**Note: Sample uses older template format

RSNA CLINICAL TRIALS METHODOLOGY WORKSHOP

(Protocol template)
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[Color-coded Timetable:
Orange Font: Draft due Sunday
Green Font: Draft due Tuesday
Blue Font: Draft due Wednesday
Black Font: Final draft due Friday]

MR Imaging of the Excitatory and Inhibitory Neurotransmitters in Knee Osteoarthritis

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***Co-investigators**, and contact info.*

Statistician

Original Date: *Insert date of final and approved protocol (blank during this workshop)*
Version Date: *Version 3, January 19, 2011*
Activation Date: *On activated protocols only (blank during this workshop)*

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Note: The Protocol Overview also serves as the basis for Poster that will be displayed on Thursday evening.

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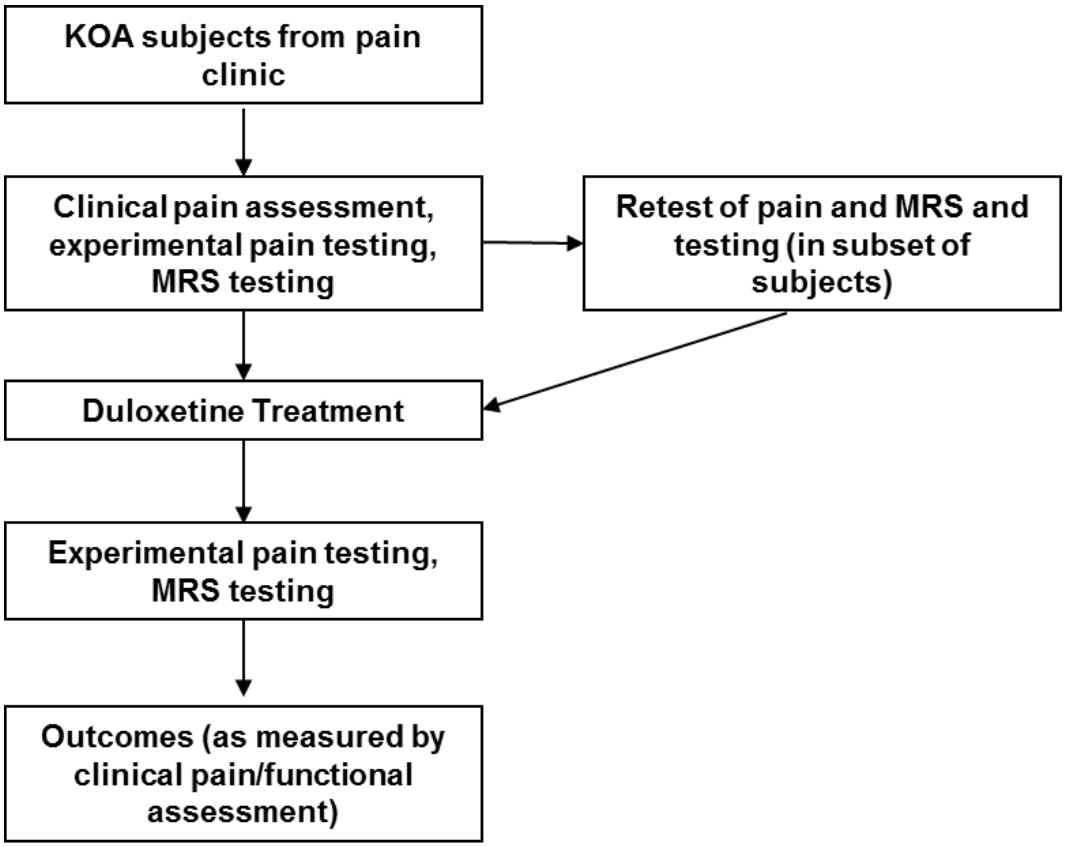
1.0 PROTOCOL ABSTRACT/OVERVIEW

SCHEMA



BACKGROUND AND RATIONALE

Osteoarthritis (OA) is a significant public health problem that is increasing in frequency, and is associated with significant direct and indirect medical costs that are only expected to increase further in the increasing elderly and obese population. Current treatments for treating pain in osteoarthritis are only modestly efficacious[1, 2]. Recent findings suggest that a subset of individuals with what have traditionally been considered "peripheral" pain states, such as knee osteoarthritis (KOA) may have prominent CNS contributions to their pain [[3-8]. Magnetic Resonance Spectroscopy (MRS) is a non-invasive imaging technique that can provide an insight to brain biochemistry. MRS studies have shown alterations in brain metabolism in a number of chronic pain states including 'Glx' which is a combined measure of glutamate (Glu) and glutamine[9-11]. Recent developments in spectroscopic methods currently allow reliable measurement inhibitory

neurotransmitters. Specifically, novel MRS editing techniques allow for quantification of -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS which is also hypothesized to be a significant mediator in chronic pain syndromes [12-16].

The overarching goal of this proposal is to correlate excitatory and inhibitory neurotransmitters with changes in clinical pain measures in KOA subjects.. The proposed studies could lead to a major paradigm shift in the diagnosis and treatment of chronic pain. For the first time, instead of considering the pain and other symptoms associated with common conditions such as KOA to be primarily due to peripheral factors, we will be able to perform neuroimaging that would identify subsets of chronic pain patients having prominent CNS contributions to their symptoms. These individuals would logically respond to markedly different classes of drug and non-drug therapies than those with primarily peripheral/nociceptive pain. The risks of the trial are minimal including the MR imaging and intervention with duloxetine which has recently been approved by the FDA for treatment of osteoarthritis.

OBJECTIVES

1. Primary Objective

Correlate baseline excitatory and inhibitory neurotransmitters as measured by MRS with clinical pain response to duloxetine intervention in KOA subjects. Primary endpoints are clinical pain levels.

2. Secondary Objectives

In a subset of the study subjects, establish the repeatability of MRS testing of excitatory and inhibitory transmitters.

Correlate changes in post-treatment MRS testing with clinical and experimental pain measures following duloxetine intervention. Secondary endpoints are follow-up MRS GABA and Glx measures and experimental pain measures.

ELIGIBILITY

Right handed individuals over age 40 that are diagnosed with unilateral, symptomatic KOA based on American College of Rheumatology (ACR) criteria[17].

STUDY DESIGN

The research team will correlate MRS measures with clinical pain response to duloxetine intervention in KOA subjects using a longitudinal study design. Trained pain researchers will administer clinical pain assessment testing, evoked pressure pain testing as well as mood testing to control for potential confounders. To evaluate the repeatability of our MRI method and experimental pain measures, we will retest the first 30 subjects to receive a second MRI scan and experimental pain pressure evaluation. The MR research technician will scan (and for the first 30 subjects, rescan) the research subjects for baseline MR spectroscopy measures of Glx and GABA.

Duloxetine will then be administered to all of the subjects over the course of eight weeks. The pain researchers will repeat clinical and experimental pain testing on the subjects. The MR research technician will scan the research subjects for post-treatment MR spectroscopy measures of Glx and GABA.

REQUIRED SAMPLE SIZE

With 80% power and 2.5% type I error rate (two-tailed), 128 patients would be needed to detect a correlation of 0.2 or greater, assuming an 80% follow-up rate.

