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# Pain-related functional interference in patients with chronic neuropathic postsurgical pain: an analysis of registry data

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**Abstract**

Although chronic postsurgical pain (CPSP) is a major health care problem, pain-related functional interference has rarely been investigated. Using the PAIN OUT registry we evaluated patients' pain-related outcomes on the first postoperative day, and their pain-related interference with daily living (Brief Pain Inventory) and neuropathic symptoms (DN4: douleur neuropathique en 4 questions) at six months after surgery. Endpoints were pain interference total scores (PITS) and their association with pain and DN4 scores. Furthermore, possible risk factors associated with impaired function at M6 were analyzed by ordinal regression analysis with PITS groups (no to mild, moderate and severe interference) as a dependent three-stage factor. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Of 2,322 patients, 15.3% reported CPSP with an average pain score ≥3 (NRS 0-10). Risk for a higher PITS group increased by 190% (OR (95%-CI): 2.9 (2.7-3.2); p<0.001) in patients with, compared to without CPSP. A positive DN4 independently increased risk by 29% (1.3 (1.12-1.45), p<0.001). Pre-existing chronic pain (3.6 (2.6-5.1); p<0.001), time spent in severe acute pain (2.9 (1.3-6.4); p=0.008), neurosurgical back surgery in males (3.6 (1.7-7.6); p<0.001) and orthopedic surgery in females (1.7 (1.0-3.0); p=0.036) were the variables with strongest association with PITS. PITS might provide more precise information about patients' outcomes than pain scores only. As neuropathic symptoms increase PITS, a suitable instrument for their routine assessment should be defined.

**Keywords:** Chronic postsurgical pain (CPSP), Neuropathic pain, Brief Pain Inventory (BPI), Pain Interference Total Score (PITS), Pain scores

## INTRODUCTION

Prophylaxis and treatment of chronic postsurgical pain (CPSP) is recognized as a health priority [31], and the diagnosis "CPSP" is now included in the upcoming ICD-11, the international classification of diseases. CPSP has been considered an iatrogenically induced chronic pain, making identification of mechanisms and risk factors pivotal in order to prevent it [13]. Severe CPSP can result in clinically relevant functional interference, and is reported by 5-10% of patients after surgery [9,13]. However, many studies focused only on pain intensity, without considering the functional consequences of severe CPSP. In particular, neuropathic pain seems to be a major problem, with patients reporting an increase in pain intensity as well as pain-related interference [2,13,17,29]. Thus, to capture the full picture of disability caused by CPSP, an assessment of patients' functional interference has been recommended [13,18].

In order to describe the characteristics of patients suffering from (neuropathic) CPSP and their functional interference as well as possible risk factors in more detail, we analyzed data from the international pain registry PAIN OUT [39]. The registry provides details of pain-related functional interference and neuropathic symptoms, based on results of the International Pain Outcomes Questionnaire administered on the first postoperative day, as well as results of the Brief Pain Inventory (BPI) and the DN4 questionnaires filled in 6 months after surgery [6,9,24].

The aim of the study was to investigate functional interference six months after surgery in a large cohort of patients undergoing medium sized to major surgery. The hypothesis was that pain intensities or the presence of CPSP are associated with pain interference total scores (PITS), and that neuropathic symptoms (positive DN4) contribute to functional interference. Furthermore, we wanted to identify potential risk factors for pain-related functional interference six month after surgery.

## METHODS

### PAIN OUT registry

Basis of this analysis is the PAIN OUT registry, which provides tools for benchmarking and quality control of postoperative pain outcomes (ClinicalTrials.gov: NCT02083835) [24,39]. Each participating center obtained ethics approval from its local ethics committee (for Bern University Hospital: KEK 074/11). Patients scheduled for elective surgery gave informed consent for this prospective observational study according to the local requirements [28].

