



RESEARCH CONSENT FORM

Protocol Title: DULOXETINE FOR TREATMENT OF PAINFUL TEMPOROMANDIBULAR JOINT DISORDER

Study No.: HP-00040504

Principal Investigator: Dr. Sharon M Gordon DDS, MPH, PhD

Sponsor: Eli Lilly and Company

You are invited to be a part of this research study because you have chronic facial pain. Chronic facial pain may be linked to Temporomandibular Joint Disorder (TMJD), which currently has no standard treatment. The purpose of this study is to see if the study drug duloxetine relieves pain of temporomandibular joint dysfunction. Before making the decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study.

If you are not completely truthful with your study doctor regarding your health history and medications, you may harm yourself by participating in this study.

The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. This form describes the study in order to help you decide about participating in the study. Please read this form carefully and ask the study dentist or study staff about anything in this form that you have questions about or do not understand. Do not sign this form unless you are satisfied with the answers to your questions and decide to be part of this study. This form describes the study to help you decide about participating in the study. You will receive a copy of this form.

PURPOSE OF STUDY

The purpose of this study is to test duloxetine (Cymbalta) as a potential treatment for chronic facial pain. Duloxetine is an antidepressant also approved by the United States Food and Drug Administration (FDA) for the treatment of chronic pain of diabetic nerves and fibromyalgia.

PROCEDURES

Your participation in this study is voluntary. The research will be conducted at the University of Maryland Baltimore UMB dental clinics. In order to participate in this study you must be at least 18 years of age or older and must have chronic facial pain for over 2 weeks. This study will test the pain relieving effect of the study drug (duloxetine) in comparison with placebo (a look alike inactive drug) at baseline and follow up for a six week period. The duration of this study is six weeks. You will have four scheduled clinic visits and three phone calls.



A) **FIRST VISIT:** This is a screening and baseline visit.

Screening Visit

The following procedures will occur during the screening visit:

- 1) You will be given a copy of this Consent Form and have it explained to you so that you understand the purpose of the study and what participation involves. If you have questions at any time during the research study, you should feel free to ask them and should expect to be given answers that you completely understand. After all of your questions have been answered, if you still wish to take part in the study, you will be asked to sign this form. You will be given a copy of the signed form to keep.

- 2) We will determine your eligibility to participate in this study by reviewing your detailed medical and dental history, pain history and your current medications.

- 3) If you are a female of child bearing potential and you are post-menopausal for less than two years you must be willing/using a medically approved method of contraception (i.e., oral, transdermal or implanted contraceptive devices, intrauterine device, diaphragm, condom, abstinence, or surgical sterility) during the entire course of the study. You must not be pregnant or breast feeding to be a part of this study. A urine pregnancy test will be taken at the initial visit and at the follow up visits.

Baseline

After you consent to participate and meet all the eligibility criteria we will provide you with the study medication and instructions. You may get the study drug or the placebo (matching pills with inactive substance). Which one you receive will be determined randomly (like the flip of a coin). You will have 50/50 chance of receiving duloxetine or placebo. This study is double blind, which means that neither you nor your study doctor will know whether you are taking duloxetine or placebo. However, this information can be obtained in case of an emergency. We will also provide acetaminophen (like Tylenol), which you might take if pain is not controlled adequately with the study drug.

1. **Questionnaires:** We will ask you to fill out questionnaires to help us understand your personality, how you cope with problems, and how you feel about yourself. Other questionnaires will ask about your mood, and your emotional well being. Also some questionnaires ask how you are feeling at the present or how you have felt over the last week or two. These surveys will be completed during your clinical visit.

2. **Clinical Examination:** We will do a head and neck and muscle exam. You will be seated in a dental chair and a dentist or clinic examiner will use their hands to apply pressure to muscles on your face, jaw, neck, shoulders, and arms. Two muscles and one tendon inside of your mouth will also be tested. For another part of the exam you will stand while the examiner presses on your hip, legs, and back. You will be asked to tell the examiner if you feel pain at each spot. We will also measure your body weight, height, blood pressure and heart rate.



3. Pressure Sensations: We will apply pressure to some muscles on your face, jaw joint, shoulder, and forearm. You will be asked to tell the examiner when you begin to feel discomfort or mild pain. As soon as you tell us you feel pain, the pressure will be removed.

