Effect of Combined Morphine and Duloxetine on Chronic Pain

NCT03249558

02/18/2022

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Detailed Protocol

I. BACKGROUND AND SIGNIFICANCE

a. Historical Background

Patients suffering from chronic pain often present with comorbidities such as depression and require multi-modality treatment including medications. Preclinical studies on the pathophysiology of pain suggests that pain symptoms may be treated by targeting distinctive underlying mechanisms, but a number of obstacles have so far made it difficult to translate preclinical findings to clinical applications (Mao, 2013). To date, several categories of medications are commonly used in chronic pain management including non-steroidal anti-inflammatory drugs, acetaminophen, opioids, antidepressants, antiepileptic drugs including gabapentinoids, and topical agents (Mao et al. 2011; Cohen, Mao, 2014). Moreover, the concept of combination drug therapy for pain management has been known for several decades, which refers to the combined use of different categories of pain medications in order to achieve improved pain relief as a primary goal (Vorobeychik et al., 2011). While opioids are strong analgesics for the treatment of moderate to severe pain, their use is often complicated by side effects and sometimes adverse outcomes such as addiction, abuse, and paradoxical opioid-induced hyperalgesia (OIH) (e.g., Mao, 2002; 2010; Chu et al., 2006, 2011; Ram et al., 2008; Chen et al., 2009). Although it is uncommon for clinicians to use opioids as a single drug treatment for chronic pain, few clinical trials have adequately assessed opioid therapies in combination with a non-opioid adjunct such as an antidepressant with regard to 1) analgesic effect, 2) side effect profile, and 3) adverse outcomes including opioid dependence and OIH. Accordingly, we propose to conduct a double-blind, randomized, and placebo-controlled clinical study in order to examine whether duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), could enhance opioid analgesia and decrease overall opioid use. We expect that this prospective human study will yield timely and much-needed clinical data on the effectiveness, or lack thereof, of adding an adjunct to opioid therapy in chronic pain management. Positive outcomes of this study will help improve opioid analgesia and reduce unnecessary opioid dose escalation.

b. Previous studies

Combination drug therapy with opioid and antidepressant – preclinical studies

A number of preclinical studies have demonstrated the efficacy of various drug combinations in rodent or primate models of tissue injury (Banks et al., 2010; Sikka et al., 2011; Li et al., 2011). In addition, combining monoamine reuptake inhibitors with morphine enhanced the morphine anti-nociceptive effect in rats (Taiwo et al., 1985; Shen et al., 2013). Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), influenced isolation-induced morphine self-administration in rodents by restoring the central serotonin function (Raz, Berger, 2010), prevented morphine tolerance in mice (Nayebi et al., 2009), and attenuated morphine withdrawal signs in neonatal rats (Sills, Fletcher, 1997; Wu et al., 2005). Moreover, maprotiline, a non-selective antidepressant, enhanced morphine antinociception when both drugs were injected intrathecally in rats (Pettersen et al., 2009). Of note, most preclinical studies on the interaction between opioid and SSRI were conducted in healthy rodents and their clinical relevance remains to be determined.

Combination drug therapy for chronic pain management – clinical studies

Although effective in some cases, using single drug therapy often fails to provide adequate analgesia for many chronic pain conditions. Indeed, clinicians regularly use more than one medication in pain treatment regimens in order to improve analgesia and/or reduce side effects. Some of the commonly used combinations of pain medications include gabapentin or pregabalin with a tricyclic antidepressant, opioid with gabapentin or a tricyclic antidepressant, and an oral medication (e.g., gabapentin) with a topical agent such as lidocaine patch or cream (Bril et al., 2011; Vorobeychik et al., 2011; McCormick et al., 2014). For example, a previous study has shown that combining gabapentin with an opioid analgesic is effective to reduce pain and produces fewer side effects (Gilron et al., 2005). Fluoxetine has also been shown to improve drug-related side effects such as morphine-induced pruritus and sedation (Erjavec et al., 2000). However, several studies using combination drug therapy have yielded either negative or equivocal results. In a study of 28 completed subjects, morphine (15-90 mg), either alone or in combination with nortriptyline (25-100 mg), produced no significant analgesic effect on sciatic pain (Khoromi et al., 2007). In another study of 16 subjects with neuropathic pain due to advanced cancer, adding amitriptyline (up to 50 mg) to opioid therapy also produced no significant pain improvement (Mercadante et al., 2002). While the number of clinical studies on combination drug therapies is still limited, several preliminary indications have emerged from these studies (Mao et al., 2011; Vorobeychik et al., 2011). **(1)** Most studies demonstrate some benefits by including gabapentinoids in combination drug therapy for pain related to diabetic neuropathy and post-herpetic neuropathy. **(2)** High concentration topical capsaicin or 5% lidocaine patch seems to be effective as add-on therapies to oral pain medications. **(3)** Most clinical studies suggest that the effectiveness of combination drug therapy is dependent on the type of pain conditions and dose regimens. Therefore, we feel that several key issues must be addressed in a combination drug therapy in order to evaluate its clinical effectiveness, including patient population, choice of medications, treatment regimen, and appropriate outcome assessment.