Data collected within this registry reflect clinical practice in perioperative (analgesic) care. Patient histories and anesthesia- and surgery-related data were collected from the records. On the first postoperative day, patients filled in the International Pain Outcome Questionnaire asking for pain intensity scores, pain-related functional interference, and side effects of treatment using a numeric rating scale NRS 0-10 [24]. Some items were addressed with yes/no answers (e.g., desire for more treatment) or a percentage scale (time spent in severe pain during the first 24 hours after surgery, pain relief).

To prevent bias, trained surveyors not involved in patients' care collected data in the participating hospitals and entered them in the web-based case report form. Composite pain scores were calculated for pain intensities reported on the first postoperative day, functional interference (mean NRS for "how pain interfered with activities in bed and out of bed, NRS for breathing deeply or coughing and sleeping") and side effects (mean NRS for dizziness, drowsiness, itching and nausea).

### Patient assessment six months after surgery

Six months after surgery, patients filled in the short form of the Brief Pain Inventory (BPI), which asked for pain intensity, pain relief experienced from analgesic treatment, and pain-related common dimensions of physical and affective interference within the previous 24 hours

[6]. Questions addressed only pain related to the previous surgery. Patients were advised not to report pain or discomfort unrelated to their surgery, such as low back pain, arthritis pain, or headache. The BPI pain score summarizes NRS scores for average, least, worst and current pain ("pain right now"). Pain-related functional interference was calculated as a pain interference total score (PITS) from the seven respective questions of the BPI [26], capturing the reactive dimension of pain, as recommended by the BPI user guide. Additionally, mean scores for the two domains *physical interference* (general activity, walking ability, work) and *affective interference* (mood, enjoyment of life, relations with other persons) were calculated. Sleep was handled as a separate third factor, as it does not improve psychometric properties of the BPI interference scale [33-35]. According to their PITS scores, patients were allocated the groups: *no interference* (PITS=0), *mild interference* (PITS >0 and <2), *moderate interference* (PITS 2-5) and *severe interference* (PITS >5), as previously published [26].

Neuropathic symptoms were assessed using the interview version of the DN4 (douleur neuropathique en 4 questions) [4,9]. Patients were categorized as DN4 positive (at least three of seven neuropathic symptoms present) or negative (fewer than three neuropathic symptoms present) [4,9]. The questionnaires were either filled in electronically by the patient after receipt of a link via e-mail or via a telephone interview.

According to the NRS score for average pain six months after surgery, patients were allocated to the groups pain-free (NRS=0), mild pain (NRS=1-2), moderate pain (NRS=3-5) or severe pain (NRS ≥6). In line with previous studies and the Initiative on Methods, Measurement and Pain Assessment (IMMPACT) recommendations, CPSP was defined as persistent "clinically meaningful pain" with an NRS score ≥3 for average pain [9,12,27]. CPSP was considered as absent when average pain was <3.

**Data analysis and statistics**

A download from the coded PAIN OUT database was performed in June 2017. Only data from hospitals contributing at least 50 complete datasets from patients having undergone major surgery in the departments of general surgery, orthopedic surgery, gynecology and neurosurgery (four surgical groups) were included. The neurosurgical group consisted of patients undergoing surgery on the spinal canal and spinal fusions. The anonymized data set provided from PAIN OUT for this statistical analysis included some but not all of the patients in the euCPSP study (enrollment 7/2011 to 12/2012), due to more rigorous inclusion criteria [9]. Based on our previous investigation showing a 5.6% incidence of neuropathic CPSP and inclusion of four surgical groups, we aimed at a sample size of at least 2,000 cases completing the BPI and DN4 questionnaires six months after surgery. We expected this would give us a representative cohort of patients (>100 patients with neuropathic CPSP) for reliable statistical analysis. An additional ethics approval was obtained for this analysis of registry data from the local ethics committee (KEK Bern: 2017-01157).

