

# Evidence for the Optimal Management of Acute and Chronic Phantom Pain: A Systematic Review

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## Abstract:

**Objectives:** The objective was to examine the evidence to determine the optimal management of phantom limb pain in the preoperative and postoperative phase of amputations.

**Methods:** Trials were identified by a systematic search of MEDLINE, review articles, and references of relevant trials from the period 1966–1999, including only English-language articles. Included trials involved a control group, any intervention, and reported phantom pain as an outcome.

**Results:** Twelve trials were identified, including 375 patients whose follow-ups ranged in duration from 1 week to 2 years. Only three randomized, controlled studies with parallel groups and three randomized crossover trials were identified. Eight trials examined treatment of acute phantom pain, including epidural treatments (three trials), regional nerve blocks (three trials), treatment with calcitonin (one trial), and transcutaneous electrical nerve stimulation (one trial). Three trials demonstrated a positive impact of the intervention on phantom limb pain, but the remainder demonstrated no difference between the intervention and control groups. Four trials examined late postoperative interventions, including transcutaneous electrical nerve stimulation (two trials) and the use of Farabloc (a metal threaded sock) and ketamine (one trial each). With regard to late postoperative interventions, three of the four trials showed modest short-term reduction of phantom limb pain. There was no relation between the quality of the trial and a positive result of the intervention.

**Conclusions:** Although up to 70% of patients have phantom limb pain after amputation, there is little evidence from randomized trials to guide clinicians with treatment. Evidence on preemptive epidurals, early regional nerve blocks, and mechanical vibratory stimulation provides inconsistent support for these treatments. There is currently a gap between research and practice in the area of phantom limb pain.

**Key Words:** Phantom limb pain—Epidural anesthesia—Nerve blocks.

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*Phantom limb pain* (PLP) is a painful sensation perceived in the missing limb after amputation.<sup>1</sup> This is distinct from stump pain, which is pain in the residual portion of the limb or stump,<sup>2</sup> and phantom limb sensa-

tion, which is any sensation (paresthesia, dysesthesia, hyperpathia) of the missing limb except pain.<sup>3</sup>

Reported rates of phantom pain range from 2% to 85%.<sup>4</sup> They vary according to whether the study was retrospective,<sup>5</sup> clearly distinguished PLP from stump pain and phantom limb sensation, sampled those seeking treatments for pain,<sup>6</sup> or involved researchers independent of treatment teams.<sup>7</sup> Prospective work suggests that in the year after amputation, 60% to 70% of amputees experience PLP,<sup>5,8</sup> but it diminishes with time.<sup>5,6</sup> In a series

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of studies 72% of amputees had PLP 1 week after amputation, 67% had pain 6 months later, and 60% had pain at 7 years.<sup>5</sup> This pain may be severe and disabling. A study of 2,694 community amputees showed that 51% experienced PLP severe enough to hinder lifestyle on more than 6 days per month, 27% for more than 15 hours per day, and a further 21% reported daily pain over a 10- to 14-hour period.<sup>7</sup> However, because that study was conducted in the early 1980s, before the increase in the availability of neuroactive agents, a new review is required.

Descriptive studies have identified factors that may contribute to the development of PLP: the degree of preamputation pain; the presence of noxious intraoperative inputs brought about by cutting skin, muscle, nerve, and bone; acute postoperative pain (including that due to proinflammatory processes<sup>9</sup>); and psychological factors.<sup>6</sup> Less work has been done to identify effective treatments.

Surveys suggest that although physicians believe treatments are effective,<sup>10</sup> fewer than 10% of patients with PLP receive lasting relief from prescribed medical treatments.<sup>7</sup> However, clinicians have been restricted by the lack of clinical trials that would aid in treatment decisions and by the absence of evidence-based treatment guidelines. In 1980 a literature review identified 43 methods for treating PLP but concluded that few produced relief and that placebo responses were common.<sup>11</sup> Treatment recommendations for PLP have suggested regimens in line with the management of neuropathic pain states,<sup>12-14</sup> although trials of treatments for neuropathic pain rarely include patients with PLP and the pathophysiology of PLP remains poorly understood.