2.0 Background and Rationale

Burden of disease

Osteoarthritis (OA) is a significant public health problem that is increasing in frequency, and is associated with staggering direct and indirect medical costs. OA is typically diagnosed when an individual presents for medical attention complaining of pain in the hip or knee. A radiograph is then performed documenting degenerative changes consistent with osteoarthritis. OA is by far the most common form of arthritis, and is rapidly increasing in frequency, in part because our population is becoming older and more obese[18]. The estimated lifetime risk for symptomatic knee OA alone is 45% [19]. The true direct and indirect costs of OA are nearly impossible to calculate, but appear to be rising exponentially. In 1994, Yelin estimated that the total overall costs of OA in the U.S. were $15.5B dollars (2005), just the cost of hospitalization for musculoskeletal procedures was estimated at $31.5B, totaling 10% of overall inpatient costs (http://www.hcup-us.ahrq.gov/reports/statbriefs/sb34.jsp). Without advances in preventing or more effectively treating OA, the magnitude of this problem will continue to grow, as the number of total joint replacements is anticipated to rise 174% for hips (572,000 per year) and 673% for knees (3.48 million per year) by 2030[20].

Our current treatments for OA are only modestly efficacious

Pain in OA is attributed to joint or bone damage, and nearly all therapies have been aimed at treating the pain derived from this peripheral structural problem including exercise, topical analgesics, oral non-steroidal anti-inflammatory drugs (NSAIDS) and opioids, local injections, and eventually replacement. While there are numerous interventions for OA, the current data suggest that our therapeutic impact is less than desirable. The first-line pharmacological treatments for this and other types of regional musculoskeletal pain are acetaminophen and NSAIDs. In meta-analyses of randomized control trials using either of these classes of drugs in OA, acetaminophen leads to an average of 4 mm improvement compared to placebo (on a 0 – 100 mm visual analog pain scale), whereas NSAID trials that do not exclude non-responders show an average of 8 mm improvement compared to placebo[1, 2].

Central pain processing and knee osteoarthritis

It has been evident for some time that peripheral factors can, at best, only partially explain the pain and other symptoms suffered by individuals with osteoarthritis (OA). Population-based studies consistently show a poor relationship between the degree of "pathology" in OA and reported pain intensity. In fact, in population-based studies approximately 30 – 40% of KOA patients with the most severe forms of radiographic knee OA (KOA; Kellgren-Lawrence grades III and IV) have no pain[21, 22]. Furthermore, many OA patients that theoretically have a pathologic process confined to one or only a few joints experience symptoms that cannot be explained by the "peripheral" model of pathogenesis. Multifocal pain in areas not generally affected by OA is common in individuals identified as having KOA[3]. Similarly, other somatic symptoms that would not be explained by a purely peripheral problem are often seen. For example, a recent study from our group showed that fatigue was a prominent problem in individuals with KOA, and in many individuals fatigue was a more functionally limiting symptom than pain[4]. Insomnia likewise occurs in a sizable proportion of OA patients, and has been shown to improve along with pain in the small proportion of individuals with KOA that

responded to opioids, suggesting that insomnia and pain may have overlapping biological underpinnings[23].

It has therefore become increasingly clear that purely "peripheral" theories regarding OA are incomplete, and recently studies have begun to explore the potential CNS contributions to this condition. Harden et. al. compared 37 subjects with KOA and 35 controls on a battery of psychophysical tests and found that the OA subjects demonstrated lower overall mechanical pain thresholds compared to controls, as well as greater mechanical and thermal temporal summation than controls, whereas there were no differences among subjects for any of the remaining experimental pain testing[5]. Gwilym and colleagues used both experimental pain testing and functional neuroimaging procedures to show augmented CNS processing of pain in 20 OA patients[6]. Perhaps the strongest evidence for CNS factors being important in OA is the finding that the drug duloxetine, a centrally acting selective serotonin and norepinephrine reuptake inhibitor (SNRI) with analgesic effects, is efficacious in individuals with KOA with 19% response rate to treatment compared to placebo however it can 8 to 12 weeks to see full effect[7]. Duloxetine is thought to act through predominately central nervous system mechanisms as pain is thought to be mediated in part through centrally acting serotonergic and norepinephric pathways [24-26].

Glutamate and pain processing

Glu is the major excitatory neurotransmitter of the mammalian central nervous system. Although the role of Glu has been firmly established in animal models of pain and nociception, relatively little work has been performed to date examining Glu levels in humans with chronic pain. It is important to note that MRS is able to provide quantitative measures of Glx which is a combined measure of glutamate and glutamine; pure Glu levels are beyond the resolution of currently available MRS methods. Elevated cerebrospinal fluid levels of Glu have been identified in both migraine and FM[27, 28]. However, levels of substances in the CSF may not be reflective of those in specific regions of the brain. Mullins was the first to use MRS to measure brain Glx levels in the setting of pain[29]. Since then, our group and several others have used MRS to show that FM patients are characterized by increased levels of Glx in brain regions known to be involved in pain processing[10, 30, 31].

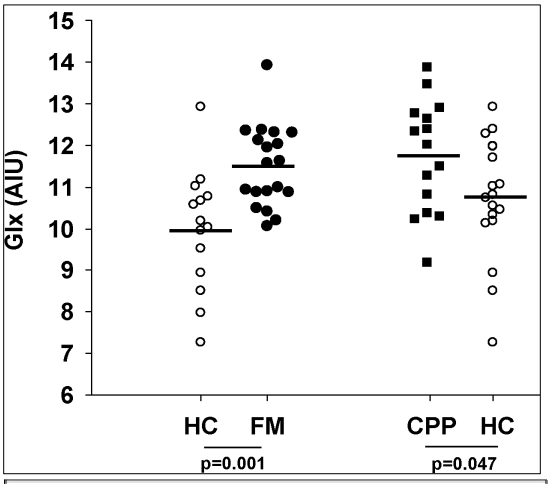


Figure 1: Elevated glutamate+glutamine (Glx) posterior insula in chronic pelvic pain (CPP) and fibromyalgia (FM) patients compared to age-matched

In a study of 19 FM subjects and 14 age and sex-matched healthy controls, we found significantly elevated levels of Glx in the posterior insula of FM subjects compared to healthy controls (Figure 1; Glx mean(SD) FM: 11.50(0.98), HC: 9.97(1.46), p=0.001). We have also collected preliminary MRS data from 15 women with chronic pelvic pain (CPP) to determine if insular Glx is elevated in this separate chronic pain state. We found elevated mean Glx levels within the posterior insula in CPP patients as compared to pain free controls (Figure 1; Glx mean(SD) CPP: 11.76(1.35), HC: 10.74(1.45), p=0.047). This would be consistent with the hypothesis that these

individuals have augmented central neural activity in pain processing regions.

As expected, FM patients in the study outlined above exhibited trends towards lower pain thresholds than HC, with FM subjects requiring less pressure (in kg) to elicit the same clinical pain level (mean pressure FM=0.55 kg [SD=0.48], HC=1.44 kg [SD=1.29], p=0.03). Both FM patients and HC with higher Glx levels displayed greater pressure pain sensitivity to lower pressure thresholds, as shown in Figure 2.

