TAXANE-INDUCED MUSCULOSKELETAL PAIN IN WOMEN WITH OVARIAN CANCER

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TAXANE-INDUCED MUSCULOSKELETAL PAIN IN WOMEN WITH OVARIAN CANCER

Taxane-induced musculoskeletal pain (TIMP) is musculoskeletal pain that includes myalgia (i.e., diffuse muscle pain, usually accompanied by malaise) and/or arthralgia (i.e., joint pain) that occurs following treatment with taxane-based chemotherapy. TIMP is a symptom that is clinically reported as negatively affecting most cancer survivors receiving taxane-based chemotherapy; however, TIMP is not comprehensively understood. The purpose of this dissertation was to conduct a cross-sectional, descriptive, correlational pilot study to describe TIMP in women with ovarian cancer who were being or had been treated with paclitaxel-containing regimens. Specific aims were to: (1) describe the TIMP symptom experience (intensity, distress, duration, location, quality, temporal pattern, aggravating and alleviating factors, and pain management); (2) describe the associations between TIMP (intensity, distress) and co-occurring symptoms (pain [general], peripheral neuropathy, impaired sleep, fatigue, emotional distress, and/or hot flashes); and (3) identify associations between TIMP (intensity, distress) and patient-reported outcomes (interference with daily activities, physical functioning, and health-related quality of life). Primary data collection was performed on a convenience sample of 15 women with ovarian cancer. Participants were recruited from an outpatient cancer clinic, local cancer support communities, and a national cancer survivors' research registry. Descriptive statistics and Spearman's correlations were used.

Findings showed TIMP is moderate to severe in intensity on average, constant, affecting a large area of the body, and aggravated by everyday walking. Greater TIMP intensity or distress was associated with greater intensity and interference of most co-

occurring symptoms and was associated with greater interference with daily activities, worse physical functioning, and worse health-related quality of life. Nurses are encouraged to comprehensively assess TIMP using structured, validated tools for pain to better intervene on aggravating and alleviating factors and pain management regimens. Prospective, longitudinal studies with larger sample sizes are needed to further understand TIMP and its impact on cancer survivors.

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LIST OF ABBREVIATIONS

Abbreviation	Term
TIMP	Taxane-induced musculoskeletal pain
IOM	Institute of Medicine
NIH	National Institutes of Health
NCI	National Cancer Institute
NINR	National Institute of Nursing Research
ACS	American Cancer Society
ONS	Oncology Nursing Society
IUSCC	Indiana University Simon Cancer Center
IRB	Institutional Review Board
DTQ	Demographic and Treatment Questionnaire
SCQ	Self-Administered Comorbidity Questionnaire
BPI	Brief Pain Inventory
NPS-CIN	Neuropathy Pain Score-Chemotherapy Induced Neuropathy Specific
PROMIS	Patient-Reported Outcomes Measurement Information System
HFRDIS	Hot Flash Related Daily Interference Scale
PF-10	Performance 10
FACT-G	Functional Assessment of Cancer Therapy- General
REDCap	Research Electronic Data Capture
HIPAA	Health Insurance Portability and Accountability
SPSS	Statistical Package for the Social Science
M	Mean
Mdn	Median
SD	Standard Deviation

CHAPTER 1

This chapter introduces the dissertation topic of taxane-induced musculoskeletal pain (TIMP) in women with ovarian cancer. The chapter provides a discussion of the significance of the topic, identifies the purpose and specific aims of the study, and outlines the study methods. In the subsequent chapters, the manuscripts related to this dissertation study are discussed.

Significance

TIMP and the TIMP Symptom Experience

TIMP is musculoskeletal pain that includes myalgia (i.e., diffuse muscle pain, usually accompanied by malaise) and/or arthralgia (i.e., joint pain) that occurs following treatment with taxane-based chemotherapy.[1] It appears to affect more than half of patients treated with taxane chemotherapy agents such as paclitaxel.[1] TIMP appears to be distinct from other common taxane-induced symptoms including peripheral neuropathy.[2-14] Peripheral neuropathy is neuropathic pain (i.e., sensory nerve involvement) with unusual or increased reaction to stimuli or loss of sensation (i.e., paresthesia and pain), characteristically occurring in the fingers and toes (i.e., “glove and stocking” distribution), persisting at rest or at night, and alleviated while walking.[15-17] In contrast, TIMP is musculoskeletal pain aggravated by movement and likely has different clinical, somatosensory, and psychological parameters that distinguish it from peripheral neuropathy.[15] Although chemotherapy-induced peripheral neuropathy is often reported as the most common taxane-related symptom, in at least one review, reports of TIMP closely approximated or exceeded the incidence of peripheral neuropathy.[18] This has important clinical implications in that treatments targeting neuropathic pain (i.e., peripheral neuropathy) may need to be different from those targeting TIMP.[19]

The TIMP symptom experience is not comprehensively understood.[2-13] In the investigator's systematic review,[20] out of 688 articles pertaining to taxane-based chemotherapy, only 12 studies (1.7%) included evaluable data related to TIMP.[2-13] Moreover, 10 of the 12 articles (83%) were clinical trials evaluating the safety, tolerability, and/or efficacy of taxane-based chemotherapy, with TIMP mentioned only as a side effect.[2, 3, 5-11, 13] All studies assessed TIMP intensity only, using a limited (i.e., not comprehensive) toxicity grading method. No studies comprehensively assessed TIMP using the common symptom assessment parameters of intensity, distress, duration, location, quality, temporal pattern, aggravating and alleviating factors, and pain management even though pain literature suggests that practitioners evaluating pain for the first time should start with multidimensional instruments to obtain an overview of the symptom.[21] Once core areas of the pain have been identified, then more specific, streamlined assessments can be used. Also, the investigator's review supported the literature which suggests TIMP is likely common[18, 22] – affecting up to 94% of patients[20] - and intensity appears to be dose dependent with doses of paclitaxel > 200mg/m^2 leading to more frequent and intense TIMP.[23] However, other details of TIMP remain unstudied and unspecified. In other non-oncology populations, such as primary care patients, musculoskeletal pain is a significant problem. It is typically localized simultaneously in both the axial (head, neck and spine, ribs, and pelvis) and peripheral (extremities) skeleton.[24] Musculoskeletal pain can also arise from the muscles, ligaments, tendons, or joints and can be localized or generalized.[25] These facts, from primary care patients, suggest there is more to be understood about TIMP than intensity ratings alone.

TIMP and Co-occurring Symptoms

TIMP likely co-occurs with symptoms such as general pain, peripheral neuropathy, impaired sleep, fatigue, emotional distress (i.e., depression and anxiety), and/or hot

flashes. Research on co-occurring cancer symptoms, or symptom clusters, suggests co-occurring symptoms may not be independent entities, but rather symptoms that interact synergistically.[26, 27] A current research priority, clusters of co-occurring symptoms have a greater adverse impact on outcomes than individual symptoms.[26] Among all cancer survivors, frequent co-occurring symptoms include pain, impaired sleep, low energy/fatigue, depression, and anxiety.[1, 26, 28-31] In addition to hot flashes, these symptoms have also been highlighted in studies specific to women with ovarian cancer. [32-35] Prolonged or ineffective management of treatment-related symptoms can contribute to treatment noncompliance, worsening of symptoms, reduced health-related quality of life, and overall poorer patient outcomes.[1] In non-oncology populations, such as primary care patients, pain and depression co-occur at a rate of 30-50%.[36, 37] In addition, many primary care patients seeking treatment for pain report significantly impaired sleep, which is known to further aggravate pain, reduce pain inhibitory responses, increase emotional distress, and reduce well-being.[38] Because TIMP has not been well researched, associations among TIMP and other co-occurring symptoms likely exist but are currently unspecified.

TIMP and Patient-reported Outcomes

TIMP is likely to be associated with patient-reported outcomes including greater interference with daily activities, poorer physical functioning, and lower health-related quality of life. Although research to date has not identified TIMP to be a dose-limiting toxicity, the myalgia and/or arthralgia experienced by patients receiving taxane-based chemotherapy can result in impaired mobility, secondary to the limitation of joint function, and the experience of pain can affect physical functioning.[1] Though it has not been widely studied, TIMP very likely undermines cancer survivors' health-related quality of life in ways that are similar to the burden of persistent musculoskeletal pain seen in non-oncology populations. Data from non-oncology populations suggest the following. Pain is among the

most common reasons for temporary and permanent work disability.[39, 40] The World Health Organization recognizes the significant contribution of musculoskeletal conditions to the global burden of disease.[38] Additionally, the Institute of Medicine (IOM) has highlighted the significant functional and economic effects of musculoskeletal pain.[41] Musculoskeletal pain is the most common, disabling, and costly of all pain complaints.[40] Pain is known to be even more prevalent in individuals with psychiatric comorbidity, specifically mood disorders, and is a strong predictor of both onset and persistence of depression; likewise, depression is a strong predictor of pain.[42] Furthermore, the comorbidity of pain and chronic conditions, such as impaired sleep and emotional distress, decrease an individual's active coping in addition to negatively impacting health-related quality of life, disability, and even response to treatment.[36, 42] These facts suggest TIMP is likely negatively associated with patient-reported outcomes. However, because it has not been comprehensively studied, the strength of the associations among TIMP and interference with daily activities, physical functioning, and health-related quality of life are unknown.

TIMP and Ovarian Cancer

Women with ovarian cancer represent an ideal population for studying TIMP for three reasons. First, ovarian cancer affects over 21,000 American women annually, with over 190,000 survivors estimated to be living in the United States in 2012, and yet ovarian cancer survivors are poorly represented in cancer research.[43, 44] Second, women with ovarian cancer do not take aromatase inhibitors, which cause musculoskeletal pain[45-47] and could confound understanding of TIMP. Third, women with ovarian cancer do not typically require prophylaxis with growth factor,[48] which causes musculoskeletal symptoms[1] and could confound understanding of TIMP.

A Comprehensive Assessment to Increase Understanding of TIMP

A comprehensive assessment of TIMP is the first logical step in building symptom science towards greater understanding of this treatment-related symptom. To improve patient-reported outcomes in cancer care, control of cancer treatment-related symptoms such as TIMP is essential.[28] However, clinical trials designed to prevent and treat symptoms require a foundational knowledge of the symptom experience as well as the type and strength of relationship with co-occurring symptoms and patient-reported outcomes. Specifically, the proposed research addressed national priorities to generate new knowledge to alleviate symptom burden and improve functioning and health-related quality of life in persons affected by cancer by describing the TIMP symptom experience (Aim 1); examining the associations between TIMP (intensity, distress) and co-occurring symptoms (Aim 2); and examining the associations between TIMP (intensity, distress) and patient-reported outcomes (Aim 3) among women with ovarian cancer who were being or had been treated with paclitaxel-containing regimens. Findings are foundational for the investigator's program of research in symptom science. Ultimately, the investigator plans to build upon her minor in epidemiology and conduct a larger, population-based, prospective, longitudinal study to expand understanding of TIMP to fully inform the development, timing, and testing of effective interventions to manage TIMP (e.g., National Institutes of Health [NIH] R01).

Topical Fit to National Priorities

This study addresses the important national research priority of symptom management set forth by the National Cancer Institute (NCI) Office of Cancer Survivorship,[49] the National Institute of Nursing Research (NINR),[50] the American Cancer Society (ACS),[51] the IOM,[52] and the Oncology Nursing Society (ONS).[53, 54] Cancer and cancer treatment-related symptoms can profoundly affect an individual's health-related

quality of life throughout survivorship.[55] This study aligns with (1) the NCI Office of Cancer Survivorship's mission to enhance quality of survival and minimize physical and psychosocial adverse effects of cancer and its treatment during survivorship;[49] (2) NINR's focus on symptom management research that will improve the understanding of symptom science and assist in developing new symptom management strategies to improve quality of life in chronic illness, including cancer;[50] (3) ACS's priority to improve health-related quality of life through symptom surveillance;[51] (4) IOM's priority for cancer care that is patient-centered in managing symptoms and side effects from treatment;[52] and (5) ONS's symptom management research priority to manage cancer symptoms and symptom clusters, as well as side effects related to cancer treatment.[53, 54] Additionally, recognition of patient-reported outcomes, supported by the NIH, is of growing research interest and requires attention to standardized measurement of health-related quality of life outcomes in populations including cancer survivors.[56-59]

Purpose and Specific Aims

Given the limitations in our knowledge about TIMP, the next logical step was to carefully study TIMP, its co-occurring symptoms, and its relationship to patient-reported outcomes. Because paclitaxel is the most common treatment for women with ovarian cancer and because this group is a poorly represented cancer population, this proposal focuses on survivors of ovarian cancer. Therefore, the **purpose** of this cross-sectional, descriptive, correlational, pilot study was to describe TIMP in women with ovarian cancer who were being or had been treated with paclitaxel-containing regimens. **Specific aims** were to:

Aim 1: Describe the TIMP symptom experience (intensity, distress, duration, temporal pattern, location, quality, aggravating and alleviating factors, and pain management);

Aim 2: Describe the associations between TIMP (intensity, distress) and co-occurring symptoms (pain [general], peripheral neuropathy, impaired sleep, fatigue, emotional distress, and/or hot flashes);

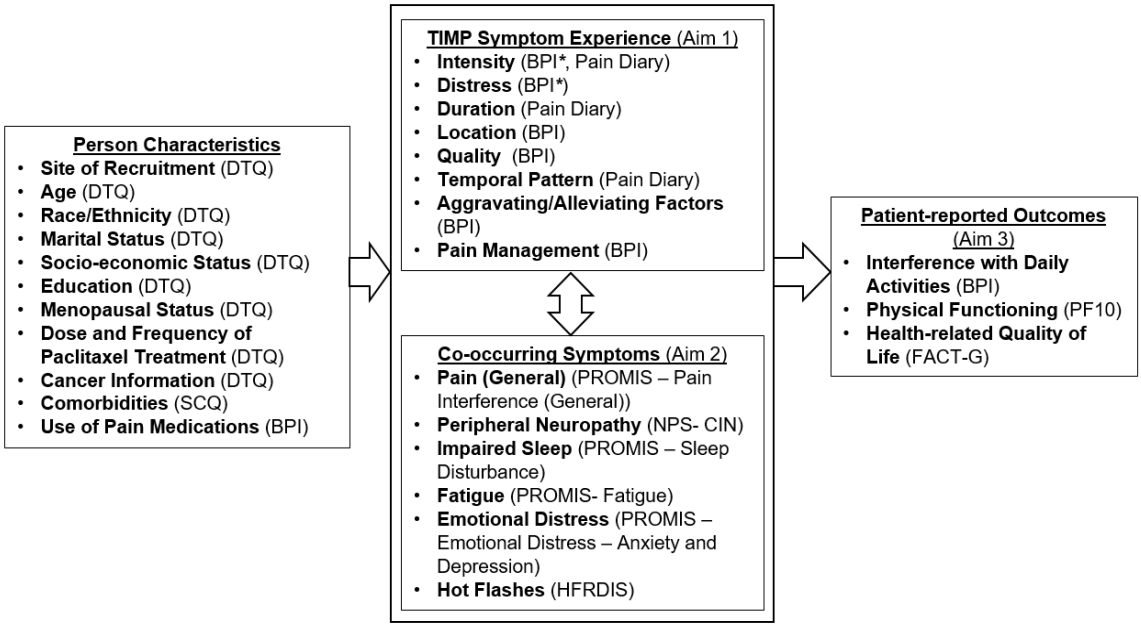
Aim 3: Identify associations between TIMP (intensity, distress) and patient-reported outcomes (interference with daily activities, physical functioning, and health-related quality of life)

Approach

Guiding Theoretical Frameworks and the Conceptual Model

The proposed research was guided by two well-established conceptual models with substantial empirical evidence for guiding this study[60-64] (Figure 1-1, below). The Theory of Symptom Management and the Theory of Unpleasant Symptoms[61, 63, 65] guide the symptom dimensions to be assessed (Aim 1), highlight the importance of evaluating co-occurring symptoms (Aim 2), and identify important patient-reported outcomes to be evaluated (Aim 3). Symptoms are subjective experiences reflective of changes occurring in physical functioning, sensations, or cognition, and they are the most frequent reason individuals seek health care.[60, 61] Both theories emphasize essential symptom management concepts including, but not limited to, personal characteristics influencing symptoms and outcomes, descriptions of the symptom experience (intensity, distress, duration, location, quality, temporal pattern, aggravating or alleviating factors, and pain management, as well as co-occurring symptoms), and associations with patient-reported outcomes.[61, 63, 65]

Figure 1-1: Multidimensional Symptom Assessment Model for TIMP



*Note: An * designates the intensity and distress measures from the BPI only will be used to identify associations with co-occurring symptoms (Aim 2) and patient-reported outcomes (Aim 3).*
DTQ= Demographic and Treatment Questionnaire; SCQ= Self-Administered Comorbidity Questionnaire; BPI= Brief Pain Inventory-Long Form; PROMIS= Patient Reported Outcomes Measurement Information System; NPS-CIN= Neuropathy Pain Score-Chemotherapy-Induced Neuropathy-Specific; HFRDIS= Hot Flash Related Daily Interference Scale; PF10= Performance 10; FACT-G= Functional Assessment of Cancer Therapy-General.

Design

This was a cross-sectional, descriptive, correlational pilot study which addressed specific Aims 1-3.

Sample

A convenience sample of 15 women were recruited from the cancer clinics at Indiana University. Data from the Indiana University Simon Cancer Center (IUSCC) clinics indicate 264 women with ovarian cancer were seen in the clinics in the last calendar year, assuring feasibility of recruitment even if accrual rates were as low as 8% in a one-year period or as low as 5% in an 18-month period.

Sample Criteria

Inclusion criteria were: (1) ≥ 21 years of age; (2) diagnosed with ovarian cancer; (3) have a history of no other cancer diagnoses (basal cell skin cancer will be allowed); (4) undergoing active treatment with paclitaxel (must have received at least one dose), or have received treatment with paclitaxel in the past; (5) report experiencing myalgia and/or arthralgia after starting paclitaxel treatment; (6) self-reported ability to read and speak English; and (7) willing and able to participate in the study. To eliminate confounding factors, exclusion criteria were: (1) confirmed bone metastases and/or (2) have received growth factor with their chemotherapy treatment.

Study Procedures

Institutional Review and Approvals

The investigator received IUSCC approval and IU Institutional Review Board (IRB) approval. Waivers of written informed consent and written authorization to use protected health information were sought from the IRB. A study information sheet was used to explain the study.

Recruitment and Verbal Consent and Authorization

To recruit potential participants, the investigator and her designee worked with a medical oncology physician at the IUSCC. The investigator or her designee was available to meet with interested women during clinics. Potential participants were identified by the physician or his designees, who briefly introduced the study to potential participants in person at the end of their clinic visits and asked if they were interested in learning more about the study. If women agreed, the investigator or her designee entered the room to provide more detailed study-related information and answered questions. The investigator or her designee carefully reviewed the Study Information Sheet including the risks,

benefits, specific activities, and voluntary nature of the study and addressed any potential questions. Interested women were asked to provide verbal consent and verbal authorization to use protected health information before research staff conducted eligibility screening. Ineligible women were informed they were ineligible and thanked for their interest. Eligible women received a copy of the Study Information Sheet and completed data collection on site or received a web link to complete the study from home. The investigator and her designee tracked reasons for disinterest and ineligibility.

