

Online Exclusive

Neuropathic Aspects of Persistent Postsurgical Pain: A French Multicenter Survey With a 6-Month Prospective Follow-Up

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Abstract: To investigate the role of peripheral neuropathy in the development of neuropathic postsurgical persistent pain (N-PSPP) after surgery, this French multicentric prospective cohort study recruited 3,112 patients prior to elective cesarean, inguinal herniorrhaphy (open mesh/laparoscopic), breast cancer surgery, cholecystectomy, saphenectomy, sternotomy, thoracotomy, or knee arthroscopy. Besides perioperative data collection, postoperative postal questionnaires built to assess the existence, intensity, and neuropathic features (with the Douleur Neuropathique 4 Questions [DN4]) of pain at the site of surgery were sent at the third and sixth months after surgery. In the 2,397 patients who completed follow-up, the cumulative risk of N-PSPP within the 6 months ranged from 3.2% (laparoscopic herniorrhaphy) to 37.1% (breast cancer surgery). Pain intensity was greater if DN4 was positive and decreased with time since surgery; it depended on the type of surgery. In pain-reporting patients, the response to the DN4 changed from time to time in about 1:4 of the cases. Older age and a low anxiety score were independent protective factors of N-PSPP, whereas a recent

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negative event, a low preoperative quality of life, and previous history of peripheral neuropathy were risk factors. The type of anesthesia had no influence on the occurrence of N-PSPP. Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00812734), NCT00812734.

Perspective: *This prospective observational study provides the incidence rate of N-PSPP occurring within the 6 months after 9 types of elective surgical procedures. It highlights the possible consequences of nerve aggression during some common surgeries. Finally, some preoperative predispositions to the development of N-PSPP have been identified.*

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Key words: *Chronic pain, postoperative, DN4, complications, nerve lesion.*

Postsurgical persistent pain (PSPP) has frequently been reported in the literature.^{16,38,43} Although this fact is now well identified for some types of surgery, there is a need for more precise information such as level of risk (especially for frequently performed procedures), intensity, and time course. The role of neuropathy needs also to be better identified, as there is growing evidence that it is one of the main mechanisms in the development of PSPP. Such a role is supported by 1) anatomic (ie, some surgeries are likely to harm nerves),^{8,61} 2) semiological (ie, neuropathic aspects have been reported in patients suffering from PSPP),^{13,26,46} and 3) exploratory arguments (ie, peripheral nerve dysfunction has been noted after certain surgeries).^{3,20,29}

The present study (“EDONIS”) is a prospective epidemiologic multicentric study of PSPP. Only certain surgical procedures were included in the project, and each procedure represented a subcohort of the whole cohort. The types of procedures were chosen to achieve 2 goals in parallel: 1) to give a precise estimate of the risk of PSPP and its neuropathic components following frequent procedures, where this the information was incomplete, and 2) to be able to conduct an analysis in which predictive factors of the occurrence of neuropathic PSPP (N-PSPP)—whatever the type of surgery—could be identified. Then, some other surgical procedures (such as thoracotomy, breast cancer surgery, and inguinal herniorrhaphy) were considered because they were already identified as inducing frequent, and often neuropathic-like, PSPP.^{1,13,46,57,64} The other procedures were chosen on the basis of case series of PSPP, or anatomic arguments for a nerve lesion during a procedure. These were sternotomy,^{13,34,45} cesarean section,⁵⁰ cholecystectomy,⁹ saphenectomy,¹³ and knee arthroscopy.^{47,73} For inguinal herniorrhaphy, it was estimated at the conception of the study that 3 types of procedures (ie, open meshless, open mesh, and laparoscopic) were equally represented in the French practice, and each represented a different cohort instead of pooling the 3 procedures. For cholecystectomy, only the laparoscopic procedure was considered, as this technique was by far the most practiced in France. The primary endpoint was to estimate the risk of N-PSPP within the 6 months following surgery. Another important endpoint was to identify risk factors of N-PSPP. To improve power and therefore predictability, the risk factor analysis was performed by pooling the different surgeries, a method used previously in risk factor analysis of PSPP.^{6,30}

Methods

Organization

This prospective observational study was approved by the appropriate institutional review boards (CCPRB d’Auvergne and CPP Sud-Est VI for amendments) and declared on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00812734) (ref. NCT00812734). The steering committee made up of the authors and a coordinating clinical research assistant (CRA) designed the study with the help of scientific collaborators, regularly followed the pattern of inclusions, and could decide to recruit new centers if necessary. It was helped by a French network of regional coordinators, each head of a Department of Anesthesia at a regional University Hospital, who contacted other sites. A regional CRA was appointed to monitor the quality of the research at each site, to mail the questionnaires, and to keep contact with the coordinating CRA. One coordinating investigator was appointed at each site.

Study Sample

The study sample consisted of all patients over 18 years of age scheduled in a recruitment center for one of the selected procedures (Table 1). To avoid inclusion bias, consecutive recruitment was required, and off-inclusion periods were defined by the coordinating CRA when centers were unable to include patients because of local constraints.

Data Collection

All the questionnaires are detailed in the Appendix. The inclusion visit was undertaken by the anesthetist at the preanesthetic visit (1–2 weeks before surgery). After providing information and obtaining verbal consent, the patient was given a preoperative questionnaire about his or her working activities and history of previous pain. The anesthetist completed the preoperative part of the medical data sheet, including the patient’s demographic data, potential symptoms of peripheral neuropathy, and possible risk factors for peripheral neuropathy. On discharge from the surgical ward, he or she completed the peri- and postoperative parts of the medical data sheet concerning general and/or locoregional anesthesia, per- and postoperative analgesia, and possible early complications.

If surgery had been completed as planned, the inclusion was confirmed to the regional CRA, who posted a questionnaire to the patient at the third and the sixth months after surgery, to be returned to the

Table 1. Study Population and Methods Used for the Sample Size Estimation

<i>PROCEDURE</i>	<i>INCLUSION CRITERIA</i>	<i>EXCLUSION CRITERIA</i>	<i>POINT ESTIMATE OF PSPP RISK [REFERENCES]</i>	<i>CORRESPONDING SAMPLE SIZES</i>
All procedures	Scheduled procedure Aged 18 or over	Expected difficulty in understanding or completing the questionnaires Patients potentially unreachable during the 6 months following surgery		
Breast cancer surgery	Total mastectomy with axillary sentinel lymph node exploration or not Total mastectomy with axillary lymph node exclusion Bilateral total mastectomy Mastectomy for T4-type breast cancer Breast tumorectomy with axillary lymph node exclusion	Total mastectomy with planned reconstruction Simple breast tumorectomy or partial mastectomy Breast tumorectomy with simple exploration of sentinel lymph node Total mastectomy unscheduled (ie, converted breast tumorectomy or partial mastectomy) Male gender	43% [22–24; 56, 71]	454
Cesarean section	No specific criterion	Procedure in emergency or during labor	5.9% [50]	103
Cholecystectomy	No specific criterion	Planned laparotomy	20% [9]	297
Inguinal herniorrhaphy (any type)	Primary herniorrhaphy Planned laparoscopy	Planned laparotomy Reoperation Surgery for eventration	30% [13, 17, 46, 49, 53, 72]	389 (for each of the 3 subcohorts)
Inguinal herniorrhaphy: open (mesh or meshless)	No specific criterion	Bilateral procedure Intraperitoneal procedure		
Knee arthroscopy	Knee arthroscopy for surgical care (including ligamentoplasty)	Exploratory arthroscopy different from further ligamentoplasty	20% [5, 63, 65, 70, 75]	297
Saphenectomy	Excision of the great or the small saphenous vein	Procedure under local anesthesia only	10% [13, 25, 48]	167
Sternotomy	No specific criterion	No specific criterion	28% [34, 45]	374
Thoracotomy	Lung or pleural surgery with opening of the rib cage by intercostal way	Exclusively endoscopic procedure	50% [28, 35, 52, 57, 62, 74]	463

coordinating center. In this questionnaire, the patient was asked if he or she felt pain in the operated area. If yes, information was asked about the intensity of this pain over the last 48 hours, with a drawn visual analog scale (VAS). Other questions concerned the time course of the pain since surgery and the clinical features, some of these being built out of the Douleur Neuropathique 4 Questions (DN4) questionnaire and included within the study's questionnaire. The DN4 is a validated tool to screen the neuropathic origin of chronic pain.¹⁰ It includes 3 items about the type of pain (burning/painful cold/electric shock), 4 items about the associated symptoms (tingling/pins and needles/numbness/itching), 2 about the existence of numbness in the painful area (on contact/on pinching), and 1 about initiation or enhancement of pain by rubbing. It was initially designed to be completed with the help of a physician, and, for the uses of this study, the questions were adapted for completion by the patient (see underlined items in the [Appendix](#)).¹¹ If documents were not completed and returned, the regional CRA contacted the patient by telephone. Throughout the follow-up period, the patient was able to visit his or her referent practitioner

for analgesic treatment if required or could request referral to the closest specialist pain center.

