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Preoperative Psychosocial and Psychophysical Phenotypes as Predictors of Acute Pain Outcomes after Breast Surgery

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Abstract

The severity and impact of acute pain after breast surgery varies markedly among individuals, underlining the importance of comprehensively identifying specific risk factors, including psychosocial and psychophysical traits. In this prospective observational study, women (n=234) undergoing breast-conserving surgery, mastectomy, or mastectomy with reconstruction completed a brief bedside quantitative sensory testing (QST) battery, along with measures of psychosocial characteristics. Postoperative pain severity, impact, and opioid use at 2 weeks were assessed using Brief Pain Inventory (BPI) and procedure-specific breast cancer pain questionnaires. Moderate-severe average pain (>3/10) was reported by 29% of patients at 2 weeks. Regression analysis of pain outcomes revealed that *pain severity* was independently predicted by axillary dissection, pre-surgical pain, temporal summation of pain (TSP), (–)positive affect, and behavioral coping style. *Pain impact* was predicted by age, education, axillary dissection, reconstruction, but also by negative affect and depression scores. Lastly, *opioid use* was predicted by age, education, axillary dissection, reconstruction, TSP and reinterpreting coping style. Our findings suggest that, individuals with certain phenotypic characteristics, including high TSP and negative affect may be at greater risk of significant pain and continued opioid use at 2 weeks after surgery, independent of known surgical risk factors.

Keywords

temporal summation of pain; mastectomy; postsurgical pain; depression; opioid analgesia

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Introduction

The effective and safe management of postsurgical pain is an important clinical goal, as an estimated 240 million surgeries are performed each year worldwide.⁶⁰ Despite increased recognition of acute⁴¹ and chronic³⁴ postsurgical pain, and much excellent study of the mechanistic underpinnings of postsurgical pain,⁷ acute postsurgical pain remains a problem²¹ for a significant minority of patients. In a recent large study in a variety of surgical types, 28% of patients (of 22,000 patients studied) still experienced moderate-severe acute pain after surgery,²⁴ and a sizable number of patients remain on long-term opioids months after orthopedic surgery.¹⁰ *Persistent* postsurgical pain development can occur after mastectomy or lumpectomy^{6, 22, 53} in a minority of patients (20–30%), and is strongly associated with acute postoperative pain,^{5, 37, 38} making the perioperative period a critical period of surveillance and potential intervention for the over 200,000 women who are diagnosed with breast cancer (BC) each year in the US, most requiring at least one surgical procedure to manage BC.¹⁸

Individual patients may experience a highly variable amount of pain, despite receiving a relatively standard painful stimulus (surgery).¹⁹ The biopsychosocial model of pain²³ acknowledges the contribution not only of *biological* differences between people, but also the *psychological* and *social* context of the pain experience. We are interested in the practical measurement of biopsychosocial phenotypes, assessed in the preoperative period, to enhance the prediction of the postsurgical pain trajectory.^{6, 52} For example, a “psychosocial phenotype” including such characteristics as enhanced negative affect, anxiety, depression, sleep disturbance, and maladaptive coping (catastrophizing) has previously been associated with greater acute pain after mastectomy.^{32, 33, 36, 42, 47} Similarly, individuals may vary in terms of how they process nociceptive stimuli, or “psychophysical phenotype”; that is, how severe and impactful a defined painful stimulus feels to them. Quantitative sensory testing (QST) systematically characterizes psychophysical responses,⁴⁹ and enhanced sensitivity on QST may be used to predict greater postsurgical pain.⁶² One particular sensory test that has shown promise is the Temporal Summation of Pain (TSP),⁵¹ which has been associated with both acute^{1,43} and chronic^{17, 44, 53} post-surgical pain.

Previous retrospective and some prospective studies have investigated risk factors for *acute* postsurgical pain, identifying younger age, female gender, preoperative pain, surgical extent, and higher anxiety as predictive.^{24, 31, 57} Given these demographic risk factors, and the prevalence of breast cancer, breast surgery is an important surgical subset for further investigation. The current study involves a pragmatic, but concise and systematic measurement of phenotypic predictors, followed by multidimensional assessment of pain-related outcomes after breast surgery, as recommended in recent consensus statements.^{15, 35} Specifically, we investigated the predictive capacity of a wide-ranging set of potential risk factors, including previously identified variables such as age and the type and extent of surgery, as well as a targeted assessment of psychosocial and psychophysical phenotype. We hypothesized that, in addition to established risk factors, individual differences in psychosocial functioning (e.g., high levels of negative affect) and psychophysical phenotype (e.g., elevated indices of sensitization) would uniquely contribute to predicting adverse pain-related outcomes following breast surgery.

Materials and Methods:

Enrollment

This prospective, observational study was approved by the Partners Healthcare/ Brigham & Women's Institutional Review Board. Female patients age 18–85 scheduled to undergo breast conserving surgery or total mastectomy with or without reconstruction, and with or without axillary evaluation, were recruited from the Weiner Center for Preoperative Evaluation (Anesthesia preoperative clinic) between 9/2014–3/2017. Patients were given basic information about the study and asked if they would be willing to learn more about it. If patients consented to be in the study, initial 5–10 minute quantitative sensory testing was performed, and they were sent initial baseline questionnaires (demographic, medical, validated psychosocial, and validated baseline pain) via secure email link to the REDcap data entry system. Patients were included in subsequent follow-up if these questionnaires were completed before the time of surgery.

General approach

In the design of this study, we considered elements appropriate to the development of a prediction model:⁴⁰ 1) prospective assessment, 2) predictors measured in isolation of outcomes, 3) inclusion of a variety of patients and surgical types in order to be generalizable, 4) simultaneous measurement of previously known risk factors together with newly identified potential risk factors, recognizing that these factors likely interact, and 5) adequate powering for a single, contextual, multivariate assessment of pain.

Surgical procedures and factors

The majority of patients enrolled were diagnosed with invasive breast cancer (77%) or Ductal Carcinoma In Situ (DCIS) (15%) and most underwent image-guided core biopsy within the month before surgery. A history of some previous breast surgery was determined (previous breast conserving surgery on the ipsilateral or contralateral side, contralateral mastectomy, or excisional biopsy on the ipsilateral or contralateral side). Patients underwent breast conserving surgery (lumpectomy/partial mastectomy), total mastectomy, or total mastectomy with reconstruction, performed by surgeons with specialty in breast (11) and/or plastic (12) surgery. Tissue expander placement comprised the majority of reconstructions. Patients were categorized as having no nodal procedure, sentinel node biopsy, or axillary dissection. Duration of surgery and surgical complications requiring immediate repeat surgery (e.g. hematoma) were recorded.

Anesthetic treatment and factors collected

Many patients received preoperative anxiolysis with midazolam (79%) followed by either general anesthesia (GA, 96.1%) or sedation (3.9%). Approximately 40% of patients had a primarily propofol-based anesthetic (>800 mg). Surgeons subcutaneously injected local anesthetic (0.25% bupivacaine) at the incision site at end of the surgery in 70% of cases. As per the practice in our institution, regional anesthesia (RA) (paravertebral or proximal intercostal blockade, $\pm$ pectoralis nerve block) was offered primarily to those undergoing mastectomy or mastectomy with reconstruction, with 25.5% of patients receiving RA.

Receipt of RA was dependent on stochastic factors such as timing of the surgery, discretion of anesthesiologists and surgeon, and availability of regional anesthesia specialists. Use of other anesthetic and analgesic agents were according to current practice and judgment of anesthesia providers, including perioperative opioid analgesics most commonly including fentanyl, hydromorphone, and morphine, and were recorded, as were non-opioid analgesics (including celecoxib (17.8%), gabapentin (13.9%), and ketamine (8.1%).

