particulate and non-particulate steroids, studies have shown that effects are not inferior.[40,41] However, if the third group involved a different target (e.g. two groups of epidural injection and one group of intramuscular injection), it was excluded. We presented the relative risk (RR) of success or improvement and the associated 95% confidence interval (CI) for dichotomous outcomes, and weighted mean differences (WMD) and 95% CI for continuous outcomes. To enhance interpretability with continuous measures for pain relief, probabilities were estimated for patient accepted symptom state of <4 (successful) or >4 in an 11-point NRS, after converting all results to the same direction. Risk differences (RD) and number needed to treat (NNT) were reported whenever pooled results were significant. Measure of heterogeneity was reported as χ^2 and inconsistency across studies as proportion of I^2. We hypothesised that SLA leads to longer pain relief and higher steroid doses are associated with better pain relief. Meta-regression was performed to assess the effect of steroid dose on the success (binary) and intensity of pain relief (continuous) between studies. As we have indicated earlier, one of the assumptions to add steroids to LA is the potential for prolonged pain relief. However, existing studies rarely, if at all, consider duration of relief as an outcome. There are variations within studies of multiple injections; some consider giving a series of injections before outcome evaluation, whereas others allow more than one repeat injection based on the initial outcome. Hence, we considered an indirect evaluation of steroid effect on duration by assessing 'success' or 'pain score' over lengths of follow-up in single injection studies using meta-regression.

Exploration of heterogeneity and subgroup analysis

As per our *a priori* hypotheses, we performed subgroup analysis based on clinical groups categorised according to the structure being targeted, and single *vs* multiple sittings of injections to the same target. The seven clinical categories considered were: (1) peripheral joint (hip, knee, shoulder joint injections, and other joint injections); (2) spinal joint/disc (facet joint or disc injections); (3) spinal nerve or epidural or intrathecal (epidural injections including transforaminal epidural); (4) peripheral nerve (nerves such as occipital nerve, suprascapular, and median nerve); (5) autonomic ganglia (stellate ganglia, celiac plexus, lumbar sympathetic block); (6) soft tissue (injections to lateral or medial elbow ligaments, subacromial bursa or

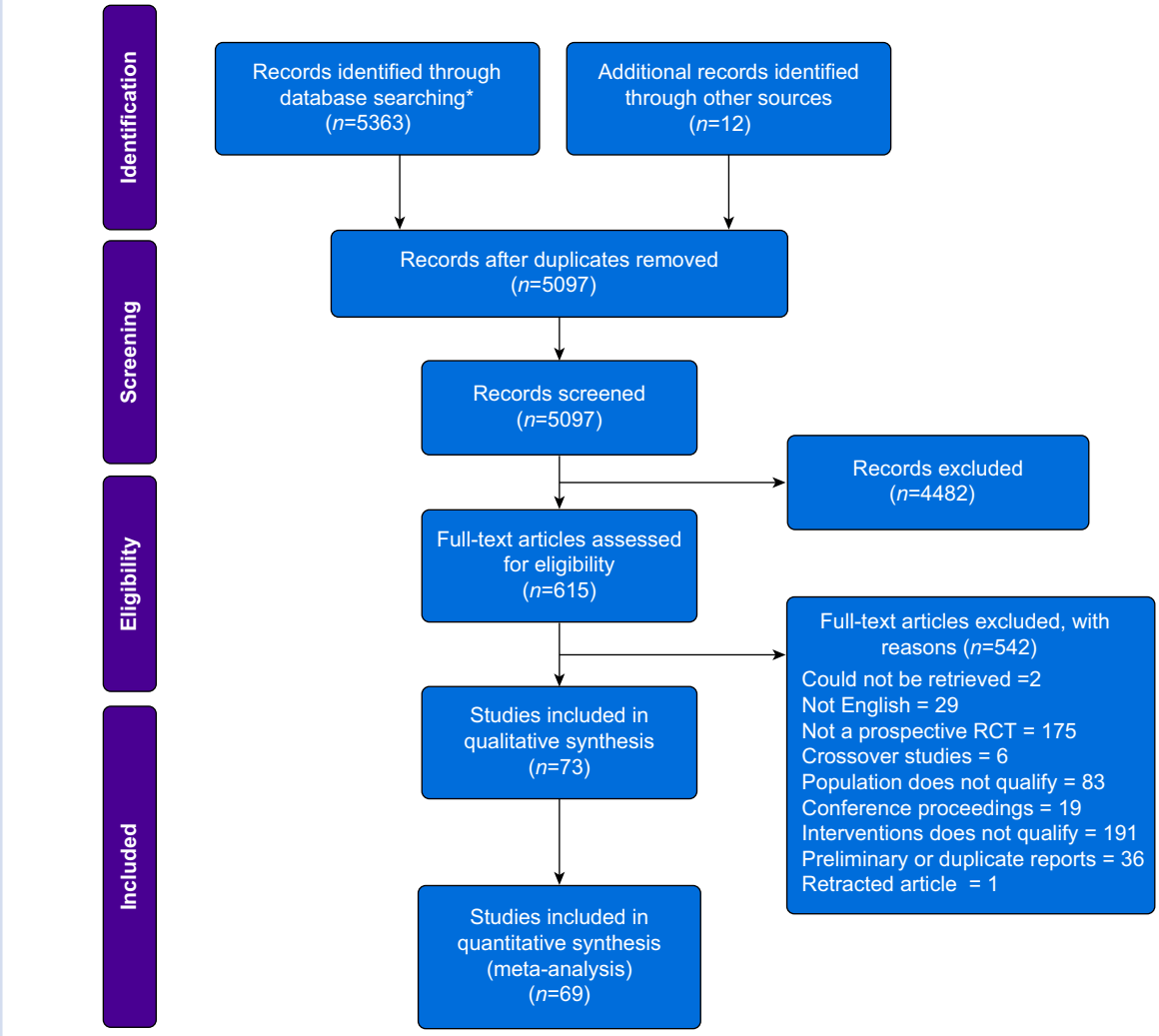

Fig 1. PRISMA Flowchart. *Latest search was carried out on May 7, 2019. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

plantar fascia); and (7) trigger point or intramuscular (injections to trigger point, piriformis muscle, or any other intramuscular injections).

Sensitivity analyses

Pain relief outcome was explored for loss to follow-up (LTFU) in studies with >5% LTFU (considered as patients missing their data from analysis for any reason) using imputation strategies described Ebrahim and colleagues[42] and Akl and colleagues[43] for continuous and dichotomous measures, respectively. For trials in which the authors report total missing participant data only, without specifying what groups and the stage the participants were missing, we considered the total sample size and the actual sample size included for final analysis and assumed that missing data were equally distributed between the arms. For trials in which the authors reported imputed analysis only, we used the imputed results for the meta-analysis. Sensitivity analysis was also carried out for a risk of bias (RoB) component, when there was substantial variability. We conducted a *post-hoc* sensitivity analysis by excluding trials that used intrathecal methylprednisolone for intractable post-herpetic neuralgia. Intrathecal steroids have a higher risk of chemical meningitis, transverse myelitis, arachnoiditis, cauda equina syndrome, lumbar radiculitis, intractable headache, and urinary retention. Its use is not recommended because of these safety concerns.[44,45]

Addressing sources of biases

Studies were assessed for RoB using a modified Cochrane RoB tool based on the components of sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data (>5% LTFU), and selective outcome reporting. Publication bias was assessed using a funnel plot and by the test of Harbord or Egger.[46] Selective outcome reporting was considered when

Table 1 Characteristics of included studies.

