A STUDY TO IDENTIFY PREDICTORS OF RESPONSE TO DULOXETINE IN BREAST CANCER PATIENTS WITH CHRONIC PAIN, UMCC 2013.044

Clinicaltrials.gov: NCT01912612

Principal Investigator	N. Lynn Henry, MD PhD
Co-Investigators	
Anesthesiology:	Steven Harte, PhD David A. Williams, PhD
Biostatistics:	Alexander Tsodikov, PhD
Medical Oncology:	Anne Schott, MD
Study Coordinators:	Katherine Scott Ryan Scott

Protocol Version 1.0: April 10, 2013	
Protocol Version 1.1: April 25, 2013	Amendment 1
Protocol Version 1.2: May 20, 2013	
Protocol Version 2.0: June 27, 2013	Amendment 2
Protocol Version 2.1: August 8, 2013	Amendment 3
Protocol Version 3.0: October 2, 2013	Amendment 4
Protocol Version 4.0: Nov 30, 2013	Amendment 5
Protocol Version 5.0: May 15, 2014	Amendment 6
Protocol Version 6.0: Sept 6, 2014	Amendment 7
Protocol Version 7.0: May 5, 2015	Amendment 8
Protocol Version 8.0: May 13, 2020	Amendment 9

Amendment 1 (4/25/2013)

Section 5.5. Added to ineligibility criterion #13 (page 12): Urine pregnancy test will be assessed at the baseline visit in women of child-bearing potential with chronic pain.

Section 8.0 (page 16). Add urine pregnancy testing at baseline visit to schedule of events. Comment at bottom states only to be done in subjects with chronic pain, not in controls.
Section 8.2 (page 18). Add urine pregnancy testing to list of events occurring at baseline visit. Should occur prior to randomization in order to confirm eligibility.

Section 8.2 (pages 21-22). Added description of the stamped mailing envelope that patients will use to return the study drug bottle at the end of the study.

Updates (5/20/2013)

Section 8.2 – clarified information about data that will be abstracted from the medical record.

Updates (5/31/2013)

Section 5.4 – revised inclusion criterion #3 to state that patients must have completed surgery, chemotherapy, and/or radiation therapy at least 12 weeks prior to study enrollment

Study synopsis (page 3) – corrected typographical error, and changed 3 months to 12 weeks in order to be consistent with change listed above in section 5.4

Amendment 2 (6/27/2013)

1. Section 5.3: Clarification of subject recruitment sites.
2. Section 5.4: Inclusion criteria #5 was changed to omit “at screening visit”. Subjects will be asked verbally to rate their pain level at the time of screening.
3. Section 5.5: Added exclusion criteria prohibiting enrollment of subjects unable to take or absorb oral medication.
4. Section 5.7: Added that subjects who discontinue study medication for more than 7 days will be removed from protocol treatment
5. Section 5.7: Clarified which subjects who discontinue therapy early should taper off study medication and which do not require a taper. Also clarified off study evaluation for those subjects who discontinue treatment early.
6. Section 6.2. Defined notation for randomization groups.
7. Section 6.4. Added information about dose given at each time point as well as instructions for taking study medication.
8. Section 6.5. Added section about dose modifications.
9. Section 8. Updated schema
10. Section 8.2. Screening. Deleted 1 week pain recall questionnaire.

11. Section 8.2 and Appendix. Added concomitant medication form to be completed by subjects at each visit.
12. Section 8.2. Deleted references to Days throughout the protocol because if subjects complete a visit early, the next time period should start the next day and should not be counted from the beginning of study treatment. For example, if subjects undergo Visit 2 assessment on day 33 instead of day 35, visit 3 should still be scheduled between 18-21 days later, not 20-23 days later as would be determined based on the start date of the first medication. In addition, medication bottles including any remaining capsules should be collected at visits 2, 3, and 4.
13. Section 8.2 and Appendix. Added medication logs for subjects to complete during each treatment period.
14. Section 8.2. Added vital sign assessment to Visit 1 for those subjects who do not undergo screening and Visit 1 on the same day.
15. Section 12. Changed database from Apolo to REDCap.
16. Made minor clarifications and corrections throughout protocol.

Amendment 3 (8/8/2013)

1. Added Ryan Scott as study coordinator.

Amendment 4 (10/2/2013)

1. Added Christine Kwiatkowski and Andrew Clauw as study coordinators on the protocol. They were previously added to eResearch and to the consent.
2. Removed the ineligibility criterion about narcotics (pages 11-12). Potential subjects are permitted to take narcotics as long as they have been on a stable dose. This change was made because of difficulty with accrual. Use of narcotics will be included as a covariate in the analysis.
3. Clarified the eligibility criteria for control subjects (page 11).
4. Clarified the procedures that control subjects will complete (section 8.2 page 18)

Amendment 5 (11/30/2013)

1. Clarified the eligibility criteria related to prior SNRI therapy (page 12)
2. Change reimbursement for screen failures.

Amendment 6 (5/15/2014)

1. Clarified the eligibility criteria related to patient-reported pain rating from average pain at least 4 out of 10 to worst pain at least 5 out of 10 (page 11). We are having difficulty with patient accrual because many patients report relatively high worst pain scores but when they are asked to provide an average pain score it is typically quite low. However we think it appropriate to accrue patients with this intermittent, relatively high pain since it is bothersome when it occurs, even though it isn't sustained.
2. Changed the eligibility criteria related to eligible timeframe for subject enrollment from 8 to 12 years (page 11). Patients are continuing to take adjuvant therapy for up to 10 years starting after completion of all local therapy and chemotherapy. We wish to include patients up to a few years beyond completion of treatment in order to include the entire treatment period.
3. Unblind patients after the completion of all 4 study assessments so that patients who wish to continue on commercial supply of duloxetine can transition seamlessly from study drug to commercial drug (page 23).

Amendment 7 (9/6/2014)

1. The intent of this amendment is to remove the placebo control from the protocol because of difficulty with accrual to the study. There were significant difficulties with recruitment of patients to the trial as originally designed, in part because a high proportion of breast cancer survivors with chronic pain require an antidepressant/anxiolytic medication and are reluctant to be on placebo for 7 weeks. Therefore the study team decided to revise the study design and convert it to a single-arm open label trial. The study objectives are unchanged: predictors of response to duloxetine in patients with chronic pain, and mechanism of action of duloxetine. The placebo effect should be equally distributed across participants with and without centralized pain, and therefore should not influence the assessment of predictors of response to duloxetine. The new design more accurately reflect real world decisions that face providers and patients when deciding whether to switch from one antidepressant medication to another based on the potential benefit-risk profile. Revision of the study led to changes in the statistical plan, as outlined in the statistical section of the protocol, and reduction in the number of planned enrolled patients with chronic pain to 84. Controls will be increased to 48 (approximately 2 controls per case). Because this is a very substantial change to the study design there are a number of changes being made in this amendment.
2. Change study title and running head
3. Update Synopsis with new trial design
4. Update section 4.0 with information provided in #1 above.
5. Update section 5.0 with new trial design.
6. Update schema with new trial design (section 5.2)
7. Clarified eligibility criteria for cases and controls (sections 5.3 and 5.4)
8. Update section 6.0 with new trial design. Information about emergency unblinding (section 6.6) was deleted.
9. Update study calendar section 8.0
10. Update schedule of assessments section 8.2 based on new trial design
11. Adjusted statistical plan (section 11) based on change in study design.
12. Update data and safety monitoring language (Section 13) to reflect the fact this will no longer be a randomized trial design.

Amendment 8 (05/05/2015)

1. Added study team member, Cindy Alsamarraie, to the cover sheet of the protocol.

Amendment 9 (5/13/2020)

1. Protocol clarification amendment to clarify trial endpoints that comprise the overall study objectives.
2. Changed names on protocol cover sheet to reflect current listing in eResearch

Table of Contents

1.0 SYNOPSIS

CLINICAL STUDY SYNOPSIS	
Title of Study	A study to identify predictors of response to duloxetine in breast cancer patients with chronic treatment-related pain
Objective	The primary objectives of this clinical trial are to (1) assess breast cancer survivors with chronic pain for the presence and degree of pain centralization and (2) identify predictors of response to the predominantly centrally-acting analgesic duloxetine in breast cancer survivors with chronic treatment-emergent pain.
Methodology	Single arm, open label study. Patients will be treated with the following: 7 weeks of duloxetine (1 week of dose escalation [30 mg/d], 4 weeks of stable dose [60 mg/d], 2 weeks of dose de-escalation [30 mg/d]).
Number of Patients	Approximately 124 patients planned (84 cases with chronic pain, and 48 controls without chronic pain)
Diagnosis and Main Criteria for Inclusion	Female outpatients, age ≥25 years, stage 0-III breast cancer, diagnosed ≥1 year prior to enrollment, who developed new or worsened chronic pain since breast cancer diagnosis that has been present for at least 12 weeks, and have a worst pain score 5-10 on a 10 point scale will be eligible for enrollment in this study
Test Product, Dosage, and Mode of Administration	Duloxetine 60 mg/d, oral administration
Duration of Treatment	Each patient will receive 7 weeks of duloxetine

2.0 INTRODUCTION

Chronic pain in Breast Cancer Survivors

Over 200,000 women are diagnosed with breast cancer each year in the United States, and more than 80% are alive 10 years after diagnosis.[1] Treatment generally includes surgery, radiation therapy, chemotherapy, and/or targeted therapies such as endocrine therapy. Choice of treatment is determined by assessing the likely benefit of each therapy for an individual patient, taking into consideration tumor characteristics and likelihood of disease recurrence, as well as patient preferences. Almost all women undergo treatment with surgical resection of their primary breast tumor, as well as limited or extensive axillary surgery. More than half of women will subsequently undergo chemotherapy, and the majority of those will receive a taxane-containing regimen, which can cause both acute pain and chronic neuropathy.[2,3]

Most long-term breast cancer survivors recover fully from treatment. However, 25-60% experience chronic pain and associated symptoms, including disturbances in energy, sleep, and mood, which negatively impact quality of life.[4-6] The etiology of these symptoms in patients that otherwise remain

free from disease recurrence is unclear, especially since all patients typically undergo similar procedures or therapy regimens. These treatments can lead to the following syndromes:

- Regional chest wall pain: Patients with breast cancer typically undergo resection of the primary breast mass as well as axillary lymph node(s). The extent of surgical resection depends on tumor burden and patient preference. Almost all patients who undergo lumpectomy, as well as a subset who undergo mastectomy, will also receive adjuvant radiation therapy. Chronic post-surgical pain has been reported to occur in 20-68% of breast cancer survivors, can occur in the breast or chest wall as well as the axilla, shoulder, and arm following surgery, and can persist for years.[5] Radiation therapy has also been associated with an increased risk of chronic breast, chest wall, and axillary pain in breast cancer survivors.[4,7] Surgery- and/or radiation-related nerve injury is believed to be the cause of the chronic pain; however, definitive evidence is lacking.[5,8-11]

- Post-chemotherapy pain: Cytotoxic chemotherapy is administered to patients with breast cancer at increased risk of disease recurrence.[12] Most adjuvant chemotherapy regimens contain a taxane. Taxanes have been demonstrated to cause acute pain in the days immediately following infusion as well as chronic sensory neuropathy in 30-40% of treated patients, which can be painful.[2,3] Chemotherapy has also been associated with a three-fold increased risk of persistent pain following breast cancer treatment, including chronic generalized arthralgias, although the etiology remains uncertain.[13,14]

- Endocrine therapy-associated arthralgias: Adjuvant endocrine therapy is recommended for almost all patients with estrogen receptor positive breast cancer because it significantly improves breast cancer outcomes.[15,16] Endocrine therapy, including tamoxifen and the aromatase inhibitors, is associated with an increased risk of musculoskeletal pain compared to placebo.[17,18] Typically the distal joints, such as the hands and feet, are affected to a greater degree than the axial skeleton or weight-bearing joints.[19] Importantly, aromatase inhibitor-associated musculoskeletal symptoms (AIMSS) occur in up to 50% of treated patients and are severe enough to result in treatment discontinuation in 20%, although the mechanism remains unknown.[20,21] Peripherally acting medications such as non-steroidal anti-inflammatory drugs (NSAID) and opioids are only modestly effective for the treatment of AIMSS.[22] We recently demonstrated in an open-label pilot clinical trial that treatment of AIMSS with the predominantly centrally-acting serotonin and norepinephrine reuptake inhibitor (SNRI) duloxetine results in a 60% decrease in average pain.[23] These findings suggest that AIMSS may be due, at least in part, to centrally-mediated mechanisms.

