Systematic review

Systematic review of management of chronic pain after surgery

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Background: **Pain present for at least 3 months after a surgical procedure is considered chronic postsurgical pain (CPSP) and affects 10–50 per cent of patients. Interventions for CPSP may focus on the underlying condition that indicated surgery, the aetiology of new-onset pain or be multifactorial in recognition of the diverse causes of this pain. The aim of this systematic review was to identify RCTs of interventions for the management of CPSP, and synthesize data across treatment type to estimate their effectiveness and safety.**

Methods: **MEDLINE, Embase, PsycINFO, CINAHL and the Cochrane Library were searched from inception to March 2016. Trials of pain interventions received by patients at 3 months or more after surgery were included. Risk of bias was assessed using the Cochrane risk-of-bias tool.**

Results: **Some 66 trials with data from 3149 participants were included. Most trials included patients with chronic pain after spinal surgery (25 trials) or phantom limb pain (21 trials). Interventions were predominantly pharmacological, including antiepileptics, capsaicin, epidural steroid injections, local anaesthetic, neurotoxins, *N*-methyl-D-aspartate receptor antagonists and opioids. Other interventions included acupuncture, exercise, postamputation limb liner, spinal cord stimulation, further surgery, laser therapy, magnetic stimulation, mindfulness-based stress reduction, mirror therapy and sensory discrimination training. Opportunities for meta-analysis were limited by heterogeneity. For all interventions, there was insufficient evidence to draw conclusions on effectiveness.**

Conclusion: **There is a need for more evidence about interventions for CPSP. High-quality trials of multimodal interventions matched to pain characteristics are needed to provide robust evidence to guide management of CPSP.**

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Introduction

Pain present for at least 3 months after a surgical procedure is described as chronic postsurgical pain (CPSP)[1]. CPSP affects between 10 and 50 per cent of patients after common operations such as mastectomy, cardiac surgery, hysterectomy, hernia repair, joint replacement, back surgery and also more minor procedures[2–8]. In a European survey[9] of surgical patients, the prevalence of moderate to severe CPSP at 12 months after operation was 11·8 per cent. Chronic pain is associated with poor general health, disability, depression[9–12] and social withdrawal, and increases the risk of further co-morbidities[13]. CPSP has been defined previously as pain that develops after surgery[5], and a proposed update to the definition includes the possibility that CPSP is pain that increases in intensity after surgery[14]. This update allows for the possibility that pain among patients who undergo surgery to relieve pain is also, appropriately, included in the definition.

Risk factors for CPSP may be genetic, psychosocial, or related to preoperative or acute postoperative pain severity[2,15]. However, certain surgical procedure-related factors are key for the development of chronic pain[16]. Surgical procedures lasting longer than 3 h may increase the risk of postoperative pain[5]. A major surgical factor in the development of chronic pain is nerve injury, and patients undergoing thoracic, breast and hernia surgery are at particular risk of neuropathic pain[8]. Inflammation resulting from intraoperative tissue injury can contribute

to central sensitization and further pain[2]. Inadequate preventive analgesia may also contribute[17].

Knowledge of determinants and predictors of CPSP can guide the development of interventions and help target care. Possible forms of management for CPSP may focus on the underlying condition that needed surgery, on the aetiology of the pain, or be multifactorial in recognition of the diverse causes of postoperative pain. Although some forms of management may have limited applicability outside of the specific condition for which they were intended, others may be transferrable, regardless of the surgical procedure.

There are systematic reviews of pharmacological and other interventions for the management of chronic pain, defined generally, or specific to the presumed mechanisms (such as neuropathic pain[17] and cancer pain[18]). A number of Cochrane reviews[17,19–29] have included studies evaluating interventions for CPSP, although this was not the primary focus of these reviews. It is rare for any review to focus specifically on chronic pain in the postoperative context. Exceptions include reviews that have focused on interventions for chronic pain after particular surgical procedures, including phantom limb pain after amputation[30] and knee replacement[31]. The aim of the present review was to identify RCTs of interventions for the management of CPSP and to synthesize data across treatment type to provide an estimate of their effectiveness and safety. In keeping with recommended practice, a systematic review is a key step toward the development of future trials to evaluate interventions for CPSP[32].

Methods

The protocol was registered in the international prospective register of systematic reviews (PROSPERO; http://www.crd.york.ac.uk/PROSPERO/) on 15 January 2015 (registration number 15957). The review was conducted in accordance with PRISMA guidelines[33].

Eligibility criteria

Published articles describing RCTs involving any intervention that aimed to provide management of CPSP were included. Eligible studies reflected PICO criteria[34]: patients aged 18 years or more and at least 90 per cent of study participants reporting CPSP; interventions for pain received by patients at a minimum of 3 months after surgery; comparison arm of placebo, usual care or an alternative pain management intervention; and outcomes were pain reported using any data collection tool(s).

