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The neuropathic component in persistent postsurgical pain: A systematic literature review ☆

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ABSTRACT

Persistent postsurgical pain (PPSP) is a frequent and often disabling complication of many surgical procedures. Nerve injury–induced neuropathic pain (NeuP) has repeatedly been proposed as a major cause of PPSP. However, there is a lack of uniformity in NeuP assessment across studies, and the prevalence of NeuP may differ after various surgeries. We performed a systematic search of the PubMed, CENTRAL, and Embase databases and assessed 281 studies that investigated PPSP after 11 types of surgery. The prevalence of PPSP in each surgical group was examined. The prevalence of NeuP was determined by applying the recently published NeuP probability grading system. The prevalence of probable or definite NeuP was high in patients with persistent pain after thoracic and breast surgeries—66% and 68%, respectively. In patients with PPSP after groin hernia repair, the prevalence of NeuP was 31%, and after total hip or knee arthroplasty it was 6%. The results suggest that the prevalence of NeuP among PPSP cases differs in various types of surgery, probably depending on the likelihood of surgical iatrogenic nerve injury. Because of large methodological variability across studies, a more uniform approach is desirable in future studies for evaluating persistent postsurgical NeuP.

1. Introduction

Persistent postsurgical pain has gained increased attention in medical research in the last decade [46]. This condition has been described by several terms; in the current review, we will use the term *persistent postsurgical pain*, abbreviated PPSP. A major reason for this increased interest is the understanding that PPSP can be a case of iatrogenic chronic pain that may be prevented upon identification of mechanisms and risk factors. However, the underlying etiology of PPSP is still unclear. PPSP has been considered neuropathic [17,23,27,39,61], and a strong association is reported between PPSP and sensory abnormalities [32], but the evidence suggests that mechanisms other than nerve injury such as inflammation [28,35,64], central sensitization [24,37,44], or a combination of these [33,51,56] play a role. In order to identify PPSP risk factors, it is essential to understand the underlying mechanisms and to elucidate whether persistent pain is due to surgical injury to the nerves, ongoing inflammatory processes, injury to the somatic or visceral structures, or other causes.

In an attempt to strengthen the criteria for what is and what is not neuropathic pain (NeuP), the International Association for the Study of Pain (IASP) recently defined NeuP as "pain caused by a lesion or disease of the somatosensory nervous system" (IASP Web site, April 2012). The article that suggested this definition also proposed a probability grading system for categorizing NeuP, which can be useful for both clinical and research purposes [57]. This probability grading is mentioned in the latest European Federation of Neurological Societies (EFNS) guidelines on NeuP assessment [15], but there is no guidance on implementation of the grading system as a result of a lack of studies documenting its effectiveness.

In order to clarify the contribution of NeuP to PPSP, we systematically reviewed the available literature on persistent pain after 11 different surgical procedures representing various anatomical locations and types of operative tissue injury in adults and adolescents, and we assessed the NeuP prevalence in these studies. On the basis of the results and the overview of the methodologies used in the identified studies, we propose recommendations for more uniform pain assessment in future studies on neuropathic PPSP.

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2. Materials and methods

2.1. Surgical procedures, literature search, and study selection

Studies assessing the occurrence and characteristics of pain after the following 11 surgical procedures were searched: (i) thoracic surgery, (ii) breast surgery, (iii) major abdominal surgery on the gastrointestinal tract, (iv) donor nephrectomy, (v) gynecologic surgery (hysterectomy and cesarean section), (vi) prostatectomy, (vii) groin hernia repair, (viii) total hip arthroplasty (THA) or knee arthroplasty (TKA), (ix) iliac crest bone harvest, (x) mandibular sagittal split osteotomy, and (xi) varicose vein stripping or ablation.

Medline (PubMed), Embase, and Cochrane CENTRAL databases were searched in June 2011 (with search update in January 2012), including the following search keywords: Mesh terms "Pain, Postoperative" and "Surgical Procedures, Operative" with "chronic pain" or "long term pain" keywords ("postoperative pain" and "surgery" with "chronic pain" in Embase).

Additionally, "Pain, postoperative"[Mesh] term was combined in a separate Medline search with one of the following: "Thoracic surgical procedures"[Mesh], "Mammaplasty"[Mesh], "Mastectomy, Segmental"[Mesh], "Abdomen/surgery"[Mesh], "Nephrectomy"[Mesh], "Hysterectomy"[Mesh], "Cesarean section"[Mesh], "Prostatectomy"[Mesh], "Hernia, Inguinal/surgery"[Mesh], "Arthroplasty, Replacement, Hip"[Mesh], "Arthroplasty, replacement, knee"[Mesh], "Ilium/surgery"[Mesh], "Mandible/surgery"[Mesh] or "Varicose veins/surgery"[Mesh]. Additional articles were retrieved from the references of the identified studies and from reviews on the topic.

Studies were included if they reported the occurrence of persistent pain after one of the above mentioned 11 surgeries, with or without assessment of sensory function. Exclusion criteria were: (1) studies with follow-up of less than 2 months (studies in which less than 10% of patients had a shorter follow-up period, but not less than 1 month, were included); (2) studies including patients younger than 13 years old; (3) studies on patients with established PPSP that did not report the frequency of persistent pain; (4) studies published before 1979 (as the first definitions of neuropathy and neuralgia were proposed by the IASP Task Force in 1979); (5) abstracts; and (6) studies/case reports including fewer than 10 patients.