Acute vs Chronic Pain

Many of the mechanisms that underlie chronic pain differ from those that underlie acute pain. Acute pain states are typically due to inflammation and/or mechanical damage in peripheral structures (i.e. nociceptive input). In chronic pain states, peripheral nociceptive input plays an important role, but there is no chronic pain condition where the degree of peripheral nociceptive input (as measured by an X-ray, MRI, or nerve conduction studies) accurately predicts whether an individual will be experiencing pain, or how severe the pain will be. Especially in population-based studies, many individuals are identified with severe peripheral abnormalities and no pain, and vice versa.[24] This discrepancy between pain and evidence of peripheral damage or inflammation is being increasingly felt to be due to central nervous system (CNS)-directed facilitation and maintenance of pain (i.e., pain centralization).

Recent evidence suggests that factors such as female gender, a prior history of pain or other CNS-mediated somatic symptoms, and inherited variants in genes associated with pain sensitivity, may constitute a pain-prone phenotype (Figure 1).[25] In these patients, subsequent exposure to a variety of pain and other stressors can lead to pain centralization, as is seen in chronic pain conditions such as fibromyalgia.[25-31] These centralized pain states are believed to be due to dysfunction of brain regions involving pain processing, mood, and level of alertness. Centralized pain is identifiable by abnormal quantitative sensory testing (QST) and abnormal CNS activation patterns on functional neuroimaging studies.[25] In addition, subsets of individuals with "traditional" peripheral pain states such as chronic low back pain and osteoarthritis can also have prominent pain centralization, such that peripheral nociceptive input (i.e., damage or inflammation in the periphery) is not the sole driver of symptom expression. The evidence for this includes epidemiologic studies, mechanistic studies (e.g., QST, functional neuroimaging, and genetic studies) and therapeutic trials (e.g., that the SNRI duloxetine decreases knee and low back pain).[32-37] Although localized inflammatory processes typically respond to standard analgesics such as NSAIDs, centralized pain generally requires treatment with therapies such as SNRIs that target abnormal levels of CNS neurotransmitters involved in the pathogenesis of centralized pain.

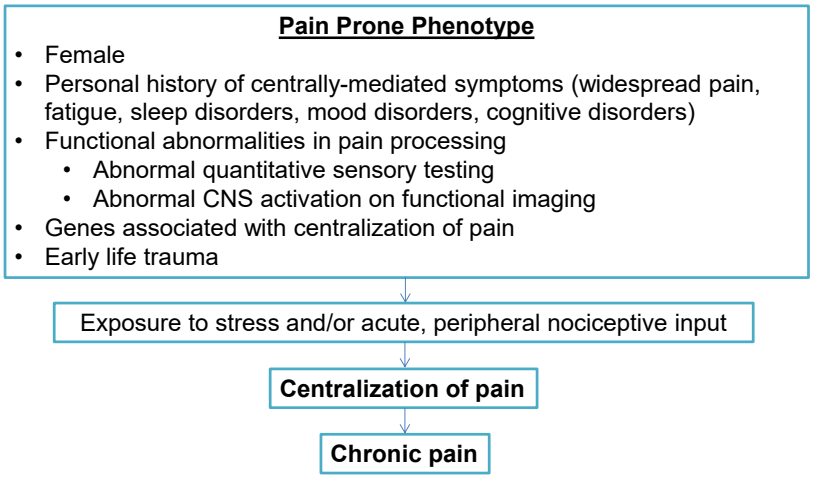

Figure 1. Model depicting centralization of pain and development of chronic pain following nociceptive input

The impact of these CNS factors on chronic pain in breast cancer has not been directly investigated. However, a number of findings suggest that similar factors may be present in breast cancer patients who develop chronic pain following surgery, chemotherapy, and/or endocrine therapy. For example, multiple factors have been shown to be associated with centralization in chronic pain syndromes. In breast cancer survivors, CNS-driven somatic symptoms, such as fatigue, sleep disturbances, cognitive dysfunction, anxiety, and depression, are common.[6] In addition, an association between chronic pain and fatigue in breast cancer survivors and a variant in the catechol-O-methyltransferase gene known to be associated with pain sensitivity has been reported.[38,39] Taken together, these results suggest that pain centralization could play an important mechanistic role in chronic pain in breast cancer survivors, which is the basis of the hypothesis underlying this clinical protocol.

Based on these preliminary data we hypothesize that a subset of breast cancer patients have a "pain-prone" phenotype and are predisposed to development of centrally-mediated treatment-related pain and co-morbid CNS-mediated somatic symptoms including fatigue, sleep disturbances, cognitive difficulties, and mood disturbances following diagnosis of their cancer. In order to investigate this hypothesis, we plan to enroll breast cancer patients with and without chronic pain on this clinical protocol. We expect to identify inter-patient differences in markers of pain centralization, including pain sensitivity, pain modulation patterns, and patient-reported symptom clusters. We will also investigate the mechanistic effects of the primarily centrally-acting analgesic duloxetine in breast cancer survivors with chronic pain, and hypothesize that response to the therapy is associated with a subject's degree of pain centralization. This knowledge could lead to individualization of therapy for the thousands of breast cancer survivors with chronic pain and lead to decreased pain and improved quality of life for these women.

Interventional Phenotyping of Centralization of Pain

Currently, there is no single biomarker of centralization of pain. However, its presence can be inferred by assessing constructs known to occur differentially in individuals with predominantly central pain (e.g., fibromyalgia, irritable bowel syndrome, temporomandibular joint disorder) versus those with predominantly peripherally maintained pain or healthy controls. The two primary methods that will be used in this trial are QST to assess pressure pain threshold and conditioned pain modulation and self-report measures to assess pain and a constellation of centrally-associated somatic symptoms

Quantitative Sensory Testing

Members of the Chronic Pain and Fatigue Research Center (CPFRC) at the University of Michigan have developed a reliable method for objectively determining pressure pain threshold in chronic pain patients. The literature on the evaluation of sensitivity to blunt pressure had previously been based on clinical methods involving manual palpation or on the use of devices termed pressure algometers or dolorimeters, and evaluated pain threshold using continuously increasing pressure. However, continuously ascending methods are vulnerable to extraneous factors such as distress. Therefore, investigators at the University of Michigan developed a computer-operated system in combination with random staircase paradigms. Delivering discrete pressure using “random” paradigms (where the test participant cannot guess what the next stimulus will be) leads to a measure of pressure pain threshold that is relatively immune to biases that confound other conventional measures of pain threshold. The results of these tests in either cross-sectional or longitudinal studies are highly correlated with changes in functional imaging activation patterns, clinical outcomes, and a number of other relevant domains.[26,40,41] These measures have been extensively used and reported in all of the CPFRC’s studies for the past decade, and have not only been shown to be less influenced by psychological factors, but also have been superior in responsiveness to change in clinical trials, and correlation with biological data in neuroimaging studies.[26,40,41] Dr. Harte and his colleagues at the University of Michigan College of Engineering developed a simple handheld device, called the Multimodal Automated Sensory Testing (MAST) System,[42,43] which provides reliable measurements of mechanical pain sensitivity. We have previously demonstrated the feasibility of using this testing in postmenopausal breast cancer patients starting AI therapy, and will employ this methodology in this study to assess pain sensitivity in breast cancer survivors with chronic pain related to treatment, as one component of assessment of pain centralization.

Threshold and suprathreshold indices of secondary hyperalgesia (i.e., as measured at a neutral site) will be assessed by pressure applied to the thumbnail, a site which was chosen because it is a neutral, pain-free site remote from the area of surgery with dense nociceptor innervation. We have extensive experience using thumbnail pressure as an evoked pain stimulus and its validity in the measurement of centralized pain has been discussed extensively.[40,44-51] Using QST, fibromyalgia patients show significantly lower pain thresholds at the thumbnail compared to age- and sex-matched healthy controls (HC) (Figure 2). We have also demonstrated that experimental pain evoked by thumbnail pressure is associated with overall body tenderness,[51] clinical pain,[40,52] and functional neuroimaging,[26] and is lowered following analgesic treatment.[53]

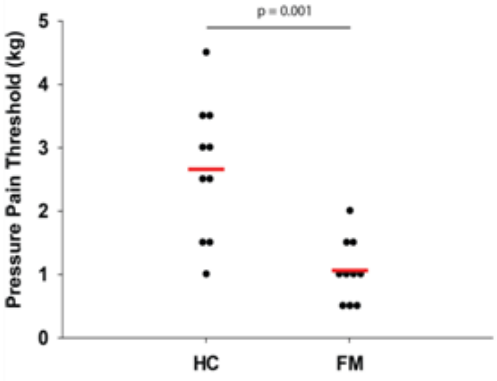

Figure 2. Fibromyalgia (FM) patients have lower pressure pain thresholds compared to healthy controls (HC). Red bars represent mean threshold.

Bilateral pressure pain testing will also be conducted using a digital algometer at the deltoid muscle to assess surgery-induced primary hyperalgesia. The inclusion of this site was based on recent evidence showing that pressure pain threshold was bilaterally reduced at the deltoid muscle in BCS compared to healthy controls, and that pressure pain threshold at the affected deltoid was negatively correlated to neck pain intensity.[54]

Abnormal pain modulation patterns have also been shown to be associated with chronic pain disorders. In healthy humans and laboratory animals, application of a painful stimulus to one part of the body produces generalized whole-body analgesia, termed conditioned pain modulation (CPM).[55,56] CPM has been consistently observed to be less efficient in approximately two-thirds of patients with centralized pain.[57-60] Less efficient CPM is believed to reflect decreased descending inhibitory pain control and is thought to be a potential marker of centralization of pain. This less efficient CPM can lead to increased sensitivity to pain, which is believed to be mediated in part by an attenuated serotonin-norepinephrine system.[61] Therefore, treatment with duloxetine, which inhibits serotonin and norepinephrine reuptake, may work in part by restoring CPM in patients with centralized pain, resulting in decreased pain. In support of this hypothesis, Yarnitsky et al recently reported that less efficient CPM was predictive of response to duloxetine in diabetic peripheral neuropathic pain.[62] CPM is assessed by testing with a unilateral painful test stimulus (black bars in Figure 3), followed by reassessment with that stimulus in combination with a contralateral painful stimulus (grey bars in Figure 3), and is defined as the pain rating with both stimuli minus the pain rating with only the unilateral stimulus. Less efficient CPM (higher/positive values) is seen in large proportions of individuals with central pain conditions such as FM and in smaller proportions of individuals with conditions such as osteoarthritis.[55-57,60,63-66] By evaluating CPM as a continuous rather than a dichotomous outcome, Yarnitsky and others have also shown that CPM magnitude is predictive of a variety of adverse pain outcomes, including chronic post-thoracotomy pain.[63,64,67]

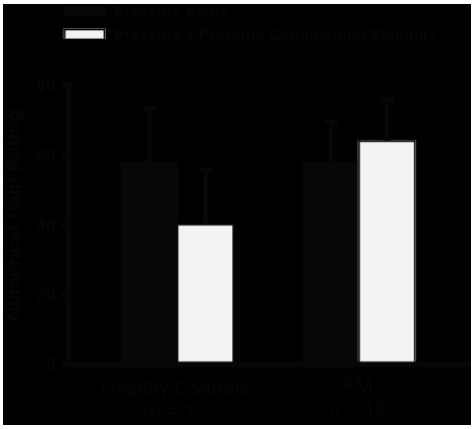

Figure 3. Comparison of CPM magnitude in healthy controls and fibromyalgia (FM) patients.