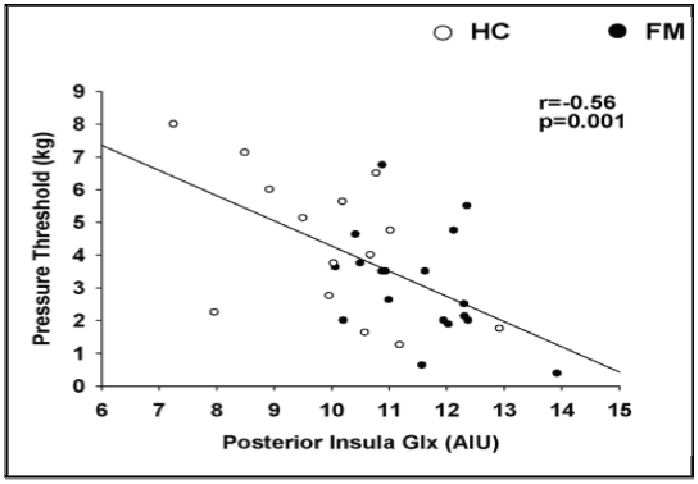


Figure 2: Correlation of Pressure Testing and Posterior Insula Glx levels in FM & HC Subjects

We showed that Glx levels in the posterior insula were related to overall pain sensitivity in both FM patients and controls. Because individuals with FM displayed decreased pain threshold, their Glx levels were correspondingly higher, but the same fundamental relationship between pain sensitivity and Glx was seen in both FM patients and healthy controls[10] This is consonant with our overall hypothesis that an increase in Glu/Glx sets the gain on pain processing in both healthy individuals and chronic pain cohorts, but any group of chronic pain patients will display an upward shift of Glu/Glx, that in turn determines their degree of hyperalgesia (i.e. sensitivity to painful stimuli).

Our group has also demonstrated that treatment of central pain patients with acupuncture and/or sham acupuncture can lead to changes in Glx levels within the posterior insula[32]. These changes in Glx are highly correlated with changes in pain: greater reductions in Glx are associated with greater reductions in both experimental and clinical pain. *In aggregate, these data suggest that elevated levels of Glx are present within the CNS of central pain patients.*

GABA and pain processing

GABA is the major inhibitory neurotransmitter in the central nervous system and its role in pain processing has been recognized for some time[12]. GABA receptors are widely distributed in the spinal cord, thalamus, and cortex, both pre- and post-synaptically. Many of the early studies showing proof of concept that GABA played a critical role in pain transmission involved demonstrating that baclofen, a GABA-B agonist, was effective in both preclinical models of acute and chronic pain[13]. These effects are likely mediated by both spinal and supraspinal GABA-B receptors[14]. GABA-B receptors are also involved in the inhibitory effects of other neurotransmitters on glutamatergic synaptic transmission, e.g. acetylcholine (via muscarinic receptors), μ-opioid receptors, endocannabinoids (via CB1 receptors) and adenosine (via A1 receptors)[15].

Perhaps the strongest and most impressive data suggesting a pivotal role for GABA deficiency in central pain states comes from the recent trials of gamma-hydroxybutyrate (GHB) in FM. Two Phase III trials showed that this compound, which is known to bind only to GHB and GABA-B receptors, is highly effective at improving pain in this condition, with an effect size larger than any of the other drugs studied in this condition. More impressively, these trials all showed similar effects ($p<.001$ for all analyses) for improvements in sleep and fatigue. This is the only drug for chronic pain that has shown simultaneous salutary effects for pain, fatigue, and sleep, suggesting it is acting on a basic underlying pathological mechanism in this central pain state[16, 33].

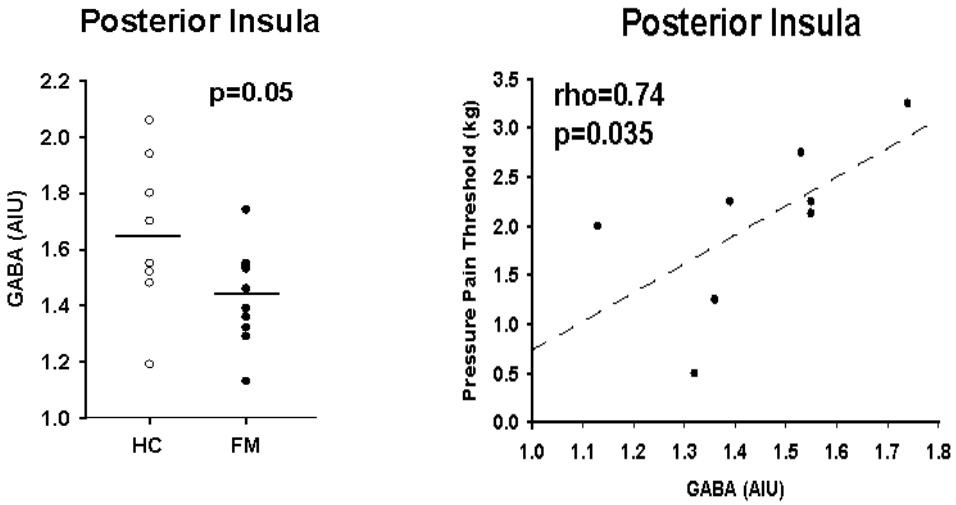


Figure 3. Decreased levels of GABA in the posterior insula in FM subjects compared to HC (left). Positive correlation of pain threshold with GABA levels in FM subjects (right).

We have preliminary data in 9 FM subjects and 8 age and sex-matched healthy controls (Figure 3.) We found a significantly lower GABA concentration in the posterior insula in fibromyalgia subjects (1.43 i.u. ± 0.16)) compared to healthy controls (1.65 i.u. ± 0.26; $p = 0.05$). FM patients with higher levels of GABA tended to have a higher pain threshold.

Significance of proposed research

Osteoarthritis is highly prevalent in the population with enormous direct and indirect costs. Traditional treatments for osteoarthritis are only modestly efficacious. The proposed studies could lead to a major paradigm shift in the diagnosis and treatment of chronic pain. For the first time, instead of considering the pain and other symptoms associated with KOA to be primarily due to peripheral factors, we will be able to perform neuroimaging testing to identify subsets of chronic pain patients that have prominent CNS contributions to their pain symptoms. These individuals would logically respond to markedly different classes of drug and non-drug therapies than those with primarily peripheral/nociceptive pain. The combination of established and novel MRS techniques will enable us to assess changes in the excitatory and inhibitory neurotransmitters in the context of chronic pain, offering new opportunities for targeted interventions in these patients. Although our project is focused on KOA, central pain components are thought to be significant in the context of neuropathic pain as well as cancer and inflammatory rheumatological diseases, widening the scope of the proposed research.

3.0 Study Objectives

The overarching goal of this proposal to correlate excitatory and inhibitory neurotransmitters with changes in clinical pain measures in KOA subjects. To this end we have formulated the following specific objectives:

3.1 Primary Objective

Correlate baseline MRS measures with clinical pain response to duloxetine intervention in KOA subjects.