2.2. PPSP prevalence

To avoid overestimation of PPSP, we compared the point prevalence of PPSP (the percentage of patients reporting pain at the time of follow-up assessment), unless stated otherwise. The cumulative pain prevalence (the percentage of patients reporting pain of certain duration at some point between the surgery and the follow-up) was reported separately if assessed in the study (see Appendices 1–11 for details). An attempt was made to extract a single point prevalence of PPSP in each study. Some studies used very loose criteria (eg, any thoracic pain [58,63], or any pain in the inguinal area including occasional pain and discomfort [13]), which might have overestimated the prevalence of PPSP, or used stringent criteria (eg, pain with intensity >3/10, or moderate to severe pain [16,29]), which might have underestimated it. Therefore, PPSP prevalence rates obtained from these studies were labeled as liberal and conservative, respectively. A separate calculation was made for conservative PPSP prevalence rate (median of standard and conservative estimates) and for liberal PPSP prevalence rate (median of standard and liberal estimates) for each surgery.

A single prevalence rate was assigned for studies with no group comparisons or nonsignificant differences among the intervention arms. If a study included 2 or more arms with differences in PPSP prevalence ($P \leqslant .05$ between groups), a separate prevalence rate was assigned to each of the subgroups.

2.3. NeuP probability

The probability of NeuP was graded by applying the NeuP probability criteria [57] to the published data in the included studies (Table 1). Patients who had had a previous surgery (history suggestive of a somatosensory lesion) and pain in the surgical or corresponding area (pain with neuroanatomically plausible distribution) were automatically classified as possible NeuP grade. The further grading to probable NeuP was stipulated on demonstration of either neuroanatomical distribution (presence of sensory disturbances concordant with the distribution of pain) or nerve lesion by confirmatory tests. Definite NeuP was the grade if both the latter criteria were fulfilled.

The prevalence of NeuP that was assessed by other methods (eg, NeuP-specific questionnaires or the authors' own definition), and reported as neuropathic by the authors, was calculated separately.

Table 1
Criteria for grading NeuP probability

Subject	
NeuP criteria	1. Pain with a distinct neuroanatomically plausible distribution (a region corresponding to a peripheral innervation territory or to the topographic representation of a body part in the CNS) 2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system (the suspected lesion or disease is reported to be associated with pain, including a temporal relationship typical for the condition) 3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test (clinical sensory examination, which may be supplemented by laboratory and objective tests, to confirm the presence of negative or positive neurologic signs concordant with the distribution of pain)[a] 4. Demonstration of the relevant lesion by at least one confirmatory test (as part of the neurologic examination, these tests confirm the diagnosis of the suspected lesion or disease)
Criteria fulfilled	NeuP probability
1 + 2 not fulfilled	Unlikely
1 + 2, without confirmatory evidence from 3 or 4	Possible
1 + 2, + either 3 or 4	Probable
1 + 2, + 3 + 4	Definite

CNS, central nervous system; NeuP, neuropathic pain.

[a] As objective testing for criterion 3, we included clinician-assessed negative and positive sensory signs, but also patient-assessed signs, when it clearly required self-examination (eg, stroking the finger over the scar or question about sensitivity of the skin to light touch). Patient-reported numbness or paresthesia did not qualify as objective sensory assessment.

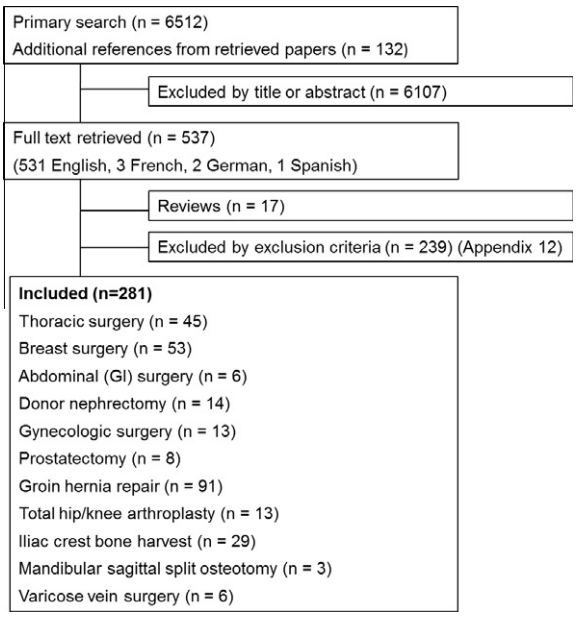

Fig. 1. Literature search and study selection (PRISMA) flowchart.

3. Results

3.1. Literature search and study characteristics

The total number of articles identified by the literature search was 5413 (PubMed) + 346 (CENTRAL) + 753 (Embase). These were skimmed by titles/abstracts, and 537 potential articles were identified. The full text of these articles was evaluated by 2 authors. Application of the exclusion criteria resulted in the final number of 281 articles relevant for the current review. Disagreements regarding individual article inclusion or exclusion were resolved by discussion among all the authors. Fig. 1 is a flowchart of the literature search. Table 2 describes the included studies by types of study design. The excluded studies are described in Appendix 12.

