

# Postamputation pain: Studies on mechanisms

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## THE 10 PREVIOUSLY PUBLISHED PAPERS ARE: (referred to in the text by Roman numerals)

- I. Nikolajsen L, Ilkjær S, Krøner K, Christensen JH, Jensen TS. The influence of preamputation pain on postamputation stump and phantom pain. *Pain* 1997; 72:393-405.
- II. Nikolajsen L, Ilkjær S, Christensen JH, Krøner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. *Lancet* 1997;350:1353-57.
- III. Nikolajsen L, Ilkjær S, Jensen TS. Effect of preoperative extradural bupivacaine and morphine on stump sensation in lower limb amputees. *Br J Anaesth* 1998;81:348-54.
- IV. Nikolajsen L, Ilkjær S, Jensen TS. Relationship between mechanical sensitivity and postamputation pain: A prospective study. *Eur J Pain* 2000;4:327-34.
- V. Nikolajsen L, Black J, Krøner K, Jensen TS, Waxman SG. Neuroma removal for neuropathic pain: efficacy and predictive value of lidocaine infusion. *Clin J Pain* 2010;26:788-93.
- VI. Black JA, Nikolajsen L, Krøner K, Jensen TS, Waxman SG. Multiple sodium channels isoforms and mitogen-activated protein kinases are present in painful human neuromas. *Ann Neurol* 2008;64:644-53.
- VII. Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain* 1996; 67:69-77.
- VIII. Nikolajsen L, Gottrup H, Kristensen AGD, Jensen TS. Memantine (a N-methyl D-aspartate receptor antagonist) in the treatment of neuropathic pain following amputation or surgery: A randomized, double-blind, cross-over study. *Anesth Analg* 2000; 91:960-6.
- IX. Nikolajsen L, Finnerup NB, Kramp S, Vimtrup A, Keller J, Jensen TS. A randomized study of the effects of gabapentin on postamputation pain. *Anesthesiology* 2006;105:1008-15.
- X. Vase L, Nikolajsen L, Christensen B, Egsgaard LL, Arendt-Nielsen L, Svensson P, Jensen TS. Cognitive-emotional sensitization contributes to wind-up-like pain in phantom limb pain patients. *Pain* 2011;152:157-62.

My PhD thesis entitled "Phantom pain in lower limb amputees", Aarhus University (1998), was based on studies I, II and III.

## INTRODUCTION

Phantom phenomena have probably been known since antiquity, but the first medical descriptions were not published until the 16th century by such authors as Ambroise Paré, René Descartes, Aaron Lemos and Charles Bell. Historically, Silas Weir Mitchell (1829-1914) is credited with coining the term "phantom limb". More than anyone else, Mitchell brought phantom limbs to the attention of the medical community. In his *Injuries of Nerves and Their Consequences* from 1872, he presented results from clinical studies of amputees and approached phantom limbs physiologically, experimentally and therapeutically (for historical review, see [51]).

In modern times, World War II, Vietnam, Israeli, Iraqi, Yugoslavian and Afghani wars have been responsible for many sad cases of traumatic amputations in otherwise healthy people [39]. Landmine explosions in Cambodia still result in many amputations [80], and during the civil war in Sierra Leone, the opposing parts performed limb amputations to terrorize the enemy [100]. Also, tragically, judicial amputations are still carried out in some societies (see [www.amnesty.org.uk](http://www.amnesty.org.uk)). The main reasons for amputation in Western countries are diabetes and peripheral vascular disease and, less often, tumours. Most of these patients are elderly and have often suffered from pain for several years prior to the amputation.

Amputation is followed by phantom phenomena in virtually all amputees. Most amputees feel that the missing limb is still present, and some even have vivid sensations of shape, length, posture and movement. Non-painful phantom sensations rarely pose any clinical problem, but 60-80% of all amputees also have painful sensations located to the missing limb. The intensity and frequency of both non-painful and painful phantom sensations usually diminish over time, but in 5-10% of patients severe phantom pain persists.

Stump pain is another consequence of trauma or surgery, but in most patients it subsides within a few weeks, and only a few patients develop chronic stump pain. Phantom sensations, phantom pain and stump pain often coexist in the same patient, and the elements may be difficult to separate.

The mechanisms underlying chronic pain in amputees are not fully known despite extensive research in the area. Experimental

animal models mimicking neuropathic pain and research in other neuropathic pain conditions have, however, contributed significantly to our understanding. It is now clear that nerve injuries are followed by multiple changes along the neuroaxis. The general view is that all these changes contribute to the experience of phantom pain, but the relative contribution of peripheral and central factors has yet to be determined.

Chronic stump and phantom pain are usually very difficult to treat. Many different treatments have been proposed, but most of the available evidence is based on small studies without controls. Until more clinical data become available, guidelines on pharmacological treatment of other neuropathic pain conditions are probably the best approximation. In general, the treatment should be non-invasive. Tricyclic antidepressants, anticonvulsants and perhaps opioids are recommended as first-line treatment. If the patient does not obtain sufficient pain relief, other drugs and drug combinations can be considered. Non-pharmacological treatments such as physical therapy, mirror therapy, sensory discrimination training and transcutaneous electrical nerve stimulation can be used as a supplement.

Phantom phenomena may also occur after the loss of other body parts, for example the breast [98,151], rectum [131] and eye [144].

The present doctoral thesis will deal only with pain after limb amputation. The following definitions will be used:

- **Phantom pain:** painful sensations referred to the missing limb.
- **Phantom sensations:** any sensation of the missing limb, except pain.
- **Stump pain:** pain referred to the amputation stump.

#### AIM OF OWN STUDIES

The primary aim of the studies that constitute this doctoral thesis was to explore some of the mechanisms involved in the development and maintenance of stump and phantom pain after amputation.

My PhD thesis from 1998 also dealt with pain after amputation. The three studies included in my PhD thesis focused on preamputation limb pain as a risk factor for the subsequent development of postamputation stump and phantom pain. The first study examined the relationship between the pain intensity before and after amputation, and also sought to clarify to what extent pain experienced before the amputation might persist as phantom pain (study I). The other two studies examined if a perioperative epidural pain treatment had any preventive effect on postamputation stump and phantom pain (study II) or abnormal sensory phenomena at the stump (study III).

Briefly, the conclusion of my PhD thesis was that preamputation pain increases the risk of postamputation pain, but at the same time the results made it clear that several other mechanisms had to be involved. Unfortunately, the two studies on prevention were negative.

The aim of the present doctoral thesis was to further explore the mechanisms underlying phantom pain. Study IV expanded on the role of preamputation sensitization for the development of postamputation pain. Studies V and VI focused on peripheral mechanisms, studies VII, VIII and IX examined spinal mechanisms, and study X dealt with supraspinal mechanisms.

#### The main questions addressed were:

- Does preamputation pain increase the risk of developing stump and phantom pain?
- Can phantom pain be prevented by a perioperative epidural blockade?
- Does afferent input from peripheral neuromas contribute to phantom pain?
- Can phantom pain be modulated by pharmacological agents that work spinally?
- Do supraspinal factors, e.g. catastrophizing, contribute to phantom pain?

My PhD thesis dealt exclusively with questions 1 and 2. In addition, my doctoral thesis also deals with questions 3, 4 and 5.

The doctoral thesis is presented as a review of the literature on stump and phantom pain after amputation. The focus will be on mechanisms, but clinical characteristics, treatment options and preventive measures will also be described in order to give a general overview of the topic.

#### CLINICAL CHARACTERISTICS

##### PHANTOM PAIN

###### Prevalence

Prevalence rates of phantom pain have been reported from a low 2-4% in early studies [49,73] up to a staggering 60-80% in recent studies (see Table 1 for details). This large variation may be attributed to differences in study populations, research design and cut-off levels for phantom pain. Studies based on medical records of pain and analgesic requirements are likely to underestimate the prevalence [16,163]. The prevalence of phantom pain does not seem to be influenced by factors such as age, gender, side and level and cause (civilian versus traumatic) of amputation [76,85,116,164]. However, a recent prospective study of 85 amputees showed that female gender and upper-limb amputation were associated with a higher risk of phantom pain [14]. Phantom pain is less frequent in very young children and congenital amputees [93,114,180], whereas older children and adolescents develop phantom pain almost to the same extent as adults [94,180].

###### Onset

Prospective studies in patients undergoing amputation mainly due to peripheral vascular disease have shown that the onset of phantom pain is usually seen within the first week after amputation [71,85,125,149], although it may also be delayed for months or even years [153]. For example, Rajbhandari et al. described a man who had undergone left below-knee amputation at the age of 13 years. Eight months before he was diagnosed with diabetes at the age of 58 years, he began to complain of a typical diabetic neuropathy pain in the phantom leg, which was followed by a similar complaint in the intact limb [142]. Similarly, in a retrospective study of individuals who were born either limb-deficient or underwent amputation before the age of 6 years, the mean time for onset of phantom pain was found to be 9 years in the group of congenital amputees and 2.3 years in the group of individuals with early amputations [114].

###### Duration

It is not possible to give exact descriptions of the time course of phantom pain, as no prospective studies with long-term (many years) follow-up exist. Prospective studies show that the preva-

lence of phantom pain only decreases slightly during a maximum follow-up period of 3.5 years [14,71,86,125,149], although the severity and frequency of phantom pain attacks gradually decrease with time in most patients. For example, in a retrospective survey of 526 veterans, phantom pain had disappeared in 16%, decreased markedly in 37%, remained similar in 44%, and increased in 3% of the respondents reporting phantom pain [173].

