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## GENERAL & SELECTED POPULATIONS SECTION

# Associations Among Sleep Latency, Subjective Pain, and Thermal Pain Sensitivity in Gynecologic Cancer

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## Abstract

**Objective.** Pain is common among women with gynecologic cancer and contributes to depressed mood, sleep disturbances, and likelihood of future chronic pain. Little is known about how psychosocial factors are associated with central sensitization of pain in gynecologic cancer. This study examined relations among depressive symptoms, sleep, subjective pain, and aftersensation pain (a proxy for central sensitization of pain) in gynecologic cancer. **Methods.** Participants were 42 women (mean age [SD] = 59.60 [10.11] years) enrolled in a randomized clinical trial examining psychological intervention effects on sleep, pain, mood, and stress hormones/cytokines in gynecologic cancer. Six to eight weeks after surgery, participants completed an assessment of depressive symptoms, sleep, and subjective pain and a temporal summation of pain protocol via quantitative sensory testing (QST). **Results.** Controlling for recent chemotherapy, history of chronic pain, and analgesic medication use, regression analyses revealed that longer sleep onset latency (SOL; $B = 3.112$, $P = 0.039$, bias-corrected and accelerated (BCa) 95% confidence interval [CI] = 0.371 to 6.014) and greater sensory pain ($B = 0.695$, $P = 0.023$, BCa 95% CI = 0.085 to 1.210) were associated with greater aftersensation pain at 15 seconds. Greater sensory pain scores were associated with greater aftersensation pain at 30 seconds ($B = 0.286$, $P = 0.045$, BCa 95% CI = 0.008 to 0.513). Depression was not associated with aftersensation pain. The overall models accounted for 44.5% and 40.4% of the variance in aftersensation pain at 15 and 30 seconds, respectively. **Conclusions.** Longer SOL and higher subjective sensory pain were related to greater aftersensation of experimentally induced pain in women postsurgery for gynecologic cancers. Interventions that improve sleep and subjective sensory pain during the perisurgical period may reduce risk for central sensitization of pain.

**Key Words:** Pain; Gynecologic Cancer; Sleep; Quantitative Sensory Testing

## Introduction

Pain is a common experience in individuals with cancer. In fact, approximately 40% of patients with cancer report experiencing pain [1]. Unlike individuals who do not have cancer, individuals with cancer typically have one or a combination of pain sources including cancer-related pain, treatment-related pain (i.e., chemotherapy, radiotherapy), and/or pain unrelated to the tumor or treatment interventions [2]. Within gynecologic cancer populations, pain is highly prevalent, with some studies finding that 50% to 94% of patients report pain symptoms [3–6] and one-third of cancer survivors report experiencing chronic

pain [7]. Therefore, pain is a crucial component of the cancer experience and should be considered in the conceptualization of treatment and disease outcomes in women diagnosed with a gynecologic malignancy.

Surgical resection is commonly the first line of treatment for many women diagnosed with gynecologic cancer. Unfortunately, surgery also leads to prevalent postoperative pain. Factors known to contribute to postoperative pain include depression [8,9], poor sleep quality [10,11], and adjuvant treatments such as chemotherapy [12] and radiation [13]. Surgical intervention and/or chemotherapy can further lead to symptoms such as cancer-induced peripheral neuropathy, which contributes to sensation loss and pain [12,14].

Above and beyond treatment side effects, psychosocial factors such as mood and sleep have also been well-documented contributors to pain in cancer patients [8,15]. Mood symptoms such as depression are highly prevalent in cancer populations, with gynecologic cancers being one of the most highly affected cancer types [16]. Importantly, depression is associated with greater perceived pain intensity [8], a relationship that is likely bidirectional. Patients recovering one to 16 weeks post–surgical resection from endometrial cancer reported higher depression in tandem with greater pain intensity [8]. In addition, individuals with gynecologic cancer who had previous chronic pain reported greater perceived pain and depression following cancer diagnosis [15]. Therefore, the impact of mood symptoms throughout the course of the cancer experience is an important consideration in pain experience and management.