Patient reported outcomes

Patient self-report data will be used to characterize pain and response to therapy, and to evaluate degree of centralization of pain, using the questionnaires listed below. The CPFRC has been involved in the development and validation of outcomes instruments for multiple chronic pain conditions.[26] These measures have been used extensively by the CPFRC with a number of subjects with a variety of pain types as well as with healthy controls. This study will also take advantage of the heightened precision associated with the static short forms developed by the NIH Roadmap initiative PROMIS.[68] PROMIS utilizes item response theory in the development of large item banks from which a relatively small number of highly informative items can be used to assess with precision a broad range of clinically relevant domains.[31,69-74]

Assessment of pain

- *Clinical Pain.* Pain severity and functional interference due to pain will be assessed using the Brief Pain Inventory (BPI),[69] which has been recommended as a measure of choice for the assessment of pain in clinical research.[75] The BPI has been extensively tested in numerous populations,[76,77] and asks patients to rate their worst, least and average pain in the last week on a 0-10 rating scale. A measure of functional interference from pain is also obtained from this measure.

Measures of centralization of pain

- The Michigan Body Map and Symptom Severity Scale, a modified version of the Wolfe Regional Pain Scale, will be used to quantify (a) any locations where patients experience pain using a checklist that allows for efficient scoring and (b) the severity of key symptoms associated with centralized pain, including fatigue, sleep disturbance, and disturbed cognitive function. Measures of pain distribution and the presence of this symptom cluster have been repeatedly found to be associated with centrally-mediated pain symptoms. [78-80]
- Qualitative Pain Characteristics. PainDETECT [70] is a 9-item measure of sensory descriptors, spatial, and temporal characteristics that has been shown to identify neuropathic components of pain in low back pain and in osteoarthritis.[34] It distinguishes neuropathic from musculoskeletal pain.
- Treatment-related toxicity. The FACT/GOG-NTX neurotoxicity module is an 11-item subscale specifically developed to address chemotherapy-associated peripheral neurotoxicity and its consequences on functional status.[71] The subscale scores correlate with objective neuropathy measures, specifically pin sensibility, strength, and deep tendon reflexes.
- Functional status, sleep, and fatigue. The following PROMIS short-forms will be used in this study: Fatigue, Sleep Disturbance, and Physical Function.[68] The 7-item Fatigue scale assesses the experience of fatigue as well as its impact on physical, mental, and social activities. The 8-item Sleep Disturbance scale assesses perceptions of sleep quality, sleep depth, and restoration associated with sleep. The 10-item Physical Function scale assesses self-reported function, including the ability to perform activities of daily living. The PROMIS scales possess favorable reliability and enhanced precision with lowered patient burden when compared to comparable legacy assessment instruments.
- Psychiatric status. The Hospital Anxiety and Depression Scale (HADS) will be used to assess anxiety and depressive symptoms.[81] The HADS is a 14 item questionnaire that has been extensively evaluated for the assessment of mood disorders in patients with cancer.[93,94]
- Cognitive dysfunction. The 38-item Multiple Abilities Self-Report Questionnaire (MASQ),[55,95,96] is comprised of five cognitive domains: language ability, visuo-perceptual ability, verbal memory, visual memory, and attention/concentration. Satisfactory reliability and validity have been demonstrated.[72,82,83]

Treatment of Chronic Pain

Many different kinds of medications are used in the treatment of chronic pain states such as fibromyalgia and irritable bowel syndrome; these medications have had varying degrees of success.[84-86] Although antidepressants are the cornerstone of many treatment paradigms, other types of agents such as anticonvulsants, antispasticity agents, anxiolytics, sedatives, and opiates are also used. Many patients with chronic pain use NSAIDs and acetaminophen[87] even though peripheral inflammation has not been demonstrated,[88] and numerous studies have failed to confirm the efficacy of these analgesics in the treatment of fibromyalgia.[89-93] These agents do, however, provide an element of protection against other peripheral pain generators such as osteoarthritis.

Antidepressants of all varieties are a common form of therapy for many chronic pain states, including fibromyalgia.[84-86,94] Most available antidepressants directly and/or indirectly increase the levels of serotonin (5-hydroxytryptamine) and/or norepinephrine in the CNS. Monoaminergic levels are increased either by inhibiting reuptake (by blocking transport proteins) or interfering with the breakdown of monoamine (by inhibiting the monoamine oxidase enzymes) after the monoamine is released into the synaptic cleft. Dual reuptake inhibitors, referred to as serotonin-norepinephrine reuptake inhibitors (SNRIs), are pharmacologically similar to tricyclic antidepressants such as amitriptyline and doxepin, exhibiting dual activity on serotonin and norepinephrine reuptake.[95] Fortunately, these newer agents are generally devoid of significant activity at other receptor systems,

resulting in diminished side effects and enhanced tolerability. Therefore, SNRIs have significant potential for the treatment of fibromyalgia and/or other chronic pain conditions.[32,35,96,97] Although the mechanism of action is uncertain, Yarnitsky and colleagues recently reported that less efficient conditioned pain modulation was predictive of response to duloxetine in diabetic peripheral neuropathic pain,[62] suggesting that increasing CNS levels of these neurotransmitters by blocking their reuptake may enhance descending analgesic pathways and decrease pain.

Duloxetine, a selective SNRI with a preferential reuptake inhibition of norepinephrine over serotonin, has been approved by the United States Food and Drug Administration for the treatment of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain. The plasma elimination half-life of duloxetine is about 12 hours. Elimination occurs mainly via the liver. A detailed description of the chemistry, pharmacology, and safety of duloxetine is provided in the Package Insert.[98]

Significance and Innovativeness of the Study

The majority of women diagnosed with early stage breast cancer in the United States have long-term disease-free survival. However, a subset develops treatment-related chronic pain, which can negatively impact quality of life and which is difficult to manage effectively. The etiology of this pain remains unexplained in the majority of cases. We hypothesize that a substantial percentage of breast cancer survivors with chronic pain has centralization of pain, and that the degree of centralization may predict responsiveness to centrally-acting analgesics such as duloxetine.

We propose to perform quantitative sensory testing and assess patient-reported pain and centrally-mediated symptoms in breast cancer survivors with chronic pain in order to determine if there is evidence of pain centralization. At the completion of this study we expect we will have investigated mechanisms that underlie both development of pain and response to the therapy, as well as identified predictors of benefit from the centrally-acting analgesic duloxetine on treatment-related chronic pain and co-morbid symptoms in breast cancer survivors. These results can potentially directly impact treatment of patients with chronic pain, as treatment with centrally-acting therapies such as duloxetine may be superior for decreasing pain and improving other symptoms compared to standard analgesics. In addition, we expect that these results will lead to additional mechanistic studies, such as investigating the role of CNS neurotransmitters in development of chronic pain and the impact of inherited genetic variants on predisposition to treatment-related pain. Ultimately, understanding the mechanisms underlying both development of chronic pain and response to therapy in breast cancer survivors could lead to individualized breast cancer treatment-decision making or preventive approaches for patients at increased risk of developing chronic pain, thereby improving quality of life.

3.0 STUDY OBJECTIVES

1) To assess breast cancer survivors with chronic pain for the presence and degree of pain centralization

(2) To identify predictors of response to the primarily centrally-acting analgesic duloxetine in breast cancer survivors with chronic treatment-emergent pain.

4.0 RESEARCH DESIGN AND METHODS

The randomized, placebo-controlled, cross-over design was originally chosen because it enables each individual who enters the study to either support or refute our primary mechanistic hypothesis. However there were significant difficulties with recruitment of patients to the trial as originally

designed, in part because a high proportion of breast cancer survivors with chronic pain require an antidepressant/anxiolytic medication and are reluctant to be on placebo for 7 weeks. Therefore the study team decided to revise the study design and convert it to a single-arm open label trial. The study objectives are unchanged. The placebo effect should be equally distributed across participants with and without centralized pain, and therefore should not influence the assessment of predictors of response to duloxetine. The new design more accurately reflect real world decisions that face providers and patients when deciding whether to switch from one antidepressant medication to another based on the potential benefit-risk profile.

5.0 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

5.1 Overview of Study Design

This is a single-center, single-arm, open-label study conducted at the University of Michigan's Chronic Pain and Fatigue Research Center (Figure 4). Patients with stage 0-III breast cancer who have chronic pain that developed or worsened since breast cancer diagnosis and whose worst pain is rated at least 5 on a 10 point Likert-type scale and who meet the other inclusion and exclusion criteria outlined in Sections 5.4 and 5.5 will be eligible to enroll in the study.

Patients with chronic pain (cases) who qualify for the study at Screening will begin a 1- to 4-week washout period (if necessary) to taper off antidepressants and other drugs that they are currently taken and that cannot be taken along with duloxetine therapy. Patients who successfully taper off all excluded medications and continue to meet all of the inclusion criteria (and no exclusion criteria) at Baseline/Randomization (Visit 1) will start treatment with duloxetine as indicated below and will undergo serial comprehensive assessment with questionnaires and QST. Patients will receive 7 weeks of duloxetine (1 week of 30 mg/d, 4 weeks of 60 mg/d, and 2 weeks of 30 mg/d). QST and questionnaires will be completed prior to initiation of treatment and after 5 weeks of treatment, before reduction in dose to 30 mg/d. Patients who are tolerating duloxetine well, want to continue therapy using commercial supply, and do not want to taper off duloxetine will not be required to take the final 2 weeks of 30 mg/d.

The duration of participation in this study for cases with chronic pain will be 5-11 weeks, depending on the time required for patients to taper off excluded medications and depending on if patients wish to remain on commercial duloxetine following assessment #2. This study will randomize approximately 84 patients with chronic pain.

Control subjects (n=48) who meet all eligibility criteria but who have average pain 0-1 on a 10 point scale will undergo assessment with questionnaires and QST at a single timepoint.

In order to account for treatment heterogeneity, for both the case and control cohorts subjects will be enrolled in equal numbers into the following treatment "bins": (1) surgery +/- radiation therapy, (2) surgery and chemotherapy +/- radiation therapy, (3) surgery and endocrine therapy +/- radiation therapy, (4) surgery, chemotherapy, and endocrine therapy +/- radiation therapy.