#### **Intensity and frequency**

Although phantom pain is seen in 60-80% of amputees, the number of patients with severe pain is rather small and in the range of 5-10%. In a prospective study of lower limb amputees, the mean intensity of pain was 22 (range 3-82) on a visual analogue scale (VAS, 0-100) 6 months after amputation [125]. Similar results were found in another prospective study [71]. In a retrospective study of 176 amputees who were asked to recall on a VAS (0-10) how much phantom pain they experienced at 6 months and 1, 2 and 5 years after amputation, the mean scores were 4, 3, 3, 2 and 1, respectively [76].

Phantom pain is usually intermittent, and only a few patients are in constant pain. Episodes of pain attacks are most often reported to occur daily, or at daily or weekly intervals [27,41,93,149,153,176]. For example, in a survey of 141 upper limb amputees, the reported duration of pain attacks was seconds or a few min. in 43% of amputees, several min. to hours in 20%, and longer in the rest of the amputees [27].

#### **Localization and character**

Phantom pain is primarily localized to the distal parts of the missing limb. In upper limb amputees, the pain is normally felt in the fingers and palm of the hand, and in lower limb amputees, it is generally experienced in the toes, foot or ankle [86,90,125]. The reason for this clear and vivid phantom experience of distal limb parts is not clear, but the larger cortical representation of the hand and foot as opposed to the lesser representation of the more proximal parts of the limb may play a role. The character of phantom pain is often described as shooting, pricking and burning. Other terms used are stabbing, pricking, pin and needles, tingling, throbbing, cramping and crushing. Some patients present with vivid descriptions such as "a hammer is slammed at my calf" and "ants are crawling around inside my foot" [41,116,125,173,180].

#### **Modulating factors**

Phantom pain may be modulated by several other internal and external factors, such as attention, distress, coughing, urination and manipulation of the stump. It is unclear whether the use of a functionally active prosthesis as opposed to a cosmetic prosthesis reduces phantom pain [78,93,105,174]. Both experimental and clinical studies have shown that there is a significant genetic contribution to the development of chronic pain, including neuropathic pain after nerve injury [126,145,158], although an inherited component is not always present. For example, Scott described a case in which five members of a family sustained traumatic amputations of their limbs. The development of phantom pain in the family members was unpredictable despite their being first-degree relatives [155]. It has been claimed that phantom pain may be provoked by spinal anaesthesia in lower limb amputees [106]. Tessler and Kleiman, however, prospectively investigated 23 cases of spinal anaesthesia in 17 patients, and only one patient developed phantom pain which resolved in 10 min. [168].

## **STUMP PAIN**

#### **Prevalence**

Not surprisingly, stump pain is common immediately after amputation [85,133]. In a prospective study of lower limb amputees, all 54 patients had some stump pain in the first week after amputation, with a median intensity of 15.5 (range 0-61) on a VAS (0-100) [125]. In some patients, the stump pain persists beyond the stage of postsurgical healing, but the prevalence varies a lot in the literature, and severe pain is only seen in 5-10% of patients (see Table 1 for details). In a survey of 78 traumatic amputees, Pezzin and associates found that 14.1% out of 78 traumatic amputees suffered from severe and constant pain in the stump after a mean of 7.5 years after amputation [135]. In another survey of 914 amputees, the prevalence of stump pain was 67.7%, but the pain was mild in most cases [48]. The prevalence of chronic stump pain is likely to be higher in war zones [80,100]. In the latter study of 40 amputees from Sierra Leone, all complained of stump pain at an average of 22 months after the amputation [100].

#### **Character and psychophysical characteristics**

Stump pain may be described as pressing, throbbing, burning or squeezing or stabbing [86]. Some patients have spontaneous movements of the stump, ranging from slight, hardly visible jerks to severe contractions. Careful sensory examination of the amputation stump may reveal areas with sensory abnormalities such as hypoaesthesia, hyperalgesia or allodynia [123].

#### **Relation between stump and phantom pain**

Stump pain and phantom pain are strongly correlated. In a survey of 648 amputees, Sherman and Sherman found that stump pain was present in 61% of amputees with phantom pain but only in 39% of those without phantom pain [163]. Similar results have been found in more recent studies (for example [27,149,153]). Temperature and muscle activity at the stump are related to phantom pain [89,161,162], and in a prospective study of 35 amputees, low mechanical thresholds (pressure algometry) at the stump were associated with stump and phantom pain 1 week after amputation [124]. However, other studies have shown that there is no simple correlation between phantom pain and sensory function of the stump [77,78].

## **PHANTOM SENSATIONS**

#### **Prevalence**

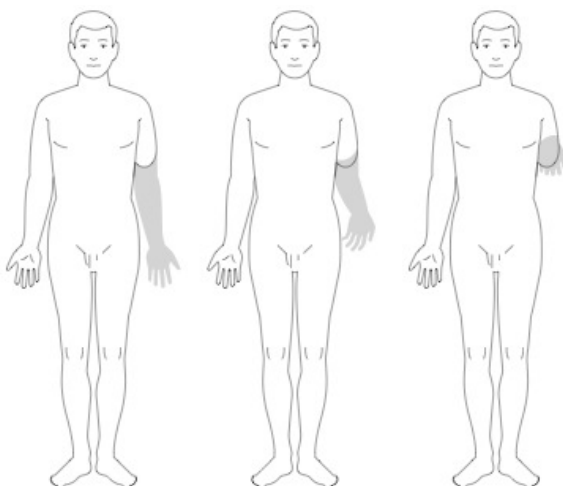
Phantom sensations are more frequent than phantom pain and are experienced by nearly all amputees (see Table 1 for details), but rarely pose any major clinical problem. Phantom pain and phantom sensations are strongly correlated. In a study by Kooijman et al., phantom pain was present in 36 out of 37 upper limb amputees with phantom sensations, but only in one out of 17 without phantom sensations [93].

#### **Onset and duration**

As for phantom pain, non-painful sensations usually appear within the first days after amputation [153]. The amputee often wakes up from anaesthesia with a feeling that the amputated limb is still there. Immediately after the amputation, the phantom limb often resembles the preamputation limb in shape, length and volume. Over time the phantom fades, shrinking to the distal parts of the limb. For example, upper limb amputees may feel the hand and fingers, and lower limb amputees may feel the foot and toes.

**Table 1**  
Prevalence of phantom pain, phantom sensations and stump pain.

Author(s)	Year	Total number of amputees	% with phantom pain	% with phantom sensations	% with stump pain
Ewalt et al.[49]	1947	2284	2	95	-
Henderson and Smyth[73]	1948	300	4	-	-
Parkes[133]	1973	46	61	-	13
Jensen et al.[85]	1983	58	72	84	57
Sherman and Sherman[163]	1983	764	85	-	58
Houghton et al.[76]	1994	176	78	82	-
Wartan et al.[173]	1997	526	55	66	56
Montoya et al.[116]	1997	32	50	81	44
Nikolajsen et al.[125]	1997	56	75	-	-
Wilkins et al.[180]	1998	33	49	70	70
Ehde et al.[41]	2000	255	72	79	74
Kooijman et al.[93]	2000	72	51	76	49
Lacoux et al.[100]	2002	40	33	93	100
Wilkins et al.[180]	2004	14	67	93	-
Ephraim et al.[48]	2005	914	80	-	68
Hanley et al.[69]	2006	57	62	-	57
Richardson et al.[149]	2006	52	79	100	52
Schley et al.[153]	2008	96	45	54	62
Bosmans and Geertzen[14]	2010	85	32	-	-
Desmond and MacLachlan[26]	2010	141	43	-	43



**Figure 1**  
This figure illustrates telescoping: a phenomenon in which the phantom hand or phantom foot gradually approaches the amputation stump.

### Character

A common position of the phantom limb in upper limb amputees is that the fingers are clenched in a fist, while the phantom limb of lower limb amputees is frequently described as toes flexed [180]. In some cases, phantom sensations are very vivid and include feelings of movement and posture; in other cases only suggestions of the phantom are felt. Telescoping (shrinkage of the phantom) is reported to occur in about one-third of patients. The phantom hand or foot gradually approaches the amputation stump and eventually becomes attached to it (Fig. 1).

Sometimes the phantom limb may even be experienced within the residual limb. It has been postulated that phantom pain prevents or retards shrinkage of the phantom, but Montoya et al. failed to find such a relation: 12 of 16 patients with phantom pain and 5 of 10 patients without pain reported telescoping [116].

### TREATMENT

Treatment of chronic pain after amputation represents a major challenge to the clinician, in particular the treatment of phantom pain. There is not much evidence from randomized trials to guide clinicians with treatment, and in addition, most studies dealing with phantom pain suffer from major methodological errors: Samples are small, randomization and blinding are either absent

Table 2

Selected studies on medical treatment of phantom pain (A, B, C refer to the different treatment arms in studies with a parallel design) \*crossover design.