3.2 Secondary Objectives

1. In a subset of the study subjects, establish the repeatability of MRS testing of excitatory and inhibitory transmitters.
2. Correlate changes in post-treatment MRS testing with clinical and experimental pain measures following duloxetine intervention.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

Right handed individuals over age 40 that are diagnosed with unilateral, symptomatic KOA based on ACR criteria[17].

Subjects will be allowed to continue on stable doses of non-opioid analgesics.

4.2 Exclusion Criteria

Inability to provide written informed consent.

Severe physical impairment precludes participation (e.g. blindness, deafness, paraplegia).

Co-morbid medical conditions that may cause significant impairment of physical functional status.

Psychiatric conditions that in the judgment of study personnel would preclude participation in this study.

Currently on centrally acting pain medication (i.e. opioids, tramadol).

History of CNS disease (infection, neoplasm, head injury, stroke or seizure disorder,

Current alcohol or substance abuse/dependence.

Pregnant or breast-feeding women.

Contraindications to MRI methods (e.g. pacemaker, claustrophobia etc.).

5. 0 Research Design and Methods

5.1 Study Design

The research team will correlate MRS measures with clinical pain response to duloxetine intervention in KOA subjects using a longitudinal study design. The collaborating pain physician will recruit KOA patients through the University of Michigan Pain & Physical Medicine Clinic. Trained pain researchers will administer clinical pain assessment testing (including The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) and the SF-36 Questionnaire), evoked pressure pain testing, as well as mood testing to control for potential confounders. To evaluate the repeatability of our MRI method and experimental pain measures, we will retest the first 30 subjects to receive a second MRI

scan and experimental pain pressure evaluation. The MR research technician will scan (and for selected subjects, rescan) the research subjects for baseline MR spectroscopy measures of Glx and GABA.

Duloxetine will then be administered to all of the subjects over the course of eight weeks. The pain researchers will repeat clinical and experimental pain testing on the subjects including patients' clinical pain score and level of disability as measure by the WOMAC and the SF-36 Questionnaire. The MR research technician will scan the research subjects for post-treatment MR spectroscopy measures of Glx and GABA.

5.2 Study Calendar / Schedule

Week	-1 to -4	0	1	1	3	7	9
Visit	Visit 1	Visit 2	Visit 3	Visit 3	Visit 4	Visit 5	Visit 6
	Preregistration	Screening	Testing	Testing	TX	TX	Final
			Baseline	Reproducibility	Follow-up	Follow-up	
Eligibility	x						
Interest	x						
MRI safety screen	x						
Informed Consent		x					
MRI safety screen		x					
History & Physical		x			x	x	
Sociodemographics		x					
Urine Pregnancy Test		x	x	x	x	x	x
ConMeds		x	x	x	x	x	x
Blood pressure		x	x	x	x	x	x
Adverse Events		x	x	x	x	x	x
Laboratory testing			x				x
Patient Reported Pain		x	x	x	x	x	x
Pain Pressure Testing			x	x			x
Pain Phenotyping			x	x			x
SF-36			x				x
WOMAC			x				x
Duloxetine					x	x	x
MRS			x	x			x

5.3 Pre-Registration Procedures (Visit 1)

The pain physician will perform the initial determination of eligibility when he/she sees his patients at the pain clinic. The pain physician will inform potentially eligible subjects about the study and ask them if they would be willing to meet with the study coordinator. The study coordinator will attend the physician's pain clinic and, during the clinic, meet briefly with willing subjects. This brief meeting will represent Visit 1, the pre-registration visit. At this pre-registration visit, the coordinator will outline the

research protocol to the subject; give the subject an informational flyer, an MRI screening safety questionnaire, and a consent form; record the subject's preferred contact information; and schedule the subject for a registration visit.

5.3 Registration Visit and Procedures (Visit 2)

At the registration visit, the coordinator will explain the protocol in greater detail and answer the potential subject's questions. The MRI screening questionnaire and consent form will be reviewed. With the subject's verbal permission, eligibility criteria will be rechecked. If the eligibility criteria are met, the subject will be asked to sign informed consent and the subject will be registered in the trial. The first 30 research subjects will receive a modified consent explain that the experimental and MRI testing will be repeated on the same day. The research coordinator will record demographic data (gender, date of birth, self-reported ethnicity, and self-reported racial group) as well as clinical and laboratory data related to the eligibility criteria (liver and renal function laboratory tests). If the liver or renal laboratory tests obtained for clinical care are not available within 35 days of the scheduled initiation of duloxetine, then the liver or renal laboratory testing will be ordered. The serum sample will be obtained by a certified phlebotomist or other qualified medical professional as a study procedure. The coordinator will schedule the research MRI examination and review with the subject pre-MRI instructions.

5.4 Research Baseline Pain Testing and MRI (Visit 3)

The research coordinator will meet the subject at the Clinical Pain and Fatigue Outpatient Research Center. Pain research technicians will administer pain pressure testing, pain/functional/mood questionnaires. The research coordinator will transport the research participant to the University of Michigan Hospital Radiology Department. The MRI research technologist will meet the research coordinator subject upon arrival at the MR3T facility and confirm consent, re-review MR safety screening questionnaire and obtain a urine pregnancy test (if the subject is a woman of child bearing potential. The MRI examination will be performed (see Section 6.11). The PI or study investigator will monitor each MR examination and observe the subjects for adverse events until the subjects leave the MR facility. Adverse events will be recorded on an adverse event form. Immediately prior to discharge from the MR facility, subjects will be given compensation as detailed in the consent form. The study coordinator will dispense 96 thirty mg tablets with instructions to take one 30 mg duloxetine pill by mouth in the morning after breakfast and one 30 mg duloxetine pill by mouth in the evening after dinner.

5.5 Reproducibility Research Baseline Pain Testing and MRI (Visit 3)

The first 30 subjects will undergo repeat pain pressure testing and MRI to be on the same day using the same testing procedures. Subjects will be given a one hour break between the pain testing and a one hour break between the MRI testing. The study coordinator will dispense 96 thirty mg tablets with instructions to take one 30 mg duloxetine pill in the morning by mouth after breakfast and one 30 mg duloxetine pill by mouth in the evening after dinner.

5.6 General Concomitant Medication and Supportive Care Guidelines (Visits 4&5)

The study coordinator will schedule the subjects to return to the pain clinic at 2 weeks and 6 weeks following initiation of duloxetine treatment. The pain physician will perform a history and physical examination including blood pressure monitoring to ensure that there are no significant side-effects as defined by change in blood pressure or pulse by 15%.

5.7 Final Pain Testing and MRI (Visit 6)

The research coordinator will meet the subject at the Clinical Pain and Fatigue Outpatient Research Center. Pain research technicians will administer pain pressure testing, pain/functional/mood questionnaires. The research coordinator will transport the research participant to the University of Michigan Hospital Radiology Department. The MRI research technologist will meet the research coordinator subject upon arrival at the MR3T facility and confirm consent, re-review MR safety screening questionnaire and obtain a urine pregnancy test (if the subject is a woman of child bearing potential. The MRI examination will be performed (see Section 5.8). The PI or study investigator will monitor each MR examination and observe the subjects for adverse events until the subjects leave the MR facility. Adverse events will be recorded on an adverse event form. Immediately prior to discharge from the MR facility, subjects will be given compensation as detailed in the consent form.