Pain and related factors measurement

Taking into account the 5 core criteria identified for the study and measurement of acute pain,³⁵ the following pre- and post-surgical assessment methods were used:

Definition of acute post-mastectomy pain (Criterion 1)—We defined significant acute pain after breast surgery as pain >3/10 (on a 0–10 rating scale) based on this being a common point of analgesic intervention, experienced in the area of the surgery including the breast, axilla, upper arm, or side of body, in the 2 weeks following lumpectomy or mastectomy, with or without reconstruction and axillary nodal procedure. Pain on the day of surgery (POD0) was collected verbally from patients in the post anesthesia care unit (PACU). Postoperative day 1 (POD1) pain scores were collected either in person if patients were in hospital or via email link from home for day surgery patients. Pain at 2 weeks was assessed by completion of questionnaires (see Domain 4 below) sent via email through REDCap system.

Common features of acute post-mastectomy pain (Criterion 2)—Surgical and anesthetic variables were collected as outlined above, recognizing the importance of subgrouping surgical procedures according to the extent of surgery. Surgical subgroups were defined as breast conserving surgery, mastectomy, and mastectomy with immediate reconstruction procedure. Node procedure categories were defined as none, sentinel node procedure, and axillary dissection.

Potential modifying factors of acute pain (Criterion 3)—Taking into account the biopsychosocial model of pain, we assessed many modulating factors, both in advance of and during the surgical procedure.

Biological: We assessed patient characteristics at the time of surgery including age, body mass index (BMI), typical amount of weekly exercise (1 point per each 15 min of mild, 2 point per each 15 min of moderate, 3 points per each 15 min of intense exercise in an average week), preexisting pain in the planned surgical area, and chronic pain in other body areas, via baseline questionnaire and from electronic medical record. Baseline general pain sensitivity was assessed using 2 brief, portable quantitative sensory tests:

1. Temporal Summation of Pain (TSP) and Painful after-Sensations (PAS): Mechanical pinprick pain was assessed as in our previous studies,^{17, 53} using standardized weighted pinprick applicators similar to those described by Rolke et al.⁴⁹ First, a single stimulation of the lowest force (128mN) pinprick was applied to the dorsal aspect of the index finger between the first and second interphalangeal joints of the left hand while resting the palm

facing downward on a flat surface. The subject then rated the pain intensity from the mechanical stimulus on a scale of 0–10. If this was rated as 0–1, the next highest force probe was tested as a single application. One of 3 designated force (128, 256 and 512mN) probes was selected: specifically, the lowest force probe to result in a mildly (1–3) painful sensation with a single application. Next, after a break of at least 10 seconds, a train of 10 stimuli was applied at the same location, at a rate of 1 stimulation/second. The subject rated pain on a scale of 0–10 after the first, fifth and tenth stimulus. After this train of stimuli, patients were asked to rate any ongoing pain remaining 15 seconds after cessation of the last stimulus (PAS), on a scale of 0–10. The same procedure was repeated on the right index finger and the third finger of the each hand, alternating sides of testing. Temporal summation of pain was calculated as the pain rating in response to the 10th stimulation minus pain rating in response to the 1st stimulation. This was calculated for each of the four finger sites and averaged.

2. Pressure pain testing methods: Pressure pain threshold and tolerance were assessed in a similar manner to our previous studies⁵³ using a digital pressure algometer (Wagner FDX, Greenwich, CT, USA) with a flat round transducer, probe area 0.785 cm². Testing sites were bilateral on the dorsal aspect of the proximal forearm approximately 3–4 cm distal to the elbow crease (extremity site) and over the trapezius muscle at the upper back approximately 2–3 cm above the scapular spine, midway between C7 prominence and humeral head (truncal site). For *pressure pain threshold* determination, pressure was increased at a steady rate of approximately 1 lb/second (0.45 kg/second) and the subject was asked to indicate when this pressure first became painful. The pressure was further increased and the subject was asked to indicate when the pain from the stimulus was no longer tolerable (*pressure pain tolerance*). Two trials were performed at each site, alternating from side to side and between extremity and truncal sites.

Psychological: Questionnaires assessing psychosocial factors were chosen based upon previous retrospective association with postoperative pain and opioid use, strong psychometric validation characteristics, and brevity. The Pain Catastrophizing Scale (PCS), which has been validated in pain patients and controls,⁵⁵ was used to measure catastrophic thinking associated with pain. Depressive symptoms, anxiety and sleep disturbance were assessed using short-form instruments from the NIH roadmap initiative, Patient Reported Outcome Measurement Information System (PROMIS), which have been extensively validated in studies comparing results with established scales, and have been calibrated on over 20,000 persons.¹² The Brief Symptom Index 18-Somatization Scale, also previously validated in pain patients,¹⁴ was used to measure somatization. The Positive Affect Negative Affect Scale (PANAS)⁵⁹ was also used. Specific coping strategies preference was also assessed using the short form of the Coping Strategies Questionnaire (CSQ).^{48,29}

Social: Ethnicity and highest educational training (1=some high school, 7= doctoral degree(s)) were assessed via questions on the baseline demographic questionnaires.

Domains of pain measurement (Criterion 4)—Several instruments were used to measure pain and its impact at baseline and following surgery: 1) A simple numerical rating

scale (NRS) was used to assess current pain at rest and with movement, as is commonly done in the course of clinical care in the perioperative period to make decisions about analgesic administration. Of note, the mode of NRS on postoperative day 1 was primarily in person for some surgical types (mastectomy with reconstruction) and electronic for others (lumpectomy and some mastectomy patients, depending on their location (hospital vs home). 2) In order to compare to other studies of acute pain, the Brief Pain Inventory (BPI) was used as our primary measure of pain at 2 weeks. The BPI instrument assesses the patient's current pain, least pain during the last week, worst pain during the last week, and self-reported average pain over the last week, with these 4 scores being averaged to give the BPI score. 3) Recognizing that pain severity, frequency, duration, and area are all important to the experience of pain, we also used the Breast Cancer Pain Questionnaire (BCPQ), first used by Gartner et al²² and in subsequent studies^{4, 53} which refers questions about pain severity and frequency directly *to the surgical area*, and distinguishes different areas that may be involved. A Pain Burden Index (PBI) can be calculated from these responses by summing the pain severity scale (0–10) at each of four locations (breast, axilla, chest wall, arm) multiplied by the frequency of the pain at each site (constantly – 5 points, daily – 4 points, occasionally – 3 points, weekly – 2 points, monthly – 1 point, and never – 0 points), thus $PBI = \sum [\text{Pain severity at each site} \times \text{frequency}]$. The expanded version of this questionnaire also includes items to estimate sensory disturbance in, function impact of, and analgesic use for pain specifically in these areas as follows:

Sensory disturbances in surgical area: Subjects reported on the BCPQ whether or not they experienced various types of sensory disturbance in the surgical area at 2 weeks after surgery, ranging from hypoesthesia (numbness, pins and needles), to spontaneous pain (painful itch, burning, electric shock sensation), to hyperalgesia and allodynia (cold pain, pain with light pressure or rubbing)(all items listed in Table 2).

Pain impact: Subjects also reported on the BCPQ the degree to which pain and discomfort in the area of surgery interfered with function including aspects of individual, social, cognitive, and emotional functioning (14 questions with ratings of how frequently difficulty experienced because of pain, see Appendix 1). These responses were summed to give a pain impact score.

Analgesic use: Subjects answered several questions, including whether they were taking any analgesics, whether they were taking these analgesics primarily for surgery-related pain, and the type of analgesic used.

Consideration of pain mechanisms (Criterion 5)—We asked patients to report presence of various sensory disturbances in the surgical area (sensory disturbance score, described above), as nervous system injury and dysfunction has previously been associated with and theorized as a potential underlying mechanism of more severe and persistent pain. Similarly, we assessed general tendency towards central sensitization using baseline QST, as well as psychosocial contributions.

Statistical analysis

Patient characteristics in different surgical groups were summarized using frequencies and percentages for categorical variables, median values with interquartile ranges (Q1–Q3) for continuous variables. The continuous variables that satisfied Shapiro-Wilk for normality test were summarized using mean values and standard deviations. Variation in simple NRS pain scores over time, state (rest, movement), and between surgical categories was investigated using repeated measures ANOVA.