Information sources and searches

MEDLINE, Embase, PsycINFO, CINAHL and the Cochrane Library were searched from inception to 23 March 2016. The search strategies were modified for different bibliographic databases (*Appendix S1*, supporting information). No language restrictions were applied. Reference lists were checked and registers inspected; grey literature (literature not formally published as journal articles) was sought in OpenGrey (http://www.greynet.org/opengreyrepository.html), a database of grey literature, on 30 March 2016. A minimum sample size was not specified in the protocol to ensure inclusion of all treatments of potential interest to clinicians and researchers working in a range of surgical specialties.

Published conference abstracts were followed up to obtain any full publications, but otherwise excluded. After completion of data extraction, relevant systematic reviews were identified from the Cochrane Database of Systematic Reviews, and included studies were reviewed to identify any studies missed in the initial searches because eligibility was not apparent from the title and abstract.

Study selection

All records identified in the search were imported into EndNote X7 (Thomson Reuters, New York, New York, USA). Abstracts or full-text articles were screened to remove obviously irrelevant reports. Reasons for excluding studies were recorded as free text in EndNote X7. This was performed by one author who was over-inclusive if eligibility was not clear. A sample of 10 per cent was double screened by a second author, which identified one eligible study that had been missed. The final selection of studies was then performed in duplicate by two authors. When there was insufficient information to determine eligibility, study author e-mail addresses were obtained and supplementary information was requested.

Data collection

Data from included studies were extracted using standard forms by one author and checked by a second author. Study setting, participant demographics, methodology, recruitment, duration, treatment characteristics, length of follow-up, outcomes, tools used to measure outcomes, and information for the risk-of-bias assessment were recorded. Authors of studies were contacted where necessary for clarification and to provide missing or incomplete data.

Outcomes

In accordance with GRADE guidelines[35] and Cochrane guidance, the total number of outcomes planned to be included in this review was limited to seven (2 primary and 5 secondary). The primary clinical effectiveness outcome was pain intensity and the primary harm outcome was serious adverse events. These reflect recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[36] and the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS)[37]. Studies were required to report the primary outcome of pain intensity to be eligible for inclusion in the review. The first secondary outcome was the presence or absence of neuropathic pain, which is particularly relevant to chronic pain after a surgical intervention[8]. The other four secondary outcomes reflected the IMMPACT core outcome domains for chronic pain clinical trials: physical functioning, emotional functioning, participants' ratings of global improvement and satisfaction with treatment, and participant disposition[36]. No limits were placed on the tools used to measure these outcomes.

Risk of bias in individual studies

Risk of bias was assessed using the Cochrane risk-of-bias tool[38]. Two authors assessed the risk of bias independently across the six domains of the tool for each study. Results are reported through graphical representation of bias judgements grouped by intervention.

Statistical analysis

In the protocol, meta-analyses were planned using RevMan 5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) with general guidance from the Cochrane Handbook[38]. For dichotomous (binary) data, the odds ratio with 95 per cent c.i. would be used. For continuous data, if outcomes were measured identically across studies, an overall mean difference and 95 per cent c.i. would be calculated. If continuous outcomes were measured differently across studies, overall standardized mean differences and 95 per cent c.i. would be calculated. For data from crossover trials, the generic inverse-variance method in RevMan 5 would be used.

Opportunities for meta-analysis were limited by heterogeneity between studies. Even when multiple studies for a particular intervention were identified, variation in modes of administration, comparator groups and/or format of outcome data precluded pooling. Thus, the majority of results are reported narratively, with results of meta-analyses described only for gabapentin and capsaicin. Planned subgroup analysis of pharmacotherapy, physical/self-management and multidisciplinary interventions was not possible owing to clinical and methodological heterogeneity. Results for pain outcome at final follow-up within individual studies are presented as reported by investigators (*Tables S1* and *S2*, supporting information).

Results

Included trials

Searches identified 17 029 articles, of which 660 were considered potentially relevant after initial screening. Author e-mail addresses were traced for 57 of 78 studies that contained insufficient information to determine eligibility, and further data were requested. Replies were received for 16 studies, and only one was eligible for inclusion. The remaining articles were assumed to be ineligible as the abstract or full text made no reference to patients having CPSP. After evaluation of full-text articles, 66 trials[39–104] with data from 3149 participants were included (*Fig. 1*).

An overall summary of trial characteristics is provided in *Table 1* and characteristics of individual trials are shown in *Tables S1* and *S2* (supporting information). *Table 2* summarizes studies according to the index surgery and intervention. Individual components of risk-of-bias assessment are provided in *Appendix S2* (supporting information).