5.8 Criteria for Removal from Study

Registered subjects will be withdrawn from the study if any of the following conditions are met:

- Baseline research MRI is not performed
- eGFR < 45 on or AST or ALT > 1.5X normal value on blood sample drawn after registration
- Subject has a positive urine pregnancy test after registration.
- Subject withdraws his/her consent.
- Exclusion criteria are discovered after registration but prior to MRI

5.9 Image Acquisition, Archiving, and Interpretation

MRI and MRS scanning protocol

All studies will be performed on a Philips Achieva 3T system using an 8 channel (Invivo Diagnostic Imaging) receive head coil. Field homogeneity will be optimized up to 2nd order using field map based shimming software (Philips 'shimtool'). One voxel will be placed for the magnetic resonance spectroscopy portion of the exam, one in the right posterior insula.

The MRI and MRS scanning protocol will consist of:

A. Survey images (1 minute).
B. SENSE Reference images (1 minute).
C. B0 field map sequence for shim adjustment (1 minute)..
D. 3D-MP-RAGE (6 minutes): Isotropic 0.9 mm resolution, 150 slices, TR/TE 8.2/3.7 ms
E. FLAIR (5 minutes): Slice Thickness/Gap 1.26/0.6mm, 300 slices, TR/TE 8000/341ms,matrix 228x226, FOV 250 x 250 matrix 192x256, FOV 184 x 230, flip angle 8˚, SENSE factor (R) 2.0.
F. Point Resolved Spectroscopy Sequence (PRESS) technique for Glx (4 minutes): Spatial localization for MRS will be achieved using the point-resolved spectroscopy sequence (PRESS), as well as 4 outer-volume suppression bands. The voxel will be placed in two supraventricular white matter regions. Single voxel spectra (TR/TE=2000/35 ms) will be acquired from the region of interest with and without 'VAPOR' water suppression with 64 averages and a total scan time of approximately 2 minutes for each voxel. The water signal will be recorded using 8

averages (scan time 16 sec). This will be used to determine Glx concentration and will be used for quantification purpose. Using the LCModel software package, the concentrations (in mM) of Glu, Gln, Glx (the sum of Glu and Gln), total NAA, lactate, as well as creatine (Cr), choline (Cho), myo-inositol (mI) will also be determined using the brain water signal as an internal intensity reference.

H. MEGA-PRESS Technique for GABA (11 minutes): MEGA-PRESS experiment for isolating -aminobutyric acid (GABA) will be performed TE= 68, TE_1= 15, TE_2 =53 msec, TR= 1.8s; 256 transients. MEGA "on/off" frequencies for GABA will be 8.3/1.9 ppm and a MEGA PRESS experiment time of 8 minutes and 32 seconds. The voxel will measure 3.0 cm x 2.0 cm x 3.0 cm. To minimize chemical shift displacement effects, high bandwidth (2.2 kHz) frequency modulated refocusing pulses will be used. GABA concentrations will be quantified in institutional units (i.u.) as the ratio between the GABA integral and the water integral multiplied by a constant factor that accounts for estimates of the T1 and T2 of water and GABA protons, estimates of the MR-visible water concentration and editing efficiency, and the number of scans in the experiment Quantification of GABA levels will be done in Matlab (The Mathworks, Natick, MA) using in-house software code.

5.10 Pain Phenotyping Measures

A. Self-report questionnaires:

Pain Distribution Measure - A modified version of the Wolfe Regional Pain Scale will be used in this study that queries for the existence of pain in 19 regions of the body using a checklist that allows for efficient scoring. For this study, a modified version of the Regional Pain Scale [34] will be used. This scale has been shown to differentiate types of pain in a large registry of over 12,000 individuals with rheumatic disorders. A second brief measure helps in differentiating "central" pain versus "peripheral" pain.

Average Clinical Pain at baseline will be assessed using the pain severity scales of the Brief Pain Inventory (BPI)[35]. The BPI, validated for use in chronic non-malignant forms of pain, asks patients to rate their current pain intensity as well as their worst, least and average pain in the last 24 hours on a 0-10 rating scale.

Pain Qualitative Characteristics. The PainDETECT is a brief 9-item measure of sensory descriptors, spatial, and temporal characteristics that has demonstrated utility in identifying central neuropathic components of pain in low back pain and in OA[6]. The PainDetect will be used in combination with a body map defining the distribution of pain.

Centrally-mediated Symptom Clusters. Given the potential patient burden associated with rigorously evaluating multiple symptom domains, this study will take advantage of the static short forms developed by the NIH roadmap initiative PROMIS. The following PROMIS short-forms will be used in this study: PROMIS-Fatigue (7-items), PROMIS-Depression (8-items), PROMIS-Anxiety (8-items), PROMIS-Sleep Disturbance (8-items), PROMIS-Wake Disturbance (8-items)(www.NIHPROMIS.org).

WOMAC: The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) will be used to assess clinical health status relevant to OA outcomes. The WOMAC is a self-administered instrument that yields a total score and subscale scores for (1) Pain, (2) Stiffness, and (3) Physical Function[36] and has an intraclass coefficient of 0.69 for pain at rest and 0.63 for pain on weight bearing in knee osteoarthritis patients[37] as well as an intra-rater coefficient of 0.73 and an inter-rater co-efficient of 0.80 in hip osteoarthritis patients [38].

SF-36 Questionnaire (SF-36): The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It measure 8 varied concepts of health: physical functioning, role limitations due to physical problems, bodily pain, general health, energy/vitality, social functioning, role limitations due to emotional problems, and mental health. Question responses are pooled to calculate sub-scales for each of these 8 domains. The SF-36 pain scale has an intra-rater coefficient of 0.77 and an inter-rater co-efficient of 0.75 in hip osteoarthritis patients [38].

Affective disease:

Anxiety Symptoms: In this trial anxiety will be assessed with the State-Trait Personality Inventory (STPI). This scale is an 80-item self-report questionnaire with eight 10-item scales for measuring state and trait anxiety, anger, depression, and curiosity. For purposes of this study, a subset of 10 items will be used that assesses state anxiety. The STPI possesses strong psychometric properties for the assessment of mood symptoms given the items have been well validated as parts of larger instruments such as the State-Trait Anxiety Inventory and the State-Trait Anger Inventory[39].

Depression: Several psychiatric conditions are known to influence pain report and are often present in pain patients. In this trial, depressive symptoms will be assessed with the Center for Epidemiological Studies Depression Scale (CES-D). This is a 20-item self-report instrument that was developed by the National Institute of Mental Health to detect major or clinical depression in adolescents and adults in both clinical and normal populations. The CES-D has 4 separate factors: Depressive affect, Somatic symptoms, Affect and cognitions, and Interpersonal relations. The questions are easily interpreted and address most of the areas included in the diagnostic criteria for depression. The CES-D has been used in urban and rural populations, and in cross-cultural studies of depression. Studies using the CES-D indicate that it has very good internal consistency and validity[40].

B. Experimental Pain testing: This will be performed using the Multimodal Automated Sensory Testing (MAST) System, a quantitative sensory testing device developed at the University of Michigan, and currently being employed in several clinical trials, including the NIH MAPP Network. Instructions for both study personnel and participants will be scripted. Participants will perform several practice sessions before testing to become familiarized with the procedures and equipment. The MAST System features a control computer that coordinates testing protocols and program execution. Operators are able to custom configure the testing algorithm and monitor test progress in real-time.