5.2 Schema

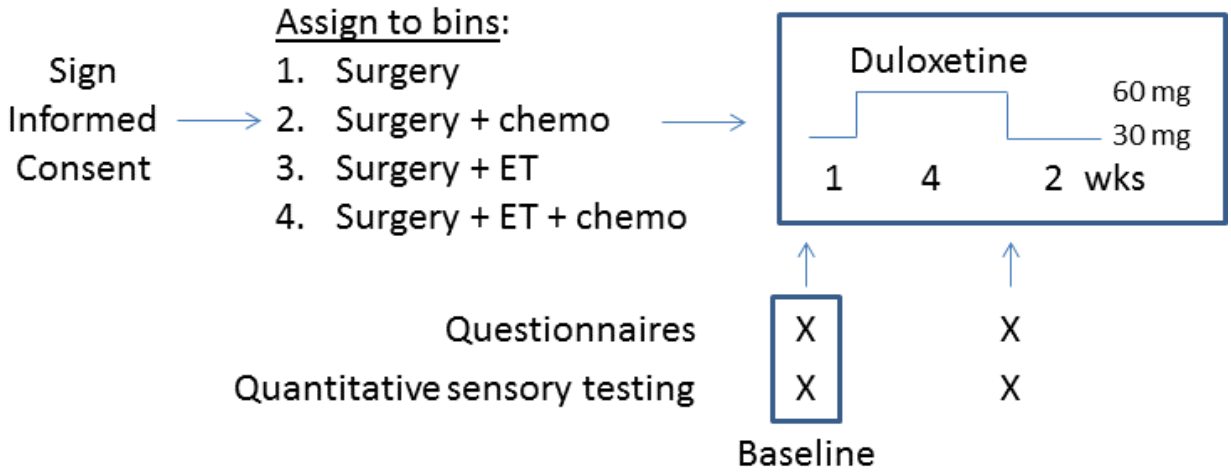

Figure 4. Schema of clinical trial design. All subjects could have received radiation therapy. Chemo: chemotherapy, ET: endocrine therapy.

5.3 Recruitment and Screening

Approximately 84 patients with chronic pain will be enrolled. Female outpatients, age ≥25, who have chronic pain of at least 3 months duration that has developed or worsened since breast cancer diagnosis, and whose worst pain is rated at least 5 on a 0-10 scale, will be eligible for enrollment in this study. Subjects will be recruited from the Breast Oncology Clinics at the University of Michigan Comprehensive Cancer Center and from the Pain Clinics at the University of Michigan. Since many patients with chronic pain are treated in the Lymphedema Clinic (Occupational Therapy), the occupational therapists will be contacted in order to identify symptomatic and therefore potentially eligible patients in their clinics. In addition, 48 controls without chronic pain who otherwise meet the following eligibility criteria (inclusion #1-3, exclusion #1, 2, 4, 5, worst pain score 0-1, and not currently on medication for pain) will be recruited and will undergo baseline evaluation.

5.4 Inclusion Criteria

To be eligible to participate in this study as a case, patients must meet the following criteria:

1. Written informed consent obtained from the patient before the initiation of any study-specific procedures
2. Female patients at least 25 years of age
3. Diagnosis of stage 0-III breast cancer within 12 years prior to enrollment. All indicated surgery, chemotherapy, and/or radiation therapy must have been completed at least 12 weeks prior to enrollment. Concomitant endocrine therapy and trastuzumab are permitted.
4. Pain that developed or worsened since breast cancer diagnosis and is not due to identifiable traumatic event or fracture
5. Patient-reported worst pain score between 5 and 10 (inclusive) on a 0-10 scale (assessed verbally)
6. Female patients must be at least 1 year postmenopausal or surgically sterile; or must agree to use a medically acceptable form of contraception
7. Willing to withdraw from selective serotonin reuptake inhibitors and tricyclic antidepressants prior to treatment initiation
8. Patients who are currently taking NSAIDs and/or opioid pain medications must remain on a stable dosage throughout the duration of the study

5.5 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study as a case:

1. Prior use of duloxetine or milnacipran.
2. Prior use of venlafaxine specifically for treatment of pain (prior use for treatment of other indications, such as hot flashes, is permitted)
3. Patients must not be taking any contraindicated medications listed on the duloxetine package insert including the following: phenothiazines, propafenone, flecanide, linezolid, or anticoagulation medication (e.g., heparin, warfarin); treatment with MAO inhibitor within 14 days prior to registration
4. Thumbnail abnormalities on either hand (such as due to chemotherapy or trauma, or artificial nails) that are likely to alter pain perception during testing
5. Peripheral sensory neuropathy at the thumbs bilaterally that interferes with function and/or activities of daily living
6. Significant risk of suicide based on the Investigator's judgment
7. History or behavior that would, in the Investigator's judgment, prohibit compliance for the duration of the study.
8. History of alcohol or other substance abuse or dependence within the year prior to registration
9. Known chronic liver disease, end stage renal disease, or creatinine clearance <30 mL/min as defined by Cockroft-Gault equation
10. Uncontrolled narrow-angle glaucoma.
11. Clinically significant coagulation disorder
12. Pregnant or breast-feeding. Urine pregnancy test will be assessed at the baseline visit in women of child-bearing potential with chronic pain.
13. Unable to take oral medications or any medical condition that would interfere with the absorption of study medication capsules.

Controls are patients without chronic pain who otherwise meet the following eligibility criteria (inclusion #1-3, exclusion #1, 2, 4, 5, worst pain score 0-1, and not currently on medication for pain)

5.6 Replacement Procedures

Patients with chronic pain who prematurely discontinue from this study after randomization may be replaced to obtain 84 completers.

5.7 Removal of Patients from Therapy

A premature discontinuation will occur when a patient who signed the informed consent form ceases participation in the study, regardless of the circumstances, before the completion of the protocol. Patients can be prematurely discontinued from the study for one of the following reasons:

- Failure to meet inclusion/exclusion criteria
- Adverse event (AE)
- Insufficient therapeutic response
- Discontinuation of study medication for more than 7 days
- Protocol violation, including lack of compliance
- Withdrawal of consent

- Other reasons, such as administrative reasons or pregnancy

All patients who prematurely discontinue from the study, regardless of the cause, should undergo a final assessment.

- Those subjects who are taking medication from the 4 week supply at the time of study discontinuation will be asked to undergo in person evaluation with QST and questionnaire completion). At that in person visit they will receive the 2 week supply of medication to taper off the study drug, will be called by the study team 1-2 weeks later to assess AEs, and will be given a stamped envelope in which to return the medication bottle. If they are not willing to return to clinic they will undergo the Final Evaluation (phone visit) and will be mailed the 2 week supply of medication to taper off the study drug. Subjects will be required to return all study drug and medication bottles.
- Those subjects who are taking medication from either the 1 week or 2 week supply at the time of study discontinuation will undergo the Final Evaluation (phone visit). No taper is required. Patients will be required to return all randomized study drug.

6.0. DESIGN

6.1 Treatments Administered

The SNRI duloxetine was chosen because it is a predominantly centrally-acting analgesic with the broadest efficacy to date (in neuropathic pain, fibromyalgia, low back pain, and osteoarthritis), and the analgesic effects have consistently been shown to be independent of anti-depressive effects.[99,100,96,101-104] SNRIs are thought to act primarily by increasing serotonin and norepinephrine transmission in the CNS, thereby augmenting and restoring pain modulation, resulting in decreased pain.[61] The majority of patients who respond to duloxetine achieve a response within 2-4 weeks of initiating therapy.[23,105] We have demonstrated the feasibility of treating cancer patients with duloxetine in trials evaluating its use for treatment of aromatase inhibitor-associated arthralgias[23] as well as chemotherapy-induced painful neuropathy.[106] This drug is also coming off patent soon so if these studies were to suggest efficacy in an identifiable subset of breast cancer patients, duloxetine would represent an inexpensive and safe treatment option, especially compared to the known toxicities associated with opioids and even NSAIDs.

Study drug in the form of capsules will be provided by the University of Michigan Investigational Drug Service. An IND waiver has been obtained from the US Food and Drug Administration.

6.2 Method of Assigning Patients to Treatment

All patients will receive the same treatment regardless of treatment “bin.” Approximately equal numbers of patients will be enrolled in each treatment “bin”, which are: (1) surgery +/- radiation therapy, (2) surgery and chemotherapy +/- radiation therapy, (3) surgery and endocrine therapy +/- radiation therapy, (4) surgery, chemotherapy, and endocrine therapy +/- radiation therapy.

6.3 Selection of Dosages in the Study

The duloxetine dosage chosen for this study is based on experience obtained in previous dose-finding and phase III studies. In a pilot study of duloxetine in aromatase inhibitor-associated arthralgias and in multiple placebo-controlled phase III clinical trials of duloxetine for a variety of chronic pain conditions, duloxetine 60 mg/d was demonstrated to be safe, generally well tolerated, and effective in the treatment of chronic pain.[32,96,102,107] Therefore, duloxetine 60 mg/d is the selected dosage for this study. Subjects will initiate treatment with 30 mg/d and then increase to 60 mg/d in order to decrease the likelihood of developing nausea. Similarly, subjects will taper off the medication

during the final two weeks of treatment in order to decrease the chance of developing withdrawal symptoms. Those subjects who prefer to remain on duloxetine following completion of the 4 week full-dose treatment period are not required to taper the medication, and can be given a prescription by their treating provider to obtain the medication through standard of care, commercial supply.

6.4 Selection and Timing of Dose for Each Patient

Patients who meet eligibility criteria at Screening will begin a 1- to 4-week washout period (if necessary) to taper off all excluded medications that are contraindicated during duloxetine therapy. Patients who successfully withdraw from all excluded medications and continue to meet all inclusion criteria (and no exclusion criteria), as well as those who were not required to withdraw from any medications, will begin treatment with duloxetine. Two prescription bottles will be dispensed at the Baseline (Visit 1); one will contain tablets for 7 days of dose escalation (30 mg duloxetine), and the other will contain a 4-week supply of stable-dose drug (60 mg duloxetine). At the Post-Treatment Evaluation (Visit 2), patients will receive 1 prescription bottle containing medication for the 14 days of dose de-escalation (30 mg duloxetine). Patients who choose to remain on duloxetine following assessment #2 can take the study supply of 30 mg duloxetine until they are able to obtain a prescription from their PCP or other treating provider.

Subjects will be instructed to take the medication each morning at approximately the same time. Subjects will be instructed to take the medication prior to study visits on the day of scheduled visits.

6.5 Dose Modifications

There will be no dose modifications for this study. If subjects develop grade 1 or 2 toxicities that are felt to be possibly, probably, or definitely related to study drug, monitor as needed until problem has resolved (i.e., Grade 0), stabilized (i.e., remains as Grade 1 or Grade 2), or is otherwise explained. If Grade 1 or Grade 2 symptoms persist, symptom management can be initiated (e.g., antiemetics). If grade 3 or 4 symptoms develop, or if grade 1 or 2 symptoms persist despite symptom management and are bothersome to the subject, the subject should be removed from protocol treatment. See section 5.7 for instructions regarding tapering of study medication.