c. Rationale for using duloxetine as an adjunct to opioid therapy

Duloxetine is an SNRI and approved by the FDA to treat diabetic neuropathic pain, fibromyalgia, and musculoskeletal pain (www.FDA.gov). In this project, we choose to study the effectiveness of duloxetine as an adjunct to opioid therapy for several reasons. **First,** SNRI such as venlafaxine has been shown to modulate morphine analgesia in a rodent neuropathy model. Its acute effect improved and chronic effect reduced morphine antinociception, respectively (Cegielska-Perun et al., 2012, 2014, 2015). Venlafaxine also attenuated morphine dependence and withdrawal in naive rats (Lu et al., 2001). Preclinical studies have shown that duloxetine also attenuated morphine tolerance and morphine withdrawal signs in rodents without persistent nociception (Ozdemir et al., 2012; Charkhpour et al, 2014). Duloxetine itself has been shown to reduce nociceptive behavior in both inflammation (Jones et al., 2005) and post-operative pain (Obata et al., 2010) models in rats. The effect of duloxetine on pain modulation may be due to its ability to increase the spinal norepinephrine level (Meske et al., 2014). Of interest to note is that, in a rat nerve injury model, morphine appears to be more effective to reduce mechanical allodynia whereas duloxetine is more effective to diminish neuroma-induced nociception (Miyazaki, Yamamoto, 2012). **Second,** duloxetine has been shown to reduce morphine requirement in patients with knee replacement surgery in a small (50 subjects) clinical study (Ho et al., 2010). An earlier human study also suggests that increasing the central serotonin level may enhance morphine analgesia (Coda et al., 1993). To our knowledge, no randomized, placebo-controlled clinical studies have been carried out to examine the effect of duloxetine on opioid analgesia in patients with chronic neck and back radicular pain symptoms. **Third**, duloxetine is an FDA-approved drug for depression and pain treatment with a relatively good safety profile (but with a warning for suicidal

risk in young subjects; www.FDA.gov). Since its approval by FDA for chronic pain treatment, duloxetine has been increasingly used in clinical settings. **Fourth,** among SNRIs including milnacipran and venlafaxine, duloxetine (60 mg, oral) has a pharmacokinetic profile that favors a chronic course of treatment with minimal day-to-day dose adjustment, including about 6 hours to reach the peak plasma level, an elimination half-life of 8-17 hours (average 12 hours), and a 50% oral bioavailability (www.FDA.gov). In comparison, milnacipran involves a more complicated titration schedule and is approved for fibromyalgia treatment whereas venlafaxine is used off-lable for pain treatment and has a rather short half-life requirig 2-3 daily doses (www.FDA.gov). Therefore, we choose to add duloxetine (generic formula; daily doing) to an opioid therapy in this clinical study. We expect that this combination therapy will enhance opioid analgesia and reduce overall opioid use, thereby diminishing opioid dependence/withdrawal and OIH.

II. SPECIFIC AIMS

This study has two specific aims:

1. To examine changes in VAS scores and to determine total versus rescue opioid use (primary outcomes) after each treatment
2. To compare secondary outcomes including a) side effect profile, b) dropout rate, c) functional status, d) physiologic opioid dependence, e) OIH, and f) urine drug screening

III. SUBJECT SELECTION

a. Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Subject is 18-70 years old.
2. Subject has chronic neck or back pain for at least 3 months.
3. Subject has a VAS ≥ 6.
4. Has not taken duloxetine in the last 3 months.
5. Has not taken an opioid in the last 3 months, but has taken one in the past without sufficient pain control OR has never taken opioids but has failed at 3 (or more) non-opioid treatments.

Exclusion Criteria:

1. Subject has major psychiatric disorders requiring recent hospitalization (within 3 months) such as major depression, bipolar disorder, schizophrenia, anxiety disorder, or psychotic disorder.
2. Subject is using illicit drugs or alcohol detected by urine toxicology/drug screen.
3. Subject has a history of alcohol use disorder within 6 months.
4. Subject is pregnant or lactating/breast feeding.
5. Subject is allergic to morphine or duloxetine.
6. Subject is on an antidepressant including SNRI, SSRI, tricyclic antidepressant.
7. Subject has a history of suicidal attempts or current suicidal ideation.
8. Subject takes monoamine oxidase inhibitors, antipsychotics, triptan drugs such as sumatriptan, lithium, linezolid, tramadol (Ultram), St. John's Wort, Kratom, CNS stimulants such as amphetamine, methylphenidate, methamphetamine, phentermine, diethylpropion, sibutramine, cocaine, or thiordazine.
9. Subject takes drugs that cause loss of potassium such as diuretics and corticosteroids.