Trial design

Trials were generally small, ranging in size from three to 250 participants (median 38). The study with three participants was a pilot trial, but a total of 18 trials recruited fewer than 20 participants. Sample size calculations were reported in 34 of 66 studies; of these, 13 failed to recruit or retain sufficient numbers of participants to meet their calculation. Authors did not always state dates of recruitment; publication dates ranged from 1989 to 2016. There has been an increase over time in the number of published trials in this field, from ten trials published before 2001 to 23 published between 2011 and 2015.

Interventions

The primary method of reporting results was grouped according to treatment type. The majority of studies evaluated pharmacological interventions, and so studies were grouped as primarily pharmacological, or as primarily physical, surgical, psychological and other (*Table 1*).

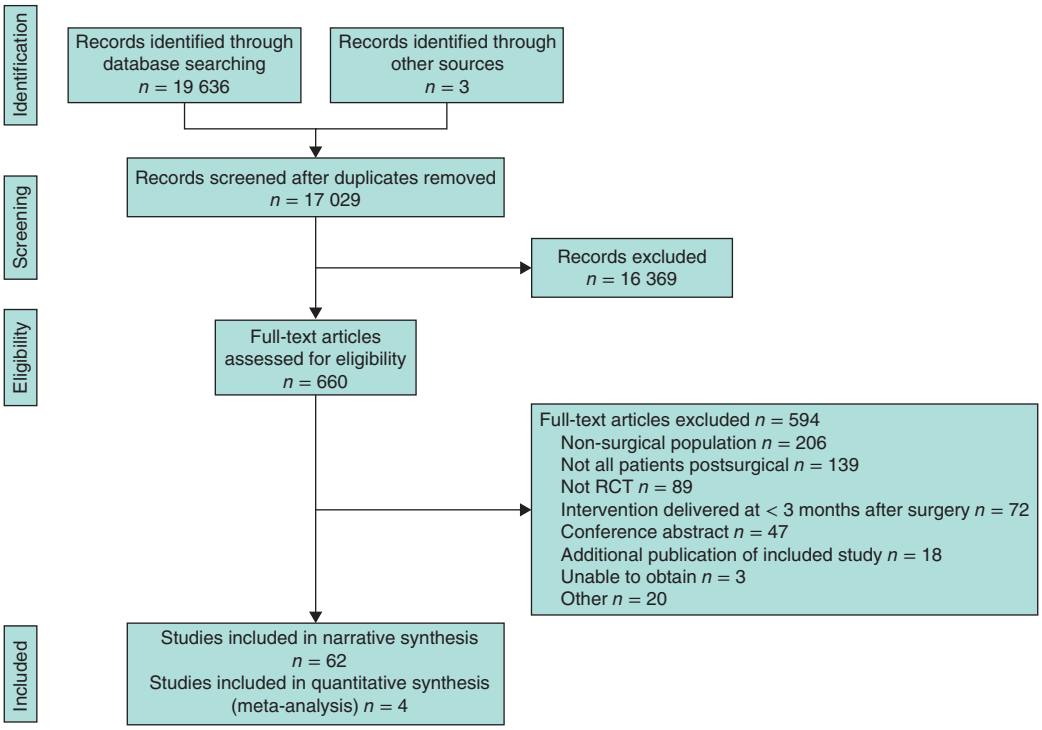

Fig. 1 Flow diagram showing selection of articles for review

Outcome measurements

A visual analogue scale (VAS) was used to assess pain intensity in 37 of 66 studies (56 per cent). Validated pain-specific tools were used infrequently; the most common was the McGill Pain Questionnaire, which was used in eight studies. Only one trial referenced IMMPACT criteria[36] for patient outcomes. In terms of presentation of the primary outcome (pain intensity) as the percentage of patients reporting 30 or 50 per cent improvement, a format preferred by both IMMPACT[105] and the Cochrane PaPaS Group[106], only a minority of authors (6 of 31 trials published after 2008) were compliant. Serious adverse events and the secondary outcomes in this review were reported inconsistently and there was no opportunity to summarize these outcomes; therefore, only pain outcomes are presented in *Tables S1* and *S2* (supporting information).

Pharmacological interventions

Antidepressants

Four trials, including data from 177 participants, evaluated the effect of antidepressants on chronic pain after amputation[39,40] or breast surgery[41,42]. Risk of bias was evident in two studies owing to incomplete outcome data[40,42], and a change to the definition of responder and potential funder bias[40]. Amitriptyline was evaluated in three trials[39,40,42], with some issues suggesting risk of bias, and venlafaxine in one trial[41] with a low risk of bias. There was no evidence that a 4–6-week course of antidepressants reduced pain intensity compared with placebo, except in one trial[42] involving 20 patients which found that patients reported lower breast scar pain intensity after 4 weeks of 100 mg/day amitriptyline compared with placebo. However, this trial also found evidence that amitriptyline resulted in more adverse events than placebo.