In the past decade clinical trials have examined treatments for PLP. Early trials concentrated on reducing established postoperative PLP, but newer approaches have used analgesic agents administered before amputation.<sup>9</sup> Treatment approaches currently are based on the assumption that long-term PLP is the result of functional or structural changes in the CNS in response to noxious somatosensory input,<sup>15</sup> and therapies are directed at early reduction of pain. Most recent trials have incorporated preamputation epidural analgesia and regional nerve blockade and have examined the impact of early intervention on reported PLP levels.

We were uncertain of the quality of evidence supporting current treatments used in the prevention of phantom pain with new amputations and the management of chronic, long-term PLP. Therefore, our aim was to examine the evidence systematically to determine the optimal management of acute and chronic PLP.

## MATERIALS AND METHODS

### Inclusion/exclusion criteria

Trials were included if they involved a control group and examined any intervention for PLP (regardless of the methodology). Interventions involving treatments before and during the amputation were included as well as treatments for chronic pain. Trials were grouped into two categories: preoperative and early postoperative interventions (at <2 weeks) or late postoperative interventions (at >2 weeks). All trials that involved the measurement of PLP as either a primary or secondary outcome were included. Only English-language articles were included. Reports of case studies were excluded.

### Identification of trials and data extraction

Trials were identified from a systematic search of the electronic database MEDLINE (with use of the terms *randomized controlled trial, controlled clinical trial, double-blind method, single-blind method, placebos, research design, comparative study, evaluation studies, follow-up studies, prospective studies, phantom limb, phantom limb pain, and human*), previous review articles, and the references of relevant trials from the period of 1966–1999. Eligibility was determined by reading all trial reports identified by the search. Experts in the area were contacted to identify missing trials or trials still in progress. Data were extracted by one of the authors (J. H.) and checked by another author (M. C.).

Information was also collected from the included trials on numbers of patients, characteristics of patients (including age, sex, and site of amputation), inclusion criteria for trial, methodology, length of follow-up, and numbers of dropouts and deaths. Details of the intervention, including time of intervention, description of intervention, control treatments, outcome measures, and overall result, were also collected.

### Quality assessment

Trials were assessed with an instrument<sup>16</sup> that measures the likelihood of bias in pain research reports in three areas: randomization, double-blinding, and withdrawals or dropouts. The assessment questions were as follows (scoring: add 1 point for an answer of “yes” and deduct 1 point for “no”).

1. Is the study randomized?
2. Is the randomization appropriate?
3. Is the study double-blind?
4. Is the double-blind method appropriate?
5. Are withdrawals and dropouts described?

It should be noted that the scores allocated to the studies included in this review might have been more a

reflection of the quality of reporting than the methodological quality of the trials themselves.

Trials were examined for sample-size calculations. Using the PLP outcome for each trial individually and the intervention–control group difference at 12 months' follow-up, we calculated the number of patients required at the commencement of the trial (without losses due to dropout or death) to examine whether this result was likely to reach statistical significance.

The outcome measures used in each trial and the description of subjects provided by the investigators reporting the studies were accepted without further analysis.

### Data analysis

We had originally planned to use formal meta-analytical techniques to quantitatively combine the results from the included trials. However, after extraction of the data from the trials, it became apparent that any technique designed to combine the results from the included trials would be invalid because of the heterogeneity in PLP outcomes and follow-up periods, which varied from 7 days to 2 years. Therefore, it was decided to present results only as a narrative summary. Descriptive data from the trials are presented as mean  $\pm$  SD.

## RESULTS

### Description of included trials

The searches yielded 186 articles, of which 165 were rejected because they were letters or reviews, the trials were descriptive and did not involve intervention, or the articles were not published in the English language ( $n = 35$ ). Of the remaining 21 articles, a further 9 were rejected because they did not describe a control group, were case reports, were an extension of a previously published study, or did not differentiate PLP from stump pain. Twelve trials<sup>17–28</sup> were included: 8 examining the treatment of acute phantom pain with preoperative, intraoperative, and early (at <2 weeks) postoperative interventions and 4 examining the treatment of chronic phantom pain with late (at >2 weeks) postoperative interventions.

In the 8 preoperative, intraoperative, and early postoperative trials (Table 1), the interventions included: epidural anesthesia,<sup>17,23,26</sup> regional nerve blocks,<sup>19,21,28</sup> intravenous calcitonin,<sup>22</sup> and transcutaneous electrical nerve stimulation (TENS)<sup>20</sup> (Table 2).