10. Subject takes digoxin, cyclosporine, methenamine, or high doses of salicylates (i.e. aspirin).
11. Subject takes anticonvulsants such as topiramate, phenytoin and zonisamide.
12. Subject has uncontrolled narrow-angle glaucoma.
13. Subject has sensory deficits on arms or Raynaud's Syndrome.
14. Subject has a pending litigation related to chronic pain condition.
15. Subject is on methadone or suboxone treatment for addiction.
16. Subject has a lifetime history of opioid addiction.
17. Subject has an allergy to morphine, duloxetine, acetazolamide, or other sulfa drugs.
18. Subject scores 18 or higher on the Screener and Opioid Assessment for Patients with Pain-Reversed (SOAPP-R) questionnaire.

All potential subjects will be reviewed by a study physician to determine inclusion. The study physician will review: 1) information obtained during the IRB approved phone screen, 2) Partners LMR and 3) medical records received from the PCP or prescribing physician. Subjects will be informed that the information obtained is solely for the purpose of making sure it is safe for them to participate in the study.

b. Source of subjects and recruitment methods

Study subjects will be recruited from: 1) pools of patients under treatment at the MGH Center for Pain Medicine, 2) MGH internal medicine department and orthopedic spine center, and 3) the local community through advertisements and physician referrals from our counterparts in the Harvard medical system including Brigham & Women's Hospital, Beth Israel and Deaconess Medical Center, Spaulding Rehabilitation Hospital, Newton-Wellesley Hospital, etc. Our established referral network and advertisement venues (e.g., RSVP: a Healthcare Database from the Partners' system including MGH and Brigham & Women's Hospital) will be used to facilitate subject recruitment.

IV. SUBJECT ENROLLMENT

a. Methods of enrollment

1. Study subjects will be recruited through advertisements, U.S. post, or in person by a study staff member at the MGH Center for Pain Medicine. Study subjects can contact the MGH Center for Translational Pain Research for information about the study.
2. The principal investigator will ask his physician colleagues working at Partners facilities to help identify their patients who may be eligible for this study. The primary healthcare provider will first explain the research study to the identified patient or give him/her a Research Invitation. If the patient is interested, the primary healthcare provider will provide the study staff's contact information or will obtain the patient's permission (verbally or by use of Research Invitation) to be contacted by study staff. If the patient's primary healthcare provider is one of the study investigators, the patient will be recruited using one of the following methods:
    i. A Research Invitation will be sent to the patient. If interested, the patient can contact the study investigator or study staff.
    ii. The study investigator can ask a physician colleague to initially explain the study to the potential subject.
    iii. The study investigator can present the study to the patient and then ask a physician colleague to re-contact the patient.

iv. The study investigator can present the study to the patient and provide the patient with the Consent Form to take home. If interested, the patient can contact the study investigator or study staff.

b. Procedures for obtaining informed consent

The potential subject will be provided with information about the research through advertisements, Research Invitations, or reading a copy of the Consent Form. The potential subject can learn more about the study including potential benefits, risks, and discomforts by speaking with the study staff. The subject will be given as much time as needed to consider participating in the study. If the subject is eligible and decides to participate, he/she will be scheduled for a visit at the MGH Center for Translational Pain Research. At the first visit, the subject will read the Consent Form and then meet with a study physician via phone call to review and discuss the details of the study that are outlined in it. Any questions pertaining to the study will be answered at that time. If the subject agrees to participate, he/she will sign the Consent Form through a survey on REDCap with Adobe sign feature using a laptop provided or personal electronic device. The study physician will then log into REDCap right after and sign their signature. Two copies of the Consent Form will be printed with signatures from the REDCap website. The subject will take one copy and the other copy will be kept in his/her study folder. Subjects will have the option to meet with a study physician who is not their pain physician.

c. Treatment Assignment and Randomization

A total of 135 subjects will be enrolled for this double-blind, randomized study. Subjects will be randomized into three groups (n=45 subjects/group) using a computer-generated randomization protocol (Randomization.com).

Group 1: morphine + placebo with acetazolamide
Group 2: morphine + duloxetine with acetazolamide
Group 3: placebo + duloxetine with acetazolamide

The duloxetine and placebo for duloxetine are specifically compounded with acetazolamide (15 mg), which will be used as a tracer to determine a subject's compliance with the study medication.

V. STUDY PROCEDURES

a. Study visits and parameters to be measured

Subjects will participate in a 10 week study consisting of three phases: Phase I is the dose titration period of 4 weeks, Phase II is the dose maintenance period of 4 weeks, and Phase III is the dose taper period of 2 weeks.

Seven office visits (screening visit, weeks 1, 3, 5, 7, 9, and end of week 10)and four follow up phone calls (weeks 2, 4, 6, and 10) will be used to collect data. Since this is a prospective study, we will be able to first determine baseline quantitative sensory testing (QST) and VAS pain score, followed by assessing their longitudinal changes at each office visit. To assess OIH, QST will be performed at each office visit before subject takes the next dose of the study drugs. We will also measure plasma morphine concentration during the titration and maintenance phase to help validate morphine intake.

Urine Screening

Subjects who are using illicit drugs detected by urine toxicology/drug screen including stimulants, benzos, alcohol, opioid (other than the study opioid), cocaine will be withdrawn from the study.

