

PROTOCOL

Project Description for IRB

Title: Pain, Psychological, and Endocannabinoid Responses to Yoga in Breast Cancer Survivors with Chemotherapy-Induced Neuropathic Pain

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Study Sites:

University of Wisconsin-Madison (lead site)

Medical College of Wisconsin (assays)

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Study Objectives

The American Cancer Society estimated there were over 3.5 million breast cancer survivors in the United States in 2016 (1). Cancer treatments such as surgery, radiation therapy, and chemotherapy may leave survivors with lasting health complications (2-5). In particular, certain chemotherapy agents (e.g., taxanes, platinum agents, vinca alkaloids) often lead to peripheral neuropathy which may persist long after treatment cessation (2, 6). Symptoms of chemotherapy-induced peripheral neuropathy (CIPN) include numbness, tingling, burning, and/or pain in a stocking-glove distribution and CIPN has been described as a predictor of lasting neuropathic pain more than 9 years post-treatment (3). In addition, it may lead to poorer psychological outcomes (i.e., depression, anxiety, sleep disturbance) and altered biological functioning such as seen in the endocannabinoid (eCB) system, a neuromodulatory system involved in numerous processes including pain modulation (2, 7). In fact, pre-clinical evidence indicated lower levels of eCB content in mice who developed pain following chemotherapy administration (8). Thus, interventions which reduce pain, perhaps by increasing eCB content, are needed.

Accordingly, one such intervention may be exercise. Studies demonstrated increased eCB content following 30 - 50 minutes of moderate exercise (9-15). Further, experimental evidence indicated an eCB mechanism for exercise induced hypoalgesia (i.e., pain reduction) following isometric exercise in healthy adults (13). In addition to stimulating the eCB system, there is pre-clinical evidence of utility of aerobic exercise in reducing neuropathic pain (16). In addition, there is some clinical evidence of neuropathic pain reduction following an aerobic exercise training program (17) or a combination of aerobic and resistance training program (18) in patients with diabetes, and attenuated symptoms of CIPN after 10 weeks of combined aerobic and resistance training (19). Further, yoga (i.e., a form of isometric exercise) has been shown to reduce pain in cancer survivors (20) and patients with chronic low back pain (21) and may improve psychological outcomes (i.e., depression) in fatigued breast cancer survivors (22). Although these investigations lend support to the hypothesis that exercise (i.e., yoga) may reduce neuropathic pain in cancer survivors with painful CIPN, current clinical evidence lacks mechanistic insight, thus more investigation is needed (23). Further, our previous research suggests increases in eCB ligands, in conjunction with pain reduction and improved psychological outcomes (i.e., depression, anxiety) following exercise in healthy adults but the eCB, pain, and psychological response to yoga is not well characterized. In turn, it may be important to compare yoga to a known effector of these variables (i.e., aerobic exercise) to gain more insight. Thus, the current proposed study will address the following aims:

Aim 1: To examine the effect of two exercise modalities (i.e., aerobic exercise, yoga) on pain and psychological responses in breast cancer survivors with CIPN.

Aim 2: To examine the effect of two exercise modalities (i.e., aerobic exercise, yoga) on eCB responses in breast cancer survivors with CIPN.

Study Significance

Breast cancer patients with CIPN were estimated to have \$16,940 higher annual healthcare costs than matched controls (24), indicating a need for low-cost treatments. CIPN is characterized by numbness, tingling, and/or pain in a stocking-glove distribution and has been associated with neuropathic pain post-treatment (3). Certain chemotherapy agents cause CIPN

with up to 50% of patients treated with platinum-based chemotherapies and up to 97% of patients treated with taxanes developing lasting CIPN (4, 5). Neuropathic pain, a severe symptom leading to functional limitations, results from damaged nociceptive neurons which alters pain perception and modulation (25). This damage may lead to central sensitization (26) through changes to the microenvironment of key areas in the pain pathway such as microglia, inflammatory markers, BDNF stimulation, and neuromodulatory substances such as the endocannabinoids (eCBs). Often, painful CIPN is accompanied by altered sensation, resulting in cold allodynia, heat hypoalgesia, and/or mechanical allodynia seen in both human and animal models (25). Further, research demonstrated up to 50% of patients who developed CIPN during treatment experienced lasting symptoms post-treatment (5). Unfortunately, current pharmacological treatment appears to be minimally effective on pain in this population (27). Traditional pain medication, such as opioids, have little impact on neuropathic pain in individuals with CIPN and only one out of six recent clinical trials demonstrated moderate efficacious effects (using duloxetine) (27). Thus, there is a strong rationale to examine exercise as medicine (i.e., to reduce pain) in this population.