In the preoperative, intraoperative, and early postoperative trials, control group patients received a placebo<sup>22</sup> consisting of a saline infusion or epidural anesthesia consisting of on-demand opioid analgesia.<sup>23</sup> Five trials involved opioid analgesia,<sup>17,18,19,21,26</sup> and one trial<sup>20</sup> used sham TENS, with and without chlorpromazine. In all trials in which epidural anesthesia was used, treatment

commenced 18 hours<sup>27</sup> to 72 hours<sup>17</sup> before surgery. In the blockade group, anesthesia commenced during the operation<sup>19,21</sup> or postoperatively.<sup>22,28</sup> Five trial reports described deaths during the follow-up periods, ranging from 2 patients<sup>20,21,28</sup> to 20 patients (36%).<sup>26</sup> Two trial reports did not include any information on dropouts or deaths.<sup>19,23</sup> Two reports noted that the final follow-ups occurred at 6 months,<sup>19,28</sup> whereas in the remainder they occurred at 12 months or (in one trial) 2 years.<sup>22</sup> One trial<sup>20</sup> excluded 13 patients whose stumps did not heal sufficiently to allow the intervention.

Four trials examined late postoperative interventions (Table 3), including TENS,<sup>24</sup> Farabloc (a metal threaded sock; Farabloc Development Corp., Coquitlam, BC, Canada),<sup>18</sup> vibratory stimulation,<sup>25</sup> and infused ketamine<sup>27</sup> (Table 4). Three trial reports described no deaths,<sup>18,24,27</sup> and in the other trial 17 people (71%) were lost to follow-up at 24 months<sup>25</sup>; follow-up ranged from immediately postintervention<sup>24,27</sup> to 24 months,<sup>25</sup> and in one trial<sup>18</sup> the time of follow-up was reported as “after 3 to 5 episodes of pain.”

### Description of included patients

Overall, there were 375 patients (both men and women), and the ages ranged from 47 to 75 years.

The preoperative, intraoperative, and early postoperative trials included 278 patients (171 men, 86 women, and 21 whose sex was not specified). The number of patients per trial ranged from 21 to 59. The majority of patients were undergoing amputations of the lower extremities, mostly below-the-knee amputations (Table 1).

The late postoperative trials included 97 patients (66 men and 31 women). The number of patients per trial ranged from 11 to 34. Time since amputation ranged from 36 days to 46 years, with a wide range in all trials (Table 3).

### Rates of phantom pain in the control group (expressed as a dichotomous variable) at various follow-ups

Three trials showed that 56%<sup>26</sup> to 82%<sup>17,23</sup> of the control group were experiencing PLP at day 7 of follow-up. At 3 months, the incidence had decreased to 50% of the control group in one trial.<sup>26</sup> By 6 months, three trials showed the incidence of PLP in the control group to be 39%,<sup>17</sup> 55%,<sup>26</sup> and 73%.<sup>23</sup> At 12 months, the incidence of PLP in the control group in five trials was 27%,<sup>17</sup> 55%,<sup>20</sup> 69%,<sup>26</sup> 73%,<sup>23</sup> and 78%.<sup>19</sup>

### Quality of included trials

Of the preoperative, intraoperative, and early postoperative trials, three included randomized, controlled parallel groups,<sup>20,26,28</sup> one was a randomized crossover trial,<sup>22</sup> one was a pseudorandomized trial in which date