You will be asked to participate in a substudy to collect blood samples. Blood collected for the purposes of this study will be tested for genetic markers, which may be related to pain and pain relief. This substudy is optional and is explained in a separate consent document. If you do not agree to participate in the substudy, you can still participate in the main study.

4. Pain Diary: You will be sent home with pain diary for you to complete daily during the entire length of the study (6 weeks). This diary needs to be completed in the upon awakening in the morning prior to taking any medications or using any caffeinated drinks. Data on your pain experience will be captured by the diary, including present pain at rest, pain over the last 24 hours, and worst and least pain during the last 24 hour period.

You will be sent home with a supply of study drug which you will bring back to your follow up visits.

B) FOLLOW UP VISITS: You will have a follow up visit on weeks 1, 3 and 6. During these follow up visits we will do the physical assessments as during the initial visit and update your medical, dental history and your medications. We will also perform a urine pregnancy test, if necessary. We will ask you about any side effects and collect your pain diary and check your study pills.

On your final visit on week 6 we will also collect your pain diary and any unused study drugs. We will call you a week after discontinuing from the drug to check how you are feeling.

C) FOLLOW UP PHONE CALLS: We will call at a scheduled time on weeks 2, 4 and 5 to check how you are feeling.

During the course of the study you will have 24/7 access to the study doctor via pager. You will need to report any changes in your general health condition, hospitalizations etc. even if it is not relevant to the study medication.

POTENTIAL RISKS/DISCOMFORTS:

There may be risks to you if you participate in this study. Potential risks associated with your participation relate primarily to the study drug duloxetine and the rescue pain medication acetaminophen. Duloxetine safety and efficacy data comes from studies of participants with depression, anxiety, pain and other studies. Duloxetine safety data also comes from over 9 million people who have taken duloxetine outside of clinical studies.



Risks and discomforts associated with duloxetine:

The following adverse events were reported from clinical trial data and are rated as very common, common, uncommon. Many of these events were also reported outside of clinical trials.

Very common side effects:

Very common (reported by at least 1 out of 10 people taking duloxetine, or greater than or equal to 10%) unpleasant experiences were: Difficulty having a bowel movement (stool), feeling sick to the stomach, headache, dry mouth, and feeling weak or tired.

Common side effects: Common (reported by between 1 out of 100 people taking duloxetine, or greater than or equal to 1% but less than 10%) unpleasant experiences were: dizziness, feeling slow or sluggish, sleepiness/excessive sleep, having trouble sleeping, diarrhea, stomach pain, intestinal gas, heavy sweating, chills, vomiting, decreased or loss of appetite, uncontrolled shaking, uneasiness and uncertainty and fear, blurry vision, loss of or decreased sex drive, aches and joint pains, abnormal skin feelings (burning, tingling, itching), weight loss, abnormal sleep, yawning, feeling jittery, feelings of irregular or forceful beatings of the heart, difficulty or failure to experience orgasm, excessive feeling of annoyance or frustration, reddening of the face, indigestion, and unusual taste in mouth.

Uncommon side effects:

Uncommon (reported by fewer 1 out of 100 people taking duloxetine, or less than 1%) unpleasant experiences were: abnormal blood test results that may indicate liver damage, blood cholesterol increased (fatty substances in the blood), menopausal symptoms, feeling abnormal, night sweats, poor quality of sleep, blood pressure increased, enlargement (increased size of eye pupils and abnormal vision, muscle tightness, fast heart rate, ear ache and ringing or booming sensation in one or both ears, ejaculation disorder, erectile dysfunction, muscle twitching, sudden involuntary jerks or twitches of the muscle, generalized state of discomfort, tiredness or illness, confusion, loss of interest, abnormal dreams, difficulty or painful urination, cold sweats, fluid loss, slow or hesitation in urinating, inability to urinate, passing a lot of urine, poor urine steam, waking at night with a need to urinate, low levels of thyroid, sore/hoarse throat, bad breath, mouth irritation grinding or clenching of teeth, feeling cold, feeling hot, belching, thirsty, stomach irritation, digestive system irritation, throat tightness, abnormal voluntary muscular movements, abnormal walk, unusual urine smell, skin sensitive to light, trouble focusing, low blood pressure upon standing and cold hands and feet, weight gain, allergic skin reactions after contact with irritant, and sexual problems.