Given the increasing use of marijuana in general population and the knowledge of a minimal impact of occasional marijuana use on opioid effects, we will use the following plan to monitor marijuana use.

a. If subjects test positive for marijuana use at the initial screening, the subjects will be given the chance to have a second urine test in one week. If the second test is negative, subjects will be allowed to participate in the study. If the urine test is positive, subjects will be withdrawn.
b. During the study, subjects take a urine drug test at each office visit. Similarly, if the subject tests positive for marijuana use at one of these office visits, the subject will be given the chance to have a second test in one week while continuing the study. If the second test is also positive, the subject will be dismissed from the study with a proper monitoring and management of withdrawal symptoms.

Screening Visit

1. Subject will meet with a study physician to review pain and medical history to confirm inclusion/exclusion criteria
2. Informed consent will be obtained by a study physician
3. Vital signs (blood pressure, oxygen saturation, and pulse) will be taken
4. Urine sample will be collected for drugs of abuse (DOA) and pregnancy test
5. The following questionnaires will be completed: Pain Questionnaire, Short-form McGill Pain Questionnaire (SF-MPQ2), Short-form 36 (SF-36), Beck Depression Inventory (BDI-II), Prescription Drug Use Questionnaire (PDUQ), Screener and Opioid Assessment for Patients with Pain- Reversed (SOAPP-R) and Anxiety Sensitivity Index (ASI)
6. Sensory test at QST site
7. QST testing

Visit 1

1. Vital signs will be taken
2. Urine sample will be collected for DOA and acetazolamide/creatinine measurement
3. Provide study medication and review medication instructions, daily pain log, and daily medication log
4. The following questionnaires will be completed: Pain Questionnaire, Short-form McGill Pain Questionnaire (SF-MPQ2), Short-form 36 (SF-36), Anxiety Sensitivity Index (ASI), Beck Depression Inventory (BDI-II), and Prescription Drug Use Questionnaire (PDUQ)
5. Schedule future study visits
6. Blood draw (10 cc) to measure plasma morphine concentration to confirm subject is not taking morphine

Visits 2, 3 and 5

1. Vital signs will be taken
2. Urine sample will be collected for DOA and acetazolamide/creatinine measurement
3. Collect and count unused study medication and provide study medication for the next phase
4. Review daily pain and medication logs and provide subject with new logs
5. The following questionnaires will be completed: Pain Questionnaire, Short-form McGill Pain Questionnaire (SF-MPQ2), Short-form 36 (SF-36), Anxiety Sensitivity Index (ASI), Beck Depression Inventory (BDI-II), and Prescription Drug Use Questionnaire (PDUQ)
6. QST testing

Visits 4

1. Vital signs will be taken
2. Urine sample will be collected for DOA and acetazolamide/creatinine measurement
3. Collect and count unused study medication and provide study medication for the next phase
4. Review daily pain and medication logs and provide subject with new logs
5. The following questionnaires will be completed: Pain Questionnaire, Short-form McGill Pain Questionnaire (SF-MPQ2), Short-form 36 (SF-36), Anxiety Sensitivity Index (ASI), Beck Depression Inventory (BDI-II), and Prescription Drug Use Questionnaire (PDUQ)
6. Perform QST
7. Blood draw (10 cc) to measure plasma morphine concentration and biomarkers

Visit 6

1. Vital signs will be taken
2. Urine sample will be collected for DOA and acetazolamide/creatinine measurement
3. Collect and count unused study medication
4. Review daily pain and medication logs
5. The following questionnaires will be completed: Pain Questionnaire, Short-form McGill Pain Questionnaire (SF-MPQ2), Short-form 36 (SF-36), Anxiety Sensitivity Index (ASI), Beck Depression Inventory (BDI-II), Clinical Opioid Withdrawal Scale (COWS), and Prescription Drug Use Questionnaire (PDUQ)
6. Perform QST
7. Remuneration form completed

Phone Calls

Trained study staff will call subjects at weeks 2, 4, 6 and 10 to monitor subject safety and compliance. Subjects will be asked about their pain, medication schedule, medication side effects, and overall health. Subjects will have an opportunity to ask questions and speak to a study physician.

Remuneration

Subjects will receive $300 for completing the study, plus $10 as a travel stipend for each office visit (up to $370). Payment will be in the form of one check which will be mailed to the subject about 4-6 weeks after their last visit.

The following guidelines have been created for cases concerning pro-rated remuneration:

1. Subjects testing positive for illicit drugs or undisclosed prescriptions or subjects who are non-compliant with the study medication schedule will receive zero payment. Non-compliance will be determined by the study physicians on a case by case basis. We cannot define an objective set of criteria for non-compliance since every scenario will differ based on study phase, potential side effects, and subject reported information (such as incomplete logs or missed phone calls, and CleverCap discrepancy).
2. Subjects who do not complete the study through their own decision will receive full payment and the travel stipend for the visits attended.
3. Subjects who are withdrawn by an investigator by no fault of their own will receive full payment for the visits attended.