The aim of our study was to investigate functional interference six months after surgery with the main hypothesis that pain and DN4 have an influence on PITS. An ordinal regression model with the factors CPSP / no CPSP (NRS average pain ≥3 or <3) and DN4 negative/positive as well as their interactions on PITS was fitted. PITS was used as a dependent three-stage factor (no to mild functional interference (PITS <2), moderate interference (PITS 2-5) or severe interference (PITS >5) [26]. Estimated odds ratios (OR) with 95% confidence intervals were reported. Additionally, a multivariate linear regression model with the factors CPSP/no CPSP and DN4 negative/positive, including their interactions, was performed as a sensitivity analysis. Estimated regression coefficients with 95% confidence intervals were calculated. Goodness-of-fit of the regression model was assessed by the coefficient of determination $R^2$.

ROC (receiver operating characteristic) analysis was used to discriminate between patients with severe interference (PITS >5) and patients with no to moderate interference (PITS ≤5) based on

average pain scores at six months. Accuracy was assessed by the area under the curve (AUC) with 95% confidence intervals (CI) and by predictive values at the chosen cut-off value of average pain. We additionally applied the ROC analysis for the cut-off PITS ≥2 versus PITS <2 to discriminate between patients who had at least moderate interference and patients who had no to mild interference.

Finally, we were interested in possible risk factors associated with impaired function six months after surgery. A multivariate ordinal regression model was set up and fitted with the three PITS groups to estimate the risk of increased pain-related interference including a pre-specified set of possible predictors as independent variables. These predictors were variables referring to patient-reported outcome evaluated on the first postoperative day (pain intensity, % of time in severe pain, side effects, a composite score of pain-related interference, satisfaction, and emotional aspects such as feeling anxious or helpless). Covariates included were pre-existing chronic pain, pre-existing opioid therapy, and surgery-related variables (surgical group, duration of surgery). As sex, age and BMI may also influence outcome, these patient characteristics were introduced as confounders into the model. Odds ratios (OR) of the risk factors and corresponding 95% CI are presented.

Continuous data and composite scores were described by mean±SD (standard deviation), and NRS scores by medians with interquartile ranges. Categorical data were presented as absolute and relative frequencies. Differences in continuous outcomes were tested by two-sided independent samples (t test or ANOVA) if the data were normally distributed; otherwise, the Mann-Whitney U test or the Kruskal-Wallis test was applied. Differences in the frequency of categorical outcomes were analyzed by the $\chi^2$ test. The significance level was set at p=0.05. To address the problem of multiple comparisons, Bonferroni correction was applied for the analysis of BPI scores/PITS in the subgroups of patients with different pain intensities and positive or negative

DN4. Statistical analyses were performed with IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY).

## RESULTS

### Study cohort and patient characteristics

In the PAIN OUT database 2,872 patients were identified who had filled in the six-month questionnaire (Figure 1). After exclusion of cases with incomplete data, 2,322 patients with completed BPI could be analyzed. Six months after surgery, 20.1% of the patients noted mild pain, 12.3% moderate pain and 3.0% severe pain (Figure 1). This resulted in 15.3% of the patients with CPSP, defined by an average pain score of NRS ≥3 at six months. Characteristics of patients with and without CPSP as well as their surgery-related and anesthesia-related data are displayed in Table 1. There was a significant difference in the incidence of CPSP between the four surgical groups (Table 1, $p<0.001$; Figure S1 in the supplemental digital content, available at http://links.lww.com/PAIN/A773). Particularly after neurosurgery and orthopedic surgery, the incidence was high. An analysis of individual surgeries revealed relatively low percentages of affected patients after laparoscopic cholecystectomy (6.5%), bariatric surgery (7.8%) and Cesarean delivery (8.1%), and increasing incidence after hernia repair (12.5%), breast surgery (14.7%), thoracotomy for lung resection (16.1%), total hip arthroplasty (20.8%), and total knee arthroplasty (30.9%).

Comorbidities did not vary between patients with and without CPSP. Pre-existing chronic pain for at least three months before surgery was more frequent in patients later suffering from CPSP than in patients without CPSP (Table 1, $p<0.001$). Most patients indicated their pre-existing pain to be located at the site of surgery (56.2%), elsewhere (15.7%), or at the site of surgery and elsewhere (28.1%). The majority of patients undergoing orthopedic surgery and neurosurgery reported pre-existing chronic pain (70.4%). Opioids were more frequently taken before surgery in patients with CPSP compared to those without CPSP (0.001; Table 1). The proportion of pa-

tients taking preoperative opioids was particularly high in orthopedic and neurosurgical patients (7.4% and 15.2%, respectively).