Similar to research on depression and pain, findings support a strong bidirectional relationship between sleep and pain in cancer [17–19]. Pain has been identified as one of the biggest contributors to sleep difficulties in cancer [20], with 45% of cancer patients with insomnia attributing much of their sleep difficulties to pain [11]. Pain may impact patients' overall sleep quality, as well as specific sleep parameters, such as sleep onset latency. In fact, prolonged sleep latency, difficulties staying asleep, and not feeling refreshed (i.e., daytime sleepiness) have all been significantly associated with cancer-related pain [21].

Prolonged sleep onset latency, in particular, is a commonly reported clinical complaint in cancer. It is typically defined as an inability to fall asleep within 30 minutes. A recent study found that approximately 40% of cancer patients reported taking greater than 30 minutes to fall asleep [22]. Similarly, 72% of patients with ovarian, peritoneal, or fallopian tube cancer reported taking more than 15 minutes to fall asleep [23], suggesting that sleep latency is an important contributor to overall sleep disturbance. Due to the prevalence of prolonged sleep latency complaints in patients with gynecologic cancer, this subcomponent of sleep was of particular interest in the current study.

In addition to sleep and mood factors, a history of chronic pain can significantly influence the pain experience in individuals diagnosed with cancer. Previous research has found that approximately 3%–10% of women diagnosed with gynecologic cancer [15,24] report chronic pain before their cancer diagnosis. Central sensitization, a heightened reactivity of the nervous system due to chronic pain, leads to greater pain sensitivity [25]. Individuals with central sensitization require less afferent input to transmit pain signals in the spinal cord, resulting in pain being maintained even with low levels of peripheral stimuli. A number of central nervous system (CNS) structures are involved in the processing of pain, stress, and emotions that may contribute to the development of central sensitization and the experience of chronic pain [26]. Among cancer patients, the experience of chronic stress, negative emotions, and pain may have important health-related implications. Chronic, long-term negative emotional states and pain may lead to hypothalamic pituitary adrenal (HPA) axis dysregulation and downstream glucocorticoid and cytokines dysregulation in a manner that facilitates tumorigenesis [27].

Although it is believed that psychosocial factors may contribute to central sensitization, little research has been devoted to this topic within gynecologic cancer. Given these relationships, the current study sought to explore the relationships among sleep onset latency, depressive symptoms, subjective pain, and quantitative thermal sensory pain responses in women following surgery for gynecologic cancer. Factors associated with pain in cancer patients (e.g., cancer type, cancer stage, treatment factors, chronic pain history, and analgesic medication use) were explored as control variables.

## Methods

### Participants

Participants were women with suspected gynecologic cancers who were enrolled in a randomized clinical trial (RCT) examining cognitive behavioral therapy (CBT) effects on sleep, pain, mood, cortisol, and cytokines in gynecologic cancers (PI: Deidre B. Pereira, PhD, R01 CA138808, 2009–2017; ClinicalTrials.gov NCT02609880). Women undergoing surgical consultation for suspected gynecologic cancer were screened for study eligibility. Inclusion criteria at enrollment were 1) suspected primary gynecologic cancer, 2) planned surgical intervention, 3) at least 18 years of age, 4) fluent in English, and 5) a positive screening for insomnia. Exclusion criteria at enrollment were 1) recurrent gynecologic cancer, 2) preoperative chemotherapy or radiotherapy, 3) medical record–documented history of seizure disorder and/or obstructive sleep apnea (OSA; i.e., diagnoses that would preclude the ability to use a manualized CBT for insomnia treatment protocol), and/

or 4) medical record–documented current, uncontrolled, severe psychopathology. Six to eight weeks after surgery, participants with pathology-confirmed gynecologic cancer underwent postsurgical psychosocial and pain assessment procedures.

## Procedures

Patients undergoing consultation at the Gynecology Oncology Clinic were screened for study eligibility. Individuals meeting the above eligibility criteria were approached by study staff and, if interested, were consented following procedures approved by the University of Florida Institutional Review Board. After consent, participants underwent a brief psychiatric screening to rule out current psychotic symptoms [28] and suicidal intent or plan [29]. Participants evidencing concern for these were withdrawn from the study (N = 4) and immediately evaluated by the Principal Investigator (DBP), a licensed psychologist, according to standard clinical guidelines to assess safety risk and determine potential interventions needed. Eligible participants completed study questionnaires, a peripheral venous blood draw by a certified hospital phlebotomist, and saliva sampling for cortisol quantitation.