Data Management

Data entry was performed using a database designed with Microsoft Access 2003 (Microsoft, Redmond, WA), which was exported to the statistical software (Statistical Analysis System, version 9.3; SAS Institute Inc, Cary, NC). Double data entry was performed for 30% of the follow-up files to check the quality of the procedure. In the case of ambiguous data, the entry was checked by the study's main coordinator (C.Dua.) at the demand of the data entry staff. A regular check and update was undertaken in tandem by the main coordinator and the biostatistician (L.O.). If the missing data were mandatory to build the primary outcome (see below), further information was collected from the patient by telephone provided the call was made not later than 3 months after the expected time of data collection. Outliers were identified and checked by telephoning either the patient or the recruiting center. Other missing data were not replaced. Finally, open answers were examined by the

main coordinator and could lead to the creation of new categorical variables.

Endpoints

The primary endpoint was to estimate the risk of N-PSPP within the 6 first postoperative months, the occurrence of N-PSPP being cumulated within 2 time points at the third and sixth months after surgery. N-PSPP was defined as self-reported pain in the operated area for which at least 4 items of the self-administered version of the DN4 were positive. The secondary endpoints were 1) to describe at each time point the characteristics of reported postsurgical pain (ie, risk level, intensity, time course) and 2) to study the possible relationship between N-PSPP and various pre- and perioperative factors.

Statistical Analysis

The quantitative data were expressed as median, interquartile range, and range for nonnormally distributed data or as mean \pm standard deviation otherwise. The categorical data were expressed as frequencies and percentages. The type I error was set at 5%. Analyses were performed using SAS, version 9.3. As the primary outcome was cumulative risk, only the patients for whom complete information was available for this outcome at the third and sixth months after surgery were considered for the analysis. This was also true for the risk-factor analysis and the description of the primary and the 2 secondary endpoints. However, some other secondary descriptive analyses included all patients, regardless of data completion. Figures were generated using Microsoft Office Excel 2003 and PowerPoint 2003 (Microsoft) and XLStat (Addinsoft, Paris, France).

The risk factor analysis was performed through a logistic regression for which the primary outcome was the dependent variable. The explicative variables were chosen on the basis of their relevance in terms of medical knowledge (see Appendix). Some were demographic or morphometric, such as the patient's age, gender, and body mass index. Most of the other preoperative variables were orientated to provide data likely to be linked to postoperative or chronic pain, such as 1) indicators from the patient history of peripheral neuropathy (ie, postherpetic neuralgia, postoperative or posttraumatic neuropathic pain, presence of neuropathic symptoms at the inclusion visit); 2) indicators of putative neurotoxic condition, ie, diagnosis of diabetes, abuse of alcohol, recent or actual anticancer chemotherapy with taxanes, platinum salts, or vinca alkaloids, exposure to toxic substances (listed in the Appendix), concomitant treatment likely to induce neuropathy (listed in the Appendix); 3) concomitant intake of opioids and of treatment for neuropathic pain (ie, "protective medications"); 4) the location of preoperative pain, if any; 5) indicators of the patient's health-related quality of life (with the Short Form [SF]-36 questionnaire),^{42,51} and psychological status, such as the Pain Catastrophizing Scale,⁶⁸ the Hospital Anxiety and Depression Scale,⁷⁹ and the report of a negative event in the past 6 months or of current engagement in a conflict. Out of these indi-

cators, the scores considered for analysis were the physical and the mental component summaries of quality of life (SF-36), the global score of catastrophizing, and the anxiety and depression scores from the Hospital Anxiety and Depression Scale. Perioperative data related to events that occurred from surgery to discharge from hospital (see Appendix). The type of anesthesia was classified in a 3-modality variable ("general," "general plus locoregional," "locoregional") in order to reduce the effect of the variability of the practices within and between surgeries. Similarly, a stratified variable was constructed for the type of postoperative analgesia that included the potency of administered analgesics (level 1: Paracetamol only; level 2: Cyclo-oxygenase inhibitor or nefopam, no opioid; level 3: Any opioid) and report of the use of postoperative locoregional analgesia. The use of intra- or postoperative ketamine and the use of intraoperative nitrous oxide were considered separately, as the literature suggested a possible protective effect against N-PSPP.^{14,69} The report of any early postoperative complication was also considered.

As the study planned a stratified sampling of different surgical procedures, relationships were expected between surgery type and other factors considered in the analysis (eg, gender). To reduce undesirable effects likely to arise in multivariate analysis (such as multicollinearity), we combined different model-building strategies. First, the number of covariates was kept as small as possible. The descriptive analysis helped to identify binary variables with very low variability, some being eliminated, others being combined to build new composite variables. The identification of the center where surgery was done was not considered, because of the large number of modalities and too obvious link with procedure. Second, continuous variables whose distribution appeared closely linked to surgery type (eg, age) were transformed into ordinal variables according to their terciles taken as cut-off values within each type of surgery, ending in a standardization regarding the type of surgery. Finally, following Hosmer and Lemeshow,³¹ we performed a selection of the variables—restricted to those for which the *P* value of the univariate Wald test did not exceed .25—through an automated backward elimination procedure with a .05 significance level to stay in the model, except for age, gender, and body mass index, which were forced into the model whatever the *P* value.

In a supplementary analysis, we aimed to identify which factors significantly explained the intensity of PSPP. For this, only the patients who reported PSPP (either neuropathic or not) at any time of measurement were considered, in order to get the gross direction and size. Depending on the distribution of the data, further inferential analyses were conducted. Where it was felt useful to clarify the presentation of data, the pain score on VAS was transformed into a 3-modalities ordinal outcome (<3 = mild pain; 3–7 = moderate pain; >7 = severe pain).¹² Comparisons were undertaken by the appropriate test. Finally, a multivariable analysis was undertaken to explain the intensity of PSPP (measured on VAS), the independent outcomes being the type of surgery, the positivity of the response to the DN4, and the

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time since surgery (third/sixth month). The model used was a linear mixed model, with the subject (into the type of surgery), and the time since surgery as random effects and the positivity of the response to the DN4 as a fixed effect. The interactions between each factor were also tested, and the model was adjusted to the level of analgesia.

Sample Size Estimation

For each subcohort, we aimed at estimating the risk of PSPP, and the sample size calculation was performed to reach a 5% precision for the width of the 95% confidence interval (CI), that is, the type I error being set at 5%. Each 95% CI was built around the point estimate of the risk of PSPP being reported in the available literature at the time of conception of the project^{5,9,13,17,22-25,28,34,35,45,46,48-50,52,53,56,57,62,63,65,70-72,74,75} (see Table 1 for details). The sample size was systematically inflated expecting 20% lost patients during the study.

Results

Flow Chart of the Cohort and Description of the Sample for Analysis

During the study, the targeted size of the recruited sample had to be adjusted, according to the results of an intermediate analysis of N-PSPP undertaken in June 2009. As the cumulative risk was higher than expected for cesarean section and saphenectomy, the sample sizes were reset at 352 and 300, respectively. For the knee arthroscopy subcohort, the study was continued over the targeted size, supported by the results of a large-sample retrospective study.³⁶ Finally, recruitment for the open meshless inguinal herniorrhaphy subcohort was stopped because only 3.9% of the expected sample could be recruited. The flow of the participants to the study is displayed in Table 2. Out of the 3,112 patients who were included from June 2006 to October 2009, the data from a complete follow-up were available for 2,397 of them (77.0%). These 2,397 patients represented the sample that was considered for the estimation of the primary outcome and the risk factor analysis. Table 2 also displays the primary outcome, that is, the cumulative risk of N-PSPP, which was estimated at 20.6% for the whole cohort (95% CI = 18.9–22.2%). Fig 1 shows the detailed reported prevalence of PSPP (depending on the response to DN4) at the 2 times of assessment. Among the patients who reported PSPP, 50.2% and 43.3% of them were considered as cases of N-PSPP respectively at the third and sixth months after surgery, according to a positive response to DN4. Whatever the results of the DN4, the risk of PSPP tended to decrease with time (34.8 and 29.5%, respectively, at the third and sixth months after surgery, for the whole cohort).