Reference	Randomization	Blinding	No. of patients	Intervention	Effect on pain
<u>Tricyclic antidepressants</u>					
Robinson et al. 2004 [150]	+	+	39	A (n=20): amitriptyline up to 125 mg/day for 6 weeks B (n=19): active placebo	-
Wilder-Smith et al. 2005 [179]	+	+ (-)	94	A (n=30): amitriptyline (mean 55 mg/day) for 1 month B (n=33): tramadol (mean 448 mg/day) C (n=31): placebo	+
<u>Gabapentin</u>					
Bone et al. 2002* [12]	+	+	19	Gabapentin/placebo for 6 weeks, 1-week washout period, maximum dose of gabapentin 2400 mg	+
Smith et al. 2005* [165]	+	+	24	Gabapentin/placebo for 6 weeks, 5-week washout period, maximum dose of gabapentin 3600 mg/day	(+)
<u>Opioids</u>					
Huse et al. 2001*[79]	+	+	12	Oral morphine/placebo for 4 weeks, 1-2-week washout phase, maximum dose of morphine 300 mg/day	+
Wu et al. 2002*[187]	+	+	32	Infusion of morphine/lidocaine/diphenhydramine over 40 min on 3 consecutive days	+(morphine)
Wu et al. 2008*[186]	+	+	60	Oral morphine/mexiletine/placebo for 8 weeks, washout period 1 week, mean dose of morphine 112 mg/day, mean dose of mexiletine 933 mg/day	+(morphine)
<u>NMDA receptor antagonists</u>					
Nikolajsen et al. 1996*[121]	+	+	11	Infusion of ketamine/placebo over 45 min, washout period 3 days	+
Eichenberger et al. 2008*[42]	+	+	20	Infusion of ketamine/ketamine and calcitonin/calcitonin/ placebo over 1 h, washout period 2 days	+(ketamine)
Nikolajsen et al. 2000*[120]	+	+	19	Oral memantine/placebo for 5 weeks, washout period 4 weeks, dose of memantine 20 mg/day	-
Maier et al. 2003[107]	+	+	36	A (n=18): memantine (30 mg/day) for 4 weeks B (n=18): placebo	-
Wiech et al. 2004*[177]	+	+	8	Oral memantine/placebo for 4 weeks, washout period 14 days, dose of memantine 30 mg/day	-

or inappropriate, controls are often lacking, and follow-up periods are short. Halbert et al. performed a systematic literature search (Medline 1966–99) to determine the optimal management of phantom pain. The authors identified 186 articles, but after exclusion of letters, reviews, descriptive trials without intervention, case reports and trials with major methodological errors, only 12 articles were left for review [67]. Since then, some well-designed studies have been published. Until more clinical data become available, treatment guidelines for other neuropathic pain conditions are probably the best approximation, especially for the treatment of stump pain [52]. A combination of medical and non-medical treatments may be advantageous. In general, treatment should be non-invasive because surgery on the peripheral or central nervous system always implicates further deafferentation and thereby an increased risk of persistent pain.

## PHARMACOLOGICAL TREATMENT

### *Tricyclic antidepressants*

At least two studies have examined the effect of tricyclic antidepressants on phantom pain. In one study, 39 patients were randomized to receive either amitriptyline or active placebo during a 6-week trial period. The dosage of amitriptyline was increased until the patient reached the maximum tolerated dose of 125 mg/day. Unfortunately, the study showed no effect of amitriptyline on pain intensity or secondary outcome measures such as satisfaction with life [150]. In another study, 49 posttraumatic amputees were randomized to receive amitriptyline (mean dose 55 mg), tramadol (mean dose 448 mg) or placebo for one month. The administration of tramadol and placebo was blinded; amitriptyline was given non-blinded as open comparison. Non-responders (less than 10 mm pain relief on a VAS from baseline to day 3) were switched to the alternative active treatment, e.g. tramadol to amitriptyline treatment and vice versa. Placebo non-responders were switched to tramadol or amitriptyline. Both tramadol and

amitriptyline almost abolished stump and phantom pain at the end of the treatment period [179].

### **Gabapentin**

The effect of gabapentin on chronic phantom limb pain has been examined in two studies. Bone et al. examined the effect of gabapentin in a double-blind, crossover study including 19 patients with phantom pain. The dose of gabapentin was titrated in increments of 300 mg to the maximum dosage of 2400 mg per day. After 6 weeks of treatment, gabapentin was better than placebo in reducing phantom pain [12]. Smith et al. administered gabapentin or placebo for 6 weeks to 24 amputees in a double-blind, crossover fashion with a maximum dose of 3600 mg. Gabapentin did not decrease the intensity of pain significantly, but the participants rated the decrease of pain as more meaningful during the treatment period with gabapentin [165]. So far, the effect of pregabalin on phantom pain has not been examined in controlled trials.

### **Opioids**

Failure to provide efficient pain relief should not be accepted until opioids have been tried. In a placebo-controlled, crossover study including 12 patients, a significant reduction of phantom pain was found during a 4-week treatment phase with oral morphine (70 mg to 300 mg/day) [79]. In another randomized, double-blind, crossover study with active placebo, 32 amputees received a 40-minute infusion of lidocaine, morphine or diphenhydramine. Compared with placebo, morphine reduced both stump and phantom pain, whereas lidocaine only reduced stump pain [187]. The effect of oral treatment with morphine, mexiletine or placebo was examined in a randomized, double-blind, crossover study including 60 amputees. Each of the three treatment periods included a 4-week titration, a 2-week maintenance and a 2-week taper phase. Postamputation pain was only significantly reduced during the treatment with morphine (mean dosage 112 mg) [186].

### **NMDA receptor antagonists**

The effect of NMDA receptor antagonists has been examined in different studies. In a double-blind, placebo-controlled, crossover trial, intravenous ketamine reduced pain, hyperalgesia and wind-up-like pain in 11 amputees with stump and phantom pain [121]. Eichenberger and colleagues studied the effect of an 1-hour infusion of ketamine alone, a combination of ketamine and calcitonin, calcitonin alone, and placebo in 20 amputees with phantom pain. Ketamine alone significantly reduced phantom pain. The combination with calcitonin provided no additional effect, and calcitonin alone had no effect on pain [42].

Three other trials have examined the effect of memantine, an NMDA receptor antagonist available for oral use. In all studies, memantine was administered in a blinded, placebo-controlled, crossover fashion to patients with established stump and phantom pain. Memantine at doses of 20 or 30 mg per day failed to have any effect on spontaneous pain, allodynia and hyperalgesia [107,120,177].

### **Other drugs**

Calcitonin significantly reduced phantom pain when used intravenously in the early postoperative phase in one study [82]. However, a more recent study found no effect of such a treatment [42]. A large number of other treatments, for example dextromethorphan, topical application of capsaicin, intrathecal opioids, various anaesthetic blocks and injections of botulinum toxin and

topiramate, have been claimed to be effective in phantom pain, but none of them have proven effective in well-controlled trials with a sufficient number of patients. An overview of selected studies on medical treatment can be seen in Table 2.

### **NON-PHARMACOLOGICAL TREATMENT**

A recent survey of treatments used for phantom pain revealed that after pharmacological treatment, physical therapy was the treatment modality most often used [69]. Physical therapy involving massage, manipulation and passive movements may prevent trophic changes and vascular congestion in the stump. Other treatments, such as transcutaneous electrical nerve stimulation, acupuncture, bio-feedback and hypnosis, may in some cases have a beneficial effect on stump and phantom pain. It has been suggested that mirror therapy can reduce phantom pain [18,35]. In a larger clinical trial of 80 amputees, however, Brodie et al. failed to find any significant effect of mirror treatment [15]. Flor's group demonstrated that sensory discrimination training obtained by applying stimuli to the stump reduced pain in 5 upper limb amputees [55]. The major advantages of most of the above-mentioned methods are the absence of side effects and complications and the fact that the treatment can be easily repeated. Most studies are, however, uncontrolled observations.

### **Surgical and other invasive treatment**

Surgery on amputation neuromas and reamputation previously played important roles in the treatment of stump and phantom pain. Today, stump revision is usually performed only in cases of obvious stump pathology, and in properly healed stumps there is almost never any indication for proximal extension of the amputation because of pain. In a recent prospective study of patients with neuropathic pain, including phantom pain, pain was only relieved in two out of six patients following surgical neuroma removal [118]. The results of other invasive techniques such as, for example, dorsal root entry zone lesions, sympathectomy and cordotomy have generally been unfavourable, and most of them have now been abandoned. Surgery may produce short-term pain relief, but the pain often reappears. Spinal cord stimulation and deep brain stimulation may be used for the treatment of phantom limb pain [9,170]. As the methods are invasive and associated with considerable costs, they should only be used for carefully selected patients.

### **GENERAL ASPECTS ON MECHANISMS**

The mechanisms underlying phantom limb pain are not fully known despite much research in the area. Results from animal models of neuropathic pain have, however, contributed further to our understanding. It is now clear that nerve injuries are followed by a number of morphological, physiological and chemical changes in both the peripheral and central nervous system (for review see [61,99]). For example, neuromas in the periphery exhibit spontaneous and abnormally evoked activity [171], which is assumed to be the result of an increased expression of sodium channels [11]. In the dorsal root ganglion (DRG) cells, similar changes occur [87]. The increased afferent barrage from neuromas and DRG cells is thought to induce long-term changes in centrally projecting neurons in the spinal dorsal horn. The pharmacology of central sensitization involves, for example, increased activity in N-methyl-D-aspartate (NMDA) receptor-operated systems, and many aspects of the central sensitization can be reduced by NMDA receptor antagonists [184].

Supraspinally, reorganization of the somatosensory cortex occurs, and it has been shown that there is a correlation between phantom pain and the amount of reorganization [58], although it is not clarified whether cortical reorganization is a causal factor, a consequence or an epiphenomenon of phantom limb pain.

Preamputation factors are also likely to contribute to the development of stump and phantom pain after amputation. Clinical studies have shown that pain before the amputation increases the risk of developing phantom pain [71,76,86,125], and that phantom pain often resembles the pain experienced before the amputation both in character and localization [75,90,125]. Some authors have explained these findings with the hypothesis that preamputation pain establishes a nociceptive engram in some cerebral structures, and that phantom pain is a reminiscence of the pain experienced in the limb before the amputation [113].

As can be seen from the foregoing, the mechanisms underlying pain in amputees are very complex (see Figs. 2 and 3 for an overview). In the following chapters, peripheral, spinal and supraspinal mechanisms will be described separately and in more detail with an emphasis on the author's own studies (V-X). To start with, the issue of preamputation pain (study I) and limb sensitization (study IV) as risk factors for the development of stump and phantom pain will be dealt with, and the possibilities of prevention by perioperative interventions will be discussed (studies II, III).