No First author, year (country/region)	Clinical diagnosis Study groups	Clinical group Target structure	No of patients randomised (analysed) Females in %		Age: Mean (SD)		Duration of chronic pain (months) Mean (SD)	
			LA + Steroid	LA Only	LA + Steroid	LA Only	LA + Steroid	LA Only
Autonomic Ganglia								
1. Stevens,[102] 2012 (USA)	Chronic pancreatitis Only study on autonomic ganglia	Celiac plexus	21 (21) 43%	19 (16) 47%	39.5 (10.9)	44.1 (12.5)	29 [13, 84]*	48 [21, 84]*
Epidural-Intrathecal								
2. Tafazal,[103] 2009 (UK)	Lumbar radicular pain	Lumbar-transforaminal	74 (70) 35%	76 (71) 36%	52.8	51	20 [7, 24.5]¶	17.8 [6, 24.5]¶
3. Manchikanti,[89] 2012a (USA)	Lumbar disc herniation and radiculitis	Caudal	60 (60) 62%	60 (60) 68%	43 (14.5)	48.7 (14.1)	81.3 (81.7)	93.4 (86.9)
4. Nam,[94] 2011 (Asia)	Lumbar scoliosis with spinal stenosis	Lumbar-interlaminar	17 (17) 76%	19 (19) 74%	75.24 (5.27)	71.58 (9.55)	7.71 (2.59)	6.74 (2.83)
5. Ng,[95] 2005 (UK)	Lumbar radicular pain	Lumbar-interlaminar	43 (43) 42%	43 (43) 47%	51.2 (14.5)	49.7 17.1	16.9 [6.25, 19.5]*	12 [6, 18.5]*
6. Rogers,[96] 1992 (UK)	Sciatica	Lumbar-interlaminar	15 (15) 53%	15 (15) 53%	42 [22, 61]¶	41 [23, 63]¶	23 [1, 240]*	25 [1, 240]*
7. Manchikanti,[79] 2012b (USA)	Chronic low back pain without disc herniation	Caudal	60 (60) 63%	60 (60) 78%	43.9 (13.1)	48.5 (15.3)	92 (85.4)	100 (87)
8. Manchikanti,[90] 2012c (USA)	Chronic low back pain – post lumbar surgery	Caudal	70 (70) 51%	70 (70) 39 %	48 (12.3)	52.4 (14.1)	160 (113.3)	152.1 (106.9)
9. Manchikanti,[86] 2012d (USA)	Chronic cervical pain – post surgery syndrome Although preliminary – has no final report not published	Cervical	28 (28) 32%	28 (28) 64%	49 (10.3)	48.3 (9.9)	111.2 (73.9)	122.3 (77.7)
10. Manchikanti,[87] 2012e (USA)	Cervical spinal stenosis Although preliminary – has no final report not published	Cervical	30 (30) 10%	30 (30) 7%	49.7 (8.9)	49.9 (8.5)	94.3 (77.4)	115.2 (89.9)
11. Kotani,[73] 2000 (Japan)	Postherpetic neuralgia Three different measures for pain (lancinating, burning, and allodynia) – primary outcome measure not specified. Global pain relief – given as two categories was considered.	Intrathecal	89 (89) 47%	91 (91) 52%	63 8	65 8	36 (19)	41 (20)
12. Rijsdijk,[99] 2013 (Other Europe)	Postherpetic neuralgia	Intrathecal	6 (6) 33%	4 (4) 50%	76§ [70, 88]¶	70§ [60, 72]¶	24§ [17.5, 50.5]¶	21.5§ [9.3, 87]¶
13. Datta,[62] 2011# (Asia)	Chronic low back pain Four groups and three steroid groups combined into one group for this review LA only considered as placebo	Caudal	152 (121) 8%	55 (42) 9%	43	41	4	4

Continued

Table 1 Continued

No First author, year (country/region)	Clinical diagnosis Study groups	Clinical group Target structure	No of patients randomised (analysed) Females in %		Age: Mean (SD)		Duration of chronic pain (months) Mean (SD)	
			LA + Steroid	LA Only	LA + Steroid	LA Only	LA + Steroid	LA Only
14. Friedly,[66] 2014 (USA)	Lumbar spinal stenosis	Lumbar-interlaminar and transforaminal	200 (193) 59%	200 (193) 52%	68 (9.8)	68 (10.2)	[3, 60]*	[3, 60]*
15. Manchikanti,[78] 2015 (USA)	Lumbar spinal stenosis	Lumbar-interlaminar	60 (60) 45%	60 (60) 68%	50 (15.3)	54.6 (13.5)	105 (87.7)	93.4 (86.9)
16. Manchikanti,[85] 2013a (USA)	Cervical disc herniation	Cervical	60 (60) 58%	60 (60) 53%	45.6 (10.4)	46.2 (10.3)	91.9 (94.5)	118.3 (98.6)
17. Manchikanti,[83] 2014a (USA)	Lumbar disc herniation and radiculitis	Lumbar-interlaminar	60 (60) 38%	60 (60) 62%	40.6 (12.5)	49 (14.1)	133.2 (108.5)	135 (120.3)
18. Manchikanti,[80] 2013b (USA)	Chronic discogenic low back pain	Lumbar-interlaminar	60 (60) 60%	60 (60) 77%	42.7 (11.4)	41.2 (11.9)	129 (90.9)	104.2 (106.5)
19. Manchikanti,[82] 2012f (USA)¶	Lumbar spinal stenosis	Caudal	50 (50) 50%	50 (50) 68%	55.7 (15.9)	56.9 (14.5)	104.9 (80.4)	94.2 (106.9)
20. Fukusaki,[67] 1998 (Japan)	Spinal stenosis Three groups†	Lumbar-interlaminar	19 (19) 32%	18 (18) 28%	72.7	69.9	NR	NR
21. Manchikanti,[81] 2014b (USA)	Chronic thoracic pain	Thoracic-interlaminar	55 (55) 56%	55 (55) 85%	40.8 (13.1)	42.8 (13.7)	91 (85.7)	103 (90.7)
22. Manchikanti,[91] 2014c (USA)	Lumbar disc herniation	Lumbar-transforaminal	60 (60) 55%	60 (60) 83%	42.6 (11.2)	43.8 (11.8)	103.8 (92.5)	98.4 (83.4)
23. Anderberg,[52] 2007 (Other Europe)	Cervical radiculopathy	Cervical-transforaminal	20 (20) 55%	20 (20) 45%	51§	51§	31§ [3, 120]*	31§ [3, 120]*
24. Manchikanti,[84] 2014d(USA)	Cervical discogenic pain	Cervical-interlaminar	60 (60) 68%	60 (60) 75%	41.8 (11.6)	44.5 (12.6)	95.8 (95.7)	100.3 (94.3)
25. Ghai,[107] 2015 (Asia)	Chronic low back with radicular pain	Lumbar parasagittal epidural	35 (35) 46%	34 (34) 56%	45.9 (13.3)	44.7 (10.5)	21.5 (14.8)	19.6 (12.5)
26. Okmen,[111] 2017 (Other Europe)	Chronic low back pain due to disc disease	Interlaminar epidural	60 (48) 52%	60 (50) 62%	51.9 (9.2)	53.8 (10.3)	14.5 (4.9)	13.9 (4.7)
27. Saqib,[114] 2016 (Asia)	Chronic low back pain	Interlaminar epidural	60 (55) (50.5%)	60 (54) (50.5%)	49.37 (10.46)	49.37 (10.46)	15.01 (9.32)	15.01 (9.32)
Peripheral Joint								
28. Henriksen,[13] 2015 (Other Europe)	Osteoarthritis	Knee-intraarticular	50 (50) 56%	50 (50) 66%	61.3 (9.9)	65.5 (8.3)	NR	NR
29. Beyaz,[56] 2012 (Asia)	Osteoarthritis Three groups†— LA only considered as placebo	Knee	25 (25) 84%	25 (25) 72%	68.6 (7.3)	70.7 (7.7)		
30. Rizk,[100] 1991# (USA)	Adhesive capsulitis Four groups; two separate LA + steroid groups for intra-articular and intrabursal injection, and one LA group. We have combined both LA + steroid for comparison. LA only considered as placebo	Shoulder	32 (29) 34%	16 (15) 56%	55 [40, 70]	55 [40, 70]	13.2§ [8, 18]*	13.2§ [8, 18]*