Mechanical Pain Sensitivity (MPS): Pain sensitivity will be assessed by applying discrete pressure stimuli to the thumbnail bed. We have extensive experience using

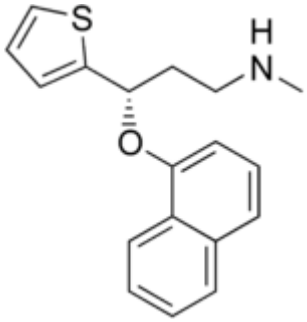
thumbnail pressure as an evoked pain stimulus. The MAST system will deliver an ascending series of 5-s duration stimuli at 25-s intervals, beginning at 0.25 kg/cm^2 and increasing in 0.25 – 0.50 kg/cm^2 intervals up to tolerance or to a maximum of 10 kg/cm^2 to the patients' dominant thumbnail. Pain intensity will be rated after each stimulus on a 0-100 numerical rating scale with 0 representing "no pain" and 100 representing "extreme pain". These ratings will be used to compute pain threshold and a psychophysical function of each subject's suprathreshold pain sensitivity. The procedure requires approximately 10 min to complete.

Diffuse Noxious Inhibitory Control (DNIC): DNIC will be induced and tested by painful pressure delivered via two MAST System thumbnail stimulators positioned on opposite thumbs. The test stimulus will be applied continuously for 30-s to the dominant thumbnail at a pressure intensity determined during PPT evaluation to elicit moderate pain. The conditioning stimulus will be applied to the opposite thumbnail at the same pressure intensity. DNIC magnitude is calculated as the difference in the mean of the three pain ratings given prior to the conditioning stimulus, and the three pain ratings given during the conditioning stimulus.

6. 0 PHARMACEUTICAL INFORMATION

6.1 Name and chemical name, molecular formula, drug classification

Duloxetine (**Cymbalta**) is a serotonin-norepinephrine reuptake inhibitor manufactured and marketed by Eli Lilly. The empirical formula is C18H19NOS•HCl, which corresponds to a molecular weight of 333.88. The structural formula is:



6.2 Mode of action

Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.

6.3 Description

Cymbalta® (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate,

6.4 How supplied

Cymbalta is available as delayed release capsules in the following strengths, colors, imprints, and presentations:

Features	**Strengths**			
	20 mg[a]	**30 mg[a]**	**60 mg[a]**	
Body color	Opaque green	Opaque white	Opaque green	
Cap color	Opaque green	Opaque blue	Opaque blue	
Cap imprint	Lilly 3235	Lilly 3240	Lilly 3237	Lilly 3270
Body imprint	20mg	30mg	60mg	60mg
Capsule number	PU3235	PU3240	PU3237	PU3270
Presentations and NDC Codes				
Bottles of 30	NA	0002-3240-30	0002-3237-30	0002-3270-30
Bottles of 60	0002-3235-60	NA	NA	NA
Bottles of 90	NA	0002-3240-90	NA	NA
Bottles of 1000	NA	0002-3240-04	0002-3237-04	0002-3270-04
Blisters ID†100	NA	0002-3240-33	0002-3237-33	0002-3270-33

[a] equivalent to duloxetine base
† Identi-Dose® (unit dose medication, Lilly)

6.5 Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [*see* USP Controlled Room Temperature].

6.6 Method and Route of administration

Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

6.7 Potential drug interactions

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

6.7.1 Inhibitors of CYP1A2

When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the Cmax was increased about 2.5-fold, and duloxetine t1/2 was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin.

6.7.2 Inhibitors of CYP2D6

Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine).

6.7.3 Dual Inhibition of CYP1A2 and CYP2D6 14

Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax.

6.7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued.

6.7.5 Lorazepam

Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

6.7.6 Temazepam

Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

6.7.7 Drugs that Affect Gastric Acidity

Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may

slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

6.7.8 Drugs Metabolized by CYP1A2

In vitro drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg twice daily).

6.7.9 Drugs Metabolized by CYP2D6

Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg twice daily) in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold.

6.7.10 Drugs Metabolized by CYP2C9

Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

6.7.11 Drugs Metabolized by CYP3A

Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

6.7.12 Drugs Metabolized by CYP2C19

Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

6.7.13 Monoamine Oxidase Inhibitors

The concomitant use of Monoamine Oxidase Inhibitors is not recommended**.**

6.7.14 Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other SSRIs, SNRIs or tryptophan is not recommended.

6.7.15 Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically

warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increase.

6.7.16 Alcohol

When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol. In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen.

6.7.17 CNS Drugs

Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action

6.8 Toxicology and Adverse Effects

6.8.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis — Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m2 basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m2 basis) did not increase the incidence of tumors.

Mutagenesis — Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility — Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m2 basis) did not alter mating or fertility.

6.8.2 Adverse Effects

Chronic Pain due to Osteoarthritis — Approximately 16.3% (39/239) of the patients who received duloxetine in 13-week, placebo-controlled trials for chronic pain due to OA

discontinued treatment due to an adverse reaction, compared with 5.6% (14/248) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 2.9%, placebo 0.8%) and asthenia (duloxetine 1.3%, placebo 0.0%). Pooled Trials for all Approved Indications — The most commonly observed adverse reactions in Cymbalta-treated patients (incidence of at least 5% and at least twice the incidence in placebo patients) were nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis.

Vital Sign Changes

In placebo-controlled clinical trials across approved indications for change from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.07 mm Hg in systolic blood pressure and 0.62 mm Hg in diastolic blood pressure compared to mean decreases of 1.31 mm Hg systolic and 0.73 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure.

Duloxetine treatment, for up to 26 weeks in placebo-controlled trials across approved indications, typically caused a small increase in heart rate for change from baseline to endpoint compared to placebo of up to 1.40 beats per minute.

Weight Changes

In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In studies of DPNP, FM, OA, and CLBP, patients treated with Cymbalta for up to 26 weeks experienced a mean weight loss of approximately 0.6 kg compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In one long-term fibromyalgia 60-week uncontrolled study, duloxetine patients had a mean weight increase of 0.7 kg. In one long-term CLBP 54-week study (13-week, placebo-controlled acute phase and 41-week, uncontrolled extension phase), duloxetine patients had a mean weight decrease of 0.6 kg in 13 weeks of acute phase compared to study entry, then a mean weight increase of 1.4 kg in 41 weeks of extension phase compared to end of acute phase.

Laboratory Changes

Cymbalta treatment in placebo-controlled clinical trials across approved indications, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients.

Electrocardiogram Changes

Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13 weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg twice daily, no prolongation of the corrected QT interval was observed.

7.0 Statistical Considerations

7.1 Study Design and Endpoints

The research team will correlate MRS measures (GABA and Glx) with clinical pain response to duloxetine intervention in KOA subjects using a longitudinal study design. The primary endpoints are clinical pain levels as measured by pain questionnaires (WOMAC). Secondary endpoints are follow-up MRS GABA and Glx measures and experimental pain measures.