To date, there is a wide range of animal evidence which supports the use of exercise to treat neuropathic pain (for a full review see Cooper et al., 2016) (16). Most models are specific to lesion damage (i.e., in mice with crushed sciatic nerve), however there is one CIPN mouse model which demonstrated preliminary efficacy for pain-reduction following an exercise program (28). However, few researchers have examined exercise-driven reductions in neuropathic pain in humans. Observational evidence demonstrated reduced risk for worsened CIPN over 1-year for patients who were highly active compared to individuals who were minimally active (29). Accordingly, interventional evidence indicated reduced side effects of CIPN after 10 weeks of home-based walking and resistance band training (19), supporting the hypothesis that exercise may reduce pain in patients with CIPN. However, little is known about exercise dose or adherence in this study, as the only measure of activity was number of steps. In diabetic patients with neuropathic pain, it appears that chronic exercise may improve “worst pain over the past month” (17) or reduce pain interference (18). Although these studies support the possibility of exercise-driven reductions in neuropathic pain, they lack control conditions, thus their results should be seen as preliminary. Regardless, these preliminary results suggest that further research exploring the role of exercise in pain reduction in individuals with neuropathic pain is needed.

One such exercise modality is yoga. Yoga has been shown to improve psychological variables such as pain and anxiety as well as improve quality of life. For example, yoga reduced pain in individuals suffering from chronic low back pain (21). Further, it was as effective as aerobic exercise in reducing pain and depression in breast cancer survivors without lymphedema (20) and may reduce anxiety in breast cancer patients undergoing treatment (30). In addition, yoga training may improve health-related quality of life, including emotional well-being, in both breast cancer and colorectal cancer survivors (31, 32). However, some results demonstrate no change in psychological outcomes after yoga training (33). Further, it is important to note that meta-analytic evidence indicates much of the literature base to be of moderate to low quality (34). Thus, more research is needed to elucidate the role of yoga on pain reduction, especially in patient populations such as breast cancer survivors with CIPN. The first step may be to understand the acute effects of yoga (i.e., immediate effects after one session) in order to inform future research in an effort to develop more efficacious interventions. Currently, it appears that yoga induces acute improvements in cognition (35) and perceived stress (36, 37) in healthy adults. However, these results have not been replicated in clinical populations. On the other

hand, researchers documented acute improvements in psychological outcomes (i.e., total mood disturbance) in patients with multiple sclerosis following yoga which paralleled improvements following 20 minutes of moderate walking (38), however pain was not assessed in this study. Participant reports of pain and distress were reduced following 15 minutes of gentle yoga after laparotomy surgery (39). Therefore, this proposed study fills a gap in the literature by examining the acute effects of yoga on pain and psychological outcomes in an under-studied clinical population (breast cancer survivors with CIPN).

Interestingly, recent research indicates exercise may reduce pain through acting on the eCB system. In brief, the eCB system is a neuromodulatory system which consists of the cannabinoid receptors CB1 and CB2 and their effectors, the endocannabinoids, N-arachidonylethanolamine (AEA, anandamide) and 2-arachidonolglycerol (2-AG) (40). When stimulated, the eCBs regulate ion channels or exert excitatory and inhibitory actions in the central nervous system and has been implicated in several processes including neuropathic pain (7, 41, 42). Previous research established increased 2-AG and AEA levels in the blood following 30-50 minutes of aerobic exercise (9, 11, 13-15). Further, evidence from our lab indicated increased eCB content following acute exercise in conjunction with acute mood improvement (9) as well as pain reduction following isometric exercise in healthy adults (13). This is important in light of evidence which indicated possible eCB dysregulation (e.g., reduced 2-AG (8) or AEA (43) content in the periphery in animals with painful CIPN. Furthermore, CB1 and CB2 receptors are located at several key locations along the pain pathway, thus exerting effects on pain transmission and control (41). Hence, interventions which target the eCB system may be important for subsequent interventions.

Given these points, there is potential for yoga to reduce pain and improve psychological outcomes by influencing the eCB system. In fact, recent pilot work in our lab indicated a small increase in AEA following yoga (measured by Cohen's d) and a small reduction in pain in healthy volunteers. Although preliminary, this lends support to our hypothesis. Further, it may be useful to compare yoga to an exercise stimulus already known to influence these variables (i.e., aerobic exercise). Therefore, this proposed study is designed to examine the pain, psychological, and eCB response to yoga compared to aerobic exercise.

Significance Statement. As established, it is important to develop targeted interventions to reduce neuropathic pain in individuals with CIPN to increase psychological well-being. It appears that yoga training may be an effective intervention to reduce pain and improve psychological outcomes by targeting the eCB system. However, before training interventions can be developed, it is important to first establish the acute psychological (i.e., pain, depression, anxiety) and eCB responses. By comparing yoga to aerobic exercise, we will begin to understand how different exercise modalities influence psychological and biological variables. Thus, these results can be used to design more effective future interventions.

Research Design and Procedures

This exploratory pilot study is a within subject, repeated measure design where participants complete a familiarization session (Study Visit #1) and pre-post measures during two study visits (Study Visit #2 and #3) (i.e., yoga and aerobic exercise.)