Pain severity at 2 weeks was evaluated by defining a dichotomous variable “moderate-severe pain”, which was equal to 1 when pain on BPI at POD 14 was ≥ 3 , and 0 if it was ≤ 2 . Pain impact score was the sum of responses to 14 items of the BCPQ (Appendix 1), and opioid use was defined as 1) reporting use of opioid-type medication at POD 14 2) for pain 3) in the surgical area. The prediction model for each of the three outcomes was built separately using the corresponding cohort.

The univariate associations between the predictors and the three outcomes (pain severity, pain impact, opioid use) were examined using Wilcoxon rank-sum test, Chi-square test, Fisher’s exact test, Kruskal-Wallis rank-sum test, or test for Spearman correlation, as appropriate. Predictors with p -value < 0.1 on univariate testing (indicating reasonable correlation with outcome), as well as having variance inflation factor less than 2.5 (as an assessment of colinearity between related variables) were included in the initial regression models.² In order to manage missing data, imputation was performed using multivariate imputation by chained equations (MICE) with 20 imputed datasets. The numbers of complete observations for each predictive factor are indicated in Tables 4, 6, and 8, unless there were no missing values for the variables in the corresponding cohort. Logistic regression and multiple linear regression were applied on the imputed datasets, and backward variable selection was used based on having p -value < 0.05 . The final models were from the pooled results from 20 imputed datasets, for each outcome respectively. To correct the over optimistic performance of the logistic models, 1000 bootstrap samples were drawn from the corresponding original cohort (Moons, et al. 2012). Both the uncorrected and corrected performance criteria including area under the curve (AUC) and Brier score of the models were reported for logistic models. AUC was used as a discrimination measure of how well the model could distinguish the two groups, while the Brier score was calculated as a calibration measure for the accuracy of the predicted probabilities. Imputation was performed using R package mice version 2.46, and all analyses were performed in R 3.4.1. All statistical tests were two-tailed with $\alpha = 0.05$. Required sample size was based on our previous cross sectional data,^{6, 17} in which roughly 35% of patients experienced clinically significant pain after breast surgery. We calculated effect sizes between pain and no pain groups for each of the psychosocial and psychophysical variables, which ranged from 0.06 to 0.70. We calculated that to detect effect sizes of 0.40 or greater, assuming 80% power and two-sided alpha level of 0.05, we would need at least 200 subjects.

Results:

Description of study sample

Women scheduled to undergo breast conserving surgery (BCS) or total mastectomy were approached at the preoperative evaluation clinic, with approximately 70% initially giving consent to participate. Of those who consented, 77% completed baseline preoperative questionnaires (n=259) sent via electronic mail link, and 80% of those completed all (n=208), and 90% completed at least some pain questionnaires at 2 weeks (n=234) (Figure 1). Two week questionnaires were sent at exactly 14 days, and if no response was obtained, a reminder email was sent after 2 days, and mean time of response to these questionnaires was 16.1 ± 3.9 days after surgery. All patients were female, with a mean age of 55.5 ± 12.3 , and were predominantly Caucasian (86.5%). Surgical indication was primarily invasive cancer (77%), but also included DCIS (15%), prophylactic mastectomy (4.5%), and benign lesions (3.5%).

Demographic, surgical and anesthetic factors

Table 1 compares baseline characteristics in three broad surgical groups (BCS, total mastectomy and total mastectomy with immediate reconstruction). There was a significantly lower age and BMI amongst those undergoing mastectomy with reconstruction, and these patients were more likely to be premenopausal. Previous breast surgery (including biopsy) was present in 38% of patients, and this was less common in patients undergoing BCS (Table 1). A larger proportion of those undergoing BCS also had a sentinel node procedure, and total surgical duration was lower amongst these patients. Importantly, there were no significant differences between the three surgical categories in terms of frequency of concurrent axillary dissection, although this was relatively uncommon (n=33). The majority of patients received a general anesthetic, while the remainder receiving regional/monitored anesthesia care (MAC) alone. Perioperative analgesia included intravenous opioids including fentanyl, hydromorphone, remifentanyl, and sufentanil, according to the anesthesia provider's choice. A minority of patients also received COX-2 inhibitors (celecoxib) (46), gabapentin (36), and ketamine (21). None of these medications were significantly associated with pain severity at any study time point. Regional anesthesia (RA) in combination with general anesthesia was available only to a subset of patients (mastectomy or mastectomy with reconstruction), and thus was differently represented amongst the surgical groups. The impact of RA in this smaller subset of patients is examined in a separate analysis. Not surprisingly, given the greater duration and extent of surgery, perioperative opioid utilization was higher amongst patients having mastectomy with or without reconstruction.

Psychosocial characteristics

Baseline psychosocial characteristics (Table 1) were notable for relatively low mean values for catastrophizing (mean $\pm$ SD: 5.7 ± 6.4), and higher than average anxiety (t score: 55.8 ± 7.5), but ratings of depressive symptoms (t score: 48.2 ± 7.1) and sleep disturbance (t score: $50.5.2 \pm 8.9$) were similar to population average (t score =50). Baseline psychosocial traits including pain catastrophizing, anxiety, depression, somatization, sleep disturbance, positive and negative affect, and predominant pain coping strategies did not differ between

breast conservation surgery, mastectomy, and mastectomy with reconstruction groups ($p>0.05$, Table 1).

Psychophysical characteristics

We used a brief, portable set of quantitative sensory tests (QSTs), including pressure threshold and tolerance testing and temporal summation of pain, similar to previous studies^{17, 53}. We observed a variable degree of sensitivity to pressure pain at non-surgical sites (forearm and trunk) among participants (Table 1). The group scheduled for mastectomy with immediate reconstruction (which also had a younger age) exhibited higher forearm pain threshold and tolerance at baseline. Temporal Summation of Pain with a repeated pinprick stimulus, and incidence of painful after-sensations after this repeated painful stimulus varied substantially among subjects (Table 1), but no differences in TSP, PAS, and truncal site (trapezius) pressure pain threshold and tolerance were observed between surgical groups.

Pre- and post-surgical pain

Intercorrelation of pain measures and baseline pain: Several instruments were used to measure pain and its impact at baseline and following surgery. Reported pain scores using these various instruments were significantly intercorrelated, both between scales and across timepoints. Although many patients reported some baseline pain in the surgical area in the last month, only 7.5% rated their baseline pain as moderate to severe in the previous week. Few subjects reported taking opioids for pain at baseline ($n=13$).

Postoperative Pain Intensity, Extent, and Location: Postoperative pain severity (Figure 2A), pain location (Figure 2B), and Pain Burden Index (PBI) (Figure 2C) varied among subjects. Pain severity at 2 weeks after surgery increased significantly from preoperative levels for any given subject (paired t test BPI ave $t=-9.8$ (208), $(-1.5, -1.0)$, $p<0.001$, paired t test PBI $t=-11.6$ (233) $(-23.5, -16.7)$). Reported pain location was primarily the breast and axilla, although pain was also reported in upper arm and side (Figure 2B). On the day of surgery (2 hours after end of surgery, post operative day (POD)0), 20% and 55% reported moderate-severe pain (at rest and with movement, respectively). Interestingly, pain at rest was reported as moderate-severe by a higher proportion on POD1 (40%) while pain with movement was reported as moderate-severe in a similar proportion (48%).

Pain in different surgical subtypes: Figure 3 shows pain severity (NRS) at different times after surgery amongst different major surgical groups: breast conserving surgery (BCS), total mastectomy, and total mastectomy with reconstruction. In order to investigate differences in pain experienced by these surgical groups over time in the acute-subacute period (baseline, post operative day POD0, POD1, POD14) and in different states (rest or movement), we used a repeated measures ANOVA. There was a significant main effect for surgical type ($F=10.6$ ($df=2$), $p<0.001$, with higher pain scores amongst those having more extensive surgery, and also a main effect for axillary dissection ($F=4.3$ ($df=1$), $p<0.039$). There was a main effect of movement ($F=151$ ($df=1$), $p<0.001$). There were also significant 2-way interactions for time and surgical type ($F=4.1$ ($df=6$), $p=0.001$), movement and surgical type ($F=4.7$ ($df=2$), $p=0.01$) and a three-way interaction for time $\times$ surgical type $\times$ movement

($F=3.5$ ($df=6$), $p=0.002$), suggesting that more extensive surgeries are associated with longer lasting acute pain and more pain with movement, within the first 2 weeks after surgery.