**TABLE 1.** Characteristics of preoperative and "early" (<2 weeks) postoperative intervention trials

Trial	Number of patients	Characteristics of patients	Methodology	Follow-up	Lost to follow-up	Quality score*
Epidural anesthesia Bach <sup>17</sup>	25	18 men, 7 women; mean age 75 yr; 25 patients distal preamputation pain; main cause was occlusive arterial disease; 11 had diabetes mellitus	Pseudo-randomization using DOB	1 wk, 6 mo, 12 mo	6 patients died	1
Jahangiri <sup>23</sup>	24	18 men, 6 women; mean age 66 yr; 15 below-knee amputation; 7 above-knee; 13 had peripheral vascular disease; 7 diabetes mellitus; 1 infected ulcer; 1 failed embolectomy	Controlled not randomized	1 wk, 6 mo, 12 mo	Did not include	0
Nikolajsen <sup>26</sup>	56*	33 men, 23 women; mean age 71 yr; 31 below-knee; 7 through-knee and 18 above-knee; no information on disease leading to amputation	Randomized controlled trial; stratified by preamputation pain, blinding of treatment assignment to staff and patients	1 wk, 3 mo, 6 mo, 12 mo	5 reamputations during follow-up; 20 deaths	5
Regional anesthesia (blockade) Elizaga <sup>19</sup>	59	53 men, 6 women; mean age 47 yr; 37 transtibial; 12 transfemoral; "a heterogeneous population (trauma, infection, chronic deformity, vascular insufficiency)"	Cohort, intraneural catheter use determined by surgeon	6 mo	Not applicable; only 9/19 treated; 12/40 controls completed the questionnaire	0
Fisher <sup>21</sup>	21	Not sure which gender; mean age 69 yr; 23 below-knee; 8 above the knee; moderate-to-severe limb pain preoperatively, resulting from occlusive vascular disease and diabetes mellitus	Not randomized, controlled trial; control group all suffered from septic gangrene	2 mo, 12 mo	2 deaths after 2 months	1
Pinzur <sup>28</sup>	21	10 men, 11 women; mean age 68 yr; amputation of lower extremity, all resulting from peripheral vascular disease	Randomized controlled trial using a table of random numbers	3 mo, 6 mo	5 patients chose not to complete the questionnaire at 3 mo, 6 mo; 2 deaths	5
Other Finsen <sup>20</sup>	51	27 men, mean age 69 yr; 24 women, mean age 79 yr; patients undergoing below-knee or through-knee amputation, caused by diabetes mellitus or atherosclerosis	Randomized controlled parallel group design	4 wk, 16 wk, 12 mo	2 deaths; 13/49 did not heal	2
Jaeger <sup>22</sup>	21	12 men, 9 women; mean age 53 yr; 15 thigh amputations, 1 hip, 4 calf, 1 elbow; 6 diabetes mellitus; 7 peripheral vascular disease; 5 cancer; 1 trauma, renal failure, and osteomyelitis	Randomized, cross-over after 2 hrs	1 wk, 6 mo, 12 mo, 24 mo	5 deaths in follow-up	3

Quality score in three parts: randomization, double-blinding, and withdrawals; 60 patients randomized but 4 withdrew before amputation.

of birth was used for allocation,<sup>17</sup> two were controlled trials,<sup>21,23</sup> and one was a trial with cohorts of intervention and control patients<sup>19</sup> (Table 1). In the late postoperative group, there were two randomized controlled crossover trials,<sup>18,27</sup> one controlled crossover trial,<sup>24</sup> and one trial with a controlled parallel group<sup>25</sup> (Table 3).

Only three trials scored the maximum five points for quality assessment<sup>18,26,28</sup>; one trial scored four

points,<sup>27</sup> one scored three points,<sup>22</sup> four scored one point, and three scored zero points. Whereas six trials were reported to be randomized, only three reports<sup>18,27,28</sup> included an adequate description of randomization. Four trials were reported to be double-blind, seven were reported to have dropouts and withdrawals, and only two included a sample-size calculation as part of the study methods.<sup>26,27</sup>

