

# BMJ Open Study protocol for a randomised, double-blind, placebo-controlled clinical trial of duloxetine for the treatment and prevention of musculoskeletal pain: altering the transition from acute to chronic pain (ATTAC pain)

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## ABSTRACT

**Introduction** Chronic musculoskeletal pain affects a substantial portion of adults visiting the emergency department (ED). Current treatment is limited in scope and does not effectively reduce musculoskeletal pain in patients. The study will evaluate the use of duloxetine, a serotonin-norepinephrine reuptake inhibitor Food and Drug Administration approved for the treatment of chronic pain, as a promising option in its prevention. The proposed study may present a well-tolerated and effective non-opioid treatment for patients with acute musculoskeletal pain that may also be effective in preventing the transition to persistent or chronic musculoskeletal pain.

**Methods and analysis** The primary outcome of this study will be to assess the tolerability and preliminary effectiveness of duloxetine in patients with acute musculoskeletal pain. The study will take place at two EDs in Rhode Island, USA. The study will involve randomisation to one of three arms: duloxetine 30 mg, duloxetine 60 mg or placebo. Tolerability will be assessed by comparing the proportion of participants that report an adverse event and that drop-out across the three study arms. Effectiveness will be determined by self-reported pain over 6 weeks of follow-up. Specifically, we will compare the proportion of participants with persistent pain (ongoing pain at 6-week follow-up), across the three study arms. 60 adults (aged 18–59) presenting to the ED with acute axial musculoskeletal pain within 7 days of onset are expected to be enrolled in the proposed study.

**Ethics and dissemination** Ethics approval was obtained by the Institutional Review Board (IRB). These results will be published in a peer reviewed scientific journal and presented at one or more scientific conferences.

**Trial registration number** NCT03315533.

## INTRODUCTION

Chronic musculoskeletal pain affects 30% of adults,<sup>1</sup> and the costs associated with treating

## Strengths and limitations of this study

- Findings of this study will address an urgent gap in non-opioid management options.
- Double blind randomised controlled trial is the most rigorous study design to address this research question.
- Potentially may have a high dropout rate.

chronic pain are immense, totalling over \$220 billion in direct health costs.<sup>2</sup> Musculoskeletal pain is one of the most common reasons to visit the emergency department (ED) with persistent and minor chronic pain presenting in a substantial proportion of patients (>20%). Individuals with chronic musculoskeletal pain often report injury as an inciting event,<sup>3</sup> and epidemiological studies have indeed demonstrated that chronic musculoskeletal pain commonly develops after common events such as motor vehicle collisions (MVCs) and episodes of acute low back pain.<sup>4–7</sup> Our preliminary work suggests that current mainstays of treatment, opioids or non-steroidal anti-inflammatory drugs (NSAIDs), do little to reduce musculoskeletal pain persistence.<sup>8</sup> Current treatment of acute musculoskeletal pain with opioids has numerous limitations, including pain worsening (opioid-induced hyperalgesia), increased risk of transition to chronic musculoskeletal pain, functional decline, dependence and/or abuse.<sup>9 10</sup>

There is an urgent need for non-opioid pain management options to reduce acute

pain and prevent the development of chronic musculoskeletal pain. This proposed altering the transition from acute to chronic pain (ATTAC pain) study will help address this critical need by evaluating the preliminary tolerability and effectiveness of a non-opioid, duloxetine—a serotonin-norepinephrine reuptake inhibitor (SNRI) marketed for the treatment of generalised anxiety disorder, major depressive disorder and chronic pain. Evidence suggests that stress systems and their interactions with neurological and immune systems play an influential role in persistent and chronic musculoskeletal pain development; serotonin and norepinephrine are important neurotransmitters in this regard.<sup>11 12</sup> The ATTAC pain study will examine whether duloxetine can reduce acute and persistent musculoskeletal pain among adults presenting to the ED with either traumatic or atraumatic (eg, lifting injury) acute musculoskeletal pain.