7.0 Concomitant Therapy

7.1 Allowable Concomitant Therapy

The following medications/therapies will be allowed for patient use during this study:

- Serotonin (*5-hydroxytryptamine*) agonists (triptans), eg, rizatriptan (Maxalt), sumatriptan (Imitrex), zolmitriptan (Zomig)
    - The use of 5-hydroxytryptamine receptor agonists (triptans) is allowed in this study; however, serotonin syndrome may occur with agents that inhibit serotonin reuptake, including duloxetine, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors). Serotonin syndrome may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Careful observation of the patient is advised if triptans are used as concomitant therapy

- Epinephrine and other adrenergic agents, e.g., epinephrine (EpiPen), pseudoephedrine (Sudafed)

    - Because duloxetine increases noradrenergic activity, epinephrine (EpiPen) should only be used in the event of a severe allergic reaction (anaphylaxis). Caution should be exercised with the use of local anesthetics that contain epinephrine, nasal decongestants that contain pseudoephedrine (e.g., Sudafed), and herbal supplements that contain stimulants (e.g., bitter orange), as these may increase heart rate or blood pressure

- Nonbenzodiazepine hypnotics, eg, zaleplon (Sonata), zolpidem (Ambien)

    - Zaleplon (Sonata) will be allowed as a first-tier selection for those patients requiring treatment of insomnia. Antihistamines and chloral hydrate are also allowed

- Nonsteroidal anti-inflammatory agents, eg, ibuprofen (Motrin), naproxen (Naprosyn), ketorolac (Toradol)

- Physical modalities

    - Modalities commonly employed during routine physical therapy, chiropractic manipulation, and/or massage therapy are allowed provided they do not involve the use of injected medications

7.2 Prohibited Concomitant Therapy

The following medications/therapies will be prohibited throughout the course of this study:

- Antidepressants, eg, escitalopram (Lexapro), venlafaxine (Effexor), milnacipran (Savella), fluoxetine (Prozac), bupropion (Wellbutrin), nortriptyline (Pamelor), monoamine oxidase (MAO) inhibitors (Parnate)

- Phenothiazines

- Propafenone and flecanide

- Antiepileptics, e.g., phenytoin (Dilantin), topiramate (Topamax), carbamazapine (Tegretol), levetiracetam (Keppra), tiagabine (Gabitril)

7.3 Treatment Compliance

Study drug compliance during any period will be closely monitored by counting the number of tablets dispensed and returned. Every effort will be made to collect all unused study drug before dispensing new study drug at each relevant visit.

8.0. Specific Methods

	Week 0		Week 1	Week 2 to Week 5	Week 6-7
	Screening		Assessment	Assessment	Final evaluation
	Screening visit		Visit 1	Visit 2	Phone
Informed consent	X				
Inclusion/Exclusion	X		X		
Discuss study procedures	X				
Urine preg test			X		
Adverse events			X	X	X
Concomitant meds	X		X	X	X
Vital signs	X		X	X	
Drug accountability				X	X
Drug dispensing			X	X	
Self-report questionnaires			X	X	
Pressure pain threshold			X	X	
CPM			X	X	
Duloxetine			←	→	
Approximate visit length	1 hour		3 hours	3 hours	0.25 hours

Washout (1-4 weeks, if necessary)

Screening Visit and Visit 1 can occur on the same day for those who do not have to withdraw from any medications.

Subjects can be evaluated up to 4 days early for visit #2. The phone call should take place 7-14 days following Visit #2.

Urine pregnancy test only in women of child-bearing potential with chronic pain. Not to be done in controls.

8.1 Vital Signs
Vital signs will be measured at every visit. The parameters include: pulse rate; systolic and diastolic blood pressure (BP); and body weight. Pulse rate and BP readings will be taken using an automated BP monitor after the patient has been sitting for 5 minutes.

8.2 Schedule of Assessments
The schedule of study procedures and assessments is tabulated by visit in the Schedule of Events in Section 8.0. The descriptions of the procedures to be completed at each visit are provided below. Control subjects will complete questionnaires and pain testing as described under screening/baseline, and then their participation in the study will be complete.

Screening
At Screening, a review of inclusion/exclusion criteria will be conducted to determine the patient's eligibility for enrollment. Study procedures will be reviewed with the patient, and documentation of informed consent will be obtained. After signing the informed consent form (ICF), patients will be assigned a unique study ID number in sequential order. Patients currently taking excluded medications will be required to complete a 1- to 4-week washout period before returning to study center for Baseline/Randomization (Visit 1).

At Screening the following procedures will be completed:

- Obtain signed and dated ICF
-
- Discuss study-specific procedures with the patient
- Review inclusion and exclusion criteria
- Question patient to ensure that the patient does not have major depression and does not have suicidal thoughts or wishes
- Record demographic information
- Record concomitant medications/therapies on concomitant medication form
- Measure vital signs, including temperature, weight, height, sitting BP, and heart rate, and record values
- Determine the required washout period and instruct the patient to taper off all excluded medications
- If washout is required, schedule an appointment for the patient to return in 1 to 4 weeks, depending on each patient's required washout period

The following data will be abstracted from the medical record: date of breast cancer diagnosis, tumor information (e.g., tumor histology, receptor status), treatment information (e.g., surgery type and dates, chemotherapy doses and dates, radiation therapy doses and dates, endocrine therapy dates), information about other medical co-morbidities.

Baseline (Visit 1)

Baseline (Visit 1) will be conducted 0 to 4 weeks (depending on the patient's washout period) after Screening to determine whether the patient is eligible to continue into the study treatment period. Those patients who do not need to discontinue any medications can proceed directly to Baseline (Visit 1). Patients who continue to meet inclusion criteria (and no exclusion criteria) will initiate treatment with duloxetine following baseline assessment. At this visit, patients will be given prescription bottles containing (1) a 1-week supply of study drug for the escalation period and (2) a 4-week supply of study drug for the treatment period, as well as the Period 1 medication log.

At Baseline (Visit 1) the following procedures will be completed:

- Review inclusion and exclusion criteria
- Assess and record baseline AEs
- Inquire as to any changes in physical symptoms, sleep and/or mood (to include suicidal ideation) (not required if screening and baseline are performed on the same day)
- Record concomitant medications/therapies on concomitant medication form
- Measure vital signs, including temperature, weight, height, sitting BP, and heart rate, and record values (not required if screening and baseline are performed on the same day)
- Perform urine pregnancy test in women of childbearing potential (not controls)
- Complete the following outcome assessments:
    - Evaluation of pressure pain threshold
    - Patient-reported outcome assessments:
        - Brief Pain Inventory (BPI)
        - Michigan Body Map and Symptom Severity Scale
        - PainDETECT
        - FACT/GOG-NTX subscale
    - Evaluation of CPM
    - Patient-reported outcome assessments
        - PROMIS (Fatigue-SF)
        - PROMIS (Sleep Disturbance-SF)
        - PROMIS (Physical Function-SF)

- Hospital Anxiety and Depression Scale (HADS)
- Multiple Ability Self-Report Questionnaire (MASQ)

(Control subjects will not participate in any additional study activities listed below.)

- Dispense the prescription bottles containing study drug for the first 5 weeks of the first treatment period (7 days of dose escalation and 28 days of full-dose treatment) and review dosing instructions. The subject should take the medication in the morning starting the morning after the baseline visit at approximately the same time each day. She should record when she took the medication on the provided Period 1 medication log. On the study visit days she should take her dose prior to the visit.

- Schedule an appointment for the patient to return in 5 weeks. This visit may be scheduled up to 4 days early.

Section 9.0 provides a detailed description of each outcome assessment.

Post-Treatment Evaluation (Visit 2)

Post-Treatment Evaluation (Visit 2) will be conducted 5 weeks after Baseline (Visit 1) to complete endpoint assessments. At this visit, patients will be given 1 prescription bottle containing the dose de-escalation for 14 days. *Visit 2 can be performed up to 4 days early (should be conducted during week 4 of full-dose treatment).*

At Post-Treatment Evaluation (Visit 2) the following procedures will be completed:

- Assess patient tolerance of medication and record AEs
- Inquire as to any change in physical symptoms, sleep, and/or mood (to include suicidal ideation)
- Record concomitant medications/therapies on concomitant medication form
- Measure vital signs and record values
- Collect study drug from the previous visit and perform drug accountability. If the subject has pills remaining, either because she missed a pill or because this visit was conducted early, the pills should not be returned to the subject.
- Complete the following outcome assessments:
    - Evaluation of pressure pain threshold
    - Patient-reported outcome assessments:
        - Brief Pain Inventory (BPI)
        - Michigan Body Map and Symptom Severity Scale

- PainDETECT
- FACT/GOG-NTX subscale

○ Evaluation of CPM

○ Patient-reported outcome assessments

- PROMIS (Fatigue-SF)
- PROMIS (Sleep Disturbance-SF)
- PROMIS (Physical Function-SF)
- Hospital Anxiety and Depression Scale (HADS)
- Multiple Ability Self-Report Questionnaire (MASQ)

- Dispense the prescription bottle containing study drug for the dose de-escalation (2 weeks) and review dosing instructions.

- For those patients who wish to continue to take commercially-available duloxetine after study completion, the patient can transition directly to duloxetine 60 mg daily using a prescription provided by her PCP or other treating physician, and she does not need to taper off and then restart drug. If she does not yet have the prescription, she will be given the two week supply of dose de-escalation study drug. Once she obtains the medication from her pharmacy she can stop the 30 mg dose and start the commercial supply.

Section 9.0 provides a detailed description of each outcome assessment.

Final Evaluation (Phone visit)

Final Evaluation (Phone visit/ET) will be conducted 7-14 days after Post-Treatment Evaluation (Visit 2). This will be the final assessment for the study. For patients who prematurely discontinue participation in the study, this will be the ET visit, and the PI will determine whether outcome assessments should be obtained at this visit in addition to the procedures listed below. Patients who have switched to commercially available duloxetine do not need to be contacted if there are no ongoing AEs that require follow-up and if they do not have study medication bottles to return.

At Final Evaluation (Phone visit/ET) the following procedures will be completed:

- Assess patient tolerance of medication and record AEs
- Inquire as to any change in physical symptoms, sleep, and/or mood (to include suicidal ideation)
- Review concomitant medications/therapies

- Remind subjects to return the study drug bottle in the stamped envelope.

Section 9.0 provides a detailed description of each outcome assessment

9.0 Outcome Measures

9.1 Primary Outcome Assessment

9.1.1 Brief Pain Inventory

The Brief Pain Inventory (BPI) is a 17-item patient self-rating scale that assessed sensory and reactive components of pain.[69] For sensory components, it addresses severity, location, chronicity, and degree of relief due to therapy. For reactive components, it assesses depression, suffering, and perceived availability of relief. Reliability has been demonstrated over short intervals using test retest item correlation; worst pain, r=0.93, usual pain, r=0.78, pain now r=0.59. It has been validated in patients with both cancer and non-cancer pain.[76,77] Ratings of pain interference with various activities increased as ratings of pain severity were higher. The proportion of patients receiving opioid analgesics also increased with increased severity rating.

The BPI uses 0 to 10 numeric rating scales for item rating because of its simplicity and lack of ambiguity. Since pain can be variable over a day, the BPI asks patients to rate their pain at the time of completing the questionnaire, and also at its worst, least, and average over the previous 24 hours. The primary endpoint for this clinical trial will be based on the 24-hour average pain as reported on the BPI. The ratings can be combined to give a composite index of pain severity. Also, using numeric 0 to 10 scales, with 0 being “no interference” and 10 being “interferes completely”, the BPI asks for ratings of the degree to which pain interferes with mood, walking and other physical activity, works, social activity, relations with others, and sleep. The mean of these scores can be used as a pain interference score.