Discontinuing duloxetine

In Eli Lilly clinical research studies, after slowly or suddenly discontinuing duloxetine treatment some subjects experience unpleasant events including the following: feeling weak or tired, dizziness, headache, feeling sick to the stomach, having trouble sleeping, diarrhea, abnormal skin



feelings (burning, tingling, and itching), vomiting, uneasiness and uncertainty and fear, irritability, heavy sweating, feeling like objects are moving around and abnormal dreams.

The other risks in the section below come from clinical trial data and from data outside of clinical trials.

Events reported outside of clinical trials

Some patients outside of clinical trials also reported the following adverse events: lockjaw, bruising, aggression and anger (particularly early in treatment or after stopping treatment) and ringing or booming sensation in or both ears when stopping treatment.

Monoamine oxidase inhibitors (MAOIs) and other medications

The use of certain medications along with duloxetine can lead to serious and sometimes fatal side effects. Please inform the study doctor or study staff of any new prescription medications, over the counter medications, or herbal remedies that you may be using.

Do not take duloxetine if you are currently taking thioridazine or a monoamine oxidase inhibitor (MAOI). Do not take duloxetine if you have taken an MAOI within the last 2 weeks or plan to take an MAOI within 5 days after the last dose of duloxetine.

Mydriasis and narrow-angle glaucoma

Enlarged (increased size) of the eye pupil (mydriasis) was uncommon in clinical trials. Increased eye pressure (glaucoma) was seen in some patients outside of clinical trials.

Patients with increased eye pressure, controlled narrow-angle glaucoma or those at risk of acute narrow-angle glaucoma should use caution when taking duloxetine.

Suicide

Duloxetine is an antidepressant. Patients with depression may experience worsening of their depression emergence of suicidal thinking and behavior or unusual changes in behavior.

Antidepressants may increase the risk of suicidal thinking and behavior in children, adolescents and young adults with depression and other psychiatric disorders. As with other antidepressants, cases of suicidal thinking and behaviors have been reported during duloxetine therapy or early after treatment discontinuation. Consider these risks when taking this medicine for depression or other psychiatric or nonpsychiatric conditions.

Tell your study doctor immediately if you have any troubling thoughts or feelings at any time. You should watch for uneasiness, uncertainty and fear, excessive feeling of annoyance or frustration, having trouble sleeping, irritability, hostility or aggressiveness, being quick to act without considering the results, restlessness with difficulty sitting, excessive or raving type behavior, as well as suicidal thinking, and to report such symptoms immediately to the study doctor. You may choose to inform your family or caregiver to be alert for these signs and symptoms.



Effects on blood sugar

Some patients on duloxetine have increased blood sugar, particularly patients with diabetes. Furthermore, in patients with diabetes and diabetic nerve damage, the use of duloxetine appears to be related to a small increase in fasting blood sugar and hemoglobin A1c. Hemoglobin A1c is an important measure of long-term diabetic control. All patients with diabetes should adequately monitor blood sugar.

Heart rate and blood pressure

Subjects taking duloxetine can occasionally have a feeling of rapid heartbeats. Duloxetine has been associated with a rise in blood pressure in some people; subjects taking duloxetine should have their blood pressure periodically monitored. Some subjects taking duloxetine, especially when first starting the drug, can experience a drop in blood pressure upon standing which may result in feeling light-headed or in fainting.

Hypersensitivity and skin reactions

Duloxetine should not be taken if you have a known allergy or hypersensitivity to duloxetine hydrochloride or any inactive ingredient. Allergic reactions with duloxetine include hives, rash, rapid skin or tissue swelling, and a severe allergic reaction. Some subjects have experienced a serious skin reaction called Stevens-Johnson syndrome (SJS) have been reported among subjects taking duloxetine. Symptoms of SJS start with a rash that spreads and develops into blisters and possible peeling of skin that could affect other body organs and lead to serious complications.

Kidney disease

Individuals with severe kidney or liver diseases may build up excessive levels of duloxetine in the blood stream, possibly causing a greater number of side effects or serious side effects.