Duloxetine is an ideal candidate intervention because (1) a large body of data support the efficacy of duloxetine in chronic pain conditions<sup>13 14</sup>; (2) duloxetine targets neurological, stress and immune mechanisms that play a critical role in chronic musculoskeletal pain development<sup>15</sup>; (3) duloxetine has been shown to reduce opioid use in other acute musculoskeletal pain settings<sup>16</sup>; (4) duloxetine reduces post-traumatic stress disorder (PTSD) symptoms in trauma survivors,<sup>17</sup> and PTSD has been shown to contribute to functional decline,<sup>18</sup> opioid/substance abuse<sup>19</sup> and chronic musculoskeletal pain development<sup>20</sup>; (5) duloxetine is well-demonstrated to be safe<sup>21</sup>; and (6) duloxetine is a generic, low cost medication (\$15–30/month).

The primary aims of the proposed study will (1) assess the tolerability of duloxetine in patients with acute musculoskeletal pain by measuring the proportion of participants who report an adverse event (AE) in the duloxetine versus placebo groups, as well as the overall drop-out rate in each study arm. Secondary outcomes of interest are: (2) the potential effectiveness of duloxetine in improving pain outcomes in patients with acute musculoskeletal pain will be indicated by examining whether duloxetine: reduces acute musculoskeletal pain symptoms (during the first 2 weeks after the ED visit), decreases the amount of rescue analgesia needed by participants after their ED visit and decreases persistent musculoskeletal pain incidence and severity 6 weeks after the ED visit.

## METHODS

### Trial design

This study is a randomised, double-blind, placebo-controlled clinical trial with three study arms. Patients will either receive 30 mg duloxetine, 60 mg duloxetine or a placebo medication.

### Settings

This study will be carried out in the EDs of Rhode Island Hospital (RIH) and The Miriam Hospital, both in Providence, Rhode Island. RIH is a large, tertiary care,

academic, level-1 trauma centre with more than 105 000 adult ED visits per year. The Miriam Hospital is a community-based academic hospital with more than 65 000 ED visits per year. Recruitment is expected to begin in February 2018 and continue for a period of about 12–18 months. We used the Standard Protocol Items: Recommendations for Interventional Trials checklist when writing our report.

### Recruitment and consent

Patients presenting to the ED will be screened by study research assistants (RAs) for potential eligibility. This study will use a convenience sample of patients who present to the ED when study RAs are available, although the times of non-coverage are rare. Using the electronic medical record (EMR) system, reports will be run on a biweekly basis to identify potential missed enrolments at each of the study sites. RAs will be stationed in the ED and review the EMR for relevant clinical history such as the chief symptom, injury history and medical history pertaining to the inclusion/exclusion criteria listed below. After the screening process is completed, if the patient is willing and eligible to participate, then written informed consent will be obtained. After informed consent has been obtained, a pregnancy test will be performed (if needed). The patient history, screening data and any other test results (eg, pregnancy test) will then be reviewed with an Medical doctor investigator. This investigator will then give final eligibility approval to proceed with randomisation and will be available by cell phone 24/7 to discuss eligibility in real time.

### Study population

Patients at Rhode Island and Miriam Hospital EDs presenting with axial musculoskeletal pain (in the back, neck or shoulder region) with pain onset in the last 7 days will be included in the study.<sup>22</sup> A shorter duration of acute pain (<7 days) was chosen for two reasons: first ED patients with acute pain, are likely to present early in the course of pain and second, a hypothesised mechanism by which duloxetine may prevent chronic pain (descending modulation) may be dependent on pain duration.<sup>23</sup> If this preliminary study is effective, subsequent studies may examine different durations of pain intensity as a moderator of treatment effect. Patients that also satisfy the following inclusion and exclusion criteria displayed in [table 1](#) will be eligible to participate in the study.