9.2 Secondary Outcome Assessments

9.2.1 Pressure Pain Threshold
Most QST will be performed using the MAST System. The MAST System is a wireless QST platform featuring a control computer, a touch screen for patient feedback, and an automated pressure actuator. Forces are delivered by a 1-cm^2 conformal-rubber probe attached to a cylindrical transducer driven by a miniature servo-motor and housed within a polyurethane case that is held comfortably in either hand. Load-cells measure each applied force while a closed-looped control system monitors and adjusts motor output ensuring accurate pressure delivery. All subjects will undergo bilateral pressure pain testing (PPT) at the thumbnail.[52] The thumbnail was chosen as a neutral, pain-free site remote from the area of surgery. Increased pain sensitivity at the thumbnail (i.e., secondary hyperalgesia) suggests a state of widespread hyperalgesia that may be indicative of centralized pain.[47,51,54,108] Subjects will undergo testing bilaterally to determine the effect, if any, of prior breast and axillary surgery on thumbnail pressure sensitivity. Testing will be counter-balanced between left and right thumbs. The MAST System will first deliver an ascending series of pressures (5-s duration; 4 kg/cm^2/s) at 25-s intervals, beginning at 0.25 kg/cm^2 and increasing in 0.25 – 0.50 kg/cm^2 intervals up to tolerance or to a maximum of 10 kg/cm^2 to the thumbnail. Pain intensity will be rated after each stimulus on a 0-100 numerical rating scale (NRS), with “0” representing “no pain” and “100” representing “extreme pain”. Patient responses obtained in the ascending series will be used to compute a set of 5-7 stimuli between that patient’s threshold and tolerance. These stimuli will then be delivered and rated 3 times each (5-s duration; 25-s inter-stimulus interval) in randomized order. These ratings will be used to compute a psychophysical function of each subject’s pain sensitivity with pressure intensity and response magnitude represented on the x- and y-

axes, respectively. These curves will be used to compare single subject and group changes in pain sensitivity longitudinally throughout the project. Pressure pain threshold and tolerance levels will also be calculated for each subject at each thumbnail.

Because we are aware that the presence of peripheral neuropathy could influence the results of PPT threshold in the thumb, we will also test this at another site not affected by peripheral neuropathy: the deltoid muscle. The inclusion of this particular site was based on recent evidence showing that pressure pain threshold was bilaterally reduced at the deltoid muscle in BCS compared to healthy controls, and that pressure pain threshold at the affected deltoid was negatively correlated to neck pain intensity.[54] Testing will be conducted using a 1 cm^2 rubber probe attached to a digital algometer. Test order will be counter-balanced between affected and non-affected sides. Pressure will be manually increased at a rate of 0.3 $kg/cm^2/s$ to a maximum 10 kg following an ascending method of limits. Subjects will indicate the point at which the pressure sensation becomes painful (pressure pain threshold) and the point in which the pain becomes intolerable (pressure pain tolerance). A tolerance of 10 kg/cm^2 will be used for patients that fail to press the button before test completion. Measurements will be conducted 3 times at each side (20-60 second inter-stimulus interval) with mean values used for analysis.

9.2.2 Conditioned Pain Modulation (CPM)

Endogenous pain modulation will be evaluated using a CPM paradigm.[63] CPM procedures incorporate a conditioning stimulus (a noxious stimulus that activates pain modulatory systems) and a test stimulus (a noxious stimulus used to evaluate the analgesic response to the conditioning stimulus). In this study, painful pressure stimuli will be delivered via two MAST actuators positioned on opposite thumbs with pressure at one thumb serving as the test stimulus and pressure at the other thumb serving as the conditioning stimulus. The test stimulus will be applied continuously for 30-s to the thumbnail of the affected side at an intensity that induces a moderate level of pain for that patient (i.e., a rating of 30-50/100). Patients will rate the intensity of the pressure at 10-, 20-, and 30-s on a NRS. CPM will be induced 5-min later by applying 60-s of continuous pressure to the thumbnail of the non-affected side at the same pain intensity as the test stimulus. CPM magnitude will be calculated as the difference in mean pain rating to the test-stimulus applied prior to and during the conditioning stimulus. Previous work by our group and others demonstrated this to be a valid method of CPM assessment in patients with chronic pain.[55-57,60,63-66]

9.3 Patient-Reported Outcome Assessments

All enrolled subjects and controls will complete the battery of questionnaires described above, which will take approximately 1 hour to complete. All questionnaires that assess self-reported pain will be completed prior to QST; the remainder will be completed between PPT and CPM assessment.

Measures of centralization of pain

- The **Michigan Body Map and Symptom Severity Scale**, a modified version of the Wolfe Regional Pain Scale, will be used to quantify (a) the locations of breast cancer treatment-related pain using a checklist that allows for efficient scoring and (b) the severity of key symptoms, including fatigue, sleep disturbance, and cognitive function. Measures of pain distribution and the presence of this symptom cluster have been repeatedly found to be associated with centrally-mediated pain symptoms. [78-80]
- Qualitative Pain Characteristics. **PainDETECT** [70] is a 9-item measure of sensory descriptors, spatial, and temporal characteristics that has been shown to identify neuropathic components of pain in low back pain and in osteoarthritis.[34] It distinguishes neuropathic from musculoskeletal pain.
- Treatment-related toxicity. **The FACT/GOG-NTX** neurotoxicity module is an 11-item subscale specifically developed to address chemotherapy-associated peripheral neurotoxicity and its consequences on functional status.[71] The subscale scores correlate with objective neuropathy measures, specifically pin sensibility, strength, and deep tendon reflexes.

- Functional status, sleep, and fatigue. The following **PROMIS** short-forms will be used in this study: **Fatigue**, **Sleep Disturbance**, and **Physical Function**.[68] The 7-item Fatigue scale assesses the experience of fatigue as well as its impact on physical, mental, and social activities. The 8-item Sleep Disturbance scale assesses perceptions of sleep quality, sleep depth, and restoration associated with sleep. The 10-item Physical Function scale assesses self-reported function, including the ability to perform activities of daily living. The PROMIS scales possess favorable reliability and enhanced precision with lowered patient burden when compared to comparable legacy assessment instruments.
- Psychiatric status. The **Hospital Anxiety and Depression Scale** (HADS) will be used to assess anxiety and depressive symptoms.[81] The HADS is a 14 item questionnaire that has been extensively evaluated for the assessment of mood disorders in patients with cancer.[93,94]
- Cognitive dysfunction. The 38-item **Multiple Abilities Self-Report Questionnaire** (MASQ),[55,95,96] is comprised of five cognitive domains: language ability, visuo-perceptual ability, verbal memory, visual memory, and attention/concentration. Satisfactory reliability and validity have been demonstrated.[72,82,83]

10.0 Safety Assessments

Patients must be seen by an appropriately trained health professional at every visit and the evaluation must be documented. The procedures discussed in section 9.0 will be performed at the designated visits.

10.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples of AEs are as follows:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the Investigator or other study personnel
- All concurrent diseases that occur after the start of the study, including any change in severity or frequency of preexisting disease
- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study

In general, AE reporting for this clinical trial will follow the University of Michigan IRBMED guidelines. However, changes in the pain or occurrence of symptoms noted in the patient's baseline self-report questionnaires will not be recorded as AEs. In addition, if patients are undergoing treatment with anticancer agents such as aromatase inhibitors, tamoxifen, bisphosphonates, and/or trastuzumab, expected side effects of these medications will not be reported to the IRB. Changes that are clinically significant, as assessed by the Investigator, or that qualify as serious will be reported as ***SAEs***.

10.2 Causality Assessment

For all AEs, the Investigator must provide an assessment of causal relationship to study drug. Causal relationship must be assessed according to the following scale:

Related:	Reasonable temporal relation to study drug administration AND cannot be reasonably explained by other factors (eg, the patient's clinical state, concomitant therapy, and/or other interventions).
Possibly Related:	Relationship to study drug cannot be ruled out.
Not Related:	Data are available to identify a clear alternative cause for the reaction (eg, positive test for viral antigen in a case of suspected drug-induced hepatitis, hemorrhage due to mechanical injury).

10.3 Severity Assessment

The Investigator will provide an assessment of the severity of each AE. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality. Severity of AEs will be graded according to CTCAE criteria, version 4.

11.0 Statistical Methods and Determination of Sample Size

The overall study objectives are broad: (1) to assess breast cancer survivors with chronic pain for the presence and degree of pain centralization and (2) to identify predictors of response to the predominantly centrally-acting analgesic duloxetine in breast cancer survivors with chronic treatment-emergent pain. In order to examine these objectives, as noted in section 9 of the protocol, the primary outcome measure is the Brief Pain Inventory and the secondary outcome measures are objective measures of pain sensitivity and other patient-reported outcomes questionnaires. These measures are used to assess patients with chronic pain who are treated with duloxetine, in order to assess change in these outcomes with therapy, and also to assess control patients without chronic pain in order to define differences in these measures between the two cohorts and to facilitate interpretation of the change in these scores in duloxetine-treated patients. These results will be used to explore centralized pain in this patient population including identification of predictors of response to duloxetine.

Primary outcome:

Change in worst pain from baseline to week 5 with 5 weeks of duloxetine therapy, using the worst pain score from the BPI

Secondary outcomes:

a. Change in average pain from baseline to week 5 with 5 weeks of duloxetine therapy, using the average pain score from the BPI
b. Change in pain interference from baseline to week 5 with 5 weeks of duloxetine therapy, using the pain interference score from the BPI

c. Change in number of sites of pain from baseline to week 5 with 5 weeks of duloxetine therapy, using the Michigan Body Map

d. Change in Fibromyalgia Severity Score from baseline to week 5 with 5 weeks of duloxetine therapy, using the Michigan Body Map and Symptom Severity Scale

e. Change in Neuropathic Pain from baseline to week 5 with 5 weeks of duloxetine therapy, using the PainDETECT

f. Change in Neuropathy from baseline to week 5 with 5 weeks of duloxetine therapy, using the FACT/GOG-NTX

g. Change in Fatigue from baseline to week 5 with 5 weeks of duloxetine therapy, using the PROMIS Fatigue 7a

h. Change in Sleep Disturbance from baseline to week 5 with 5 weeks of duloxetine therapy, using the PROMIS Sleep Disturbance 8b

i. Change in Physical Function from baseline to week 5 with 5 weeks of duloxetine therapy, using the PROMIS Physical Function 10a

j. Change in Anxiety from baseline to week 5 with 5 weeks of duloxetine therapy, using the Hospital Anxiety and Depression Scale

k. Change in Depression from baseline to week 5 with 5 weeks of duloxetine therapy, using the Hospital Anxiety and Depression Scale

l. Change in the 5 components of Cognitive Difficulties from baseline to week 5 with 5 weeks of duloxetine therapy, using the Multiple Ability Self-Report Questionnaire

m. Change in pain sensitivity from baseline to week 5 with 5 weeks of duloxetine therapy, using the Pain50 assessed using quantitative sensory testing

n. Change in CPM from baseline to week 5 with 5 weeks of duloxetine therapy, using quantitative sensory testing

Exploratory analyses:

*Assessment of Centralized Pain***.** Centralized pain will be assessed within the unsupervised classification paradigm. Measures of pain centralization (pain severity (BPI) and distribution (Michigan Body Map)), symptom severity scale, neuropathic pain (PainDETECT), functional status (PROMIS), anxiety and depression (HADS), cognitive measures (MASQ), and experimental pain (QST)) will be treated as a multivariate phenotype informing about the latent centrality status of the subject. Demographic (e.g., age, BMI) and clinical (treatment “bin”) variables will be added as covariates. We will assume that the hypothesized centrality status is expressed by a latent variable specific to the subject, a random effect.