**Neuropathic symptoms six months after surgery**

The DN4 was filled in by 2,066 patients (Figure 1). Six months after surgery, neuropathic pain was reported by 39.8% of the patients with CPSP. Neuropathic pain was more frequent in patients suffering from severe CPSP (58.2%) than from moderate CPSP (38.7%; p=0.004 compared to severe pain) or mild pain (25.0%; p<0.001 compared to moderate pain). Interestingly, some patients who indicated no pain at all reported three or more neuropathic symptoms (2.8%; p<0.001 compared to mild pain). Neuropathic pain qualities differed by type of surgery, with 36.8% of the patients having a positive DN4 after thoracotomy, 33.3% after neurosurgical back surgery, 20.2% after knee arthroscopy, 18.3% after breast surgery and 17.0% each after total hip arthroplasty, total knee arthroplasty and Cesarean delivery. In particular, some women after Cesarean delivery and breast surgery categorized in the group "no CPSP" indicated neuropathic symptoms, with a positive DN4 in 15.7% of the women after Cesarean delivery and 13.5% after breast surgery.

Table S1 in the supplemental digital content gives further details of patient characteristics and results of patient-reported outcomes evaluated on the first postoperative day, for the groups with or without CPSP and negative or positive for DN4 (available at http://links.lww.com/PAIN/A773).

**Interaction of PITS with pain scores and DN4 sores**

The PITS differed in patients with no pain, mild, moderate and severe pain six months after surgery, with 0.2%, 2.4%, 21.4% and 61.4% reporting severe pain-related interference (Figure 2A; p<0.001). Thus, high PITS were also present in some patients allocated to the no pain, mild and moderate pain groups according to their average pain score at six months. In contrast, 1.4%

of the patients with moderate CPSP and 1.8% of the patients with severe CPSP did not report any functional interference.

In each of the subgroups with no pain, mild, moderate or severe pain, those subjects presenting with a positive DN4 were more impaired than those with a negative DN4 (Figure 2B). The ordinal regression analysis using PITS as a three-stage factor (no to mild functional, moderate or severe interference) revealed that in case of a positive DN4, there was a 29% increased risk for a higher PITS group (OR=1.29 (1.12-1.45); p<0.001), which was comparable in patients with CPSP (1.27 (1.10-1.51)) and with no CPSP (1.31 (1.01-1.53)). In patients with CPSP, the risk for a higher PITS group was increased by 190% (OR=2.9 (2.7-3.2); p<0.001) compared to those without CPSP. An interaction between CPSP and DN4 was not detected (p=0.807). For sensitivity analysis, we performed an additional approach using multivariate linear regression analysis. In a patient with "average" pain scores at six months (mean pain score of the whole cohort NRS=0.93), an increase of one point in the DN4 score resulted in a 0.26 higher PITS score on average ($ß_{DN4}$=0.26 (0.21-0.30); p<0.001). Conversely, if average pain increased by one point in a patient with average neuropathic symptoms (mean DN4 score of the whole cohort 0.92), PITS scores were on average 0.70 higher ($ß_{avg.pain}$=0.79 (0.66-0.74); p<0.001). There was a positive interaction between DN4 and pain scores regarding PITS; however, the combined additional influence was rather small ($ß_{DN4*avg.pain}$=0.02 (0.003-0.036); p=0.021). The coefficient of determination revealed a good fit in the model with $R^2$=0.68, i.e. 68% of the variation of PITS was explained by average pain and DN4 score in the model.

Comparing the domains of pain-related physical and affective interference, patients with neuropathic CPSP reported higher composite scores for affective and physical interference and composite pain scores as well as higher scores for the seven individual measures of interference compared to those with DN4-negative CPSP (Figure 3).