### Randomisation and study intervention

The active drug arms will consist of duloxetine extended release capsules. Active drug dosing will consist of either 30 mg or 60 mg per dose daily for 14 days starting in the ED. Study medication, including both duloxetine and placebo, will be compounded by the Investigational Drug Service (IDS) pharmacy at each of the study sites. All medication will be compounded in batches and packaged in bulk containers for storage at the IDS pharmacy. The containers will be labelled with a lot number

**Table 1** Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>▶ Age 18 to 59</li> <li>▶ Alert and oriented</li> <li>▶ Axial musculoskeletal pain (back, neck, shoulders)</li> <li>▶ Present to the Emergency Department (ED) with acute (present for <math>\leq 7</math> days) musculoskeletal pain and have a current pain score of <math>\geq 4</math></li> </ul>	<ul style="list-style-type: none"> <li>▶ Age <math>&lt; 18</math> or <math>&gt; 59</math></li> <li>▶ Musculoskeletal pain lasting <math>&gt; 7</math> days</li> <li>▶ Emergency Department (ED) pain score <math>&lt; 4</math></li> <li>▶ Chronic pain: Self-reported pain present on most days of the week, for 3 months or longer</li> <li>▶ Fracture (except fracture of the phalanges)</li> <li>▶ Substantial soft tissue injury*</li> <li>▶ History of coronary artery disease, including previous Myocardial Infarction (MI), Angina, Percutaneous transluminal coronary angioplasty (PCTA), etc.</li> <li>▶ History of renal failure (acute or chronic), congestive heart failure, glaucoma, seizure disorder, suicidal ideation, mania or psychotic disorder</li> <li>▶ Prisoner or in police custody</li> <li>▶ Does not have a telephone or regular internet access and email address</li> <li>▶ Unable to speak and read English</li> <li>▶ Blood pressure reading(s) in ED that, when considered in the context of patient history, in the investigator's judgement exceeds acceptable level</li> <li>▶ Currently taking a monoamine oxidase inhibitor or other medication with substantial interaction with duloxetine</li> <li>▶ Pregnant or breast feeding</li> <li>▶ Chronic daily opioid use</li> <li>▶ Previously on duloxetine or previous allergic reaction to duloxetine</li> <li>▶ Antidepressant use within 2 weeks of study start (4 week if Prozac)</li> <li>▶ Severe allergy to lactose</li> <li>▶ Intoxicated</li> </ul>

\*Giant abrasion: road rash to a surface area that is great than  $15 \times 15$  cm in area. Large avulsion-type injury: skin with or without subcutaneous tissue torn off an area of skin  $> 5 \times 5$  cm. Giant laceration: lacerations greater than 20 cm in length. Many lacerations: greater than four lacerations requiring sutures. Burn: any partial thickness burn  $> 3$  cm<sup>2</sup>.

and expiration date and stored at room temperature. Once a patient's history and screening results have been cleared by the study investigator, the participant will be randomised by the study site IDS to receive duloxetine (30 mg or 60 mg) versus placebo, using a randomisation schedule with permuted block sizes stratified on gender and the type of musculoskeletal pain (traumatic or atraumatic) as the type of pain/injury may be predictive of whether or not the participant responds to treatment. At the time of patient discharge from the study site, the study site IDS will dispense a 14-day supply of study medication. This medication will be prescribed by the treating physician. Participants will be offered a copy of the package insert for duloxetine.

### Assessments

All study data are collected by direct data entry using REDCap software. This software is located on a secure server at RIH. This system is password protected and protected by backup to hard drive. If the internet at an ED site is temporarily unavailable, data will be collected via back-up paper forms and subsequently entered into

the database. The study team has expertise in the use of such software for previous randomised controlled trials (RCT). Identifying information will only be kept until a patient has completed all follow-up evaluations, after which it will be destroyed. Paper survey forms will be labelled with participant study identification number only.