7.2 Objectives and Analysis Plans

The null hypothesis is that there is no association between the MRS parameters (Glx and GABA) with the change in WOMAC pain score; the alternative hypothesis is that there is an association. We will fit general linear models, with the dependent variable being the change in WOMAC pain score (pre-treatment minus post-treatment), and the independent variables being patient age, depression score, anxiety score, baseline WOMAC pain score, and each of the two MRS scores of GABA and Glx (separate models for each). We will also include two-way interaction terms, as the sample size permits. To test for normality of the change in WOMAC pain scores, we will examine Q-Q plots of the data, or other similar plots; standard transformations will be considered if the data differ markedly from a normal distribution. The fit of the model will be evaluated using various standard methods including an examination of residual values and estimation of the coefficient of determination A t-test, or partial test, will be used to determine if the regression coefficient for the MRS score differs from zero, after controlling for the other variables in the model. A significance level of 0.025 will be used for each MRS score (two-tailed test).

A similar model will be fit to test whether the change in WOMAC pain score is correlated to the change in MRS score (pre-treatment minus post-treatment). We will fit generalized linear models, with the dependent variable being the change in WOMAC pain score (pre-treatment minus post-treatment), and the independent variables being patient age, depression score, anxiety score, baseline WOMAC pain score, and the change in the MRS scores.

7.3 Sample Size Considerations

The following table summarizes the sample size required to detect various correlations between MRS scores and change in WOMAC scores as a function of the lost to follow-up rate [41].

	# pt if no lost to FU	# pts if 10% lost to FU	# pts if 20% lost to FU	# pts if 30% lost to FU
r=0.1	422	465	507	549
r=0.2	106	117	128	138
r=0.3	47	52	57	62

With 80% power and 2.5% type I error rate (two-tailed), 128 patients would be needed to detect a correlation of 0.2 or greater, assuming an 80% follow-up rate.

For the proposed modeling, which includes at least 5 possible predictors per model, a sample size of 128 would be adequate to avoid overfitting.

8.0 Adverse Events; Safety Issues

Adverse events (AEs) are a routine part of every clinical trial. There is language available that you may copy and paste into this overview and the following sections. However, it is critical to determine how AEs are managed at your institution and to utilize institution-specific language.

7.1 Definition of Adverse Events and Potential Risks (1. Comprehensive Adverse Events and Potential Risks List and 2. Agent Specific Adverse Events List)

7.2 Definition of Serious Adverse Events (Serious Adverse Events List)

A Serious Adverse Event (SAE) is an injury or illness that:

Causes death

Is life threatening, even if temporary in nature

Results in permanent impairment of a bodily function or permanent damage to a body structure

Necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure

An increased level of care (e.g., unscheduled admission, transfer from a routine inpatient bed to an intensive care unit, etc.).

Events meeting the criteria for an SAE require notification of the sponsor and the reviewing IRB within the specified timeframe identified in section 8.4.1.1.

7.3 Adverse Events Characteristics

7.3.1 Grading of Adverse Events

7.3.2 Definition of Expected / Unexpected (Anticipated / Unanticipated) Adverse Events

7.3.3 Attribution of Adverse Events

Attribution of the AE:

Definite – The AE *is clearly related* to the study intervention.
Probable – The AE *is likely related* to the study intervention.
Possible – The AE *may be related* to the study intervention.
Unlikely – The AE *is doubtfully related* to the study intervention.
Unrelated – The AE *is clearly NOT related* to the study intervention.

7.4 Adverse Event Reporting

7.4.1 When and How to Report Adverse Events

It is the responsibility of the investigator to document all Adverse Events (AEs) which occur during the course of the study.

7.4.1.1 Expedited Adverse Event Reporting

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

7.4.1.2 Protocol-specific Expedited Adverse Event Reporting Exclusions

7.4.1.3 Routine Adverse Event Reporting

8.0 Ethical Considerations (Including Informed Consent)

[Note to CTMW Participants: In addition to the relevant sections below (8.1 to 8.5), fill out the 2-page "Template For Basic Elements of Informed Consent" at the end of this Word document.]

8.1 Protection of Patient Rights

The risk of the MR procedure itself is minimal particularly since no contrast is to be administered which has the potential of allergic reaction. Patients will be screened to ensure no contraindications for MRI (such as pacemakers). Trained technologists will perform the studies and trained medical personal will be present in the event of unexpected outcome. Crash cart resources are present located just outside the MR scanner suite. The MR imaging suite is located in the hospital with access to medical care if necessary.

The risk of duloxetine treatment is low. The most common complications associated with duloxetine are generally mild and include: nausea, fatigue, and constipation. More serious problems such as gastric ulcer, suicide attempt and myocardial infarction are infrequent. Subjects will be screened including baseline liver and renal labs to ensure no contraindications to duloxetine or potential interactions with existing medications.

Questionnaires: Subjects may refuse to answer any question on the questionnaires or surveys if they find the questions too probing or uncomfortable to answer.

Blood drawing: Only individuals skilled in the process of blood drawing will be used to take your blood sample. Pressure will be applied to the site to reduce the risk of bruising. Sterile technique will be used to reduce the risk of infection.

Tender Point/Dolorimeter Exams/Pressure Pain Testing: Researchers have been educated in how to perform these tests safely. The research subject may stop the tests at any time if the test becomes too uncomfortable.

8.2 Confidentiality

We will not identify data collected during the subject's participation in this study with personal identifying information. Data collected during this study will be kept either in a locked file cabinet or a password-protected database.

8.3 Inclusion of Women and Minorities

The racial, gender and ethnic characteristics of the proposed subjects reflect the demographics of the patient population of the surrounding area. However, extra efforts will be made to recruit women and minorities. Children will be excluded from the study. No exclusion criteria shall be based on race, ethnicity, or gender.

8.4 Audit and Monitoring

This study uses a longitudinal, multi-point interaction with the research subjects with low risk to participants. Subjects will be monitored for adverse events and side-effects during the follow-up clinical appointments with the pain physician. In the unlikely occurrence of an adverse event felt to be related to the study protocol, it will be reported to the University of Michigan IRB and R & D service. If subjects are judged to be experiencing an adverse event from the study and are clinically stable, they will be referred back to their primary care physician for further evaluation and follow-up. If the subject is considered to be clinically unstable, the subject will be referred to the closest emergency room. A monthly meeting will be held with the PI, co-PIs and study coordinators to review and ensure the integrity of the collected data.

9.0 Data Management; Administrative Issues

Brief description of how data (including image data) will be collected and where it will be stored.

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11.0 APPENDICES

11.1 Glossary of Terms

11.2 Case Report Forms

11.3 Informed Consent Document

RSNA Clinical Trials Methodology Workshop

Template For
Basic Elements of Informed Consent
45 CFR Part 46.116 (A)

Your Informed Consent document must address the 8 basic elements listed in Section a below. The first 4 elements will be specific to your protocol. Text approved by your local IRB for the last 4 elements should be available from your institution.

Your Informed Consent document should also address the 6 additional elements listed in Section b below, if they are relevant to your clinical trial.

For purposes of the RSNA CTMW, please write a few sentences for each of the 8 basic elements, and any of the 6 additional elements that are relevant, in language understandable by the potential subjects for your clinical trial.