Participant Population

We will recruit breast cancer survivors who report having painful CIPN, are at least 6 months post-active cancer treatment, and who are at least 18 years old. In addition, participants will obtain physician permission to participate in yoga and aerobic exercise sessions and agree to use the safety stop feature on the treadmill if needed before enrolling in the study. Participants will be excluded if they meet any of the following criteria: undergoing chemotherapy or radiation treatment for cancer, presence of an uncontrolled medical condition, stroke or myocardial infarction in the past 6 months, pregnant or planning to become pregnant, have severe mobility constraints, history of lightheadedness or fainting during blood draw or exercise, or history of chest pain during exercise. Participants will complete each study visit at the same time of day and will be asked to refrain from eating within 2 hours and exercising within 24 hours of study visit #2 or study visit #3.

Sample Size Justification

Based on a previously published clinical study suggesting large reductions in pain following yoga (39), a statistical power analysis was performed for sample size estimation based on a large effect size. Using Cohen's f effect size (ES) of .4, alpha = .05, and power = .80, the total sample size needed for this study is N = 10 (GPower 3.1). We will recruit up to 30 individuals to account for participant attrition and for those who may be excluded at the familiarization session.

Reasons for exclusion include inability to complete exercise sessions, neuropathic pain which developed from something other than chemotherapy treatment, or if a participant reports she did not receive a chemotherapy agent that is known to cause neuropathy.

Inclusion Criteria

Inclusion criteria will be as follows:

- A diagnosis of breast cancer (stage 0-III),
- no evidence of active disease (i.e., recurrence, bone metastases, etc),
- presence of painful polyneuropathy, with onset coinciding or developing after receiving chemotherapy agents that in the opinion of the research team is likely to have caused such symptoms,
- at least six months since last active cancer treatment, with no further planned treatment (Note. active treatment is defined as surgery, chemotherapy, or radiation),
- the participant agrees to use the safety stop feature on the treadmill if needed,
- at least 18 years of age,
- and their physicians has provided consent for them to participate in yoga and aerobic exercise sessions.

Note. The inclusion criteria “the participant agrees to use the safety stop feature on the treadmill if needed” and “and their physicians has provided consent for them to participate in yoga and aerobic exercise sessions” were added at the request of the UW Carbone Cancer Center PRMC. Their correspondence is included in the supplementary section of the IRB application.

Exclusion Criteria

Exclusion criteria will include:

- undergoing current chemotherapy or radiation treatment for cancer,
- taking anticoagulant therapy,

- uncontrolled medical conditions (i.e., uncontrolled hypertension, heart disease, stage 4 liver disease, end-stage renal disease, end-stage pulmonary disease, etc),
- stroke or myocardial infarction in the past 6 months,
- being pregnant or planning to become pregnant,
- severe mobility constraints (e.g., confined to a wheelchair),
- having a history of light headedness or fainting during blood draws or physical activity,

Identification and Recruitment of Participants

Volunteers will be recruited from the breast cancer population in Dane County, WI. They will be 18 years or older, have received a diagnosis of stage 0-III breast cancer, have no evidence of active disease, report the presence of painful polyneuropathy with onset coinciding or developing after receiving chemotherapy agents that in the opinion of the research team is likely to have caused such symptoms, and be at least six months from their last cancer treatment with no further planned treatment. Flyers will be posted around the community (e.g., grocery stores, gas stations, etc.), and local cancer support organizations (e.g., Gilda's Club, Carbone Cancer Center) and be posted on the social media sites (e.g., Facebook) of local cancer organizations. Further, flyers may be handed out at local breast cancer events (e.g., Relay for Life, etc). In addition, participants will be recruited from local health clinics (e.g., UW Pain Clinic, UW Breast Center). Recruitment methods specific to local health clinics will include posting flyers, asking staff to distribute flyers to interested participants, and direct physician recruitment. Individuals directly recruited from physicians will complete a paper permission-to-contact form. A member of the research team will collect the permission-to-contact forms in person and all forms will be stored in a locked cabinet in the Exercise Psychology Lab until the participant has been screened or the study is complete. Volunteers will complete a phone screen prior to Study Visit #1 to determine eligibility. Participants must agree to use the safety stop feature of the treadmill if needed before enrolling. If participants meet all other eligibility requirements, participants will be asked to provide evidence of physician permission to participate in the yoga and aerobic exercise sessions. To do this, the researcher will ask for oral consent for HIPPA authorization so the researcher may contact their doctor and request a signed participation permission form. As such, during the phone screen, participants will be asked to give oral consent for HIPPA authorization, will be asked to provide their provider's name, clinic, and their own date of birth (DOB).

Participant DOB is needed in order to communicate with their provider. In turn, the researcher will call the participant's provider to request their signed consent that the participant is safe to be able to participate in this study. The researcher will e-mail, fax, or drop off the permission form (depending on the requirements of the clinic) and obtain the signed form by fax or in-person pick up (no identifiable and health information will be sent over e-mail). In the event a provider does not consent to this procedure, the research team will re-contact the potential participant and request they obtain permission from their doctor on their own and bring the signed form to the first study session. In this event, or if participants are uncomfortable providing the necessary information, participants will be mailed (standard or e-mail) a physician permission form for them to fill out with their doctor. They will be required to bring the signed form to the first session before they can enroll in this study. During the phone screening, participants will be asked about their readiness for physical activity using the PAR-Q. If a participant responds 'Yes' (indicating a contraindication to exercise) to any of the seven questions on the PAR-Q (e.g., having a bone, joint, cardiac, or other medical condition that a doctor has said may be worsened by physical activity; having a history of chest pain during physical activity; taking medications

for any chronic diseases such as high blood pressure or diabetes), this will be discussed with their physician when obtaining physician permission to participate in the study using the procedures described above.