During the ED visit, participants will complete survey questions regarding somatic and psychological symptoms,<sup>24 25</sup> pain and pain-related symptoms,<sup>26</sup> general health and medication history,<sup>27</sup> drug use<sup>28</sup> and a demographic questionnaire. To increase adherence to the protocol, participants will be directed to download an optional MediSafe application onto their smartphone to serve as a daily reminder to take to study medication. Standard procedures to operationalise methods to reduce the magnitude of the placebo effect will also be taken. This is valuable to increase study power, as the placebo effect generally biases study results toward the null.<sup>29 30</sup> These methods include: using patient reported ratings (investigator cannot cause inflation of scores); excluding

**Table 2** Study assessments and timing

Measure	Domain	In-person ED*	SMS/Web Days: 3, 10, 17	Phone Days: 7, 14, 21	In-person Week 6
Demographic information	General	•			
Crash history	Distress	•			
Peritraumatic distress	Distress	•			
Life orientation test–revised survey	Optimism	•			
Drug abuse screening test (DAST-10)	Substance Use	•			
Numeric Rating Scale, Regional Pain Scale	Pain	•			•
Short form health survey, Ver. 2 (SF-12v2)	General health	•			
Centre for Epidemiologic Studies Depression Scale	Depression	•			•
Somatic symptoms	Somatisation	•			•
Neuropathic pain diagnostic questionnaire (DN4)	Pain	•			
Pain catastrophising scale	Catastrophising				
Medication use	Medication use	•	•	•	•
Adverse event assessment	Safety	•	•	•	•
Pain frequency, intensity	Pain		•	•	•
Brief pain inventory	Pain			•	•
National Epidemiologic Survey on Alcohol and related conditions (NESARC), questions on opioid misuse	Substance use				•
Impact of events scale revised	Post Traumatic Stress Disorder (PTSD)				•
New injuries or health problems	General			•	•
Healthcare usage, disability, litigation	General			•	•
Missed work or usual activities	General			•	•

patients with mild severity (more likely to respond to placebo); minimising extraneous contact with investigative staff (perceived as therapeutic); and emphasising the concept of a placebo.

Following discharge, the patient will receive follow-up assessments via internet based surveys and phone to monitor for AEs and evaluate patient outcomes. The patient will also return to the study site for an in-person follow-up interview 6 weeks after their initial ED visit. Both the participant and interviewer will be blinded to randomisation. Participants reporting AEs may have their dosage advanced more slowly, or the next dose reduced or held as appropriate. If necessary, patients will be maintained on a lower dose, or their dose will be readvanced depending on the nature of the side effect(s). Patients who decline further participation and patients experiencing adverse effects that in the opinion of study investigators indicate that study drug should be stopped will be discontinued or tapered from study medication. [Table 2](#) outlines the intended schedule of surveys and follow-up procedures after consent is obtained:

### Outcomes measured and statistical analyses

#### Primary outcome

Overall tolerability will be assessed by (1) the proportion of participants in each treatment arm reporting

adverse side effects and (2) the proportion of participants that drop-out due to side effects in the first 21 days of study assessments. Duloxetine will be considered acceptable if the drop-out rate differs by  $\leq 25\%$  in duloxetine arms versus the control arm and if the rate of AEs in the duloxetine treatment arms is  $\leq 25\%$  metrics chosen based on differences observed in numerous clinical trials of opioids and duloxetine conducted in patients with musculoskeletal pain.<sup>31</sup> We will also explore adherence as a marker of tolerability. Adherence will be defined as successfully taking  $\geq 70\%$  of the study drug (average at least 5 out of 7 weekly doses) for the duration of the 2-week study drug protocol. Adherence will be determined by performing a pill count at the in-person visit at week 6. (If participants do have remaining medications, we will assist with safe medication disposal at the time of this visit.)