Additionally, the applicant worked with Rare Patent Voice, LLC©[66] to recruit potential participants. Rare Patient Voice, LLC© is a research company focused on promoting health outcomes in patients with rare disorders. Rare Patient Voice, LLC© has a registry of over 900 ovarian cancer survivors who have agreed to be contacted for future studies.[66] The investigator also used additional recruitment methods (see below Potential Problems and Alternative Solutions) because monthly accrual was not reached in the first three months.

Data Collection

Eligible women could take part in a study visit at the cancer clinic, preferably the same day recruitment occurred. At the visit, the investigator or her designee provided specific instructions to prevent participant confusion about which symptom was being evaluated in a given questionnaire. Women spent approximately 20 minutes completing questionnaires via a secure, web-based database. Women were given a TIMP Pain Diary with instructions for completing it during their next full cycle of paclitaxel (2 minutes each day for 28 days) and returning it in a pre-addressed, stamped envelope. If participants could not stay to complete the questionnaires, they received a web link to complete questionnaires at home (or given paper copies, if that was their preference, to take home to complete and return by mail with the TIMP Pain Diary). If eligible participants wanted to

speak to a member of the study team before agreeing to participate, they were contacted by the e-mail (e-mails were sent using IU Outlook) or telephone number provided on the Screening and Eligibility Form for follow up and additional information. If participants were agreeable to participating in the study after additional follow up, they either received a web link to complete questionnaires online at home or were mailed paper copies to be returned to the study team by mail. Participants received a $25 gift card for their time, effort, and any travel expenses incurred. Gift cards were mailed after the TIMP Pain Diaries (and other paper forms, if used) were returned. The investigator made reminder/troubleshooting calls and e-mails to those participants who do not return their diaries.

Additionally, Rare Patient Voice, LLC© sent a mass e-mail message to their ovarian cancer registry explaining the study. A link to the study materials in the REDCap database was included in the mass e-mail message. Potential participants were able to download and review the Study Information Sheet as well as the Authorization Form so they could read more about the study, the requirements for participation, and be provided with contact information for follow up if necessary. If women chose to proceed, screening and eligibility questions were asked next. Based upon the potential participant's responses, eligibility was determined within REDCap. Ineligible women received a message informing them they were ineligible and thanking them for their interest in the study. Eligible women were directed to the subsequent section where they acknowledged they were providing consent and authorization to use protected health information by clicking on appropriate buttons. Participants were guided through each of the questionnaires as they provided their responses by direct data entry. Upon completion of the questionnaires, participants were informed they must also complete the TIMP Pain Diary in order to complete the study and receive a gift card. Women were informed that daily e-mail links would be sent to them for the next 28 days. Daily links asked women to

record their pain intensity (morning and bedtime) for the previous day. After 28 days, when the diaries were completed, participants were mailed a $25 gift card at the mailing address provided in REDCap. Rare Patient Voice, LLC© participants were given the option to forgo providing their mailing address if they chose to have their responses remain anonymous; however, this prohibited the study team from providing the participant with the gift card incentive as payment for their time and effort. This was explained in the initial mass e-mail message describing the study to potential participants. Finally, if Rare Patient Voice, LLC© participants provided their mailing address and symptom scores on questionnaires were elevated, participants were notified by letter accompanying the gift card incentive. The letter encouraged participants to follow up with their healthcare provider. Letters were not provided to those who chose to remain anonymous when completing the study.

Measures

Measures are described below. Special instructions were provided at the top of all TIMP-specific measures to prompt participants to focus on TIMP-specific pain.

Person Characteristics

Demographic information including site of recruitment, age, race/ethnicity, marital status, socio-economic status (employment and ability to pay for basics), education, and menopausal status was self-reported and recorded by participants using the Demographic and Treatment Questionnaire (DTQ). Disease and treatment-specific information including the dose and frequency of paclitaxel treatment (and the date of last treatment) and cancer information (date of cancer diagnosis, stage of disease, and dates and types of treatments including surgery, chemotherapy, and radiation) was also self-reported and recorded by participants using the DTQ. Comorbidities were evaluated using the Self-Administered Comorbidity Questionnaire (SCQ) modified. On this 12-item validated tool, respondents

mark “yes” or “no” as to whether they have each of 12 health conditions and, if *yes*, whether they are receiving treatment for it (*yes/no*) and whether it limits their activities (*yes/no*). A maximum of 3 points are given to conditions that are present, being treated, and limiting current activities. Therefore, higher scores indicate greater comorbidity. Cronbach’s alpha, including among cancer patients, was 0.94.[67] This tool has been modified to include six additional conditions affecting women, including fibromyalgia, lupus, thyroid disease, seizures, headaches, and an option for “other.” Conditions that may impact reports of musculoskeletal pain (e.g., arthritis, fibromyalgia) were assessed. Finally, use of pain medications was assessed using 2 items on the Brief Pain Inventory (BPI) – Long Form.[68] This 32-item validated tool for pain assesses use of pain medications (i.e., *yes*/*no* do you have pain requiring medication and an open-ended item where participants indicate names of treatments or medications used for pain), pain intensity, distress, duration, location, quality, aggravating or alleviating factors, and pain management in the past week. The BPI has been used in patients with pain related to chronic conditions (e.g., cancer, osteoarthritis, low back pain), or acute conditions (e.g., postoperative pain). Cronbach’s alpha has ranged from 0.77 to 0.91.[68]

The TIMP Symptom Experience

Intensity: Two methods were: (1) the mean of BPI items #1 to #4[68] and (2) TIMP Pain Diary prospective ratings of TIMP intensity at two daily time points (upon waking and before going to bed) over 28 days (one chemotherapy cycle). Distress was measured using BPI item #5,[68] which asked participants to rate distress caused by TIMP on a 0-10 scale. Duration was assessed using the TIMP Pain Diary as the total number of days and the total number of nights with pain reported. Location was assessed by asking participants to shade relevant parts of BPI item #6,[68] the body diagram. Quality was evaluated using BPI item #7,[68] where participants circled adjectives to describe their TIMP.

Temporal pattern was evaluated using the TIMP Pain Diary intensity ratings over time. Aggravating/alleviating factors were assessed using BPI items #8 to #11,[68] where participants open-endedly reported what makes their TIMP better or worse; indicated, on a 0 to 100 scale, the percentage of relief from pain treatments or medications; and circled, from a list of possible choices, methods that relieved pain. Finally, pain management was evaluated using BPI items #12 to #14,[68] which provided categorical options assessing period of pain relief provided by medications and frequency of pain medication. In addition, BPI items #15 to #19[68] included yes/*no* items about pain management and BPI item #20[68] was an open-ended question about medications not prescribed by the doctor and taken for pain by the participant.

Co-occurring Symptoms

Pain (general): PROMIS – Pain Interference (General) – Short Form 8a, an 8-item validated tool for pain interference not related to TIMP (e.g., headache), this shortened tool correlated r=0.95 with items from the original tool. Item responses (1=*not at all* to 5=*very much*) are summed and higher scores indicate greater pain interference. Alpha for scores that were +/- 2 standard deviations from the mean were 0.11 to 0.99.[57] Peripheral neuropathy: Neuropathy Pain Score (Chemotherapy-Induced Neuropathy-Specific) (NPS-CIN), is a 6-item validated tool for chemotherapy-induced peripheral neuropathy pain with Cronbach's alpha=0.96. Item responses (0=*not at all* to 4=*excruciating*) are summed and higher scores indicate greater pain.[69] Impaired sleep: PROMIS – Sleep Disturbance – Short Form 8a, is an 8-item validated tool. This shortened tool correlated r=0.96 with items from the original tool. Item responses (1=*not at all* to 5=*very much*) are summed and higher scores indicate greater sleep disturbance. Alpha for scores that were +/- 2 standard deviations from the mean were 0.88 to 0.97.[57] Fatigue: PROMIS – Fatigue – Short Form 8a, is an 8-item validated tool. This shortened tool correlated r=0.76 with items from the

original tool. Item responses (1=*not at all* to 5=*very much*) are summed and higher scores indicate greater fatigue. Alpha for scores that were +/- 2 standard deviations from the mean were 0.95 to 1.00.[57] Emotional distress: PROMIS – Emotional Distress – Anxiety – Short Form 8a and the PROMIS – Emotional Distress – Depression – Short Form 8a are each 8-item scales. Each of these shortened tools correlated r=0.96 with items from the original tool. Item responses (1=*not at all* to 5=*very much*) are summed and higher scores indicate greater anxiety or depression. Alphas for scores that were +/- 2 standard deviations from the mean were 0.62 to 0.98 for anxiety and 0.47 to 0.99 for depression.[57] Hot flashes: The Hot Flash Related Daily Interference Scale (HFRDIS) is a 10-item scale measuring how much hot flashes interfere with 9 daily activities and quality of life over the past two weeks. Item responses (0 (*not at all*) to 10 (*completely interfered*) are summed and higher scores indicate greater hot flash interference.[70] Cronbach's alphas are consistently > .90.[71] PROMIS measures are advantageous because they: (1) are from standardized scales that have been widely used in various populations, including cancer;[57-59] (2) have been used in prior work conducted by Dr. Kroenke (committee member),[72] both independently and in combination with the investigator; and (3) will allow for future comparison with other non-cancer populations.

Patient-reported Outcomes

Interference with daily activities associated with TIMP was evaluated using the arithmetic mean of the 7 BPI interference items.[68] Cronbach's alphas have ranged from 0.77 to 0.91[68] Physical functioning: The Performance 10 (PF10) is a valid and reliable 10-item scale that is the physical functioning subscale of the MOS-SF-36, one of the most commonly used measures of health-related quality of life.[73, 74] Cronbach's alphas generally exceed 0.90.[73, 74] Health-related quality of life: The Functional Assessment of Cancer Therapy-General (FACT-G) is a valid 28-item tool assessing physical well-being,

social/family well-being, emotional well-being, and functional well-being. Item responses (0=*not at all* to 4=*very much*) yield total scores ranging from 0 to 112, with higher scores indicating higher health-related quality of life. Cronbach's alpha is 0.89.[75]

Analysis

Data Entry and Management

Data was entered into a secure, web-based REDCap[76] (Research Electronic Data Capture) database. Data not directly entered by participants was entered by the investigator and double-checked after two weeks elapsed. REDCap servers are secure and aligned with Health Insurance Portability and Accountability Act (HIPAA) regulations. REDCap incorporates real-time validation rules (with automated data type and range checks) at the time of entry. Prompts alerted the respondent if any items were missed. Data was exported for analysis to SPSS® version 24. Case summaries detected missing items or out-of-range values. Only diaries with at least 90% of all possible ratings were used, as previously done in Dr. Carpenter's (Co-chair) studies.[77-79]

Data Analysis

Person characteristics were evaluated using frequencies (nominal/ordinal) and descriptive statistics (interval/ratio). Information was used to describe the sample in the dissertation publications.

Aim 1 Analysis

Aim 1 Analysis: Describe the TIMP symptom experience (intensity, distress, duration, location, quality, temporal pattern, aggravating and alleviating factors, and pain management). Descriptive statistics, including frequencies, percentages, mean, median, mode, standard deviations, and 95% confidence intervals, were produced to describe

each dimension of the symptom experience. **Intensity:** BPI intensity ratings were reported as mean, median, mode, standard deviation, and range. TIMP Pain Diary ratings were reported as morning, nighttime, and combined mean, median, mode, standard deviation, and range for the 28 days. **Distress:** Individual scores on this 0-10 scale were analyzed and presented as mean, median, mode, standard deviation, and range. **Duration:** TIMP Pain Diary intensity ratings across 56 possible time points (28 days x 2 daily time points) were presented as a total overall percentage of time points where pain was present. For example, women rating intensity $\geq$ 1 at all 56 time points (28 days x 2 daily time points) would score as pain duration 100%, those with ratings $\geq$ 1 on 28 of 56 time points as pain duration 50%. If only morning or night pain was recorded, the duration was considered to be one-half day. **Location:** The body diagram was divided into 8 sections including: (1) anterior head and neck; (2) posterior head and neck; (3) anterior thorax; (4) posterior thorax; (5) right shoulder, arm, elbow, forearm, wrist, hand; (6) left shoulder, arm, elbow, forearm, wrist, hand; (7) right hip, thigh, knee, leg, ankle, foot; and (8) left hip, thigh, knee, leg, ankle, foot. Frequencies and percentages were calculated in accordance with categorical variables for both the total number of areas reported by the women and the number of women reporting pain in each area. **Quality:** BPI descriptors endorsed were given a value of 1. This allowed calculation of percentages of women who endorsed each descriptor, the ability to summarize the top 3 to 5 descriptors, and total the number of descriptors endorsed (mean, median, standard deviation, range). **Temporal pattern:** The mean weekly morning and nighttime intensity ratings (with 95% confidence intervals) were graphed over time for the entire sample as well as each individual. **Aggravating and alleviating factors:** Answers to categorical and BPI open-ended questions were coded using basic content analysis to develop commonly occurring categorical themes and analyzed by frequencies and percentages. Percentages of BPI pain relief ratings were described as such, along with frequencies and mean, median, standard deviation, and

range. **Pain management:** BPI questions 12 to 14 were analyzed according to frequencies and percentages for the categorical options given for period of pain relief provided by medications and frequency of pain medication. Questions 15 to 19 were coded categorically and were evaluated using frequencies and percentages. Question 20 was analyzed using basic content analysis to develop commonly occurring categorical themes for classes and/or names of specific medications, which were further described by frequencies and percentages. Coding for all content analyses used in the Aim 1 analysis were verified by Drs. Carpenter (Co-chair) and Otte (Co-chair) and disagreements resolved through discussion.

Aim 2 Analysis

Aim 2 Analysis: Describe the associations between TIMP (intensity, distress) and co-occurring symptoms (pain [general], peripheral neuropathy, impaired sleep, fatigue, emotional distress, and/or hot flashes). Spearman's correlations were used to measure the magnitude of the relationships among TIMP (intensity, distress) and pain (general) interference, peripheral neuropathy intensity, impaired sleep intensity, fatigue intensity, emotional distress (i.e., anxiety and depression) intensity, and hot flash interference. Means, standard deviations, and correlations were reported. Positive correlations indicated that greater TIMP intensity and/or distress was correlated with greater (i.e., worse) intensity or interference of co-occurring symptoms. The magnitude (r), direction (+/), and significance (*p* value) of each relationship were described.

Aim 3 Analysis

Aim 3 Analysis: Identify associations between TIMP (intensity, distress) and patient-reported outcomes (interference with daily activities, physical functioning, and health-related quality of life). As shown in Figure 1-1 above, TIMP intensity and distress

were evaluated in relation to outcomes (interference with daily activities, physical functioning, and health-related quality of life). Spearman's correlations were used to measure the magnitude of the relationships among TIMP intensity and distress and interference with daily activities, physical functioning, and health-related quality of life. Means, standard deviations, and correlations were reported. Positive correlations indicated that greater TIMP intensity and/or distress was correlated with greater interference with daily activities, physical functioning, and/or health-related quality of life. The magnitude (r), direction (+/-), and significance (*p* value) of each relationship were described. Correlations involving FACT-G total scores will be completed with and without the FACT-G pain item to identify if conceptual overlap occurs when including the pain item. If so, this item will be removed from FACT-G total scores for the analyses.

Potential Problems and Alternative Solutions

Additional recruitment methods included expanding recruitment to other sites in the Indianapolis area. Participants could also self-refer to the study by telephoning the project office. This occurred if patients were referred by physicians or in response to local cancer care clinics and ovarian community support groups who had the study's advertisement available for pick-up, posted the advertisement, and/or shared study contact information with ovarian cancer survivors during routine communications. Physicians could also directly refer patients by telephoning the project office. Also, organizations such as the American Cancer Society, Little Red Door, Cancer Support Community, and Ovar'Coming Together were contacted. If agreeable, these organizations distributed the flyer and/or the same mass e-mail used for the Rare Patient Voice, LLC© registry to advertise the study. Potential participants were able to self-refer and complete eligibility questions by clicking the REDCap link provided in the e-mail.

Conclusions and Future Research

This was the first study to fully characterize the symptom experience, co-occurring symptoms, and patient-reported outcomes of TIMP in ovarian cancer survivors. Findings from the proposed study provide an important foundation for the investigator's program of research in symptom science. Ultimately, the investigator plans to build upon her minor in epidemiology and conduct a larger, population-based, prospective, longitudinal study to expand understanding of TIMP to fully inform the development, timing, and testing of effective interventions to manage TIMP (e.g., NIH R01).

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CHAPTER 2

This chapter focuses on the state of the science of TIMP and serves as a call to action for a comprehensive understanding of TIMP and suggests cancer nurses must contribute to national initiatives to improve patient-reported outcomes by addressing TIMP symptom management needs and associated health-related quality of life outcomes in cancer survivors.

Total cancer mortality in the United States has declined and, thus, cancer survival rates have improved correspondingly.[1, 2] However, increased survivorship is offset by multiple, persistent treatment-related symptoms.[3] Taxane-induced musculoskeletal pain (TIMP) is defined as arthralgia (i.e., joint pain) and/or myalgia (i.e., diffuse muscle pain, usually accompanied by malaise) related to the administration of taxane-based chemotherapy.[4] Paclitaxel is one of the most widely prescribed taxane agents in clinical practice and is predominately administered in populations of breast, ovarian, and non-small cell lung cancer.[5] Across all populations of paclitaxel-treated patients, TIMP is likely common[6, 7] and intensity appears to be dose dependent with doses of paclitaxel > 200mg/m^2 leading to more frequent and intense TIMP.[4] However, other common symptom assessment parameters such as distress, timing, quality, and concurrence (i.e., co-occurring symptoms) of TIMP appear to be unstudied and unspecified and, although TIMP is likely common,[6, 7] true estimates of TIMP prevalence appear to be unknown.

In other non-oncology patient populations, such as those seen in primary care settings, musculoskeletal pain is a significant problem. It is typically localized simultaneously in both the axial (head, neck and spine, ribs, and pelvis) and peripheral (extremities) skeleton, affecting both areas of the body.[8] Musculoskeletal pain can also arise from the muscles, ligaments, tendons, or joints and can be localized or generalized.[9]

These facts regarding persistent musculoskeletal pain in primary care suggest there is more to be understood about TIMP that is not adequately captured by intensity ratings alone. Because TIMP may importantly affect the health-related quality of life of cancer survivors, careful and comprehensive research examination of TIMP is warranted.[4, 10, 11]

Conceptual Framework

To improve both health-related quality of life and patient-reported outcomes in cancer care, control of cancer treatment-related symptoms, such as TIMP, is essential.[12] Symptoms are subjective experiences reflective of changes occurring in biophysical functioning, sensations, or cognition, and they are the most frequent reason individuals seek health care.[13, 14] The University of California San Francisco Theory of Symptom Management and Lenz's Theory of Unpleasant Symptoms are well-established theoretical frameworks with substantial empirical evidence for guiding a comprehensive assessment addressing the complexity of symptoms.[13-17] These two theories are particularly suitable for guiding symptom management research in populations including those diagnosed with cancer.[14, 15, 17] Both theories emphasize essential symptom management concepts including, but not limited to, contextual considerations (i.e., person, environment, health, and illness variables), descriptions of the symptom experience (i.e., intensity, distress, timing, quality, and concurrence variables), and the impact of symptoms on selected outcomes (i.e., health-related quality of life, functional status, emotional status, need for additional treatment, and discontinuation of treatment or dose adjustment).[13, 14, 16, 18] Thus, both the University of California San Francisco Theory of Symptom Management and Lenz's Theory of Unpleasant Symptoms provide comprehensive and theoretical symptom assessment frameworks appropriate for guiding research, and they were combined to develop a conceptual framework which guided this review. See Figure 2-1. In this framework, four types of contextual variables

such as person variables (e.g., age) or illness variables (e.g., comorbid conditions) may influence the experience of TIMP, which may, in turn, influence outcomes.