Instruments

Demographic and Pain History Form. The demographic and pain history form consists of questions asking about age, sex, ethnicity, history of pain, current health history, past health history, etc., and will be used to describe the sample. This form will be administered at Study Visit #1 only and will include a question on the chemotherapy drug(s) they received and will be used to corroborate eligibility during the Study Visit #1 (see section below).

Heart Rate. Heart rate will be collected continuously using a Bluetooth enabled Polar Heart Rate monitor to quantify the intensity of the study tasks. Heart rate will be measured during Study Visit #2 and #3.

Menstrual Cycle Log. The menstrual cycle log charts the length and regularity of the menstrual cycle and type and dosage of any birth control medications.

painDETECT. The PD-Q (42) is an instrument designed to measure the presence of neuropathic pain. Participants complete four sections: pain diagram (i.e., neuropathic pain sites on the body), pain intensity (acute and chronic), pain course (persistent pain or pain attacks), and pain gradation. In the pain diagram section, participants mark where on their body they feel pain. In the pain intensity section, participants mark their pain on a scale from 0 “none” to 10 “max” on how intense their pain is at this moment, at its strongest, and on average. In the pain course section, participants indicate if their pain is persistent, persistent with pain attacks, or pain attacks with or without pain in between. Finally, participants complete the pain gradation section which measures pain characteristics and consists of 7 items rated on a 6 point scale ranging from “never” to “very strongly.” Participants will complete the PD-Q during Study Visit #1 only.

Pain Catastrophizing Scale. The PCS (44) is a 13-item scale rated on a 5 point scale. This instrument measures the extent that an individual magnifies their experience of pain. Items are rated on a scale ranging from 0 “Not at all” to 4 “all the time” with higher scores indicating higher catastrophizing. Participants will complete the PCS during Study Visit #1 only.

Pain Diagram. The pain diagram (43) contains two diagrams of the body (i.e., posterior and anterior views). Participants use colored markers to indicate the location and quality (i.e., aches, burning, stabbing, etc.) of all of the types of pain (e.g., back pain, headaches, etc) they have experienced in the past 4 weeks. This questionnaire will be administered at Study Visit #1 only.

Physical Activity Measurement. Physical activity levels will be assessed objectively (i.e., via accelerometry) and subjectively (i.e., via self-report).

Accelerometry. Participants will be provided with an accelerometer (Actigraph GT3X+, Actigraph, Pensacola, FL) at the end of the Study Visit #1, which they will be required to wear on a belt around their waist for one week. Participants will be given instructions on the proper use of the accelerometer and will also be given a log to track their wear time during the week.

Simple Physical Activity Questionnaire. The SIMPAQ (48) is an interview tool designed to measure time spent in bed, time spent exercising, and time spent in physical activity. Participants' physical activity level will be measured at Study Visit #2 only.

Profile of Mood States. The POMS (45) is a 65-item questionnaire using a 5-point Likert-type scale ranging from 0 "not at all" to 4 "extremely." It will be used to determine the mood state of participants which include: tension, depression, confusion, anger, fatigue, vigor, and total mood disturbance. Internal consistencies for the subscales on the POMS range from .84 to .95 (42). To assess the mood-response to exercise, participants will complete the POMS pre- and post-exercise (Study Visit #2 and #3).

Ratings of Perceived Exertion (RPE). A validated RPE scale (46) will be used to measure the perceived intensity of the exercise during Study Visit #2 and #3. The scale ranges from 6 "no exertion at all" to 20 "maximal exertion."

Short-Form McGill Pain Questionnaire. The SF-MPQ (47) is a 15-item survey with items rated on a 4-point scale ranging from 0 "none" to 3 "severe." Eleven items assess the intensity of sensory components of pain and four items assess the intensity of affective components of pain. In addition, a Present Pain Index (PPI) and a Visual Analogue Scale (VAS) are included in the questionnaire. This questionnaire will be administered pre- and post-exercise during Study Visit #2 and #3 to assess the pain response to exercise.

State-Trait Anxiety Inventory. The STAI Form Y-1 (49) is a 20-item questionnaire designed to measure state anxiety. Items ranged from 1 "almost never" to 4 "almost always" with higher scores indicating higher anxiety. The internal consistency for the STAI ranges from .86 to .95. Participants will complete the STAI pre- and post-exercise during Study Visit #2 and #3.

VAS Neuropathic Pain Sensations. Visual analog scales (VAS) will be used to assess the intensity of the following sensations specific to neuropathic pain: pins and needles, tingles, stinging, and electrical pain sensations. This questionnaire will be administered pre- and post-exercise during Study Visit #2 and #3.