<b>Supraspinal mechanisms:</b>
Reorganization and hyperexcitability changes of the somatosensory cortex and other regions including the thalamus
Catastrophizing and other psychological factors
<b>Spinal mechanisms:</b>
NMDA receptor activation
Expansion of receptive fields
Loss of inhibitory interneurons
Activation of glial cells
<b>Peripheral mechanisms:</b>
Neuroma formation
Changed ion channel expression
Alteration of receptor proteins
Ectopic discharge from severed nerve endings
Sympathetic activation
<b>Preamputation mechanisms:</b>
Pain before amputation
Genetics
Psychosocial factors

**Figure 2**  
An overview of the proposed mechanisms involved in phantom pain.

## PREAMPUTATION MECHANISMS

### PREAMPUTATION PAIN AS A RISK FACTOR

Retrospective [76,94] as well as prospective studies [71,86,125] pointed to pain before the amputation as a risk factor for phantom pain. In a retrospective study of 176 lower-limb amputees, a significant relation was found between preamputation pain and

phantom pain in the first 2 years after amputation in vascular amputees, but in traumatic amputees phantom pain was only related to preamputation pain immediately after the amputation [76].

Jensen et al. carried out the first prospective study on the relation between preamputation pain and phantom pain. Fifty-eight lower-limb amputees were followed for 2 years. After 6 months, phantom pain was more frequent in patients who had pain on the day before the amputation compared to those without pain; there was no relation between preamputation pain and phantom pain after 2 years. The intensity of pain was not recorded in that study [86].

In study I, fifty-six patients scheduled for lower-limb amputation were asked about pain before the amputation and after 1 week, 3 and 6 months. The intensity of pain was recorded on a VAS (0-100). Phantom pain was more frequent after 1 week and 3 months, but not after 6 months in patients who had moderate to severe preamputation pain (VAS > 20) compared to patients with less preamputation pain (VAS < 20) [125]. More recently, Hanley et al. recorded data about pain before and after amputation in 57 lower-limb amputees and showed that the intensity of preamputation pain was a predictor of phantom pain after 24 months [71].

Still, the relation between preamputation pain and phantom pain is not simple. In study I, some patients with severe preoperative pain never developed phantom pain, while others with only modest preoperative pain developed severe phantom pain [125]. Also, patients with traumatic amputations, including those who never experienced pain before the amputation, develop phantom pain to the same extent as patients with long-standing preamputation pain who undergo amputation for medical reasons. Lacoux et al. examined 40 upper-limb amputees who had lost their limbs following injury by a machete, axe or gunshot during the civil war in Sierra Leone. About half of the amputees (56%) lost their limbs at the time of injury (primary), while the remainder had an injury and a subsequent amputation at a hospital on average 10 days after the injury (secondary). It is reasonable to assume that the latter group suffered from severe pain between the two events. However, there was no correlation between the development of phantom pain and whether the amputation was primary or secondary [100].

Another issue concerns to what extent pain experienced before the amputation may persist as phantom pain. Striking case reports show that phantom pain may mimic preamputation pain in both character and localization [75,90,125]. In a retrospective study, 68 amputees were questioned about preamputation pain and phantom pain from 20 days to 46 years after amputation. Fifty-seven per cent of those who had experienced preamputation pain claimed that their phantom pain resembled the pain they had before the amputation [90].

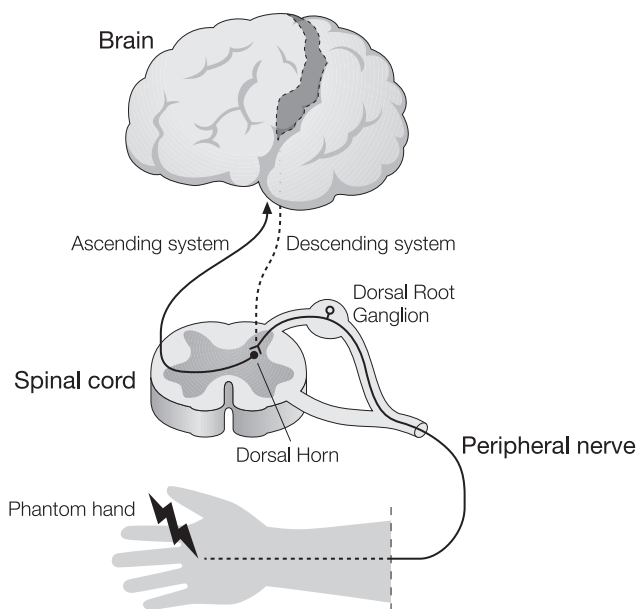
The number of patients with similar descriptions of preamputation pain and phantom pain was much lower in two prospective studies [86,125]. In the latter of the two studies, 10 different word descriptors, the McGill Pain Questionnaire and the patients' own words were used to characterize the pain before and after amputation. The location of the pain was also recorded. Six months after the amputation, 41% of patients claimed that their phantom pain was similar to the pain they had experienced before the amputation, but the actual similarity when comparing pre- and postamputation descriptions of pain was not higher in patients who claimed similarity than in those who found no similarity between their phantom pain and preamputation pain (study I [125]).

### PREAMPUTATION LIMB SENSITIZATION

Long-term and intense nociceptive input from the periphery, such as preamputation pain, may induce central sensitization. Besides pain, the clinical manifestations of central sensitization include lowered pain thresholds (hyperalgesia), pain evoked by non-noxious stimuli (allodynia) and pain elicited by repeated pricking stimuli (wind-up-like pain) [20]. Study IV examined whether pre-amputation signs of sensitization, as reflected by lowered mechanical thresholds at the limb, were related to postamputation stump and phantom pain. Pressure pain thresholds at the limb, obtained by using a pressure algometer, were examined in 35 patients before and 1 week and 6 months after amputation. There was an inverse relation between preamputation thresholds and stump and phantom pain after 1 week, but not after 6 months [124].

The importance of preinjury sensitization for the subsequent development of pain is supported by the experimental literature. For example, it has been shown that a thermal injury applied to the hindpaw before sectioning the sciatic and saphenous nerves shortens the onset and enhances the severity of autotomy (i.e. self-mutilation), which may represent a behavioural model of phantom pain in the rat [91].

Prevention of phantom pain by perioperative interventions  
The idea of using perioperative analgesic interventions in order to prevent the development of phantom limb pain is prompted by the finding that pain experienced before the amputation is a risk factor for the development of phantom pain. The hypothesis is that phantom pain can be prevented by reducing preamputation pain. Table 3 shows an overview of studies on the prevention of phantom pain (for review, see [190]).



**Figure 3**  
A schematic figure of the areas involved in the development of phantom pain.

### Epidurals

The first study on the prevention of phantom pain was carried out by Bach et al.: 25 patients were randomized by birth year to either epidural pain treatment 72 hours before the amputation (11 patients) or conventional analgesics (14 patients). All patients had spinal or epidural analgesia for the amputation, and both groups received conventional analgesics to treat postoperative pain. Blinding was not described. After 6 months, the incidence of phantom pain was lower among the patients who had received the preoperative epidural blockade [4].

Jahangiri et al. examined the effect of perioperative epidural infusion of diamorphine, bupivacaine and clonidine on postamputation stump and phantom pain. Thirteen patients received epidural treatment 5-48 hours preoperatively and for at least 3 days postoperatively. A control group of 11 patients received opioid analgesia on demand. All patients had general anaesthesia for the amputation. The incidence of severe phantom pain was lower in the epidural group 7 days, 6 months and 1 year after amputation. The study was not randomized or blinded [83].

Schug et al. presented in a letter results from a study in which 23 patients had either epidural analgesia before, during and after the amputation (eight patients), intra- and postoperative epidural analgesia (seven patients) or general anaesthesia plus systemic analgesia (eight patients). After 1 year, the incidence of phantom pain was significantly lower among the patients who received pre-, intra- and postoperative epidural analgesia compared with patients who received general anaesthesia plus systemic analgesia [156]. Several abstracts with similar study designs have claimed a preventive effect of perioperative epidurals, but the results have never been published in articles.

Study II was a randomized, double-blind, placebo-controlled study in which 60 patients scheduled for lower limb amputation were randomly assigned into one of two groups: a blockade group that received epidural bupivacaine and morphine before the amputation and during the operation (29 patients) and a control group that received epidural saline and oral or intramuscular morphine (31 patients). Both groups had general anaesthesia for the amputation, and all patients received epidural analgesics for postoperative pain management. Patients were interviewed about their preamputation pain on the day before the amputation and about stump and phantom pain after 1 week, 3, 6 and 12 months. Median duration of the preoperative epidural blockade (blockade group) was 18 hours. After 1 week the percentage of patients with phantom pain was 51.9 in the blockade group and 55.6 in the control group. Subsequently, the figures were (blockade/control): at 3 months, 82.4/50; at 6 months, 81.3/55; and at 12 months, 75/68.8. The intensity of stump and phantom pain and consumption of opioids were also similar in the two groups at all four postoperative interviews [122]. These findings are confirmed by a more recent retrospective review of 150 amputees, in which there was no difference in the incidence of phantom pain 24 months after the amputation among those who had received epidural, spinal or general anaesthesia for the amputation [130]. Thirty-one patients, all recruited from the above-mentioned randomized study [122], underwent quantitative sensory testing before, 1 week and 6 months after amputation. There was no difference between the two groups (epidural blockade vs. control) in any of the postoperative assessments as regards pressure pain thresholds (pressure algometry), touch and pain detection thresholds (von Frey filaments), thermal sensibility (thermal rolls) and allodynia and wind-up-like pain (study III [123]).