Antiepileptics

Eight trials including data from 338 participants evaluated the effects of antiepileptic medications on CPSP. The largest number of studies for any one technology was for gabapentin (6 studies, 293 participants with pain after amputation[43,44], breast cancer surgery[45], sternotomy[46] and spinal surgery[47,48]). Four trials were at risk of bias owing to issues relating to blinding[48], blinding and randomization[45], incomplete outcome data[44], and blinding and single-authored article[47]. Meta-analysis using the generic inverse-variance method was possible for the primary outcome for one subgroup only (gabapentin *versus* placebo for 6 weeks) involving two crossover trials with 43 patients[43,44]. This demonstrated a within-person mean difference in pain intensity measured on a VAS and numerical

Table 1 Overall summary of trial characteristics

Trial design	Parallel design (41), crossover study (25)
No. of arms	Two arms (53), three arms (12), five arms (1)
Countries	USA (21), Germany (8), Denmark (7), Iran (3), China (2), Egypt (2), Finland (2), France (2), Italy (2), Korea (2), Sweden (2), Turkey (2), Belgium (1), Canada (1), Israel (1), Mozambique (1), The Netherlands (1), Norway (1), Serbia (1), Spain (1), Switzerland (1), UK (1), international multisite (1)
Surgery types	Spinal surgery (25), amputation (21), breast cancer surgery (8), inguinal hernia repair (3), neck dissection for cancer (2), knee replacement (1), sternotomy (1), abdominal surgery (1), shoulder surgery (1), various surgical procedures (3)
Interventions	
Pharmacological	Antidepressants as analgesics (4), antiepileptics (8), capsaicin (3), epidural steroid injections and associated interventions (11), local anaesthetic (11), neurotoxins (3), *N*-methyl-D-aspartate receptor antagonist (7), opioids (6), calcitonin (1), naloxone as an adjuvant to morphine (1)
Physical, surgical, psychological and other pain management	Acupuncture/dry needling (2), exercise (4), limb cover/liner for patients who had undergone amputation (2), spinal cord stimulation (5), further surgery (2), laser therapy (1), magnetic stimulation (1), mindfulness-based stress reduction (1), mirror therapy for amputation (1), sensory discrimination training (1), joint manipulation (1), combined package of hot packs, ultrasound treatment and transcutaneous electrical nerve stimulation (1)
Comparator interventions	Active treatment (31), placebo or sham (31), usual care (2), waiting list (1), no treatment (1)

Values in parentheses are number of studies.

rating scale score of −1·12 (95 per cent c.i. −1·89 to −0·36; $I^2 = 53$ per cent), favouring gabapentin (*Fig. S1*, supporting information). Similar results are reported in a Cochrane review[30] and no studies additional to those included in the previous review were identified. The two trials that compared gabapentin with non-steroidal anti-inflammatory drugs (NSAIDs) found that gabapentin provided more effective pain relief after 1 month[46] and 6 months[48] of treatment. An 8-week course of gabapentin was found to be superior to a stellate ganglion block using bupivacaine in a trial involving 60 patients after mastectomy[45]. The addition of 1 month of oral gabapentin to standard epidural corticosteroids was found to result in lower pain at 6 months compared with epidural corticosteroids alone after spinal surgery[47].

One trial[49] with a low risk of bias found no differences in pain relief between levetiracetam and placebo over 4 weeks of treatment. Pain relief after taking pregabalin for 7 weeks for chronic pain after abdominal surgery was compared with placebo in a study of 13 patients[50]; results favouring the treatment group must be interpreted with caution as the trial was terminated early by the industry sponsor.

Capsaicin

Three trials including data from 174 participants evaluated capsaicin for relief of chronic pain after inguinal hernia repair[51], mastectomy[52], and diverse procedures for cancer[53]. All studies were at risk of bias because of issues relating to blinding of a preparation with a burning sensation and erythema. One study[52] was also at risk of bias owing to selective reporting. The trial[51] assessing a single 60-min application of a capsaicin patch (8 per cent) found no evidence of pain relief compared with placebo after 3 months. Two trials[52,53] of low-dose (0·075 per cent) capsaicin topical cream applied four times daily for 6–8 weeks reported some evidence of reduced pain intensity compared with placebo. Meta-analysis suggested a modest positive effect of capsaicin topical cream on the proportion of patients reporting pain improvement (odds ratio 2·64, 95 per cent c.i. 1·02 to 6·86; $I^2 = 0$ per cent) (*Fig. S2*, supporting information), although caution is warranted owing to risk of bias and, as a previous Cochrane review[107] advised, the total number of events was too few to be reliable. In both trials, a commonly reported side-effect was local skin reaction.