Quantitative Sensory Testing (QST). Pain sensitivity will be assessed via QST which represents a non-invasive set of psychophysical tests that are designed to measure different aspects of the sensory nervous system (50, 51). Pre-clinical and clinical research indicates that breast cancer survivors with CIPN experience altered sensations such as cold allodynia, heat hypoalgesia, and/or mechanical allodynia (25). By using standardized procedures (51, 52), researchers and clinicians can examine these altered sensations through testing the function of specific nerve fibers. Further, these methods can help us understand the role of peripheral (i.e., excitability of peripheral nerves) or central sensitization (i.e., excitability of neurons in the central nervous system) in pain transmission. By using QST to evaluate pain responses, we will gain deeper insight into the treatment potential of exercise in this population. Therefore, our QST protocol will involve the assessment of mechanical allodynia and hyperesthesia, mechanical pain threshold, thermal (hot and cold) pain thresholds, pressure pain threshold, vibration detection threshold, and mechanical temporal summation.

- Mechanical allodynia (presence of pain in response to a stimulus that would be rated non-painful under normal conditions) and hyperesthesia (perception of sensation out of proportion to the applied stimulus) will be assessed by applying stimuli to both the control and test site. Participants will be asked to rate their pain (i.e., intensity, unpleasantness) after each stimulus. Mechanical allodynia will be assessed by applying light touch, using a Q-tip, on a 2-cm area of skin for approximately 2 s (43). Hyperesthesia will be assessed by a pinprick test using the Neuropen. The Neuropen is a spring-loaded device in which a pin (diameter less than 0.4 mm) is placed inside a guide which allows relative standardization of the degree of force applied (approx. 40 g) (53).
- Pain sensitivity, or a heightened pain response, will be assessed by determining pain thresholds to different stimuli. Pain thresholds will be assessed by applying, to a site close to the affected area (e.g., wrist or ankle areas), von Frey filaments (for mechanical pain threshold), a Medoc Thermal Sensory probe (for thermal pain thresholds), and an algometer (for pressure pain threshold) until the participant indicates the stimulus to be painful.
- Mechanical temporal summation, which is a measure of central sensitization, will be assessed using a standardized protocol on both the control and test sites (51). In order to determine summation, participants will rate pain intensity and unpleasantness after a single mechanical stimuli (i.e., pinprick) and after a series of 10 administered at 1-second intervals.
- Vibration detection threshold is indicative of activation of nerve fibers which do not typically transmit pain information. However, under some pathological conditions, such as CIPN, these fibers begin to send pain signals. It will be determined using a Rydel-Seiffer (R-S) graduated tuning fork which has a graduated scale (1-8) that, when activated, accurately represent the amplitude of vibration (54). The activated R-S tuning fork will be placed on the skin and participants will indicate when the vibration is no longer felt. The research assistant will record the visible score from the fork at that instant.

A test site (i.e., a site near the affected area such as wrist or ankles) and a control site (i.e., non-painful site on the opposite limb) will be chosen for each participant during the familiarization session. In addition to this, participants will undergo practice tests using an abbreviated protocol prior to experimental testing. The researchers will instruct participants to report anytime they experience “intolerable pain” which is defined as the point at which they do not want the test to continue. Upon report of “intolerable pain,” the test will immediately stop, and the patient can decide to continue to the next test or to skip the remaining tests. Dr. Nalini Sehgal will provide training for these procedures.

Procedures

Prior to attending the study visits, volunteer eligibility will be determined through a preliminary phone screen. If the volunteer is eligible, they will be scheduled for the familiarization session. Eligibility will be further assessed at the familiarization session (Visit 1) to ensure that the participant understands how to use the safety features on the treadmill, and the participant’s pain is neuropathic and results from chemotherapy administration. Upon completion of the familiarization session, participants will be scheduled for Study Visit #2 and will be asked to refrain from exercise for 24 hours and to refrain from drinking or eating (except for water) for 2

hours prior to their study visit. Participants will attend one familiarization session, 45 minutes long, and two study visits, each 60-75 minutes long, to complete both the yoga and aerobic exercise sessions. There will be between 2 and 7 days between Study Visit #2 and Study Visit #3. All visits will be completed independently and participants will spend a total of 165-195 minutes completing this study. Session order (experimental vs. aerobic exercise) will be randomized and counter-balanced. See Figure 1 for a schematic of the study procedures.

The exercise stimuli will be matched on session duration (i.e., 40 minutes) and session intensity (using the ratings of perceived exertion scale, RPE).