Participants underwent surgical resection approximately one week later. Six to eight weeks after surgery, participants returned to the Gynecologic Oncology Clinic for a routine postsurgical visit with their medical team, at which time they also completed a study visit, which included questionnaires, a peripheral venous blood draw, saliva sampling for cortisol quantitation, and quantitative sensory testing. Data for the current analyses were drawn from this postsurgical assessment, given that sensory testing was not completed at the presurgical assessment. All data were collected before randomization for the intervention component of the study.

## Measures

The Medoc Thermal Sensory Analyzer (TSA-2001, Ramat Yishai, Israel) was used to test induced sensory pain in the participants. Previous research has found thermal threshold to be higher in individuals with cancer compared with age-matched controls, indicating that patients with cancer may have small-fiber sensory dysfunction [30]. Per the protocol, heat was applied alternately to the dominant and nondominant palms with stimuli continuously increasing from 45°C to 52°C. Participants rated their pain (0 = no pain, 100 = worst imaginable pain) during testing, as well as 15 and 30 seconds after stimulus removal (aftersensation pain).

The McGill Pain Questionnaire (MPQ) is a 20-question survey that asks the participant to select the word that best describes their perceived level of pain. In addition to an overall pain score, the questionnaire has four subscales (sensory, affective, evaluative, and miscellaneous pain) [31]. Higher scores represent greater subjective pain. In a sample of individuals with acute and/or chronic pain, the MPQ demonstrated extremely high internal consistency (Cronbach's alpha = 0.98) [32], which is similar to the present sample (MPQ Total Score: Cronbach's alpha = 0.92; Sensory subscale: Cronbach's alpha = 0.87). The Sensory subscale was chosen for examination in this study because it assesses pain location, pattern, quality, and intensity; as such, it was determined to give the most comprehensive assessment of subjective pain experience in our sample.

The Pittsburgh Sleep Quality Index (PSQI) [33] was used to assess sleep disturbance. The PSQI measures self-reported sleep quality within the last month and yields a Global Index Score and seven sleep component scales. Global Index Scores range from 0 to 21, with higher scores indicating greater sleep impairment. A score greater than 5 is indicative of clinically significant sleep disturbances. This inventory has demonstrated good internal consistency for the PSQI Global Index Score in both the original validation population (Cronbach's alpha = 0.80) and cancer samples (Cronbach's alpha = 0.81) [33,34]. The sleep component scales have also displayed adequate internal consistency (Cronbach's alpha = 0.70 to 0.78). In the current sample, participant data yielded internal consistency scores similar to previous research (PSQI Global Index Score: Cronbach's alpha = 0.69; Sleep Latency subscale: Cronbach's alpha = 0.87). The Sleep Latency scale was used as a predictor for several reasons: 1) it maps closely onto one of the core required diagnostic criteria for insomnia in the Diagnostic and Statistical Manual of Mental Disorders [35] and 2) prolonged sleep onset latency is common in women with cancer [36] and individuals undergoing chemotherapy [37].

The Beck Depression Inventory–II (BDI-II) is a 21-question inventory that assesses cognitive and somatic depressive symptomology [38]. Scores range from 0 to 63, with higher scores indicative of greater depression. The BDI-II has shown good internal consistency across a community sample of adults (Cronbach's alpha = 0.90) [38]. The current sample demonstrated similar and adequate psychometric properties (Cronbach's alpha = 0.83).

Control variables were abstracted via medical record review. Cancer-related control variables included presence of poor-prognosis gynecologic cancer types (i.e., fallopian tube/ovarian cancer [yes] vs all others [no]), presence of advanced cancer (i.e., stages III/IV [yes] vs stages I/II [no]) [39], receipt of highly invasive surgery (i.e., exploratory laparotomy/total abdominal hysterectomy with bilateral salpingo oophorectomy [yes] vs robotic-assisted surgeries [no]), recent receipt of any adjuvant chemotherapy, and presence of any acute postsurgical complications (e.g., hypoxia, emesis). History of chronic pain was also explored as a potential control variable. This was determined via a semistructured sleep and pain interview. Individuals who endorsed a history of chronic pain predating cancer diagnosis (i.e., fibromyalgia, sciatica, neuropathy, arthritis) were classified as having a positive history of chronic pain.