Epidural injections and associated interventions

Eleven trials including data from 886 participants evaluated epidural injections and associated interventions after spinal surgery[54–64]. Risk of bias was evident in ten studies relating to allocation concealment[54–56,64], blinding[54,58,61], incomplete outcome data[54,57,61,63], selective reporting[56,57,59,62] and single-authored article[63]. Two trials[55,56] comparing epidural injections with, and without steroids found no difference in pain relief between groups. The addition of steroids to 3-monthly morphine epidural injections was not found to influence pain intensity after 6 months[59]. A three-arm trial[63] involving 206 patients evaluated epidural injections of 1 mg indomethacin, 2 mg indomethacin and 80 mg methylprednisolone, and found that all treatments resulted in a similar pain reduction. Two trials evaluating epidural injections of steroids (prednisolone acetate) *versus* saline alone produced contrasting results: one[57] noted no benefit at 120 days and the other[58] reported a reduction in pain at 18 months after multiple epidural injections. The addition of hyaluronidase to an epidural steroid injection was found to lead to lower pain intensity at 4 weeks[62] and 12 months[60], and a combination of hyaluronidase and triamcinolone provided more effective pain relief for 12 weeks than either agent alone[61]. Two trials reported that adding percutaneous adhesiolysis to an epidural injection

Table 2 Summary of included studies according to the index surgery and intervention

	Amputation	Spinal surgery	Breast cancer	Abdominal surgery	Hernia repair	Knee replacement	Neck dissection	Sternotomy	Shoulder surgery	Mixed
Pharmacological interventions										
Antidepressants	2[39,40]		2[41,42]							
Antiepileptics	2[43,44]	2[47,48]	2[45,49]	1[50]				1[46]		
Capsaicin			1[52]		1[51]					1[53]
Epidural injection and associated interventions		11[54–64]								
Local anaesthetic	4[70–73]	2[67,68]	2[45,74]		2[65,66]					1[69]
Neurotoxins	1[77]					1[75]	1[76]			
NMDA receptor antagonist	6[78–83]									1[69]
Opioids	4[40,70,71,84]	1[59]	1[85]							
Other	1[78]									1[86]
Physical, surgical, psychological and other interventions										
Acupuncture/dry needling							1[88]		1[87]	
Exercise	1[91]	3[89,90,92]								
Limb cover/liner	2[93,94]									
Spinal cord stimulation		5[95–99]								
Surgery		2[90,95]								
Other	2[102,104]	3[92,100,103]	1[101]							

Nine trials[40,45,59,69–71,90,92,95] were included twice or more as they evaluated interventions which fall into different categories. NMDA, *N*-methyl-D-aspartate.

led to better pain relief at 6 months[64] and 12 months[54] after treatment.

Local anaesthetics

Eleven trials including data from 324 participants assessed the effectiveness of local anaesthetics in providing pain relief after inguinal hernia repair[65,66], spinal surgery[67–69], amputation[70–73] and breast cancer surgery[45,74]. Risk of bias was evident in three studies, and concerned incomplete outcome data[73], random sequence generation and blinding[45], and early trial termination[65]. Interventions assessed included lidocaine block[65], repeated epidural nerve blocks[68], stellate ganglion block[45,74], bupivacaine[72], intravenous lidocaine[67,69,70], ropivacaine[73], oral mexiletine[71] and lidocaine patch[66].

Five trials evaluated local anaesthetic nerve blocks. No difference in pain intensity was found after ultrasound-guided lidocaine nerve block compared with placebo block[65] or after repeated epidural sympathetic nerve block compared with saline blocks[68]. A trial[45] of stellate ganglion blocks for pain after breast surgery found that they were inferior to gabapentin; another trial[74] noted that pain relief at 8 weeks was improved with ultrasound guidance compared with unguided blocks. One trial[72] found that injections of bupivacaine into contralateral painful muscle sites that mirror phantom limb pains were more effective at providing pain relief than placebo saline injections.

Five trials evaluated systemic administration of intravenous local anaesthetic or oral mexiletine. Two trials[67,69] found that intravenous lidocaine did not reduce pain intensity compared with saline, and one[70] reported that it reduced stump pain, but not phantom limb pain. A pilot trial[73] of three patients reported that ropivacaine reduced phantom limb pain after 12 weeks, although no statistical tests were performed on this small patient sample. An 8-week course of oral mexiletine was found to have no effect on pain intensity compared with placebo in a trial with 60 patients[71].

A single trial[66] of 21 patients evaluated lidocaine patches (5 per cent); applied for 2 weeks, they were found to produce similar results to placebo patches.