This variable will be used as an effect modifier in a regression model linking the primary response of pain severity and other response variables with the phenotype variables. The resultant mixture of regression models where the latent centrality variable will be shared by all regression models within the subject will be fit by the EM algorithm with iterative imputation of the latent centrality status. Regression models for each response variable will be of the generalized linear models (GLM) family. The data will have ample information to bear on the distribution of patients over the latent classes as the model will borrow strength from all contributing GLMs. The model will be refined in layers by adding response and predictor variables deemed informative of the latent centrality. The performance of the model will be measured by the Akaike Information Criterion (AIC). A threshold of 2 per 1 degree of freedom will be applied to AIC differences between models as a measure of significant difference between models. The model showing the highest AIC will be selected as the best model for subsequent analysis and prediction. The latent centrality status will be predicted for each subject by a Bayesian argument using the best model. Continuous, ordered categorical and binary latent centrality status will be explored in search for the model that provides the best explanation for the heterogeneity of pain responses in the breast cancer survivors.

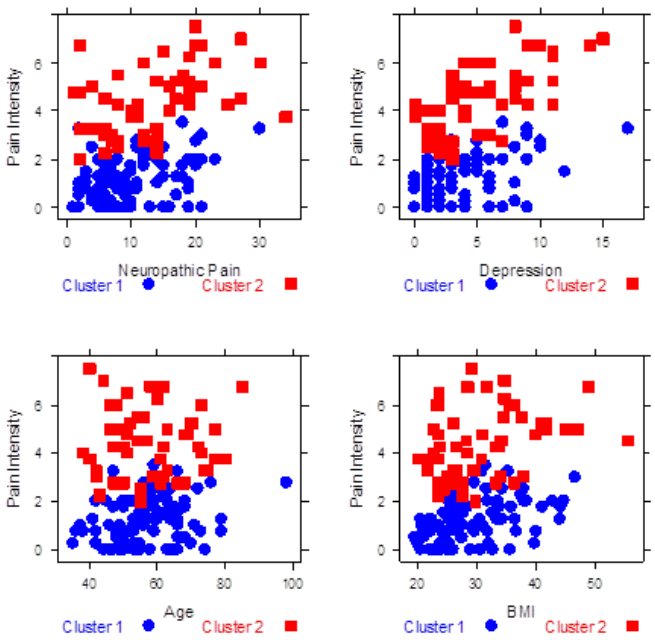

Fig. 5. Clustering of 199 BCS using a mixture of 2 (pain ~ phenotype + treatment + demographics) regression models. Red high pain latent cluster is loosely identified with predicted centralized pain classification, and the blue cluster with non-centralized. Note that none of the phenotype variables taken alone serves as a particularly good surrogate for the classification, and the mixture approach that borrows strength across various phenotypes is essential.

As an illustration of the method we fitted a binary centrality status (central vs. non-central) model (a mixture of two different latent linear regression models specific for the centrality class) to cross-sectional pain severity data on 199 breast cancer patients from an unpublished cross-sectional study we conducted on breast cancer survivors 1-3 years following diagnosis. PainDETECT, age, BMI, HADS depression and anxiety, sleep disturbance, fatigue, Perceived Stress Scale, and treatment bin (listed in Figure 4) were used as explanatory phenotype variables. The model resulted in identification of two clusters (cluster 1: 64% of patients; cluster 2: 36%) of breast cancer patients defined by dissimilar regression relationships between pain and phenotype and clinical variables. Cluster 2 is characterized by persistently higher levels of pain (Figure 5). Age, BMI and fatigue are significant variables in Cluster 1 while neuropathic pain and depression mark Cluster 2 regression. While in the data analysis we will favor continuous characterization of centrality, this binary model is used as a source of information for the power analysis below. Using the AIC criterion, the two-cluster model is significantly better than the homogeneous patient population (one regression, no latent heterogeneity explained by centrality). We note that treatment was not significant (p=0.39), in line with our hypothesis of common pain mechanism regardless of the type of insult.

Analysis. The planned sample size for Aim 1 is 132 (84 cases and 48 controls). For Aim 2, latent dichotomous pain centrality status will be hypothesized and regressed on explanatory variables including the ones involved in the CNS pain regulation. We will assume that the causality of the effect of the centrality block of variables on the Duloxetine (DLX) treatment outcome will follow through the centrality status. In addition to the random effect representing the interaction between the drug effect and the

central status, subject specific random intercept will be introduced to model correlation due to repeated measurements. A generalized linear mixed model will be used with the two response variables (self-report pain questionnaires and experimental pain testing scores). The form of the link function and variable transformations will be determined based on the data using AIC criteria. A full likelihood model-based approach will be used to fit the model. Hypotheses will be tested by the likelihood ratio test. A clinically relevant response is defined as 50% reduction in pain within the patient. The following effects are hypothesized based on our pilot studies: Central patients will constitute approximately 30% of the breast cancer population; 10% of non-central patients are hypothesized to show clinically relevant improvement under DLX while the rate of at least 70% is hypothesized in the central group. Overall, this leads to the expected 28% response rate. Placebo effects in this kind of studies are expected not to exceed 3%. Conservatively we would be looking to detect improvement over twice the expected placebo rate (6%). Using a two-sided test for the proportion of improvement vs. 6% at alpha=0.05 we will have the power of 81% with 21 patients in each “bin” (total of 84 patients).

12.0 Data Handling

MICHRs Data Management (DM) unit supports research at the University of Michigan by providing expertise in all areas of data management, from study start to completion, meeting best practices and ensuring data integrity. DM works closely with each study team to help develop an efficient method of data collection and management based on project needs, following Standard Operating Procedures and Good Clinical Practice. The unit creates study-specific data collection instruments either as paper or electronic Case Report Forms (CRFs). Database development is done using web-based applications. Throughout the life of the project, this unit provides the necessary services and expertise to help manage and report data. DM will track and store Case Report Forms, perform data entry and provide a number of reports to monitor data quality and study progress. The Data Management Unit also works collaboratively with other MICHR units to provide researchers with comprehensive services needed to effectively conduct research. The self-report data will be collected via REDCap, an electronic data capturing system developed at Vanderbilt University. REDCap is an open-source, secure, web-based application designed to support data capture for research studies, and is provided through MICHR. REDCap provides: 1) an intuitive interface for data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields within electronic forms. Servers are physically located in the UM Medical School Information Systems data center. Physical security for the databases is provided in a professionally managed and equipped tier-2 data center with tightly controlled access. Remote data access employs SSL encryption and 2-tier Kerberos and UMHS level 2 password challenges via LDAP authentication. Access to the application, the database, and the underlying systems infrastructure comply with industry best practices, supporting HIPAA security and privacy requirements and the HITECH Act. Backup of data is managed by MSIS, and vulnerability testing is performed regularly. Daily backups and VM snapshots of the application and database servers are stored on a remote storage device.

13.0 Data and Safety Monitoring

This is a phase II trial that does not require an independent data and safety monitoring board because it is designed to look at mechanism of effect rather than efficacy. Monitoring of accrual and adverse events will be performed by UM investigators and research personnel during (1) routine weekly Breast Oncology Program research meetings which are attended by faculty and staff, research nurses, and data management and regulatory personnel from the University of Michigan Clinical Trials Office and (2)

quarterly Chronic Pain and Fatigue Research Center meetings which are attended by the co-Investigators and study coordinator listed on the protocol. In addition, the trial will be monitored quarterly by the UM Comprehensive Cancer Center DSMB per institutional guidelines.

14.0 REFERENCE LIST

1. American Cancer Society: Breast Cancer Facts & Figures 2009-2010. Available at: http://www.cancer.org/Research/CancerFactsFigures/BreastCancerFactsFigures/breast-cancer-facts--figures-2009-2010. Accessed August 25, 2011.

2. Loprinzi CL, Reeves BN, Dakhil SR, et al. Natural history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCTG N08C1. J Clin Oncol 2011;29:1472-8.

3. Pachman DR, Barton DL, Watson JC, Loprinzi CL. Chemotherapy-induced peripheral neuropathy: prevention and treatment. Clin Pharmacol Ther 2011;90:377-87.

4. Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. Jama 2009;302:1985-92.

5. Andersen KG, Kehlet H. Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. J Pain 2011;12:725-46.

6. Bower JE. Behavioral symptoms in patients with breast cancer and survivors. J Clin Oncol 2008;26:768-77.

7. Peuckmann V, Ekholm O, Rasmussen NK, et al. Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. European journal of pain (London, England) 2009;13:478-85.

8. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618-25.

9. Steegers MA, Wolters B, Evers AW, Strobbe L, Wilder-Smith OH. Effect of axillary lymph node dissection on prevalence and intensity of chronic and phantom pain after breast cancer surgery. J Pain 2008;9:813-22.

10. Jung BF, Herrmann D, Griggs J, Oaklander AL, Dworkin RH. Neuropathic pain associated with non-surgical treatment of breast cancer. Pain 2005;118:10-4.

11. Cross NE, Glantz MJ. Neurologic complications of radiation therapy. Neurol Clin 2003;21:249-77.

12. Carlson RW, Allred DC, Anderson BO, et al. Invasive breast cancer. J Natl Compr Canc Netw 2011;9:136-222.

13. Loprinzi CL, Duffy J, Ingle JN. Postchemotherapy rheumatism. J Clin Oncol 1993;11:768-70.

14. Sheridan D, Foo I, O'Shea H, et al. Long-Term Follow-Up of Pain and Emotional Characteristics of Women After Surgery for Breast Cancer. J Pain Symptom Manage 2012.

15. Oxford. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.

16. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 2010;28:3784-96.

17. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60-2.

18. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793-802.

19. Mao JJ, Stricker C, Bruner D, et al. Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors. Cancer 2009;115:3631-9.

20. Henry NL, Giles JT, Ang D, et al. Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. Breast Cancer Res Treat 2008;111:365-72.

21. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation due to treatment-emergent symptoms in early-stage breast cancer. J Clin Oncol 2012;30:936-42.

22. Crew KD, Greenlee H, Capodice J, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol 2007;25:3877-83.

23. Henry NL, Banerjee M, Wicha M, et al. Pilot study of duloxetine for treatment of aromatase inhibitor-associated musculoskeletal symptoms. Cancer 2011;117:5469-75.

24. Odding E, Valkenburg HA, Algra D, Vandenouweland FA, Grobbee DE, Hofman A. Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam Study. Annals of the rheumatic diseases 1998;57:203-8.

25. Clauw DJ. Fibromyalgia: an overview. Am J Med 2009;122:S3-S13.

26. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333-43.

27. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders--pathways of vulnerability. Pain 2006;123:226-30.

28. Tracey I, Bushnell MC. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? J Pain 2009;10:1113-20.

29. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152:S2-15.

30. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med 2000;160:221-7.

31. Williams DA, Schilling S. Advances in the assessment of fibromyalgia. Rheum Dis Clin North Am 2009;35:339-57.

32. Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: A 13-week, randomized, placebo-controlled trial. Pain 2009;146:253-60.

33. Wolfe F, Hauser W, Hassett AL, Katz RS, Walitt BT. The development of fibromyalgia - I: examination of rates and predictors in patients with rheumatoid arthritis (RA). Pain 2011;152:291-9.

34. Gwilym SE, Keltner JR, Warnaby CE, et al. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. Arthritis Rheum 2009;61:1226-34.

35. Skljarevski V, Ossanna M, Liu-Seifert H, et al. A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. Eur J Neurol 2009;16:1041-8.