**TABLE 2.** Interventions and outcome of the preoperative and “early” (<2 weeks) postoperative intervention trials

Trial (year)	Treatment	Timing of intervention	Outcomes	Results	Overall result	Adverse events
<b>Epidural anesthesia</b>						
Bach <sup>17</sup>	Lumbar epidural blockade vs. meperidine, paracetamol, aspirin	Pre-op for 72 hr	PLP (no. patients), phantom sensation (no. patients), stump pain (no. patients)	At 1 week and 6 months post-op, more patients in control group had PLP, same result at 12 months but not statistically significant	-	None reported
Jahangiri <sup>23</sup>	Epidural infusion of bupivacaine, clonidine, diamorphine vs. opioid analgesia	24–48 hr pre-op and for 3 days post-op	PLP (no. patients), stump pain (no. patients), phantom limb (no. patients)	More patients in the control group than study group experience PLP at 6 and 12 months follow-up	+	Two patients developed urinary retention, and two patients developed fecal incontinence (short-term)
Nikolajsen <sup>26</sup>	Epidural bupivacaine + morphine vs. epidural saline + morphine; difference was for preoperative treatment	18 hr pre-op, post-op both groups received bupivacaine	PLP (VAS), PLP (no. patients), adverse events, stump pain (VAS)	No effect on PLP at all follow-up periods, no effect on stump pain	-	6 febrile patients (1 with meningitis and the other a subcutaneous abscess)
<b>Regional anesthesia (blockade)</b>						
Elizaga <sup>19</sup>	Regional analgesia + opioid analgesics vs. opioid analgesics	During operation	Mean opioid requirements, phantom limb sensations, pain (no. patients), pain scale (VAS)	No differences between the groups for PLP at 6 months, occurrence of PLP had no relation to preamputation limb pain, level of amputation	-	Pruritis and drowsiness were more frequent in treatment group but did not reach significance
Fisher <sup>21</sup>	Continuous postoperative regional analgesia vs. parenteral opioid analgesia	During operation	PLP for intervention group only, parenteral narcotic doses 72 hr post-op	No results comparing PLP at 2 months or 12 months in the intervention vs. control group	NA	No complications resulting from the operation
Pinzur <sup>28</sup>	Infusion of bupivacaine hydrochloride vs. saline infusion	Post-op for 72 hr	Morphine use 1, 2 days post-op, McGill questionnaire for PLP	No significant difference between the groups at 3 or 6 months	-	No complications with catheters or use of patient-controlled analgesia, no wound infections
<b>Other</b>						
Finsen <sup>20</sup>	TENS vs. sham TENS vs. sham TENS + chlorpromazine	Post-op TENS	PLP (no. patients), subjective effect of TENS	Less PLP reported by TENS group at 16 weeks; no differences between the groups for phantom pain at 12 months	-	None reported
Jaeger <sup>22</sup>	Salmon calcitonin (s-CT) vs. control (saline)	Post-op infusions	Percentage of patients with pain relief of more than 50%, number of patients who were pain free	s-CT reduced PLP regardless of order of s-CT infusions and control infusions; longer-term follow-up results not controlled	+	With CT infusion, headache (n = 2), vertigo (n = 2), nausea (n = 6), vomiting (n = 5), augmentation of phantom sensation (n = 4), hot/cold flashes (n = 4), drowsiness (n = 2)

PLP, phantom limb pain; VAS, visual analog scale; TENS, transcutaneous electrical nerve stimulation; -, no difference between intervention and control; +, positive for intervention.

### Phantom limb pain outcomes (descriptive)

Investigators in six trials<sup>17,19–21,23,26</sup> reported PLP as a dichotomous variable (that is, presence or absence of PLP), those in three trials measured PLP with a visual analog scale,<sup>19,26,27</sup> and those in three measured PLP with the McGill pain questionnaire.<sup>24,27,28</sup> In three trials, the outcome measure was PLP pain relief, and this was measured either with a visual analog scale<sup>18</sup> or with a dichotomous variable.<sup>22,25</sup> Several trials included other

outcomes, including stump pain, phantom sensation, and opioid use; only one study<sup>22</sup> included “reduction in pain of 50%,” which has previously been recommended as a preferred pain outcome.<sup>29</sup> In the reports of two studies,<sup>18,25</sup> the title referred to phantom pain but the outcome mentioned was “pain relief,” and we assumed this was relief from PLP as opposed to relief from stump pain. None of the trials included measures of function or activities of daily living.