Pain-related outcomes: sensory disturbance and pain impact: To further characterize the pain experienced at 2 weeks after surgery, subjects were also asked to report sensory disturbances, ranging from negative symptoms (numbness) to positive symptoms (hyperalgesia) in the surgical area (Table 2). There was a significant positive correlation between reported overall pain severity (BPI) and degree of sensory disturbance (Spearman $Rho .499$, $p<0.001$) (Figure 4A).

Subjects reported the degree to which pain and discomfort in the area of surgery interfered with various aspects of individual, social, cognitive, and emotional functioning (14 questions on BCPQ, rating how frequently difficulty experienced because of surgical pain, see Appendix 1). This pain impact score (mean 22, range 14–56) was also significantly associated with pain severity (Spearman 0.552 $p<0.001$) (Figure 4B). Sensory disturbance score did not significantly differ between main surgical groups (mean $\pm$ SD: BCS: 3.7 ± 2.0 , Mastectomy: 3.6 ± 2.3 , Mastectomy with Reconstruction: 4.4 ± 2.5 , Kruskal-Wallis ANOVA, $p=0.06$), but was significantly higher for those who had axillary dissection (mean $\pm$ SD: 5.0 ± 1.7) than sentinel node (3.9 ± 2.3) or no axillary surgery (3.3 ± 2.0) (Kruskal-Wallis ANOVA, $p=0.002$).

Predictors of pain severity, pain impact, and opioid use at 2 weeks after surgery

Pain severity: We were interested in assessing pain at 2 weeks after surgery, as this may represent an important turning or inflection point, when patients follow-up with providers, and expectations are that pain has mostly resolved. Approximately 30% of subjects reported moderate to severe pain ($>3/10$) at 2 weeks (BPI). Table 3 shows the univariate analysis of association of preoperatively measured variables with moderate-severe pain (BPI $>3/10$) at 2 weeks. Among demographic variables, younger age and higher BMI were associated with moderate-severe pain, as was higher baseline pain. Axillary dissection was associated with moderate-severe pain, but surgical subtype was not. Higher baseline depression, sleep disturbance, and somatization were also associated with moderate-severe pain, as were higher values on several pain coping scores including catastrophizing, praying, and behavioral coping strategies. Positive affect was inversely associated with moderate-severe pain. Among the psychophysical tests, both Temporal Summation of Pain (TSP) and Painful After-Sensations (PAS) were associated with moderate-severe pain, while pressure pain threshold at both sites was not, and pressure pain tolerance at the truncal site was only weakly associated (Table 3).

Logistic regression was performed to assess factors that *independently* predicted moderate-severe pain ($>3/10$) (Table 4). Axillary dissection, baseline pain and interference were predictive, as was lower positive affect, higher behavioral coping score, and higher TSP (Table 4). More specifically, having axillary dissection increased the odds of having moderate-severe pain (OR: 4.42), while positive affect (PANAS) decreased odds of moderate-severe pain (OR: 0.93). BPI interference (OR 1.04), TSP (OR 1.36), and

behavioral coping (OR 1.21) also increased odds of having moderate-severe pain. The unadjusted area under the curve (AUC) and Brier score were 0.8057 and 0.1550, respectively. The bootstrap-adjusted AUC and Brier score were 0.7803 and 0.1696.

Pain impact: Subjects were asked to rate the impact of pain in the surgical area on several aspects of normal functioning, including items related to affect, ability to concentrate, relate with others, and participate in valued activities (see Appendix 1). Table 5 shows the univariate analysis of preoperatively measured variables that were significantly correlated with greater pain impact, including preoperative pain, age, and many psychosocial and surgical variables. Again, to assess factors that independently predicted impact of pain, a subsequent multivariable linear regression was performed (Table 6). Amongst demographic variables, age (−0.12) and educational level (0.59) were independent predictors of pain impact. Baseline pain severity (0.77), presence of reconstruction (2.89), axillary dissection (2.91), as well as higher depression (0.41), and negative affect (0.24) were also independently associated with greater pain impact at 2 weeks. The linear regression model had adjusted R-squared of 0.44¹¹.

Opioid utilization at 2 weeks after surgery: Subjects were asked about their analgesic use at two weeks, with 129 reporting some analgesic use, and 62 reporting taking opioids for surgical-related pain. This included 5 who had been taking opioids for pain related to their breast cancer preoperatively, and 2 who had been taking opioids for another reason preoperatively. On univariate analysis, age, menopausal status, lower education, and race were associated with opioid use at 2 weeks, as were baseline pain severity and baseline opioid use, but other chronic pain was not (Table 7). Concurrent reconstruction or axillary dissection were both associated with higher rates of opioid use (Table 7, Figure 5). Many psychosocial factors were associated with opioid use, including baseline catastrophizing, depression, anxiety, sleep disturbance, and affect, as were certain pain coping strategies. There was also an association of temporal summation of pain with opioid use, but other psychophysical tests were not associated (Table 7).

In order to determine independent predictors of opioid use at 2 weeks, logistic regression was performed (Table 8). Lower age (OR: 0.96) and education (OR: 0.72), higher baseline pain severity (OR: 1.22) and opioid use (OR: 18.63), mastectomy surgery with reconstruction (OR: 2.88), and axillary dissection (OR: 4.22) were all independently predictive of opioid use at 2 weeks (Table 8). In addition, psychosocial variables including preoperative depression score (OR: 1.11), and reinterpreting coping style (OR: 1.17), as well as higher baseline temporal summation of pain (OR: 1.24) were also independently predictive of opioid use at 2 weeks (Table 8). The unadjusted area under the curve (AUC) and Brier score were 0.8377 and 0.1376, respectively. The bootstrap adjusted AUC and Brier score were 0.8032 and 0.1566.

Discussion:

In this prospective observational study, we used comprehensive preoperative patient phenotyping to identify independent predictors of pain and opioid outcomes in the first 2 weeks after breast surgery. As in previous studies, preoperative pain, younger age, and

surgical factors accounted for some of the variance in the experience of postoperative pain. In addition, specific psychosocial variables, most notably affect and depression, were also independently predictive of pain severity, impact and opioid use. Interestingly, a simple preoperative bedside assessment of mechanical temporal summation of pain (TSP) was also an independent predictor of moderate-severe pain severity and opioid use at 2 weeks.

Temporal Summation of Pain (TSP)

QSTs like TSP have been used to characterize the psychophysical profile of patients with chronic pain, with TSP being higher among chronic pain patients relative to pain-free controls. Both static (e.g., pain thresholds) and dynamic (e.g., repeated stimulation paradigms such as TSP) QSTs have been associated with greater postsurgical pain, accounting for up to 50% of the variance between patients,⁶² although the overall predictive value has been somewhat mixed.^{46, 51} In particular, dynamic sensory tests reflecting an individual patient's balance of endogenous inhibitory (e.g. Conditioned Pain Modulation (CPM))⁶⁴ and facilitatory (e.g., TSP) pain-modulatory mechanisms⁵¹ may help predict responses to postsurgical pain.