Table 3 describes the demographic, morphometric, psychometric, and medical outcomes identified pre- and perioperatively in the sample of patients who completed follow-up. The sample was representative of the French surgical population, as there were a minimum of 4 centers per surgery, and a total of 40 centers recruited patients

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retained for the final analysis. Two combined outcomes, history of peripheral neuropathy and putative neurotoxic condition, were considered to reduce the number of covariates in further multivariate analysis.

PSPP and N-SPPP-Related Outcomes

Table 4 shows the results of both the univariate and multivariate analyses conducted to identify risk factors for the occurrence of N-PSPP. Among the studied factors, those that were found to favor the occurrence of N-PSPP were all the types of surgery different from laparoscopic inguinal herniorrhaphy (which was taken as the reference), history of peripheral neuropathy, a negative event in the past 6 months, and a low preoperative health-related quality of life (for both physical and mental components). Factors found to protect from N-PSPP were higher age (ie, over the third tercile within each subcohort) and low anxiety score. Unless significance was reached for the catastrophizing pain score, no conclusion could be drawn, because only the cases with missing observations had a risk significantly inferior to the reference class. Also, the CIs of the adjusted odds ratio were wide for the types of surgery because of the number of modalities, thus lowering the number of cases of N-PSPP. As the gender was forced into the model and was strongly associated with the type of surgical procedure, same analysis was undertaken to check the quality of the whole model by withdrawing the cases for which the surgery was naturally dependent on gender (ie, breast cancer surgery, cesarean section, and all inguinal herniorrhaphies). This showed no major difference in the results, as the only factor for which significance was lost was a negative event in the past 6 months; the adjusted odds ratio for male gender was .751 (95% CI = .551–1.024, $P = .07$). Finally, the quality of the model fit was assessed using the Hosmer and Lemeshow's test, with a chi-square of 9.89 (df = 8) and a corresponding P value of .272 meaning that the goodness of fit is not rejected; the area under the receiver operating characteristic curve was .762 (95% CI = .745–.779).

Pain Intensity

Among the 917 observations for which PSPP was reported and a pain score on VAS was available, the intensity of PSPP could be described, depending on the neuropathic characteristics of pain, according to the patient's response on the self-reported DN4 questionnaire and the time of measurement (Figs 2 and 3). Four subgroups of patients were identified, depending on the response to DN4 (positive or negative) and on the time of measurement. In 25.7% of the cases, the response to DN4 changed from one time to the other ("drift"). In general, the rate of severe pain and of moderate-to-severe pain was higher when the response to DN4 was positive (ie, N-PSPP). Except in the subgroup in which the response to DN4 drifted from negative to positive (Fig 3, bottom), pain intensity tended to decrease with time, but the decrease was not significant in the subgroup in which the response to DN4 was

Table 2. Flow Chart and Primary Outcome

	CESAREAN SECTION	INGUINAL HERNIORRHAPHY (LAPAROSCOPIC)	INGUINAL HERNIORRHAPHY (OPEN MESH)	BREAST CANCER SURGERY	CHOLECYSTECTOMY	SAPHENECTOMY	STERNOTOMY	THORACOTOMY	KNEE ARTHROSCOPY	ALL SURGERIES POOLED
Inclusion phase										
Screened for inclusion (scheduled surgery)	475	183	533	544	326	481	445	691	546	4,224
Not included	84	27	159	102	72	176	50	277	165	1,112
Missed preinclusion	46	16	49	11	9	63	24	175	75	468
Patient's refusal at first proposal	6	7	34	25	24	84	3	32	3	218
Patient's planned moving	4	0	3	1	2	5	0	2	3	20
Patient <18 years old	0	0	2	0	0	1	0	0	0	3
Patient's difficulty understanding	3	0	15	30	23	6	0	23	2	102
Patient's resignation before surgery	2	2	2	0	0	0	0	1	4	11
Surgery in emergency	4	0	0	0	0	1	0	2	0	7
Cancelled or delayed surgery	2	0	2	8	4	2	10	6	7	41
Change in type of surgery	0	0	4	7	2	0	0	5	1	19
Initial case report form uncompleted or lost	10	2	4	10	1	9	11	5	58	110
Surgery under local anesthesia	0	0	37	0	0	0	0	0	0	37
Other	7	0	7	10	7	5	2	26	12	76
Included	391	156	374	442	254	305	395	414	381	3,112
Third month after surgery										
Incomplete information about postsurgical pain	101 (25.8)	18 (11.5)	120 (32.1)	81 (18.3)	41 (16.1)	38 (12.5)	49 (12.4)	75 (18.1)	21 (5.5)	544 (17.5)
Incomplete sheet	0	3	3	4	2	3	3	9	5	32
No return	101	15	117	77	39	35	46	66	16	512
Sixth month after surgery										
Incomplete information about postsurgical pain	136 (34.8)	28 (17.9)	46 (12.3)	65 (14.7)	20 (7.9)	55 (18.0)	38 (9.6)	78 (18.8)	24 (6.3)	490 (15.7)
Incomplete sheet	1	6	5	5	3	5	5	2	4	36
No return	135	22	41	60	17	50	33	76	20	454
Third and sixth months after surgery										
Complete follow-up at both times	233 (59.6)	126 (80.8)	242 (64.7)	337 (76.2)	212 (83.6)	240 (78.7)	341 (86.3)	312 (75.4)	354 (92.9)	2,397 (77.0)
Cumulative risk of N-PSPP	24.5 (18.9–30)	3.2 (.1–6.2)	12.4 (8.2–16.5)	37.1 (31.9–42.2)	7.5 (4–11.1)	19.2 (14.2–24.1)	16.7 (12.8–20.7)	32.7 (27.5–37.9)	15.8 (12–19.6)	20.6 (18.9–22.2)

NOTE. Flow chart of the patients from the time of screening to the end of the follow-up, that is, at the sixth month after surgery. The primary outcome, which is the cumulative risk of postsurgical neuropathic pain (N-PSPP), defined on the basis of self-report by the patient of persistent pain at the operated site with 4 or more positive items at the DN4 questionnaire, is also shown with its 95% CI (in parentheses).



Figure 1. Description of the reported prevalence for PSPP for each subcohort and for the whole cohort, depending on the time of assessment (ie, at the third and sixth months after surgery, hereby named M3 and M6, respectively), and the response to the DN4 (positive: likely to be neuropathic). Prevalence is expressed as percentage of the patients for which complete information about PSPP was available at each time.

positive at both times (bottom left). The level of analgesia, taken as a rate of the respective levels of analgesia, changed between the 2 observations only in the subgroup drifting from a positive to a negative response to DN4. Considering the whole observations, the level of analgesia was significantly lower when the response to DN4 was negative ($P < .0001$, chi-square test). Finally, a mild ($R^2 = .09$) but significant ($P < .0001$, analysis of variance) positive correlation was found between the level of treatment and the intensity of pain.

The results of the linear mixed model used to explain the intensity of PSPP showed a significant effect for the type of surgery ($P < .0001$), response to DN4 ($P < .0001$), the time since surgery ($P = .0002$), and the interaction type of surgery \times time since surgery ($P < .0001$). Pain scores were higher when the DN4 was positive for the observation than when negative (mean scores = 2.9 vs 1.7, respectively). They were higher at the third month after surgery than at the sixth month (mean scores = 2.3 vs 2.0, respectively). The types of surgery were ranked

according to the mean pain scores in this decreasing order: knee arthroscopy, thoracotomy, saphenectomy, sternotomy, breast cancer surgery, cholecystectomy, inguinal herniorrhaphy (open mesh, laparoscopic), and cesarean section. The post hoc comparisons (Tukey-Kramer test) showed a difference between knee arthroscopy and 5 other types of surgery, and between cesarean and 4 other types of surgery. The interaction was only quantitative, with a significant decrease of pain scores with time for sternotomy only. The results of this multivariable analysis were not changed when the level of analgesia was added to the model; this variable had also a significant effect ($P < .0001$).