3.2. Characterization of included surgery types

The types of surgical procedures in the individual studies are described in Appendices 1–11. Briefly, thoracic surgery included open thoracotomies ($n = 20$) and video-assisted thoracoscopies (VATS) ($n = 2$), sternotomies ($n = 14$), comparison of open thoracotomy to VATS ($n = 6$), and comparison of sternotomy to thoracotomy or sternothoracotomy ($n = 2$). Breast surgery included interventions for breast cancer ($n = 46$), breast augmentation ($n = 6$), and breast reduction ($n = 1$). Abdominal surgery included colon/rectum resections ($n = 5$) and mixed population of lower and upper gastrointestinal surgeries ($n = 1$). Donor nephrectomy included open (including finger-assisted) surgeries ($n = 4$), laparoscopies ($n = 4$) or both ($n = 4$). Gynecologic surgery included hysterectomies (abdominal or vaginal) ($n = 6$), cesarean sections ($n = 4$), both ($n = 1$), and other major gynecologic surgeries ($n = 2$). Prostatectomy included radical prostatectomies for prostate cancer ($n = 8$). Groin hernia repair included femoral hernia repairs ($n = 2$) and inguinal hernia repairs via open ($n = 42$), laparoscopic ($n = 14$) or both ($n = 33$) approaches. THA/TKA section included THA ($n = 7$), TKA ($n = 4$), or both ($n = 2$). Iliac crest bone harvest included procedures for spine fusions ($n = 17$), maxillary/mandibular reconstructions ($n = 5$), or mixed indications ($n = 7$). Mandibular sagittal split osteotomy procedure was performed for correction of mandibular retrognathia or for mandibular advancement/setback surgery ($n = 3$). Varicose vein surgery section included vein stripping ($n = 3$) and radiofrequency ablation procedures ($n = 3$).

3.3. Prevalence of PPSP

PPSP conservative and liberal prevalence rates and follow-up period ranges are summarized in Table 3. The highest prevalence of PPSP was found after thoracic and breast surgeries (34.5% and 31.0%), followed by THA/TKA and iliac crest bone harvest (19.8% and 18.7%); similar PPSP prevalences were found after prostatectomy (14%), gynecologic surgery (13.7%), abdominal surgery (11%), mandibular osteotomy (10%), and donor nephrectomy (9.6%); the lowest PPSP was reported with groin hernia repair (7%) and varicose vein surgery (4.7%) (Fig. 2). The detailed characterization of the individual studies included in the current review is available in Appendices 1–11.

3.4. NeuP probability

A quantitative summary of NeuP prevalence, evaluated with the NeuP probability grading system and other NeuP assessment methods, was performed for surgeries for which probable/definite NeuP prevalence was available from more than 2 studies to avoid small-sample bias. Only 4 surgical groups fulfilled this criterion. The relative prevalence of NeuP among patients with PPSP, assessed with the grading system vs other assessment methods

Table 2
Included studies.[a]

Type of surgery	Study design				
	Prospective PPSP assessment, no group comparison	Retrospective PPSP assessment, no group comparison	Prospective PPSP assessment, group comparison	Retrospective PPSP assessment, group comparison	Not clear
Thoracic surgery	16	12	11	8	–
Breast surgery	9	27	13	4	1
Abdominal surgery	2	2	2	–	–
Donor nephrectomy	2	8	1	3	–
Gynecologic surgery	4	4	5	–	–
Prostatectomy	3	–	5	–	–
Groin hernia repair	22	25	40	6	3
THA/TKA	4	5	4	–	–
Iliac crest bone harvest	3	15	5	4	1
Mandibular osteotomy	1	2	–	–	–
Varicose vein surgery	3	2	–	–	1

PPSP, persistent postsurgical pain; THA, total hip arthroplasty; TKA, total knee arthroplasty.
[a] Data are presented as the number of studies per study design for each surgical group. The total number of studies for each surgical group may exceed the number of included studies because some studies included 2 groups or consisted of 2 phases.

Table 3
Prevalence of PPSP

Surgery type	No. of studies used in PPSP prevalence calculation	Sample size, median no. of patients (range)	Time from surgery to pain assessment	PPSP prevalence %, conservative approach[a] (median, IQR)	PPSP prevalence %, liberal approach[b] (median, IQR)	Extreme estimates of PPSP prevalence, by only stringent and loose criteria[c] (median, range)	No. of studies not included in PPSP analysis[d]
Thoracic surgery	44	86 (23–1080)	2 mo–12 y	34.5 (21–52)	37 (23.5–52)	27 (9–70); 34 (15–81)	1 (Appendix 1)
Breast surgery	53	106 (22–3253)	2 mo–35 y	31 (21.5–47.3)	41 (24.3–49)	18 (3.1–34); 43 (3.1–77)	0
Abdominal surgery	6	86 (22–286)	1–10 y	11 (4.7–18)	11.5 (3.5–18)	6.9 (6.3–7.6); 8 (4.6–11.5)	0
Donor nephrectomy	12	75 (53–359)	1.5 mo–15 y	9.6 (3.2–25)	21.3 (3.7–33)	11 (3–26); 44.5 (22–60)	2 (Appendix 4)
Gynecologic surgery	13	90 (36–1135)	3–24 mo	13.7 (7.8–17.3)	17 (11.5–34.5)	8.2 (6–18); 32 (9.2–40)	0
Prostatectomy	8	95 (24–179)	2.5–6 mo	14 (8–36)	21 (10.4–36)	2; 29 (n = 1 in each)	0
Groin hernia repair	89	266 (22–5524)	1.5 mo–12 y	7 (2.5–19)	12 (4.4–23.6)	2.5 (0–31); 11 (1.2–91)	2 (Appendix 7)
THA/TKA	13	142 (20–7230)	4 mo–8 y	19.8 (11.7–27.7)	27 (12.5–39.1)	13 (12–26); 36 (27–63)	0
Iliac crest bone harvest	29	94.5 (10–414)	3 mo–13 y	18.7 (12.5–28.3)	23.5 (14.7–35.1)	15.5 (10–25); 41.5 (11–55)	1 (Appendix 9)
Mandibular osteotomy	1	20	12 mo	10	10	NA	2 (Appendix 10)
Varicose vein surgery	6	83.5 (35–126)	3 mo–11 y	4.7 (4–13)	4.7 (4–13)	NA	0