Neurotoxins

Three trials including data from 91 participants evaluated botulinum toxin A injections for chronic pain after knee replacement[75], neck dissection[76] and lower limb amputation[77]. One study[77] had evidence of bias relating to incomplete outcome data. In patients with knee replacement treated with botulinum toxin A, pain intensity was reduced compared with that in the placebo group after 2 and 7 months, with no increase in adverse events[75]. In a dose-finding study[76] involving patients with chronic pain after neck dissection, a lower dose of botulinum A toxin was associated with reduced pain intensity. There was little evidence that botulinum A was more effective than lidocaine/Depo-Medrol® (Pharmacia & Upjohn, New York, New York, USA) injection after 6 months in a pilot trial of patients with phantom limb pain[77].

N-methyl-D-aspartate receptor antagonists

Seven trials, including data from 122 participants, evaluated *N*-methyl-D-aspartate (NMDA) receptor antagonists. One study[78] had evidence of risk of bias relating to blinding and incomplete outcome data. No differences in pain relief after 3–5 weeks of memantine compared with placebo were found in four trials[79–82] involving patients with pain after amputation. Three studies, involving 11–20 patients each, evaluated ketamine alone or in conjunction with calcitonin with placebo for patients with phantom limb pain[78,83] or pain after diverse procedures[69]. All trials provided evidence that the intervention reduced pain intensity, although follow-up was short (80 min to 48 h).

Opioids

Six trials including data from 297 participants evaluated opioids for chronic pain after amputation[40,70,71,84], breast surgery[85] and spinal surgery[59]. Opioids evaluated included tramadol[40], oral morphine[71,84,85], morphine infusion[70] and epidural morphine[59]. In three trials, risk of bias was noted relating to blinding[84], incomplete outcome data[40] and selective reporting[59]. Compared with placebo, oral morphine was found to provide better pain relief at 4–6 weeks[70,71,84], although a common side-effect was constipation. Trials evaluating 4 weeks of tramadol compared with placebo[40], 6 weeks of morphine compared with gabapentin with, or without NSAIDs[85], and 3-monthly injections of epidural morphine and steroids compared with steroids alone[59], found no differences in pain intensity between treatment groups.

Other pharmacological interventions

One trial[78], with risk of bias relating to blinding and incomplete outcome data, evaluated intravenous calcitonin for phantom limb pain in 20 patients, and found no effect up to 48 h after infusion compared with saline. Another trial[86], with no clear evidence of risk of bias, evaluated low doses of oral/or intravenous naloxone as a supplement in 12 patients whose severe CPSP was already managed by continuous intrathecal morphine administration. No evidence of an effect on pain relief was found after two 3-week sessions on differing doses of the drug across a 9-week period

Physical, surgical, psychological and other interventions

Acupuncture/dry needling

No evidence of differences in pain relief was found in a trial of 20 patients comparing dry needling and physiotherapy with physiotherapy alone for pain after shoulder surgery[87]. Another trial[88] involving 70 patients with chronic pain after neck dissection reported that acupuncture resulted in better pain relief than usual care after 42 days. Neither participants nor assessors were blinded and this may have introduced bias.

Exercise

Four trials[89–92] involving 323 participants evaluated exercise interventions, often as a component of a broader package of care. Two studies were at risk of bias owing to lack of blinding[90,92]. No evidence of differences in pain relief was found in trials comparing 3 months of exercise with, and without hyperextension exercises after lumbar surgery[89], and 3 weeks of exercise combined with a cognitive intervention compared with lumbar fusion after disc herniation surgery[90]. A 4-week training programme of progressive muscle relaxation, mental imagery and phantom exercises was found to be more effective at relieving phantom limb pain than a general exercise programme[91]. A trial[92] of treatment of pain after laminectomy found that 8 weeks of low-tech exercises (McKenzie-type and spinal stabilization training exercise) or high-tech exercises (cardiovascular, isotonic and isokinetic exercises) resulted in a reduction in pain-related disability compared with no treatment.

Limb cover/lining

One trial[93] with 57 patients reported that non-invasive limb covering for 12 weeks compared with sham limb covering did not reduce phantom limb pain. Another trial[94] involving 30 patients, which was at risk of bias owing to incomplete outcome data, found evidence that a stump liner worn by amputees for 2 weeks reduced pain compared with a placebo liner.

Spinal cord stimulation

Five trials including 260 participants assessed the impact of spinal cord stimulation (SCS) on chronic pain after spinal surgery. Two studies[95,96] had a risk of bias related to blinding, and another[97] owing to blinding and commercial interests. Two trials found that patients who received SCS for 6 months reported better pain relief than those who had conventional management (100 patients)[97] or reoperation (60)[95]. Subcutaneous stimulation as adjunct therapy to SCS was noted to provide better relief of back pain, but not leg pain, compared with sham treatment in a trial of 20 participants[96]. Burst SCS was found to be more effective at providing pain relief after 1 week than tonic or placebo SCS[98]. In a trial involving 15 patients[99], there was no difference in pain after 2 weeks on stimulation with 1000- *versus* 500-Hz bursts.