Discussion

In a similar way to other types of chronic pain, the neuropathic aspect of PSPP may be a factor of severity and chronicization.^{7,44} In this study, the major role of this aspect was confirmed, as about half the cases of PSPP were identified as N-PSPP, thus highlighting the

Table 3. Description of the Analyzed Sample

	CESAREAN SECTION	INGUINAL HERNIORRHAPHY (LAPAROSCOPIC)	INGUINAL HERNIORRHAPHY (OPEN MESH)	BREAST CANCER SURGERY	CHOLECYSTECTOMY	SAPHENECTOMY	STERNOTOMY	THORACOTOMY	KNEE ARTHROSCOPY	ALL SURGERIES POOLED
Number of patients	233	126	242	337	212	240	341	312	354	2,397
Recruiting centers										
Number of centers	7	4	6	5	7	5	4	6	4	40
Number of patients per center*	33.3 (14–83)	31.5 (13–46)	40.3 (18–82)	67.4 (2–164)	26.5 (12–73)	48 (21–146)	85.3 (40–206)	52 (12–124)	88.5 (14–189)	59.9 (9–206)
Demographic/morphometric										
Age (years)	32.1 ± 5	55.9 ± 12.3	59.6 ± 14.1	56.4 ± 13	53.5 ± 15.1	50.9 ± 13.2	64.6 ± 12.3	59.7 ± 11.6	45.6 ± 13.3	53.5 ± 15.5
Male gender	0 (0)	122 (96.8)	219 (90.5)	0 (0)	66 (31.1)	74 (30.8)	230 (67.4)	206 (66)	258 (72.9)	1,175 (49)
Weight (kg)	74.8 ± 14	75.5 ± 9.2	74.5 ± 11.4	68.6 ± 14.5	73.5 ± 16.4	72.4 ± 14.4	77.2 ± 15.9	72.1 ± 14	76.7 ± 13.1	73.8 ± 14.3
Height (cm)	163 ± 6.5	174.7 ± 6.4	172.5 ± 7.7	162.5 ± 6.8	165.9 ± 9.1	167.9 ± 8.5	168.2 ± 8.7	169.3 ± 8.5	172.5 ± 8.1	168.2 ± 8.8
Body mass index	28.2 ± 5.1	24.7 ± 2.7	25 ± 3.5	26 ± 5.1	26.6 ± 4.8	25.7 ± 4.7	27.3 ± 5.3	25.1 ± 4.2	25.8 ± 4.1	26.1 ± 4.7
History of peripheral neuropathy										
Postsurgical/traumatic pain with positive DN4	62 (26.6)	27 (21.4)	63 (26)	125 (37.1)	38 (17.9)	112 (46.7)	60 (17.6)	93 (29.8)	83 (23.4)	663 (27.7)
Zoster	9 (3.9)	7 (5.6)	19 (7.9)	31 (9.2)	11 (5.2)	25 (10.4)	20 (5.9)	26 (8.3)	13 (3.7)	161 (6.7)
Symptoms of neuropathy before surgery	29 (12.4)	19 (15.1)	47 (19.4)	100 (29.7)	22 (10.4)	98 (40.8)	31 (9.1)	64 (20.5)	30 (8.5)	440 (18.4)
History of any type of peripheral neuropathy	69 (29.6)	30 (23.8)	74 (30.6)	142 (42.1)	45 (21.2)	122 (50.8)	78 (22.9)	111 (35.6)	93 (26.3)	764 (31.9)
Reported pain before surgery										
None	118 (50.6)	46 (36.5)	86 (35.5)	155 (46)	81 (38.2)	104 (43.3)	207 (60.7)	180 (57.7)	71 (20.1)	1,048 (43.7)
Distant from site of surgery	75 (32.2)	18 (14.3)	35 (14.5)	68 (20.2)	21 (9.9)	50 (20.8)	59 (17.3)	64 (20.5)	33 (9.3)	423 (17.6)
Location not reported	31 (13.3)	24 (19)	44 (18.2)	58 (17.2)	45 (21.2)	47 (19.6)	37 (10.9)	45 (14.4)	65 (18.4)	396 (16.5)
Close to the site of surgery	0 (0)	33 (26.2)	74 (30.6)	42 (12.5)	17 (8)	20 (8.3)	12 (3.5)	21 (6.7)	163 (46)	382 (15.9)
At the site of surgery	9 (3.9)	5 (4)	3 (1.2)	14 (4.2)	48 (22.6)	19 (7.9)	26 (7.6)	2 (.6)	22 (6.2)	148 (6.2)
Putative neurotoxic condition										
HIV infection	1 (.4)	0 (0)	4 (1.7)	1 (.3)	0 (0)	0 (0)	0 (0)	1 (.3)	0 (0)	7 (.3)
Alcohol abuse	0 (0)	6 (4.8)	35 (14.5)	16 (4.7)	12 (5.7)	5 (2.1)	31 (9.1)	56 (17.9)	25 (7.1)	186 (7.8)
Anticancer chemotherapy†	0 (0)	0 (0)	0 (0)	82 (24.3)	0 (0)	1 (.4)	0 (0)	38 (12.2)	0 (0)	121 (5)
Other favoring medical condition†	19 (8.2)	2 (1.6)	18 (7.4)	24 (7.1)	17 (8)	9 (3.8)	82 (24)	41 (13.1)	7 (2)	219 (9.1)
Exposure to toxics†	0 (0)	1 (.8)	13 (5.4)	5 (1.5)	3 (1.4)	1 (.4)	3 (.9)	26 (8.3)	7 (2)	59 (2.5)

Table 3. Continued

	CESAREAN SECTION	INGUINAL HERNIORRHAPHY (LAPAROSCOPIC)	INGUINAL HERNIORRHAPHY (OPEN MESH)	BREAST CANCER SURGERY	CHOLECYSTECTOMY	SAPHENECTOMY	STERNOTOMY	THORACOTOMY	KNEE ARTHROSCOPY	ALL SURGERIES POOLED
Concomitant favoring medications†	0 (0)	0 (0)	10 (4.1)	5 (1.5)	3 (1.4)	7 (2.9)	31 (9.1)	18 (5.8)	3 (.8)	77 (3.2)
Risk factor for neural aggression of any type	19 (8.2)	9 (2.4)	55 (14)	118 (32)	33 (10.8)	22 (7.1)	121 (30.5)	136 (34.6)	37 (4.8)	550 (18.1)
Other environmental factors										
Smoker	26 (11.2)	24 (19)	35 (14.5)	35 (10.4)	36 (17)	30 (12.5)	43 (12.6)	171 (54.8)	70 (19.8)	470 (19.6)
Concomitant opioids	0 (0)	2 (1.6)	5 (2.1)	19 (5.6)	2 (.9)	5 (2.1)	14 (4.1)	18 (5.8)	16 (4.5)	81 (3.4)
Concomitant protective medications†	5 (2.1)	4 (3.2)	17 (7)	68 (20.2)	7 (3.3)	8 (3.3)	33 (9.7)	30 (9.6)	30 (8.5)	202 (8.4)
Psychological indicators										
Engagement in a conflict	3 (1.3)	1 (.8)	2 (.8)	2 (.6)	3 (1.4)	2 (.8)	7 (2.1)	7 (2.2)	6 (1.7)	33 (1.4)
Negative event in the past 6 months	43 (18.5)	21 (16.7)	51 (21.1)	104 (30.9)	40 (18.9)	54 (22.5)	59 (17.3)	75 (24)	80 (22.6)	527 (22)
SF-36: physical component summary	39.4 ± 8.8	47.3 ± 7	45.2 ± 8.7	47.1 ± 10	46.9 ± 9	49.5 ± 7.7	41.0 ± 10.2	46.2 ± 9.2	41.2 ± 8.7	44.5 ± 9.6
SF-36: mental component summary	47.7 ± 9.8	49.3 ± 9.7	49.3 ± 10	40.4 ± 11.8	44.7 ± 10.9	46.8 ± 10.6	42.5 ± 11.3	42.2 ± 11	48.3 ± 10.4	45.2 ± 11.2
Catastrophizing pain score	14.0 ± 10.7	11.8 ± 10.7	12.2 ± 11.7	14.7 ± 12.7	17.8 ± 13.4	13.9 ± 11.2	15.0 ± 12.8	16.0 ± 11.9	13.5 ± 11.3	14.5 ± 12
HADS: anxiety score	7 [5–10] (1–17)	6 [4–9] (0–16)	7 [4–9] (0–18)	10 [7–12] (0–21)	8 [6–10] (0–21)	8 [5–10] (1–19)	9 [5–12] (0–20)	8 [6–11] (0–21)	7 [5–10] (0–20)	8 [5–11] (0–21)
HADS: depression score	3 [2–6] (0–23)	3 [1–5] (0–11)	4 [1–6] (0–13)	4 [2–7] (0–19)	3 [2–6] (0–24)	4 [2–7] (0–20)	5 [2–8] (0–21)	4 [2–7] (0–18)	4 [2–6] (0–16)	4 [2–7] (0–24)
Intraoperative conditions										
Anesthesia										
General	4 (1.7)	120 (95.2)	78 (32.2)	328 (97.3)	209 (98.6)	171 (71.3)	341 (100)	219 (70.2)	236 (66.7)	1,706 (71.2)
General plus locoregional	3 (1.3)	6 (4.8)	109 (45)	9 (2.7)	3 (1.4)	1 (.4)	0 (0)	93 (29.8)	31 (8.8)	255 (10.6)
Locoregional	226 (97)	0 (0)	55 (22.7)	0 (0)	0 (0)	68 (28.3)	0 (0)	0 (0)	87 (24.6)	436 (18.2)
Nitrous oxide	3 (1.3)	115 (91.3)	53 (21.9)	98 (29.1)	103 (48.6)	94 (39.2)	1 (.3)	36 (11.5)	211 (59.6)	714 (29.8)
Ketamine	1 (.4)	79 (62.7)	49 (20.2)	162 (48.1)	75 (35.4)	13 (5.4)	60 (17.6)	126 (40.4)	112 (31.6)	677 (28.2)
Postoperative conditions										
Postoperative analgesia†										
Level 1, no locoregional	23 (9.9)	10 (7.9)	30 (12.4)	24 (7.1)	10 (4.7)	36 (15)	77 (22.6)	2 (.6)	52 (14.7)	264 (11)
Level 2, no locoregional	45 (19.3)	32 (25.4)	66 (27.3)	116 (34.4)	40 (18.9)	117 (48.8)	12 (3.5)	7 (2.2)	112 (31.6)	547 (22.8)