4. Subjects who fail to return the loaned CleverCaps will not receive payment to allow for the purchase of replacements.
5. Subjects who test positive for marijuana will be allowed to re-take the urine test in one week or at the next scheduled visit. If the second test is negative they will be allowed to continue in the study. If the second test is positive they will be withdrawn from the study and will not receive payment.

All prorated remuneration will be documented via progress notes and kept with the subject's research folder.

The pro-rated remuneration for visits attended is as follows:

1.

Screening Visit:	$40 + $10 travel stipend or parking pass
Visit 1:	$50 + $10 travel stipend or parking pass
Visit 2:	$40 + $10 travel stipend or parking pass
Visit 3:	$40 + $10 travel stipend or parking pass
Visit 4:	$50 + $10 travel stipend or parking pass
Visit 5:	$40 + $10 travel stipend or parking pass
Visit 6	$40 + $10 travel stipend or parking pass

b. Drugs to be used:

Dose of study medications

Group 1: Extended release morphine (15 mg) + placebo with acetazolamide (15 mg): Subjects will be titrated onto extended release morphine until their pain level is reduced to a VAS ≤ 3 or until the maximal tolerable dose (up to 60 mg/day) is reached. The placebo will be a sugar pill and will be compounded with acetazolamide (15 mg).

Group 2: Extended release morphine (15 mg) + duloxetine (30 mg) with acetazolamide (15 mg): Subjects will be titrated onto extended release morphine until pain level is reduced to a VAS ≤ 3 or until the maximal tolerable dose (up to 60 mg/day) is reached. Subjects will be titrated onto duloxetine until they have reached 60 mg/day. The duloxetine will be compounded with acetazolamide (15 mg).

Group 3: Placebo + duloxetine (30 mg) with acetazolamide (15 mg)The placebo will be a sugar pill. Subjects will be titrated onto duloxetine until they have reached 60 mg/day. The duloxetine will be compounded with acetazolamide (15 mg).

Morphine placebo and duloxetine placebo will have similar weight and packaging to the true morphine and true duloxetine in order to maintain blinding for subjects and study staff. The morphine/morphine placebo pills will be packaged in a different colored capsule than the duloxetine/duloxetine placebo so subjects can differentiate between the two pills. All medications will be taken orally, and will be prepared, dispensed, and coded by the MGH Research Pharmacy. The assignment will not be disclosed to the study subject or study staff.

Rescue medication:

Subjects in all three groups will be asked to stay on the same non-opioid pain medications, if any, without change once the study starts. Although no progression of overall pain condition is expected for study subjects, there may be sporadic breakthrough pain on top of an otherwise stable pain condition (i.e., no worsening of underlying pathology). This would be more likely to occur in the

doluxetine and placebo group. Subjects will be titrated onto the rescue medication and will be allowed to take up to two 15 mg instant release morphine pills/day, so that the total maximum dose of morphine (extended release + instant release) is 90 mg/day. Subjects will be tapered off the rescue morphine before they finish the study. To avoid overdosing, subjects will be instructed to wait at least 2 hours after taking their other study medication (extended release morphine or placebo) before taking the rescue dose. They will also be asked to wait at least 2 hours before taking the next dose of the study medication.

Medication schedule:

Subjects will participate in this 10 week study that consists of three phases: Phase I is the dose titration period of 4 weeks, Phase II is the dose maintenance period of 4 weeks, and Phase III is the dose taper period of 2 weeks. Study medications will be dispensed at weeks 1, 3, 5, 7, and 9. For the subject's safety, study medication for the titration and maintenance periods will be dispensed with up to an additional three days of medication; this will prevent medication withdrawal if the subject has to reschedule a visit. Subjects will take the medication according to the table below:

TITRATION PERIOD					
Week	**Extended Release Morphine (15mg) or Placebo**		**Rescue medication: Instant Release Morphine (15 mg)**	**Week**	**Duloxetine or Placebo (30mg)**
	Morning	Evening	As needed		Evening
1	0	1	≤1	1	1
2	1	1	≤2	2	2
3	1	2	≤2	3	2
4	2	2	≤2	4	2

MAINTENANCE PERIOD					
Week	**Extended Release Morphine (15mg) or Placebo**		**Rescue medication: Instant Release Morphine (15 mg)**	**Week**	**Duloxetine or Placebo (30mg)**
	Morning	Evening	As needed, no more than 2 pills/day		Evening
5-8	2	2	≤2	5-8	2

TAPER PERIOD						
Day	**Extended Release Morphine (15mg) or Placebo**		**Day**	**Rescue medication: Instant Release Morphine (15 mg)**	**Day**	**Duloxetine or Placebo (30mg)**
	Morning	Evening	As needed, no more than 1 pill/day			Evening
56-60	1	2	56-62	≤1	56-62	1
61-65	1	1	63, 65, 67, 69	0	63, 65, 67, 69	0
66-69	0	1	64, 66, 68	≤1	64, 66, 68	1

Study drug compliance

We will use the following methods to monitor subjects' compliance with the study medication:

1. We will provide study subjects with a log sheet to record their daily medication intake (date and time). Study subjects will be asked to bring the medication and log to each scheduled study visit. The medication will be counted to make sure the returned quantity matches the balance between total given and taken based on the log sheet.
2. Study medication vials will be secured with a CleverCap Pro which is a tamper resistant electronic cap that dispenses medication at a pre-set interval and a pre-set amount.