**Prediction of PITS by pain scores**

ROC analysis showed good discrimination between patients with severe interference and patients with PITS ≤5 according to the average pain score at six months (n=2,322 with completed BPI; AUC (95% CI): 0.94 (0.91-0.97), p<0.001). Using the cut-off value defined for CPSP in this trial, the negative predictive value was 99.3% (1,952 of 1,966 patients). In contrast, the positive predictive value amounted to only 29.3%, as only 104 patients suffering from CPSP reported severe functional interference. By choosing a cut-off of PITS <2 versus PITS ≥2 to discriminate between patients with clinically relevant interference and those without, comparably good prediction could be confirmed using average pain (AUC (95% CI): 0.94 (0.92-0.96), p<0.001).

**Variables associated with pain-related interference 6 months after surgery**

Multivariate ordinal regression analysis revealed younger age, preexisting chronic pain before surgery, percentage of time suffering from severe pain in the first 24 hours after surgery, duration of surgery, as well as *feeling anxious* as variables significantly associated with PITS (Table 2). Furthermore, we found an interaction between surgery and sex; therefore, males and females in the four surgery groups were analyzed separately. Males undergoing neurosurgery had a nearly 3.6 times increased risk of higher PITS compared to the reference group (males undergoing general surgery), while the risk for females was 1.9 times higher. For males and females after orthopedic surgery, the OR amounted to 1.38 and 1.77, respectively (Table 2).

**Analgesics 6 months after surgery**

Six months after surgery, 17.4% of all patients reported the intake of analgesics, in most cases non-opioid analgesics. Use of opioid medication was more frequent in patients with higher PITS (Table 3). In the patient group with severe pain-related functional interference, more than

a quarter took WHO II or WHO III opioids, whereas percentages were lower in the groups with moderate, mild or no functional interference ($p<0.001$).

## DISCUSSION

Pain-related functional interference in patients suffering from (neuropathic) CPSP was analyzed in a large patient cohort six months after surgery. CPSP and a positive DN4 were independently associated with patients' increased pain-related functional interference six months after surgery. The risk increase due to CPSP did not depend on the DN4 status (i.e., was the same for patients with positive or negative DN4) and the risk increase due to DN4 was the same for patients with or without CPSP. Of the patients suffering from CPSP, 29% reported severe pain-related interference.

We focused on PITS encompassing the physical and affective dimensions, as the impact of chronic pain states on activities of daily living seems to be more meaningful than pain intensity scores alone [18]. Additionally, the outcome *functional interference* might better capture the social consequences of a chronic pain state [13,18].

### CPSP: Previous research

The definition of CPSP in the new ICD-11 indicates a clear time interval (at least 3 months following surgery) for diagnosis of CPSP [31]. The time interval was a variable inconsistently used in previous publications, thus explaining some of the variance in reported incidence of CPSP [13,21,36]. Some working groups defined CPSP as any pain (NRS/VAS >0), resulting in high proportions of patients affected by CPSP [7,10,11,16]. Others used NRS ≥3 or NRS ≥4 as cut-offs [1,9,14,27,37]. If we apply a cut-off of 4 instead of 3 for classification of CPSP in our study, 200 (9.8%) instead of 338 patients would be allocated to the CPSP group.

In contrast, no cut-offs for pain intensity are given in the ICD-11 definition of CPSP. Instead, it is emphasized that pain should have a significant impact on quality of life [19,36], which might reflect the complexity of pain, with not only its sensory dimension but additional psycho-social consequences. Not considering function or even the multidimensionality of persistent pain may lead to erroneous conclusions regarding the pathophysiological mechanisms involved, and thus lead to an inadequate treatment approach [19,36]. In the present analysis, PITS significantly varied between the groups with no, mild, moderate and severe pain. However, existence of CPSP does not automatically imply moderate or severe functional impairment. This underlines previous results showing that pain intensity and physical functioning are only moderately related [32].