### Statistical Analysis

Analyses were conducted using IBM SPSS, version 24. Descriptive statistics were first performed to examine the distribution of data and to ensure that the assumptions of normality were met. We then explored the relationship between the aforementioned potential control variables and aftersensation pain using Pearson correlation analyses. Variables associated with aftersensation pain at $P < 0.10$ were included as control variables in subsequent regression equations. Given that pain medication use, chemotherapy, and history of chronic pain have well-established relationships with aftersensation pain/QST responses [40,41], they were entered as control variables as a conservative measure regardless of their relationship with aftersensation in the current sample.

Due to the non-normality of the data, multivariate hierarchical regression analyses with bootstrapping were conducted. Two regression analyses were performed. In the first equation, aftersensation pain at 15 seconds was regressed on control variables in Block 1, and sleep latency, sensory pain, and depressive symptoms in Block 2. The second equation regressed aftersensation pain at 30 seconds with the same control and psychosocial variables.

## Results

Of the 115 participants who were enrolled in the parent study at presurgery, 54 patients were eligible to complete postsurgery measures to determine continued study eligibility. Reasons for ineligibility included benign disease (N = 27), ineligible inclusionary cancer diagnosis (N = 9), lost to follow-up (N = 3), participant-initiated withdrawal (N = 15), and Principal Investigator–initiated withdrawal (N = 7). Reasons for participant-initiated withdrawal included competing demands, poor health, residence greater than 100 miles from the hospital, and deeming study procedures too demanding. Principal investigator–initiated withdrawals included mental health concerns and nonadherence. Of the 54 eligible participants, four women did not complete the QST protocol. Of the 50 women who completed the QST protocol, three did not complete questionnaires, three did not complete the sleep and pain interview, and two had unusable QST data due to device malfunction. Of these 42 participants, postsurgical study procedures detected previously undiagnosed OSA in five women; furthermore, seven participants lacked sleep diary–confirmed insomnia. However, these participants were retained for the present analyses given nonsignificant associations between aftersensation pain at 15 seconds and 1) presence of OSA ($r(42) = -0.112$, $P = 0.479$) or 2) lack of clinical insomnia ($r(42) = -0.210$, $P = 0.182$). Furthermore, there was no association between aftersensation pain at 30 seconds and 1) presence of OSA ($r(42) = 0.000$, $P = 1.00$) or 2) lack of clinical insomnia ($r(42) = -0.187$, $P = 0.235$). Thus, the final sample consisted of 42 participants.

**Table 1.** Participant demographics (N = 42)

| | No., % | M (SD) |
|---|---|---|
| Age, y | | 59.60 (10.11) |
| Race | | |
| African American | 4, 9.5 | |
| Asian | 1, 2.4 | |
| Caucasian | 37, 88.1 | |
| Education | | |
| High school/GED | 16, 38.1 | |
| More than high school | 25, 59.5 | |
| Unknown | 1, 2.4 | |
| Marital status (married) | 29, 69.0 | |
| Presence of poor prognosis cancer type (yes) | 8, 19.0 | |
| Presence of advanced cancer stage (yes) | 9, 21.4 | |
| Recent receipt of chemotherapy (yes) | 16, 38.1 | |
| Receipt of highly invasive surgical procedure (yes) | 19, 45.2 | |
| History of chronic pain (yes) | 21, 50.0 | |
| Analgesic use immediately before QST (yes) | 13, 31.0 | |

GED = general educational development; QST = quantitative sensory testing.

Most of the sample had endometrial cancer (76.2%) and stage I or II pathology (78.5%). In addition, 19 participants (45.2%) had a highly invasive exploratory surgical procedure, 15 (35.7%) had begun chemotherapy at the time of postsurgical study assessment, and five (11.9%) had acute postsurgical complications. Half of the study participants (N = 22, 50.0%) had a history of chronic pain, including fibromyalgia, sciatica, neuropathy, and/or arthritis, before being diagnosed with cancer (Table 1). There were no significant differences between women with and without histories of chronic pain in aftersensation pain at 15 seconds ($t(40) = 0.989$, $P = 0.329$) or 30 seconds ($t(40) = 1.419$, $P = 0.164$). Before quantitative sensory testing, 13 participants (31.0%) had taken analgesic medication. The most common analgesics used were oxycodone/APAP, hydrocodone/APAP, and ibuprofen.