### Other nerve blocks

Others have examined the effect of peri- or intraneural blockade on phantom pain. Fischer and Meller (1991) introduced a catheter into the transected nerve sheath at the time of amputation and infused bupivacaine for 72 hours in 11 patients. None of the patients developed phantom pain during a 12-month follow-up [53]. Two retrospective studies have found negative and positive effects, respectively, of a similar treatment [47,64]. Pinzur et al. prospectively randomized 21 patients to continuous postoperative infusion of either bupivacaine or saline, but failed to find any difference between the two groups with regard to the incidence

of phantom pain after 3 and 6 months [136]. Lambert et al. compared two techniques of regional analgesia: 30 patients were randomized to epidural bupivacaine and diamorphine started 24 hours before the amputation and continued for 3 days postoperatively or an intraoperative perineural catheter for intra- and postoperative administration of bupivacaine. All patients had general anaesthesia for the amputation. The pre-, peri- and postoperative epidural pain treatment was not superior to the intra- and postoperative perineural pain treatment in preventing phantom pain as the incidence of phantom pain was similar in the two groups after 3 days, 6 and 12 months [102].

**Table 3**

**Summary of studies on the prevention of phantom pain (A, B, C refer to the different treatment arms in each study) \*retrospective study.**

Reference	Randomization	Blinding	No. of patients	Intervention	Long-term effect
<u>Epidural analgesia</u> Bach et al. 1988[4]	+	?	25	A (n=11): epidural bupivacaine and morphine for 72 h before amputation B (n=14) systemic analgesia	+
Jahangiri et al. 1994[83]	-	-	24	A (n=13): epidural bupivacaine, clonidine and diamorphine for 24-48 h before amputation and continued 72 h after amputation B (n=11): systemic analgesia	+
Schug et al. 1995[156]	-	-	23	A (n=8): epidural bupivacaine and morphine for 24 h before, during and after amputation B (n=7): epidural bupivacaine and morphine during and after amputation C (n=8): systemic analgesia	+
Nikolajsen et al. 1997[122]	+	+	60	A (n=29): epidural bupivacaine and morphine for 18 h before, during and 166 h after amputation B (n=31): systemic analgesia before amputation, epidural bupivacaine and morphine 166 h after amputation	-
Ong et al. 2006*[130]	-	-	150	A (n=21): epidural anaesthesia B (n=81): spinal anaesthesia C (n = 48): general anaesthesia	-
<u>Epidural vs. perineural analgesia</u> Lambert et al. 2001[102]	+	-	30	A (n=14): epidural bupivacaine and diamorphine for 24 h before, during and 72 h after amputation B (n=16): perineural block with bupivacaine for 72 h after amputation	-
<u>Epidural +/- epidural ketamine</u> Wilson et al. 2008[182]	+	+	53	A (n=24): Epidural bupivacaine and ketamine for 48-72 h after amputation B (n=29): Epidural bupivacaine and saline for 48-72 h after amputation	-
Perineural analgesia Fischer and Meller 1991[53]	-	-	11	A (n=11): nerve sheath block with bupivacaine for 72 h after amputation	+

**Table 3 - continued**

**Summary of studies on the prevention of phantom pain (A, B, C refer to the different treatment arms in each study) \*retrospective study.**

Reference	Randomization	Blinding	No. of patients	Intervention	Long-term effect
<u>Epidural +/- epidural ketamine</u> Elizaga et al. 1994*[47]	-	-	21	A (n=9): perineural block with bupivacaine for at least 72 h after amputation B (n=12): systemic analgesia	-
Pinzur et al. 1996[136]	+	+	21	A (n=11): perineural block with bupivacaine for 72 h after amputation B (n=10): perineural block with saline for 72 h after amputation	-
Grant and Wood 2008*[64]	-	-	64	A (n=33): perineural block with bupivacaine for 3.4 days after amputation B (n=31): conventional analgesia	+
Borghi et al. 2010[13]	-	-	71	A (n=71): perineural block with ropivacaine for 30 days after amputation	+
<u>Medical interventions</u>					
Dertwinkel et al. 2002[25]	-	-	28	A (n=14): intravenous ketamine during and for 72 h after the amputation B (n=14, historical control)	+
Hayes et al. 2004[72]	+	+	45	A (n=22): intravenous ketamine during and for 72 h after the amputation B (n=23): intravenous saline during and for 72 h after the amputation	-
Schley et al. 2007[152]	+	+	19	A (n=10): memantine 20 - 30 mg/day for 4 weeks after amputation B (n=9): placebo for 4 weeks after amputation	-
Nikolajsen et al. 2006[119]	+	+	46	A (n=23): gabapentin 1800 mg/day for 30 days after amputation B (n=23): gabapentin 1800 mg/day for 30 days after amputation	-

In a very recent study by Borghi et al., interesting results have been reported following a prolonged infusion of local anaesthetics via a perineural catheter. Seventy-one patients received perineural infusion of ropivacaine 0.5% for a median period of 30 days (range 4-83 days) after the amputation. The infusion of ropivacaine was discontinued at regular intervals, but restarted if the intensity of phantom pain exceeded 1 on a 5-point verbal scale. The prevalence of severe to intolerable phantom pain was only 3% after 12 months [13].

**Medical interventions**

A few studies have examined the effect of medical interventions applied in the peri- and postoperative period. In an open study with historical controls, Dertwinkel et al. suggested that ketamine infused intraoperatively and for 72 hours after the amputation could reduce phantom pain [25]. A randomized, double-blind trial including 45 patients found no effect of a similar treatment [72]. In another double-blind study, 19 patients with acute traumatic amputation of the upper extremity were randomized to either memantine 20-30 mg daily or placebo for 4 weeks after the amputation. All patients received postoperative analgesia by continuous brachial plexus analgesia. Memantine treatment reduced

phantom pain after 4 weeks and 6 months, but not after 12 months [152]. In a randomized, blinded, placebo-controlled study, gabapentin administered daily during the first 30 days after amputation had no effect on phantom pain (study IX [119]).

**DISCUSSION OF OWN RESULTS AND CONCLUSION ON PREAMPUTATION MECHANISMS**

Study I showed that pain before the amputation increases the risk of phantom pain [125] in accordance with other studies on the subject. The study also showed that pain experienced before the amputation may persist as phantom pain, but in the majority of patients there was no similarity between the pain before and after the amputation. These findings were in contrast with a retrospective study by Katz and Melzack [90]. It therefore seems that retrospective memories about pain should be interpreted with care [125].

Preamputation mechanisms do play a role for the development of phantom pain, and this was further supported by the finding that mechanical thresholds at the limb obtained before amputation were inversely related to stump and phantom pain one week after the amputation (study IV [124]). No other studies with a similar design have been carried out in amputees, but

clinical studies involving other surgical procedures have shown that preoperative responses to noxious stimuli may predict postoperative pain (for review, see [63]).

Studies II and III prospectively examined the effect of a perioperative epidural blockade on phantom pain and abnormal sensory phenomena at the stump but found no effect of such a treatment [122,123]. These findings are in contrast with several other studies on the prevention of phantom pain by epidurals. Many of the studies published on this subject do, however, suffer from methodological flaws such as lack of randomization and blinding.

The issue of epidurals in the prevention of phantom pain is still a matter of great debate, yet it is unlikely that a short-lasting perioperative epidural treatment will have a major impact on pain after amputation. Many amputees have suffered from ischaemic pain for months or years and are likely to present with neuronal sensitization before surgery, and postoperatively afferent noxious barrage from the periphery is likely to outlast the duration of the epidural block. In this respect, the results by Borghi et al. are of great interest as patients were treated with a perineural block for a median period of 30 days [13]. Epidurals and other nerve blocks are effective in the treatment of stump pain in the immediate postoperative period, but more well-designed controlled trials are needed to evaluate the potential of perioperative treatment regimens for the reduction of chronic phantom pain.

Based on the literature and the findings in studies I-IV, it can be concluded that preamputation mechanisms play a role for the development of phantom pain, although it is evident that other mechanisms are involved.

## PERIPHERAL MECHANISMS

### CLINICAL OBSERVATIONS

Several clinical observations suggest that mechanisms in the periphery (i.e. in the stump or in central parts of the sectioned afferents) play a role for the phantom limb concept.

- Phantom limb pain is significantly more frequent in amputees with long-term stump pain than in those without persistent pain [27].
- Stump pathology with increased stump sensibility is linked to phantom pain [169].
- Tapping of neuromas may increase phantom pain [128].
- Phantom pain can be modulated by sensory discrimination training at the stump [55].
- Temperature and muscle activity at the stump are related to phantom pain [89,161,162].
- Phantom pain and pressure pain thresholds at the stump are inversely correlated early after amputation [124].
- Phantom pain is increased by perineuromal injections of gallamine [17] and norepinephrine [103] and reduced by injections of lidocaine [17].
- Regional anaesthesia may evoke [110,132] and reduce [7] phantom pain.

The clinical observation that stump temperature is related to phantom pain suggests that the sympathetic nervous system is involved [89,161]. For example, Katz studied 28 amputees of whom 11 experienced phantom pain, nine experienced phantom sensations and eight experienced no phantom phenomena. The temperature was significantly lower at the stump than at the contralateral limb in the groups with phantom phenomena, but

not among amputees without phantom phenomena [89]. Whether this difference in temperature represents a pain-generating mechanism or is a result of pain per se is not clear. More recently, Lin et al. demonstrated a dose-dependent increase in stump pain by perineuromal injections of norepinephrine. There was a partial reversal of the pain by pretreatment with phentolamine, an  $\alpha$ -adrenergic antagonist [103].

Experimental studies have shown that the interaction between sympathetic efferent nerve fibres and afferent sensory neurons takes place both in the periphery [171] and in DRG cells [29].