Continued

Table 1 Continued

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			LA + Steroid	LA Only	LA + Steroid	LA Only	LA + Steroid	LA Only
31. Flanagan,[65] 1988 (UK)	Hip osteoarthritis 3 groups[†]	Hip	12 (12) NR	12 (12) NR	NR	NR	NR	NR
32. Lambert,[74] 2007[#] Canada	Osteoarthritis hip	Hip	31 (31) 50%	21 (19) 68%	65.6 (11)	56.9 (11)	51 (39)	51 (56)
33. Prestgaard,[113] 2015[#,†] (Other Europe)	Adhesive capsulitis shoulder	Shoulder	42 (39) (64%)	40 (36) (65%)	53.2 (6.9)	55.4 (6.5)	3.77 (1.15)	3.75 (1.4)
34. Spolidoro Paschoal,[115] 2015 (South America)	Osteoarthritis	Hand-intraarticular	30 (30) (100%)	28 (30) (93%)	60.7 (9.1)	60.7 (7.3)	4.7 (4.2)	5.2 (3.0)
Peripheral nerve								
35. Karadas,[70] 2011 (Other Europe)	Carpal tunnel syndrome	Median nerve	33 (33) 88%	32 (32) 88%	46.35 (12.38)	46.75 (5.83)	9.4 (3.477)	10.25 (2.03)
36. Ashkenazi,[54] 2008 (USA)	Transformed migraine Pain relief reported as number of pain-free days[‡]	Occipital	19 (19) 37%	18 (18) 78%	40.7 (8.9)	41.9 (11.3)	276 (156)	228 (144)
37. Dammers,[61] 1999 (Other Europe)	Carpal tunnel syndrome	Median	30 (30) 80	30 (30) 86	53	51	32	25
38. Armstrong,[53]2004[#] (USA)	Carpal tunnel syndrome After two weeks assessment the randomization was opened and LA group allowed steroid injection	Median	43 (43) 81%	38 (38) 74%	51.9 (13.3)	51.2 (10.4)	NR	NR
39. Eker,[64] 2012 (Other Europe)	Peripheral neuropathic pain (posttraumatic)	Peripheral nerve-various	44 (44) 39%	44 (44) 34%	51.8 (14.7)	57.8 (13.9)	12.9 (20.2)	9.7 (20.2)
40. Dilli,[63] 2013[#] (USA)	Migraine	Occipital	35 (33) 86%	35 (30) 71%	44 (11)	42 (16)		
41. Kashipazha,[71] 2014 (Other Europe)	Migraine	Occipital	24 (24) 83%	24 (24) 88%	37 (4.41)	37.04 (9.93)	NR	NR
42. Ambrosini,[51] 2005[#] (Other Europe)	Cluster headache LA only considered as placebo	Occipital	13 (13) NR	10 (10) NR	47.5[§] [26, 52][¶]	35[§] [24, 43][¶]	NR	NR
43. Labat,[109] 2016 (Other Europe)	Pudendal neuralgia	Pudendal nerve block	66 (66) 57%	68 (68) 60%	57 (13)	57 (12.7)	50 (59.7)	36 (42.3)
44. Kim,[116] 2018 (Asia)	Osteoarthritis	Genicular nerve block	24 (24) (100%)	24 (24) (96%)	65.8 (9.2)	66.5 (4.7)	54 (24)	66 (26.4)
45. Mol,[117] 2018 (Other Europe)	Abdominal pain due to anterior cutaneous nerve entrapment syndrome	Anterior cutaneous nerve	68 (68) (76%)	68 (68) (73%)	43[§] [18, 78][¶]	46[¶] [18, 79][¶]	15[§] [1, 120][¶]	14[§] [1, 120][¶]
46. Salman Roghani,[118] 2018 (Asia)	Carpal tunnel syndrome, three groups – two steroid groups combined as one group	Median nerve	69 (64) (72%)	33 (30) (82%)	66 (13)	63.4 (10)	NR	NR

Continued

Table 1 Continued

No First author, year (country/region)	Clinical diagnosis Study groups	Clinical group Target structure	No of patients randomised (analysed) Females in %		Age: Mean (SD)		Duration of chronic pain (months) Mean (SD)	
			LA + Steroid	LA Only	LA + Steroid	LA Only	LA + Steroid	LA Only
Soft tissue structure								
47. Price,[98] 1991[#] (UK)	Lateral epicondylitis Periarticular structure: three groups[†] LA only considered as placebo We have combined both LA + steroid for comparison	Elbow ligaments-lateral	59 (58) 46%	29 (29) 38%	47[§]	46[§]	20[§] [6, 150][*]	16[§] [4, 152][*]
48. Baumgarten,[55] 2007[¶] (USA)	Trigger finger Two parallel diabetic groups compared with and one non-diabetic group. LA only considered as placebo	Flexor tendon sheath	16 (16) 63%	14 (14) 50%	62.9 (9)	61.4 (9.1)		
49. Bahari,[77] 2003 (Asia)	Medial epicondylitis	Elbow ligaments-medial	20 (20) 30%	20 (20) 20%	42.55 (8.89)	42.7 (7.49)		
50. Thomson,[104] 2013 (UK)	Morton neuroma	Subcutaneous neuroma	64 (61) 84%	67 (64) 85%	54.7 (17.4)	51.6 (12.9)	NR	NR
51. Alvarez,[50] 2005 (Canada)	Rotator cuff tendinosis	Subacromial bursa	31 (30) 52%	31 (28) 35%	50 (15)	46 12	44 (44)	17.4 (28.6)
52. Crawford,[59] 1999 (UK)	Heel pain Four groups – only two groups considered for this review	Heel pad	27 (26) 60%	27 (26) 77%	59.41 (11.84)	56.88 (13.02)	11.65 (19.49)	18.96 (25.72)
53. Wolf,[15] 2011[#] (USA)	Lateral Epicondylitis 3 groups[†]– LA only considered as placebo	Elbow ligaments-lateral	9 (9) NR	9 (9) NR	49	49		
54. Kiter,[72] 2006 (Asia)	Plantar heel pain Three groups[†] Pain relief only reported at 6 months[‡]	Plantar fascia	15 [¶]NR	15 [¶]NR	50.7	50.7	19.3 [6, 180][*]	19.3 [6, 180][*]
55. Holt,[69] 2013 (UK)	Shoulder arthropathy	Subacromial bursa	19 (19) 58%	21 (20) 71%	61.5 (5.8)	56 (11.3)	15.9 (6.1)	10.7 (5)
56. Torstensson,[105] 2009 (Other Europe)	Pregancy-induced chronic back pain	Sacrospinous ligaments	18 (18) 100%	18 (18) 100%	32.3[§] [28.1, 37.9][¶]	32.2[§] [29.5, 36.3][¶]	4.3[§] [2.3, 6.5][¶]	4.1[§] [2.7, 6.4][¶]
57. Stahl,[101] 1997[#] (Israel)	Medial epicondylitis	Elbow ligaments-medial	30 (30) 20%	30 (30) 27%	43 (1.22)	41.3 (1.48)	4.33 (0.25)	4.72 (0.25)
58. Blair,[57] 1996 (USA)	Subacromial impingement syndrome Outcome reported at difference time point for the two groups[‡]	Subacromial bursa	19 (19) 79%	21 (21) 81%	56 [32, 81][¶]	57 [33, 81][¶]	8 [3, 24][*]	8 [3, 22][*]
59. Luukkainen,[76] 2002 (Other Europe)	Non-spondyloathropathic pain sacroiliac joint	Sacroiliac ligaments	13 (13) 77%	11 (11) 64%	50.3 [38, 68][¶]	49.3 [23, 62][¶]	64 [8, 180][*]	52 [8, 180][*]
60. Lindenhovius,[75] 2008 (USA)	Lateral epicondylitis	Elbow ligaments-lateral	31 (24) 55%	33 (27) 55%	50	50	3 [0.5, 5][*]	2 [0.5, 5][*]