**TABLE 3.** Characteristics of the "late" (>2 weeks) postoperative intervention trials

Trial	Number of patients	Characteristics of patients	Time since amputation	Methodology	Follow-up	Lost to follow-up	Quality score
Conine <sup>18</sup>	34	28 men, 6 women; 10 above-knee; 14 below-knee; 5 above-elbow; 3 below-elbow; 2 shoulder disarticulation	1–40 yr	Double-blind, randomized, cross-over design	Duration of 3–5 episodes of pain	None	5
Katz <sup>24</sup>	28	18 men, 10 women; upper and lower extremity amputation; 12 peripheral vascular disease; 9 trauma; 3 arterial thrombosis; 2 tumor; 1 radiation; 1 polio	36 days–46 yr	Controlled cross-over design	Postsession, no longer-term follow-up	None	0
Lundeberg <sup>25</sup>	24	12 men, mean age 56 yr; 12 women, mean age 61 yr; all had previously had TENS for at least 2 months—unsatisfactory; no information on disease leading to amputation	6 mo–24 yr	Controlled trial (subjects own controls)	3 mo, 6 mo, 12 mo, 18 mo, 24 mo	3 at start, 9 at 3 mo, 12 at 6 mo, 16 at 12 mo, 17 at 18 mo and 24 mo	1
Nikolajsen <sup>27</sup>	11	8 men, 3 women; mean age 47 yr; upper and lower extremity amputations; main reason for amputation was cancer	Not provided; duration of pain 0.75–11 yr	Double-blind, randomized cross-over design	80 minutes	None	4

Quality score in three parts: randomization, double-blinding, and withdrawals. TENS, transcutaneous electrical nerve stimulation.

### Effect on phantom pain

#### Acute pain

Most trial investigators attempted to reduce perioperative pain and evaluated whether early pain control had an impact on acute and chronic pain.

**Epidural Anesthesia.** Investigators in three trials assessed preoperative epidural pain relief and were unable to provide evidence to support its routine use (Table 5). The results of two studies involving small numbers suggested that epidural analgesia may help but were inconsistent: one showed relief at 7 days, 6 months, and 1 year

**TABLE 4.** Interventions and outcomes of the "late" (>2 weeks) postoperative intervention trials

Trial	Treatment	Outcomes	Results	Overall result	Adverse events
Conine <sup>18</sup>	Farabloc—a linen fabric with ultrathin steel threads, to be worn over the stump	PLP relief level (VAS)	21/34 patients reported their greatest PLP relief during Farabloc intervention	+	No adverse events
Katz <sup>24</sup>	Two sessions, one with low-frequency, high-intensity auricular TENS, the other placebo stimulation	Phantom limb intensity, McGill Pain Questionnaire rating indexes	No difference in PLP intensity during the sessions, decrease in PRI-S, PRI-T scores after TENS	+	None reported
Lundeberg <sup>25</sup>	Placebo stimulation vs. vibratory stimulation, generally at the site of pain	Modified McGill Pain Questionnaire	PLP reduction was inversely proportional to intensity of pain before treatment; more patients experienced pain relief in the intervention period	–	Most (71%) stopped because treatment was ineffective, or experiencing more pain, or pain difficult to tolerate
Nikolajsen <sup>27</sup>	Intravenous infusion of ketamine or saline	Phantom pain and stump pain (VAS), McGill Pain Questionnaire, pressure–pain thresholds, wind-up–like pain, thermal stimulation, temporal summation of heat-induced pain, reaction time	Use of ketamine resulted in a decrease in the rating of stump and phantom pain (both VAS and McGill Pain Questionnaire). Ketamine increased pressure–pain thresholds and decreased wind-up–like pain.	+	Insobriety (6 patients); discomfort (3 patients)

PLP, phantom limb pain; VAS, visual analog scale; TENS, transcutaneous electrical nerve stimulation; PRI-S, pain relief index—sensory; PRI-T, pain relief index—total; +, positive for intervention; –, no difference between intervention and control.

**TABLE 5.** Summary of simplified results for all follow-up periods, together with the quality score for each included trial

Trial (year)	Early follow-up*	Late follow-up*	Quality score†
Early postoperative interventions			
Epidural anesthesia			
Bach <sup>17</sup>	- (7 d)	+ (6 mo) - (12 mo)	1
Jahangiri <sup>23</sup>	+ (7 d)	+ (6 mo) + (12 mo)	0
Nikolajsen <sup>26</sup>	- (7 d) - (3 mo)	- (6 mo) - (12 mo)	5
Regional anesthesia			
Elizaga <sup>19</sup>		- (14-20 mo)	0
Fisher <sup>21</sup>	- (intervention group only)		1
Pinzur <sup>28</sup>	- (3 mo)	- (6 mo)	5
Other			
Finsen <sup>20</sup>	- (during first 4 wk)	+ (16 wk) - (over 12 mo)	
Jaegar <sup>22</sup>	+ (48 hr)		3
Late postoperative interventions			
Conine <sup>18</sup>		+ (3-4 episodes of pain)	5
Katz <sup>24</sup>		+ (10 min postintervention)	0
Lundeberg <sup>25</sup>		+ (at start) - (6-24 mo)	1
Nikolajsen <sup>27</sup>		+ (up to 80 minutes)	4

\*+, positive for intervention; -, no difference between intervention and control.