There were no significant relationships between aftersensation pain at 15 seconds or 30 seconds and history of chronic pain, presence of advanced cancer stage, presence of poor-prognosis cancer, receipt of highly invasive surgery, or analgesic use immediately before testing (all $P > 0.10$) (Table 2). However, recent receipt of chemotherapy was significantly associated with greater aftersensation pain at 15 seconds ($r(42) = 0.309$, $P = 0.047$), but not with aftersensation pain at 30 seconds ($r(42) = 0.260$, $P = 0.096$).

Greater aftersensation pain at 15 seconds and 30 seconds was associated with greater MPQ[1] Sensory pain scores (15 seconds: $r(42) = 0.486$, $P = 0.001$; 30 seconds: $r(42) = 0.439$, $P = 0.004$) and greater PSQI Sleep Latency subscale scores (15 seconds: $r(42) = 0.422$,

1. The total MPQ score was also significantly correlated with aftersensation at 15 seconds ($r(42) = 0.455$, $P = 0.002$, and 30 seconds, $r(42) = 0.377$, $P = 0.014$).

**Table 2.** Correlations between aftersensation pain and variables of interest

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Aftersensation 15 s | 1 | 0.842** | –0.154 | 0.238 | –0.061 | –0.038 | 0.309* | 0.164 | –0.064 | 0.486** | 0.422** |
| 2. Aftersensation 30 s | 0.842** | 1 | –0.219 | 0.223 | 0.064 | 0.119 | 0.260 | 0.227 | –0.099 | 0.439** | 0.358* |
| 3. History of chronic pain | –0.154 | –0.219 | 1 | 0.072 | –0.401* | –0.048 | –0.196 | 0.258 | 0.216 | 0.122 | –0.085 |
| 4. Presence of advanced cancer stage | 0.238 | 0.223 | 0.072 | 1 | 0.325* | 0.125 | 0.663** | –0.235 | 0.175 | 0.149 | 0.257 |
| 5. Presence of poor-prognosis cancer | –0.061 | 0.064 | –0.401* | 0.325* | 1 | 0.202 | 0.485** | –0.214 | 0.099 | –0.217 | –0.046 |
| 6. Receipt of highly invasive surgical procedure | –0.038 | 0.119 | –0.048 | 0.125 | 0.202 | 1 | –0.023 | –0.195 | 0.158 | 0.031 | –0.067 |
| 7. Recent receipt of chemotherapy | 0.309* | 0.260 | –0.196 | 0.663** | 0.485** | –0.023 | 1 | 0.005 | –0.019 | 0.049 | 0.069 |
| 8. Analgesic use immediately before QST | 0.164 | 0.227 | 0.258 | –0.235 | –0.214 | –0.195 | 0.005 | 1 | –0.200 | 0.164 | 0.033 |
| 9. Depressive symptoms | –0.064 | –0.099 | 0.216 | 0.175 | 0.099 | 0.158 | –0.019 | –0.200 | 1 | 0.282 | 0.230 |
| 10. MPQ Sensory | 0.486** | 0.439** | 0.122 | 0.149 | –0.217 | 0.031 | 0.049 | 0.164 | 0.282 | 1 | 0.368* |
| 11. PSQI Sleep Latency | 0.422** | 0.358* | –0.085 | 0.257 | –0.046 | –0.067 | 0.069 | 0.033 | 0.230 | 0.368* | 1 |

*$P < 0.05$; **$P < 0.01$.