Surgery

No evidence of differences in pain relief was found when lumbar fusion was compared with exercise for chronic pain after disc herniation surgery in a trial of 60 participants[90]. In a trial[95] involving 60 patients with failed back surgery syndrome, less pain relief after 6 months was reported by patients who had reoperation than was reported by patients who had SCS.

Other interventions

No evidence of differences in pain relief were found in a trial of cutaneous magnetic stimulation for 24 h compared with sham treatment after spinal surgery in 17 patients[100]. Four weeks of laser therapy compared with placebo laser therapy was found to reduce mastectomy pain at 12 weeks in a trial of 61 participants[101]. An unblinded trial that included ten patients[102], which was at risk of bias, found that 2 weeks of sensory discrimination training led to a reduction in phantom limb pain at 3 months compared with comprehensive psychophysiological assessment. One trial[103] with 40 patients, reported that 8 weeks of mindfulness-based stress reduction following spinal surgery led to better pain relief after 12 weeks compared with that in the waiting list control group. However, the trial was at risk of bias because of lack of blinding and incomplete outcome data. In a three-arm trial[104] that included 22 patients with phantom limb pain, mirror therapy was found to reduce pain intensity after 4 weeks compared with sham mirror therapy and mental visualization. The study was at risk of bias owing to lack of blinding. A trial[92] involving patients with pain after laminectomy found that an 8-week course of joint manipulation did not reduce pain-related disability compared with no treatment. The same trial also found no difference between a combined package of hot packs, ultrasound treatment and transcutaneous electrical nerve stimulation, and no treatment.

Discussion

The best evidence to guide the implementation of effective interventions comes from their evaluation in high-quality randomized trials, and ultimately in systematic reviews and meta-analyses. Given the prevalence and impact of CPSP, it is imperative to establish robust methods for its management. This systematic review aimed to provide a comprehensive evaluation of the evidence base for the management of CPSP. Although some of the interventions identified were procedure-specific, others had wider applicability to other types of CPSP. However, owing to heterogeneity in the interventions and trial design, pooling of data in meta-analysis was rarely possible or warranted. Of the 66 included trials, most evaluated pharmacological interventions. For all interventions, there was insufficient evidence to draw conclusions on effectiveness or harm.

There are few systematic reviews in the field of CPSP, with existing reviews focusing on predictors[108], characteristics[8] and prevention[109–112]. The previous reviews that have evaluated treatments have been procedure-specific, focusing on chronic pain after total knee replacement[31] and phantom limb pain[30]. This contrasts with other areas of pain research in which numerous systematic reviews[21,22,113–116] of treatments have been published. Typically, the focus of a review is on a defined condition (such as fibromyalgia, back pain) or a presumed mechanism of chronic pain (for example neuropathic pain). Patients with CPSP are, of course, embedded within broader trials investigating chronic pain, but it has not previously been possible to identify these patients.

This review highlighted some difficulties with conducting a broad systematic review of CPSP. First, there was heterogeneity in the definition of CPSP within research studies; some trials included only patients with neuropathic pain and there was variability across studies in key eligibility criteria, such as duration and severity of pain. Second, one-third of the studies included in the review evaluated interventions for phantom limb pain. Although previous reviews of CPSP have also included amputation[109,111], the commonality in the aetiology of phantom limb pain and other forms of CPSP could be questioned. However, phantom limb pain was included as the aim of this review was to provide a broad overview of interventions for chronic pain in the surgical context. The identification of interventions that show effectiveness in one well studied surgical model could provide directions for the evaluation of interventions for CPSP in other surgical areas.

It is important to acknowledge the limitations of this review when interpreting the results. Searches yielded a large volume of literature and therefore initial eligibility screening was performed in duplicate for only 10 per cent of the studies; this may have increased the risk of eligible studies being discarded[117]. However, the final selection of studies was undertaken by two reviewers in accordance with guidance from the Cochrane Handbook[38]. Given the hidden nature of patients with CPSP included within other trials, relevant studies were often difficult to identify from titles and abstracts, and required investigation of the full text to establish whether or not patients were likely to have CPSP. Although the search terms identified a large volume of literature, search of relevant Cochrane reviews identified three other relevant studies that were not identified in the initial searches. This highlights the difficulty of conducting such a systematic review owing to limited reference to the

patient sample by conventional means – there is no medical subject heading (MeSH) for CPSP, so indexers and even study authors did not necessarily use CPSP as a descriptor or keyword. Limits were not placed on the tools used to assess secondary outcomes and the resulting heterogeneity precluded their inclusion in analysis. Adverse events were found to be poorly and inconsistently reported. This has previously been described as a common issue in chronic pain trials[30], and poor reporting precluded conclusions about intervention safety in this review. Opportunities for meta-analysis were limited because of variability in the identified interventions, and conclusions are predominantly based on narrative synthesis. However, this review has produced a comprehensive overview of the evidence for management of CPSP, and the findings have a number of methodological and clinical implications.