#### Secondary outcomes

1) Acute pain relief assessment: the measured outcome variable is self-reported axial pain (0–10 numeric rating scale (NRS)). These are obtained over time, and thus we will use mixed effects models with random intercepts to account for subject effects and the correlation among repeated measurements within a subject. The study is powered to detect a 33% difference in pain



scores between groups, a change that has been previously established to represent a clinically important measurement in pain outcomes.<sup>32</sup> Models will be developed which include as independent variables the treatment group and the time (day of the assessment). We will assess the effect of the intervention on acute pain (Days 3, 7, 10, 14, 17, 21, 42). The effect of the intervention on acute pain will be assessed by comparing the pain score slopes (pain decline) between the two groups in the model:

$$P_{ij} = \beta_0 + \alpha_{0i} + \beta_1 \text{Group}_i + \beta_2 \text{Day}_i + \beta_3 (\text{Group}_i \times \text{Day}_i) + \epsilon_{ij}$$

Where  $P_{ij}$  is the pain score for the  $i$ th individual at time point  $j$ ,  $\beta$ s denote fixed effects,  $\alpha_{0i}$  is the random intercept for the  $i$ th individual and  $\epsilon$  corresponds to random errors. (both  $\alpha$  and  $\epsilon$  are zero centred and normally distributed).

2) Persistent to moderate severe axial musculoskeletal pain: the measured outcome variable will be assessed at 6 weeks. Six weeks is a time of importance because chronic pain trajectories are established about 6 weeks after acute injury or reporting acute musculoskeletal pain (such as an MVC),<sup>33 34</sup> allowing for greater statistical power in this pilot study—more participants are likely to complete follow-up at 6 weeks than 6 months. Moderate to severe axial musculoskeletal pain was defined as a pain score of  $\geq 4$  out of 10 on the NRS in the back, neck or shoulders (axial).<sup>35</sup> Moderate to severe axial musculoskeletal pain was chosen as the primary outcome because it is associated with risk for chronic pain development<sup>36</sup> and because it of its clinical relevance. The presence of moderate to severe musculoskeletal pain correlates with other patient-centred outcome measures such as impaired function.<sup>37</sup> We will compare the proportion of participants with moderate to severe (NRS  $\geq 4$ ) axial pain at week 6 ( $\chi^2$  test) between treatment groups. We will use a mixed model with random effects (as outlined above) to compare and determine the effect of treatment on musculoskeletal pain scores across time, up to week 6, accounting for baseline pain scores and change in time.

3) Rescue analgesia use: we will use participant report of prescription opioids, NSAIDs and other treatments for pain. We will determine if participants have used opioids within the past week and past 24 hours. We will then further assess the type, dose, frequency and quantity taken on average in the past week and past 24 hours. For opioids, we will estimate average morphine equivalent daily dose.

### Sample size calculation

For the primary aim, tolerability, it was determined that 12 participants per group would be required to detect a 25% difference in AEs (primary outcome), assuming a background rate of 10% AEs in the control group ( $\alpha=0.05$  and  $\beta=0.90$ , two-sided test of proportions). To assess a 25% difference in the proportion of participants dropping out of the study, 20 participants per group is required, ( $\alpha=0.05$  and  $\beta=0.90$ , two-sided test of proportions). This

assumes a drop-out rate in the control group of 33%, typical of randomised controlled trials (RCTs). Therefore, a total of 60 participants will be recruited into the study ( $n=20$  per arm). The sample size is not based on pain outcomes, as those are secondary endpoints in this pilot feasibility study.

### Monitoring

The research committee of the University Emergency Medicine foundation will serve as the Data Safety Monitoring Board (DSMB). The DSMB will be used to review and approve the study protocol prior to the start of the study. It will conduct an unblinded analysis after 30 patients have conducted outcome assessments through day 21 and determine whether it is safe to continue the trial after this stage. In case of any serious adverse events (SAEs), the DSMB will convene.

The study principal investigator (PI) will monitor for AEs that change study risk level. If an AE occurs which changes the study risk level, the study PI will immediately report this event to the institutional review board, inform any coinvestigators, and oversee the process of modifying the study at the study site(s) as appropriate to address the change in risk. SAEs will be monitored by the study site investigative teams in real time throughout the trial.

### Patient and public involvement

The patients and public were not involved in the planning of this study.

### Ethics and dissemination

These results will be published in a peer reviewed scientific journal and presented at one or more scientific conferences.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This work was approved by the Institutional Review Board of the Miriam Hospital (Federal Wide Assurance FWA00003538).

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