Purpose and Specific Aims

Therefore, because it is imperative that symptom research reflects the complex nature of symptoms, the purpose of our paper was to systematically review the literature examining the state of the science around TIMP. Specific aims were to evaluate: (1) the conceptual clarity of TIMP; (2) descriptions of the TIMP symptom experience, including intensity, distress, timing, quality, and symptom concurrence; (3) contextual variables influencing TIMP including person, environment, health, and illness variables; and (4) the impact of TIMP on selected outcomes including health-related quality of life, functional status, emotional status, need for additional treatment, and discontinuation of treatment or dose adjustment. Findings from the review would therefore help to better delineate the framework (see Figure 2-1).

Methods and Search Strategy

Inclusion and Exclusion Criteria

Relevant studies addressing TIMP were identified using a comprehensive and systematic approach. Inclusion criteria were: full-text articles, published in a peer-reviewed journal; population specific to adult cancer survivors aged 18 and older; evaluated TIMP; and English language. Exclusion criteria were: case reports, review articles, cost-effectiveness trials, study populations including metastatic patients or patients with bone metastasis (i.e., patients diagnosed with Stage IV cancer), and studies including regimens with treatments or therapeutic interventions having known skeletal side effects (such as aromatase inhibitors or growth factor). The rationale for exclusion was to ensure that any reported arthralgia or myalgia could be exclusively

attributed to the taxane agent rather than to metastases or other forms of therapy. Studies evaluating neuropathy (peripheral nerve pain) were also excluded. No limits were placed on year published and the search was current as of August 4, 2014. Peer-reviewed literature was searched using the PubMed database. The search terms used were (pain or myalgia or arthralgia or musculoskeletal) and taxane and neoplasm. Reference lists of all relevant review articles were searched for additional, applicable citations (i.e., “spooling”) before being excluded.

Articles were identified for inclusion by the primary author. A subset (2%) of articles were discussed with both co-authors before being eliminated for not meeting inclusion criteria. As shown in Figure 2-2, 688 articles were identified and their titles and abstracts screened for exclusion. Of these, 676 were excluded, leaving a total of 12 articles. Common reasons for exclusion were a failure to address or report TIMP, sample populations comprised of participants with bone metastasis, and sample populations comprised of participants classified as metastatic, whether or not stage or site of metastases was reported.

Data Abstraction

The data were abstracted and organized into five separate tables consistent with the review aims. All abstracted data were verified by a second reviewer. The first table used in the analysis included a general overview of the studies including: focus (TIMP or toxicity as a primary vs. secondary focus), type of taxane (docetaxel; paclitaxel; or nanoparticle, albumin-bound paclitaxel), dose and frequency of taxane, other chemotherapy regimen agents assessed and premedications administered (when discussed), cancer type(s), number of subjects, and specification of time points for TIMP data collection. The second table used during analysis included all identified terms describing TIMP, consistent with Aim 1. The third table showed the dimension(s) of the

symptom experience (intensity and measure used, distress, timing, quality, and symptom concurrence) addressed for each TIMP term used (Aim 2). If symptom intensity was assessed for a given TIMP term(s), measures used to evaluate intensity were listed in the table. The fourth table (Aim 3) listed person variables (demographic, psychological, sociological, and physiological), environment variables (situational, physical, social, and cultural), and health and illness variables (risk factors, injuries, or disabilities), the contextual variables that might influence TIMP. The fifth table used during the analysis (Aim 4) showed the impact of TIMP on selected outcomes including health-related quality of life, functional status, emotional status, requirement of additional treatment, and discontinuation of treatment or dose adjustment. Only data from the first three of these five tables are reported in this paper because so few of the included studies evaluated contextual variables influencing TIMP or the impact of TIMP on the pre-specified, selected outcomes. See Tables 2-1- 2-3.

Results

Critiquing the Evidence (Synthesis/Overall Purpose)

As shown in Table 2-1, a very limited number of studies were identified.[19-30] Most studies were conducted in the United States,[19, 21, 25, 28, 29] 42% (n = 5), or Europe,[20, 22, 24, 27, 30] 42% (n = 5). Year published ranged from 1997 to 2013, with 83% (n = 10) of studies published in the year 2000 or later. Studies were evenly split relative to focus, with 50% (n = 6) having a primary focus on TIMP or cancer treatment-related toxicity[21, 26-30] and 50% (n = 6) having a secondary focus on TIMP or treatment-related toxicity.[19, 20, 22-25]

Paclitaxel was the most commonly evaluated taxane agent, used in 83% (n = 10) of studies.[19-21, 23, 24, 26-30] Docetaxel was used in 8% (n = 1),[22] and nanoparticle, albumin-bound paclitaxel was used in 8% (n = 1) of studies.[25] Paclitaxel was administered at

doses greater than 200mg/m^2 in 33% (n = 4) of the studies.[19, 27-29] The most frequently administered dose of paclitaxel was 175mg/m^2, given in 42% (n = 5) of studies.[20, 23, 24 ,26, 30] When specified, cycles of paclitaxel were usually administered every 21 days (every 3 weeks).[19, 20, 22-30] Across all studies, there was an average of two additional chemotherapy regimen agents assessed (range = 0-5). Only two studies[23, 30] evaluated paclitaxel alone, and no other oral or intravenous chemotherapy regimen agents. Premedications were described in 58% (n = 7) of studies[19, 23, 24 ,27-30] and included dexamethasone, diphenhydramine, chlorpheniramine, and cimetidine as well as other non-specified H_2 receptor antagonists and corticosteroids.

Breast cancer was the most commonly evaluated cancer type, assessed in 42% (n = 5) of studies.[20-22, 25, 29] Other cancer types included ovarian, assessed in 25% (n = 3) of studies,[23, 26, 30] non-small cell lung cancer (25%, n = 3),[19, 27, 28] and small-cell lung cancer (8%, n = 1).[24] Half of studies (n = 6) had sample sizes of 35 or fewer,[19, 21, 23-25, 30] and half (n = 6) had sample sizes greater than 50.[20, 22, 26-29] Time points for collecting assessments of TIMP, reported in 50% (n = 6) of studies,[21, 23, 25, 27-29] varied across this subset; 2 (17%)[23, 25] occurred after each chemotherapy cycle, 2 (17%)[27, 29] occurred throughout chemotherapy cycles, 1 (8%)[21] occurred during the last cycle of chemotherapy, and 1 (8%)[28] occurred after 2 cycles of pre-operative chemotherapy and again after 3 cycles of post-operative chemotherapy. The studies specifying that assessments of TIMP were collected throughout chemotherapy cycles[27, 29] did not specify the exact intervals the assessments of TIMP were collected.

Terms Describing TIMP (Aim 1)

As shown in Table 2-2 (Aim 1), 6 different terms (adverse event, complication, side effect, symptom, syndrome, and toxicity) were used to describe TIMP. Although the

individual studies used from 1 to 5 different terms, TIMP was described as a toxicity in 92% (n = 11).[19, 20, 22-30]

Descriptions of the Symptom Experience (Aim 2)

As shown in Table 2-3 (Aim 2), 83% (n = 10) of studies[19, 20, 22-28, 30] used the terms arthralgia and/or myalgia to signify TIMP. Across studies, the average number of terms used to signify TIMP was 2.6 (range = 2-4). Other less commonly used terms for TIMP included bone pain and/or joint pain, used in 25% (n = 3) of studies.[21, 25, 29]

No studies evaluated all dimensions of the TIMP symptom experience. Intensity was measured in all studies, most commonly with the National Cancer Institute Common Toxicity Criteria, used in 50% (n = 6) of studies.[19, 25-29] The World Health Organization Dose Limiting Toxicity scale was used in 33% (n = 4) of studies.[20, 23, 24, 30] Intensity severity ranged from mild (Grade 1) to life-threatening (Grade 4). Among the terms arthralgia, myalgia, and bone pain, TIMP was estimated across the various studies to affect from 1.3% to 94% of study subjects. The intensity measure was not specified in 17% (n = 2) of studies.[21, 22] In one study[29] there was a conceptual-operational mismatch between the terms arthralgia and myalgia and the results from a linear analog scale for flu-like symptoms, and therefore intensity grading was not reported for these TIMP terms. Distress was reported in only 8% (n = 1) of studies.[21] Similarly, timing, for only three of four total TIMP terms used, was addressed in only 8% (n = 1) of studies,[29] and quality was addressed in only 8% (n = 1) of studies.[21] Concurrence (co-occurring symptoms) was not addressed by any of the studies included in our review.

Contextual Variables Relating to TIMP (Aim 3)

Person, health, and illness domains influencing TIMP were addressed in only 17% (n = 2) of studies.[26, 29] No physical, social, or cultural variables comprising the environment domain were evaluated by any study included in our review.

Of those reporting person domains potentially influencing TIMP, one study[26] found arthralgia and myalgia caused by paclitaxel did not vary between older and younger groups of patients. This finding suggests that age may not be a risk factor for treatment-related symptom severity (p = .57) in women with ovarian cancer undergoing chemotherapy. Another study[29] addressed the influence of physiological variables (also within the person domain) by evaluating plasma levels of inflammatory cytokines in relation to incidence and timing of musculoskeletal pain in breast cancer patients receiving chemotherapy. Increases in interleukin (IL)-10 correlated strongly and positively with joint pain (p = .003) in those who received weekly paclitaxel. In the 3-weekly paclitaxel group, IL-8 correlated positively with “flu-like” symptoms (p = .008).[29] This same study[29] was also the only study to assess risk factors relating to TIMP by addressing correlations among paclitaxel, the release of inflammatory cytokines, and musculoskeletal symptoms, and their findings suggested that inflammatory cytokine release induced by paclitaxel may be a risk factor for musculoskeletal symptoms in breast cancer patients who are undergoing treatment with taxane-based chemotherapy.

Status Outcomes of TIMP (Aim 4)

No studies addressed all of the outcomes of TIMP specified in our model. Most studies did not address health-related quality of life outcomes at all, and only 8% (n = 1) of studies partially addressed these outcomes.[21] This study,[21] which partially addressed health-related quality of life outcomes, was a qualitative evaluation of symptoms

experienced by women undergoing chemotherapy and descriptions of how treatment-related symptoms, including bone pain while on paclitaxel, affected quality of life emerged as a major theme and was discussed. This same study[21] was also the only study to partially address functional status (8%) and emotional status (8%). Additional treatment for TIMP was addressed in 17% (n = 2) of the studies, including intravenous analgesics[23] and non-steroidal analgesics.[24] Non-steroidal analgesics were reported to be effective in managing complaints of TIMP;[24] efficacy of intravenous analgesics was not reported.[23] Discontinuation of treatment or dose adjustment was a reported consequence in only 17% (n = 2) of studies.[23, 25] Discontinuation of treatment was reported in one study,[23] for one participant receiving paclitaxel, secondary to severe arthralgia and myalgia, and another study[25] found that dose reduction was required for one participant with complaints of severe myalgia from nanoparticle, albumin-bound paclitaxel.

Discussion

Our review of the very limited research on TIMP had four major findings. First, research to date has involved inconsistent use of terms signifying TIMP, and this lack of conceptual clarity has been impeding our understanding of true estimates of prevalence of this cancer treatment-related symptom. Second, assessment of TIMP has largely been limited to symptom intensity. Third, most research to date has not examined contextual variables influencing TIMP, and fourth, most research to date has not evaluated the impact of TIMP on outcomes. Each of these findings is discussed below.

First, research to date has been inconsistent in its use of terms to signify TIMP. Conceptual clarity is necessary to move forward with cancer symptom management research regarding the assessment of TIMP; for a concept such as TIMP to be solid and strong, it must clearly name that to which it refers (there must not be an excess of terms

referring to TIMP), it must be clearly defined, and its use in theory should be clear so that anyone can understand exactly what is being described, explained, or predicted.[31] In most current research, arthralgia and myalgia may be listed separately or alone or these terms may even be grouped with a common neurotoxicity known as chemotherapy-induced peripheral neuropathy.[4] Chemotherapy-induced peripheral neuropathy may appear to be similar to arthralgia and myalgia in that it is pain caused by many of the same chemotherapy agents; however, chemotherapy-induced peripheral neuropathy includes sensory nerve involvement with unusual or increased reaction to stimuli or a loss of sensation (paresthesias and pain).[32] Furthermore, these symptoms commonly occur in the fingers and toes, thus presenting with a characteristic “glove and stocking” distribution.[33] Inconsistent use of TIMP terms and a lack of research defining and differentiating TIMP from chemotherapy-induced peripheral neuropathy perpetuates a lack of conceptual clarity surrounding TIMP and has, in some cases, precluded notions regarding the relevancy of non-neuropathic pain components (TIMP) associated with chemotherapy. In turn, this negatively impacts health care providers’ ability to assess and manage TIMP effectively in clinical practice. These assertions are supported by a recent exploratory study[34] evaluating symptom patterns indicative of neuropathic or musculoskeletal pain, or both, in cancer patients; one major finding was that, although chemotherapy-induced neuropathy-associated pain is usually regarded as neuropathic, movement-associated pain in approximately 60% of patients points to a musculoskeletal pain component as evidenced by a subgroup of patients with different clinical, somatosensory, and psychological parameters. Furthermore, one characteristic of musculoskeletal pain is its association with weight bearing or physical exercise which is different from persisting pain occurring at rest or at night that alleviates while walking and is characteristic of neuropathic pain.[34] Interestingly, anxiety was higher in patients with musculoskeletal pain components which could be explained by anxiety as a known

risk factor for musculoskeletal pain where activation of the sympathetic nervous system releases stress hormones leading to impairment of muscle functioning essential for control of movements and posture.[34, 35] Therefore, one can infer that true estimates of prevalence cannot be determined without conceptual clarity of TIMP, and the recognition of TIMP as separate and distinct from other types of treatment-related pain as has been suggested by recent literature.

Second, most research has involved a limited evaluation of TIMP. Assessment of TIMP in our review was largely limited to symptom intensity. Indeed, this finding supports literature suggesting that most models of symptoms focus on one symptom and, specifically, on the intensity of the symptom and not on its other features, such as distress, timing, quality, or concurrence.[17] Theoretical models such as the Theory of Symptom Management and the Theory of Unpleasant Symptoms, which helped to define our conceptual framework for this review, demonstrate the importance of fully evaluating all dimensions of the symptom experience in order to comprehensively understand a symptom and to inform the development of efficacious interventions. No studies comprehensively assessed TIMP using the common symptom assessment parameters of distress, timing, quality, and concurrence even though pain literature suggests health care providers evaluating pain for the first time should start with multidimensional instruments to obtain an overview of the symptom.[36] Once core areas of the pain have been identified, then more specific, streamlined assessments (i.e., intensity and interference with functional status, only) can be used. Finally, it is important to note that addressing the dimension of symptom concurrence (both commonly co-occurring symptoms and the concept of cancer treatment-related symptom clusters) is a current research priority.[15, 37-40] Therefore, more thorough reporting of all symptom experience dimensions of TIMP is critical.

Finally, studies did not examine contextual variables influencing TIMP or address the impact of TIMP on selected outcomes. Person, environment, health, and illness variables serve as a reminder of the contextual considerations potentially capable of influencing symptoms.[14] Therefore, these contextual variables must be evaluated in research on TIMP. To illustrate, a woman's experience of TIMP may vary according to her age, reproductive status, and genetic risk factors (person domain); cultural beliefs about the meaning of her symptom or whether she is evaluated in a clinic or her home (environmental domain); and her current state of health or diagnosis (health and illness domains).[14] Similarly, outcomes (both positive and negative) must also be assessed in evaluations of TIMP. Even when a disease is treated and/or controlled (survivorship), symptoms can remain a continued concern.[13] Research suggests that symptoms may be associated with work impairments, resulting in a loss of work days or increased worker compensation.[13, 16] Overall, the lack of research addressing both contextual variables and outcomes relative to TIMP limits the ability of scientists and clinicians to understand the full impact of TIMP in cancer survivors undergoing taxane-based chemotherapy treatment.

Strengths and Limitations

To the best of our knowledge, this is the first comprehensive review to synthesize the literature on TIMP. However, there were limitations to our review. First, only the PubMed database was searched for relevant studies and it is possible that some articles were missed. PubMed provides access to bibliographic information including over 24 million citations and MEDLINE.[41] The PubMed database was selected because biomedical topics and the sciences are the primary foci of articles contained in this database and these content areas directly related to the topic for this systematic review. Thus, it was reasonable to believe our search strategy effectively captured most, if not

all, of the evidence regarding TIMP and any additional articles that may have been acquired from searching a database other than PubMed, such as CINAHL, would not significantly alter the overall conclusions of our review. However, a larger review including multiple databases is likely needed to ascertain the full extent of this literature.

Second, most studies were conducted in the United States[19, 21, 25, 28, 29] or Europe,[20, 22, 24, 27, 30] which limits the generalizability of our findings. International studies were retrieved from the search strategy previously described and were considered for inclusion in our review. Of note, these studies were eliminated on the basis of the pre-specified exclusion criteria; the inclusion of growth factor in treatment regimens was the primary indication for exclusion of these studies. Third, the population for most studies was predominately female as breast cancer was the most commonly evaluated cancer type[20-22, 25, 29] and ovarian cancer was the second most commonly evaluated cancer type.[23, 26, 30] Because paclitaxel is predominately administered in populations of breast, ovarian, and non-small cell lung cancer, it was not surprising sample populations were mostly female. Therefore, gender may prove an important demographic variable in evaluating TIMP.

Finally, two studies[21, 25] included in our review used the term bone pain in their assessment of treatment-related symptoms. Because these studies also included the terms myalgia and joint pain (terms highly consistent with the definition of musculoskeletal pain), they were included in our review. It is possible that the assessments from these studies may have additionally included measurement of a different symptom (i.e., bone pain). However, this limitation does not significantly detract from the important findings of our review regarding the limited nature of research on TIMP. In particular, research to date has involved inconsistent use of terms signifying TIMP, which has impeded our understanding of true estimates of prevalence;

assessment of TIMP has largely been limited to symptom intensity; most research to date has not examined contextual variables influencing TIMP; and most research to date has not evaluated the impact of TIMP on outcomes.

Conclusions

TIMP is a treatment-related symptom that oncology health care providers need to address in order to improve health-related quality of life in cancer survivors undergoing taxane-based chemotherapy. In research on TIMP, there has been little consistency in terms, and measurement has largely been limited to toxicity grading scales. Overall, little is known about TIMP. Future research should focus on comprehensive descriptions of TIMP, including evaluation of all dimensions of the symptom experience as well as the contextual variables influencing TIMP and the impact of TIMP on outcomes in cancer survivors. Consideration should be given to type of taxane agent (preferably with an emphasis on paclitaxel since it is the most commonly prescribed), as well as to the type of cancer to be evaluated. Sample populations with minimal confounding influences on the experience of musculoskeletal pain should be evaluated, at first, in order to capture the richest and most clear picture of TIMP possible. It is only with information gleaned from this type of foundational and multidimensional research that new strategies for better management of TIMP can be developed, our understanding of the mechanisms underlying TIMP can be improved, and the role that TIMP likely assumes in the cancer treatment-related symptom clusters (both known and unknown) that are experienced by cancer survivors undergoing taxane-based chemotherapy can be clearly elucidated.