Previous studies of *persistent* postsurgical pain have investigated TSP using several modalities (heat, mechanical stimulation), testing in both surgical and nonsurgical areas. Mechanical TSP on the affected knee predicted chronic pain after knee arthroplasty,⁴⁴ on the thigh predicted pain after hip arthroplasty²⁸, and on previous Cesaerean-Section scar predicted subsequent acute pain after repeat C-section⁴³. Similarly, mechanical TSP on the hand^{17, 53} showed an independent association with chronic pain after breast surgery. Importantly, in previous studies of *acute* postoperative pain, TSP assessed using a mechanical stimulus (but not a heat stimulus) predicted acute post-thoracotomy pain.⁶¹ TSP evoked by a prolonged pressure stimulus also independently predicted post-knee arthroplasty pain and opioid utilization.¹ Interestingly, in a recent study of acute post mastectomy pain, investigators found that CPM, but *not* TSP, was predictive of worst pain 1 day after surgery, and only amongst those without preexisting pain.⁵⁰ Important methodological differences, which may explain this apparent discrepancy from the current study include that Ruscheweyh and colleagues assessed TSP on the forearm with only a single weight mechanical probe (256mN), calculated a windup ratio, predicting worst pain at 1 day after surgery rather than average pain score at 2 weeks. From a practical standpoint, we chose a TSP protocol that had shown association with pain after breast surgery previously, was portable and brief, and amenable to testing in a clinical setting, finding that this was predictive of both pain severity and opioids use 2 weeks after surgery.

Preoperative QSTs may discern aspects of pain processing that are not evident from clinical interview or questionnaires responses, potentially contributing uniquely to personalization of care in the perioperative period, similar to the strategy proposed in neuropathic pain patients.²⁰ Surgery and the management and study of postoperative pain may be a useful space for understanding the predictive potential for QSTs, in that the timing of injury is known, and patients may be tested in advance, allowing a prospective, mechanism-based approach for intervention in different patients who have a predominance of certain responses.⁴⁵

Surgical factors

A number of important surgical factors (e.g., axillary dissection, reconstruction) impact early postoperative pain severity.³⁶ In particular, axillary dissection is consistently associated with greater acute pain,⁹ as in the present study. Irritation or damage to the intercostobrachial nerve (ICBN) has also been cited as a potential driver of pain after breast surgery,³⁰ although one study suggested that ICBN handling may not be as important as previously thought.³ Breast reconstruction has also been associated with greater pain.⁵⁸ We also found greater pain at rest and with movement among patients having reconstruction immediately after surgery (POD 0,1), although reconstruction was not a predictor of moderate-severe pain at 2 weeks in the regression analysis. However, it did predict greater pain impact and opioid use at 2 weeks. As reconstruction options have evolved, other studies have investigated differences in pain associated with different types of reconstruction. One recent study found that autologous flap reconstruction (deep inferior epigastric perforator flap (DIEP), superficial inferior epigastric perforator flap (SIEA), and pedicle transverse rectus abdominis musculocutaneous flap (PTRAM)) may be associated with less pain at one week than tissue expander and implant.³⁶ Others have suggested that placement of subpectoral implants (vs prepectoral) produces more pain.⁶⁵ Our sample largely received subpectoral tissue expanders, leaving us unable to make distinctions between reconstruction types.

Psychosocial factors and pain

Psychological distress is a substantial contributor to individual differences in the experience of both acute and chronic pain generally¹¹ and in pain after breast cancer surgery.⁵² In one study, the diagnosis of breast cancer (and presumed stress surrounding this diagnosis) increased the likelihood of pain persistence, compared to surgery for benign breast disease.¹⁶ Anxiety has been shown to predict greater persistent post-mastectomy pain,³⁸ while a measure of psychological robustness predicted lower incidence.⁸ Higher levels of depressive symptoms^{39, 53, 54} have also been associated with persistent pain after mastectomy, as has the number of antidepressants used.⁵⁶ Some have speculated that pain-related or pain-specific variables (such as pain catastrophizing) may be more predictive than general psychological measures,²⁵ although we did not observe this. These various measures (anxiety, depression, distress, negative affect) are often moderately to strongly inter-correlated, raising the possibility that the one which is most predictive in the context of a multivariate regression may vary across samples, depending on several factors, such as the mean group score on those variables, and presence of other measured similar variables. For example, in the present study, pain catastrophizing scores, which were relatively low, although correlated with pain, did not emerge as independently predictive, while depression did, in contrast to our cross-sectional study.¹⁷ In that study, catastrophizing was associated with chronic pain and depression was not, possibly because PCS scores were relatively higher and depression scores (Beck depression index) lower.

Methodological considerations in acute pain measurement

The reported incidence of pain after breast surgery has varied widely, perhaps due to the variety of definitions and measures of pain. Using any pain (>0/10) as the criterion to define

pain will obviously lead to higher rates than using a higher threshold to estimate “clinically significant” pain (i.e. $>3/10$). We found that at 2 weeks very few patients report an average pain of 0/10 (8%), while a sizable proportion of patients who reported pain greater than 0, but $\leq 3/10$ (60%). We considered that a pain score from 1–3 is clinically considered mild, and distinct from what is commonly accepted as “moderate-severe” pain ($>3/10$). While we used the BPI as the primary pain outcome at 2 weeks, other measures have certain advantages: the NRS is in widespread clinical use, and the Breast Cancer Pain Questionnaire has greater specificity to surgically related pain, pain impact, and sensory dysfunction. We utilized all three measures in order to take advantage of their various strengths. Interestingly, some recent studies assess daily pain over a prolonged period in order to model pain trajectory after surgery,^{26,57} indicating superiority of a change-point model to fit the data, and revealing pain severity fundamentally changes between days 10 and 21 after surgery.²⁶ Our primary assessment timepoint (2 weeks) falls within this range, and thus may represent a meaningful point in recovery. From a practical standpoint, it falls close to the first follow-up appointment with the surgical team, when the patient is attempting to return to “normal life”, and self-managing pain at home.

Limitations

There are several important limitations to consider. First, patients who declined participation cited feeling overwhelmed and anxious about the upcoming surgery (and generally the diagnosis of breast cancer) as a reason for non-participation, potentially skewing the sample studied toward lower-catastrophizing, less anxious patients. Second, the racial make-up was predominantly non-Hispanic white, potentially restricting generalizability. Third, the QST assessment did not include CPM or thermal modalities of testing, and thus cannot speak to their predictive value for acute pain after breast surgery. Given a pragmatic focus, a more extensive QST was not feasible. Fourth, we did not assess pain at a sufficient frequency to make a meaningful assessment of different daily pain trajectories between patients. Fifth, the limited application of regional anesthesia to this mixed surgical cohort precluded meaningfully investigation of its influence. Finally, we included patients who had previous breast surgery, which allows greater generalizability but also increases sample variability.

Conclusion

In order to adequately treat postsurgical pain in any individual, assessing variability in pain processing is essential.^{27, 63} Inclusion of simple psychosocial and psychophysical assessment, or “phenotyping” in studies may allow estimation of important differences in pain processing between individuals,¹³ informing more accurate prediction of which patients may struggle with pain in the early postoperative period, and allow better targeting of trials of novel analgesic drugs or therapies in “high-risk” samples, increasing study power.⁶⁶ This phenotyping of patients is a step towards greater personalization of care, and may allow more effective and targeted preventive perioperative planning.

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Appendix 1:: Pain impact questions from the Breast Cancer Pain Questionnaire (BCPQ)

Subjects answered the following questions at 2 weeks following surgery via email link to electronic Redcap survey. Pain impact score= sum of ratings on these 14 items Below is a list of statements. Please indicate how you have been feeling during the last month:

1=never 2=to some degree 3=quite a bit 4=very much

I often say no to taking part in leisure activities because of discomfort due to my surgery.

My discomfort affects interactions with friends and family.

My discomfort gets me down

My discomfort after the surgery is a burden for my family and friends

My discomfort after the surgery makes me nervous

My discomfort after the surgery is an unpleasant reminder of my illness

My discomfort after the surgery for breast cancer is the reason I don't do the things I want to do

I sometimes think that pain could be an indication that I still have breast cancer

Discomfort consumes my daily life

My discomfort makes me feel like I am a bad partner

I have difficulty concentrating

I have more difficulty concentrating now than before my surgery for breast cancer

I feel that I don't have the energy to solve problems

I feel that I quickly get mentally fatigued after surgery

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Perspective: We measured differences in the psychosocial and psychophysical processing of pain amongst patients before breast surgery using simple validated questionnaires and brief quantitative sensory testing. Independent of younger age and procedural extent (axillary surgery and reconstruction), affect and greater temporal summation of pain predicted acute postoperative pain and opioid use.