†Quality score reported on a 0-to-5 scale, with 5 the highest score possible and indicating the least likelihood of bias.<sup>16</sup>

postoperatively.<sup>23</sup> The other<sup>17</sup> showed less PLP in the intervention group at 1 week, 6 months, and 1 year, and the difference reached significance only at 6 months. However, the largest of the studies showed no difference in phantom pain at 7 days, 3 months, 6 months, and 12 months.<sup>26</sup> A significant factor in this study<sup>26</sup> was the loss of 5 patients with reamputations and 20 deaths by 12 months. Adverse events associated with epidurals occurred in two studies, with 6 of 56 patients developing febrile illnesses,<sup>26</sup> and among the intervention patients, urinary retention and fecal incontinence developed in two patients each.<sup>23</sup>

**Regional Nerve Blocks.** Three trials assessed sciatic or posterior tibial nerve blocks with perineural<sup>21,28</sup> and intraneural<sup>19</sup> bupivacaine blocks, either at the time of surgery or immediately postoperatively (Table 5). With this approach, short-term pain relief was achieved; less morphine was used for 2 or 3 days,<sup>28</sup> and opioid needs were decreased at 3 days postoperatively.<sup>21</sup> Despite these early benefits, there was no difference in pain between the intervention and control groups in the postacute period in the two studies.

The remaining early treatment trials assessed intravenous salmon calcitonin (200 IU)<sup>22</sup> and early TENS.<sup>20</sup> Intravenous calcitonin reduced PLP in the early postoperative period, but PLP on longer-term follow-up was not adequately controlled.<sup>22</sup> TENS was assessed in the 2-week postoperative period, and although the treated group had less pain at 4 weeks, by 12 months there was no difference between the groups<sup>20</sup> (Table 5).

#### Late pain treatments

When PLP persists longer than 6 months, the prognosis for spontaneous improvement is poor and treatment is considered difficult.<sup>14</sup> Four trials were performed to assess treatments that were initiated in the late postoperative phase. Three of these<sup>18,25,27</sup> included only subjects with chronic pain (that is, pain lasting  $\geq 6$  months), and the remaining trial was conducted with outpatients whose amputations had occurred between 36 days and 46 years previously.<sup>24</sup>

Investigators examined the efficacy of TENS in two trials, Farabloc (a metal threaded sock) in one, and infused ketamine in another.<sup>27</sup> Farabloc,<sup>18</sup> low-frequency TENS applied to the ear,<sup>24</sup> and ketamine<sup>27</sup> provided a modest short-term reduction in the intensity of PLP and paresthesia. The remaining trial<sup>25</sup> examined TENS at the site of pain, but findings were inconclusive because of the large dropout rate over the follow-up period.

## DISCUSSION

Phantom limb pain is difficult to treat, and our review identified significant limitations with the literature rather than effective treatments. Because of their poor quality and contradictory results, the randomized and controlled trials did not provide evidence to support any particular treatment of PLP either in the acute perioperative period or later. Other reviews of treatments for chronic pain conditions have commented on the paucity of trials to assist clinicians.<sup>30</sup> The gap between practice and research in the area of PLP is marked, and no trials examined commonly recommended oral drugs such as membrane stabilizers or tricyclic antidepressants.<sup>13,14</sup>

The majority of trials examined the short-term and long-term impact of regional anesthesia (epidurals and nerve blocks), and with the exception of one trial<sup>23</sup> there was no evidence of success of the interventions. The limited success of preemptive epidurals as a way of managing both acute and chronic phantom pain is surprising and contrasts with a growing body of work in animal and other clinical settings.<sup>31</sup> The aim of preemptive epidurals is to avert long-term spinal sensitization by blocking, in advance, the cascade of intraneuronal responses that take place in the spinal cord after peripheral injury. Retrospective clinical studies have suggested that PLP is more likely to occur in amputees who had severe pain before and immediately after amputation; thus, effective preoperative and intraoperative treatments might reduce later pain.<sup>8</sup> It is possible, however, that these treatments, although beneficial for the acute nociceptive pain associated with the loss of the limb, are often not truly preemptive. For many patients the amputation is a last resort, preceded by a prolonged period of pain while salvage is attempted.