The clinical observation that phantom pain can be reduced by regional anaesthesia is of great interest as there is an ongoing discussion to what extent phantom pain is dependent on afferent input from the periphery. Birbaumer et al. studied the effect of regional anaesthesia on phantom pain and cortical reorganization in upper-limb amputees and found that a brachial plexus blockade abolished pain and cortical reorganization in three out of six amputees with phantom pain. Cortical reorganization was unchanged in the three amputees whose pain was not reduced by the brachial plexus blockade [7]. This suggests that afferent input from the periphery is important for the phantom pain experience in some – but not all – amputees.

## PERIPHERAL NERVE INJURY AND NEUROMAS

### Experimental studies

Following injury to peripheral nerve fibres a series of structural and functional changes are seen. These changes include blockade of axonal transport, accumulation of channel-loaded transport vesicles, membrane remodelling and altered gene expression, leading to ectopic discharges and changed responsiveness of receptors and channels at damaged nerve endings [28,61,184].

A particularly important aspect of pain in nerve injury, including postamputation pain, is the sprouting of peripheral nerve fibres. When a peripheral nerve is cut, numerous fine processes (“sprouts”) start to grow from the proximal end, i.e. the part still connected to the cell body. Under normal conditions these sprouts will elongate to form connections with their appropriate peripheral targets. This is not possible after limb amputation, and in consequence the regenerating sprouts will form a tangled mass at the nerve end, a so-called “amputation neuroma” [101]. At the molecular level, the blindly ending transected axons within the neuromas contain an abnormal accumulation of sodium channels [23,30] and associated molecules, such as ankyrin G [96] and contactin [160] that enhance the expression of functional channels in the axon membrane. This accumulation may play a role for the hyperexcitability and spontaneous discharge noted within injured nerves [112]. Animal models of neuropathic pain have shown ectopic discharge in both axotomized unmyelinated C-fibres, thinly myelinated A $\delta$ -fibres, A $\beta$ -afferents, intact neighbouring C-fibres and DRG cells (for review see [28]).

Only few studies have examined ectopic discharge in humans. In a classical study, Nyström and Hagbarth made intraneural microelectrode recordings from the transected nerves in two amputees with ongoing pain in their phantom foot and hand, respectively. The recordings revealed prominent spontaneous activity. Percussion of neuromas produced increased nerve fiber discharges and an augmentation of phantom pain [128]. Similar results have been found by others [127].

### Clinical studies on neuroma removal

If phantom pain is driven by afferent input generated ectopically in primary sensory afferent neurons, as suggested by experimen-

tal and clinical studies, a logical approach would be to remove the painful neuromas. In fact, several studies have reported promising results of neuroma removal on neuropathic pain following various nerve injuries, including amputation [38,92,97]. For example, Sehirlioglu et al. retrospectively studied 75 lower-limb amputees who underwent neuroma removal and reported that all patients were free of any pain symptoms after a mean follow-up period of 2.8 years [157].

However, the effect of surgical excision remains controversial. Study V studied the effect of neuroma removal on stump and phantom pain in six patients with verified peripheral nerve injury pain and palpable neuromas, of which four were upper-limb amputees. Pain was recorded before and 1, 3 and 6 months after the operation, and quantitative sensory testing was carried out before and 3 months after surgery. Neuroma removal resulted in a reduction of stump and phantom pain and brush-evoked allodynia in two patients (both amputees). One of those patients had a prior poor response to neuroma removal. Pain worsened in one of the six patients [118]. Thus, these results suggest that pain may be driven by other factors than afferent input from neuromas. One possibility is that DRG cells constitute a source of ectopic activity that is not eliminated by surgery [28,104].

#### **Lidocaine**

Experimental studies have documented that lidocaine, a non-specific sodium channel blocker, silences ectopic discharge from neuromas and DRG cells [32], and in human studies intravenous lidocaine has been shown to reduce spontaneous and evoked neuropathic pain [62,187]. Study V examined if the analgesic response to a preoperative intravenous infusion of lidocaine could predict the outcome of neuroma removal. Lidocaine (5 mg·kg<sup>-1</sup>) or saline (placebo) was administered over the course of 30 min. in a randomized, double-blind manner on two separate examination days before surgery. Wind-up-like pain was elicited before and 20 min. after the start of the infusion. The analgesic effect of lidocaine or saline was calculated as the difference in evoked pain intensity before and during the infusion. Lidocaine reduced wind-up-like pain in two patients, but there was no consistent relationship between the effect of lidocaine and the outcome of surgery: one patient responding to the lidocaine infusion experienced pain relief after neuroma removal, but in the second patient the pain worsened [118]. Thus, the effect of systemically administered lidocaine did not predict the outcome of surgery. One explanation is that recurrent neuromas continue to be a source of ectopic output.

Others examined the effect of lidocaine on chronic stump and phantom pain after amputation. Jacobson et al. found that intrathecal lidocaine reduced stump pain in three out of eight amputees whereas intrathecal fentanyl abolished the pain in all amputees [81]. More recently, Wu et al. randomized 32 amputees to receive either intravenous lidocaine, morphine or active placebo in a double-blind, crossover study. Stump pain was reduced both by morphine and lidocaine, while phantom pain was reduced only by morphine [187]. The findings in the two latter studies suggest that the mechanisms underlying stump pain and phantom pain may differ. A final support of the role of ion channels in the stump as a source of pain is demonstrated by the pain reduction following perineuronal injection of lidocaine [17].

#### **SODIUM CHANNELS**

There are nine distinct isoforms of sodium channels, and of those Nav1.3, Nav1.7, Nav1.8 and Nav1.9 are likely to be involved in neuropathic pain (for review see [33]). Experimental studies have

shown a prominent expression of Nav1.7, Nav1.8 [36] and Nav1.9 in uninjured nociceptive neurons in the DRG, and that the presence of Nav1.3 is upregulated after peripheral axotomy [10]. The expression of sodium channels in human neuromas have until recently only been examined in two studies, which demonstrated upregulation of Nav1.7 and Nav1.8 [8,95]. In addition to changes in sodium channel expression, there are also changes in Ca<sup>++</sup> and K<sup>+</sup> channels that may contribute to abnormal activity in afferent fibres [1,33]. The excitability of the cell is not only determined by the number of ion channels but also by channel kinetics. Pro-inflammatory cytokines, intracellular mitogen-activated protein (MAP) kinases and other mediators have been shown to modulate channel kinetics, resulting in an increased excitability [129].

Black and co-workers examined the expression of sodium channels Nav1.1, Nav1.2, Nav1.3, Nav1.6, Nav1.7, Nav1.8 and Nav1.9 and two MAP kinases, activated p38 and ERK1/2 in seven painful neuromas and control nerve tissue obtained from five patients (four were amputees). The results demonstrated for the first time an expression of Nav 1.3 and MAP kinases in painful neuromas. Also, there was an enhanced expression of Nav1.7 and Nav1.8 in neuromas when compared with control nerve tissue obtained more proximally from the same nerve. There was no association between the presence or absence of any particular sodium channel isoform or MAP kinases and the degree of pain or the response to neuroma removal (study VI [11]).

#### **DISCUSSION OF OWN RESULTS AND CONCLUSION ON PERIPHERAL MECHANISMS**

The outcome in study V was less positive than the outcome reported in other studies [38,92,97]. This difference may be related to patient selection and study design. For example, in the retrospective study by Sehirlioglu et al., which was based on a review of medical records, amputees were diagnosed with a neuroma if they had a painful swelling in the stump [157]. Studies based on review of medical records are likely to underestimate the incidence of pain. Study V also had some limitations. First, only a limited number of patients were included, and second, the follow-up period was only 6 months. Also, it is possible that a greater efficacy of surgical removal might have been demonstrated if the neuromas had been shown to be a focus of pain via a focal preoperative diagnostic block. The lack of prediction of outcome by systemically administered lidocaine may be explained by output from DRG cells and recurrent neuromas.

Black and co-workers showed an enhanced expression of sodium channels Nav1.3, Nav1.7, Nav1.8 and two MAP kinases and thus confirmed and expanded the findings by others that sodium channels and MAPK pathways play a role for neuropathic pain, including phantom pain (study VI [11]).

Based on the literature and studies V and VI, it can be concluded that peripheral mechanisms play a role for the phantom pain experience. However, it is very likely that other mechanisms are involved as peripheral blocks and neuroma removal do not always alleviate the pain [7,118].

#### **SPINAL MECHANISMS CLINICAL OBSERVATIONS**

Clinical observations indicate that spinal factors are involved in the generation of phantom limb pain [3,19,137]. For example, phantom limb pain may appear or disappear following spinal cord neoplasia. Aydin and colleagues described a woman who suffered from phantom limb pain following lower limb amputation at the age of 5 years. At the age of 65 years, the pain gradually disap-

peared, paralleling the evolution of cauda equina compression due to an intraspinal tumour. The phantom limb pain gradually reappeared after surgical removal of the tumour [3]. Other studies have shown that spinal anaesthesia may modulate phantom pain [106,154,168].

Although direct evidence for spinal mechanisms in human amputees is limited, experimental data based on animal models show that spinal changes are likely to play an important role for neuropathic pain, including phantom pain.

#### CENTRAL SENSITIZATION

Experimental studies have shown that increased activity in peripheral nociceptors can induce long-term changes in the synaptic responsiveness of neurons in the dorsal horn of the spinal cord, a process known as central sensitization. Central sensitization has several features including increased spontaneous activity of dorsal horn neurons, increased response to afferent input, after-discharges following repetitive stimulation and an expansion of peripheral receptive fields (for review see [99]).