Continued

Table 1 Continued

No First author, year (country/region)	Clinical diagnosis Study groups	Clinical group Target structure	No of patients randomised (analysed) Females in %		Age: Mean (SD)		Duration of chronic pain (months) Mean (SD)	
			LA + Steroid	LA Only	LA + Steroid	LA Only	LA + Steroid	LA Only
61. McCleane,[60] 1998[#] (Other Europe)	Sacroiliac pain-chronic Three groups[†] LA only considered as placebo	Sacroiliac ligaments	15 (15) 80%	15 (15) 87%	47	36	43 [4, 140][*]	41 [13, 60][*]
62. Akgun,[49] 2004 (Other Europe)	Subacromial impingement syndrome Three different outcomes measures for pain (rest; activity; sleep) – primary outcome measure not specified. Resting VAS scores considered	Subacromial bursa	16 (16) 75%	16 (16) 63%	48.5 (8.5)	47.5 (9.5)	19 (12.2)	11.8 (7.8)
63. Plafki,[97] 2000 (Other Europe)	Subacromial impingement syndrome Three groups[†] LA only considered as placebo	Subacromial bursa	40 (40) 30%	10 (10) 40%	43.5[§] [27, 63][¶]	43.5[§] [27, 63][¶]	16.8	16.8
64. Rah,[14] 2012[#] (Asia)	Post stroke hemiplegic shoulder pain	Subacromial bursa	30 (29) 64%	30 (29) 62%	56.6 (12.5)	54.9 (10.6)	6.6 (4.3)	7 (3.4)
65. Penning,[112] 2014[#,†] (Other Europe)	Subacromial impingement	Subacromial bursa	53 (53) NR	55 (55) NR	NR	NR	NR	NR
66. Lizano-Diez,[110] 2017[#] (Other Europe)	Morton's neuroma	Neuroma	20 (16) 60%	21 (19) 80%	57.7 (9.8)	60.7 (11.6)	21.6 (20.8)	20.58 (14)
Spinal joint								
67. Glemarac,[108] 2018 (Other Europe)	Low back pain with transitional vertebra	Painful location steroid injection	8 (7) NR	8 (8) NR	41.7 (11.8)	43.7 (19.1)	56.7 (53.6)	46.7 (68.7)
68. Manchikanti,[88] 2007 (USA)	Chronic low back pain –facet joint Has four groups; separate analysis for groups without sarapin reported Preliminary report	Facet-lumbar medial branch	15 (15) 53%	15 (15) 47%	44 (16.3)	56 (15.6)	120 (118.3)	189 (175.5)
69. Manchikanti,[92] 2012g (USA)	Chronic thoracic pain-facet joint	Facet-thoracic medial branch	50 (50) 38%	50 (50) 62%	42.8 (12.3)	44.7 (11.7)	77 (73.6)	78 (68.8)
Trigger point/intramuscular								
70. Venancio,[106] 2008 (South America)	Myofascial pain and headaches Three groups[†] Baseline parameters not provided separately[‡]	Trigger points	15 (15) NR	15 (15) NR	NR	NR		
71. Misirlioglu,[93] 2015 (Other Europe)	Piriformis syndrome	Piriformis muscle	25 (22) 92%	25 (25) 68%	47.2 (13.4)	45.5 (14.1)	23.6 (30.5)	17.4 (28.6)
72. Garvey,[68] 1989 (USA)		Trigger points	14 (14) NR	13 (13) NR	38	38	NR	NR

Continued

Table 1 Continued

No First author, year (country/region)	Clinical diagnosis Study groups	Clinical group Target structure	No of patients randomised (analysed) Females in %		Age: Mean (SD)		Duration of chronic pain (months) Mean (SD)	
			LA + Steroid	LA Only	LA + Steroid	LA Only	LA + Steroid	LA Only
	Low back pain-chronic Four groups, only two groups considered for this review							
73. Bourne,[58] 1984 (UK)	Chronic low back pain, oldest included report: three groups – two steroid groups combined as one group	Trigger points	34 (34) NR	23 (23) NR	43.5	39.5	150	72

LA, local anaesthetic; No., number; NR; not reported; SD, standard deviation.
* Range.
¶ Inter-quartile range.
§ Median.
# LA was considered as placebo.
† Three study groups, but only two groups considered for this review.
‡ Study not considered for quantitative analysis.

outcomes described in the Methods section were not reported in the Results section of the same study report.[47]

Rating of quality of evidence

The quality of evidence was summarised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and presented as a summary of findings (SoF) table.[48]

No patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

We identified 5097 potential trials of which 615 full-text articles were screened and 73 trials were included in our systematic review (Fig 1). The weighted kappa score for agreement on full text selection was 0.84, indicating almost perfect agreement. The characteristics of included studies are provided in Table 1.[13–15,49–80,81–118] LA was considered as placebo in 20% (15 of 73) studies,[14,15,51,53,55,60,62,63,74,98,100,101,110,112,113] whereas the remaining studies used LA as control. Use of a suitable form of image guidance was reported by 36 studies (49%). The studies included different types of injections for CNCP conditions and were categorised into the following clinical subgroups: epidural and intrathecal injections (n=26),[52,62,66,67,73,78–87,89–91,94–96,99,103,107,111,114] spinal joint or disc procedures (n=3),[88,92,108] peripheral intra-articular injections (n=7),[13,56,65,74,100,113,115] peripheral nerve injections (n=12),[51,53,54,61,63,64,70,71,109,116–118] soft tissue and periarticular injections (n=20),[14,15,49,50,55,57,59,60,69,72,75–77,97,98,101,104,105,110,112] injections on autonomic ganglia/nerve (n=1),[102] and trigger point or intramuscular injections (n=4).[58,68,93,106] There were six studies which contained more than one steroid groups – using either two different steroids or two different doses, and we combined them as one group of SLA for analysis.[58,62,97,98,100,118] Out of 73 studies, 69 studies were included for meta-analysis, and the following four were excluded from analysis and the reasons for exclusion are noted in Table 1. Ashkenazi and colleagues[54] compared SLA and LA for greater occipital nerve block in patients with transformed migraine and reported no significant difference in the mean headache-free days. Venancio and colleagues[106] randomized headache patients with trigger points to SLA, LA, and dry needling group, and assessed pain using modified symptom severity scale and found no difference between the groups at 12 weeks. Blair and colleagues[57] compared SLA and LA for subacromial injection with a mean duration of follow-up reported as 33 and 28 weeks, respectively, and noted significant improvements in the SLA group. Kiter and colleagues[72] randomised patients with plantar heel pain to injection with peppering technique to SLA, LA, and autologous blood groups. At 6 months after injection, all three groups reported good responses for pain relief with no differences between them.[72] All study outcomes are summarised in Table 2.

Pain relief

As the initial step, we separately pooled outcomes reported between 2–6 weeks and 2–4 months. However, the test for interaction for subgroup effects was not statistically significant, both for pain success (binary) or decrease in pain scores (continuous). Hence, we report them as single pooled analysis for both. Moderate quality of evidence showed that SLA resulted in slightly better success than LA (42 trials, 3586 patients, RR=1.14; 95% CI, 1.03 to 1.25; I^2=72%, NNT: 13; Fig 2, Appendix S2). However, the absolute RD decreased by nearly 50% and the NNT increased to 22, with the removal of two studies by Kotani and colleagues[73] and Rijsdijk and colleagues,[99] reporting on the use of intrathecal methylprednisolone for intractable post-herpetic neuralgia. This *post-hoc* sensitivity analysis (Appendix S3) is both methodologically and clinically meaningful because despite the spectacular results by Kotani and colleagues,[73] the study by Rijsdijk and colleagues[99] had to be stopped for futility and safety concerns. Moreover, it has never been replicated and intrathecal steroid[99] is not commonly used for CNCP for safety concerns.[45,119] Similar recommendation has been made by the Neuropathic Pain Special Interest Group of International Association for the Study of Pain in their recent recommendations.[120] For pain relief expressed as MD using 0–10 NRS, among 54 studies with 4416 patients, intensity of end pain score with SLA was less by 0.44 units (0.64, 0.24), I^2=76% (Fig 3). The proportion of patients achieving a patient accepted symptom state (pain score of <4 in 0–10 NRS) indicated an RD of 8.8% (4.6%, 13%), favouring SLA with an NNT of 12.