**Table 3.** Predicting aftersensation pain at 15 and 30 seconds

| | 15-Second Aftersensation | | | | | | 30-Second Aftersensation | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% Bootstrap CI for *B* | | | | | | 95% Bootstrap CI for *B* | | |
| Predictor | $\Delta R^2$ | *F* | *β* | Lower | *B* (SE) | Upper | $\Delta R^2$ | *F* | *β* | Lower | *B* (SE) | Upper |
| Block 1 | 0.142 | 2.105 | | | | | 0.176 | 2.708 | | | | |
| Recent receipt of chemotherapy | | | 0.278 | –0.931 | 7.020 (4.45) | 15.490 | | | 0.209 | –1.314 | 2.348 (1.89) | 6.110 |
| History of chronic pain | | | –0.152 | –11.921 | –3.729 (4.45) | 5.566 | | | –0.253 | –6.411 | –2.755 (1.96) | 1.133 |
| Analgesic medication use immediately before QST | | | 0.202 | –4.838 | 5.361 (5.09) | 15.781 | | | 0.291 | –0.804 | 3.432 (2.22) | 7.942 |
| Block 2 | 0.303** | 4.684 | | | | | 0.228** | 3.958 | | | | |
| Recent receipt of chemotherapy | | | 0.243 | –0.366 | 6.132 (3.69) | 13.808 | | | 0.179 | –1.118 | 2.002 (1.68) | 5.443 |
| History of chronic pain | | | –0.108 | –10.011 | –2.646 (3.99) | 5.430 | | | –0.222 | –6.214 | –2.420 (1.97) | 1.567 |
| Analgesic medication use immediately before QST | | | 0.069 | –6.807 | 1.828 (4.08) | 9.428 | | | 0.176 | –2.013 | 2.074 (2.15) | 6.608 |
| Depressive symptoms | | | –0.209 | –1.032 | –0.456 (0.30) | 0.174 | | | –0.175 | –0.412 | –0.169 (0.13) | 0.118 |
| MPQ Sensory | | | 0.431 | 0.085 | 0.695 (0.29) | 1.210 | | | 0.399 | 0.008 | 0.286 (0.13) | 0.513 |
| PSQI Sleep Latency | | | 0.284 | 0.371 | 3.112 (1.44) | 6.014 | | | 0.214 | –0.464 | 1.041 (0.69) | 2.271 |

CI = confidence interval; MPQ = McGill Pain Questionnaire; PSQI = Pittsburgh Sleep Quality Index; QST = quantitative sensory testing.
*$P < 0.05$; **$P < 0.01$.

$P = 0.005$; 30 seconds: $r(42) = 0.358$, $P = 0.020$). Depressive symptoms were not associated with aftersensation pain (Table 2).

After controlling for recent receipt of chemotherapy, history of chronic pain, and analgesic medication use immediately before QST, bootstrapped linear regression analyses revealed that greater sleep onset latency ($B = 3.112$, $P = 0.039$, bias-corrected and accelerated (BCa) 95% confidence interval [CI] = 0.371 to 6.014) and greater MPQ Sensory pain ($B = 0.695$, $P = 0.023$, BCa 95% CI = 0.085 to 1.210) were independently associated with greater aftersensation pain at 15 seconds (Table 3). Results from the second model revealed that only Sensory pain ($B = 0.286$, $P = 0.045$, BCa 95% CI = 0.008 to 0.513) was significantly associated with aftersensation at 30 seconds (Table 3). Depression was not significantly associated with aftersensation pain at either 15 seconds ($B = –0.456$, $P = 0.113$, BCa 95% CI = –1.032 to 0.172) or 30 seconds ($B = –0.207$, $P = 0.167$, BCa 95% CI = –0.412 to 0.118). The overall models explained 44.5% of the variance in aftersensation pain at 15 seconds and 40.4% of the variance in aftersensation pain at 30 seconds.

## Discussion

The current study examined whether greater self-reported sensory pain and longer sleep onset latency were associated with aftersensation pain above and beyond known factors that contribute to pain following surgical resection for gynecologic malignancy. Of the 42 participants in the study, 50% had a history of chronic pain, 35.7% of participants underwent adjuvant chemotherapy, 19.1% had stage III or IV cancer, and 45.2% underwent highly invasive surgeries.

The results of the current study indicate that after controlling for recent receipt of chemotherapy, analgesic medication use before QST, and history of chronic pain, longer sleep onset latency and greater sensory pain significantly predicted greater aftersensation pain at 15 seconds. Both effect sizes were in the medium to large effect size range. Only greater sensory pain significantly

predicted greater aftersensation pain at 30 seconds. Although sleep onset latency did not significantly predict aftersensation pain at 30 seconds, the relationship between the variables remained positive ($B = 1.041$). This nonsignificant relationship may be due to the lower pain ratings given at 30 seconds resulting in a floor effect and greater difficulty identifying significant relationships between variables. Overall, these findings are consistent with the literature indicating that sleep disturbances, particularly longer sleep latency, are significantly related to greater perceived pain in patients with cancer [21].