Highlights:

- prospective comprehensive preoperative assessment using brief validated tools
- psychosocial and psychophysical phenotype measured in parallel with treatment variables
- detailed assessment of postoperative pain severity, impact, and opioid use
- axillary dissection and reconstruction predicted greater pain severity and opioid use
- baseline affect and temporal summation of pain uniquely added to prediction of pain

Figure 1: Recruitment, enrollment and inclusion of participants.

N given refers to numbers completing different questionnaires at each timepoint.

Figure 2: Characterization of Pain 2 weeks after surgery.

Patients reported severity (**A**) of pain in surgical area using the Brief Pain Inventory (BPI), which rating increased from baseline to 2 weeks postoperatively (paired t test = -9.8 (208), (CI: -1.5, -1.0), $p < 0.001$). Patients also rated the location (**B**) of pain using the Breast Cancer Pain Questionnaire (BCPQ), which was most common in breast and axilla. On the BCPQ, patients rated the severity and frequency of pain at each site, allowing calculation of (**C**) the Pain Burden Index (PBI) = $\sum [\text{Pain score at each site} \times \text{frequency}]$, which was increased from baseline at 2 weeks (paired t test = -11.6 (233) (CI: -23.5, -16.7)). Box indicates group means and whiskers standard deviation, and dots indicate individual scores of participants.

Figure 3: Pain at rest and with movement in different surgical subgroups over time.

Patients rated current pain at rest (A) and with movement (B) using the numerical rating scale (NRS) (0–10) at baseline and various times after surgery: on post operative day (POD) 0 (day of surgery, 2 hours after surgical end), POD 1 (24 hours after surgical end), and 2 weeks after surgery (POD14). Pain varied by surgical type ($F=10.6$ ($df=2$), $p<0.001$, with movement ($F=151$ ($df=1$), $p<0.001$), and there was a significant three-way interaction (time $\times$ surgical type $\times$ movement, $F=3.5$ ($df=6$), $p=0.002$), suggesting that more extensive surgeries are associated with longer acute pain and produced more pain with movement during the first 2 weeks after surgery. Y axis indicates % of each surgical group, and numbers on columns indicate actual number of patients.

Figure 4: Correlation of pain Severity with sensory disturbance and pain impact.

Using the Breast Cancer Pain Questionnaire, patients answered questions regarding pain severity in the surgical area, but also different type of sensory disturbances in the surgical area (Table 2) and impact on aspects of their life (Appendix A). Pain severity was moderately correlated with the sensory disturbance score (**A**) (Spearman Rho 0.499, $p < 0.001$) and the pain impact score (**B**) (Spearman Rho 0.552, $p < 0.001$).

Figure 5: Incidence of analgesic use at 2 weeks after surgery.

Using the Breast Cancer Pain Questionnaire, patients provided information about their use of any analgesic, as well as specifically about opioid analgesics, 2 weeks after surgery. More extensive surgery (**A**) including reconstruction ($p=0.002$) and (**B**) axillary dissection ($p<0.001$) was associated with higher likelihood of opioid use (right side of each graph) (see also Table 7 for further statistical testing).

Table 1:

Comparison of patient characteristics by surgical group

Patient characteristics	All Patients, N=259	Breast Conserving Surgery	Mastectomy	Mastectomy with immediate reconstruction	P-value
N	259	137(53%)	38 (15%)	84 (32%)	
Age ¹	55.6 (12.4)	59.8 (10.9)	55.3 (15.0)	48.8 (10.2)	<0.0001
BMI	25.6 (22.9–31.1)	26.9 (23.6–32.5)	27.2 (24.0–34.4)	23.7 (21.9–27.6)	0.395
Education	5 (5–6)	5 (4–6)	5 (4–6)	5 (5–6)	0.424
Exercise	12.0 (6.0–19.5)	12.0 (5.0–19.0)	14.5 (6.3–21.0)	12.3 (8.8–19.3)	0.669
Race					
AA	7 (2.7)	6 (4.4)	0 (0.0)	1 (12)	0.0095
Caucasian	223 (86.4)	117 (85.4)	28 (73.7)	78 (94.0)	
Asian	5 (1.9)	3 (2.2)	1 (2.6)	1 (1.2)	
Hispanic/Latina	11 (4.3)	7 (5.1)	4 (10.5)	0 (0.0)	
Mixed Race	8 (3.1)	2 (1.5)	3 (7.9)	3 (3.6)	
Other	4 (1.6)	2 (1.5)	2 (5.3)	0 (0.0)	
Menopausal status					
Premenopausal	78 (30.4)	26 (19.1)	12 (31.6)	40 (48.2)	<0.0001
Peri-menopausal	31 (12.1)	11 (8.1)	5 (13.2)	15 (18.1)	
Postmenopausal	148 (57.6)	99 (72.8)	21 (55.3)	28 (33.7)	
Baseline pain					
Baseline pain (BPI average)	0.5 (0.0–1.5)	0.5 (0.0–1.3)	1.0 (0.6–2.6)	0.4 (0.0–1.5)	0.458
BPI fct impairment (0–35)	1 (0–7)	0 (0–7)	5 (0–15)	0 (0–5)	0.745
Other chronic pain	103 (39.9)	53 (38.7)	18 (47.4)	32 (38.6)	0.597
Taking painkillers	102 (40.2)	51 (38.6)	19 (50.0)	32 (38.1)	0.405
Taking opioid painkillers	13 (5.0)	5 (3.7)	5 (13.2)	3 (3.6)	0.075
Psychosocial traits					
Catastrophizing (PCS)	4 (1–8)	3 (0–8)	3 (1–10)	5 (1–9)	0.123
PROMIS Anxiety	56 (51–60)	55 (51–59)	56 (54–60)	58 (53–60)	0.866
PROMIS Depression	48 (43–52)	48 (43–52)	48 (46–52)	49 (43–53)	0.563
PROMIS Sleep	51 (9)	51 (8)	49 (9)	51 (10)	0.508
PANAS positive affect	35 (30–39)	35 (30–39)	35 (32–40)	35 (29–39)	0.842
PANAS negative affect	17 (13–20)	16 (13–20)	17 (13–22)	17 (14–20)	0.638
Somatization (BSI)	7 (6–8)	6 (6–8)	7 (6–9)	7 (6–8)	0.565
Diverting coping	3 (0–6)	3 (0–6)	2 (0–6)	3 (0–6)	0.509
Reinterpreting coping	1 (0–3)	0 (0–3)	1 (0–3)	1 (0–3)	0.301
Catastrophizing coping	0 (0–2)	1 (0–2)	1 (0–2)	0 (0–2)	0.625
Ignoring coping	5 (2–6)	5 (2–7)	5 (2–6)	4 (2–7)	0.304
Praying coping	3 (0–5)	2 (0–4)	3 (0–5)	3 (0–5)	0.495