Yoga Task: The yoga task will consist of 44 minutes of Iyengar yoga in a sound-dampened chamber. The yoga session will be pre-recorded and led by a certified yoga instructor who has previously worked with individuals with chronic medical conditions. The yoga task will consist of 7 minutes of light intensity poses (i.e., RPE 10-11) followed by 32 minutes of moderate intensity poses (RPE 12-14). The cool-down will consist of 5 minutes of light intensity poses (RPE 10-11). Participants will follow the pre-recorded video and will be instructed to participate to the best of her ability. Heart rate (HR) will be recorded continuously through a heart rate monitor and the session intensity and pain intensity will be recorded every five minutes. Session intensity will be monitored using the ratings of perceived exertion scale (RPE) (46). Pain intensity will be recorded using one item rated on a 0-10 scale from the painDETECT (42): “How would you assess your pain now, at this moment?” Participants will be encouraged to work at a moderate intensity for the 32 minute time period.

Aerobic Exercise Task: The aerobic exercise task will consist of 44 minutes of aerobic exercise (i.e., walking) on a stationary treadmill. To match the yoga session, participants will undergo a 5-minute light intensity warm up (i.e., RPE 10-11) after which they will engage in 30 minutes of walking or jogging at a moderate intensity (i.e., RPE 12-14). Finally, participants will complete a 5 minute cool down at a light intensity (i.e., RPE 10-11). This procedure was based off previous research in our lab which demonstrated a significant increase in eCBs using this exercise stimulus. HR will be recorded continuously and RPE and pain intensity will be collected at 5-minute intervals. ***{Note: both exercise modalities have been employed in previous research in our lab without incident}***

Visit 1

During this session, participants will complete several questionnaires and be familiarized with the QST protocol. The questionnaires will include: informed consent, demographic and pain history questionnaire, the menstrual cycle log, the painDETECT, the Pain Catastrophizing Scale, and the Pain Diagram. Participants' questionnaires will be examined to determine the presence of chemotherapy-induced neuropathic pain as indicated by the painDETECT, Pain Diagram, and participant report of chemotherapy agent (found on the demographic and pain history form). If participants are found to be eligible, they will partake in the remaining procedures. If participants are found to be ineligible, they will be thanked for their participation and compensated \$15 for their time. The remaining familiarization procedures include recording their age, blood pressure, height, and weight. Further, patients will be familiarized with the pain testing and exercise protocols. In order to be familiarized with the pain testing, participants will undergo an

abbreviated QST protocol. Subsequently, participants will walk on the treadmill for 5 minutes (aerobic task) and will practice the different yoga poses (yoga task) in order to be familiarized with the exercise stimuli. Thus, participants will have a better understanding of what to expect in the coming study visits. Lastly, participants will be asked to wear an accelerometer for 7 days to objectively determine average levels of physical activity. Participants will also be asked to complete an activity log in conjunction with wearing the accelerometer. Participants will return the accelerometers and activity logs one week later when they return for their second visit.

Visit 2

Participants will be randomly assigned to complete the yoga or aerobic task prior to coming in for Study Visit #2. All study visits will be completed in the Exercise Psychology Laboratory in the University of Wisconsin-Madison Natatorium building (note: numerous exercise studies have been completed in this lab without incident). Upon arrival, participants will complete the Simple Physical Activity Questionnaire (SIMPAQ) and a packet of mood questionnaires consisting of: the short-form McGill Pain Questionnaire (SF-MPQ), the Profile of Mood States (POMS), the State-Trait Anxiety Inventory (STAI), and 4 visual analog scales (VAS) which measure different aspects of neuropathic pain (i.e., pins and needles, tingles, stinging, electrical pain sensations) after which they will be outfitted with a heart rate monitor and a research assistant will explain the RPE scale. Next, participants will have their blood drawn (5 ml) and will undergo the QST protocol. They will then be informed of their study visit task (yoga or aerobic exercise task) and be instructed to complete the task in a sound-dampened chamber (yoga) or on the treadmill (aerobic exercise). Immediately upon task completion, the participants will have their blood drawn (5 ml) and will undergo the QST protocol. Lastly, the participants will complete the same questionnaires listed previously (SF-MPQ, POMS, STAI, and the pain sensation VASs). Blood samples will be prepared for analysis within 10 minutes of collection (see 'Endocannabinoid Assays' section below).

Visit 3

Participants will complete the task that was not assigned to them during study visit #1 (yoga or aerobic exercise). Although they will not complete the informed consent, demographic questionnaire, or the SIMPAQ, all procedures will be similar. Participants will complete the following questionnaires: SF-MPQ, POMS, STAI, and VASs, complete the QST protocol, and have their blood drawn prior to engaging in their assigned task. Participants will wear a HR monitor during the task and will be asked their RPE every 5 minutes during the task. Upon task completion, participants will undergo a blood draw, the QST protocol, and complete the same questionnaires listed previously. See Figure 1 for a schematic of the study visit protocol. Participants will receive a \$65 gift card upon completion of all three study visits.

Endocannabinoid Assays

Blood samples will be collected using EDTA containing tubes (BD Vacutainer, K3E EDTA K3) and centrifuged within 10 minutes of collection. Separated plasma will be frozen at -80 C until analysis. Analysis will be conducted at the Medical College of Wisconsin under the supervision of Dr. Cecilia Hillard. The analysis will quantify the plasma concentrations of eCBs (AEA and 2-AG) and their related biolipids (PEA, OEA, 2-OG) using an isotope-dilution, electrospray ionization liquid chromatography/mass spectrometry of the daughter ions (LC-ESI-MS-MS). The

PI and Dr. Hillard have collaborated on a number of previous studies using a standardized protocol (13).