**Pain-related interference and (neuropathic) CPSP**

Few working groups investigated sensory dysfunction, frequently interpreted as an indicator of neuropathic pain, in patients without CPSP [17,23,38]. However, quantitative sensory testing and pressure algometry in patients after inguinal herniotomy did not demonstrate differences between patients with, versus without, pain [23]. Hypoesthesia and tactile allodynia in the incisional area were detected in about half of the patients in both groups, showing low specificity of neuropathic symptoms for CPSP. Other authors described an association between self-reported sensory disturbances and CPSP, but no difference in QST measures in cohorts with and without CPSP [17]. The present results confirm sensory dysfunction in some patients with no pain; however, it has to be stated that the DN4 is not specifically validated in this patient group not reporting pain. The finding that DN4-positive CPSP resulted in higher PITS than DN4-negative CPSP underlines the fact that neuropathic pain is more disabling than pain without neuropathic symptoms [9,13,29]. Additionally, the negative impact of neuropathic symptoms on function was not restricted to patients with CPSP, but was also observed in patients with pain scores of NRS <3.

In some studies acute neuropathic pain after surgery and persistent chronic neuropathic pain were associated [13,22,25]. A positive DN4 during the immediate postoperative period seems to be a risk factor for neuropathic CPSP and adds to the list of other well-described variables associated with CPSP [2,22,25,29]. Thus, early detection and treatment of neuropathic pain within the first days after surgery might provide an opportunity to initiate early treatment in order to avoid later interference with function.

Prevalence estimates of neuropathic pain depend on the screening instrument used – either specific neuropathic questionnaires or more sophisticated neurophysiological methods [13]. No comprehensive physical examination is included in PAIN OUT. A misclassification of some subjects might be possible if only the DN4 is applied [13,30], although this instrument has been used successfully in previous trials [2,3,22,25]. Overall, the role of neuropathic pain questionnaires and their performance in the perioperative setting has to be clarified [13,30], and suitable instruments for assessing neuropathic symptoms as part of clinical routine should be defined.

**Variables associated with increased pain-related interference**

Regression analysis revealed roughly the same variables associated with high PITS as previously described for CPSP. Presence of pre-existing chronic pain before surgery is a well-recognized risk factor for CPSP [7,9]. The present data confirm an association with high PITS as well. There is disagreement over whether pain after surgery is a new instance of pain or a continuation of pre-existing chronic pain [20]. In the Tromsø study, 74.1% of the individuals having preoperative pain at the surgical site responded that chronic postoperative pain was not a continuation of previous pain, as the type of pain had changed [16]. In particular, patients undergoing joint replacement frequently report long-lasting preoperative chronic pain (e.g., osteoarthritis) at the surgical site [16].

Severe acute postoperative pain after surgery has often been often been linked to CPSP; however, as pointed out before, the duration of severe acute pain during the first 24 hours after surgery

proved to be more meaningful than pain intensity [9]. Particularly interesting is the interaction between sex and type of surgery. High PITS in males after neurosurgical back surgery are striking. We do not have any information on patients' occupational (physical) burden or disability (mean age of neurosurgical patients is 57). This may differ between males and females. As the overall number of neurosurgical patients was relatively small, results have to be verified in a larger cohort with a more detailed evaluation of patient characteristics.

**Limitations and strengths**

These registry data are based on patient-reported outcomes assessed by validated questionnaires. Some psychological factors – such as pain catastrophizing, pain expectation as well as pain sensitivity – were not considered, although they have previously been linked to high postoperative pain intensity and the development of CPSP. In addition, only clinical data of the first postoperative day were considered to assess acute pain. The investigated cohort underwent various surgical procedures, and results may differ for different surgical subgroups.

A large cohort of patients representing everyday clinical practice was analyzed, using the BPI. Its psychometric adequacy has been demonstrated in patients suffering from cancer and chronic non-cancer pain and it is recommended by IMMPACT [8]. Although the BPI was used to assess physical and emotional functioning after mastectomy in one study before [15], most previous trials focused on unidimensional pain assessment only, which does not fully reflect the complex interplay between biological, psychological and environmental factors [5]. In contrast, the BPI addresses one key aspect of recovery after surgery – the return to normal activities of daily living [26] – thus meeting the respective criteria mentioned in the ICD-11 definition.