PPSP, persistent postsurgical pain; IQR, 25%–75% interquartile range; NA, no liberal or conservative estimates of PPSP available; THA, total hip arthroplasty; TKA, total knee arthroplasty.
Note: Where possible, a single point prevalence of PPSP was extracted for each study.
[a] PPSP prevalence rates by conservative approach were calculated from combining studies with standard and stringent criteria for PPSP (see Materials and Methods).
[b] PPSP prevalence rates by liberal approach were calculated from combining studies with standard and loose criteria for PPSP (see Materials and Methods).
[c] The extreme prevalence rates of PPSP were calculated from reports based on only conservative and liberal criteria.
[d] Data reported in another study or inconsistent data reporting.

was 66% vs 52% after thoracic surgery, 68% vs 74% after breast surgery, 31% vs 45% after hernia surgery, and 6% vs 9% after THA/TKA. The absolute prevalence of NeuP (number of patients with NeuP as % of the whole study group) assessed with both approaches is presented in Fig. 3. Phantom breast pain, which fulfills the criteria of probable NeuP, was assessed in 15 studies in breast surgery section. The mean prevalence of phantom breast pain after mastectomy was 12.4% (range 0–43%).

The types of sensory assessment, upon which it was possible to grade the NeuP probability, are summarized in Table 4. Objective sensory testing included any clinical examination to assess sensory disturbances, including self-examination by patients, as well as quantitative sensory testing. Only studies that reported the co-occurrence of sensory dysfunction and persistent pain could be used to estimate the prevalence of probable/definite NeuP. The number of studies that evaluated NeuP with other methods, ie, NeuP-specific questionnaires (eg, DN4, PainDETECT) or pain descriptors (descriptive characteristics like burning or pricking pain, numbness, or the McGill Pain Questionnaire), are also summarized in Table 4. Individual study details, NeuP assessment methodology, and probability grading, as well as methods for assessing NeuP that did not meet NeuP grading criteria, are summarized in Appendices 1–11.

4. Discussion

Persistent pain after surgery is common and is often reported as neuropathic [39]. The results of our study indicate that surgeries performed in the thoracic/breast area result in similar PPSP prevalences of about 30–35%; bone and joint surgeries in similar PPSP prevalences of about 20%; and surgeries on abdominal visceral structures in PPSP of about 10–14%.

4.1. NeuP probability and mechanisms in PPSP

The prevalence of probable/definite NeuP among patients with PPSP after thoracic and breast surgeries was very similar, 66% and 67.7%, respectively. This suggests a high probability of iatro-

Fig. 2. Prevalence of PPSP after 11 types of surgery. Data presented as median, interquartile percentiles, and ranges of PPSP prevalence by conservative estimation. Persistent pain after mandibular osteotomy is based on a single study. PPSP, persistent postsurgical pain; THA, total hip arthroplasty; TKA, total knee arthroplasty.

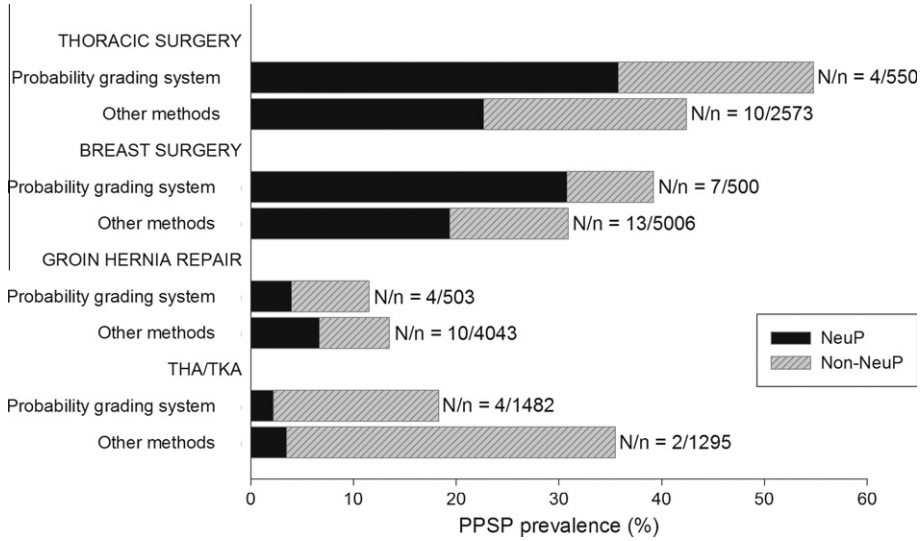

Fig. 3. Neuropathic PPSP prevalence. Comparison of absolute NeuP vs non-NeuP prevalence assessed by NeuP probability grading system and by other methods. The number of studies/patients based on which the mean prevalence was calculated are provided on the right side of each bar. PPSP, persistent postsurgical pain; NeuP, neuropathic pain; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Table 4
Summary of pain and sensory function assessment in NeuP.