Secondary outcomes

Moderate quality of evidence showed no significant functional improvement between groups for chance of success (RR=1.04; 95% CI, 0.96 to 1.12; Appendices S2 and S4) and a very small difference in ODI scores with SLA (WMD −1.77 points on ODI; 95% CI, −2.99 to −0.56 points; Appendices S2 and S5). There were no significant differences in global patient improvement or satisfaction (RR=1.16; 95% CI, 0.96 to 1.40; Table 2, Appendix S6) and QoL scores (WMD 2.59 points on a 0–100 scale; 95% CI, −0.71 to 5.89; Table 2, Appendix S7). We observed that clinically relevant adverse effects were not reported by a large majority of studies. Among adverse effects reported by more than two studies, there were no differences (Appendix S8).

Additional analyses

No subgroup effects were detected for pain relief between different clinical categories (Fig 4 and Appendix S9), and single *vs* multiple injection (Table 2). The number of studies in some of the groups were small, such as peripheral intra-articular (n=7), autonomic ganglia (n=1), and trigger points or intramuscular (n=4). Because this was a secondary analysis and also because of the small number of studies, the individual group results must be interpreted with caution. Although meta-regression did not find significant association between dose of steroids and success of pain relief (P=0.10, Appendix S10a), in trials reporting pain scores, higher dose of steroids was associated with a small (less than 2 points – clinically insignificant as it is less than MID) reduction in pain scores (P=0.002, Appendix S10b). Meta-regression did not find significant association between pain relief and length of follow-up among trials with single injection (Appendices 11a and 11b).

Assessment of bias

Among potential risk of domains, nearly half of the studies were at risk of selection bias in the domain of allocation concealment (Appendices S12a and S12b). Less than 25% studies suffered from attrition bias and sensitivity analyses based on imputations for LTFU patients did not change the effect sizes for pain success or scores significantly. We did not find evidence of publication bias both by visual inspection of funnel plots and testing. Among studies included for binary outcome of successful pain relief and comparison of pain scores, the Harbord's test (P=0.76; Appendix S13a) and Egger's test (P=0.42; Appendix S13b) were not significant, respectively.

Discussion

Our review and meta-analysis comparing LA with SLA found that only one in 13 individuals might have successful pain relief with the addition of steroids in CNCP. With the removal of two studies of intrathecal injection of steroids, the effect size nearly reduced by 50% (only one in 22 had success). The decrease in pain scores of 0.44 units in 0–10 NRS was less than clinically meaningful. There were no differences in physical functioning, global improvement or satisfaction or QoL. Our analyses also do not support the hypothesis that addition of steroids may prolong pain relief, or that higher doses of steroids are associated with better success.

Because of the rate at which the interventional pain injections have increased over the past several years,[121,122] calls to improve the quality of studies and for appropriateness of their use have been made.[122–124] Ideally, all medical interventions need to go through proof-of-concept testing to establish biological efficacy, followed by assay testing to establish the extent of biological activity. These stages of testing allow confirmation of biological activity and internal validity of a treatment and establish target structures, potentially phenotypical variations in response, and dose–therapeutic relationship.[125,126] However, the biological underpinnings of steroid injections are unclear because they have never been tested in appropriate preclinical models or for assay sensitivity. Moreover, there is lack of clarity and consensus on the technical aspects, diagnostic criteria, definition of success, frequency, number, or timing of interventions.[4,124] In addition, there is a higher chance of placebo response in chronic pain,[127] with or without an injection.[128] As LA can have biological response, we think it is inappropriate to consider them as placebo (inactive) comparators.

Once we appreciate that both comparators are active, it is pertinent to consider their mechanisms of action in CNCP. Apart from the anti-inflammatory effect, other postulated mechanisms of steroids include membrane stabilisation, inhibition of neuropeptide synthesis, and blocking of ectopic signals.[129,130] However, similar effects that go beyond the reversible conduction blockade such as suppressing ectopic discharges and decreasing sensitisation, have been postulated for LA alone.[28,131] It is possible that both can unwind sensitisation of chronic pain signals involved in neuroplasticity.[22,132,133] However, the neural correlates underlying such phenomenon are poorly studied.[134] Clinically, the predominant use of LA alone injections in CNCP have been for

Table 2 Summary of results. CI, confidence interval; LA, local anaesthetic; MD, mean difference; NNT, number needed to treat; NRS, numerical rating scale; ODI, Oswestry Disability Index; RD, risk differences; RR, risk ratios.

Outcome	Number of trials (participants)	Results Effect size (95% CI)	Inference and observation
Success of pain relief expressed as RR	42 (3586), 2 weeks to 4 months	RR=1.14 (1.03–1.25) I^2=72%; NNT, 13	Slightly better success with LA + steroid No significant publication bias
Reduction in pain expressed using 0–10 NRS	54 (4416), 2 weeks to 4 months	MD=−0.44 (−0.64 to −0.24), I^2=76%	Small improvement in pain relief with LA + steroid No significant publication bias
Proportion of patients achieving success based on responder analysis of pain score comparison	54 (4416), 2 weeks to 4 months Dichotomised using end score of ≤3 in 0–10 NRS	RD=8.8% (4.6%–13.0%); NNT, 12	Better success with LA + steroid
Secondary outcomes			
Improvement in physical function expressed as RR	21 (2301), longest follow-up outcome	RR=1.04 (0.96–1.12), I^2=34%	No difference No significant publication bias
Improvement in physical function expressed as MD in ODI%	36 (3315), longest follow-up outcome	MD=−1.77 (−2.99 to −0.56), I^2=73%	Better improvement with LA + steroid No significant publication bias
Global improvement or Patient satisfaction expressed as RR	8 (806), longest follow-up outcome	RR=1.16 (0.96–1.40), I^2=51%	No difference
Quality of life expressed as MD using 0–100 scale	9 (963), longest follow-up outcome	MD=2.59 (−0.71 to 5.89), I^2=30%	No difference
Adverse effects expressed as RR			
Serious effects needing surgery or hospitalisation	2 (426), longest follow-up outcome	RR=1.45 (0.53–3.96), I^2=0%	No difference
Facial flushing	5 (652), longest follow-up outcome	RR=3.44 (0.89–13.28), I^2=0%	No difference
Cutaneous atrophy	2 (213), longest follow-up outcome	RR=1.97 (0.84–4.60), I^2=0%	No difference
Headache	2 (494), longest follow-up outcome	RR=1.83 (0.74–4.55), I^2=0%	No difference
Swelling	2 (455), longest follow-up outcome	RR=2.00 (0.18–21.87), I^2=0%	No difference
Subgroup analysis for exploration of heterogeneity			
Effect within subgroups of single *vs* multiple injections on the success of pain relief	Single injection, 19 (4014), longest follow-up outcome	RR=1.38 (1.06–1.79), I^2=63%; NNT, 8.5	Higher success with LA + steroid
	Multiple injection, 25 (2611), longest follow-up outcome	RR=1.10 (0.98–1.23), I^2=71% Interaction test, P=0.24	No difference No subgroup effect
Effects within subgroups of single *vs* multiple injections on decrease in pain score	28 (1699), longest follow-up outcome	MD=−0.59 (−1.03 to −0.15), I^2=84%	Better pain relief with LA + steroid
	27 (3530), longest follow-up outcome	MD=−0.14 (−0.39 to 0.10), I^2=74% Interaction test, P=0.09	No difference No subgroup effect
Success of pain relief based on subgroup of clinical conditions	44 (3625), longest follow-up	RR=1.16 (1.05–1.29), I^2=68%; NNT, 12.1 Interaction test, P=0.07	No significant outcome in any category No subgroup effect
Reduction in pain expressed using 0–10 NRS based on subgroup of clinical conditions	54 (4401), longest follow-up	MD=−0.33 (−0.56 to −0.10), I^2=80% Interaction test, P=0.64	No significant outcome in any category No subgroup effect
Sensitivity analyses and meta-regression			
Effect of steroid dose on the success of pain relief	42 trials, longest follow-up outcome	P=0.10	No effect
Effect of steroid dose on reduction of pain score	54 trials, longest follow-up outcome	P=0.002	