CleverCaps also record when the dose is dispensed so study staff will review these times and compare them to the subject's daily medication log.

3. The duloxetine and placebo for duloxetine are specifically compounded with acetazolamide (15 mg), which will be used as a tracer to determine a subject's compliance with the study medication. We will collect a urine sample at each visit and test for levels of acetazolamide and creatinine. An acetazolamide/creatinine ratio will be used to determine if the subject has been taking the study medication containing acetazolamide if the cut-off ratio is set at 1. The urine samples will be sent to WuXi AppTec for the acetazolamide analysis. Blood will also be drawn at two visits to monitor the morphine plasma level.

Noncompliance with medication and study visits, which affects the subject's health or data integrity, may require withdrawal from the study.

c. Electronic medical record

When subjects enroll in this study, a notation will be made in their electronic medical record, which associates the subject with the study. We will also upload a copy of their signed Consent Form. Once subjects are associated with the study, anytime they are admitted to a Partners Hospital or visit a Partners Hospital Emergency Department, the study doctors will be alerted electronically.

d. Hospital Admissions Alert System

MGH uses an electronic system that automatically alerts your study doctors if you are admitted to a Partners Hospital or if you visit a Partners Hospital Emergency Department. The study doctors can know if you experience any side effects or other problems while partaking in the study.

e. Devices to be used

Medoc Thermal Sensory Analyzer (TSA), a thermal quantitative sensory testing device. This device is FDA approved in diagnosing neuropathic pain syndromes. The MGH Bioengineering Department inspects this device annually.

f. Procedures/surgical interventions

QST is a commonly used pain assessment tool both for human pain studies and clinical diagnosis. The thermode-skin interface will change temperature at 1 ºC/second from a baseline of 32 ºC to a maximum of 53 ºC. The subject can withdraw from the stimulation at any time. The following are examples of QST using heat stimulation.

<u>To detect heat pain threshold</u>, a contact thermode will be placed to a designated body part (e.g., forearm). Subjects will stop the stimulation by pressing a button when pain is first felt. This same test will be repeated three times with a 20 second interval and the average of three threshold temperatures from these tests will be used as the pain threshold temperature (in degrees Celsius).

<u>To detect heat pain tolerance</u>, a contact thermode will be placed to a designated body site (e.g., forearm). Subjects will stop the stimulation by pressing a button when the pain is no longer tolerable. This same test will be repeated three times with a 1 minute interval and the average of three threshold temperatures from these tests will be used as the pain tolerance temperature (in degrees Celsius).

<u>To examine windup (temporal summation of second pain)</u>, a train of four identical stimuli at 47 ºC (supra-threshold heat stimulation), separated by a 2.2 second interval between each stimulus, will be applied. Subjects will be asked to rate pain intensity by VAS following each of the four stimuli. The test will also be repeated three times.

To detect diffuse noxious inhibitory control (DNIC), we will use a protocol described in a recent study (Ram et al, 2009) and that has been employed in our research center. Four heat stimuli (HS) of 47 ºC, each lasting 4 seconds, will be delivered according to pre-set intervals. Subjects will be asked to rate the pain (VAS) after each heat stimuli. Pain score in response to the first heat stimulus will serve as baseline (Trial 1). The second heat stimulus (Trial 2) will be delivered during the final 4 seconds of a 30 second period when the subject's hand (opposite to the side of QST) is immersed in a cold water (12 ºC) bucket. Two additional heat stimuli will be delivered at 15 and 30 seconds after removal of the hand from cold water (Trial 3 and Trial 4, respectively). Pain scores from Trials 2-4 will be compared with the baseline (Trial 1) to determine the degree of DNIC (Ram et al, 2008). This same test will be repeated three times and the average of these tests will be used.

g. Data to be collected

Seven office visits (screening visit, weeks 1, 3, 5, 7, 9, and end of week 10) and four follow up phone calls (at weeks 2, 4, 6, and 10) will be used to collect data.

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected

- Pain Questionnaire and Follow-up Pain Questionnaire
- Beck Depression Inventory (BDI-II)
- Short-form 36 (SF-36)
- Anxiety and Sensitivity Index (ASI)
- Short-form McGill Pain Questionnaire (SF-MPQ2)
- Prescription Drug Use Questionnaire (PDUQ)
- Clinical Opiate Withdrawal Scale (COWS)
- Screener and Opioid Assessment for Patients with Pain- Revised (SOAPP-R)
- Neurological examination including a detailed sensory examination (e.g., von Frey, cotton swab, pinprick, tuning fork, alcohol wipe)
- A check on routine vital signs (blood pressure, pulse, blood oxygen level)
- Urine drug and pregnancy tests
- Acetazolamide/creatinine ratio
- CleverCap
- Blood plasma drug concentration
- Pain and medication log

QST will include the following:

- Heat pain threshold, heat pain tolerance, windup, and DNIC. A cut-off of 53 ^{0}C will be preset to avoid tissue damage.

b. Study endpoints

Aim 1 (primary outcomes)

1. *Changes in VAS pain score after each treatment*- we will make both within group and between group comparisons of VAS changes. VAS scores from a given study group will be compared across various time points (e.g., weeks 0, 4, 8, and 10). VAS scores will also be compared among the three groups at the same time points (weeks 0, 4, 8, and 10).
2. *Overall opioid dose (extended release morphine + rescue immediate release morphine) and rescue opioid dose (immediate release morphine)*- we will compare overall opioid

dose between the morphine/duloxetine group and the morphine/placebo group and compare rescue dose among all three groups.