Implications for Practice

Recognition of patient-reported outcomes, supported by the National Institutes of Health, is of growing research interest and requires attention to health-related quality of life

outcomes in populations including cancer survivors.[11, 42] Cancer and cancer treatment-related symptoms can profoundly affect an individual's health-related quality of life throughout their survivorship trajectory.[10] In order to improve patient-reported outcomes in cancer care, control of treatment-related symptoms is essential. Further research about TIMP will address national priorities for generating new knowledge to advance symptom science. Importantly, these national priorities include the National Cancer Institute's Office of Cancer Survivorship mission to enhance the quality of survival and minimize the physical and psychosocial adverse effects of cancer and its treatment that are experienced during survivorship in persons with cancer,[43] and the National Institute of Nursing Research Strategic Plan priority of Advancing Quality of Life through symptom management.[44] Comprehensive assessment of and research about TIMP will address several national priorities for generating new knowledge to advance symptom science and will be directly relevant to the care of cancer survivors undergoing taxane-based chemotherapy. Oncology nurses must contribute to national initiatives to improve patient-reported outcomes by addressing the symptom management needs and health-related quality of life outcomes of cancer survivors.

Figure 2-1: Conceptual Framework

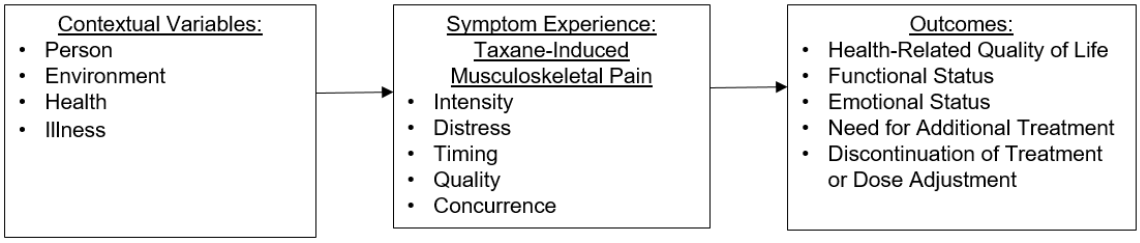

Figure 2-2: Flow Diagram

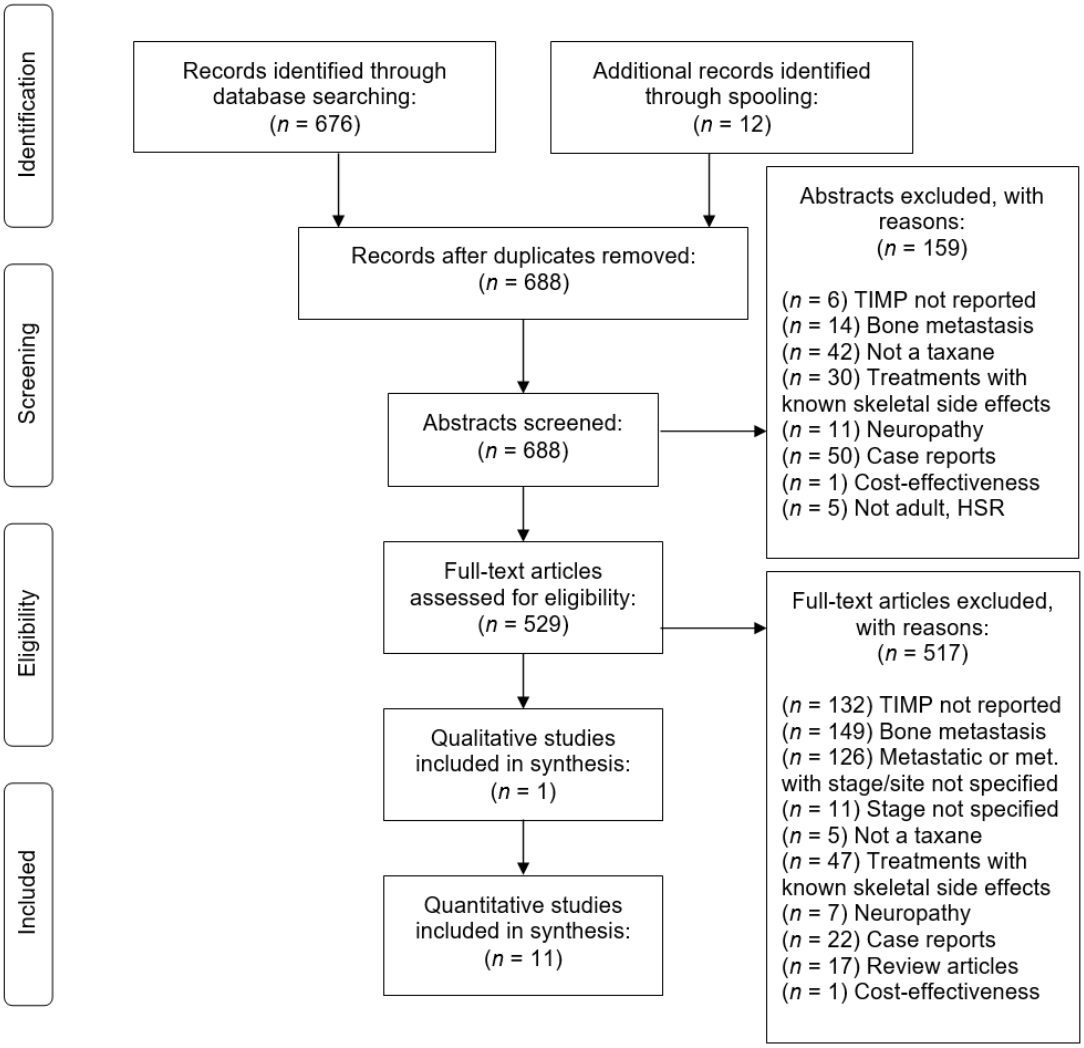

Table 2-1: Evaluation Matrix for Critiquing the Evidence (Synthesis/Overall Purpose)

Author, year, country	Focus		Type of Taxane			Dose and frequency	Other chemotherapy regimen agents assessed and premedications administered (when discussed)	Cancer type	*n*	Time points specified
	1°	2°	Doce-taxel	Pacli-taxel	Paclitaxel protein - bound particles; albumin - bound					
Altorki et al., (2003), US[19]		X		X		225 mg/m^2 q 21 days x 2 cycles	carboplatin, celecoxib dexamethasone, diphenhydramine, H_2 receptor antagonist	NSCLC	*n* = 29, 38% female	
Boccardo et al., (2010), Italy[20]		X		X		175 mg/m^2 q 3 weeks x 4 cycles	epirubicin, cyclophosphamide, methotrexate, 5 – fluorouracil, and vinorelbine	Breast	*n* = 244, 100% female	
Boehmke & Dickerson, (2005), US[21]	X			X		Dose and frequency NS; 4 cycles	adriamycin and cyclophosphamide	Breast	*n* = 20, 100% female	28 weeks post-diagnosis (during the last cycle of chemo)
Bulent et al., (2013), Turkey[22]		X	X			100 mg/m^2 q 3 weeks x 3 cycles or 75 mg/m^2 q 3	cyclophosphamide, doxorubicin, 5-fluorouracil, and epirubicin	Breast	*n* = 539, 100% female	

						weeks x 4 cycles				
Gallardo - Rincon et al., (2003), Mexico[23]		X		X		175 mg/m^2 q 3 weeks x 3- 6 cycles	None dexamethasone, chlorpheniramine, cimetidine	Ovarian	*n* = 30, 100% female	Toxicity recorded after each cycle (q 3 weeks) and expressed as percenta-ge of 149 total cycles
Gatzemeier et al., (1997), Germany[24]		X		X		175 mg/m^2 q 3 weeks; total # cycles NS	carboplatin and oral etoposide premedications given but not specified	SCLC	*n* = 35, 13% female	
Kaklamani et al., (2012), US[25]		X			X	260 mg/m^2 q 3 weeks x 4 cycles	oral lapatinib	Breast	*n* = 30, 100% female	Toxicity recorded after each cycle (q 3 weeks) and expressed as percenta-ge of total sample/ grade

Kurtz et al., (2011), International group[26]	X			X		175 mg/m^2 q 3 weeks x 6 or more cycles	carboplatin and pegylated liposomal doxorubicin	Ovarian	*n* = 157, 100% female	
O'Brien et al., (2003), Netherlands [27]	X			X		200 mg/m^2 q 21 days x 3 cycles	Carboplatin dexamethasone, diphenhydramine, cimetidine	NSCLC	*n* = 57, 33% female	Toxicity monitored throughout chemo and expressed as percentage (over all cycles) of total sample/ grade
Pisters et al., (2000), US[28]	X			X		225 mg/m^2 q 21 days x 2 cycles pre-op and 3 cycles post-op	Carboplatin dexamethasone, diphenhydramine, H_2 receptor antagonist	NSCLC	*n* = 94, 31% female	Toxicity expressed as percentage of total sample/ grade at pre-op and post-op chemo
Pusztai et al., (2003), US[29]	X			X (n = 70)		225 mg/m^2 q three weeks (# cycles NS) or 175 mg/m^2 q 3 weeks (# cycles NS) or	cyclophosphamide, doxorubicin, and 5-fluorouracil (*n* = 20) dexamethasone, diphenhydramine,	Breast	N = 105 *n* = 90, 100% female	Toxicity monitored throughout chemo and expressed

						80 mg/m^2 weekly (# cycles NS)	cimetidine (paclitaxel groups) and dexamethasone, ondansetron, lorazepam (non-paclitaxel group)		(breast cancer); *n* = 15, 100% female healthy controls	as change in intensity over one cycle
Trope et al., (1997), Norway and Sweden[30]	X			X		175 mg/m^2 q 3 weeks x 6 to 9 cycles	None corticosteroids, diphenhydramine, and cimetidine	Ovarian	*n* = 35, 100% female	

Abbreviations: US = United States, blank = not addressed, X = addressed, q = every, x = for, NSCLC = non-small cell lung cancer, NS = not specified, # = number, SCLC = small cell lung cancer

Table 2-2: Terms Describing TIMP (Aim 1)

First Author, and year	Adverse event	Complication	Side effect	Symptom	Syndrome	Toxicity
Altorki, 2003[19]	X					X
Boccardo, 2010[20]			X			X
Boehmke, 2005[21]				X		
Bulent, 2013[22]						X
Gallardo-Rincon, 2003[23]						X
Gatzemeier, 1997[24]			X			X
Kaklamani, 2012[25]	X					X
Kurtz, 2011[26]			X			X
O'Brien, 2003[27]						X
Pisters, 2000[28]		X				X
Pusztai, 2003[29]	X		X	X	X	X
Trope, 1997[30]						X

Abbreviations: X = term used, blank = term was not used

Table 2-3: Descriptions of the Symptom Experience (Aim 2)

First Author, and Year	Terms Used	Intensity	Distress	Timing	Quality	Concurrence
Altorki, 2003[19]	myalgia/arthralgia	X; NCI				
Boccardo, 2010[20]	arthralgia/myalgia	X; WHO				
Boehmke, 2005[21]	bone and joint pain	X; NS	X		X	
Bulent, 2013[22]	arthralgia/myalgia	X; NS				
Gallardo-Rincon, 2003[23]	myalgia/arthralgia	X; WHO				
Gatzemeier, 1997[24]	arthralgia/myalgia	X; WHO				
Kaklamani, 2012[25]	bone pain myalgia	X; NCI				
Kurtz, 2011[26]	arthralgia/myalgia	X; NCI				
O'Brien, 2003[27]	arthralgia myalgia motor toxicity	X; NCI X; NCI X; NCI				
Pisters, 2000[28]	myalgia/arthralgia	X; NCI				
Pusztai, 2003[29]	muscle aches joint pain flu-like symptoms muscle aches/pain	X; LAS X; NCI in 30-day diary (*n* = 30)		X X X		
Trope, 1997[30]	arthralgia/myalgia	X; WHO				

Abbreviations: X = addressed, NCI = National Cancer Institute Common Toxicity Criteria, blank = not addressed, WHO = World Health Organization Dose Limiting Toxicity, NS = not specified, LAS = Linear Analog Score

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CHAPTER 3

This chapter presents results from the dissertation research study, "Taxane-induced Musculoskeletal Pain in Women with Ovarian Cancer," and provides a description of the symptom experience and the associations with co-occurring symptoms.

More than 22,000 women in the United States are newly diagnosed with ovarian cancer each year.[1, 2] Treatment for ovarian cancer generally consists of surgery and chemotherapy and although many women respond well to these treatments initially, the majority experience disease recurrence after the first-line therapy, requiring ongoing chemotherapy treatment.[3-5] Because there have been few appreciable therapeutic breakthroughs (i.e., intraperitoneal chemotherapy, dose dense paclitaxel, and the addition of bevacizumab) over the last ten years, discussions between patients and providers about quality of life vs. length of life have become increasingly important. Prior work demonstrates women with advanced or recurrent ovarian cancer would be willing to accept reductions in progression-free survival time in return for improvements in chemotherapy side effects.[6] As such, management of cancer treatment-related symptoms is an essential component of cancer care[7] to improve health-related quality of life especially in ovarian cancer where women are living with active disease.

One cancer treatment-related symptom affecting women with ovarian cancer is taxane-induced musculoskeletal pain (TIMP). TIMP is musculoskeletal pain that includes myalgia (i.e., diffuse muscle pain, usually accompanied by malaise) and/or arthralgia (i.e., joint pain) that affects more than half of patients following treatment with taxane-based chemotherapy agents such as paclitaxel.[8] A recent systematic review suggested the TIMP symptom experience is not comprehensively understood.[9] The review included 12 available studies. Most (83%) were clinical trials evaluating the safety, tolerability, and/or

efficacy of taxane-based chemotherapy, with TIMP mentioned only as a side effect and not fully described.[10-21] Specifically, the review revealed that the TIMP symptom experience has not been comprehensively assessed using the common parameters of intensity, distress, duration, location, quality, temporal pattern, aggravating and alleviating factors, and pain management. Literature suggests that providers evaluating pain for the first time should start with multidimensional instruments to obtain an overview of the symptom.[22] Once core areas of the pain have been identified, then more specific, streamlined assessments can be used. These gaps in the literature suggest there is more to be understood about TIMP and its impact on the patient experience.

Although TIMP is not well understood, it likely co-occurs with other symptoms commonly affecting cancer survivors. Research on co-occurring cancer symptoms, or symptom clusters, suggests co-occurring symptoms may not be independent entities, but rather symptoms that interact synergistically.[23-26] Among all cancer survivors, frequent co-occurring symptoms include pain, impaired sleep, low energy/fatigue, depression, and anxiety.[7, 8, 23, 26-29] These symptoms as well as hot flashes have also been highlighted in studies specific to women with ovarian cancer.[30-33] Prolonged or ineffective management of treatment-related symptoms can contribute to treatment noncompliance, worsening of symptoms, reduced health-related quality of life, and overall poorer patient outcomes.[8] Because TIMP has not been well researched, associations among TIMP and other co-occurring symptoms likely exist but are currently unspecified.

Ovarian cancer survivors are an ideal population for studying TIMP because they (1) are poorly represented in cancer symptom research, (2) often receive paclitaxel throughout survivorship, (3) frequently report TIMP, and (4) rarely receive other medications that are also known to cause treatment-related musculoskeletal pain (e.g., aromatase inhibitors, growth factor therapy).[34-40] Therefore, the purpose of this cross-

sectional, pilot study was to obtain preliminary data to describe TIMP and associations between TIMP (intensity, distress) and other co-occurring symptoms in women with ovarian cancer who were being or had been treated with paclitaxel-containing regimens.

Methods

Sample and Setting

A convenience sample of women with ovarian cancer were recruited from an outpatient cancer clinic in the Midwest, local cancer support communities, and a national cancer survivors' research registry between December 1, 2015 and October 14, 2016. Eligible subjects were: (1) $\geq$ 21 years of age; (2) diagnosed with ovarian cancer; (3) had a history of no other cancer diagnoses (basal cell skin cancer was allowed); (4) undergoing active treatment with paclitaxel (must have received at least one dose) or received treatment with paclitaxel in the past; (5) experiencing myalgia and/or arthralgia after starting paclitaxel treatment; (6) able to read and speak English; (7) willing and able to participate in the study; (8) without bone metastases; and (9) not using and did not anticipate using growth factors with chemotherapy. The latter two were to avoid other known sources of musculoskeletal pain in this population.

Study Procedures

The study was approved by the university Scientific Review Committee (SRC) and Institutional Review Board (IRB). A waiver of written informed consent and written authorization to use protected health information for screening and data collection was granted. All women received study information and provided verbal informed consent and verbal authorization to use protected health information before being screened for eligibility. Completion of study measures confirmed their consent to participate in the study.

Women were recruited in three ways. First, during a clinic visit, a member of the research team identified potential participants, briefly introduced the study, assessed interest, and obtained verbal consent and authorization before completing eligibility screening. Second, a member of the research team contacted local support communities who agreed to send e-mail blasts to potentially eligible women and post flyers on research and communication boards. Interested women self-referred to the study and the above procedures to share study information, assess interest, and complete screening were done electronically, online. Third, a member of the research team contacted a national research registry, Rare Patient Voice, LLC©, which agreed to send e-mail blasts to potentially eligible women.[41] Rare Patient Voice, LLC© is a registry of people who have agreed to be contacted about participating in research studies. Interested women self-referred to the study and the above procedures were done electronically, online.

Eligible women received study measures in one of two ways. Those recruited from clinic had the option to receive paper copies of the study information sheet, questionnaires, and daily pain diary which they could fill out in the clinic or at home and return in a pre-paid mailer. They also had the option to fill out measures electronically, online. Those recruited via community agencies or Rare Patient Voice, LLC© only had the option to fill out measures electronically. Those women who chose to complete measures electronically did so by receiving a web-based link to a secure Research Electronic Data Capture (REDCap) data collection database, which was included in the e-mail blast.[42] Those who completed online questionnaires and agreed to complete the online pain diary received daily e-mails for 28 days to remind them to complete the diary.

Participants received a $25 gift card for their time and effort upon completion of the TIMP Pain Diary. Women who did not want to provide their name and mailing address or did not complete the TIMP Pain diary did not receive the gift card.

Data Entry and Management

Data were entered into the secure, web-based REDCap database.[42] Data not directly entered by participants was entered by the study team and double-checked after two weeks had elapsed. REDCap servers are secure and aligned with HIPAA regulations. REDCap incorporates real-time validation rules (with automated data type and range checks) at the time of entry. Data were exported for analysis to SPSS® version 24. Only diaries with at least 90% of all possible ratings were used.

Measures

Demographic and treatment information were self-reported, and were not verified against medical records. Demographics included age, race, ethnicity, marital status, employment status, socio-economic status, education, and menopausal status. Treatment information included date of diagnosis, stage of cancer, total number of chemotherapy cycles planned and received, chemotherapies received and currently taking, other treatments received for ovarian cancer diagnosis (i.e., surgery and/or radiation), and date of last paclitaxel treatment.