Table 3. Continued

	CESAREAN SECTION	INGUINAL HERNIORRHAPHY (LAPAROSCOPIC)	INGUINAL HERNIORRHAPHY (OPEN MESH)	BREAST CANCER SURGERY	CHOLECYSTECTOMY	SAPHENECTOMY	STERNOTOMY	THORACOTOMY	KNEE ARTHROSCOPY	ALL SURGERIES POOLED
Level 3, no locoregional	140 (60.1)	72 (57.1)	89 (36.8)	186 (55.2)	154 (72.6)	87 (36.3)	249 (73)	97 (31.1)	139 (39.3)	1,213 (50.6)
Locoregional plus level 1–2	3 (1.3)	10 (7.9)	35 (14.5)	3 (9)	2 (.9)	0 (0)	0 (0)	31 (9.9)	9 (2.5)	93 (3.9)
Locoregional plus level 3	22 (9.4)	2 (1.6)	22 (9.1)	8 (2.4)	6 (2.8)	0 (0)	3 (.9)	175 (56.1)	42 (11.9)	280 (11.7)
Ketamine	2 (.9)	1 (.8)	1 (.4)	1 (.3)	1 (.5)	3 (1.3)	0 (0)	76 (24.4)	0 (0)	85 (3.5)
Complication†	12 (5.2)	5 (4)	10 (4.1)	11 (3.3)	11 (5.2)	7 (2.9)	114 (33.4)	96 (30.8)	8 (2.3)	274 (11.4)

Abbreviation: HADS, Hospital Anxiety and Depression Scale.
 NOTE: Description of the sample used for the calculation of the primary outcome and the risk factor analysis. Numerical data are expressed as mean ± standard deviation or median [interquartile range] (range). Categorical data are expressed as number of patients and percentage (%).
 *Data expressed as mean (range).
 †See Methods section for description.
 ‡See Appendix for method of collection.

consequences of nerve aggression during surgery. The primary outcome, the cumulative risk of N-PSPP within 6 months, was chosen as a compromise between the current definition of PSPP,⁴³ the ability to express the initial aggression suffered by the nerves, and feasibility. Although it may not represent the real risk of later transformation into chronic pain, it could be taken into account for further preventive clinical trials. In addition to the prospective design, which gives information regarding the evolution of pain over time, the large size of the analyzed sample provided high precision about the incidence of N-PSPP. In addition, the rates of PSPP observed were consistent with those reported in the literature at the third and sixth months after breast cancer surgery,^{22-24,60,71} thoracotomy,^{20,33,37} open mesh inguinal herniorrhaphy,^{4,49,53} and sternotomy.^{27,39}

The main limitation of the study was the absence of clinical examination of the patients, as N-PPSP was identified by a self-administered questionnaire, although the DN4 had already been used in a large nationwide survey to estimate the prevalence of chronic pain.¹¹ Ideally, each patient reporting PSPP should have had a validated diagnosis, according to standardized procedures including quantitative sensory testing (QST),³² but this was not the purpose of this epidemiologic study. Systematic QST has already been used in a large prospective cohort of patients followed up to 6 months after inguinal herniorrhaphy to identify exploratory outcomes associated to persistent pain,⁴ and such tools should be applied in future cohort studies on PSPP.

Also, our results illustrate how PSPP is likely to affect daily life and how long the pain lasts over time. It is possible that only a minority of patients would suffer life-disturbing chronic pain, because PSPP as reported at the sixth month was rarely severe, in accordance with previously published data.^{13,26,28,33,39,45,54,62,74} Furthermore, PSPP tended to decrease with time after surgery, a fact also already reported.^{20,24,33,39}

Our observations about the analgesic medication reported by the patients must be interpreted with caution, as no guideline was given for pain relief. The positive correlation between the respective intensities of pain and treatment may suggest that pain relief was not optimal. Finally, the drifts observed in responses to the DN4 among patients reporting PSPP could be explained either by some instability in the symptoms used to build the DN4 or by the natural evolution of the disease. For example, dynamic allodynia may appear within several weeks after thoracotomy.²⁰ These drifts justified constructing the risk factor analysis on a cumulative incidence calculated out of a smaller sample but with a complete follow-up.

Two final limitations must be addressed. The type of breast cancer surgeries considered may be restrictive, but conservative surgeries were not uniform at the conception of the study. This choice was made in order to reduce heterogeneity and to avoid including patients with unplanned simple tumorectomies, as such procedures are not reported to induce PSPP. The recent expansion of conservative surgery may increase the risk after breast cancer surgery in the future. Also, a high rate of

Table 4. Risk Factor Analysis for Neuropathic Postsurgical Persistent Pain

FACTOR	MODALITY	NUMBER OF PATIENTS		UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS (AFTER SELECTION)	
		WITH N-PSPP	NO N-PSPP	ODDS RATIO (95% CI)	P VALUE	ODDS RATIO (95% CI)	P VALUE
Age	Lower third	210	570	Ref.	<.0001	Ref.	<.0001
	Median third	165	649	.69 (.55-.87)		.65 (.51-.85)	
	Upper third	118	685	.47 (.36-.60)		.44 (.33-.58)	
Gender	Female	318	904	Ref.	<.0001	Ref.	.093
	Male	175	1,000	.50 (.41-.61)		.78 (.58-1.04)	
Body mass index	Lower third	175	623	Ref.	.375	Ref.	.906
	Median third	154	652	.84 (.66-1.07)		.94 (.72-1.23)	
	Upper third	164	629	.93 (.73-1.18)		.97 (.75-1.27)	
Type of surgery	Herniorrhaphy, laparoscopic	4	122	Ref.	<.0001	Ref.	<.0001
	Cesarean section	57	176	9.87 (3.49-27.90)		9.31 (3.11-27.85)	
	Herniorrhaphy, open mesh	30	212	4.31 (1.484-12.52)		4.89 (1.65-14.46)	
	Breast cancer surgery	125	212	17.97 (6.48-49.81)		15.93 (5.43-46.77)	
	Cholecystectomy	16	196	2.49 (.81-7.61)		2.34 (.73-7.43)	
	Saphenectomy	46	194	7.23 (2.54-20.57)		6.40 (2.16-18.98)	
	Sternotomy	57	284	6.12 (2.17-17.22)		6.65 (2.31-19.14)	
	Thoracotomy	102	210	14.80 (5.32-41.17)		15.99 (5.62-45.54)	
	Knee arthroscopy	56	298	5.73 (2.03-16.13)		6.00 (2.09-17.23)	
History of peripheral neuropathy	No	270	1,363	Ref.	<.0001	Ref.	<.0001
	Yes	223	541	2.08 (1.70-2.55)		1.65 (1.31-2.07)	
Reported pain before surgery	None	189	859	Ref.	.007	NP	
	Distant from the site of surgery	106	317	1.52 (1.16-1.99)			
	Location not reported	97	299	1.48 (1.12-1.95)			
	Close to the site of surgery	75	307	1.11 (.83-1.50)			
Risk factor for neural aggression	No	359	1,488	Ref.	.012	NP	
	Yes	134	416	1.34 (1.07-1.67)			
Smoking habit	No	371	1,556	Ref.	.001	NP	
	Yes	122	348	1.47 (1.16-1.86)			
Concomitant opioids	No	468	1,848	Ref.	.021	NP	
	Yes	25	56	1.76 (1.09-2.86)			
Concomitant protective medications	No	441	1,754	Ref.	.058	NP	
	Yes	52	150	1.38 (.99-1.92)			
Engagement in a conflict	No	488	1,876	Ref.	.442	NI	
	Yes	5	28	.69 (.26-1.79)			
Negative event in the 6 past months	No	339	1,531	Ref.	<.0001	Ref.	.021
	Yes	154	373	1.87 (1.49-2.33)		1.34 (1.05-1.71)	
SF-36: physical component summary (PCs)	Lower third	197	566	Ref.	<.0001	Ref.	.001
	Median third	155	613	.73 (.57-.92)		.76 (.59-1.00)	
	Upper third	123	643	.55 (.43-.71)		.56 (.42-.74)	
	Missing data	18	82	.63 (.37-1.08)		.68 (.37-1.25)	
SF-36: mental component summary (MCs)	Lower third	223	540	Ref.	<.0001	Ref.	.001
	Median third	137	631	.53 (.41-.67)		.61 (.47-.81)	
	Upper third	115	651	.43 (.33-.55)		.65 (.48-.89)	
	Missing data	18	82	.53 (.31-.91)		NC	
Catastrophizing pain score	Lower third	114	609	Ref.	<.0001	Ref.	.027
	Median third	160	585	1.46 (1.12-1.91)		1.12 (.84-1.49)	
	Upper third	196	528	1.98 (1.53-2.57)		1.26 (.94-1.68)	
	Missing data	23	182	.68 (.42-1.09)		.60 (.36-1.00)	
HADS: anxiety score	Lower third	98	695	Ref.	<.0001	Ref.	0
	Median third	172	586	2.08 (1.59-2.73)		1.68 (1.25-2.27)	
	Upper third	213	542	2.79 (2.14-3.63)		1.98 (1.43-2.75)	
	Missing data	10	81	.88 (.44-1.75)		.89 (.43-1.85)	
HADS: depression score	Lower third	130	688	Ref.	<.0001	NP	
	Median third	140	599	1.24 (.95-1.61)			
	Upper third	210	540	2.06 (1.61-2.63)			
	Missing data	13	77	.89 (.48-1.66)			