36. van Meurs JB, Uitterlinden AG, Stolk L, et al. A functional polymorphism in the catechol-O-methyltransferase gene is associated with osteoarthritis-related pain. Arthritis Rheum 2009;60:628-9.

37. Tegeder I, Costigan M, Griffin RS, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 2006;12:1269-77.

38. Fernandez-de-Las-Penas C, Fernandez-Lao C, Cantarero-Villanueva I, et al. Catechol-O-methyltransferase genotype (Val158Met) modulates cancer-related fatigue and pain sensitivity in breast cancer survivors. Breast Cancer Res Treat 2011;133:405-12.

39. Henry NL, Clauw DJ. Thinking beyond the tumor to better understand chronic symptoms in breast cancer survivors. Breast Cancer Res Treat 2012;133:413-6.

40. Geisser ME, Gracely RH, Giesecke T, Petzke FW, Williams DA, Clauw DJ. The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome. European journal of pain (London, England) 2007;11:202-7.

41. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. J Neurosci 2007;27:10000-6.

42. Kruger GH, Harte SE, Ischesco E, et al. Multimodal automated quantitative sensory testing system for pain research. J Medical Devices 2011;5:abstract.

43. Harte SE, Mitra M, Ichesco EA, al. E. Development and validation of a pressure-type automated quantitative sensory testing system for point-of-care assessment. Medical and Biological Engineering and Computing 2013;in press.

44. Geisser ME, Strader Donnell C, Petzke F, Gracely RH, Clauw DJ, Williams DA. Comorbid somatic symptoms and functional status in patients with fibromyalgia and chronic fatigue syndrome: sensory amplification as a common mechanism. Psychosomatics 2008;49:235-42.

45. Geisser ME, Glass JM, Rajcevska LD, et al. A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. J Pain 2008;9:417-22.

46. Giesecke J, Reed BD, Haefner HK, Giesecke T, Clauw DJ, Gracely RH. Quantitative sensory testing in vulvodynia patients and increased peripheral pressure pain sensitivity. Obstet Gynecol 2004;104:126-33.

47. Giesecke T, Williams DA, Harris RE, et al. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. Arthritis Rheum 2003;48:2916-22.

48. Gracely RH, Grant MA, Giesecke T. Evoked pain measures in fibromyalgia. Best Pract Res Clin Rheumatol 2003;17:593-609.

49. Petzke F, Harris RE, Williams DA, Clauw DJ, Gracely RH. Differences in unpleasantness induced by experimental pressure pain between patients with fibromyalgia and healthy controls. European journal of pain (London, England) 2005;9:325-35.

50. Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain 2003;105:403-13.

51. Petzke F, Khine A, Williams D, Groner K, Clauw DJ, Gracely RH. Dolorimetry performed at 3 paired tender points highly predicts overall tenderness. J Rheumatol 2001;28:2568-9.

52. Harris RE, Gracely RH, McLean SA, et al. Comparison of clinical and evoked pain measures in fibromyalgia. J Pain 2006;7:521-7.

53. Harris RE, Sundgren PC, Pang Y, et al. Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. Arthritis Rheum 2008;58:903-7.

54. Fernandez-Lao C, Cantarero-Villanueva I, Fernandez-de-las-Penas C, Del-Moral-Avila R, Menjon-Beltran S, Arroyo-Morales M. Widespread mechanical pain hypersensitivity as a sign of central

sensitization after breast cancer surgery: comparison between mastectomy and lumpectomy. Pain medicine (Malden, Mass 2011;12:72-8.

55. Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. Pain 1979;6:305-27.

56. Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. Pain 1979;6:283-304.

57. Wilder-Smith CH, Robert-Yap J. Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. World J Gastroenterol 2007;13:3699-704.

58. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. The Clinical journal of pain 1997;13:189-96.

59. Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain 1997;70:41-51.

60. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005;114:295-302.

61. Williams DA, Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. J Pain 2009;10:777-91.

62. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. Pain 2012;153:1193-8.

63. Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Pain 2008;138:22-8.

64. Granot M, Weissman-Fogel I, Crispel Y, et al. Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: do conditioning stimulus painfulness, gender and personality variables matter? Pain 2008;136:142-9.

65. Peters ML, Schmidt AJ, Van den Hout MA, Koopmans R, Sluijter ME. Chronic back pain, acute postoperative pain and the activation of diffuse noxious inhibitory controls (DNIC). Pain 1992;50:177-87.

66. Kosek E, Ordeberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain 2000;88:69-78.

67. Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. Pain 2009;144:16-9.

68. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol 2010;63:1179-94.

69. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain 1983;17:197-210.

70. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911-20.

71. Cella D, Peterman A, Hudgens S, Webster K, Socinski MA. Measuring the side effects of taxane therapy in oncology: the functional assesment of cancer therapy-taxane (FACT-taxane). Cancer 2003;98:822-31.

72. Seidenberg M, Haltiner A, Taylor MA, Hermann BB, Wyler A. Development and validation of a Multiple Ability Self-Report Questionnaire. J Clin Exp Neuropsychol 1994;16:93-104.

73. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. Journal of health and social behavior 1983;24:385-96.

74. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54:1063-70.

75. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105-21.

76. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004;5:133-7.

77. Tittle MB, McMillan SC, Hagan S. Validating the brief pain inventory for use with surgical patients with cancer. Oncol Nurs Forum 2003;30:325-30.

78. Wolfe F. Pain extent and diagnosis: development and validation of the regional pain scale in 12,799 patients with rheumatic disease. J Rheumatol 2003;30:369-78.

79. Wolfe F, Rasker JJ. The Symptom Intensity Scale, fibromyalgia, and the meaning of fibromyalgia-like symptoms. J Rheumatol 2006;33:2291-9.

80. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010;62:600-10.

81. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.

82. Donovan KA, Small BJ, Andrykowski MA, Schmitt FA, Munster P, Jacobsen PB. Cognitive functioning after adjuvant chemotherapy and/or radiotherapy for early-stage breast carcinoma. Cancer 2005;104:2499-507.

83. Jim HS, Donovan KA, Small BJ, Andrykowski MA, Munster PN, Jacobsen PB. Cognitive functioning in breast cancer survivors: a controlled comparison. Cancer 2009;115:1776-83.

84. Buskila D. Drug therapy. Baillieres Best Pract Res Clin Rheumatol 1999;13:479-85.

85. Leventhal LJ. Management of fibromyalgia. Ann Intern Med 1999;131:850-8.

86. Lautenschlager J. Present state of medication therapy in fibromyalgia syndrome. Scand J Rheumatol Suppl 2000;113:32-6.

87. Wolfe F, Anderson J, Harkness D, et al. Health status and disease severity in fibromyalgia: results of a six-center longitudinal study. Arthritis Rheum 1997;40:1571-9.

88. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997;4:134-53.

89. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis Rheum 1986;29:1371-7.

90. Quijada-Carrera J, Valenzuela-Castano A, Povedano-Gomez J, et al. Comparison of tenoxicam and bromazepan in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. Pain 1996;65:221-5.

91. Russell IJ, Fletcher EM, Michalek JE, McBroom PC, Hester GG. Treatment of primary fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam. A double-blind, placebo-controlled study. Arthritis Rheum 1991;34:552-60.

92. Wolfe F, Zhao S, Lane N. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. Arthritis Rheum 2000;43:378-85.

93. Yunus MB, Masi AT, Aldag JC. Short term effects of ibuprofen in primary fibromyalgia syndrome: a double blind, placebo controlled trial. J Rheumatol 1989;16:527-32.

94. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999;83:389-400.

95. Sanchez C, Hyttel J. Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. Cell Mol Neurobiol 1999;19:467-89.

96. Arnold LM, Clauw DJ, Wohlreich MM, et al. Efficacy of duloxetine in patients with fibromyalgia: pooled analysis of 4 placebo-controlled clinical trials. Prim Care Companion J Clin Psychiatry 2009;11:237-44.

97. Mease PJ, Clauw DJ, Gendreau RM, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial. J Rheumatol 2009;36:398-409.

98. Cymbalta package insert, http://www.cymbalta.com/index.jsp, accessed 12/1/2011.

99. Marangell LB, Clauw DJ, Choy E, et al. Comparative pain and mood effects in patients with comorbid fibromyalgia and major depressive disorder: secondary analyses of four pooled randomized controlled trials of duloxetine. Pain 2011;152:31-7.

100. Marcus DA. Duloxetine use in painful conditions. Expert opinion on pharmacotherapy 2011;12:1333-40.

101. Pritchett YL, McCarberg BH, Watkin JG, Robinson MJ. Duloxetine for the management of diabetic peripheral neuropathic pain: response profile. Pain medicine (Malden, Mass 2007;8:397-409.

102. Skljarevski V, Zhang S, Desaiah D, et al. Duloxetine Versus Placebo in Patients With Chronic Low Back Pain: A 12-Week, Fixed-Dose, Randomized, Double-Blind Trial. J Pain 2010.

103. Sullivan MD, Bentley S, Fan MY, Gardner G. A single-blind, placebo run-in study of duloxetine for activity-limiting osteoarthritis pain. J Pain 2009;10:208-13.

104. Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006;67:1411-20.

105. Bradley LA, Wohlreich MM, Wang F, et al. Pain response profile of patients with fibromyalgia treated with duloxetine. The Clinical journal of pain 2010;26:498-504.

106. Smith EML, Pang H, Cirrincione C, et al. CALGB 170601: A phase III double blind trial of duloxetine to treat painful chemotherapy-induced peripheral neuropathy. J Clin Oncol 2012;30 (Suppl):Abstr CRA9013.

107. Henry NL, Banerjee M, Wicha M, et al. Pilot study of duloxetine for treatment of aromatase inhibitor-associated musculoskeletal symptoms. Cancer 2011.

108. Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis Rheum 2005;52:1577-84.

15.0 APPENDICES

The following documents have been attached as appendices to this protocol:

1. Brief Pain Inventory (BPI)
2. Michigan Body Map
3. Symptom Severity Scale
4. PainDETECT
5. FACT/GOG-NTX
6. PROMIS (Physical function-SF)
7. PROMIS (Fatigue-SF)
8. PROMIS (Sleep disturbance-SF)
9. Hospital Anxiety and Depression Scale (HADS)
10. Multiple Ability Self-Report Questionnaire (MASQ)
11. Demographics
12. Cymbalta (duloxetine) Highlights of Prescribing Information
13. Concomitant medication form
14. Medication log

Concomitant Medications

Subject ID: _____ **Date:** _____

Please list any prescription and nonprescription drugs, vitamins and dietary supplements that you have taken since your last clinic visit.

Drug name	Total Daily Dosage	Why do you take the medication?	Is this a medication you take daily?	Start Date (if not a daily medicine)	End Date (if not a daily medication)

Reviewed by: _____

Medication Log

Subject ID: _____

Please record when you take your study medication on this log. You should take your medication in the morning at approximately the same time each day, including the days that you have your study visits.

Please list any problems that you had (e.g., forgot to take medication, too much nausea, etc) in the comments box. If you are having side effects that are causing you to not take the medication, please call Dr. Henry at 734-936-6000.

Date	Bottle Number	Time	Comments	Date	Bottle Number	Time	Comments
	1				2		
	1				2		
	1				2		
	1				2		
	1				2		
	1				2		
	1				2		
	2				2		
	2				2		
	2				2		
	2				2		
	2				2		
	2				2		
	2				2		
	2				2		
	2						
	2						
	2						
	2						
	2						
	2						
	2						

Reviewed by: _____