Serotonin Syndrome

One of the ways that duloxetine treats illnesses is by increasing serotonin, a chemical in the brain and other parts of the body. If there is too much serotonin, a condition called serotonin syndrome may develop. Symptoms of serotonin syndrome may include confusion, fever, heavy sweating, fast heart rate, rapid changes in blood pressure, excessive sweating, fast heart rate, rapid change in blood pressure, excessive feeling of annoyance or frustration, feeling jittery, constant muscle tightness, sudden involuntary jerks or twitches of the muscle, uncontrolled shaking, and restlessness with difficulty sitting still. Serotonin syndrome has been reported in some subjects taking duloxetine. One of the most important causes for serotonin syndrome is if duloxetine is given along with other drugs, which increase Serotonin. These drugs could include certain drugs used to treat pain (for example, tramadol), certain antidepressants and mood disorder drugs, and certain drugs used to treat migraines (for example, triptans).

Abnormal bleeding

As with other similar medications (SSRI's and SNRIs), duloxetine may increase the risk of bleeding events. The use of certain drugs with duloxetine may increase the risk of bleeding



events. Bleeding events related to SSRI and SNRI use have ranged from bruising, nose bleeds, internal bleeding to life threatening hemorrhages. Bleeding events related to SSRI and SNRI use have ranged from bruising, nose bleeds, internal bleeding to life-threatening hemorrhages.

Hallucinations and/or confusion

Subjects taking duloxetine and other similar medications have reported hallucinations and/or confusions.

Mania/hypomania

Subjects taking duloxetine and other similar medications have reported excessive or raving type behavior (mania or hypomania). Duloxetine should be used cautiously in subjects with a history of mania.

Seizures

Duloxetine and other similar medications (SSRI's) can cause subjects, especially those having or prone to having seizures, to have sudden attacks of the disorder. Duloxetine therefore should be used cautiously in subjects with a history of seizure disorder.

Overdose

In clinical trials, overdoses of duloxetine, alone or with other drugs, have been reported with none being fatal. Outside of clinical trials, overdose of duloxetine, usually when taken with other medications, have resulted in death at doses as low as 1000 mg (approximately 17 X60 mg tablets). Some of the signs of the overdose (duloxetine alone or with mixed drugs) are sleepiness/excessive sleep, serotonin syndrome, coma, seizures, fast heart rate, and vomiting.

Placebo risk

At any time during the study, you may experience a return or worsening of symptoms if you are on placebo. You will have acetaminophen to take home to use as a rescue analgesic for unrelieved pain.

Risks commonly associated with acetaminophen (Tylenol) are:

The most common side effects associated with the use of acetaminophen may include, but are not limited to: 1) lightheadedness, 2) dizziness, 3) allergic reaction, 4) skin rash, or 5) liver damage.

If you consume 3 or more alcoholic drinks every day, ask the study doctor whether you should take acetaminophen or other pain relievers/fever reducers because acetaminophen may cause liver damage. Taking more than the recommended dose (overdose) may cause liver damage

Other research related risks:

The possibility exists that other side effects that are unknown to us at this time could also occur. It is very important that you tell the study staff immediately about any side effects you



experience. Please call us if you think anything unusual has happened because of your study participation.

Survey questionnaires may include specific question about how you feel and about your life experiences. Reading or answering these questions may cause you some discomfort. Your participation in this study is completely voluntary and you may refuse to answer any question or stop at any time.

If you become pregnant while you are participating in this study, it could be dangerous for the baby. You must use birth control to be sure that you do not become pregnant. The only birth control methods that work well enough to be sure that you will not become pregnant are oral contraceptives ("the pill"), intrauterine devices (IUDs), contraceptive implants under the skin, or contraceptive injections, and condoms with foam.

The risks will be minimized by careful screening at the initial visit. In the instance of an allergic reaction to the study you have to discontinue the drug and report immediately to the study doctor and you will be treated symptomatically. You may have minimal risk of pain and discomfort during clinical examination.

Although we will make every effort to protect your confidentiality, there is always the possibility of a breach of confidentiality. We will minimize this risk by using subject codes instead of names on forms, keeping locked and coded files and limiting access to the file.

POTENTIAL BENEFITS

The benefits of participating in this study may be potential for pain relief. It is possible that the exam may identify an unknown dental condition requiring care. In this event we will inform you and provide a referral to an appropriate dental or medical provider. Your participation may help the investigators better understand the causes and risk factors of chronic TMJD and response to duloxetine. However, you may receive no benefit from participating.

ALTERNATIVES TO PARTICIPATION

The following alternative procedures or treatments are available if you choose not to participate in this study: The alternative is to not participate in this study and receive other potential treatments. If you are a student or employee of UMB, your decision to participate or not will have no bearing on your academic or employment status at UMB.

