Biopsychosocial influence on shoulder pain: Rationale and protocol for a pre-clinical trial

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ABSTRACT

Background: Chronic musculoskeletal pain conditions are a prevalent and disabling problem. Preventing chronic musculoskeletal pain requires multifactorial treatment approaches that address its complex etiology. Prior cohort studies identified a high risk subgroup comprised of variation in *COMT* genotype and pain catastrophizing. This subgroup had increased chance of heightened pain responses (in a pre-clinical model) and higher 12 month post-operatives pain intensity ratings (in a clinical model). This pre-clinical trial will test mechanisms and efficacy of personalized pain interventions matched to the genetic and psychological characteristics of the high-risk subgroup.
Methods: Potential participants will be screened for high risk subgroup membership, appropriateness for exercise-induced muscle injury protocol, and appropriateness for propranolol administration. Eligible participants that consent to the study will then be randomized into one of four treatment groups; 1) personalized pharmaceutical and psychological education; 2) personalized pharmaceutical and general education; 3) placebo pharmaceutical and psychological education; 4) placebo pharmaceutical and psychological education. Over the 5-day study period participants will complete an exercise-induced muscle injury protocol and receive study interventions. Pain and disability assessments will be completed daily, with primary outcomes being duration of shoulder pain (number of days until recovery), peak shoulder pain intensity, and peak shoulder disability. Secondary outcomes include inflammatory markers, psychological mediators, and measures of pain sensitivity regulation.
Conclusion: This pre-clinical trial builds on prior cohort studies and its completion will provide foundational data supporting efficacy and mechanisms of personalized interventions for individuals that may be at increased risk for developing chronic shoulder pain.
Trial registration: ClinicalTrials.gov registry, NCT02620579 (Registered on November 13, 2015).

1. Introduction

Chronic musculoskeletal pain conditions are among the most prevalent and disabling medical problems experienced by individuals in the United States. Chronic pain affects 100 million people in the United States (U.S.) and produces annual costs up to $635 billion, exceeding the prevalence and costs of heart disease, cancer, and diabetes [1,2]. These costs are largely driven by musculoskeletal pain conditions. The burden of chronic pain is a global concern; in 2012 the Global Burden of Disease Study identified musculoskeletal pain as a primary contributor to years lived with disability worldwide [3]. The Institute of Medicine (IOM) has identified pain relief tailored to specific characteristics as a high priority for future research and practice initiatives, but very few accepted treatment models exist [1].

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Preventing the development of chronic pain conditions is a high priority initiative for improving patient care. Unfortunately, current knowledge of mechanisms involved in the transition to chronic pain is limited, which decreases options for effective treatment of pain. Studies targeting validated risk factors that confer increased risk of experiencing chronic pain provide a unique opportunity to vertically advance the field. Indeed, interventions tailored to specific risk factor characteristics (i.e. personalized or precision medicine) hold great promise in reducing the impact of chronic pain [4,5]. Personalized medicine via identification of genetic risk factors has been successfully implemented for select areas of cardiac medicine [6–9] and oncology [10–12]. However, similar successes have not been achieved for pain treatment when focusing on genetic risk factors alone [5]. Because of their complex biopsychosocial etiologies, personalized interventions for chronic pain conditions will require identification of genetic factors in combination with psychological, environmental, and/or social risk factors [4]. We recently implemented this multiple risk factor approach in validating a high-risk subgroup comprised of psychological and genetic factors [13].

One component of this high risk subgroup, the *catechol-O-methyltransferase (COMT) gene*, encodes the COMT enzyme, which metabolizes catecholamines. *COMT* polymorphisms and haplotypes associated with low COMT activity have been linked to pain sensitivity and increased risk of multiple musculoskeletal pain conditions [14–16]. The impact of *COMT* on pain modulation occurs via multiple pathways, including endogenous μ-opioid function [17,18] and the beta-adrenergic system [19–22]. *Pain catastrophizing*, the psychological component of the high risk subgroup, is a negative cognitive style, comprised of pain-related rumination, magnification, and helplessness/pessimism, that leads to the perception that the experienced pain is beyond the control of the individual and will result in the worst possible outcome [23]. Pain catastrophizing has a well-established link to pain perception and disability in multiple pain populations [24–26], including shoulder pain as evidenced by our earlier studies [27,28]. In our pilot studies [29,30] we demonstrated an interaction between *COMT* genotype and pain catastrophizing as a stronger predictor of shoulder pain and disability than either factor alone [31]. In a pre-clinical cohort in whom shoulder pain was induced by eccentric exercise, we identified a subgroup comprised of *COMT* genotype associated with low enzyme activity plus elevated pain catastrophizing that was at higher risk for increased pain intensity and delayed recovery from the induced injury. This high risk subgroup was then validated by demonstrating that the subgroup experienced significantly poorer 12-month postsurgical outcomes in a separate clinical shoulder pain cohort [13].