Aim 2 (secondary outcomes)-We will compare secondary outcomes among three groups including:

1. Side effect profile
2. Dropout rate using Kaplan Myer survive curve
3. Functional status and co-morbidities (scores on questionnaires)
4. Opioid dependence
5. OIH- we will compare QST responses along with VAS changes across three groups including changes in:
   a. Heat pain threshold
   b. Temporal summation and DNIC
   c. Mechanical pain threshold (von Frey filament)
   d. Pain location and quality as compared to pre-existing pain (e.g., aching vs. burning pain, localized vs. diffuse pain based on questionnaires
6. Urine drug screening

c. Statistical methods

Our research center has used Redcap as the database for several previous and ongoing clinical studies. For this study, we will also use Redcap to setup and maintain a designated research database. The statistical packages will include both descriptive and quantitative data analyses using Sigma Stat (version 11) with the significance level at $P< 0.05$. Ms. Trudy Poon (20% effort), a statistician in our department, will be available for consultation. Descriptive analysis will be used to analyze the data obtained from various questionnaires (e.g., SF-MPQ-2; SF-36). Percent (%) changes in each category will be analyzed using the *Chi*-square test. Quantitative analysis will be used to analyze the data obtained from QST and VAS. **(A)** The Mann Whitney U test will be used to analyze the non-parametric data (e.g., results from the von Frey filament test). **(B)** For the parametric data, two-way repeated measure analysis of variance (ANOVA) will be used to examine differences across multiple groups at a given time point (between-group comparison) or across different test points for a given group (within-group comparison). The *post hoc* Waller-Duncan k-ratio t-test will be used to determine the source(s) of differences. Since ANOVA analyses do not take into consideration the fixed (e.g., drug dose) versus random (pain duration, age, etc.) effects on study outcomes, we will also use a simple mixed effects modeling (SPSS program) to analyze the interception among these factors. **(C)** Spearman Correlation Coefficient test will be used to examine correlations between clinical data (e.g., VAS change) and QST data. We will recruit equal numbers of male and female subjects so if there is sufficient statistical power for subgroup analysis, we will also analyze the sex/gender and ethnicity differences in our research data.

d. Power analysis

Estimation of group size (power analysis): Since VAS score change is a primary study outcome and previous studies have suggested that a VAS change of 2 points (or 30% from baseline) could be considered as clinically meaningful (Farrar et al., 2001; Cepeda et al., 2003; Grilo et al., 2007; Turk et al., 2008; Dworkin et al., 2009; Chen et al., 2009), we will use this parameter as the basis of power analysis. Thus, a group size of 37 subjects will have 80% power assuming that the standard deviation is less than 2 points (VAS). We anticipate a dropout rate of around 20%. Accordingly, we will recruit up to 45 subjects for each study group. If the dropout rate increases above 20%, we will add more subjects in each group to replace the dropouts beyond the estimated

20% rate. Since **a)** the MGH pain clinic alone receives over 15,000 visits per year, **b)** other pain clinics in the Boston area have a similar number of chronic pain patient visits (e.g., Brigham & Women's Hospital and Beth Israel Deaconess Medical Center), and **c)** we have established a referral network and have recruited about 500 subjects in our OIH studies, we are confident that we will be able to recruit the proposed number of subjects for this project.

VII. RISKS AND DISCOMFORTS

a. Complications of surgical and non-surgical procedures

1. Risks of QST

   Common: Heat stimulation for pain threshold and tolerance tests, although transient may elicit pain. Heat stimulation may cause temporary skin sensitivity similar to mild sunburns. Immersion of a hand into a cool water (12 ^{0}C) bucket can be uncomfortable for subjects, particularly for those with pain in their upper extremities.
   Uncommon: If a skin change persists, the subject will be withdrawn from the study and proper treatment will be given or the subject will be referred to a dermatologist.

2. Risks of blood drawing

   Subjects may experience slight pain, discomfort, bleeding, bruising or, rarely, an infection from the blood draws. A total of 20 cc of blood will be drawn over the course of the study.

b. Drug side effects and toxicities

1. Morphine

   Common side effects: decreased blood pressure, sleepiness, dizziness, drowsiness, dry mouth, upset stomach or throwing up, hard stools (constipation), headache, feeling tired or weak, abdominal pain, sweating, and pruritis.
   Uncommon side effects: bronchospasm, change in pulse, hives, trouble breathing, loss of appetite, blurred or double vision, nervousness, sweating, and chills.