Continued

Table 2 Continued

Outcome	Number of trials (participants)	Results Effect size (95% CI)	Inference and observation
			Although statistically significant, the decrease in pain scores are not clinically meaningful
Effect of steroids on the duration: as success over length of follow-up in single injection studies	19 trials, longest follow-up outcome	P=0.88	No effect
Effect of steroids on the duration: as decrease in pain scores over length of follow-up in single injection studies	28 trials, longest follow-up outcome	P=0.54	No effect

diagnostic purpose.[135] However, their duration of relief in CNCP can outlast the expectation in a diagnostic injection. Hence diagnostic blocks with LA may be of limited value, often overshadowed by their therapeutic benefit,[5,135–138] unless the intent is to follow with an intervention of different nature, such as a neuro-ablative procedure. In an RCT involving 378 patients of non-specific chronic low back pain, patients having lidocaine paraspinal injections with standard treatment had a significantly higher rate of response compared with sham injections or standard treatment alone.[136] In their recent update on evidence-based interventional guidelines according to clinical diagnoses, Huygen and colleagues[137] note several spine interventions for which the structure can be injected by LA with or without steroid.

Several studies and reviews, both for spine and non-spine CNCP interventions, have considered it important to evaluate the effectiveness of steroids as a therapeutic agent. Individual reviews within specific populations have not been conclusive, and our review represents a broader, systematic updated overview, on the effect of adding steroids to LA for CNCP. In a systematic review restricted to epidural injections, Bicket and colleagues[28] observed that the absolute benefit favouring epidural non-steroid over non-epidural injections was greater (RR=0.27; 0.15 to 0.39) than the difference between epidural steroid and epidural non-steroid (RR=0.04; −0.01 to 0.10), suggesting the target of injection is important, and steroids do not add value to the injected solution. Similar contrasting results have been observed in other population groups by other reviews.[32] In another review, Zhai and colleagues[139] looked specifically at RCTs for patients with chronic back and radicular pain of disc herniation or radiculitis and observed that 42% of SLA and 40% of LA had significant pain relief, with similar pain scores and functional improvement. Such observations have been made in previous reviews of lumbar radiculopathy and spinal stenosis, and also in mixed spinal populations.[140,141] Steroids are also added to blocking peripheral nerve blockade (PNB) for chronic pain.[142] Bhatia and colleagues[142] pooled five studies to compare steroid *vs* non-steroid groups and observed steroids to decrease pain relief by 1.3 points in a 0–10 NRS (I^2=89%). However, we found that even within the subgroup of PNB, the results were not significant for both success (n=7) (Fig 4) or pain scores (n=6) (Appendix S9). Although earlier, smaller studies with PNB for headache have observed superior results with SLA,[63,71] the recommendations on PNB by the American Headache Society suggests using steroids only for cluster headache,[143] as there is no consensus.[54,144] It is surprising that steroids are considered for neural blockade even when a specific structure conveys the pain signal and is not directly involved in pathogenesis. For example, genicular nerve blockade with SLA was observed to have similar effect as ablation in a small RCT.[145] However, a subsequent RCT demonstrated that steroids did not have any additional effect than LA blockade.[116] Similarly, multiple studies have used SLA for celiac plexus blocks with an intention to prolong pain relief.[146] However, the only RCT comparing triamcinolone and bupivacaine with only bupivacaine for celiac plexus block (chronic pancreatitis) found no differences in the success rate.[147] We found it surprising that there was not a single RCT evaluating the role of steroids in sympathetic blocks, given that nearly 50% pain physicians add them,[148] including near highly vascular structures.[149] Other common conditions in which steroid injections are considered include epicondylitis, and bursa injections, which we considered under soft tissue structures. We found no significant

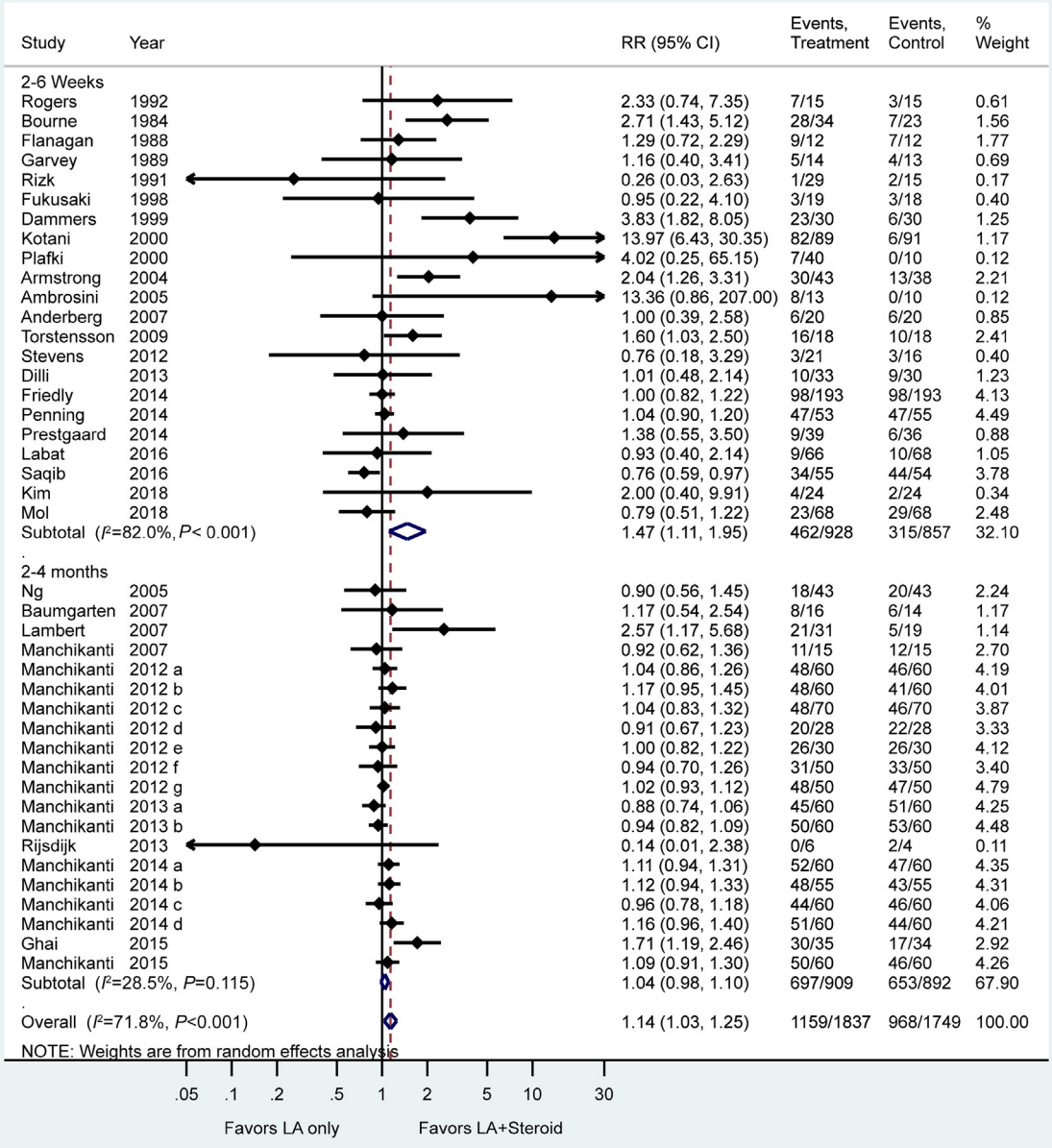

Fig 2. Comparison of successful pain relief. Interaction test P=0.07 for subgroups of 2–6 weeks *vs* 2–4 months follow-up among 42 trials (22 *vs* 20 trials, of which five trials reported pain at both time points, and we used the data at the earliest follow-up only). CI, confidence interval; RR, relative risk.