Comorbidities were evaluated using the 12-item validated Self-Administered Comorbidity Questionnaire (SCQ) modified. Respondents marked “yes” or “no” as to whether they had each of 12 health conditions and, if *yes*, whether they were receiving treatment for it (*yes/no*) and whether it limited their activities (*yes/no*). A maximum of 3 points are given to conditions that are present, being treated, and limiting current activities. Therefore, higher scores indicate greater comorbidity. Cronbach’s alpha, including among cancer patients, was 0.94.[43] This tool was modified to include six additional conditions affecting women, including fibromyalgia, lupus, thyroid disease, seizures, headaches, and an option for other.

TIMP Symptom Experience

The 32-item validated Brief Pain Inventory – Long Form assessed use of pain medications (i.e., yes/no do you have pain requiring medication) and pain intensity, distress, duration, location, quality, aggravating or alleviating factors, and pain management. The BPI has been used in patients with pain related to chronic conditions (e.g., cancer, osteoarthritis, low back pain), or acute conditions (e.g., postoperative pain). Cronbach's alpha has ranged from 0.77 to 0.91.[44]

The TIMP Pain Diary is a standard 28-day symptom reporting diary. Participants were asked to report their morning and nighttime TIMP on a scale of 0 (not at all intense) to 10 (extremely intense). Women who completed the diary on paper forms were asked to fill it out twice per day (once in the morning to reflect the previous night's pain and once in the evening to reflect the day's pain). Those who completed the diary electronically provided ratings for the previous day and night at the same time. Additionally, participants were asked to check *yes/no* did you receive paclitaxel chemotherapy today. Those women who were not on active treatment while completing the diary checked "no" for all 28 days of the TIMP pain diary.

Intensity. BPI intensity ratings (on a 0-10 scale) were comprised of the worst, least, and average pain in the past week as well as current pain both at the individual item level and as the BPI total score (i.e., the average of all four BPI intensity items). Participants were asked to do their best to provide these intensity ratings in thinking only about their TIMP and not in thinking about any other types of daily pain (e.g., headache) not related to TIMP that they may have been experiencing. There were also TIMP Pain Diary prospective ratings of TIMP intensity (on a 0-10 scale) upon waking and before going to bed.

Distress. Distress was measured using a single item which asked participants to rate distress caused by TIMP on a 0-10 scale.

Duration. Duration was assessed using the TIMP Pain Diary and reported as the total number of days and the total number of nights with pain reported. TIMP Pain Diary intensity ratings across 56 possible time points (28 days x 2 daily time points) were analyzed as a total overall percentage of time points where pain was present. For example, women rating intensity $\geq$ 1 at all 56 time points (28 days x 2 daily time points) would score as pain duration 100%, those with ratings $\geq$ 1 on 28 of 56 time points as pain duration 50%. If only morning or nighttime pain was recorded, the duration was considered to be one-half day (i.e., 1 time point).

Location. Location was assessed by asking participants to shade relevant parts of the BPI body diagram. The body diagram was divided into 8 sections including: (1) anterior head and neck; (2) posterior head and neck; (3) anterior thorax; (4) posterior thorax; (5) right shoulder, arm, elbow, forearm, wrist, and hand; (6) left shoulder, arm, elbow, forearm, wrist, and hand; (7) right hip, thigh, knee, leg, ankle, and foot; and (8) left hip, thigh, knee, leg, ankle, and foot.

Quality. Quality was assessed using the BPI which asked participants to endorse adjectives describing their TIMP. BPI descriptors endorsed were given a value of 1. This allowed calculation of percentages of women who endorsed each descriptor, the ability to summarize the top 3 to 5 descriptors, and the total number of descriptors endorsed.

Temporal Pattern. Temporal pattern was assessed using the 28-day TIMP Pain Diary morning, nighttime, and combined intensity ratings over time.

Aggravating/alleviating Factors. Aggravating/alleviating factors were assessed using several questions from the BPI and included: (1) open-ended participant responses

indicating what makes their TIMP better or worse; (2) responses indicating, on a 0 to 100 scale, the percentage of relief from pain treatments or medications; and (3) responses indicating, by selecting from a list of possible choices, methods relieving pain.

Pain Management. Pain management was also assessed using several questions from the BPI and included: (1) categorical options assessing period of pain relief provided by medications and frequency of pain medication; (2) yes/no items about pain management; and (3) an open-ended question about medications not prescribed by the doctor, but taken for pain.

Co-occurring Symptoms

PROMIS – Pain Interference (General) – Short Form 8a, is an 8-item validated tool that was used to assess for pain interference, which is considered an important pain-related dimension that complements intensity ratings,[45] not related to TIMP. Participants were asked to do their best to provide pain interference ratings in thinking only about their other types of everyday pain not related to TIMP (e.g., headache), and not in thinking about their TIMP. Item responses (1=*not at all* to 5=*very much*) are summed and higher scores indicate greater pain interference. This shortened tool, tested in populations with a variety of diseases including cancer, correlated r=0.95 with items from the original tool and alphas for scores +/- 2 standard deviations from the mean were 0.11 to 0.99.[46]

Neuropathy Pain Score (Chemotherapy-Induced Neuropathy-Specific) (NPS-CIN), is a 6-item validated tool that has been used to measure chemotherapy-induced peripheral neuropathy pain. Item responses (0=*not at all* to 4=*excruciating*) are summed and higher scores indicate greater pain. Cronbach's alpha was 0.96 in a sample of cancer patients receiving taxane (i.e., paclitaxel or docetaxel) or platinum chemotherapy (i.e., cisplatin,

oxaliplatin, or carboplatin) and included multiple cancer types (breast, lung, gastrointestinal, head and neck, genitourinary, gynecologic, and "other").[47]

PROMIS – Sleep Disturbance – Short Form 8a, is an 8-item validated tool used to assess sleep disturbances. Item responses (1=*not at all* to 5=*very much*) are summed and higher scores indicate greater sleep disturbance. This shortened tool, tested in populations with a variety of diseases including cancer, correlated r=0.96 with items from the original tool. Alphas for scores +/- 2 standard deviations from the mean were 0.88 to 0.97.[46]

PROMIS – Fatigue – Short Form 8a, is an 8-item validated tool used to measure fatigue. Item responses (1=*not at all* to 5=*very much*) are summed and higher scores indicate greater fatigue. This shortened tool, tested in populations with a variety of diseases including cancer, correlated r=0.76 with items from the original tool. Alphas for scores +/- 2 standard deviations from the mean were 0.95 to 1.00.[46]

PROMIS – Emotional Distress – Anxiety – Short Form 8a, is an 8-item scale used to assess anxiety. Item responses (1=*not at all* to 5=*very much*) are summed and higher scores indicate greater anxiety. This shortened tool, tested in populations with a variety of diseases including cancer, correlated r=0.96 with items from the original tool. Alphas for scores +/- 2 standard deviations from the mean were 0.62 to 0.98.[46]

PROMIS – Emotional Distress – Depression – Short Form 8a, is an 8-item scale used to assess depression. Item responses (1=*not at all* to 5=*very much*) are summed and higher scores indicate greater depression. This shortened tool, tested in populations with a variety of diseases including cancer, correlated r=0.96 with items from the original tool. Alphas for scores +/- 2 standard deviations from the mean were 0.47 to 0.99.[46]

The Hot Flash Related Daily Interference Scale (HFRDIS) is a 10-item scale measuring how much hot flashes interfere with nine daily activities and quality of life over

the past two weeks. Item responses (0 (*not at all*) to 10 (*completely interfered*) are summed and higher scores indicate greater hot flash interference.[48] Cronbach's alphas, in both cancer patients and healthy women, are consistently >.90.[49]

Cronbach's alphas for the standardized questionnaires that were used in this study were not performed due to the fact that this was a pilot study with a small sample size and any reported alphas would likely be unreliable.

Data Analysis

A description of the sample was analyzed using descriptive statistics appropriate for the level of measurement (i.e., means, standard deviations, frequencies, and percentages). Person characteristics were evaluated using frequencies and descriptive statistics. For both the TIMP symptom experience and co-occurring symptoms analyses, missing data points were handled by exclusion of cases pairwise.[50]

TIMP Symptom Experience

Intensity. BPI intensity ratings were analyzed as mean, median, mode, standard deviation, and range. TIMP Pain Diary ratings were analyzed for morning, nighttime, and combined mean, median, mode, standard deviation, and range for the 28 days. Intensity ratings were also examined in relation to BPI cutpoints of mild (0-4), moderate (5-6), and severe (7-10) pain.[51]

Distress. Distress was analyzed as mean, median, mode, standard deviation, and range.

Duration. Duration as a total overall percentage of time points where pain was present (e.g., women rating TIMP intensity $\geq$ 1 at all 56 time points [28 days x 2 daily time

points] would score as having constant pain with a duration of pain at 100% of recorded time points) was evaluated using frequencies and percentages.

Additionally, commonly occurring phenotypes were developed to group women according to intensity and distress of their reported TIMP. Frequencies and percentages where analyzed to develop the emerging phenotypes (i.e., mild, mild to moderate, moderate to severe, severe, or variable mix of intensities and distress). Similarly, across the dimensions, patterns of intensity, distress, and duration of TIMP were also analyzed using frequencies and percentages.

Location. Frequencies and percentages were calculated in accordance with categorical variables for both the total number of areas (mean, median, mode, standard deviation, and range) reported by the women and the total number of women reporting pain in each area.

Quality. Frequencies and percentages were analyzed for women who endorsed each descriptor and the top 3 to 5 descriptors. The total number of descriptors endorsed were analyzed as mean, median, mode, standard deviation, and range.

Temporal Pattern. Temporal patterns for morning, nighttime, and combined TIMP were graphed over time for the entire sample as well as each individual.

Aggravating/alleviating Factors. Answers to categorical and BPI open-ended questions were coded using basic content analysis to develop commonly occurring categorical themes (total number of themes and range) and were analyzed by frequencies and percentages. Percentages of BPI pain relief ratings were described as such, along with frequencies and mean, median, mode, standard deviation, and range.

Pain Management. Questions evaluating period of pain relief were analyzed according to frequencies and percentages for the categorical options given for period of

pain relief provided by medications and frequency of pain medication. Questions evaluating pain management were coded categorically (yes/no) and evaluated using frequencies and percentages. Open-ended responses about medications not prescribed by the doctor and taken for pain were analyzed using basic content analysis to develop commonly occurring categorical themes for classes and/or names of specific medications, which was further described by frequencies and percentages. Coding for all content analyses used in the TIMP symptom experience analysis were verified by the authors and disagreements were resolved through discussion.

Co-occurring Symptoms

Spearman's correlations were used to assess the relationships between TIMP intensity and distress and co-occurring symptoms. Positive correlations indicated greater TIMP intensity or distress was correlated with greater (i.e., worse) intensity or interference of co-occurring symptoms.

Results

Description of the Sample

Figure 3-1 shows the accrual flow from the 432 women who self-referred to the study or were approached for participation in the study to those who completed baseline questionnaires and the TIMP Pain Diary. The sample size for this pilot study included a total of 15 participants completing baseline questionnaires and 11 of those also completing the 28-day TIMP Pain Diary. Of the 15 women who participated in the study, *n*=3 were recruited from the cancer clinic and *n*=12 were recruited from either the Rare Patient Voice, LLC© registry or local cancer support communities. The low clinic recruitment was due to changes in physician coverage and a reduction in the patient volume seen at the clinic.

Women were on average 56 years of age. As shown in Table 3-1, most were non-Hispanic, White, married or living with a partner, retired from work, and had completed some years toward an undergraduate degree. Most had a diagnosis of stage III or IV ovarian cancer, had received surgery and chemotherapy, and self-reported they had received paclitaxel chemotherapy in the past. Slightly more than half (62%; *n*=8) had received paclitaxel chemotherapy in the past (rather than currently) with a mean of 2.1 years since their last paclitaxel treatment. Commonly reported treatments received (in addition to paclitaxel) included carboplatin (67%; *n*=10), bevacizumab (20%; *n*=3), gemcitabine (13%; *n*=2), and doxorubicin (13%; *n*=2). Other commonly self-reported comorbid conditions among the women included hypertension (40%; *n*=6), osteoarthritis or degenerative arthritis (33%; *n*=5), and back pain (40%; *n*=6).

TIMP Symptom Experience

Intensity. Table 3-2 displays mean BPI TIMP intensity ratings at their worst and least, on average, and "now" as well as for the total score and diary pain ratings. Using established cutpoints for mild, moderate, and severe pain and BPI pain ratings, over half of women reported their average TIMP as moderate or severe (53%). Using established cutpoints for mild, moderate, and severe pain and morning, nighttime, and combined diary pain ratings, most women reported TIMP as mild (83%, 58%, and 64%, respectively). The proportion of women who had moderate or severe pain on the BPI total score was higher (46%) than the proportion of women who had moderate or severe pain on the combined diary (36%).

Distress. The mean distress level reported by women was 4.7 (*Mdn*=5*,* mode=5, *SD*=2.4*,* and range: 0-8). Using reported distress levels and the established cutpoints for mild, moderate, and severe pain, women were grouped into phenotypes. Most (40%; *n*=6) women reported their TIMP was a variable mix of distress and intensity (i.e., ratings were

in mild [0 to 4] to severe [7 to 10] range). Other phenotypes included: mild, where all ratings were in the mild range (0 to 4) (27%; *n*=4); mild to moderate, where all ratings were in mild (0 to 4) or moderate range (5 to 6) (20%; *n*=3); moderate to severe, where all ratings were in moderate (5 to 6) or severe range (7 to 10) (7%; *n*=1); and severe, where all ratings were in severe range (7 to 10) (7%; *n*=1).

Duration. For the 11 women completing pain diaries, nearly half (45%, *n*=5) reported their duration of pain was 100% (i.e., TIMP was present at an intensity level $\geq$ 1 at all recorded time points) of the time, 36% (*n*=4) reported their duration of pain was at least 70% of the time (but not constant), and 18% (*n*=2) reported their duration of pain was less than 50% of the time.

Furthermore, summarizing across intensity, distress, and duration, over a quarter (27%) of women reported TIMP that was moderate to severe in intensity on average, constant (i.e., pain was $\geq$ 1 at all recorded time points), and moderate to severely distressing. Other phenotype patterns were reported among the women and varied considerably.

Location. The proportion of women who endorsed pain in each of the 8 sections is shown in Table 3-3. The mean total number of areas endorsed by women was 3.7 (*Mdn*=3.5*,* mode=2 and 4, *SD*=2.1, and range: 1-8). Pain was most often situated in the lower extremities followed by the upper extremities*).* Most (79%; *n*=11) women identified TIMP as present in 2 to 5 of the locations on the body diagram.

Quality. The proportion of women who endorsed each of the 15 TIMP descriptors is shown in Table 3-4. “Aching” was endorsed most (93%; *n*=11) by the women. “Throbbing,” “nagging,” “miserable,” and “tender” were the other top 5 descriptors. The mean total number of descriptors endorsed by women was 8.3 (*Mdn*=9*,* mode=9, *SD*=3.3,

and range: 4-15). Most (75%; *n*=9) women reported more than 5 descriptors characterizing the quality of their TIMP.

Temporal Pattern. Morning, nighttime, and combined TIMP intensities over 28 days were graphed and analyzed. There was considerable individual variability in TIMP over time both within and across individuals. No clear temporal pattern emerged across all individuals. See Figure 3-2.

Aggravating/alleviating Factors. The average amount of pain relief in the last week provided by pain treatments or medications was 46% (*Mdn*=45%, Mode=50%, *SD*=25.3, and range: 0-100). Open-ended responses to the question of what makes the pain better included: rest (60%; *n*=9); medications both oral and topical (53%; *n*=8), and heat (47%; *n*=7). Including rest, medications, and heat, women reported a total of 6 different types of alleviating factors (*M*=1.9, *Mdn*=2.0, Mode=1.0, *SD*=1.0, and range: 1-4). Open-ended responses to the question of what makes the pain worse included: walking (50%; *n*=7); standing (21%; *n*=3), lifting or bending (21%, *n*=3), and sitting or lying for too long (21%; *n*=3). Including walking, standing, lifting or bending, and sitting or lying for too long, women reported a total of 9 different types of aggravating factors (*M*=1.5, *Mdn*=1.0, Mode=1.0, *SD*=0.74, and range: 0-3). When asked, women most frequently reported using warm compresses (67%; *n*=10), relaxation techniques (53%; *n*=8), and distraction (33%; *n*= 5) as alternative methods for pain relief. Massage was entered by the only participant who endorsed "other."

Pain Management. Most (67%; *n*=10) women reported taking pain medicine only when necessary and most (54%; *n*=7) did not take pain medicine every day. The sample was almost evenly split between women who did not feel they required a stronger type of pain medication (57%; *n*=8) and those that did (43%; *n*=6). Women taking pain medication for treatment of TIMP most frequently reported that it took 1 hour (20%; *n*=3) or 4 hours

(20%; *n*=3) before pain returned; however, most (71%; *n*=10) women did not feel they needed to take more pain medication than was prescribed by their doctor and none of the women were concerned they were using too much pain medication. Only two women reported having side effects from their pain medication (14%) and these included: constipation, somnolence, and pruritus. Most (93%; *n*=13) women reported they did not feel they required further information about their pain medication. When asked about medications not prescribed by a doctor but taken to help relieve pain, women reported using nonsteroidal anti-inflammatory agents such as acetaminophen, aspirin/paracetamol/caffeine, ibuprofen, and naproxen to help relieve their pain.

Co-occurring Symptoms

Descriptive statistics including mean scores and range of scores for other symptom measures are shown in Table 3-5. Since a PROMIS symptom score ≥ 55 is indicative of a clinically relevant symptom,[52] the median scores suggest that the majority of patients also had substantial pain interference, fatigue, and sleep problems. Spearman's correlations are shown in Table 3-6. Greater TIMP intensity or distress was associated with greater intensity and interference of co-occurring symptoms. The exception was hot flash interference and morning, nighttime, and combined pain diary intensity ratings. Greater pain diary intensity was related to less hot flash interference. Additionally, with the exception of sleep disturbance, the strength of most correlations was medium to large. In general, the diary intensity ratings did not correlate as strongly as the BPI did with co-occurring symptoms.

Discussion

The results of this pilot study provide new findings of the multi-dimensional description of TIMP in women with ovarian cancer. In this small sample, there was a

great deal of variability in individual's experiences of TIMP. The most common TIMP intensity and distress phenotypes which emerged among the women in our study were those with a variable mix for intensity and distress from TIMP and those with mildly intense and mildly distressing TIMP. However, 27% had a more severe phenotype with constant TIMP that was moderately to severely intense and distressing. There was also considerable individual variability in TIMP over time both within and across individuals with no clear temporal patterns in TIMP. Second, most women experienced pain at multiple body sites, indicating the more diffuse rather than localized nature of TIMP. Furthermore, TIMP's intensity, near constant duration, aching nature, diffuse location in the body, variable temporal pattern, and fact that everyday functions such as walking and sitting were aggravating factors indicate a similarity between TIMP and other types of chronic musculoskeletal pain (i.e., osteoarthritis) and suggest TIMP may negatively impact functioning. The latter is supported by high PROMIS interference scores. These findings illustrate the importance of addressing TIMP in clinical practice and in future research.

Similar to previous clinical reports of TIMP, pain medications were often insufficient to fully alleviate TIMP, another analogy with chronic pain. Recommendations for management of chronic pain consider a multi-faceted approach to achieve therapeutic goals. While pharmacotherapy is an important component of chronic pain management, alternative therapies such as exercise, yoga, acupuncture, and massage play a complementary role.[53] These attributes of and recommendations regarding chronic pain management may provide direction for future studies evaluating the role of complementary pain management therapies in addition to pharmacotherapy for better TIMP management.