Surgery type	NeuP assessment methodology (no. of studies)					
	Objective sensory testing	NeuP-specific questionnaires	Pain descriptors	No specific NeuP assessment	Unclear methodology	Phantom sensations/ pain
Thoracic surgery	10	5	20	16	2	–
Breast surgery	21	2	25	6	2	18/15
Abdominal surgery	0	0	5	1	0	2
Donor nephrectomy	1	1	1	7	2	–
Gynecologic surgery	2	0	7	4	1	–
Prostatectomy	0	0	0	8	0	–
Groin hernia repair	12	1	27	54	3	–
TKA/THA	4	3	2	7	1	–
Iliac crest bone harvest	3	0	14	8	5	–
Mandibular osteotomy	3	0	1	0	0	–
Varicose vein surgery	3	0	3	1	0	–

NeuP, neuropathic pain; THA, total hip arthroplasty; TKA, total knee arthroplasty.
Note: The total number of studies for each surgical group may exceed the number of included studies because some studies have used more than one methodology to assess sensory function or NeuP.

genic nerve damage during surgical procedures in the thoracic area. Indeed, most of the studies refer to perioperative intercostal nerve damage as the major pain mechanism after thoracic surgery [6,19,52] and to intercostobrachial nerve injury for ipsilateral axillary and arm pain after mastectomy or axillary lymph node dissection [49,55,59,62], although other pain mechanisms are suggested after both thoracic [28,54] and breast surgeries [35,61,62].

In patients with PPSP after groin hernia repair, the prevalence of probable/definite NeuP was 30.5%. After gynecologic surgery, in one study that estimated probable/definite NeuP [11], the prevalence was 33%. These findings suggest that NeuP-generating mechanisms after lower abdominal surgeries exist, although they may not be responsible for most of PPPS cases. The majority of persistent pain cases after hernia repair are probably musculoskeletal or caused by hernia recurrence or retracted testis [31]; however, pain after intraoperative injury of the ilioinguinal, the iliohypogastric, and the genitalis nerves have been reported [3,12]. Postherniotomy patients frequently exhibit sensory disturbances [1,2,4], but the dispute whether these are due to direct nerve damage or the result of central sensitization after ongoing peripheral inflammatory processes is still ongoing.

In THA/TKA, despite a rather high PPSP occurrence, the prevalence of probable/definite NeuP among PPSP patients was only 5.7%. Probable/definite NeuP prevalence after iliac crest bone harvest, based on limited data, was 16% [20,36]. This suggests that inflammatory components in the muscle or the periosteum seem to predominate as pain-generating mechanisms in bone and joint surgeries. Intraoperative nerve damage may occur to peroneal and tibial nerves during TKA [30], and to sciatic, femoral, and obturator nerves during THA [25], although most of these cases fully recover. Sensory testing could not reveal any specific type of nerve injury that correlated with chronic pain after TKA [47].

After sagittal split osteotomy damage to the inferior alveolar nerve, the long buccal nerve and the lingual nerve have been reported [5], with up to 95% prevalence of inferior alveolar nerve injury and a very high incidence of sensory changes in the immediate postoperative period [34,48]. However, it is difficult to draw conclusions on the prevalence of NeuP after this surgery because only one study had systematically identified NeuP. There were no suffi-

cient data to estimate the prevalence and the mechanisms of NeuP after varicose vein surgery, prostatectomy, or donor nephrectomy.

4.2. Challenges in applying the NeuP probability grading system

The classic presentation of NeuP is characterized both in descriptive terms (eg, burning, pricking pain, or numbness) and sensory signs (loss or gain of sensation); however, the specificity and the sensitivity of these are suboptimal. The pain descriptors are not considered in the NeuP grading system, but even the sensory signs may in some cases manifest as a consequence of sensitization due to nociceptive/inflammatory sensory input. The NeuP grading system also lacks "negative scoring" or "negative predicting factors" to consider other pain generators, or preexisting pain. Therefore, pain in the area of sensory abnormality after nerve injury may occasionally be classified as probable or definite NeuP, despite being of nociceptive origin (eg, ongoing local inflammation).

4.3. Alternative methods of NeuP assessment

The methodology to assess NeuP varied across studies. Some studies have used pain descriptors, NeuP-specific questionnaires, or combinations as an alternative or in addition to sensory testing (Table 4). The comparison of NeuP grading as proposed by Treede et al. [57] with other methods (Fig. 3) demonstrates that for thoracic and breast surgeries, the relative prevalence of NeuP among PPSP cases is similar. However, in PPSP after hernia repair and THA/TKA, the relative prevalence of NeuP detected by other methods is about 50% higher. This may suggest that descriptive neuropathic features in these conditions are more frequent than ongoing pain accompanied by objective sensory disturbances in the painful area, and caution should be exercised in interpreting NeuP diagnoses that are based on pain descriptors. NeuP-specific questionnaires may also fail to identify 10–20% of patients with clinician-diagnosed NeuP [15], and therefore they cannot be used solely as NeuP diagnostic tools. Some NeuP-specific questionnaires include sensory examination subscales (assessed by the patient or the clinician)—for example, Douleur Neuropathique en 4 questionnaire (DN4) [9], Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) [7] and the self-report S-LANSS tool [8], Neuropathic Pain Questionnaire (NPQ) [40], PainDETECT questionnaire [22], and Neuropathic Pain Symptom Inventory (NPSI) [10]. Reporting chronic pain co-occurrence with the sensory disturbance items of these questionnaires would allow identification of probable NeuP cases.