"§46.116 General requirements for informed consent.

No investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Section (a):

1. **Statement that study involves research; explanation of purpose(s) and expected duration of participation; description of procedures and identification of experimental procedures.**

To look for brain metabolites and pain measures in people with knee osteoarthritis before and after administration of duloxetine. Duloxetine is a FDA approved pain medication for the treatment of osteoarthritis. Brain metabolites are naturally occurring compounds in the brain that are responsible for brain activity and brain structure. We will use 3 Tesla magnetic resonance (MRI) scanner to look at specific

metabolites that are thought to be involved in pain conditions such as knee osteoarthritis. We will compare the brain metabolites of people with ALS to those of people who do not have ALS and are healthy volunteers. You will be enrolled in the study for 9 weeks. You will have a baseline MRI test, pain pressure testing and questionnaires. You will then be administered duloxetine, a pain medicine for a period of 8 weeks. You will have 2 follow-up appointments with the pain physician to assess for potential side-effects. At the end of the study, you will have a follow-up MRI, pain pressure testing and questionnaires.

If you meet the criteria for knee osteoarthritis and agree to participate in this study, you will:

Have a registration visit at the Clinical Fatigue and Pain Research Center that will last approximately one hour and will include: Informed consent process, review of clinical and laboratory data and MRI safety screening. You will also be screened for study inclusion and exclusion criteria. If the liver or renal laboratory tests obtained for clinical care are not available within 35 days of the scheduled initiation of duloxetine, then the liver or renal laboratory testing will be ordered. The serum sample will be obtained by a certified phlebotomist or other qualified medical professional as a study procedure. The coordinator will schedule the pain testing and research MRI examination and review the pre-testing and pre-MRI instructions.

Have a baseline testing visit (a measurement to serve as the basis to compare later measurements) at the Clinical Fatigue and Pain Research Center that will last approximately 2 hours and will include: pressure pain testing (approximately 20 minutes, see description below), a tender point exam and dolorimeter exam (see dolorimeter exam, below). The below tests will be repeated at the end of 8 week trial of duloxetine.

- Be given a dolorimeter examination to test your pain sensitivity wherein varying degrees of pressure will be applied to four different portions of your body. To do this, the research assistant will place a pressure gauge with a rubber tip on your skin around various sites on your body. Pressure will be applied to each of these sites slowly. You will be asked to state when this pressure begins to cause discomfort. When the pain at a site becomes intolerable, the gauge will be removed and another area of your body will be tested. The exam will take about 5 minutes to perform. In addition you will be given a tender point exam as part of the diagnostic criteria for fibromyalgia and to assess your sensitivity to pressure. This is a standard clinical procedure during which the researcher will apply pressure with his (her) thumb to specific pre-established points on your body. You will tell the researcher whether the pressure results in pain or tenderness. This test will be performed at baseline, prior to each MRI scan and at the study close-out visit.

- Have your sensitivity to pressure assessed by conducting a series of pressure sensitivity tests. For pressure testing, we will apply 2 sequences of different 5-second pressures to your thumbnails. The first sequence will determine the

range of pressures you find tolerable. This range will be determined by starting with a very low intensity of pressure, and increasing step by step, according to your rating of pain intensity. The second pressure sequence will apply pressures of random intensities based on the ratings you gave in the first sequence. The entire pressure pain testing session will last approximately 20 minutes. This testing will occur at baseline prior to the MRI scan and at the study close-out visit.

- Be asked questions regarding the overall quality and intensity of your pain. In addition you will complete survey questionnaires and maintain a record of medications and other treatments used during the study period.

Have a Magnetic Resonance Imaging (MRI) scans taken at the University of Michigan University Hospital Department of Radiology: one at baseline and one following the duloxetine treatment. The MRI scan will include MR spectroscopy which is a recent research method, which makes it possible to observe metabolites in the brain. This technique is non-invasive and requires you to lie motionless in the scanner for 40 to 45 minutes.

Have two follow-up visits at 2 weeks and 6 weeks following the start of duloxetine with the pain physician for a history and physical to assess for side effects. A questionnaire will be administered at both time points to assess for severity of pain.

Females of childbearing potential will be required to undergo urine pregnancy testing.

2. Description of risks or discomforts to subject.

The known or expected risks are:

Duloxetine: The most common complications associated with duloxetine are generally mild and include: nausea, fatigue, and constipation. More serious problems such as gastric ulcer, suicide attempt and myocardial infarction are infrequent.

Blood draw: There is a small chance of pain, infection or clotting into the area from which the blood was taken; more rarely, serious skin infections or nausea and vomiting may occur. If persisting pain or redness in the area is noted, this may require medical or surgical treatment. Withdrawing blood may also induce lightheadedness or fainting.

MRI:

- There are known risks to the magnet's ability to pull metal objects toward it. This pull can cause metal objects in the body (e.g., surgical clips or staples) to move, causing bleeding or disruption of surrounding tissue. Metal objects carried or worn by a person (e.g., jewelry, hair clips, tools) can be pulled

toward the magnet; if they are free to fly through the air there is the danger that someone could get hurt if the moving object struck them. The MRI can cause pacemakers or stimulators implanted in the body to malfunction. There is also a risk that metallic objects in or on your body may be heated by the radio waves, possibly causing burns.

- The MRI scanner is tunnel-shaped and has a diameter of about one and one-half-feet. There is a minor risk of discomfort or anxiety from being in the confined space of the MRI scanner. The MRI is known to produce a rhythmic and loud noise. It is extremely important that you lie still throughout the MRI procedure.
- There is the potential that a MRI scan may reveal an abnormality that is already in your brain, such as a cyst or tumor. Many such abnormalities are not medically significant, but you may want to investigate them further.

  Such a finding might require additional studies, and maybe even treatment, neither of which would be paid for by the investigators, the sponsor, or the University of Michigan.
- No adverse effects from the static magnetic field have been reported in people. However, there could be unknown risks. In particular, because the risk to the fetus is not known, women who are pregnant or think they may be pregnant are excluded from the study.
- You may experience some discomfort or pain while lying in one position in the MRI scanner.

Questionnaires: Some questions may be
may cause discomfort. You will not be required to submit any personal identifying information on the questionnaires.

Tender Point / Dolorimeter Exams: The tender point exam may cause discomfort at the testing sites and the dolorimeter exam may result in discomfort or bruising at the site of testing.

Pressure Pain Testing: You may feel immediate discomfort and some possible short-term thumb tenderness.

3. Description of benefits to subject or to others.

You may not receive any personal benefits from being in this study nor will you be informed of any specific research results. However, it is possible that you may experience a reduction or elimination of symptoms due to duloxetine. The information obtained from your taking part in this research study may help to benefit others in the future and may be used in future research studies.

4. Disclosure of alternative procedures, if appropriate.

5. Description of the extent to which confidentiality will be maintained.

6. For research involving more than minimal risk, explanation as to whether compensation and medical treatments are available if injury occurs.

7. Explanation of whom to contact if questions arise about the research or the subjects' rights or whom to contact if research-related injury occurs.

8. Statement that participation is voluntary, that refusal to participate involves no penalty or loss of benefits, and that subject may discontinue at any time.

Section (b):
Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects to be involved in the study."