Data Analysis

The design of this study is an exploratory within subject, repeated measure design where participants complete pre-post measures during two study visits (i.e., aerobic and yoga tasks). Descriptive statistics will be reported on the demographic variables (i.e., age, ethnicity, height, etc.) and CIPN (i.e., painDETECT and pain diagram questionnaires) to characterize the sample. RPE and HR data will be summarized to describe the exercise stimuli. We will conduct condition (aerobic, yoga) x time (pre-, post-) repeated measures ANOVAs to determine the influence of yoga and aerobic exercise on pain (QST outcomes, SF-MPQ, and VASs), psychological outcomes (POMS, STAI), and eCBs (2-AG, AEA). Further, effect sizes for pre-post changes in dependent variables will be calculated using Cohen's d to understand the strength of the effect. Significant interaction effects will be examined using simple effects and Holm's procedure will be applied. Data which violate the assumption of normality will be logarithmically transformed.

Study Coordination

This study will involve collaboration between the University of Wisconsin-Madison and the Medical College of Wisconsin. The University of Wisconsin-Madison will serve as the lead site for this study, thus Dr. Kelli Koltyn, PI, will oversee all study activities. In addition, she will be responsible for coordinating between UW-Madison and the Medical College of Wisconsin.

Procedures involving recruitment will be conducted at the University of Wisconsin-Madison and will be supervised by Dr. Kelli Koltyn. Data collection and data analysis will be conducted at UW-Madison under the supervision of Dr. Kelli Koltyn. Analysis of the blood samples will be conducted at the Medical College of Wisconsin under the supervision of Dr. Cecillia Hillard. These samples will be shipped to Dr. Hillard who will supervise the eCB assays. Dr. Koltyn and Dr. Hillard will communicate using email throughout the duration of eCB assay process. Dr. Koltyn has visited Dr. Hillard's lab several times and they have previously collaborated in eight prior studies.

Data Collection

Data will be collected through self-report, QST, and biological samples. The informed consent documents (hard copy), which include the participant's name and assigned identifier, will be stored in a locked cabinet in the PI's office located in the Kinesiology Department at the University of Wisconsin-Madison Natatorium building. These will be separate from the other study documents and only the PI will have access. All data will be coded using a personal identifier assigned to the participant after informed consent is signed, thus all collected data will be coded. All information collected on paper (i.e., age, HR, height, RPE, weight, questionnaire data, QST variables), besides the informed consent, will be stored in a locked cabinet in the Exercise Psychology Lab, which is part of the Kinesiology Department. Note: any personal health information collected will be self-report rather than through medical records and will be recorded on the demographic and pain history form. Thermal pain threshold will be recorded via Medoc software and files will be stored on a password protected secure server in the Exercise Psychology Lab. Similarly, accelerometer data will be stored on the same password protected secure server in the Exercise Psychology Lab. The accelerometer only collects information regarding physical activity behaviors (e.g., minutes per day spent in light-intensity activity, minutes per day spent in moderate-intensity physical activity, sedentary minutes per day). Data

downloaded from the device will be linked to each participants' unique study ID number. No information or data goes to the company (ActiGraph) that produces/sells the devices. After the devices are returned and downloaded, data will be deleted off of the accelerometer. Data will be imputed into a computer for data analysis where it will be stored in a secured file on the Exercise Psychology Lab server which is located in a password protected area with firewall protection and backed up daily. All team members will have access to the coded information located in the Exercise Psychology Laboratory. Biological samples (blood samples) will be stored in a freezer in the Biodynamics Laboratory located in the Natatorium at the University of Wisconsin-Madison after which they will be transferred to a container of dry ice and driven by the PI to Dr. Hillard's laboratory at the Medical College of Wisconsin. The blood samples then will be stored in Dr. Hillard's lab after which they will be exhausted. The blood samples will contain only the participant ID number, time of collection, and session date; thus, participants will not be able to be identified. Moreover, data for eligible participants will be kept and secured in a locked file cabinet in the Exercise Psychology Lab until the participant has either completed the study, removed themselves from participation, or is excluded from participation. If participants give consent to be contacted for future research, their contact information and screening data will be stored in a locked cabinet in the PI's office once the study is complete (see "Permission to Contact for Future Research List" section below for more information). All other screening data for eligible participants will be shredded upon participant completion, dropout, or exclusion of the study. Phone screening data from any interested potential participants not meeting inclusion criteria will be shredded immediately. Biological samples will be exhausted upon completion of endocannabinoid assay. Any link between coded data and directly identifiable data (i.e., names/phone number/email on the informed consent) will be shredded after 7 years. Coded data includes all data collected for the purposes of the study (i.e., questionnaire data, exercise data, accelerometer data, eCB results, and QST data) and will be kept indefinitely.