improvement in pain scores (Appendix S9) or in the success rate (Fig 4). Similar observations have been made about inconsistent or no effects of steroids on these conditions in multiple previous reviews specific to such population.[26,150] Despite evidence and recommendations, physicians continue to use steroids in trigger point injections. As observed in the review by Cummings and White,[12] we found no evidence to support the use of steroids in trigger point injections, including for deep myofascial trigger points such as in piriformis syndrome.[93] Systematic reviews of multiple studies,[151] and recent RCTs[13] have found no consistent evidence to support the use of steroids in intra-articular injections for osteoarthritis.[151] We also observed that there is no association between the dose of steroid and clinical outcomes (Table 2 and Appendices S10a and S10b), and the statistical significance achieved for pain scores (Appendix S10b) was not clinically meaningful. Recent guidelines for spine injections do not recommend, doses exceeding 40 mg for

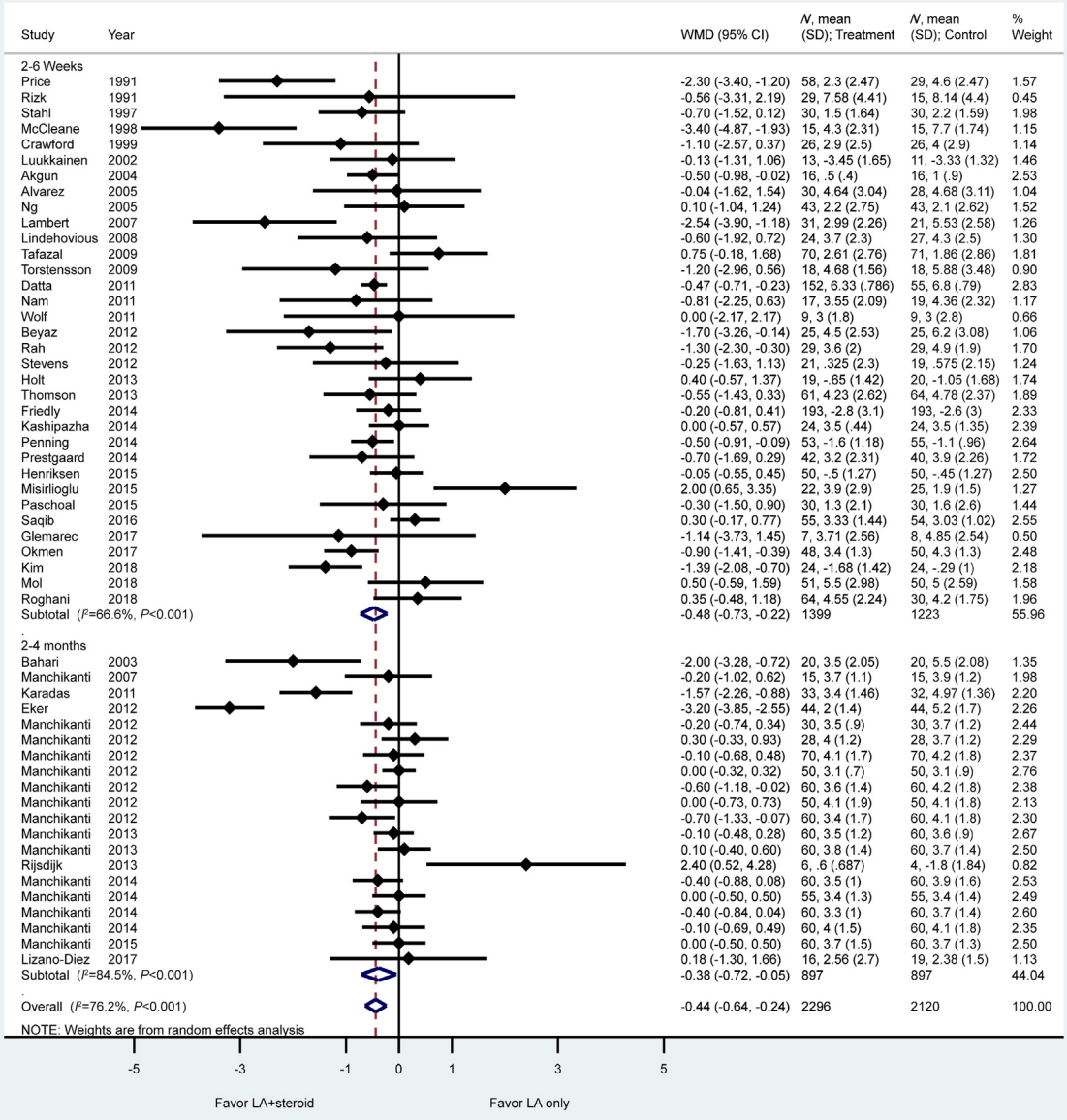

Fig 3. Comparison of pain reduction on an 11-point scale. Interaction test $P=0.94$ for subgroups of 2–6 weeks *vs* 2–4 months follow-up among 54 trials (34 *vs* 20 trials, of which 19 trials reported pain at both time points, and we used the data at the earliest follow-up only). Change scores were used if both end scores and change scores were reported (44 trials with end scores *vs* 10 trials with change scores). SD, standard deviation; WMD, weighted mean difference.

methylprednisolone acetate, 20 mg of triamcinolone, and 10 mg for dexamethasone,[152] consistent with recent studies in non-spine population.[118]

Apart from the clinical subgroups we explored for subgroup analysis, some consider other determinants to be important for success.[153] For example, in ESI such determinants could include the route of injection; image guidance; epidural approach; radicular *vs* non-radicular pain; based on underlying pathology; and the number of injections. It is likely that image guidance to deeper structures improves precise delivery and could influences outcomes, especially with ESI.[154] However, in clinical practice, there is wide variability in the route and techniques used. A 2002 national level survey in the USA reported that only 39% academic centres as compared with 79% private practices use fluoroscopy for cervical epidural injections.[155] Similarly, a 2020 survey from Canada indicated that only 55% of physicians involved in spinal injections use image guidance (fluoroscopy or CT scan).[156] The advantage of image guidance on pain relief or function in superficial myofascial structures is uncertain.[157,158] In their recent Cochrane review, Oliveira and colleagues[159] looked at ESIs for lumbosacral radicular pain and compared steroid