4.4. Methodological considerations in PPSP assessment

This systematic review demonstrated considerable inconsistencies in the definition and assessment of PPSP. Table 3 illustrates the pain prevalence differences, derived from the use of stringent or loose criteria for PPSP. Fig. 2 presents wide PPSP prevalence ranges, and differences in study design and patient risk factors are likely to contribute to this variability. A recent large-scale study demonstrated that the methodology of pain assessment may result in a 50% difference in PPSP reporting in the same patient population [32]. Different follow-up periods may also contribute to the variability; despite few studies demonstrating that PPSP prevalence may stay unchanged [50] or increase over time [41,42], most longitudinal studies demonstrate a decrease in PPSP prevalence [14,26,43,53]. The minimal follow-up period after surgery is also important; some studies have used a chronic pain cutoff period of 2 months or less; however, recent IMMPACT recommendations suggest $\geqslant$3 months' duration requirement for chronic pain [18].

An important epidemiological consideration is the inconsistent use of the terms *incidence* and *prevalence*. Incidence is defined as the fraction of a group of people initially free of the outcome of interest that develops the clinical condition over a given period of time [21], ie, the most correct epidemiological term for PPSP. There is, however, a considerable diversity in assessing and reporting point or cumulative prevalence vs incidence, which could further contribute to inconsistencies. Reporting cumulative prevalence may result in overestimation of PPSP, as it incorporates patients who developed transient pain after surgery.

Another important but largely ignored consideration is the development of similar types of pain in the general population. Vilholm et al. have demonstrated that in age-matched women who did not undergo mastectomy, the incidences of chest and shoulder pain were considerable [60].

4.5. Limitations

Although we undertook a broad literature search strategy, some of the included studies were not identified by the primary search but rather were retrieved from reference lists of other articles. Therefore, we cannot be certain that we have identified all the relevant studies.

4.6. Summary and recommendations

This systematic literature review assesses the prevalence of PPSP and highlights the differences in NeuP prevalence after different surgical procedures. The likelihood of iatrogenic nerve injury and subsequent NeuP varies among surgical procedures, and these findings may have important implications for the prevention and treatment of this type of chronic pain. However, only in a minority of studies was it possible to obtain a reliable estimate of a neuropathic component in PPSP. Moreover, we emphasize the lack of uniformity in reporting the prevalence and characteristics of PPSP—a consequence of methodological inconsistencies among studies. One of the most comprehensive definitions, proposed by Macrae [45], classifies PPSP as "pain developed after surgery and of at least 2 months' duration, when other causes of pain have been excluded, and the possibility that the pain is continuing from a preexisting problem were explored and excluded." It was used in some of the studies; however, its requirements may be extremely challenging to apply in clinical studies, especially in retrospective ones. Moreover, a recent article indicated that many studies reporting using this definition did not use appropriate methodology to fulfill its criteria [32].

On the basis of our findings, we suggest considering the following requirements in future studies aiming to investigate the incidence of neuropathic PPSP. The definition of PPSP should include a temporal and anatomical relationship to surgery. Pain should be considered PPSP if it has developed after surgery, persists for more than 3 months after surgery, and is present in the operated area or in the corresponding innervation territory. The studies should report the intensity of pain, the percentage of patients with persistent pain, and co-occurrence of pain with objective sensory disturbances. Finally, the functional impairment caused by PPSP, although beyond the scope of this article, is another important aspect that has been repeatedly recommended for capturing the full picture of disability caused by PPSP [38].

Conflict of interest statement

The authors have no conflicts of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2012.09.010.

