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# Sex differences in pain sensitivity, pain modulation, and predictors of pain intensity in patients with opioid-treated chronic lower back pain

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**SEX DIFFERENCES IN PAIN SENSITIVITY, PAIN MODULATION, AND  
PREDICTORS OF PAIN INTENSITY IN PATIENTS WITH OPIOID-TREATED  
CHRONIC LOWER BACK PAIN**

by

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B.A., Yale University, 2015

Submitted in partial fulfillment of the  
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Master of Science

2021



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**ABSTRACT**

**Purpose:** The aim of this study is to explore differences between males and females with opioid-treated chronic lower back pain in order to gain a greater understanding of how these factors may affect treatment and inform approaches to clinical care.

**Methods:** 175 participants who completed a baseline visit for a trial comparing the effectiveness of mindfulness meditation (MM) to Cognitive Behavioral Therapy (CBT) for the treatment of chronic lower back pain in adults taking a moderate to high dose of opioid medication were included in the study. Participants provided demographic information, completed a series of baseline questionnaires regarding their pain, psychological status, and medication use, and underwent assessments of pain sensitivity and pain modulation.

**Results:** Analysis by t-test demonstrated that women reported greater pain intensity and pain interference than their male counterparts. Women also reported lower pressure pain thresholds and greater sensitivity to mechanical pinprick stimuli. The association between pain intensity and pain interference was found to differ significantly by sex, with pain interference more strongly associated with increased levels of pain intensity in males compared to females.

**Conclusions:** In accordance with the available literature, women reported greater pain intensity, pain interference, and pain sensitivity than male participants. The weaker association between pain intensity and pain interference in women suggests that pain interference may be more mechanistically complex in this group, possibly with a greater role of psychosocial and other biological factors. Overall, these findings lend further support to the theory that certain biological and psychological factors which are known to differ between men and women appear to mediate the individual experience of pain.

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## LIST OF ABBREVIATIONS

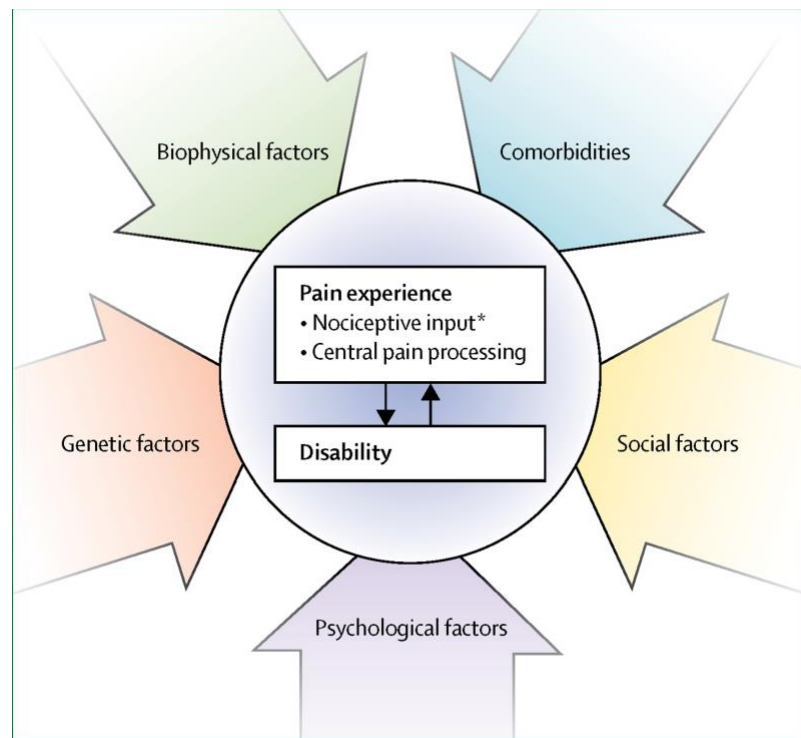
BPI .....	Brief Pain Inventory
CBT .....	Cognitive Behavioral Therapy
CDC .....	Centers for Disease Control and Prevention
COMM.....	Current Opioid Misuse Measure
CPAQ-R.....	Chronic Pain Acceptance Questionnaire - Revised
CPM .....	Conditioned Pain Modulation
HADS .....	Hospital Anxiety and Depression Scale
HADS-A .....	Hospital Anxiety and Depression Scale – Anxiety Subscale
HADS-D .....	Hospital Anxiety and Depression Scale – Depression Subscale
hsCRP.....	high-sensitivity C-reactive protein
MAAS.....	Mindful Attention Awareness Scale
MED .....	Morphine Equivalent Dose
MM .....	Mindfulness Meditation
NSAID .....	Non-Steroidal Anti-Inflammatory Drug
ODI.....	Oswestry Disability Index
PCS.....	Pain Catastrophizing Scale
PPT .....	Pressure Pain Threshold
QST.....	Quantitative Sensory Testing
SUD.....	Substance Use Disorders
TLFB .....	Timeline Follow-Back