These predictive findings provided the impetus to transition our biopsychosocial influence on shoulder pain (BISP) project to an intervention phase, which will advance scientific understanding of personalized or precision treatment options for musculoskeletal pain. The intervention phase will consist of using the pre-clinical model to determine the mechanisms and efficacy of pain interventions matched to the genetic and psychological characteristics of the high-risk subgroup. The purpose of this protocol paper is to describe the rationale, methods, and data analysis for the BISP pre-clinical proof of concept trial (NCT02620579).

2. Methods

2.1. Overview

Fig. 1 provides an overview of the study design following CONSORT recommendations [32] and Table 1 provides the enrollment, intervention, and assessment schedule following SPIRIT recommendations [33]. This study has been approved by the University of Florida Institutional Review Board and all participants will provide informed consent before being enrolled. Potential participants will be screened and those meeting the high-risk criteria will be randomized into one of four intervention groups created by crossing two pharmacologic
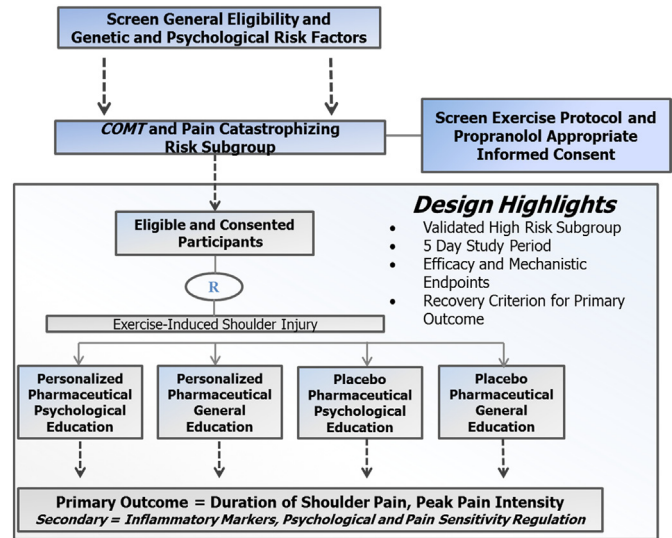

Fig. 1. Overview of biopsychosocial influence on shoulder pain design.

conditions (propranolol vs. placebo) with two education conditions (psychological intervention vs. general education), with assigned treatments administered four consecutive days. Participants will then have shoulder pain induced via exercise-induced muscle injury. This pre-clinical model was selected because it controls the injury mechanism, allows for high treatment fidelity, and has an established translational link to a post-operative clinical model [13]. The pre-clinical model also offers logistical advantages and allows us to monitor inflammatory processes, psychological factors, and pain sensitivity regulation. The primary statistical analysis will determine whether the combined personalized intervention group experienced shorter shoulder pain duration, lower peak pain intensity, or lower upper-extremity disability. The combined personalized intervention versus the combined placebo

Table 1
Schedule of enrollment, interventions, and assessments for biopsychosocial influence on shoulder pain pre-clinical trial.

Time point[a]	Study period								
	Enrollment		Allocation	Post-allocation					Close-out[b]
	−7d +	−3d	0d	0d	1d	2d	3d	4d	5d +
Enrollment									
High risk screen	X								
Eligibility screen		X							
Informed consent		X							
Allocation			X						
Interventions									
Propranolol				X	X	X	X		
Psychological education					X	X	X		
Placebo				X	X	X	X		
General education					X	X	X		
Assessments									
Demographic				X					
Pain intensity and disability				X	X	X	X	X	X
Physical impairment				X	X	X	X	X	
Psychological and pain sensitivity				X	X	X	X	X	
Inflammatory markers				X	X		X	X	
Global ratings and blinding								X	

[a] Time point units are days (d).
[b] Participants continued to be followed after last post-allocation day if they do not meet pain recovery criterion for pain intensity and disability measures only.