Prior studies have been limited in describing TIMP, focusing principally on pain intensity[9] rather than a broader range of dimensions such as distress, duration, location, quality, temporal pattern, aggravating and alleviating factors, and pain management.

Moreover, even the studies evaluating pain intensity[10, 16-20] have used common oncology toxicity grading scales which are limited in two ways. First, toxicity scales are typically four points and therefore, do not allow comparison to standard 11-point numeric pain rating scales. Second, toxicity scales are unidimensional and do not capture distress, duration, temporal pattern, and other important aspects of a symptom. As such, our study findings provide a more detailed description of TIMP that is useful for assessing and managing this type of treatment-related pain. In addition, our study findings may serve as a benchmark or comparison for future TIMP studies.

The few studies that have assessed TIMP distress, quality, and temporal pattern provide some comparison for our findings. Boehmke & Dickerson[12] described distress and quality of "bone pain" following paclitaxel chemotherapy in women with breast cancer. In this qualitative study, distress was described as "severely affecting" the women and pain quality was described as severe and "jabbing." Pusztai et al.[20] identified the temporal pattern of "muscle aches" increased following paclitaxel chemotherapy, peaked between days 3 to 5, and resolved by the end of the cycle. Although these findings present a potential temporal pattern of TIMP in those who are actively receiving treatment with paclitaxel-containing regimens, our study supports that TIMP may be present well beyond completion of paclitaxel chemotherapy. In our study, women who were off paclitaxel for an average of two or more years continued to report TIMP.

Findings from our study also suggest that, although there are few studies describing TIMP, TIMP may mimic pain that is analogous to the pain experienced in osteoarthritis. Qualitative work describing osteoarthritic pain[54] reveals its complex nature which is not adequately assessed by intensity ratings alone. Additionally, this pain is described as numerous and differing in intensity, duration, depth, type of occurrence, impact, and rhythm as well as in painful sensations and associated symptoms;

furthermore, this pain is described as being worsened by physical activity including the activities required for everyday functioning.[54] Our study findings add to the literature by further describing TIMP and supporting the need for further research which should include prospective, longitudinal studies describing TIMP and its variability with the addition of a non-cancer control group with chronic musculoskeletal pain (i.e., osteoarthritis) to establish common patterns and any differences.

Our pilot findings also suggest TIMP, like other cancer treatment-related symptoms, may occur within a symptom cluster of general pain, peripheral neuropathy, sleep disturbance, anxiety, depression, fatigue, and hot flashes. Our results revealed a paradoxical finding with worse hot flash interference associated with worse pain when using the BPI pain ratings, but less hot flash interference was associated with worse pain when using the diary pain ratings. This may be a chance finding due to our small pilot sample (with even less reporting hot flashes) or it may be in some way attributable to the cross-sectional vs. longitudinal difference in the pain measures. However, our findings are otherwise consistent with the symptom science literature supporting patients with chronic conditions such as cancer experience an array of multiple co-occurring symptoms.[26] In the latest expert panel proceedings and recommendations on advancing symptom science through symptom cluster research, two of the three most common symptom clusters identified were: (1) fatigue, pain, depression, and sleep disturbance; and (2) anxiety and depression. These clusters were identified from studies mostly involving cancer patients.[26] Similarly, sleep disturbance, pain, anxiety, depression and fatigue are five of the most prevalent, chronic, disabling, and under-treated symptoms in both the general population and in clinical practice.[52] In a sample of Veteran patients with chronic musculoskeletal pain, Davis et al.[52] identified that sleep disturbance, pain, anxiety, depression, and fatigue commonly cluster with the norm being a

polysymptomatic patient, whereas only about 1 in 10 patients were monosymptomatic. Collectively, these studies, in cancer and chronic musculoskeletal pain, support the preliminary relationships between TIMP intensity and distress and other co-occurring symptoms that were identified by our study. Although Davis et al.[52] provided preliminary evidence in support for the calculation of a composite (i.e., sleep disturbance, pain, anxiety, depression, and fatigue) symptom score derived from PROMIS measures that could be used clinically to address multiple co-occurring symptoms, further evidence on how to optimally assess and manage co-occurring symptoms or symptom clusters in clinical practice requires further research.

Our study had several strengths including being the first study to attempt to describe multiple dimensions of TIMP in a sample of women with ovarian cancer. Before now, details such as intensity, distress, duration, location, quality, temporal pattern, aggravating and alleviating factors, and pain management have been unspecified in the literature. Our study also provides new understanding of how TIMP intensity and distress are associated with co-occurring symptoms in women with ovarian cancer who were being or had been treated with paclitaxel chemotherapy.

Study findings should be interpreted in the context of some study limitations. First, because this was a small pilot study, we recommend replication in a larger sample. Also, because of the small pilot sample, we were unable to control for potential confounding influences in the analyses. Second, the study focused on women with ovarian cancer to better understand this particular patient population, but this limits generalizability to other cancers. Third, comorbid conditions such as osteoarthritis or degenerative arthritis, or back pain, which were present in our sample of women, may have impacted our ability to distinguish TIMP from these chronic pain conditions. Although we asked patients to answer TIMP-related questionnaires in thinking about

their TIMP, it is unknown whether all women were able to delineate this difference as instructed. Future prospective, longitudinal studies comparing chronic musculoskeletal pain with TIMP will delineate differences between these conditions. Fourth, although the term TIMP suggests musculoskeletal pain caused by taxane chemotherapy agents, our study did not attempt to identify causation. Rather, we only intended to describe muscle and/or joint pain reported by women following paclitaxel (assumed to be TIMP) and the associations between this type of pain and other co-occurring symptoms. Finally, differences between women who were actively undergoing treatment and those who had been treated in the past were not compared within the context of our study's findings; furthermore, this treatment information (nor demographic information) was not verified against medical records.

Implications for Nursing

Oncology nurses play an important role in managing distressing symptoms and nurses should continue to assess this symptom in a multi-dimensional context (as is recommended for initial descriptions of pain) to better intervene on aggravating and alleviating factors and pain management regimens. One important finding from this pilot study was that the TIMP pain diary did not perform as well as the standardized questionnaires and therefore, nurses should use caution when recommending patients keep a TIMP pain diary at home. Pain diaries may not be as helpful in assessing and managing TIMP because of the constant (i.e., chronic) nature of TIMP pain, which was identified in our study. Additionally, TIMP diaries may only provide useful information in populations of women who are on active treatment vs. women who have been treated with paclitaxel chemotherapy in the past, as was the majority of women who participated in our study. Finally, associations between TIMP intensity and distress and co-occurring symptoms are likely and nurses should assess for and include these relationships in

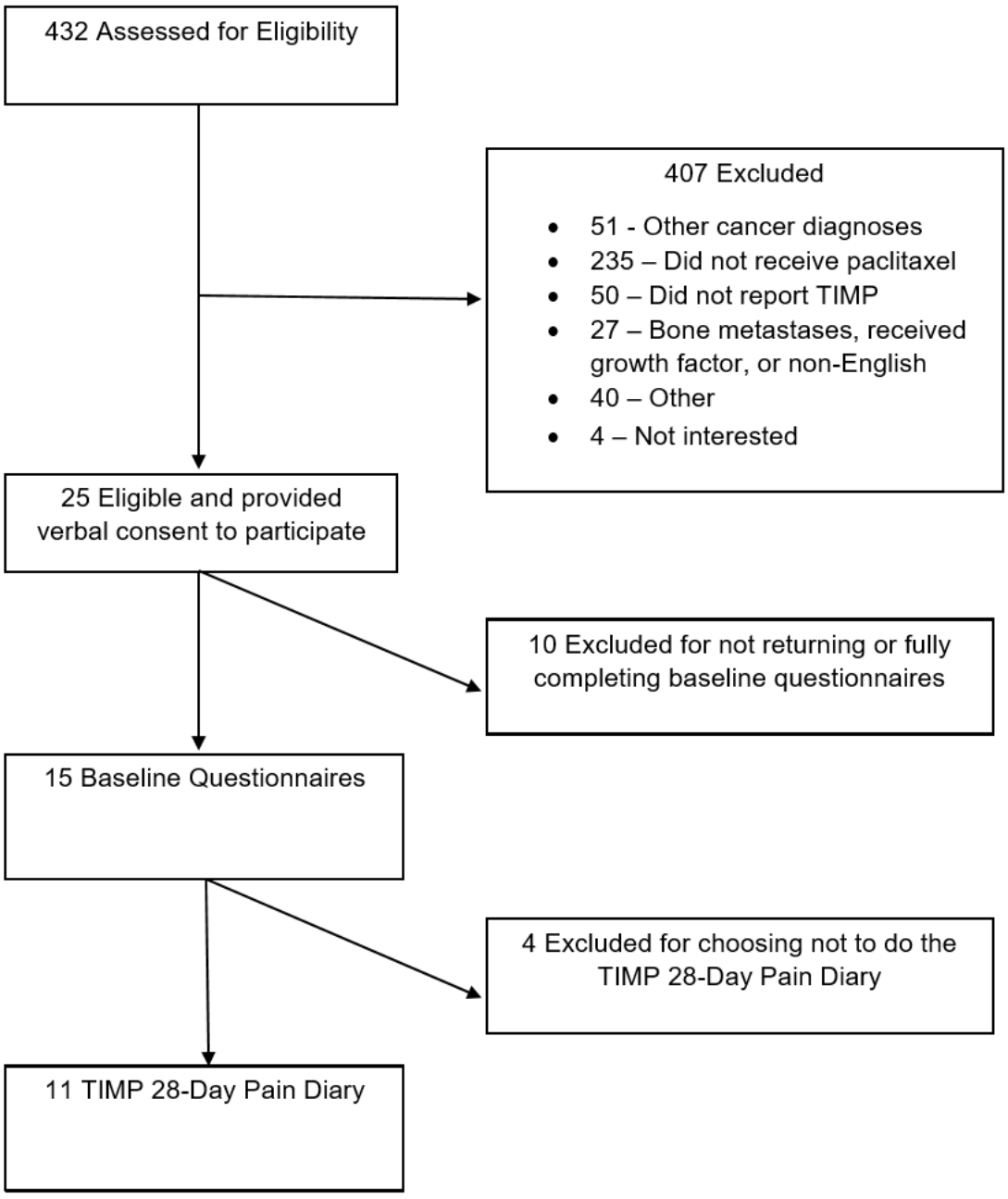
clinical care and in future research on symptom clusters specific to ovarian cancer survivors.

Conclusion

Among women with stage III to IV ovarian cancer who were being or had been treated with paclitaxel-containing regimens, TIMP is moderate to severe in intensity on average for most women and is moderately distressing. TIMP intensity and distress are also associated with co-occurring symptoms including general pain, peripheral neuropathy, sleep disturbance, anxiety, depression, fatigue, and hot flashes. Multidimensional, comprehensive descriptions of the TIMP symptom experience and the associations between TIMP intensity and distress and co-occurring symptoms should be replicated in studies with larger sample sizes. A prospective, longitudinal study with a comparison group of non-cancer women with chronic musculoskeletal pain would provide additional details about the TIMP symptom experience and its variability and could improve management of this symptom in ovarian cancer survivors.

Figure 3-1

Study Accrual Flow Diagram



Note. TIMP= Taxane-induced musculoskeletal pain

Figure 3-2

Patterns Endorsed by Participants to Describe Temporality of TIMP (N=11)

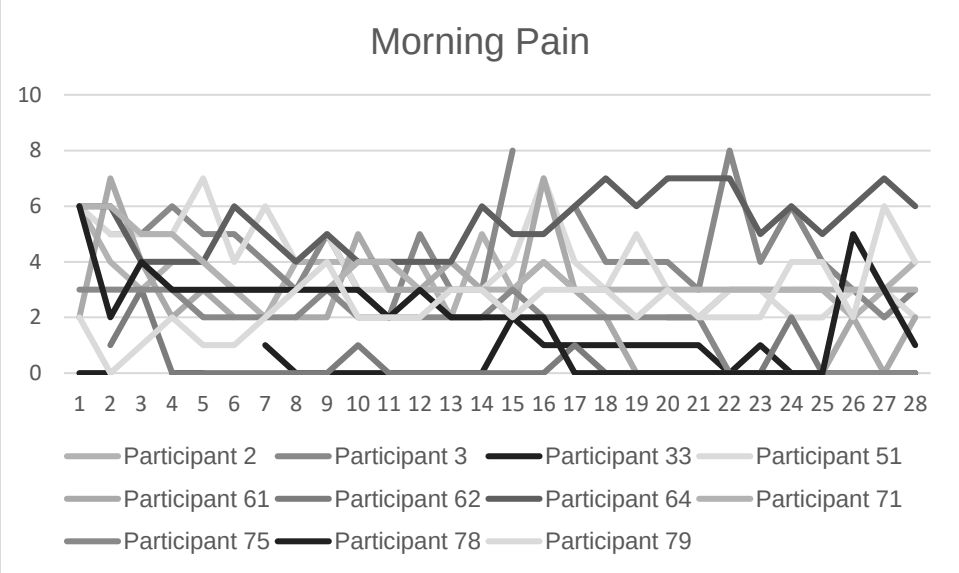


Figure 3-2a: Temporal Patterns for Morning TIMP

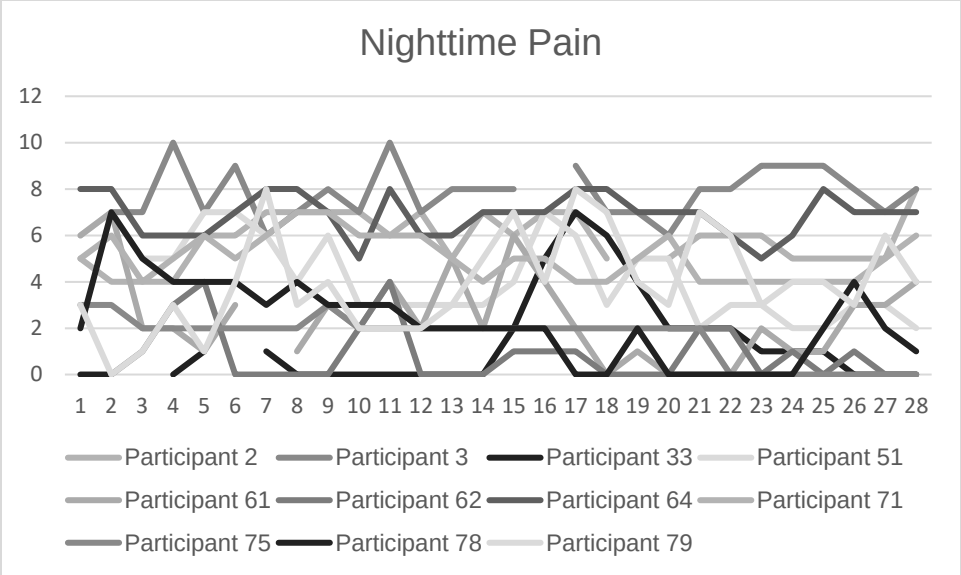


Figure 3-2b: Temporal Patterns for Nighttime TIMP

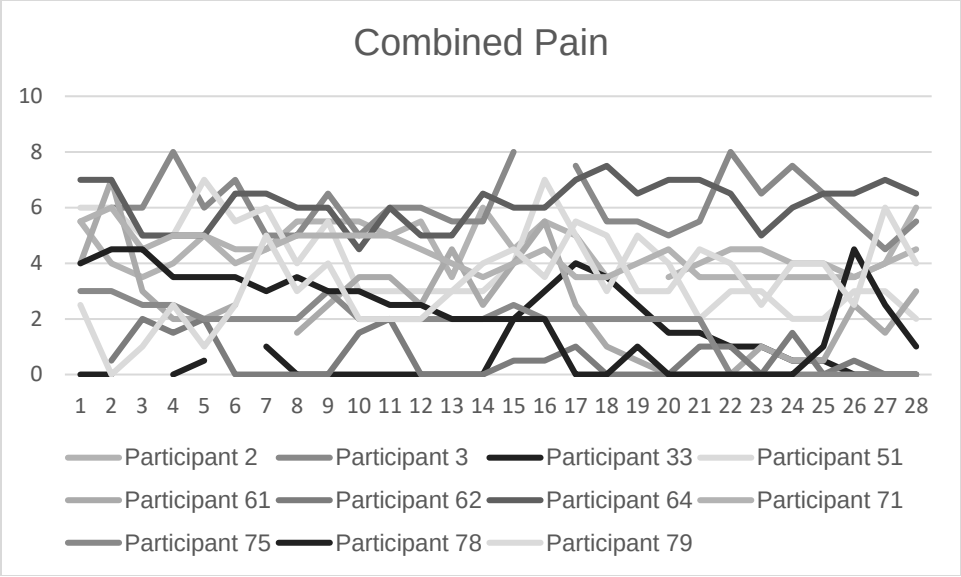


Figure 3-2c: Temporal Patterns for Combined TIMP

Table 3-1

Sample Demographic and Treatment Characteristics (N=15)

	% (n)
Race and Ethnicity	
Black or African American, Not Hispanic or Latino	6.7% (*1*)
White or Caucasian, Not Hispanic or Latino	86.7% (*13*)
More than one race	6.7% (*1*)
Marital Status	
Single	13.3% (*2*)
Married or partnered	73.3% (*11*)
Widowed	13.3% (*2*)
Employment	
Full-time	20.0% (*3*)
Unemployed	13.3% (*2)*
Retired	40.0% (*6)*
Other	26.7% (*4*)
Education	
Some high school	20.0% (*3*)
High school degree	26.7% (*4*)
Some undergraduate	46.7% (*7*)
Undergraduate degree	6.7% (*1*)
Stage of Cancer	
I	0% (*0*)
II	6.7% (*1*)

III	73.3% (*11*)
IV	20.0% (*3*)
Treatment	
Surgery and chemotherapy	93% (*14*)
Surgery, radiation, and chemotherapy	7% (*1*)
Treatment	
Actively receiving paclitaxel	20% (*3*)
Treated with paclitaxel in the past	80% (*12*)

Table 3-2

Descriptive Statistics for TIMP Pain Intensity Questionnaire and Diary

	Mean	*Median*	Mode(s)	*SD*	Range	% mild	% moderate	% severe
BPI Ratings[1]								
Worst	5.8	7	3, 8	2.4	2-9	33%	13%	53%
Least	2.6	2	3	2.3	0-7	80%	7%	13%
Average	4.3	5	3, 5	2.3	1-8	47%	33%	20%
Now	4.1	4	3,6	2.6	0-8	60%	20%	20%
Total	4.2	4	2	2.0	2-8	53%	33%	13%
Diary Ratings[2]								
Morning	2.7	3	3	2.0	0-8	83%	14%	3%
Nighttime	3.9	4	2	2.7	0-10	58%	20%	22%
Combined	3.3	3.5	0	2.2	0-8	64%	27%	9%

Note. BPI= Brief Pain Inventory; *SD*= standard deviation

[1]n=15

[2]n=11

Table 3-3

Body Locations where TIMP was Experienced by Participants (N=14)

	% (n)
Left hip, thigh, knee, leg, ankle, foot	93% (*13*)
Right hip, thigh, knee, leg, ankle, foot	79% (*11*)
Posterior head and neck	50% (*7*)
Left shoulder arm, elbow, wrist, hand	50% (*7*)
Right shoulder, arm, elbow, wrist, hand	43% (*6*)
Posterior thorax	29% (*4*)
Anterior thorax	21% (*3*)
Anterior head and neck	14% (*2*)