Only three trials included patients with CPSP after various surgical procedures; the remainder focused on one surgery type. Of these, the majority of trials were conducted to evaluate treatments for phantom limb pain and failed back surgery syndrome, which is likely to reflect the historical recognition of these pain conditions[118,119]. Although an encouraging temporal increase in the number of trials conducted was identified, the paucity of research into the management of CPSP, particularly after operations other than amputation and spinal surgery, highlights the need for further research. The majority of trials in this review evaluated pharmacological interventions, reflecting the commonplace role of these therapies in the management of chronic pain. There was insufficient evidence to evaluate the effectiveness of any treatment modality in reducing CPSP. It has previously been proposed that commonly prescribed pharmacological treatments are insufficient to treat chronic non-cancer pain when used in isolation[120]. Given the complex and multifactorial nature of CPSP, an individualized and multimodal model of care may be required, as recommended more widely for chronic non-cancer pain[120].

Similar to a previous review of interventions for phantom limb pain[30], the present analysis identified the need for more methodological rigour in the reporting and conduct of randomized trials in this field. This need is highlighted by the unclear or high risk of bias rating assigned to many aspects of the included trials. Frequently encountered issues included lack of transparency, as shown by lack of preregistration of trials or publication of trial protocols, failure to report conduct/results according to CONSORT standards[121–123], and limited and variable assessment of pain and adverse events. IMMPACT recommendations[36] suggest the use of a comprehensive approach to pain assessment in clinical trials addressing chronic pain. Many of the trials included in this review were conducted before publication of the IMMPACT recommendations in 2003. However, the trials conducted and published after the IMMPACT guidance generally limited their outcome assessment to pain intensity. Inconsistent reporting of the secondary outcomes of interest precluded their analysis, highlighting the need for standardization of outcomes assessment. For many included trials, sample sizes were small and duration of follow-up was short, limiting the conclusions that can be drawn about the therapeutic benefit of interventions in the context of chronic pain.

For many included trials, threats to both internal and external validity existed. Reports of trials did not always include a sample size calculation. The inclusion criteria did not specify an *a priori* sample size, owing to the heterogeneity of the definition of CPSP and the range of potential interventions. Such a broad approach allowed this review to meet the intended aim of comprehensiveness, and to identify and present all trials within this complex and evolving field, including those in which events led to early trial termination or lower recruitment than planned. In keeping with recommendations in the Cochrane risk-of-bias tool, sample size was not considered to present a risk of bias *per se*[124], although small studies do not improve the precision of estimates. The relatively small sample sizes in some of the studies that met the inclusion criteria, as well as the high risk of bias among many of the largest trials, impacted on both results and generalizability.

In addition to issues of bias in trial conduct and reporting, the authors were initially keen to report on the quality of the evidence, potentially using GRADE. However, this was not possible because of the inability to estimate effects of treatments: all findings would have been downgraded for quality owing to the absence of evidence for synthesis. However, as this field develops and more trials emerge, it would be expected that new reviews will report effect estimates and examine the quality of the evidence.

This review highlights the need for more evidence about interventions for CPSP, and a focus not on the presumed pathological mechanism or location of pain, but on the relationship of pain to surgery. Many patients experience CPSP and it is imperative that evidence-based interventions are offered to these individuals to improve postoperative outcome. Trials to date have focused on pharmacological interventions, and no trials have been conducted to evaluate multimodal interventions matched to pain characteristics for the management of CPSP. Given the complexity of pain that extends or emerges after surgery, individualized interventions should be developed and evaluated. High-quality trials of these interventions

are needed to provide a robust evidence base to guide the management of CPSP.

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Supporting information

Additional supporting information may be found online in the supporting information tab for this article:

Appendix S1 Search terms (Word document)

Appendix S2 Risk of bias by intervention type (Word document)

Table S1 Characteristics of included studies evaluating pharmacological interventions (Word document)

Table S2 Characteristics of included studies evaluating physical, surgical, psychological and other interventions (Word document)

Fig. S1 Forest plot showing trials of gabapentin *versus* placebo for treatment of chronic phantom limb pain (Word document)

Fig. S2 Forest plot for trials of low-dose capsaicin *versus* placebo for treatment of chronic postsurgical pain after cancer surgery (Word document)