References

[1] Aasvang EK, Brandsborg B, Christensen B, Jensen TS, Kehlet H. Neurophysiological characterization of postherniotomy pain. PAIN® 2008;137:173–81.
[2] Aasvang EK, Brandsborg B, Jensen TS, Kehlet H. Heterogeneous sensory processing in persistent postherniotomy pain. PAIN® 2010;150:237–42.
[3] Aasvang EK, Kehlet H. The effect of mesh removal and selective neurectomy on persistent postherniotomy pain. Ann Surg 2009;249:327–34.
[4] Aasvang EK, Kehlet H. Persistent sensory dysfunction in pain-free herniotomy. Acta Anaesthesiol Scand 2010;54:291–8.
[5] Bagheri SC, Meyer RA, Khan HA, Wallace J, Steed MB. Microsurgical repair of the peripheral trigeminal nerve after mandibular sagittal split ramus osteotomy. J Oral Maxillofac Surg 2010;68:2770–82.
[6] Benedetti F, Vighetti S, Ricco C, Amanzio M, Bergamasco L, Casadio C, Cianci R, Giobbe R, Oliaro A, Bergamasco B, Maggi G. Neurophysiologic assessment of nerve impairment in posterolateral and muscle-sparing thoracotomy. J Thorac Cardiovasc Surg 1998;115:841–7.
[7] Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. PAIN® 2001;92:147–57.
[8] Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. J Pain 2005;6:149–58.
[9] Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lanteri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). PAIN® 2005;114:29–36.
[10] Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lanteri-Minet M, Collin E, Grisart J, Boureau F. Development and validation of the Neuropathic Pain Symptom Inventory. PAIN® 2004;108:248–57.
[11] Brandsborg B, Dueholm M, Nikolajsen L, Kehlet H, Jensen TS. A prospective study of risk factors for pain persisting 4 months after hysterectomy. Clin J Pain 2009;25:263–8.
[12] Butters M, Redecke J, Koninger J. Long-term results of a randomized clinical trial of Shouldice, Lichtenstein and transabdominal preperitoneal hernia repairs. Br J Surg 2007;94:562–5.
[13] Chowbey PK, Garg N, Sharma A, Khullar R, Soni V, Baijal M, Mittal T. Prospective randomized clinical trial comparing lightweight mesh and heavyweight polypropylene mesh in endoscopic totally extraperitoneal groin hernia repair. Surg Endosc 2010;24:3073–9.
[14] Courtney CA, Duffy K, Serpell MG, O'Dwyer PJ. Outcome of patients with severe chronic pain following repair of groin hernia. Br J Surg 2002;89:1310–4.
[15] Cruccu G, Sommer C, Anand P, Attal N, Baron R, Garcia-Larrea L, Haanpaa M, Jensen TS, Serra J, Treede RD. EFNS guidelines on neuropathic pain assessment: revised 2009. Eur J Neurol 2010;17:1010–8.
[16] Cunningham J, Temple WJ, Mitchell P, Nixon JA, Preshaw RM, Hagen NA. Cooperative hernia study. Pain in the postrepair patient. Ann Surg 1996;224:598–602.
[17] Duale C, Guastella V, Morand D, Cardot JM, Aublet-Cuvelier B, Mulliez A, Schoeffler P, Escande G, Dubray C. Characteristics of the neuropathy induced by thoracotomy: a 4-month follow-up study with psychophysical examination. Clin J Pain 2011;27:471–80.
[18] Dworkin RH, Turk DC, Peirce-Sandner S, Burke LB, Farrar JT, Gilron I, Jensen MP, Katz NP, Raja SN, Rappaport BA, Rowbotham MC, Backonja MM, Baron R, Bellamy N, Bhagwagar Z, Costello A, Cowan P, Fang WC, Hertz S, Jay GW, Junor R, Kerns RD, Kerwin R, Kopecky EA, Lissin D, Malamut R, Markman JD, McDermott MP, Munera C, Porter L, Rauschkolb C, Rice AS, Sampaio C, Skljarevski V, Sommerville K, Stacey BR, Steigerwald I, Tobias J, Trentacosti AM, Wasan AD, Wells GA, Williams J, Witter J, Ziegler D. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. PAIN® 2012;153:1148–58.
[19] Eisenberg E, Pultorak Y, Pud D, Bar-El Y. Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). PAIN® 2001;92:11–7.
[20] Fernyhough JC, Schimandle JJ, Weigel MC, Edwards CC, Levine AM. Chronic donor site pain complicating bone graft harvesting from the posterior iliac crest for spinal fusion. Spine (Phila Pa 1976) 1992;17:1474–80.
[21] Fletcher RH, Fletcher SW. Clinical epidemiology: the essentials. Baltimore, MD: Lippincott Williams & Wilkins; 2005.
[22] Freynhagen R, Baron R, Gockel U, Tolle TR. PainDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911–20.
[23] Gottrup H, Andersen J, Arendt-Nielsen L, Jensen TS. Psychophysical examination in patients with post-mastectomy pain. PAIN® 2000;87:275–84.
[24] Gottschalk A, Smith DS, Jobes DR, Kennedy SK, Lally SE, Noble VE, Grugan KF, Seifert HA, Cheung A, Malkowicz SB, Gutsche BB, Wein AJ. Preemptive epidural analgesia and recovery from radical prostatectomy: a randomized controlled trial. JAMA 1998;279:1076–82.
[25] Goulding K, Beaule PE, Kim PR, Fazekas A. Incidence of lateral femoral cutaneous nerve neuropraxia after anterior approach hip arthroplasty. Clin Orthop Relat Res 2010;468:2397–404.
[26] Goulet JA, Senunas LE, DeSilva GL, Greenfield ML. Autogenous iliac crest bone graft. Complications and functional assessment. Clin Orthop Relat Res 1997;339:76–81.
[27] Guastella V, Mick G, Soriano C, Vallet L, Escande G, Dubray C, Eschalier A. A prospective study of neuropathic pain induced by thoracotomy: incidence, clinical description, and diagnosis. PAIN® 2011;152:74–81.
[28] Hamada H, Moriwaki K, Shiroyama K, Tanaka H, Kawamoto M, Yuge O. Myofascial pain in patients with postthoracotomy pain syndrome. Reg Anesth Pain Med 2000;25:302–5.
[29] Holmich LR, Breiting VB, Fryzek JP, Brandt B, Wolthers MS, Kjoller K, McLaughlin JK, Friis S. Long-term cosmetic outcome after breast implantation. Ann Plast Surg 2007;59:597–604.
[30] Horlocker TT, Hebl JR, Gali B, Jankowski CJ, Burkle CM, Berry DJ, Zepeda FA, Stevens SR, Schroeder DR. Anesthetic, patient, and surgical risk factors for neurologic complications after prolonged total tourniquet time during total knee arthroplasty. Anesth Analg 2006;102:950–5.
[31] Haapaniemi S, Nilsson E. Recurrence and pain three years after groin hernia repair. Validation of postal questionnaire and selective physical examination as a method of follow-up. Eur J Surg 2002;168:22–8.
[32] Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population: prevalence and predictors in the Tromsø study. PAIN® 2012;153:1390–6.
[33] Ju H, Feng Y, Yang BX, Wang J. Comparison of epidural analgesia and intercostal nerve cryoanalgesia for post-thoracotomy pain control. Eur J Pain 2008;12:378–84.
[34] Jaaskelainen SK, Teerijoki-Oksa T, Virtanen A, Tenovuo O, Forssell H. Sensory regeneration following intraoperatively verified trigeminal nerve injury. Neurology 2004;62:1951–7.
[35] Kairaluoma PM, Bachmann MS, Rosenberg PH, Pere PJ. Preincisional paravertebral block reduces the prevalence of chronic pain after breast surgery. Anesth Analg 2006;103:703–8.
[36] Kalk WW, Raghoebar GM, Jansma J, Boering G. Morbidity from iliac crest bone harvesting. J Oral Maxillofac Surg 1996;54:1424–9.
[37] Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996;12:50–5.
[38] Kehlet H, Bay-Nielsen M, Kingsnorth A. Chronic postherniorrhaphy pain—a call for uniform assessment. Hernia 2002;6:178–81.
[39] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618–25.
[40] Krause SJ, Backonja MM. Development of a neuropathic pain questionnaire. Clin J Pain 2003;19:306–14.
[41] Kroner K, Knudsen UB, Lundby L, Hvid H. Long-term phantom breast syndrome after mastectomy. Clin J Pain 1992;8:346–50.
[42] Kroner K, Krebs B, Skov J, Jorgensen HS. Immediate and long-term phantom breast syndrome after mastectomy: incidence, clinical characteristics and relationship to pre-mastectomy breast pain. PAIN® 1989;36:327–34.
[43] Landreneau RJ, Mack MJ, Hazelrigg SR, Naunheim K, Dowling RD, Ritter P, Magee MJ, Nunchuck S, Keenan RJ, Ferson PF. Prevalence of chronic pain after pulmonary resection by thoracotomy or video-assisted thoracic surgery. J Thorac Cardiovasc Surg 1994;107:1079–85.
[44] Lavand'homme PM, Roelants F, Waterloos H, Collet V, De Kock MF. An evaluation of the postoperative antihyperalgesic and analgesic effects of intrathecal clonidine administered during elective cesarean delivery. Anesth Analg 2008;107:948–55.
[45] Macrae WA. Chronic pain after surgery. Br J Anaesth 2001;87:88–98.
[46] Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth 2008;101:77–86.
[47] Martinez V, Fletcher D, Bouhassira D, Sessler DI, Chauvin M. The evolution of primary hyperalgesia in orthopedic surgery: quantitative sensory testing and clinical evaluation before and after total knee arthroplasty. Anesth Analg 2007;105:815–21.
[48] Monnazzi MS, Real-Gabrielli MF, Passeri LA, Gabrielli MA. Cutaneous sensibility impairment after mandibular sagittal split osteotomy: a prospective clinical study of the spontaneous recovery. J Oral Maxillofac Surg 2012;70:696–702.
[49] Paredes JP, Puente JL, Potel J. Variations in sensitivity after sectioning the intercostobrachial nerve. Am J Surg 1990;160:525–8.