2. Duloxetine

   Common side effects: drowsiness, dry mouth, nausea, constipation, loss of appetite, tiredness, sweating, and lightheadedness.
   Uncommon side effects: headache, muscle ache, diarrhea, vomiting, heartburn, stomach ache, decreased interest in sex, dizziness, weakness, trouble breathing, dark-colored urine, and tremor.

3. Acetazolamide- It is important to note that associated side effects are on-target, dose-related effects so using ultra low, sub-therapeutic doses will reduce the risk of experiencing side effects. Clinical doses range from 250-1000 mg/dose and subjects will only be taking a maximum dose of 30 mg/day.

   Common side effects: tingling, nausea, fatigue, weight loss, dizziness, lightheadedness, or increased urination.

   Uncommon side effects: transient myopia, sensitivity to light, hives, headache, and glucose or blood in urine.

c. Device complications/malfunctions

The QST device (Medoc) is FDA-approved and is inspected on a routine schedule established by the MGH Bioengineering Department.

d. Psychosocial (non-medical) risks

1. Morphine- feelings of euphoria or dysphoria, dependence, and addiction.
2. Duloxetine- worsening depression and emergence of suicidality.

e. Radiation risks

Not applicable.

VIII. Potential Benefits

a. Potential benefits to participating individuals

Study subjects randomized into the medication groups taking morphine + placebo, morphine + duloxetine or placebo + duloxetine may have pain relief from the study medication.

b. Potential benefits to society

We expect for this study to yield important data regarding the effectiveness, or lack thereof, of adding an adjunct to opioid therapy in chronic pain management. Positive outcomes will help improve the overall effectiveness of clinical opioid therapy and reduce unnecessary opioid dose escalation.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data

The PI, study staff and an independent Data and Safety Monitoring Board (DSMB) will monitor the validity and integrity of the data and adherence to the IRB-approved protocol. The department statistician will also monitor the source data and help with the data analysis upon request. The study staff will review the accuracy and completeness of study documents, source documents and informed consent on a weekly basis after data is collected. Any issues are immediately reported to the PI, as the PI is ultimately responsible for monitoring the quality of the data and study outcomes throughout the study. The PI, co-investigators and study staff also meet on a monthly basis to review adherence to the protocol and any other matters regarding the study. The DSMB meetings will take place annually or more often as needed. DSMB meeting minutes will be provided upon request.

b. Safety monitoring

A Data and Safety Monitoring Board will be formed to monitor the study progress. The Board will consist of (3-5) members with experiences in opioid therapy, pain management, regulatory oversight, and patient safety. These members are not associated with this research project and thus will work independently of the PI. They are qualified to review the patient safety data generated by this study because of their unique expertise in the area of pain management and clinical studies.

The PI will monitor this study for safety. Subjects will be discontinued from the study if, during the study, they develop profound sedation, dizziness, constipation, dry mouth, or symptoms of serotonin syndrome. Cumulative Minor Deviation and Adverse Event logs will be submitted at continuing review if there are events to report. A VAS pain score greater than 6 would also trigger withdrawal from the study.

The Beck Depression Inventory (BDI) will be scored based on the user manual to monitor reports of mood changes, depression, and suicidal ideation. If a subject scores within the moderate

depression category or indicates suicidal ideation, a study staff member will recommend that he or she talk to a professional caregiver about depression. Study physicians will be paged immediately if a subject scores within the severe depression category, answers 2 or 3 on Question 9 or reports any signs of spontaneous suicidality. Steps such as referring the subject to the ED, Urgent Care Clinic, or PCP will be taken following this evaluation. MGH Acute Psychiatric Services (APS) will be informed about this study and the possibility that such subjects may be presented to the APS.

Subjects who cannot tolerate the study drugs or are noncompliant will be safely withdrawn from the study. Up to three visits will be scheduled to provide the subject with a medication taper schedule and to collect any unused study medication. A study physician will be present, and visits may include additional study procedures (i.e. QST) at the discretion of the PI.

Subjects will fill out questionnaires regarding opioid dependence/withdrawal. Study physicians will be paged immediately if a subject scores within the moderate to severe dependence/withdrawal categories or if a subject has symptoms of opioid withdrawal (e.g., yawning, tearing, agitation, diarrhea, abdominal cramping). The study physician will contact the subject's treating physician to manage the withdrawal such as using clonidine. If the withdrawal symptoms are severe and urgent, the subject will be directed to the local emergency department. The study physician will contact the ED team to report the subject's condition including the history of participating in this study to facilitate the management. Additional information, advice or guidance can be provided by a study physician at the subject's request.

A study physician will be available 24/7 by page to address any concerns or issues with subjects (e.g. side effects, adverse events, study medication instructions, etc.). If necessary, the subject will be referred for further evaluation and treatment including referral to emergency room visits.

Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines.Any mild or moderate events will be reported to the PHRC and NIH in a progress report at the annual continuing review.

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