Table 4. Continued

FACTOR	MODALITY	NUMBER OF PATIENTS		UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS (AFTER SELECTION)	
		WITH N-PSPP	NO N-PSPP	ODDS RATIO (95% CI)	P VALUE	ODDS RATIO (95% CI)	P VALUE
Anesthesia	General	349	1,357	Ref.	.51	NI	
	General plus locoregional	59	196	1.17 (.86–1.60)			
	Locoregional	85	351	.94 (.72–1.23)			
Perioperative ketamine	No	344	1,376	Ref.	.273	NI	
	Yes	149	528	1.13 (.91–1.40)			
Nitrous oxide	No	365	1,318	Ref.	.038	NP	
	Yes	128	586	.79 (.63–.99)			
Postoperative analgesia	Level 1, systemic only	38	226	Ref.	.016	NP	
	Level 2, systemic only	109	438	1.48 (.99–2.21)			
	Level 3, systemic only	257	956	1.60 (1.10–2.32)			
	Locoregional plus levels 1-2	16	77	1.24 (.65–2.34)			
	Locoregional plus level 3	73	207	2.10 (1.36–3.24)			
Postoperative ketamine	No	463	1,849	Ref.	.001	NP	
	Yes	30	55	2.18 (1.38–3.44)			
Postoperative complication	No	437	1,686	Ref.	.955	NI	
	Yes	56	218	.99 (.73–1.35)			

Abbreviations: Ref., reference; NP, not passed (ie, excluded from the model); NI, not included in the model ($P > .25$ in the univariate analysis); NC, not calculated; HADS, Hospital Anxiety and Depression Scale.

NOTE. The relation between predetermined factors and the primary outcome (ie, the report of neuropathic pain in the operated area either at the 3rd or at the 6th month after surgery) was tested by univariate analyses (chi-square test). Then, a logistic regression was performed with explicative outcomes (factors) selected out of the results either of the univariate analyses or intentionally forced into the model.

missing reports after cesarean section was noted, probably because of the burden of child care. As nonresponders are more likely to be painless cases, the observed risk may be overestimated.

Although the potential risk of PSPP is now widely admitted, the mechanisms involved are still a matter of debate, as processes linked to tissue repair might still be active months after surgery. After thoracotomy, for example, only half of the cases of PSPP were considered as neuropathic.⁶⁷ PSPP can therefore be considered a “mixed pain syndrome,” in which neuropathic pain represents 1 component. Physicians encountering PSPP should be aware of the likelihood of a peripheral neuropathic origin, and the neuropathic aspect of pain should be validated following a stepwise diagnosis with examination, screening tools, and QST as much as possible.³²

The question of which nerves are responsible for N-PSPP has been addressed following thoracotomy, during which harm to the intercostal nerve(s) has been evidenced.^{8,20,61} For other surgeries, some terminations have also been cited.^{2,15,19,47,66,73,77} An unresolved issue is the nature (crush, transection, or constriction) and the time of appearance (intraoperative or delayed) of the nerve lesion responsible for N-PSPP. Intraoperative nerve crushing has been suspected during thoracotomy,⁶¹ whereas cases of neuromas and nerve entrapments into fibrosis have been reported in patients suffering from refractory N-PSPP.^{66,78}

The risk factor analysis may be a useful tool to screen predisposition to neuropathic pain and possible preventive strategies. The large size of the analyzed sample and the prospective design allowed testing of a panel of factors large enough to cover most current hypotheses. The design of this study is in accordance with

a recently published framework to establish core risk factor and outcome domains for epidemiologic studies.⁷⁶ As the aim was not to detect early postoperative predictors of neuropathic pain, postoperative factors were intentionally not included in the model; furthermore, clinical outcomes linked to nerve damage such as numbness were already used to build the primary outcome.

A lower risk of postsurgical persistent pain in older patients has already been noted in inguinal herniorrhaphy⁴⁹ and breast cancer surgery.^{26,60} The protective effect of age on neuropathic pain has been previously shown in a rat model, and many possible mechanisms have been listed, such as the thickness of the nerve sheath, fewer large myelinated axons, differing extents of nerve injury, a weaker glial activation, or impairment of cognition.⁵⁹

The role of low quality of life, anxiety, and history of negative events were expected, because previous literature has already highlighted the importance of the patient's psychological state in the development of chronic pain.³⁰ PSPP might also be favored by catastrophizing,⁵⁵ and to other preoperative markers linked to it, such as fear of the long-term consequences of the operation, optimism, or pain vigilance and awareness.^{40,58} Our findings must be tempered by the quantity of missing data, and by the competition between all the psychometric factors within the model, whereas little is known about the relations these factors have with each other in this particular population. On the other hand, the predictive role of previous history of neuropathy may illustrate a predisposition, either with a genetic or environmental background, to the development of N-PSPP, although no preclinical or clinical data are