Patient characteristics	All Patients, N=259	Breast Conserving Surgery	Mastectomy	Mastectomy with immediate reconstruction	P-value
Self-statements coping	5 (3–8)	5 (3–8)	5 (4–7)	6 (4–8)	0.397
Behavioral coping	5 (3–7)	5 (2–7)	6 (4–7)	5 (3–7)	0.202
Psychophysical traits					
FA Threshold	5.0 (1.9)	4.9 (1.8)	4.6 (1.9)	5.4 (1.9)	0.037
FA Tolerance	7.7 (2.9)	7.2 (2.7)	7.2 (3.1)	8.5 (3.1)	0.005
Trap Threshold	7.5 (3.3)	7.5 (3.5)	6.8 (3.3)	7.9 (2.8)	0.238
Trap Tolerance	10.5 (3.9)	10.3 (4.0)	9.9 (3.9)	11.1 (3.8)	0.207
TSP	1.9 (1.0–3.8)	2.3 (1.3–4.0)	1.5 (0.8–2.9)	1.8 (1.0–3.2)	0.698
PAS	67/255(26%)	41/135 (30%)	8/37 (22%)	18/83 (22%)	0.289
Surgical variables					
Previous breast surgery	98 (38.0)	43 (31.6)	20 (52.6)	35 (41.7)	0.043
Bilateral procedure	47 (18.2)	3 (2.2)	9 (23.7)	35 (42.2)	<0.0001
Surgical duration	120 (68–180)	79 (54–121)	113 (81–146)	204 (157–341)	0.004
Sentinel node procedure	135 (52.1)	92 (67.2)	14 (36.8)	29 (34.5)	<0.0001
Axillary dissection procedure	32 (12.4)	13 (9.5)	8 (21.1)	12 (14.3)	0.214
Anesthetic variables					
Sedation only	6 (2.3)	6 (4.4)	0 (0.0)	0 (0.0)	<0.0001
Regional anesthesia+ sedation	10 (3.9)	7 (5.2)	2 (5.4)	1 (1.2)	
General anesthesia only	184 (71.9)	121 (89.0)	17 (46.0)	46 (55.4)	
General and Regional anesthesia	56 (21.9)	2 (1.5)	18 (48.7)	36 (43.4)	
Intraoperative IV MME	16.7 (10.2–22.7)	12.7 (10.0–19.2)	20.0 (12.9–25.0)	22.0 (15.3–26.7)	<0.0001
PACU IV MME	2.7 (0.0–7.8)	2.5 (0.0–7.6)	2.7 (0.0–6.3)	5.3 (1.7–8.0)	<0.0001

Values reported are median (25–75 percentile) or N (%)

¹ Mean and standard deviations

MME= morphine mg equivalents

Table 2:

Proportion of subjects reporting various sensory disturbances at 2 weeks after surgery

Sensory disturbance	% Reporting
Numbness	65
Pins and needles	43
Electric shock	40
Painful itch	22
Burning	34
Cold pain	9
Pain with light pressure	41
Pain with rubbing area	64

Table 3:

Univariate Association of predictors with moderate-severe pain at 2 weeks after surgery

Patient Characteristics	All	Mild or no pain (BPI ave 3/10)	Moderate-severe pain (BPI ave >3/10)	P-value
N	208	148, 71%	60, 29%	
Age	55 (46–65)	58 (48–66)	52 (44–63)	0.043
BMI	25.5 (23.0–31.1)	25.1 (22.8–30.1)	27.5 (23.9–32.0)	0.031
Education, N=207	5 (5–6)	5 (5–6)	5 (5–6)	0.211
Exercise	12.0 (6.0–19.3)	12.0 (6.8–19.3)	12.0 (6.0–19.3)	0.882
Race				
AA	2 (1.0)	1 (0.7)	1 (1.7)	0.502
Caucasian	183 (88.0)	132 (89.2)	51 (85.0)	
Asian	5 (2.4)	3 (2.0)	2 (3.3)	
Hispanic/Latina	10 (4.8)	8 (5.4)	2 (3.3)	
Mixed Race	6 (2.9)	3 (2.0)	3 (5.0)	
Other	2 (1.0)	1 (0.7)	1 (1.7)	
Menopause status, N=207				0.175
Premenopausal	59 (28.5)	39 (26.5)	20 (33.3)	
Peri-menopausal	28 (13.5)	17 (11.6)	11 (18.3)	
Postmenopausal	120 (58.0)	91 (61.9)	29 (48.3)	
Baseline pain				
Baseline Average pain (BPI), N=203	0.5 (0.0–1.5)	0.3 (0.0–1.0)	1.3 (0.0–2.9)	<0.0001
Baseline pain interference (0–35) (BPI), N=206	0.5 (0.0–7.0)	0.0 (0.0–4.0)	7.0 (0.0–14.3)	<0.0001
Other chronic pain, N=207	82 (39.6)	57 (38.5)	25 (42.4)	0.608
Taking painkillers, N=205	81 (39.5)	56 (38.4)	25 (42.4)	0.594
Surgical Type				
Breast Conserving Surgery	117 (56.2)	85 (57.4)	32 (53.3)	0.811
Mastectomy	25 (12.0)	18 (12.2)	7 (11.7)	
Mastectomy with reconstruction	66 (31.7)	45 (30.4)	21 (35.0)	
Axillary dissection N=207	27 (13.0)	13 (8.8)	14 (23.3)	0.005
Previous breast surgery, N=207				
None	126 (60.9)	93 (62.8)	33 (55.9)	0.247
Excisional biopsy	40 (19.3)	30 (20.3)	10 (16.9)	
BCS or Mastectomy	41 (19.8)	25 (16.9)	16 (27.1)	
Psychosocial traits				
Catastrophizing (PCS)	4.0 (1.0–8.0)	3.5 (0.0–7.0)	4.0 (1.0–10.3)	0.319
PROMIS Anxiety	17 (13–20)	17 (13–19)	17 (14–20)	0.288
PROMIS Depression	11 (9–14)	11 (9–14)	12 (10–15)	0.011
PROMIS Sleep	21 (15–25)	20 (15–25)	23 (16–27)	0.030
PANAS positive affect	35 (31–40)	36 (31–40)	34 (29–38)	0.049

Patient Characteristics	All	Mild or no pain (BPI ave 3/10)	Moderate-severe pain (BPI ave >3/10)	P-value
PANAS negative affect	16 (12–20)	16 (12–20)	17 (14–21)	0.171
Somatization (BSI) N=207	7 (6–8)	6 (6–8)	8 (6–10)	0.0001
Diverting coping, N=203	3 (0–6)	3 (0–6)	3 (0–6)	0.643
Reinterpreting coping, N=205	1 (0–3)	1 (0–3)	1 (0–3)	0.376
Catastrophizing coping, N=202	0 (0–2)	0 (0–2)	1 (0–3)	0.002
Ignoring coping, N=203	5 (2–6)	4 (2–6)	6 (3–7)	0.085
Praying coping, N=202	3 (0–5)	2 (0–5)	3 (2–5)	0.0469
Self-statements coping, N=205	6 (3–8)	5 (3–8)	6 (4–8)	0.067
Behavioral coping, N=205	5 (3–7)	5 (2–7)	6 (4–8)	0.016
Psychophysical traits				
FA Threshold N=207	4.9 (3.8–6.2)	4.9 (3.8–6.2)	4.5 (3.7–6.1)	0.401
FA Tolerance N=207	7.6 (5.7–9.5)	7.6 (5.8–9.7)	7.6 (5.5–9.2)	0.552
Trap Threshold N=205	7.5 (5.4–10.0)	7.7 (5.6–10.7)	6.9 (5.0–8.7)	0.102
Trap Tolerance N=205	10.7 (7.8–14.0)	11.5 (8.4–14.1)	9.9 (7.1–13.3)	0.097
TSPN=207	1.9 (1.0–3.8)	1.8 (1.0–3.5)	3.1 (1.3–4.5)	0.012
PAS N=206	0 (0–0.3)	0 (0–0)	0 (0–0.4)	0.037

Table 4:

Multivariate logistic regression of predictors of moderate-severe pain at 2 weeks after surgery

Covariates	Odds Ratio	95% Confidence Interval	P-value
Baseline pain	1.31	(1.00, 1.72)	0.049
Baseline pain interference	1.04	(1.01, 1.08)	0.011
Axillary dissection	4.42	(1.69, 11.54)	0.003
PANAS positive affect	0.93	(0.88, 0.99)	0.022
Behavioral coping	1.21	(1.06, 1.37)	0.005
Baseline TSP	1.36	(1.12, 1.65)	0.002

Table 5:

Univariate Association of predictors with Pain Impact at 2 weeks

Patient Characteristics	Pain Impact, N=216	P-value
Age	−0.43	<0.0001
BMI	−0.06	0.3771
Education, N=214	0.16	0.0231
Exercise	0.02	0.8029
Baseline pain severity (BCPQ), N=215	0.29	<0.0001
Catastrophizing (PCS)	0.34	<0.0001
PROMIS Anxiety	0.44	<0.0001
PROMIS Depression	0.47	<0.0001
PROMIS Sleep	0.27	<0.0001
PANAS positive affect	−0.28	<0.0001
PANAS negative affect	0.46	<0.0001
Somatization (BSI) N=214	0.37	<0.0001
Diverting coping, N=210	0.05	0.5108
Reinterpreting coping, N=211	0.1	0.145
Catastrophizing coping, N=209	0.21	0.0023
Ignoring coping, N=210	−0.11	0.1132
Praying coping, N=209	0.12	0.0964
Self-statements coping, N=212	−0.04	0.5678
Behavioral coping, N=211	0.02	0.806
FA Threshold N=214	−0.06	0.419
FA Tolerance N=214	−0.01	0.9222
Trap Threshold N=213	−0.05	0.4834
Trap Tolerance N=213	−0.03	0.6333
TSP N=214	−0.04	0.5382
PAS N=212	−0.02	0.7227
Categorical variables	Tests used	P-value
Race, N=215	Kruskal-Wallis rank sum test	0.2856
Menopause, N=215	Kruskal-Wallis rank sum test	<0.0001
Other chronic pain, N=215	Wilcoxon rank-sum test	0.7012
Taking painkillers, N=212	Wilcoxon rank-sum test	0.7288
Reconstruction	Wilcoxon rank-sum test	<0.0001
Surgical Type	Kruskal-Wallis rank sum test	<0.0001
Axillary dissection, N=215	Wilcoxon rank sum test	0.0009
Previous breast surgery, N=215	Wilcoxon rank sum test	0.8401

Table 6.

Linear regression estimates of predictors for Pain Impact at 2 weeks

Covariates	Estimate	95% Confidence Interval	P-value
Age	−0.12	(−0.19, −0.05)	0.0004
Education	0.59	(0.04, 1.14)	0.0342
Baseline pain	0.77	(0.35, 1.19)	0.0004
Axillary dissection	2.91	(0.70, 5.12)	0.0100
Negative affect (PANAS)	0.24	(0.08, 0.40)	0.0032
Depression	0.41	(0.21, 0.60)	<0.0001
Reconstruction	2.89	(1.23, 4.56)	0.0007

Table 7.

Univariate association of predictors with opioid use at 2 weeks

Patient Characteristics	Total (N=234)	Yes opioids (N=62, 27%)	No opioids (N=172, 73%)	P-value
Age	56 (47–66)	51 (43–59)	59 (50–67)	0.0003
BMI	25.5 (22.9–30.7)	26.4 (22.6–32.3)	25.3 (23.0–30.2)	0.2347
Education, N=232	5 (5–6)	5 (4–6)	5 (5–6)	0.038
Exercise	12.0 (6.0–19.0)	12.5 (6.0–19.8)	12.0 (6.8–19.0)	0.7442
Race, N=233				
AA	4 (1.7)	2 (3.2)	2 (1.2)	0.0707
Caucasian	204 (87.6)	55 (88.7)	149 (87.1)	
Asian	5 (2.1)	1 (1.6)	4 (2.3)	
Hispanic/Latina	10 (4.3)	0 (0.0)	10 (5.8)	
Mixed Race	7 (3.0)	4 (6.5)	3 (1.8)	
Other	3 (1.3)	0 (0.0)	3 (1.8)	
Menopause, N=232				
Premenopausal	68 (29.3)	23 (37.7)	45 (26.3)	0.092
Peri-menopausal	30 (12.9)	10 (16.4)	20 (11.7)	
Postmenopausal	134 (57.8)	28 (45.9)	106 (62.0)	
Baseline Pain				
Baseline pain severity N=233	0 (0–2)	1 (0–3)	0 (0–2)	0.0002
Other chronic pain, N=233	93 (39.9)	26 (41.9)	67 (39.2)	0.7044
Baseline Opioids	9 (3.8)	7 (11.3)	2 (1.2)	0.0016
Psychosocial traits				
Catastrophizing (PCS)	4 (1–8)	6 (3–10)	3 (0–7)	0.0004
PROMIS Anxiety	17 (13–20)	18 (14–21)	16 (12–19)	0.0037
PROMIS Depression	11 (9–14)	13 (10–17)	11 (9–14)	0.0002
PROMIS Sleep	21 (15–25)	23 (19–28)	20 (15–25)	0.0008
PANAS positive affect	35 (30–40)	35 (26–38)	35 (31–40)	0.0366
PANAS negative affect	17 (13–20)	17 (16–21)	16 (12–20)	0.0106
Somatization (BSI) N=231	7 (6–8)	7 (6–9)	7 (6–8)	0.1516
Diverting coping, N=227	3 (0–6)	3 (1–6)	3 (0–6)	0.2281
Reinterpreting coping, N=226	1 (0–3)	1 (0–3)	0 (0–3)	0.0536
Catastrophizing coping, N=226	0 (0–2)	1 (0–4)	0 (0–2)	0.0044
Ignoring coping, N=226	5 (2–6)	4 (2–6)	5 (2–7)	0.3896
Praying coping, N=226	3 (0–5)	3 (2–5)	2 (0–4)	0.032
Self-statements coping, N=229	5 (3–8)	5 (3–7)	5 (3–8)	0.707
Behavioral coping, N=227	5 (3–7)	6 (4–7)	5 (2–7)	0.1153
Psychophysical traits				
FA threshold, N=232	4.8 (3.7–6.1)	4.4 (3.8–6.2)	4.9 (3.8–6.1)	0.7211
FA tolerance, N=232	7.4 (5.5–9.4)	7.1 (5.7–10.1)	7.5 (5.5–9.2)	0.9929

Patient Characteristics	Total (N=234)	Yes opioids (N=62, 27%)	No opioids (N=172, 73%)	P-value
Trap threshold, N=230	7.2 (5.1–9.7)	7.3 (5.2–9.2)	7.2 (5.0–10.0)	0.8679
Trap tolerance, N=230	10.5 (7.4–13.8)	10.5 (7.4–13.8)	10.5 (7.4–13.9)	0.8206
TSP, N=232	1.8 (1.0–3.8)	2.8 (1.3–4.0)	1.6 (1.0–3.6)	0.093
PAS, N=230	0.0 (0.0–0.3)	0.0 (0.0–0.3)	0.0 (0.0–0.1)	0.2876
Surgical Type				
Breast Conserving Surgery	130 (55.6)	23 (37.1)	107 (62.2)	0.0013
Mastectomy	31 (13.2)	9 (14.5)	22 (12.8)	
Mastectomy with reconstruction	73 (31.2)	30 (48.4)	43 (25.0)	
Reconstruction (Y), N=233	73 (31.3)	29 (46.8)	44 (25.7)	0.0022
Axillary dissection (Y), N=233	28 (12.0)	16 (26.2)	12 (7.0)	<0.0001
Previous breast surgery, N=233				
None	143 (61.4)	32 (52.5)	111 (64.5)	0.0801
Excisional biopsy	43 (18.5)	17 (27.9)	26 (15.1)	
BCS or Mastectomy	47 (20.2)	12 (19.7)	35 (20.3)	

Table 8.

Multivariate logistic regression for predictors of opioid use at 2 weeks

Covariates	Odds Ratio	95% Confidence Interval	P-value
Age	0.96	(0.93, 0.99)	0.0114
Education	0.72	(0.54, 0.95)	0.0189
Baseline pain severity	1.22	(1.02, 1.46)	0.0307
Baseline opioids	18.63	(3.11, 111.62)	0.0015
Axillary dissection	4.22	(1.55, 11.47)	0.0050
Surgical type			
Breast conserving surgery	Ref	Ref	Ref
Mastectomy	0.88	(0.26, 2.99)	0.8361
Mastectomy with reconstruction	2.88	(1.24, 6.69)	0.0144
Depression	1.11	(1.03, 1.20)	0.0078
Reinterpreting coping	1.17	(1.01, 1.37)	0.0392
Baseline TSP	1.24	(1.02, 1.50)	0.0278