In most of the studies examining treatments for acute PLP, the control group received active treatment with opioid analgesics. This may have been more effective than a placebo control. However, in analgesia trials in which treatments with adverse effects are used, strategies (such as the use of a range of doses or an active placebo or comparison of two drugs) have been suggested for preventing spurious findings of efficacy.<sup>32</sup>

Aggressive pain management may be introduced at a late stage, when pain is already entrenched. One trial of infused intravenous ketamine<sup>27</sup> showed promising results by reducing phantom and stump pain. Although this trial was small, it was of good methodological quality. As the outcome reported was pain only 80 minutes after the intervention, the clinical application of these results is unclear, and it warrants further investigation.

This review was limited by the poor quality of the included trials. Only 12 controlled trials could be identified, and the variety of PLP outcome measures prevented us from examining the extent of the effect of treatment on pain. Only two trial reports<sup>26,27</sup> were explicit about the sample-size calculation and power for the study. The investigators in one<sup>26</sup> of these had calculated that they would need 27 patients in each group to detect a 40% difference in PLP (power of 0.80). However, because allowance was not made for dropouts and deaths, these investigators would not have had sufficient statistical power to detect this difference. The remaining trials failed to provide any information on the size of the difference that they would have been able to detect given their sample size. In addition, because of the small num-

ber of participants in most trials, those with dichotomous primary outcomes would have needed large differences between the intervention and control groups to detect an effect from the intervention. Only two trials used a double-blind design. No trials tested the adequacy of patient-blinding, although the incidence of side effects in treatment and placebo groups would differ. Side effects are thought to enhance the placebo effect by implying potency.<sup>32</sup> This review was limited to trials published in the English language. Because of the amount of detailed translation required and limited resources, it was not possible to specifically search for or translate studies reported in other languages.

There are particular challenges associated with examining PLP. First, the amputation rate for Australia is approximately 24 to 27 people per 100,000 people in any given year, making it difficult to recruit adequate numbers of amputees in a reasonable time frame from one location.<sup>33</sup> Second, the mortality rate is high among patients who undergo amputation. Figures from the United States show that among patients aged 80 years or more who underwent a lower-extremity amputation, the 5-year survival rate was 25%.<sup>34</sup> In the largest of the identified trials, one third of those randomized had died at 12 months.<sup>26</sup> Last, with interventions designed to examine preoperative and perioperative treatments, it is ethically unacceptable to provide a true placebo treatment by withholding analgesics. Recognizing that obtaining adequate sample size is likely to be a problem, we support suggestions that data on pain treatments be reported in a form that can be dichotomized for use in meta-analysis. In trials examining preoperative and intraoperative interventions, dichotomous outcomes such as presence or absence of PLP are appropriate. In trials of established PLP outcomes, the use of visual analog scales is useful, along with dichotomized measures such as the number of patients with more than 50% pain relief.<sup>15</sup> Furthermore, only patients with moderate pain or pain in excess of 30 mm on a baseline visual analog scale should be included,<sup>29</sup> because adequate sensitivity in trials of analgesics for acute pain depends on patients' experiencing at least moderate pain before treatment.<sup>35</sup>

The implications of this systematic review for clinical practice are problematic. In early PLP (<2 weeks post-operatively), no treatments are clearly more effective than administration of opioid analgesics. Thus, clinicians could decide to use opioid analgesics at a dose that should offer adequate pain relief with an acceptable level of risk of adverse effects. For late PLP (>2 weeks post-operatively), there is some evidence suggesting consideration of Farabloc. It is unclear how readily regimens suggested for other neuropathic pain states can be applied to patients with PLP.

The major conclusion is regarding research: further, adequately designed studies of therapeutic regimens for PLP are required.

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