One aspect of central sensitization is the "wind-up" phenomenon (increased activity in dorsal horn neurons following repetitive C-fibre stimulation) [34,184]. In humans, wind-up-like pain can be elicited by repeatedly pricking the affected skin area [44]. Besides pain, other clinical manifestations of central sensitization include a reduction in pain thresholds (hyperalgesia) and pain evoked by non-noxious stimuli (allodynia) (for review see [20]). Allodynia may be explained by a phenotypic switch of large A $\beta$ -fibres into nociceptive-like nerve fibres. Substance P is normally expressed in small afferent A $\delta$ - and C-fibres but following nerve injury, substance P may be expressed in large A $\beta$ -fibres [108]. This plastic change in the functional organization of the spinal cord with phenotypic switch of A $\beta$ -fibres may contribute to pain after nerve injury (for review see [28]).

Clinical signs of central sensitization are common in amputees. For example, wind-up-like pain was demonstrated in eight out of 11 amputees with stump and phantom pain (study VII [121]). In another study, hyperalgesia at the stump, as reflected by reduced pressure pain thresholds, was related to phantom pain 1 week after amputation (study IV [124]).

#### N-METHYL-D-ASPARTATE RECEPTOR

Central sensitization is dependent on the activation of the N-methyl-D-aspartate (NMDA) receptor (for review see [185]). Afferent input from nociceptive primary afferents will induce the release of glutamate, substance P and other neurotransmitters, which in turn will recruit the AMPA and neurokinin (NK1) receptors on second order neurons. The NMDA receptor, also situated on second order neurons, is inactive under normal conditions, but sustained barrage from the periphery results in its activation. Activation of the NMDA receptor leads to a cascade of intracellular events, which include calcium release and the activation of a variety of enzymes and protein kinases, including protein kinase C (PKC). PKC phosphorylates the NMDA receptor, releasing the magnesium (Mg<sup>+</sup>) plug within the NMDA channel. Altered mRNA expression is another consequence of NMDA receptor activation [134].

Studies on animal models of neuropathic pain have shown that the clinical manifestations of central sensitization can be blocked by NMDA receptor antagonists [109,147,189]. For example, Mao et al. showed that intrathecal treatment with dextrorphan or ketamine reduced pain-related behaviours in a rat model of peripheral mononeuropathy [109].

Ketamine, an anaesthetic agent with NMDA-blocking properties, was also reported to reduce wind-up like pain, allodynia and spontaneous pain in clinical studies on different neuropathic pain conditions [5,43,44,50,111], and Stannard and Porter reported excellent results of intravenous ketamine in three amputees with phantom pain [166].

A double-blind, placebo-controlled, crossover trial studied the effect of ketamine on stump and phantom pain, pressure pain thresholds, wind-up-like pain, thermal stimulus response curve and temporal summation of heat stimuli in 11 amputees. The amputees received a 45-min infusion of either ketamine (0.5mg/kg) or saline at two test sessions, separated by at least 3 days. Stump and phantom pain were recorded at intervals before, during and after the infusion using the VAS and McGill Pain Questionnaire. Quantitative sensory testing was carried out before and during the infusion. Ketamine significantly reduced spontaneous stump and phantom pain, pressure pain thresholds and wind-up-like pain, but had no effect on the response to thermal stimuli (study VII [121]). Unfortunately, ketamine is only available for injection and its use is limited because of side effects.

Experimental studies have shown that memantine, an NMDA receptor antagonist available for oral use, reduces manifestations of central sensitization. For example, memantine reduced thermal and mechanical hyperalgesia in a rat model of peripheral mononeuropathy [46].

One clinical study failed to find any effect of memantine in patients with postherpetic neuralgia [45]. Based on the clear analgesic effect of ketamine on postamputation pain, the effect of memantine on pain, allodynia, wind-up-like pain, and thresholds to mechanical stimuli was examined in 19 patients with chronic neuropathic pain after surgery (15 were amputees). Memantine was administered in a blinded, placebo-controlled, crossover fashion. The daily dose of memantine/placebo was increased from 5 to 20 mg during a 5-week treatment period. A washout period of 4 weeks was followed by another 5-week treatment period with the opposite drug. Memantine did not affect any of the outcome parameters, including pain (study VIII [120]). More recent studies examining the effect of memantine on phantom limb pain also failed to find any effect of the drug [107,177].

#### OTHER SPINAL MECHANISMS

Several other biological events are involved in the induction and maintenance of central sensitization (for review see [99,146]). Spinal glial cells are activated following nerve injury, which leads to the release of chemical mediators, including interleukin-1, TNF- $\alpha$  and BDNF [22]. These mediators act on other glial cells and on spinal neurons, and as a result the spinal excitability is increased. Peripheral nerve injury also promotes a selective loss of inhibitory GABAergic and glycinergic interneurons [117]. Spinal opioid receptors are downregulated [172] and, in addition, cholecystokinin, an endogenous inhibitor of the opiate receptor, is upregulated in injured tissue [178], thereby exacerbating the effect of disinhibition.

A mechanism that may be of special relevance to phantom pain is a functional reorganization of the spinal cord with an expansion of receptive fields. Deafferented nerve cells exhibit increased excitability, and silent cells are recruited in the spinal cord [31,188].

#### *Gabapentin*

Gabapentin exerts its analgesic effect mainly by binding to the  $\delta 2\alpha$ -subunit of voltage-gated calcium channels in neurons in the

dorsal horn [21]. Presynaptic binding results in a decreased release of the excitatory amino acid glutamate, and postsynaptic binding may affect glutamate currents at the NMDA receptor site. Thus, both pre- and postsynaptic binding may reduce glutamate-induced central sensitization and pain (for review see [60]).

Gabapentin has proved its efficacy in several neuropathic pain conditions, but two previous studies on the use of gabapentin on chronic phantom pain did not agree on the effect of the drug [12,165]. In study IX, 46 lower-limb amputees were randomized to either gabapentin or placebo for the first 30 days after amputation. The first dose of 300 mg gabapentin/placebo was given on the first postoperative day, and the dosage was gradually increased until the maximum of 2400 mg was reached. The intensity, frequency and duration of phantom pain attacks were recorded daily in the first 30 days and after 3 and 6 months. The intensity of stump pain was also recorded and sensory testing of the stump was performed, including recording of allodynia, pressure pain thresholds and wind-up-like pain. The two treatment groups were similar in almost all outcome parameters. Thus, early and prolonged treatment with gabapentin did not seem to reduce the incidence of phantom pain [119].

#### DISCUSSION OF OWN RESULTS AND CONCLUSION ON SPINAL MECHANISMS

Study VII showed that the NMDA receptor antagonist ketamine reduced spontaneous stump and phantom pain and abnormal sensory phenomena [121]. The positive effects of ketamine are in line with both previous [5,43,44,50,111,166] and more recent [42] studies on the effect of ketamine on different neuropathic pain conditions, including phantom pain. The finding that ketamine increased mechanical thresholds but had no effect on thermal stimuli is consistent with findings by others [44,50]. One explanation may be that peripheral mechanical stimuli may be more effective than thermal stimuli in driving dorsal horn neurons and central sensitization.

Three studies, including study VIII, failed to demonstrate any beneficial effect of memantine on phantom pain [107,120,177]. The lack of effect may have several explanations, including the low number of participating patients (19, 36 and eight, respectively). It is possible that memantine may have an effect in a subgroup of patients, or that higher doses of memantine would have produced better results. Another more likely explanation is that the mechanisms underlying phantom pain are so complex that NMDA antagonism alone is not sufficient to eliminate the pain.

Study IX failed to find any effect of early treatment with gabapentin on phantom pain. It cannot be excluded that the use of higher doses and a longer treatment period would have provided more positive results. So far, only one study has suggested that gabapentin may indeed be effective in the treatment of phantom pain. In the study by Bone et al., gabapentin was not superior to placebo until after 6 weeks of treatment [12]. It is possible that treatment with one single drug may not be capable of reducing such a complex pain phenomenon as phantom pain.

Based on the literature and studies VII-IX, it can be concluded that spinal mechanisms, including activity at the NMDA receptor, play a role for phantom pain. However, the complexity of phantom phenomena and the modification of phantom pain by internal factors (attention, distraction, stress) indicate that supraspinal structures are involved.

## SUPRASPINAL MECHANISMS

### CLINICAL OBSERVATIONS

A number of observations in amputees support the involvement of supraspinal changes.

- The complex and vivid sensations that characterize phantom phenomena (e.g. telescoping and spontaneous movements of the phantom) suggest that cortical structures are involved.
- Phantom pain is sometimes similar to the pain experienced in the limb before the amputation [90,125].
- Spinal anaesthesia does not always eliminate phantom pain [6].
- Phantom pain may be modulated by attention and distraction.
- Some amputees experience an increase in phantom pain when observing or imagining another person in pain ("sympnaesthesia for pain") [54].
- There is a significant relation between stress and phantom pain [2].
- Preoperative coping strategies, especially catastrophizing, predict the level of phantom pain after amputation [148].

The various supraspinal factors will be described in more detail below. Emphasis will be given to cortical reorganization and pain catastrophizing.

### CORTICAL REORGANIZATION

#### *Experimental studies*

Studies in adult monkeys have demonstrated functional and structural changes of the primary somatosensory (SI) cortex subsequent to amputation and deafferentation. Merzenich et al. examined the cortical representations of the hand after amputation of one or two digits using microelectrode mapping techniques. The representations of adjacent digits and palmar surfaces expanded topographically to occupy most or all of the cortical territories formerly representing the amputated digits [115]. Pons et al. reported an even larger cortical reorganization following deafferentation of the dorsal root, with the representation of the cheek taking over the cortical hand and arm in the range of centimetres [139].