Table 3-4

Descriptors Endorsed by Participants to Describe TIMP Quality (N=12)

	% (n)
Aching	92% (*11*)
Throbbing	75% (*9*)
Nagging	75% (*9*)
Miserable	75% (*9*)
Tender	67% (*8*)
Exhausting	58% (*7*)
Tiring	58% (*7*)
Penetrating	58% (7)
Gnawing	50% (*6*)
Sharp	50% (*6*)
Shooting	42% (*5*)
Stabbing	33% (*4*)
Burning	33% (*4*)
Numb	33% (*4*)
Unbearable	25% (*3*)

Table 3-5

Descriptive Statistics for Other Symptom Measures

Measure	*Mean*	*Median*	Mode(s)	*SD*	Range
PROMIS – Pain Interference (General)[1]	59.9	60.3	64	6.2	49-69
NPS-CIN[2]	12.5	11.0	9, 10	4.8	6-24
PROMIS- Sleep Disturbance[1]	57.9	58.2	52	6.1	47-72
PROMIS- Fatigue[1]	58.9	60.8	63	7.8	41-69
PROMIS- Anxiety[1]	53.2	52.8	37	10.8	37-68
PROMIS- Depression[1]	50.4	50.8	38	10.4	38-66
HFRDIS[3]	29.1	15	N/A	32.8	0-82

Note. SD= standard deviation: PROMIS= Patient-reported Outcomes Measurement Information System; NPS-CIN = Neuropathy Pain Score (Chemotherapy-Induced Neuropathy-Specific); HFRDIS = Hot Flash Related Daily Interference Scale; N/A= not applicable

[1]n=15

[2]n=14

[3]n=7 reported hot flashes

Table 3-6

Spearman Correlations between TIMP Intensity and Distress and Other Symptoms

	PROMIS – Pain Interference (General)	NPS-CIN	PROMIS-Sleep Disturbance	PROMIS-Fatigue	PROMIS-Anxiety	PROMIS-Depression	HFRDIS[1]
BPI Intensity							
Worst	.45	.29	.17	.45	.33	.23	.32
Least	.69**	.49	.20	.70**	.72**	.64*	.42
Average	.80**	.65*	.28	.67**	.61*	.52*	.47
Now	.63*	.41	.29	.37	.33	.34	.18
Total	.74**	.51	.25	.62*	.54*	.50	.39
Diary Intensity							
Morning	.22	.49	.27	.61*	.51	.19	-.80
Nighttime	.30	.54	.19	.66*	.50	.20	-.80
Combined	.27	.54	.22	.64*	.49	.15	-.80
BPI Distress	.74**	.45	.32	.47	.50	.54*	.29

Note. BPI= Brief Pain Inventory; TIMP= Taxane-induced musculoskeletal pain; PROMIS= Patient-reported Outcomes Measurement Information System; NPS-CIN = Neuropathy Pain Score (Chemotherapy-Induced Neuropathy-Specific); HFRDIS = Hot Flash Related Daily Interference Scale; * = correlation is significant at the 0.05 level; ** = correlation is significant at the 0.01 level

[1]n=7 reported hot flashes

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CHAPTER 4

This chapter presents results from the dissertation research study "Taxane-induced Musculoskeletal Pain in Women with Ovarian Cancer," and presents the associations between TIMP and patient-reported outcomes.

Ovarian cancer has the highest mortality of all gynecological cancers, due in large part to the often asymptomatic presentation of women during the early stages of the disease.[1, 2] As a result, over 60% of women are diagnosed at an advanced stage.[1, 2, 3] After initial surgery and chemotherapy, disease recurrence occurs in most women and, thus, most women experience life with active disease requiring ongoing treatment.[3-5] These facts about women with ovarian cancer bring discussions about health-related quality of life to the forefront in clinical practice.[6]

In research, health-related quality of life generally consists of an individual's physical functioning and emotional, social, and psychological well-being. Measures of health-related quality of life typically evaluate the extent to which an individual's disease and/or treatment affect these important dimensions.[2, 7, 8] Symptom burden is an important variable impacting health-related quality of life.[2, 9] Treatment-related symptoms such as taxane-induced musculoskeletal pain (TIMP) (i.e., pain including myalgia and/or arthralgia and affecting more than half of patients treated with taxane-based chemotherapy) are likely to impact health-related quality of life of ovarian cancer survivors. Attention to TIMP and the impact of TIMP on patient-reported outcomes is especially important in ovarian cancer survivors where inclusion of patient-reported outcomes is an important endpoint, in clinical trials and in discussions with healthcare providers about therapy options and plans of care.[8, 10]

Background of the Problem

TIMP is likely to be associated with patient-reported outcomes including greater interference with daily activities, poorer physical functioning, and lower health-related quality of life. Although research to date has not identified TIMP to be a dose-limiting toxicity, the myalgia and/or arthralgia experienced by patients receiving taxane-based chemotherapy can result in impaired mobility, secondary to the limitation of joint function, and the experience of pain can affect physical functioning.[11] Though it has not been widely studied, TIMP very likely undermines cancer survivors' health-related quality of life in ways that are similar to the burden of persistent musculoskeletal pain seen in non-oncology populations.

Data from non-oncology populations suggest the following facts about pain. Pain is among the most common reasons for temporary and permanent work disability.[12, 13] The World Health Organization recognizes the significant contribution of musculoskeletal conditions to the global burden of disease.[14] Additionally, the Institute of Medicine (IOM) has highlighted the significant functional and economic effects of musculoskeletal pain.[15] Musculoskeletal pain is the most common, disabling, and costly of all pain complaints.[13] Pain is known to be even more prevalent in individuals with psychiatric comorbidity, specifically mood disorders, and is a strong predictor of both onset and persistence of depression; likewise, depression is a strong predictor of pain.[16] Furthermore, the comorbidity of pain and chronic conditions, such as impaired sleep and emotional distress, decrease an individual's active coping in addition to negatively impacting health-related quality of life, disability, and even response to treatment.[16, 17] These facts suggest TIMP is likely negatively associated with patient-reported outcomes. However, because it has not been comprehensively studied, the strength, direction, and significance of associations

between TIMP and interference with daily activities, physical functioning, and health-related quality of life are currently unknown and unspecified in the literature.

Therefore, the purpose of this paper was to identify associations between TIMP (intensity and distress) and patient-reported outcomes (i.e., interference with daily activities, physical functioning, and health-related quality of life) in women with ovarian cancer who were being or had been treated with paclitaxel-containing regimens.

Methods

Design, Setting, and Participants

This was a cross-sectional, descriptive, correlational pilot study describing TIMP in women with ovarian cancer. Participants were a convenience sample of women with ovarian cancer who were recruited from an outpatient cancer clinic in the Midwest, local cancer support communities, and a national cancer survivors' research registry between December 1, 2015 and October 14, 2016. Inclusion criteria for participation in our study are described in full detail in Chapter 3 of the dissertation.

Data Collection

The study was approved by the Scientific Review Committee and Institutional Review Board. Details regarding the procedures for data collection are fully described in Chapter 3.

Measures

Participants completed questionnaires and a 28-day TIMP Pain Diary.

Demographic and treatment information were self-reported and were not verified against medical records. All collected demographic and treatment variables are reported in full detail in the text and tables of Chapter 3. Additionally, comorbidities were evaluated

using the 12-item validated Self-Administered Comorbidity Questionnaire (SCQ) modified. Cronbach's alpha, including among cancer patients, was 0.94.[18]

TIMP Intensity and Distress

TIMP intensity was assessed using the 32-item validated Brief Pain Inventory – Long Form (BPI) and a standard 28-day TIMP symptom reporting diary. Cronbach's alpha for the BPI – Long Form has ranged from 0.77 to 0.91.[19] On the BPI, participants rated worst, least, average, and current (now) pain intensity. On the TIMP Pain Diary, participants were asked to report the intensity of their morning and nighttime TIMP on a scale of 0 (not at all intense) to 10 (extremely intense). Those on active treatment were given a place to specify whether or not they had received treatment with paclitaxel chemotherapy on that day.

TIMP distress was measured using a single item which asked participants to rate distress caused by TIMP on a 0-10 scale. Anchors were not at all distressing to extremely distressing.

Patient-reported Outcomes

Interference with daily activities. Interference with daily activities was evaluated with the seven BPI interference items. Participants rated how much TIMP interfered with seven daily activities including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. Response options were 0 (does not interfere) to 10 (completely interferes). The interference score was calculated as the mean of the interference items. Higher scores indicate worse interference with daily activities. Cronbach's alphas, including among cancer patients, have ranged from 0.77 to 0.91.[19]

Physical function. The Performance 10 (PF10) is a valid and reliable 10-item scale that is the physical functioning subscale of the MOS-SF-36, one of the most

commonly used measures of health-related quality of life.[20, 21] The scale assesses the extent to which health limits physical activities. Higher scores reflect higher physical functioning. Cronbach's alphas generally exceed 0.90.[20, 21]

Health-related quality of life. Health-related quality of life was evaluated using the Functional Assessment of Cancer Therapy-General (FACT-G), which is a valid 28-item tool assessing physical well-being, social/family well-being, emotional well-being, and functional well-being. Item responses (0=*not at all* to 4=*very much*) yield total scores ranging from 0 to 112. Higher scores indicate higher quality of life. Cronbach's alpha was 0.89.[22]

Data Analysis

A description of the sample, including demographic and treatment information, was analyzed using descriptive statistics appropriate for the level of measurement. Missing data points for all of the analyses were handled by exclusion of cases pairwise.[23]

TIMP Intensity and Distress

BPI intensity ratings (analyzed as mean, median, mode, standard deviation, and range) and TIMP Pain Diary intensity ratings for morning, nighttime, and combined morning and nighttime pain (mean, median, mode, standard deviation, and range) for the 28 days were analyzed. Also, all intensity ratings were examined in relation to BPI cutpoints[24] of mild (0-4), moderate (5-6), and severe (7-10) pain. Distress was analyzed as mean, median, mode, standard deviation, and range. Commonly occurring phenotypes were established to group the women according to the severity of both the intensity and distress of their reported TIMP. Phenotypes were established by using the BPI intensity items and the distress item. Frequencies and percentages were analyzed for the phenotypes including mild, mild to moderate, moderate to severe, severe, and variable.

Patient-reported Outcomes

Spearman's correlations were used to measure relationships between TIMP (intensity and distress) and patient-reported outcomes (interference with daily activities, physical functioning, and health-related quality of life). Positive correlations indicated that greater TIMP intensity and/or distress was correlated with greater interference with daily activities, worse physical functioning, and/or worse health-related quality of life. The magnitude (r), direction (+/-), and significance (*p* value) of each relationship was analyzed and reported.

Patient-reported outcomes measures were also described across each of the phenotypes (i.e., mild, mild to moderate, moderate to severe, severe, and variable). Descriptive statistics included mean, standard deviation, and range along with 95% confidence intervals across each of the outcome measures (interference with daily activities, physical functioning, and health-related quality of life).

Results

Descriptive statistics describing the demographic and treatment characteristics of our sample are fully described in detail in Chapter 3 of the dissertation. The sample was comprised of women who were on average 56 years of age. Most were non-Hispanic, White, married or living with a partner, retired from work, and had completed some years toward an undergraduate degree. Most had a diagnosis of stage III or IV ovarian cancer, had received surgery and chemotherapy, and self-reported they received paclitaxel in the past with a mean of approximately 2 years since their last paclitaxel treatment.

TIMP Intensity and Distress

Table 4-1 shows BPI TIMP intensity ratings and distress ratings for each subject as well as the phenotype groupings. Most (40%; *n*=6) women described TIMP intensity

and distress as variable (i.e., ratings were in the mild [0 to 4] to severe [7 to 10] range). Other phenotypes included: mild, where all ratings were in the mild range (0 to 4) (27%; *n*=4); mild to moderate, where all ratings were in the mild (0 to 4) or moderate range (5 to 6) (20%; *n*=3); moderate to severe, where all ratings were in the moderate (5 to 6) or severe range (7 to 10) (7%; *n*=1); and severe, where all ratings were in the severe range (7 to 10) (7%; *n*=1).

Patient-reported Outcomes

Spearman's correlations are shown in Table 4-2. Greater TIMP intensity and distress was associated with greater interference with daily activities, worse physical functioning, and worse health-related quality of life. Across all outcomes, the strength of nearly all correlations was medium to large. In general, the diary intensity ratings did not correlate as strongly or as significantly as the BPI ratings with patient-reported outcomes.

Patient-reported outcomes across phenotypes are shown in Table 4-3. This table also shows the pattern of greater TIMP intensity and distress being associated with greater interference with daily activities, worse physical functioning, and worse health-related quality of life.

Discussion

Two important findings are as follows. First, participant ratings and phenotypes showed large variability in TIMP intensity and distress. Second, greater TIMP intensity and distress were associated with worse patient-reported outcomes. This was true for the correlational matrix and when examining outcomes by phenotypes.

The first finding supports previous literature identifying large variability in reports of TIMP intensity and distress.[25-36] Furthermore, the large variability in phenotypes for TIMP intensity and distress are consistent with two of the most recent systematic

reviews of TIMP[37, 38] and other supporting literature which suggests TIMP is likely common[39, 40] – affecting up to 94% of patients.[37] Chiu et al[38] identified percentages of taxane-induced arthralgia and myalgia ranged from 2.8% to 72%. Also, intensity appears to be dose dependent with doses of paclitaxel > 200mg/m^2 leading to more frequent and intense TIMP.[38, 41] Although dose of paclitaxel was not a variable assessed in this pilot study and comparisons between those women who were on active treatment and those women who were treated in the past were not made here due to the small sample size, this may have been a contributing factor to the large variation seen across phenotypes for TIMP intensity and distress. A prospective, longitudinal study (where differences in TIMP intensity and distress can be evaluated and compared across those on active treatment versus those who have received treatment with paclitaxel in the past but still report TIMP) seems to be the best recommendation for future research studies in order to better understand the seemingly variable and non-uniform nature of TIMP intensity and distress.

The second finding is also consistent with other literature identifying greater pain intensity and distress are associated with worse patient-reported outcomes. The literature on chronic pain suggests pain is among the most common reasons for temporary and permanent work disability[12, 13] and musculoskeletal pain, specifically, is the most disabling and costly of all pain complaints[13] (i.e., those with more constant, chronic pain are more likely to experience interference with daily activities [e.g., work inside or outside the home] and physical functioning as well as health-related quality of life). The total mean years since last paclitaxel treatment for women in our sample was approximately 2 years. Because our sample included more women who had been treated with paclitaxel in the past compared to those on active treatment, our sample may have included more women experiencing a more chronic type of pain. Our correlative findings where greater intensity or distress of TIMP was associated with greater interference with

daily activities, worse physical functioning, and worse health-related quality of life suggest these facts about chronic pain and chronic musculoskeletal pain in particular may be applicable to TIMP experienced by ovarian cancer survivors. Pain is also known to be even more prevalent in individuals with psychiatric comorbidity and is a strong predictor of onset and persistence of depression; likewise, depression is a strong predictor of pain.[16] Comorbidity of pain and chronic conditions (e.g., sleep disturbance, anxiety, and depression) decrease active coping and negatively impact health-related quality of life, disability, and even response to treatment.[16, 17] Our correlations support these facts may be true in our sample of women and may support patient-reported outcomes measures as an important endpoint in ovarian cancer clinical trials and in discussions with healthcare providers about therapy options and plans of care.[8, 10] A prospective, longitudinal study continues to be the best recommendation for future research studies not only to better understand the seemingly variable and non-uniform nature of TIMP intensity and distress, but also the duration and temporal pattern of TIMP in order to better understand any underlying chronicity of TIMP and the role this chronicity may play in the associations between TIMP intensity and distress and patient-reported outcomes measures.

Collectively, these findings add to the symptom science literature describing the TIMP symptom experience in cancer survivors and its likely impact on patient-reported outcomes. Additionally, these findings come at a time when recognition of patient-reported outcomes is of growing research interest and requires attention to standardized measurement of health-related quality of life outcomes, as used in our study, in populations including cancer survivors.[42-44]

Strengths and Limitations

These preliminary findings provide new understanding of how TIMP intensity and distress are associated with patient-reported outcomes including interference with daily

activities, physical functioning, and health-related quality of life in women with ovarian cancer who were being or had been treated with paclitaxel chemotherapy. Information presented in this paper is important for nurses in understanding best clinical practice for TIMP symptom management in this population.

Findings should be interpreted in the context of some limitations. This was a small pilot study and because of the small pilot sample, we were unable to control for potential confounding influences in the analyses. We recommend replication in a larger sample. Also, the study focused on women with ovarian cancer which limits generalizability to other types of cancer. Comorbid conditions such as osteoarthritis or degenerative arthritis or back pain, which were present in our sample of women, may have impacted our results; although we asked participants to answer TIMP-related questionnaires in thinking about their TIMP, it is unknown whether all women responded as instructed. Finally, differences between women who were actively undergoing treatment and those who had been treated in the past were not compared within the context of the findings presented in this paper.

Implications for Research to Advance Practice

Attention to TIMP and the impact of TIMP on patient-reported outcomes is important in ovarian cancer survivors. Inclusion of patient-reported outcomes as an endpoint in cancer clinical trials and in discussions with healthcare providers about therapy options and plans of care[8, 10] is especially important in the case of ovarian cancer survivors who experience disease recurrence and life with active disease. Our pilot study provides preliminary evidence about the associations between TIMP intensity and distress and patient-reported outcomes including interference with daily activities, physical functioning, and health-related quality of life and health-related quality of life, in particular, appears to be an important patient-reported outcome to evaluate in women

with ovarian cancer. Replication of our findings in larger sample sizes is recommended; however, TIMP may negatively impact the health-related quality of ovarian cancer survivors and these associations and potential impact on patient-reported outcomes measures should be considered by providers in clinical practice.

Table 4-1

TIMP Phenotypes Based on BPI Intensity Ratings and Distress Ratings (N=15)

	BPI Intensity Ratings					Phenotype				
Participant Number	Worst	Least	Average	Now	Distress	Mild	Mild to Moderate	Moderate to Severe	Severe	Variable
51	3	3	3	2	3	X				
62	3	0	2	3	3	X				
73	2	0	3	1	0	X				
75	3	3	3	0	4	X				
33	5	0	1	1	5		X			
78	6	2	5	6	5		X			
79	3	3	5	3	5		X			
27	7	7	7	7	6			X		
49	8	7	8	8	8				X	
2	9	3	6	6	7					X
3	8	5	8	4	5					X
61	8	1	3	4	6					X
64	8	2	5	6	5					X
71	7	1	1	3	0					X
72	7	2	5	8	8					X

Note. TIMP= Taxane-induced musculoskeletal pain; BPI= Brief Pain Inventory; Participant data are sorted according to phenotype and then participant number; Mild= all ratings in mild range (0 to 4); Mild to moderate= all ratings in mild (0 to 4) or moderate range (5 to 6); Moderate to severe= all ratings in moderate (5 to 6) or severe range (7 to 10); Severe= all ratings in severe range (7 to 10); Variable= ratings from mild (0 to 4) to severe (7 to 10) range.