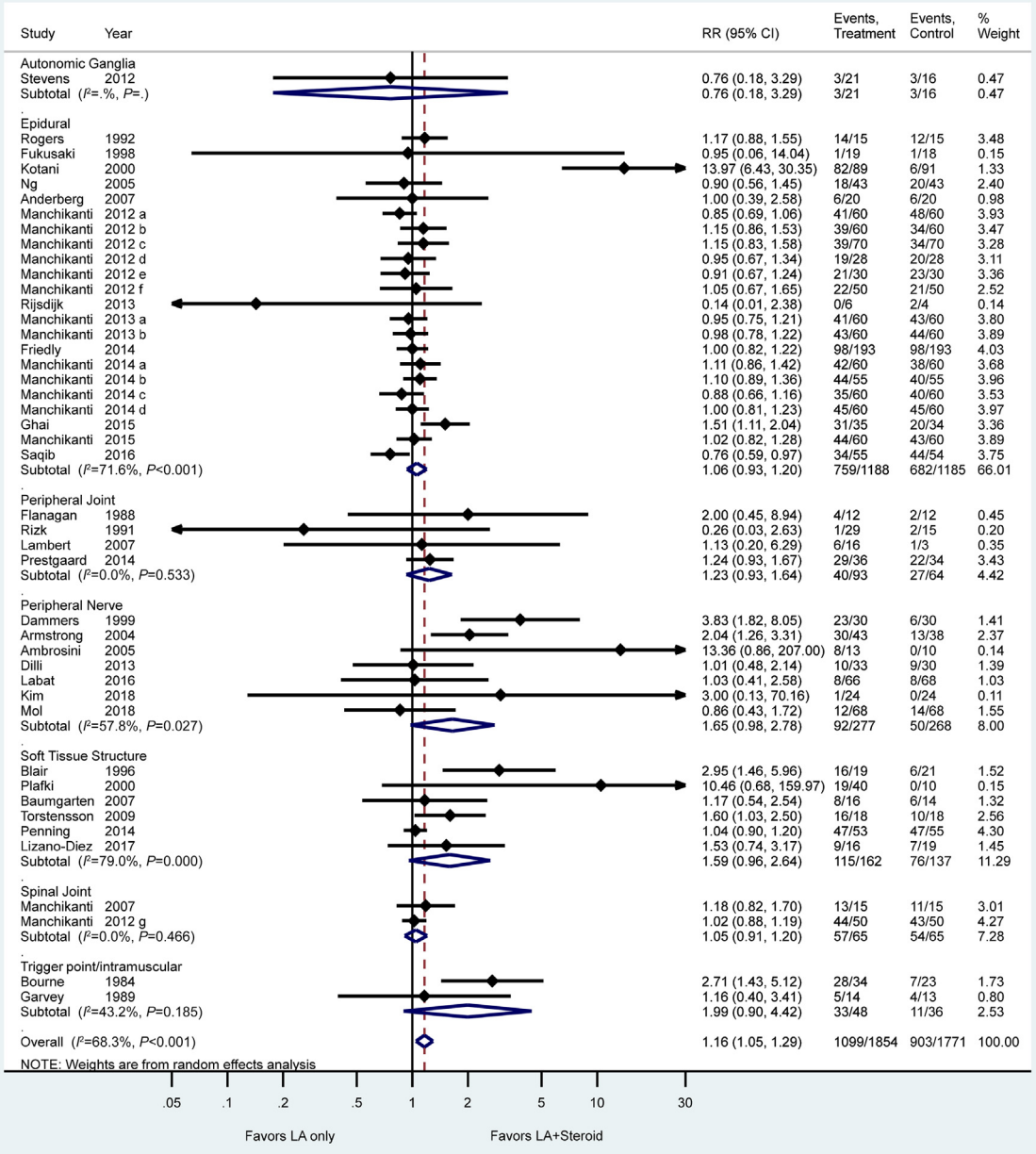

Fig 4. Comparison of successful pain relief as subgroup analysis in clinical categories. Subgroup analysis of different clinical conditions for pain at the longest follow-up (Interaction test P=0.07). CI, confidence interval; RR, relative risk.

agents with all non-steroid agents. Although short-term improvement in leg pain was observed, they found no subgroup differences based on approach or image guidance.[159] In our review we observed that repeat injections are not helpful. In a large observational study, Friedly and colleagues[160] reported that patients with repeat ESIs were more likely to use higher opioid doses, possibly as a reflection of low therapeutic response. Previous attempts at identifying responders to ESI with laboratory markers and imaging studies was inconclusive.[161] It is possible that factors outside of this review (such as sub-acute pain),[162] or other patient-level factors not yet recognised could indicate success with steroids.[150,151,163]

Adverse events and acceptable risks

Our review did not find significant differences, most likely as a result of methodological considerations and study limitations. As such, RCTs are not ideal to capture adverse effects related

to therapy,[164] and most adverse effects are under-reported.[165] However, steroid injections have a multitude of side-effects, both small and potentially devastating.[25] These adverse effects can be both absolute and dose related.[166–168] Soft tissue atrophy and alopecia are some of the local effects.[169,170] Higher doses lead to more sustained adrenal insufficiency with both epidural and intra-articular injections.[171,172] Hormonal changes could lead to abnormal vaginal bleeding, variations in blood sugar, infections, skin changes, weight gain, and osteoporosis, and vertebral fractures.[6,167,173] Unfortunately, the multidisciplinary working recommendations to minimise the risk of devastating neurological complications with ESIs do not include dose reduction, or even avoidance of steroids, if appropriate on patient, or clinical considerations.[25]

Clinical practice implications

Clarifying what is a therapeutic procedure, as defined by the agent injected, is essential for practice, regulatory, and billing purposes. It is also challenging to integrate this in the context of patient preferences, and relative choices. For example, in lumbar spinal stenosis, no pharmacological therapies are reliably effective for pain relief.[174] A popularly cited study indicated no difference between LA and SLA, but more than 3-point decrease from the baseline pain scores in both groups with nearly 50% patients having >30% pain relief in both groups at 6 weeks, consistent with our review results.[66] It is not surprising given such observation in a previous systematic review,[175] and also as recently substantiated by a recent three-arm RCT (published during our peer review) comparing tumour necrosis factor-alpha *vs* LA and steroid *vs* LA alone, in patients of lumbar spinal stenosis with unilateral radicular pain. There were no significant differences in the pain scores and functional improvement with the steroid group compared with LA alone at 1, 3, and 6 months.[176]

Limitations

Our review attempted to cover a broad nature of CNCP conditions, and some may consider it inappropriate to combine them because of heterogeneity in population, study, and techniques. Our comparators were both active, and hence this review cannot be helpful to assess the efficacy of either one of that separately as compared with a placebo or sham injection. We need to also consider that, despite being level 1 evidence, RCTs may have limitations such as small sample size, population unrepresentative of clinical practice, apart from other challenges involved in placebo control and blinding.[177]

Conclusions

Across a whole range, there is minimal benefit by adding steroids to local anaesthetics for chronic non-cancer pain injections, and there is clear potential for harm. Injection of local anaesthetics alone may be used, not just for diagnosis but also therapy. Physicians should consider a shared decision based on patient preferences. If steroids are used, one must avoid high doses and series of injections.

Transparency declaration

The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination declaration

Dissemination of results to study populations is not applicable.

Authors' contributions

Study conception and design: HS, JB, JP, LT
Acquisition of data: HS, LW, AK, PH, ES, VB, EZ, MB
Analysis of data: HS, LW
Interpretation of data: HS, JB, LW, AK, PH, ES, VB, EZ, JP, MB, LT
Literature search: RC
Drafting of the manuscript: all authors.

Declarations of interest

HS is supported by the Canadian Anesthesia Research Foundation through the Career Scientist Award, 2018–2020. The review was initially submitted as SH MSc thesis in 2015. However, there have been substantial changes to methods, and also the results as we have added nine new studies to this review. https://macsphere.mcmaster.ca/handle/11375/18440 Only a partial and preliminary report of this review and meta-analysis was presented as an abstract and received the Best of the Meeting award at the American Society of Regional Anesthesia and Pain Medicine (ASRA) 2018 meeting. https://www.asra.com/page/2692/best-of-meeting-awards.

All other authors declare no competing interests.

Acknowledgements

We declare no funding associated with this work. We thank Harman Chaudhry, Division of Orthopaedic Surgery, University of Toronto, Toronto, ON, Canada; and Dr Isabel Kim, Division of Internal Medicine, University of British Columbia, Vancouver, BC, Canada, for their contribution to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.06.062.

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Handling editor: Jonathan Hardman