Permission to Contact for Future Research List

A permission to contact list will be generated from participants who provide consent to be contact for future studies. This list will consist of the contact information and screening data from only these individuals. The information will be stored in a locked cabinet in the PI's office. Only participants who are interested in the current study will be on the "permission to contact for future research" list and only the study team will have access to this list. Further, it will only be used to recruit for similar studies in the Exercise Psychology Laboratory. The list will be destroyed after 5 years. Generating this list will be helpful in recruiting breast cancer survivors with CIPN for future studies conducted by Dr. Koltyn's Exercise Psychology Lab.

Sample/Specimen Collection

Blood samples will be collected by a trained phlebotomist using EDTA containing tubes (BD Vacutainer, K3E EDTA K3) and centrifuged. Plasma will be frozen at -80 C in a freezer in a designated area on the UW-Madison campus until all samples are collected. All samples will be driven by the PI to Dr. Hillard's lab at the Medical College of Wisconsin and will be stored in a freezer until analysis. No samples will include identifiable information and the results from the eCB assays will be shared between study team members using the participant ID numbers.

Study Procedures

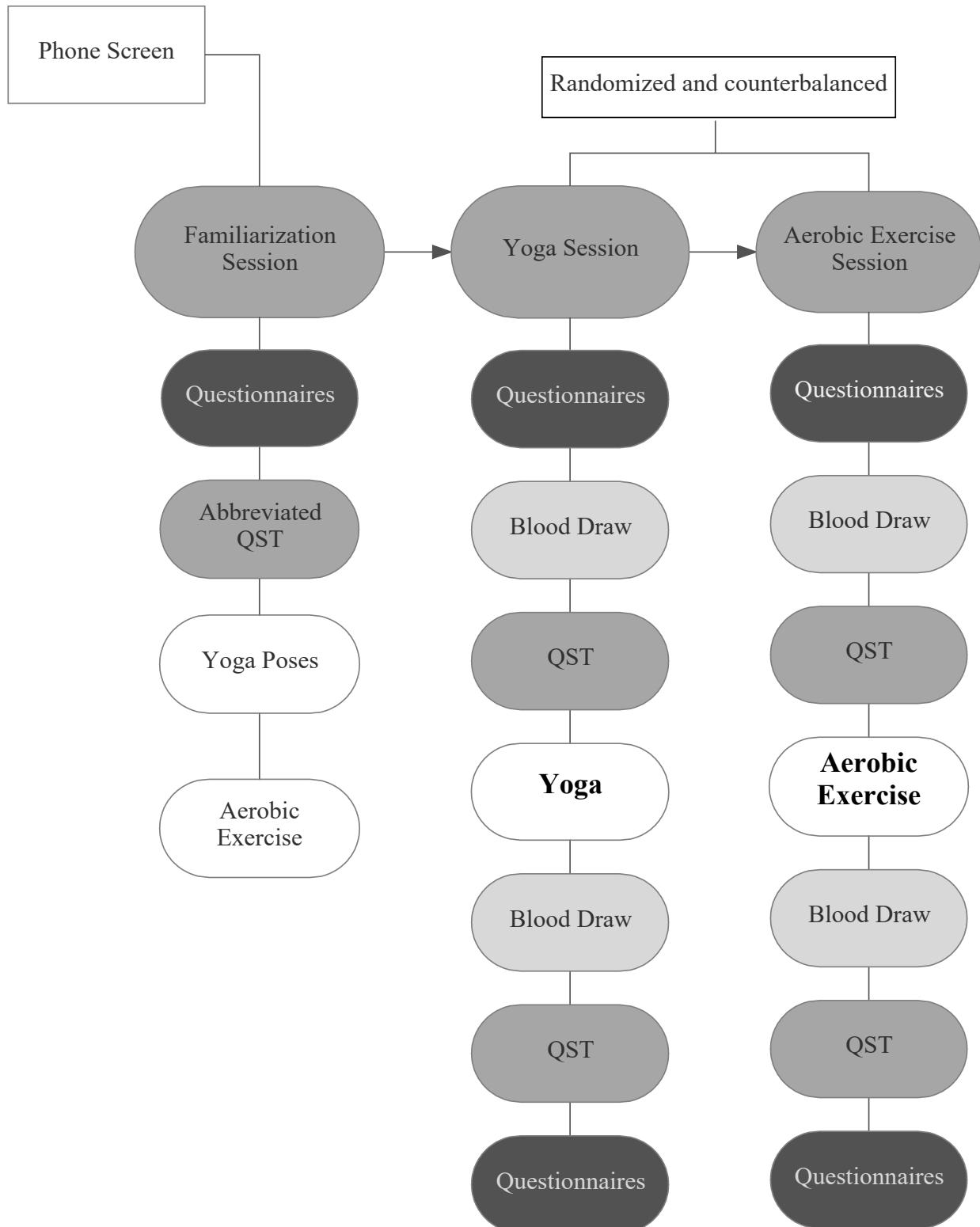


Figure 1. Study flow chart.

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