As noted above, individuals with more clinical sensory pain had significantly higher aftersensation pain at both 15 and 30 seconds. The significant relationship between sensory pain and aftersensation pain is not surprising as previous literature has found that central sensitization is a common feature in chronic pain patients, purported to be related to central nervous system plasticity [42]. These results suggest that participants with more clinical pain showed central sensitization related to poorer endogenous inhibitory control of pain. Importantly, this study extends the robust literature of central sensitization in chronic pain patients to individuals undergoing cancer surgery.

Depressive symptoms were not a significant predictor of aftersensation pain in this sample. This may be due to the low prevalence of clinically significant depressive symptoms in our sample, possibly due to time of measurement. Postsurgical study assessment occurred six to eight weeks after surgery. Only eight participants (19%) reported depressive symptoms above minimal levels. There were no significant differences in aftersensation pain at 15 seconds ($t(40) = -0.295$, $P = 0.770$) or 30 seconds ($t(40) = 0.229$, $P = 0.820$) between groups reporting minimal depressive and mild to severe depressive symptoms. Relatedly, depressive symptoms were not significantly associated with any of the control variables or other predictors (Sleep Latency, Sensory pain). Greater depressive symptoms had nonsignificant relationships with history of chronic pain, greater sleep onset latency, greater Sensory pain, and nonusage of analgesics before QST ($r = 0.200$–$0.282$). These small to medium effect sizes may have failed to reach significance due to low statistical power associated with our small sample size.

Our findings failed to find significant relationships between aftersensation pain and cancer type, cancer stage, or highly invasive surgery. Only recent receipt of adjuvant chemotherapy was significantly related to aftersensation pain at 15 seconds. The significant relationship found between aftersensation pain and chemotherapy adds to the body of literature implicating chemotherapy as a contributor to cancer-related pain and peripheral neuropathy [25]. The lack of statistically significant findings between aftersensation pain and cancer type/stage and surgical invasiveness may also be due to the time of measurement. The biobehavioral effects of cancer type/stage and surgical invasiveness on aftersensation pain may have been greater with QST administration closer in time to surgery (e.g., two weeks vs six to eight weeks). However, the ethical concerns of administering a temporal summation of pain protocol to patients only several weeks after a major surgery may preclude testing this hypothesis. Participants receiving adjuvant chemotherapy completed at least one chemotherapy cycle between surgery and postsurgical study assessment. Most of these participants were also scheduled for additional cycles after postsurgical study assessment. Thus, the biobehavioral effects of chemotherapy on aftersensation pain may have been stronger and more persistent compared with the other control variables.

In cancer patients, longer sleep onset latency may be due to maladaptive thoughts, pain, and health concerns [11]. Behavioral interventions that target these factors may provide a unique pathway to assist in reducing subjective pain via improving sleep quality. Previous research has found cognitive behavioral therapy to be effective in reducing sleep disturbances and perceived pain [43,44]. The use of imagery and coping skills training has also been found to reduce sleep disturbances and pain in cancer patients [45]. Future research should explore whether interventions that improve sleep and subjective pain may contribute to lower pain sensitivity and better quality of life in gynecologic cancer.

Study limitations include a small and relatively homogeneous sample. Most participants were Caucasian, married, and diagnosed with early-stage endometrial cancers. Therefore, we cannot generalize to larger and more diverse samples of women with gynecologic cancer. However, this study is the first to the authors' knowledge to perform quantitative sensory testing in a sample of women undergoing surgical resection for gynecologic malignancy and may provide a foundation for better understanding of the potential pain mechanisms associated with gynecologic cancer. In particular, the ability to examine quantitative and self-reported pain following gynecologic surgery elucidates potential pathways that may be targeted for intervention during and after cancer treatment.

### Clinical Significance

The results from this study extend previous research implicating clinical pain and sleep disturbance in central sensitization as a key mechanism in chronic pain [26]. By identifying those with greater sleep disturbances and greater reported subjective pain, we may be able to identify women at risk for central sensitization of clinical pain in gynecological cancer.

## Conclusions

Longer sleep onset latency and higher subjective sensory pain were related to greater aftersensation of experimentally induced pain in women postsurgery for gynecologic

cancers. The results suggest that women with more cancer-related pain show symptoms of central sensitization and poor endogenous inhibitory control of pain. Interventions that improve sleep and subjective sensory pain during the perisurgical period may reduce risk for central sensitization of pain.

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