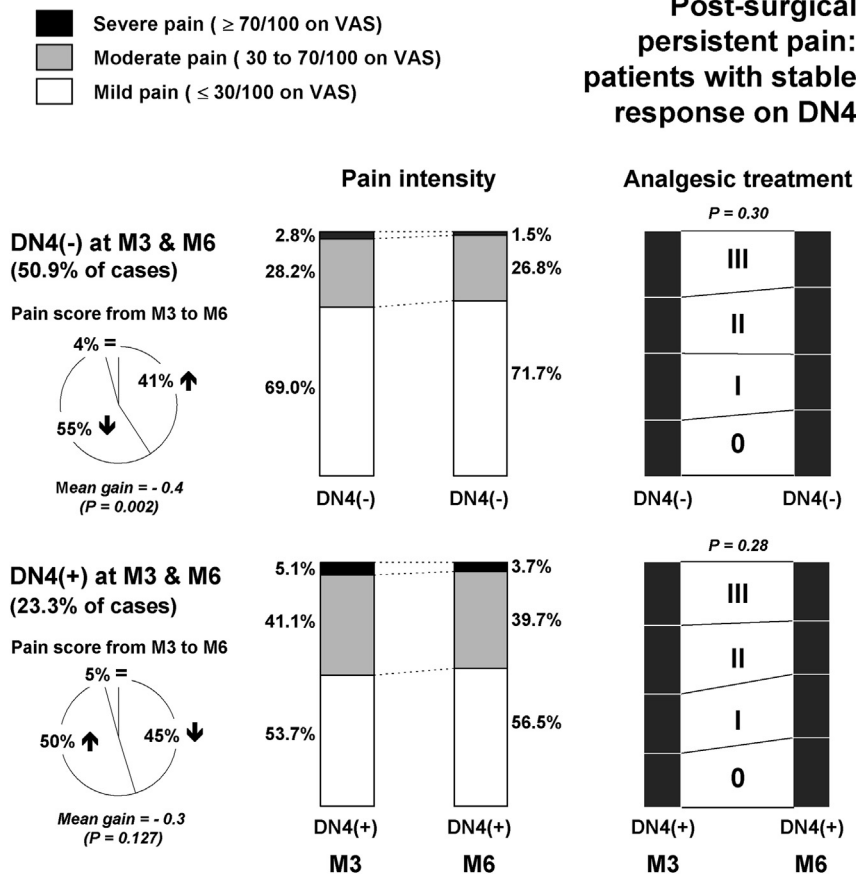


Figure 2. Description of the intensity and time course (ie, at the third and sixth months after surgery, labeled M3 and M6, respectively) of PSPP, in patients who reported PSPP at any time of measurement and quoted their pain on a VAS. Cases of PSPP are classified according to the neuropathic characteristics of pain, according to the response on the self-reported DN4 questionnaire (DN4(+): positive response; DN4(-): negative response). The 2 subgroups of cases for which the response on the DN4 was the same at both times are shown (top and bottom: negative and positive response at both times, respectively). The following information is given for each subgroup: left, distribution of the cases depending on the direction of change for pain score (\uparrow , increase; \downarrow , decrease; =, stable) and the mean increase in pain score between the 2 times; middle (100% stacked columns), intensity of PSPP, classified by severity; right (100% stacked columns), level of analgesic medication (see the Methods section for definition of levels 0, I, II, and III). Between-time comparisons were undertaken with the Wilcoxon paired test and the chi-square test.

available to argue for this hypothesis. The high reported rate of previous neuropathy may have resulted from an oversensitive method of investigation, so further studies should aim at a better precision regarding this point.

Despite promising results in different surgical models using perioperative ketamine, locoregional anesthesia, or nitrous oxide,^{14,18,41} none of the anesthetic techniques considered in our analysis could be found to be significantly protective. As these drugs/techniques are known to act strictly as a blocker of central sensitization, they may be active on the global aspects of PSPP but they may not be good candidates for preventing neuropathic processes. It must be added that in thoracotomy, perioperative ketamine was found unable to prevent PSPP.²¹

Although the present study provides important information about N-PSPP, knowledge must be improved by further research on the topic. The accuracy of screening self-questionnaires for neuropathic pain is imperfect, and more information is needed about the likelihood of N-PSPP to turn into chronicity. For this, large cohorts with a long follow-up or large population surveys—if

possible with a confirmation of the diagnosis by clinical examination and QST—are mandatory. As anesthetic techniques appeared unlikely to prevent N-PSPP, further preventive trials should probably focus on either the initiation of lesion (nerve-protective surgical strategies) or on psychological interventions. Finally, the predictive role of previous history of neuropathy should be further explored, in particular in the field of genetics.

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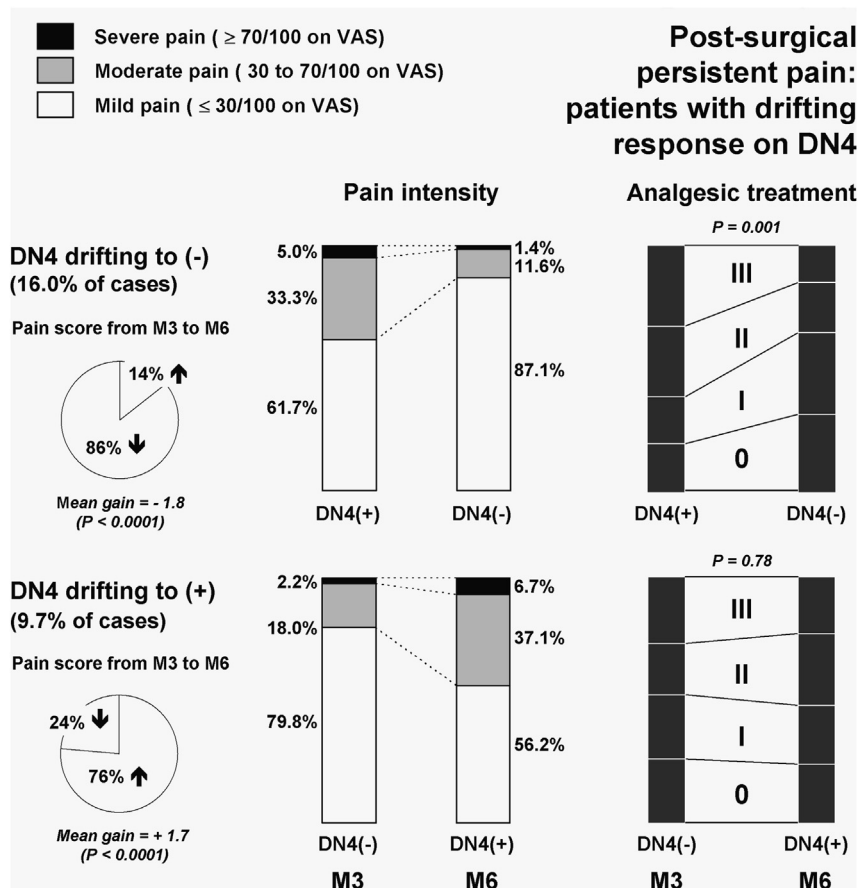


Figure 3. Description of the intensity and time course (ie, at the third and sixth months after surgery, labeled M3 and M6, respectively) of PSPP, in patients who reported PSPP at any time of measurement and quoted their pain on a VAS. Cases of PSPP are classified according to the neuropathic characteristics of pain, according to the response on the self-reported DN4 questionnaire (DN4(+): positive response; DN4(-): negative response). The 2 subgroups of cases for which the response on the DN4 was drifting from M3 to M6 are shown (top and bottom: drifting to a negative and to a positive response, respectively). The following information is given for each subgroup: left, distribution of cases depending on the direction of change for pain score (↑, increase; ↓, decrease; =, stable) and mean gain of pain score between the 2 times; middle (100% stacked columns), intensity of PSPP, classified by severity; right (100% stacked columns), level of analgesic medication (see the Methods section for definition of levels 0, I, II, and III). Between-time comparisons were undertaken with the Wilcoxon's paired test and the chi-square test.

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Appendix: Medical Pre-Operative Data

To be filled by the investigator

- Date of the inclusion visit (DD/MM/YYYY)
- First name (three first letters)
- Second name (two first letters)
- Date of birth (DD/MM/YYYY)
- Gender (male/female)
- Weight (kg)
- Height (m/cm)

Inclusion Criteria

(Must be yes for each item)

- Age \geq 18 (yes/no)
- Elective surgery in accordance to the EDONIS project (yes/no)
- Patient's consent to participate (yes/no)

Exclusion Criteria

(Must be no for each item)

- Difficulty understanding the questionnaires or the protocol (yes/no)
- Planning on moving house within the next 6 months (yes/no)
- Male gender (for mastectomies) (yes/no)

Clinical Data

Symptoms of Peripheral Neuropathy? (Yes/No)

- If yes, any motor symptom? (yes/no)
 - If motor symptom, precise: paralysis/paresis (yes/no); amyotrophy (yes/no); fasciculation (yes/no); loss of tendon reflexes (yes/no)
 - If motor symptom, comments (about the localisation or else)
- If yes, any sensitive symptom? (yes/no)
 - If subjective sensitive symptom, precise: paresthesia (yes/no); dysesthesia (ie, evoked by contact) (yes/no); ongoing pain (ie, burning, electric-shock-like or squeezing) (yes/no)
 - If objective sensitive symptom, precise: alteration of superficial sensitivity (yes/no); alteration of deep sensitivity (yes/no)
 - If motor symptom, comments (about the localization or else)
- If yes, any neurovegetative symptom? (yes/no)
 - If neurovegetative symptom, precise: vasomotor (oedema, cyanosis) (yes/no); trophic (skin dryness or scaliness) (yes/no); depilation or nails fragility (yes/no); orthostatic hypotension (yes/no)
 - If neurovegetative symptom, comments (about the localization or else)

Risk Factors for Peripheral Neuropathy

- History of herpes zoster? (yes/no)
- History of HIV infection? (yes/no)
- History of diabetes? (yes/no)
 - If yes: type? (I/II)
 - If yes: year of the diagnosis (YYYY)

- If yes, associated lesions: retinal (yes/no); renal (yes/no); coronaries (yes/no); dysautonomia (yes/no); other (*give details*)
- Actual addiction? (yes/no)
 - If yes: tobacco (yes/no; number of pack-years)
 - If yes: alcohol (yes/no; number of daily units)
 - If yes: other (*give details*)
- History of radiotherapy? (yes/no)
- History of anticancer chemotherapy? (yes/no)
 - If yes: *provide the name of the drugs*
- History of any other disease that may induce peripheral neuropathy (ie, systemic disease, cancer)? (yes/no)
 - If yes: *give details*
- Actual or recent intake of any treatment that may induce peripheral neuropathy? (yes/no)
 - If yes: almitrin (yes/no), disulfiram (yes/no), chloroquine (yes/no), metronidazole (yes/no), thalidomide (yes/no), amiodarone (yes/no), isoniazid (yes/no), nitrofurantoin (yes/no), antiviral nucleoside analogue (yes/no)
- Actual or recent exposure to chemical substances that may induce peripheral neuropathy (ie, organophosphates, arsenic, thallium...)? (yes/no)
 - If yes: *give details*
- Any other relevant concomitant treatment: name/daily doses/way of administration/date of initiation/ongoing?/date of discontinuation

Pre-Operative Questionnaire

To be filled by the patient, with possible help of the investigator

Underlined: items of the self-administered DN4.