[50] Picchio M, Palimento D, Attanasio U, Matarazzo PF, Bambini C, Caliendo A. Randomized controlled trial of preservation or elective division of ilioinguinal nerve on open inguinal hernia repair with polypropylene mesh. Arch Surg 2004;139:755–8.
[51] Pluijms WA, Steegers MA, Verhagen AF, Scheffer GJ, Wilder-Smith OH. Chronic post-thoracotomy pain: a retrospective study. Acta Anaesthesiol Scand 2006;50:804–8.
[52] Rogers ML, Henderson L, Mahajan RP, Duffy JP. Preliminary findings in the neurophysiological assessment of intercostal nerve injury during thoracotomy. Eur J Cardiothorac Surg 2002;21:298–301.
[53] Stammberger U, Steinacher C, Hillinger S, Schmid RA, Kinsbergen T, Weder W. Early and long-term complaints following video-assisted thoracoscopic surgery: evaluation in 173 patients. Eur J Cardiothorac Surg 2000;18:7–11.
[54] Steegers MA, Snik DM, Verhagen AF, van der Drift MA, Wilder-Smith OH. Only half of the chronic pain after thoracic surgery shows a neuropathic component. J Pain 2008;9:955–61.
[55] Tasmuth T, Kataja M, Blomqvist C, von Smitten K, Kalso E. Treatment-related factors predisposing to chronic pain in patients with breast cancer—a multivariate approach. Acta Oncol 1997;36:625–30.
[56] Tiippana E, Nilsson E, Kalso E. Post-thoracotomy pain after thoracic epidural analgesia: a prospective follow-up study. Acta Anaesthesiol Scand 2003;47:433–8.
[57] Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630–5.
[58] van Gulik L, Janssen LI, Ahlers SJ, Bruins P, Driessen AH, van Boven WJ, van Dongen EP, Knibbe CA. Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. Eur J Cardiothorac Surg 2011;40:1309–13.
[59] Vecht CJ, Van de Brand HJ, Wajer OJ. Post-axillary dissection pain in breast cancer due to a lesion of the intercostobrachial nerve. PAIN® 1989;38:171–6.
[60] Vilholm OJ, Cold S, Rasmussen L, Sindrup SH. The postmastectomy pain syndrome: an epidemiological study on the prevalence of chronic pain after surgery for breast cancer. Br J Cancer 2008;99:604–10.
[61] von Sperling ML, Hoimyr H, Finnerup K, Jensen TS, Finnerup NB. Persistent pain and sensory changes following cosmetic breast augmentation. Eur J Pain 2011;15:328–32.
[62] Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: a survey of 282 women. PAIN® 1996;66:195–205.
[63] Wildgaard K, Ravn J, Nikolajsen L, Jakobsen E, Jensen TS, Kehlet H. Consequences of persistent pain after lung cancer surgery: a nationwide questionnaire study. Acta Anaesthesiol Scand 2011;55:60–8.
[64] Wright D, Paterson C, Scott N, Hair A, O'Dwyer PJ. Five-year follow-up of patients undergoing laparoscopic or open groin hernia repair: a randomized controlled trial. Ann Surg 2002;235:333–7.