COSTS TO PARTICIPANTS

There is no cost for you to participate in this study. The study drug, study related procedures, study visits and parking will be provided at no charge to you or your insurance company.

PAYMENT TO PARTICIPANTS

If you enroll in this study, the tests and procedures are being performed for research purposes only. Your cost for participating in this project will be your transportation to and from the



University of Maryland Dental School. The University will cover the cost of parking on campus during the clinical research visit (up to 3 hours). You will be paid \$300 for your participation in this 6-week study as follows:

- 1) \$100 will be paid at the end of first 3 weeks: Payable as \$50 for completion of first two weeks and \$50 for the follow up visit.
- 2) \$200 will be paid at the end of second 3 weeks: Payable as \$50 for completion of each follow up phone call and \$100 at the final visit.

If you withdraw from the research project, or if the investigator terminates your participation prior to completion, you will be paid for the portions of the research project you have completed.

CONFIDENTIALITY

The data from the study may be published. However, you will not be identified by name. Your personal information will not be given out unless required by law. Everyone using study information will work to keep your personal information confidential. People designated from the institutions where the study is being conducted, the sponsor and the FDA (Food and Drug Administration) may inspect sections of your medical and research records related to the study.

RIGHT TO WITHDRAW

Your participation is voluntary. You may choose not to participate now or at any time without penalty or loss of benefits to which you are otherwise entitled. If you decide to stop participating in this study, if you have questions or concerns at any time, or if you need to report an injury related to the research, please contact: Dr. Sharon Gordon 410-706-6345 during the day and at 410-389-1432 after working hours.

In addition to the risks described in this form, there may be unknown risks/discomforts involved in participating in the study. Study staff will update you in a timely way on any new information that may affect your health, welfare, or decision to stay in this study. The investigator Sharon Gordon or sponsor can decide to withdraw you from the study at any time. You could be removed from the study for reasons related solely to you (for example, not following study-related directions from the Investigator, a treatment becomes available for you which may be better for you than the care available in the study, or you have a serious reaction during the study). Also, the entire study may be stopped by the sponsor, the Investigator, the Institutional Review Board, the facility where the study is being carried out, or the University. The sponsor may also decide to stop the Investigator's participation in the study. In that case, your participation will end unless another investigator is identified and approved by the sponsor and the Institutional Review Board.

If you are injured because of study participation, you will receive emergency medical care if needed and you will receive assistance in getting other medical care as needed. You or your insurance carrier will be billed for the cost of care, just as you would be billed for any other



medical care. If you incur uninsured medical costs, they are your responsibility. The study staff can give you more information about this if you have a study injury.

As a participant, you are not waiving any of your legal rights. You can seek legal compensation for any injury that may occur to you during the study as a result of an error by a member of the research staff, the sponsor, or others.

Members of the Institutional Review Board (IRB) or the Human Research Protections Office can answer your questions and concerns about your rights as a research subject.

The IRB office number is 410-706-5037.

UNIVERSITY STATEMENT CONCERNING RESEARCH RISKS

The University is committed to providing participants in its research all rights due them under State and federal law. You give up none of your legal rights by signing this consent form or by participating in the research project. Please call the Institutional Review Board (IRB) if you have questions about your rights as a research participant.

The research described in this consent form has been classified as greater than minimal risk by the IRB of the University of Maryland, Baltimore (UMB). The IRB is a group of scientists, physicians, experts, and other persons. The IRB's membership includes persons who are not affiliated with UMB and persons who do not conduct research projects. The IRB's decision that the research is minimal risk does not mean that the research is risk-free. You are assuming risks of injury as a result of research participation, as discussed in the consent form. If you are harmed as a result of the negligence of a researcher, you can make a claim for compensation. If you have questions, concerns, complaints, or believe you have been harmed through participation in this research study as a result of researcher negligence, you can contact members of the IRB or the staffs of the Human Research Protections Office (HRPO) to ask questions, discuss problems or concerns, obtain information, or offer input about your rights as a research participant. The contact information for the IRB and the HRPO is:

University of Maryland School of Medicine
Human Research Protections Office
BioPark I 800 W. Baltimore Street, Suite 100
Baltimore, MD 21201
410-706-5037



Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

If you agree to participate in this study, please sign your name below.

Participant's Signature

Date: _____

Investigator or Designee Obtaining Consent
Signature

Date: _____