Working Activities

- Are you at the moment out of work? (yes/no)
- If yes, for what reason? (medical decision for stopping work/accident at work/other)
- Are you engaged in a conflict with any social organism or with the company that employs you? (yes/no)
- Have you, suffered from any negative event in the 6 past months, such as a death or conflict in family, or loss of your job? (yes/no)

Pain in the Past (Anterior to 1 Month)

- Have you undergone any surgical procedures in the past? (yes/no)
- If yes, how many?
- Have you already suffered from pain after trauma or a surgical procedure? (yes/no)
- If yes, how strong was it? (mild/moderate/strong/very strong/unbearable)
- How long did the longest episode of pain last? (1 hour/1 day/1 week/1 month/more)
- When did it occur? (last month/last year/before last year)
- Did the pain affect your day life? (not at all/a few/a lot)
- Where was it located? (diffuse/at the operated area*/elsewhere*; *: *give precision*)

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- Was the pain like: burning? (yes/no); painful cold? (yes/no); electric shock? (yes/no)?
- Was it associated with any of these symptoms: tingling? (yes/no); pins and needles? (yes/no); numbness? (yes/no); itching? (yes/no)
- Did the skin in the painful area feel numb at contact? (yes/no); at pinching? (yes/no)
- Was the pain initiated or enhanced by rubbing? (yes/no)
- Did you take any medication for pain? (yes/no)
- If yes, for how long? (1 day/1 week/1 month/more)
- Which medication(s) did you take? (yes/no); for each following item:
 - oral morphine (Morphine, Skenan, Moscontin)
 - tramadol (Topalgic)
 - amitriptyline (Laroxyl), clomipramine (Anafranil), imipramine (Tofranil)
 - paroxetine (Deroxat), sertraline (Zoloft), venlafaxine (Effexor)
 - gabapentin (Neurontin)
 - carbamazepine (Tegretol), topiramate (Epitamax), clonazepam (Rivotril)
 - other pain killer (*give the name*)
- Did you undergo any of these techniques to relieve pain: peripheral nerve block? (yes/no); transcutaneous electrical nerve stimulation? (yes/no); other? (yes/no)
- Did you suffer from other painful or unpleasant episode? (yes/no)
- If yes, was it: migraine? (yes/no); depression? (yes/no); anxiety ? (yes/no); obsessive-compulsive disorder? (yes/no); other ? (yes/no; *give details*)

Current Pain (in the Past Month)

- Are you suffering from pain right now? (yes/no)
- If yes, how strong is it? (mild/moderate/strong/very strong/unbearable)
- When did it start? (less than 1 week ago/1 week ago/1 month ago)
- Does the pain interact with your day life? (not at all/a few/a lot)
- Where is it located? (diffuse/at the operated area*/ elsewhere*; *: *give precision*)
- Is the pain like: burning? (yes/no); painful cold? (yes/no); electric shock? (yes/no)?
- Is it associated with any of these symptoms: tingling? (yes/no); pins and needles? (yes/no); numbness? (yes/no); itching? (yes/no)
- Is the skin in the painful area numb on contact? (yes/no); on pinching? (yes/no)
- Is the pain initiated or enhanced by rubbing? (yes/no)
- Do you take any medication for pain? (yes/no)
- If yes, since when? (1 day/1 week/1 month/more)
- Which medication(s) are you taking? yes/no for each item:
 - oral morphine (Morphine, Skenan, Moscontin)
 - tramadol (Topalgic)
 - amitriptyline (Laroxyl), clomipramine (Anafranil), imipramine (Tofranil)
 - paroxetine (Deroxat), sertraline (Zoloft), venlafaxine (Effexor)

Neuropathic Postsurgical Persistent Pain

- gabapentin (Neurontin)
- carbamazepine (Tegretol), topiramate (Epitamax), clonazepam (Rivotril)
- other pain killer (*give the name*)
- Have you undergone any of these techniques to relieve pain: peripheral nerve block? (yes/no); transcutaneous electrical nerve stimulation? (yes/no); other? (yes/no)

Peri and Post-Operative Data

To be filled by the investigator at discharge from hospital

- Date of surgery (DD/MM/YYYY)

General Anaesthesia

- Intravenous anaesthetics: thiopental (yes/no); propofol (yes/no); etomidate (yes/no); other (yes/no)
- Opioid agents: sufentanil (yes/no); fentanyl (yes/no); alfentanil (yes/no); remifentanil (yes/no)
- Halogenated agents (yes/no)
- Nitrous oxide (yes/no)
- Myorelaxants (yes/no)

Locoregional Anaesthesia

- Time course: perioperative (yes/no); peri- and postoperative (yes/no); postoperative (yes/no)
- Type: infiltration (yes/no); spinal anaesthesia (yes/no); epidural or spinal-epidural (yes/no); peripheral block* (yes/no); *: *if yes, give details*
- Catheter? (yes/no)
- Block under general anaesthesia? (yes/no)
- Method used to improve nerve block: search for paresthesia (yes/no); nerve stimulator (yes/no); ultrasound (yes/no)

Co-Analgesia and Antihyperalgesia

- Intra-operative ketamine (yes/no)
- Post-operative ketamine (yes/no)
- Clonidine (yes/no)
- Gabapentin (yes/no)

Peri- and Post-Operative Analgesia

- paracetamol? (yes/no)
- NSAID? (yes/no)
- nefopam? (yes/no)
- opioids? (yes/no)
- others? (*give details*)

Post-Operative Complications

- If any, give details.

Analgesia at Discharge (if any)

- paracetamol? (yes/no)
- NSAID? (yes/no)
- nefopam? (yes/no)
- tramadol? (yes/no)
- dextropropoxyphene? (yes/no)
- other opioids? (yes/no)

- others? (*give details*)
- Date of discharge (DD/MM/YYYY)
- Decision to follow-up (yes/no)
 - *If no, give the reason*

Follow-Up Questionnaire

Mailed to the patient 3 and 6 months after surgery, to be filled by him/her and mailed back to the Clinical Investigation Centre

Underlined: items of the self-administered DN4.

- Date of surgery (DD/MM/YYYY)
- Date of response to the present questionnaire (DD/MM/YYYY)
- Do you feel any pain in the area where surgery was undertaken? (yes/no; *if yes, go straight to the question §*)
- What was the average intensity of pain over the last 48 hours? (to be indicated by a vertical mark on a 100-mm horizontal line labelled at the left "no pain at all" and at the right "the worst pain imaginable")
- Has the intensity of the pain changed since surgery? (yes/no)
- Did the pain start several days or weeks after your return to home? (yes/no)
- Does the pain feel different than it did immediately after surgery? (yes/no)

- Has the pain any of the following characteristics: burning? (yes/no); painful cold? (yes/no); electric shock? (yes/no)
- Is the pain associated, in the same area, to any of the following symptoms: tingling? (yes/no); pins and needles? (yes/no); numbness? (yes/no); itching? (yes/no)
- Is the skin in the painful area numb at contact? (yes/no)
- Is the skin in the painful area numb on mild pinching? (yes/no)
- Is the pain initiated or enhanced by rubbing? (yes/no)
- § Have you taken any medication for pain in the last past month? (yes/no)
- If yes, which medication(s) did you take? (yes/no); for each following item:
 - oral morphine (Morphine, Skenan, Moscontin)
 - tramadol (Topalgic)
 - amitriptyline (Laroxyl), clomipramine (Anafranil), imipramine (Tofranil)
 - paroxetine (Deroxat), sertraline (Zoloft), venlafaxine (Effexor)
 - gabapentin (Neurontin)
 - carbamazepine (Tegretol), topiramate (Epitamax), clonazepam (Rivotril)
 - other pain killer (*give the name*)
- Have you suffered from any other health disorder in the month following surgery? (yes/no; if yes, give details)