#### *Clinical studies*

Studies in humans using different cerebral imaging techniques have confirmed that cortical reorganization takes place after amputation [66,68,88,175]. Flor's group has shown in several studies that there is a correlation between phantom pain and the amount of reorganization [56,57]. For example, phantom pain and cortical reorganization were absent in five congenital amputees, but in nine traumatic amputees phantom pain was positively related to cortical reorganization [57].

The functional relationship between phantom pain and cortical reorganization has been examined in at least two studies. Birbaumer et al. found that a brachial plexus blockade abolished pain and reorganization in three out of six upper-limb amputees [7]. In a randomized double-blind crossover study of 12 amputees, pain and cortical reorganization were reduced during treatment with morphine, but not during treatment with placebo [79].

It has been suggested that referred sensations in the phantom (i.e. painful or non-painful referred sensations in the phantom that can be elicited by stimulating areas adjacent to but also far from the amputated limb) are a perceptual correlate of the

reorganizational processes in the SI cortex [143]. On the other hand, it was shown that referred sensations in upper-limb amputees can be elicited from the toe, which is far removed from the representation of the arm [65]. This suggests that other areas must be involved in the generation of referred sensations.

#### OTHER SUPRASPINAL MECHANISMS

Reorganization has also been observed at more subcortical levels [188]. In adult monkeys with therapeutic amputations of the hand, an expansion of afferents into portions of the cuneate nucleus of the brainstem related to the amputated hand was demonstrated [59].

Davis et al. recorded thalamic neuronal responses to stimuli applied at the stump in six amputees. The results showed an unusually large thalamic stump representation, suggesting that the representation of the stump region had expanded into the original limb region of the thalamus. In the same study, thalamic microstimulation elicited phantom sensations in four of the six amputees. This indicates that the thalamic representation of the amputated limb remains functional, and that neuronal activity in this region may give rise to sensations perceived as originating from the missing limb [24].

In another study, imaging techniques were used to examine the thalamus in 28 amputees with unilateral amputations. A decrease in the grey matter of the thalamus contralateral to the side of amputation was found when compared to healthy controls. The decrease was correlated with the time span after the amputation, but was not related to the frequency or magnitude of coexisting phantom pain [37].

#### AFFECTIVE AND EMOTIONAL ASPECTS OF PHANTOM PAIN

It is likely that reorganization following amputation occurs not only for the areas involved in the sensory-discriminative aspects of pain, but also for those areas involved in the affective and emotional aspects of pain [181]. A large number of imaging studies have shown that several supraspinal areas such as the insula, the anterior cingulate cortex and the frontal cortices are involved in the modulation of nociceptive stimuli [138,140,159].

Studies in amputees have shown that depressive symptoms [48], affective distress [26] and coping strategies [70,74,84] are associated with phantom pain. In a prospective study, 59 amputees were interviewed before and 6 months after amputation. High levels of passive coping strategies, especially catastrophizing, before the amputation were found to be associated with increased levels of phantom pain at the 6-month follow-up [148]. Pain catastrophizing (i.e. a coping style characterized by excessive negative thoughts and emotions) may be a specific supraspinal mechanism which contributes to phantom pain through increased facilitation and/or impaired modulation of nociceptive signals. Vase and co-workers investigated whether pain catastrophizing, controlled for anxiety and depression [141], was associated with phantom pain, wind-up-like pain and sensory thresholds in a group of 24 upper-limb amputees (16 with and eight without phantom pain) at an average of 15.5 years after amputation. Catastrophizing was significantly associated with phantom pain and accounted for 35% of the variance. There was also a significant relation between catastrophizing and wind-up-like pain in 17 non-medicated amputees (study X [169]).

#### DISCUSSION OF OWN RESULTS AND CONCLUSION ON SUPRASPINAL MECHANISMS

Study X confirmed and expanded the findings by others that phantom pain is mediated by a complex interaction of multiple

factors. The association between pain catastrophizing and wind-up like pain may have several explanations. Pain catastrophizing is a personal trait and is likely to precede wind-up-like pain. When present, the two are likely to reinforce each other [40]. Also, it has been shown that there is an overlap between the brain activation associated with catastrophizing and that associated with wind-up like pain [167]. The link between catastrophizing, wind-up like pain and phantom pain suggests an alternative explanation to the more classical concept that wind-up-like pain and phantom pain are driven from peripheral ectopic foci. In the context of catastrophizing, it is possible that central hyperexcitability exerts a descending facilitating effect on spinal cord neurons, thereby contributing to phantom pain. Cognitive or behavioral treatments of pain catastrophizing may be one way to modulate phantom pain. Based on the literature and the findings in study X, it can be concluded that supraspinal mechanisms play a major role for phantom phenomena, including pain.

#### CONCLUDING REMARKS AND FUTURE DIRECTIONS

My PhD thesis from 1998 showed that preamputation pain increases the risk of pain after amputation (study I). A perioperative epidural blockade did not reduce the incidence of phantom pain or abnormal sensory phenomena (studies II and III).

The present doctoral thesis further explored some of the mechanisms underlying phantom pain. Study IV showed that preamputation sensitization as reflected by lowered mechanical thresholds at the stump was related to stump and phantom pain one week after amputation. Studies V and IV focused on peripheral mechanisms. Sodium channels were upregulated in human neuromas, suggesting that afferent input from peripheral neuromas contributes to phantom pain. Neuroma removal, however, did not always alleviate phantom pain. The modulation of phantom pain by pharmacological agents that work spinally was examined in studies VII, VIII and IX. Study VII showed that phantom pain was reduced by a ketamine, a NMDA-receptor antagonist. Memantine, another NMDA-receptor antagonist, and gabapentin, a drug working by binding to the  $\delta 2\alpha$ -subunit of voltage-gated calcium channels, had no effect on phantom pain. Study X dealt with supraspinal factors and showed that catastrophizing was associated with phantom pain and wind-up-like pain.

Based on the literature and the results from the above-mentioned studies, it can be concluded that several mechanisms are involved in the development and maintenance of phantom pain. It is possible that the first changes take place in the periphery where nerve endings are sensitized by preamputation pain and nerve transection. The clinical observation that phantom pain can develop immediately after the amputation (i.e. within hours) suggests, however, that other factors than the formation of neuromas and upregulation of sodium channels contribute to the early development of phantom pain. The lack of elimination of chronic phantom pain by peripheral blocks and neuroma removal also suggests that more central changes are involved. Spinal sensitization is important, not least because blockade of the NMDA receptor results in a reduction of phantom pain. The complexity of phantom phenomena and the association between catastrophizing and phantom pain indicate that supraspinal changes play a significant role for phantom pain.

The relative contribution of peripheral, spinal and supraspinal factors is still unclear. It is likely that the relative contribution of the different mechanisms may vary from one amputee to another, and, furthermore, that it may change over time in the individual patient.

**Future studies should address the questions below:**

- Does intraoperative handling of the large nerves (ligation vs. transection) affect outcome?
- Can phantom pain be prevented by a very long-lasting peripheral postoperative blockade?
- Is a low-dose infusion of ketamine effective in the treatment of phantom pain if the treatment is continued for days or weeks?

Further understanding of the underlying mechanisms will hopefully lead to a better treatment of phantom pain for the benefit of our patients.

**LIST OF ABBREVIATIONS**

AMPA = $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
BDNF = Brain-derived neurotrophic factor
DRG = Dorsal root ganglion
ERK = Extracellular signal-regulated kinases
GABA = $\gamma$ -aminobutyric acid
MAP = Mitogen-activated protein
mRNA = messenger Ribonucleic acid
NMDA = N-methyl-D-aspartate
NK-1 = Neurokinin 1
PKC = Protein kinase C
TNF- $\alpha$ = Tumor necrosis factor- $\alpha$
VAS = Visual analogue scale
NRS = Numeric rating scale

**SUMMARY**

Amputation is followed by both painful and non-painful phantom phenomena in a large number of amputees. Non-painful phantom sensations rarely pose any clinical problem, but 60-80% of all amputees also experience painful sensations (i.e. phantom pain) located to the missing limb. The severity of phantom pain usually decreases with time, but severe pain persists in 5-10% of patients. Pain in the residual limb (i.e. stump pain) is another consequence of amputation. Both stump and phantom pain can be very difficult to treat. Treatment guidelines used for other neuropathic pain conditions are probably the best approximation, especially for the treatment of stump pain.

The aim of the present doctoral thesis was to explore some of the mechanisms underlying pain after amputation. Ten studies were carried out (I-X).

My PhD thesis from 1998 dealt with pain before the amputation and showed that preamputation pain increases the risk of phantom pain after amputation (I). A perioperative epidural blockade, however, did not reduce the incidence of pain or abnormal sensory phenomena after amputation (II, III).

The importance of sensitization before amputation for the subsequent development of pain is supported by study IV, in which pressure pain thresholds obtained at the limb before amputation were inversely related to stump and phantom pain after 1 week.

Afferent input from the periphery is likely to contribute to postamputation pain as sodium channels were upregulated in human neuromas (VI), although neuroma removal did not always alleviate phantom pain (V).

Sensitization of neurons in the spinal cord also seems to be involved in pain after amputation as phantom pain was reduced by ketamine, an NMDA-receptor antagonist. Another NMDA-receptor antagonist, memantine, and gabapentin, a drug working by binding to the  $\delta 2\alpha$ -subunit of voltage-gated calcium channels, had no effect on phantom pain (VII-IX).

Supraspinal factors are also important for pain after amputation as catastrophizing was associated with phantom pain (X).

In conclusion, the present doctoral thesis confirmed and expanded the findings by others that several mechanisms are involved in the development and maintenance of phantom pain. A better understanding of the underlying mechanisms will hopefully lead to improved treatment of pain after amputation in the future.

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