## Conclusions

An analysis of registry data revealed that CPSP and a positive DN4 were independently associated with patients' increased pain-related functional interference six months after surgery. Future studies on CPSP should focus on pain-related functional interference instead of only pain scores. As a positive DN4 is an independent risk factor for increased PITS, also in patients with mild or no pain six months after surgery, we need better and earlier identification of patients with neuropathic symptoms.


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**Figure Legends**

**Figure 1**

**Flow chart with number (%) of patients.** CPSP, chronic postsurgical pain; BPI, Brief Pain Inventory.

**Figure 2**

**Pain Interference Total Scores of the BPI (PITS) six months after surgery.** (A) Patients with no, mild, moderate and severe average pain (ANOVA: $p<0.001$). The numbers beneath the x-axis represent the number of patients in each group. (B) Patients with no, mild, moderate and severe pain with either negative or positive DN4. Scatter dot plots with mean and 95% CI; dashed blue lines refer to the PITS of NRS=2 presenting the cut-off between mild and moderate pain related functional interference, and PITS of NRS=5 presenting the cut-off between moderate and severe pain related functional interference.

**Figure 3**

**Results of the BPI six months after surgery for patients without and with CPSP, either with negative or positive DN4.** (A) BPI pain scores, (B) BPI physical interference, (C) BPI affective interference. (D) Pain Interference Total Score (PITS) for the four groups, grey-tones refer to patients no CPSP/DN4-, with no CPSP/DN4+, with CPSP/DN4- and with CPSP/DN4+ (left to right). Box ($1^{st}/3^{rd}$ quartiles and median), whiskers (10-90% percentile), +: mean NRS score. * $p<0.05$; ** $p<0.0001$ refer to comparison of CPSP with negative versus positive DN4, corrected for multiple testing (15 tests).

**Table 1**: Patient characteristics, surgery-related and anesthesia-related data of patients with CPSP or without CPSP six months after surgery.

| | | No CPSP | CPSP | p [a] |
|---|---|---|---|---|
| Females | n (%) | 1289 (86.0) 678 (82.4) | 210 (14.0) 145 (17.6) | 0.021 |
| Males | n (%) | 51.8 (51.1-52.5) 81.9 (80.9-83.0) | 51.7 (50.1-53.4) 81.3 (79.1-83.5) | 0.887 0.627 |
| Age | years | 169.3 (168.9-169.7) | 169.7 (168.8-170.6) | 0.360 |
| Weight | kg | | | |
| Height | cm | | | |
| **Patients' history** | | | | |
| Patients with pre-existing chronic pain [b] | | | | |
| Yes | n (%) | 704 (36.1) | 238 (67.2) | <0.001 |
| No | n (%) | 1247 (63.9) | 116 (32.8) | |
| Pain scores [c] | NRS | 6.0 (4.0/8.0) | 7.0 (5.0/8.0) | <0.001 |
| Opioids before surgery [d] | n (%) | 65 (3.3) | 36 (10.3) | <0.001 |
| Substance abuse [e] | n (%) | 29 (1.4) | 9 (4.2) | 0.002 |
| Affective disorders [e] | n (%) | 144 (8.6) | 32 (10.6) | 0.252 |
| **Surgical group** | | | | |

| | | | | |
|---|---|---|---|---|
| General surgery [f] | n | 826 (90.4) | 88 (9.6) | <0.001 |
| (%) | | 493 (75.5) | 160 (24.5) | |
| Orthopedic surgery | n | 585 (89.0) | 72 (11.0) | |
| (%) | | 63 (64.3) | 35 (35.7) | |
| Gynecology | n | | | |
| (%) | | | | |
| Neurosurgery | n | | | |
| (%) | | | | |
| **Duration of surgery** min | | 144.6 (140.6-148.5) | 150.1 (141.5-158.7) | 0.382 |

Data presented as n (%), mean (95% CI) or median NRS ($1^{st}/3^{rd}$ quartile). Data refer to 2322 questionnaires if not otherwise indicated. a: $\chi^2$ test, T-test or Mann-Whitney U test; b: refers to 2305 patients; c: refers to patients reporting chronic pain before surgery, d: refers to 2302 patients; e: refers to 1930 patients; f: includes thoracic surgery, CPSP for thoracic surgery 15.9%.