Table 4-2

Spearman's Correlations: TIMP Intensity and Distress with Patient-reported Outcomes

	BPI Interference[1]	PF 10[2]	FACT-G Total Score[2]	FACT-G Physical[2]	FACT-G Social[2]	FACT-G Emotional[2]	FACT-G Functional[2]
BPI Intensity[1]							
Worst	.59*	-.44	-.46	-.55*	-.32	-.52*	-.30
Least	.67**	-.77**	-.80**	-.67**	-.78**	-.63*	-.51
Average	.74**	-.76**	-.79**	-.86**	-.63*	-.60*	-.54*
Now	.64*	-.50	-.54*	-.73**	-.35	-.54*	-.38
Total	.76*	-.66**	-.74**	-.83**	-.58*	-.67**	-.46
Diary Intensity[1]							
Morning	.35	-.53	-.46	-.29	-.55	-.37	-.43
Nighttime	.39	-.57	-.52	-.41	-.49	-.40	-.32
Combined	.39	-.57	-.49	-.38	-.50	-.40	-.34
BPI Distress[1]	.81**	-.62*	-.67**	-.76**	-.48	-.68**	-.47

Note. TIMP= Taxane-induced musculoskeletal pain; BPI= Brief Pain Inventory; PF 10= Performance 10; FACT-G= Functional Assessment of Cancer Therapy- General;

[1]higher scores = worse outcomes

[2]higher scores = better outcomes

*p < 0.05; **p < 0.01.

Table 4-3

Patient-reported Outcomes across Phenotypes for TIMP Intensity and Distress

	Mild *n*=4 *M (SD):* range	Mild to Moderate *n*=3 *M (SD):* range	Moderate to Severe *n*=1 *M*	Severe *n*=1 *M*	Variable *n*=6 *M (SD):* range
BPI-Interference[1,3]	*1.5 (1.9):* 0.3 to 4.3	*4.3* (*2.3)*: 2.3 to 6.9	*7.3*	*8.4*	*5.1* (*3.1)*: 0.0 to 8.3
PF10[2,3]	*21.3* (*4.6)*: 15 to 26	*18.3* (*6.5)*: 12 to 25	*16*	*10*	*17.7* (*3.5)*: 14 to 24
FACT-G Total Score[2,4]	*89.8* (*16.2)*: 66 to 101	*65* (*18.7)*: 44 to 80	*46*	*37*	*73.8* (*14.7)*: 63 to 102
FACT-G Physical[2,4]	*24* (*2.2)*: 21 to 26	*15.7* (*4.6)*: 13 to 21	*12*	*12*	*17.3* (*5.1)*: 13 to 26
FACT-G Social[2,4]	*25.3* (*3.6)*: 20 to 28	*21.3* (*8.1)*: 12 to 27	*8*	*11*	*24.2* (*3.1)*: 20 to 28
FACT-G Emotional[2,4]	*22* (*3.3)*: 17 to 24	*16.7* (*4.2)*: 12 to 20	*9*	*8*	*17.8* (*2.7)*: 14 to 22
FACT-G Functional[2,4]	*18.5* (*7.9)*: 8 to 25	*11.3* (*4.5)*: 7 to 16	*17*	*6*	*14.5* (*5.7)*: 11 to 26

Note. TIMP= Taxane-induced Musculoskeletal pain; BPI= Brief Pain Inventory; PF 10= Performance 10; FACT-G= Functional Assessment of Cancer Therapy- General; *M*= mean; *SD*= standard deviation, CI= confidence interval

[1]n=14

[2]n=15

[3]higher scores = worse outcomes

[4]higher scores = better outcomes

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CHAPTER 5

The purpose of this dissertation was to address a gap in the cancer literature regarding the symptom experience of TIMP in women with ovarian cancer who were being or had been treated with paclitaxel-containing regimens. The Aims of this study provided new information regarding TIMP by (1) describing the TIMP symptom experience (intensity, distress, duration, location, quality, temporal pattern, aggravating and alleviating factors, and pain management); (2) identifying the associations between TIMP (intensity, distress) and co-occurring symptoms (pain [general], peripheral neuropathy, impaired sleep, fatigue, emotional distress, and/or hot flashes); and (3) identifying the associations between TIMP (intensity, distress) and patient-reported outcomes (interference with daily activities, physical functioning, and health-related quality of life). The dissertation results are presented in this dissertation in three manuscripts. Manuscript 1 (Chapter 2), which has been published in Cancer *Nursing*, is a review of the state of the science of TIMP[1]; Manuscript 2 (Chapter 3) is a presentation of the description of the TIMP symptom experience and the associations between TIMP (intensity, distress) and co-occurring symptoms; and Manuscript 3 (Chapter 4) is the presentation of the associations between TIMP (intensity, distress) and patient-reported outcomes. This final chapter synthesizes the key findings from all three manuscripts, the strengths and limitations of the dissertation study, and recommendations for future research.

Synthesis of Key Findings

First, the need for research describing TIMP was identified by the primary author through an extensive literature search. In research on TIMP, authors provide little consistency in the use of terms to signify muscle and/or joint pain following taxane chemotherapy.[1] Also, measurement has been largely limited to toxicity grading scales which provides a limited assessment of the TIMP symptom experience (i.e.,

assessments are largely limited to intensity) and, subsequently, these assessments do little to inform potentially effective interventions for managing TIMP. Research on descriptions of TIMP should initially include an evaluation of all dimensions of the symptom experience including intensity, distress, duration, location, quality, temporal pattern, aggravating and alleviating factors, and pain management. Furthermore, research which provides a better understanding of the associations between TIMP and co-occurring symptoms and TIMP and patient-reported outcomes is important in informing the development, timing, and testing of interventions to manage TIMP. Guided by the Theory of Symptom Management and the Theory of Unpleasant Symptoms, [2-4] this manuscript provided the initial next steps in quantifying preliminary descriptions of the dimensions of the TIMP symptom experience and associations between TIMP and co-occurring symptoms and TIMP and patient-reported outcomes to better understand TIMP and to positively impact the health-related quality of life of cancer survivors. Quantifying the preliminary description of TIMP and the associations between TIMP and co-occurring symptoms and TIMP and patient-reported outcomes was accomplished through the completed pilot study described in Chapter 3.

Second, through data analysis of the proposed pilot study, a multi-dimensional description of TIMP in women with ovarian cancer who were being or had been treated with paclitaxel-containing regimens was completed. A key feature of this description was the large variability seen in the women's experiences of TIMP intensity and distress. However, for most women included in this study, the clinical presentation of TIMP included pain that was mild to severe in intensity, nearly constant in duration, aching in nature, diffusely located throughout the body, variable in temporal pattern, aggravated by everyday functions such as walking and sitting, and not fully relieved by pain medications. Prior research on TIMP is limited in its descriptions of TIMP[1, 5] and, before now, specific

details of TIMP intensity, distress, duration, location, quality, temporal pattern, aggravating and alleviating factors, and pain management have been unspecified in the literature. The multi-dimensional description of TIMP this dissertation provides is useful for assessing and managing this type of treatment-related pain and may serve as a benchmark or comparison for future prospective, longitudinal TIMP research studies.

Third, associations between TIMP (intensity, distress) and co-occurring symptoms were identified. This dissertation has provided preliminary evidence that greater TIMP intensity and distress was associated with greater intensity or interference of co-occurring symptoms, suggesting TIMP, like other cancer treatment-related symptoms, may occur within a symptom cluster of general pain, peripheral neuropathy, sleep disturbance, anxiety, depression, fatigue, and hot flashes. These findings support the idea that assessment of co-occurring symptoms should be incorporated into clinical care in order to better delineate appropriate treatment options. Learning from patients which symptoms co-occur reliably and are distressing continues to remain an important priority for future research studies.[6]

Finally, associations between TIMP (intensity, distress) and patient-reported outcomes were identified. This dissertation has provided preliminary evidence that greater TIMP intensity and distress was associated with greater interference with daily activities, worse physical functioning, and worse health-related quality of life. Research on chronic pain suggests pain is among the most common reasons for temporary and permanent work disability[7, 8] and musculoskeletal pain, in particular, is the most disabling and costly of all pain complaints.[8] Furthermore, co-morbidity of pain and chronic conditions such as depression are known to decrease active coping and negatively impact health-related quality of life, disability, and response to treatment.[9, 10] Correlative evidence from this dissertation identifying greater TIMP intensity and distress was associated with

greater interference with daily activities, worse physical functioning, and worse health-related quality of life suggests facts about chronic pain and chronic musculoskeletal pain and its impact on patient outcomes may be applicable to the TIMP experienced by women with ovarian cancer. Recognition of patient-reported outcomes and their use in clinical research remains an important priority, especially in studies of cancer survivors. Additional studies focusing on the socioeconomic and social impact of TIMP in this population of cancer survivors is needed.

Strengths and Limitations of the Dissertation

This dissertation addressed the important national research priority of symptom management set forth by the National Cancer Institute (NCI) Office of Cancer Survivorship,[11] the National Institute of Nursing Research (NINR),[12] the American Cancer Society (ACS),[13] the Institute of Medicine (IOM),[14] and the Oncology Nursing Society (ONS).[15] Additionally, this dissertation used patient-reported outcomes measures at a time when recognition of patient-reported outcomes, supported by the National Institutes of Health (NIH), is of growing research interest and requires attention to standardized measurement of health-related quality of life outcomes in populations including cancer survivors.[16-19]

This dissertation was also the first study to fully describe the TIMP symptom experience including the dimensions of intensity, distress, duration, location, quality, temporal pattern, aggravating and alleviating factors, and pain management in women with ovarian cancer who were being or had been treated with paclitaxel-containing regimens. Before now, these dimensions of TIMP have been unspecified in the literature. Additionally, this dissertation was the first study to identify associations between TIMP (intensity, distress) and co-occurring symptoms and TIMP (intensity, distress) and patient-reported outcomes. Preliminary findings identified by this dissertation provide a new

understanding of the dimensions of TIMP; how TIMP intensity and distress are associated with co-occurring symptoms including general pain, peripheral neuropathy, impaired sleep, fatigue, emotional distress, and hot flashes; and how TIMP intensity and distress are associated with patient-reported outcomes including interference with daily activities, physical functioning, and health-related quality of life.

The findings of this dissertation should be interpreted within the context of its limitations. This was a small pilot study which limited the ability to control for potential confounding influences in the analyses. Replication of study findings in larger samples with a comparison group of non-cancer women with chronic musculoskeletal pain is recommended. Women with ovarian cancer were the focus of this dissertation, which limits the generalizability of the findings to other types of cancer survivors also treated with paclitaxel-containing regimens and experiencing TIMP. Due to the sample size and because potential confounding influences could not be controlled for in the analyses, comorbid conditions, such as osteoarthritis or degenerative arthritis or back pain which were present in our sample of women, may have influenced the results. Participants in this study were asked to answer all TIMP-related questionnaires in thinking about their TIMP, but it is unknown whether all participants responded as instructed or had the ability to distinguish between the types of pain they were experiencing. Finally, due to the small sample size, differences between women who were actively undergoing paclitaxel treatment and those who had been treated in the past were not compared within the context of the findings presented in this dissertation.

Recommendations for Future Research

Future research describing TIMP and the associations between TIMP and co-occurring symptoms and TIMP and patient-reported outcomes is warranted in cancer survivors. The findings from this dissertation largely illustrated the appreciable variability

in clinical reports of TIMP. Prospective, longitudinal studies describing TIMP and its variability could improve the assessment and management of this treatment-related symptom in cancer survivors. The addition of a non-cancer control group with chronic musculoskeletal pain is also recommended. In addition, a prospective, longitudinal approach would provide the perspective to best inform the development, timing, and testing of effective interventions to manage TIMP in cancer survivors. Learning from patients which symptoms co-occur reliably and are distressing continues to remain an important priority for future research studies, [6] and additional research on TIMP is well aligned with this important recommendation for symptom science research. Similarly, recognition of patient-reported outcomes and their use in clinical research remains an important research priority.[16-19] Additional research on TIMP is also well aligned with this recommendation from NIH. Finally, this dissertation provided the first multi-dimensional description of TIMP and this description may serve as a benchmark or comparison for future TIMP research studies.

Conclusions

Cancer and cancer treatment-related symptoms can profoundly affect an individual's health-related quality of life throughout survivorship.[20] Healthcare providers, and oncology nurses in particular, play an important role in assessing and managing distressing treatment-related symptoms experienced by cancer survivors. This dissertation called attention to TIMP, an important treatment-related symptom experienced by cancer survivors, and provided the initial steps toward better understanding the dimensions of this symptom and the associations between this symptom and co-occurring symptoms and patient-reported outcomes. Among women with ovarian cancer who were being or had been treated with paclitaxel-containing regimens, TIMP is mild to severe in intensity and is moderately distressing. TIMP intensity and distress are associated with co-occurring

symptoms and patient-reported outcomes. Future research describing the multidimensional experience of TIMP and the associations between TIMP and co-occurring symptoms and TIMP and patient-reported outcomes is warranted to positively impact the health-related quality of life of cancer survivors affected by TIMP.

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CURRICULUM VITAE

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EDUCATION

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07/2017 Doctor of Philosophy (Ph.D.) in Nursing Science, Minor in Epidemiology, Indiana University, Indianapolis, IN

05/2013 Master of Science in Nursing (MSN), Adult and Gerontology Nurse Practitioner, Indiana University, Indianapolis, IN

UNDERGRADUATE

05/2006 Bachelor of Science in Nursing, Purdue University, West Lafayette, IN

PROFESSIONAL EXPERIENCE

Research

08/2014 – 06/2016 Graduate Research Assistant, Center for Research & Scholarship (Dr. Janet Carpenter), Indiana University School of Nursing, Indianapolis, IN

05/2013 – 05/2015 Predoctoral Fellow, Behavioral Cooperative Oncology Group, Indiana University School of Nursing, Indianapolis, IN

05/2013 – 08/2014 Graduate Research Assistant (Dr. Julie Otte), Indiana University School of Nursing, Indianapolis, IN

Clinical

06/2009 – 03/2013 Registered Nurse, Outpatient Oncology Chemotherapy Infusion, Indiana University Health University Hospital, Indianapolis, IN

10/2008 – 05/2009 Registered Nurse/Oncology Nurse Clinician, Outpatient Oncology Clinic, University of Louisville Hospital, Louisville, KY

05/2006 – 10/2008 Registered Nurse, Inpatient Medical/Surgical Oncology Unit, University of Kentucky Hospital, Lexington, KY

LICENSURE & CERTIFICATION

2009 – present Oncology Certified Nurse (OCN®), Oncology Nursing Certification Corporation

2009 – present Registered Nurse (RN), Indiana State Board of Nursing

2009 – 2015 Chemotherapy and Biotherapy Provider, Oncology Nursing Society

2006 – 2009 Registered Nurse (RN), Kentucky State Board of Nursing

PROFESSIONAL ORGANIZATIONS

2015 – present Member, Midwest Nursing Research Society

2014 – present Member, American Society for Pain Management Nursing

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2014 – present Member, Sigma Theta Tau International Honor Society of Nursing, Alpha Chapter

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2012 – present Member, Oncology Nursing Society

2008 – 2009 Member, Oncology Nursing Society

ACADEMIC & PROFESSIONAL HONORS

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2014 – 2015	Predoctoral Fellowship, Behavioral Cooperative Oncology Group, Indiana University School of Nursing, Indianapolis, IN
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2013	Academic Achievement Award, Indiana University School of Nursing, Indianapolis, IN
2002	National Society of Collegiate Scholars, Purdue University, West Lafayette, IN
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PUBLICATIONS

Peer Reviewed (articles)

Carter-Harris, L., **Davis, L.L.**, & Rawl, S.M. (2016). Lung cancer screening participation: Developing a conceptual model to guide research. *Research and Theory for Nursing Practice*, 30(4), 333-352. PMID: 28304262

Otte, J.L., **Davis, L.L**., Carpenter, J.S., Krier, C., Skaar, T., Rand, K.L., Weaver, M., Landis, C., Cherynak, Y., & Manchanda, S. (2016). Sleep disorders in breast cancer survivors. *Supportive Care in Cancer*, 24(10), 4197-4205. PMID: 27146391

Davis, L.L., Kroenke, K., Monahan, P., Kean, J., & Stump, T.E. (2016). The SPADE symptom cluster in primary care patients with chronic pain. *The Clinical Journal of Pain*, 32(5), 388-393. PMID: 26295379

Davis, L.L., Carpenter, J.S., & Otte, J.L. (2016). State of the science: Taxane-induced musculoskeletal pain. *Cancer Nursing,* 39(3), 187-196. PMID: 26034876

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Philips, C.R. & **Davis, L.L.** (2015). Psychosocial interventions for adolescents and young adults with cancer. *Seminars in Oncology Nursing*, 31(3), 242-250. PMID: 26210202

Peer Reviewed (abstracts)

Davis, L.L. & Carpenter, J.S. (2015). A Systematic Review of Interventions for Treatment-related Symptoms in Ovarian Cancer. *Oncology Nursing Forum*, 42(2), E128.

Davis, L., Otte, J., & Carpenter, J. (2013). Symptom Management in Ovarian Cancer: A Review of the Theory of Symptom Self-Management. *Oncology Nursing Forum,* 40(6), E427.

Davis, L. & Carpenter, J.S. (2012). Mindfulness-based Stress Reduction in Oncology Patients: Development of a Tool for Self-directed Patient Care Decisions. *Oncology Nursing Forum*, 39(6), E513.

PRESENTATIONS

Peer Reviewed

Otte, J. L., Manchanda, S., Skaar, T., Rand, K., Weaver, M., Chernyak, Y., **Davis, L.**, Krier, C., Carpenter, J. S. (Jun. 2015). "Oncology provider knowledge and practice for sleep problems in cancer patients and survivors," poster presentation, *American Academy of Sleep Medicine, Seattle, WA*.

Davis, L.L., & Carpenter, J.S. (Apr. 2015). "A Systematic Review of the Quality of Non-pharmacologic Interventions for Treatment-Related Symptoms in Ovarian Cancer," podium presentation, *Oncology Nursing Society, Orlando, FL*.

Davis, L.L., Otte, J.L., & Carpenter, J.S. (Apr. 2015). "State of the Science: Taxane-Induced Musculoskeletal Pain," poster presentation, *Midwest Nursing Research Society, Indianapolis, IN*.

Otte, J.L., Manchanda, S., Rand, K.L., Skaar, T., Weaver, M., Krier, C., **Davis, L.**, & Carpenter, J.S. (Apr. 2015). "Preferred Treatments for Sleep Complaints by Breast Cancer Survivors," poster discussion, *Midwest Nursing Research Society, Indianapolis, IN*.

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Davis, L.L., Otte, J.L., & Carpenter, J.S. (Jun. 2014). "Taxane-Induced Musculoskeletal Pain: An Integrative Review," poster presentation, *St. Vincent Health, Indianapolis, IN*.

Davis, L.L., Otte, J.L., & Carpenter, J.S. (Jun. 2014). "Taxane-induced Musculoskeletal Pain in Women with Ovarian Cancer: An Integrated Conceptual Model for Guiding Research in Oncology Symptom Management," poster presentation, St. Vincent Health, Indianapolis, IN.

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FUNDING

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Doctoral Degree Scholarship in Cancer Nursing Renewal	American Cancer Society	$15,000	2016 - 2017
Doctoral Degree Scholarship in Cancer Nursing	American Cancer Society	$30,000	2014 - 2016
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Research Incentive	IU School of Nursing	$20,000	2013 - 2015

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Predoctoral Fellow, IU	Behavioral Cooperative Oncology Group	$60,536	2013 - 2015

COMMUNITY INVOLVEMENT

11/2014	Volunteer, Discovery Ball Fundraiser, American Cancer Society, Indianapolis, IN
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