**Table 2:** Results of the multivariate ordinal regression analysis. Patients (n=1495) were allocated to PITS groups (no to mild functional interference, moderate interference, severe interference).

| **Variables** | **OR** | **95% CI** | **P** |
|---|---|---|---|
| Pre-existing chronic pain: yes vs. no (reference) | 3.61 | 2.56-5.08 | <0.001 |
| Preoperative opioids: yes vs. no (reference) | 1.47 | 0.83-2.58 | 0.178 |
| Duration of surgery (min) | 1.002 | 1.000-1.004 | 0.020 |
| Time in severe pain D1 (%) | 2.90 | 1.32-6.39 | 0.008 |
| Satisfaction with pain treatment D1 (NRS) | 0.95 | 0.88-1.03 | 0.181 |
| Pain relief D1 (%) | 1.21 | 0.59-2.49 | 0.593 |
| Desire for more treatment D1: yes vs no (reference) | 0.95 | 0.57-1.58 | 0.836 |
| Pain interferences composite score, D1 (NRS) | 1.06 | 0.96-1.17 | 0.237 |
| Feel anxious D1 (NRS) | 1.11 | 1.03-1.19 | 0.005 |
| Feel helpless D1 (NRS) | 0.96 | 0.89-1.03 | 0.228 |
| Adverse events D1 (number of episodes) | 1.05 | 0.96-1.14 | 0.239 |
| Younger age (years) | 1.01 | 1.001-1.02 | 0.033 |
| BMI ($kg/m^2$) | 1.01 | 0.98-1.03 | 0.566 |
| General surgery & male (reference) | 1 | | |
| General surgery & female | 0.484 | 0.276-0.850 | 0.012 |
| Gynecological surgery & female | 0.755 | 0.432-1.319 | 0.324 |
| Orthopedic surgery & male | 1.383 | 0.829-2.308 | 0.214 |
| Orthopedic surgery & female | 1.772 | 1.038-3.023 | 0.036 |
| Neurosurgery & female | 1.889 | 0.861-4.144 | 0.113 |
| Neurosurgery & male | 3.565 | 1.686-7.538 | 0.001 |

D1; first postoperative day

**Table 3**: Number (%) of patients allocated to the groups with no (PITS=0), mild (PITS >0 and <2), moderate (PITS 2-5) and severe pain-related functional interference (PITS >5) taking analgesics according to WHO classification I-III, taking co-analgesics, having physiotherapy and/or other measures six months after surgery.

| **Functional interference** | **None** n=1423 | **Mild** n=485 | **Moderate** n=291 | **Severe** n=117 |
|---|---|---|---|---|
| Analgesics [a] n (%) | 35 (2.5) | 105 (21.6) | 172 (59.1) | 90 (76.9) |
| | 31 (2.2) | 98 (20.2) | 129 (44.3) | 58 (49.6) |
| WHO I | 0 (0.0) | 3 (0.6) | 18 (6.2) | 6 (5.1) |
| WHO II | 4 (0.3) | 4 (0.8) | 22 (7.6) | 25 (21.4) |
| WHO III | 0 (0.0) | 1 (0.2) | 16 (5.5) | 7 (6.9) |
| Co-analgesics [b] | 4 (0.3) | 31 (6.4) | 37 (12.7) | 8 (6.8) |
| Physiotherapy [b] | 1 (0.07) | 10 (2.1) | 5 (1.7) | 8 (6.8) |
| Others, e.g. acupuncture [b] | | | | |

Of the 2322 patients with completed BPI, six did not provide information on analgesic therapy. Thus, data refer to 2316 patients. Multiple answers were possible. a: refers to WHO analgesics and co-analgesics; b: alone or in combination.

**Figure 1**