## INTRODUCTION

### ***The Health Burden of Chronic Lower Back Pain***

Low back pain is a leading cause of disability in the United States and a major contributor to disease burden worldwide (Maher et al., 2017; US Burden of Disease Collaborators, 2013). Approximately one-fourth of U.S. adults have experienced low back pain within the past three months, with half of adults reporting low back pain within a given year (Deyo et al., 2006; Lawrence et al., 2008). Low back pain is typically classified as chronic when it persists for a duration of three months or more, which occurs in up to 15% of all cases. Chronic lower back pain is associated with a variety of comorbidities and sequelae, such as other musculoskeletal pain conditions, sleep disturbances, anxiety and depression, as well as substance use disorders (Deyo et al., 2015; Gore et al., 2012). The majority of cases of low back pain are classified clinically as nonspecific in nature or lacking an identifiable nociceptive cause. Only a small proportion of persistent cases can be directly linked to conditions such as vertebral fractures, spinal stenosis, infection, inflammatory conditions, or malignancies (Hartvigsen et al., 2018; Maher et al., 2017). Pain in other areas of the body and general physical and mental health issues tend to be more common in people reporting low back pain (Hartvigsen et al., 2018). The pain and comorbid conditions may act in synergy to amplify the effects of each condition or disease alone, resulting in a complex constellation of symptoms in which psychological, social, and biophysical factors impact quality of life and

function. (Hartvigsen et al., 2013, 2018). Over time, changes in the central and peripheral nervous system in response to nociceptive input can lead to altered pain-processing mechanisms and hypersensitivity, which may fundamentally impact an individual's experience of pain and the associated level of functional disability (Hartvigsen et al., 2018; McGreevy et al., 2011).



**Figure 1. Contributors to low back pain and disability.** An illustration of the multiple factors that contribute to the development of low back pain and disability. This model does not represent interactions between contributing factors (Hartvigsen et al., 2018).

### ***Treatment of Chronic Lower Back Pain***

In spite of the prevalence of chronic pain and its inextricable link to the human experience, the medical subspecialty of pain management and pain research as scientific disciplines are relatively new (Tompkins et al., 2017).

While the medicalization of pain and its management – which countered the previous notion of pain as a simple consequence of the aging process – helped to contribute to greater knowledge of its underlying pathophysiology and exploration of various treatment strategies, the complexity of biopsychosocial factors and variation between individuals remain particularly challenging for modern healthcare providers (Hartvigsen et al., 2013; Tompkins et al., 2017). The ability to identify individuals who are at higher risk for developing chronicity after presenting with acute pain and clear evidence regarding the steps that may be taken to prevent such an outcome are also major challenges in the treatment of pain (Koes et al., 2006). In spite of the various obstacles to effective chronic pain management, the inadequate treatment of pain may lead to significant physiological, psychological, social, and economic consequences that increase morbidity and mortality and decrease quality of life (Sarzi-Puttini et al., 2012). Current guidelines acknowledge the necessity of addressing biological, psychological, and social patient factors in lieu of a strictly biomedical approach, as well as patient centered pain care consistent with the individual’s history and goals in order to improve function (Chou et al., 2009; Hylands-White et al., 2017; Sarzi-Puttini et al., 2012).

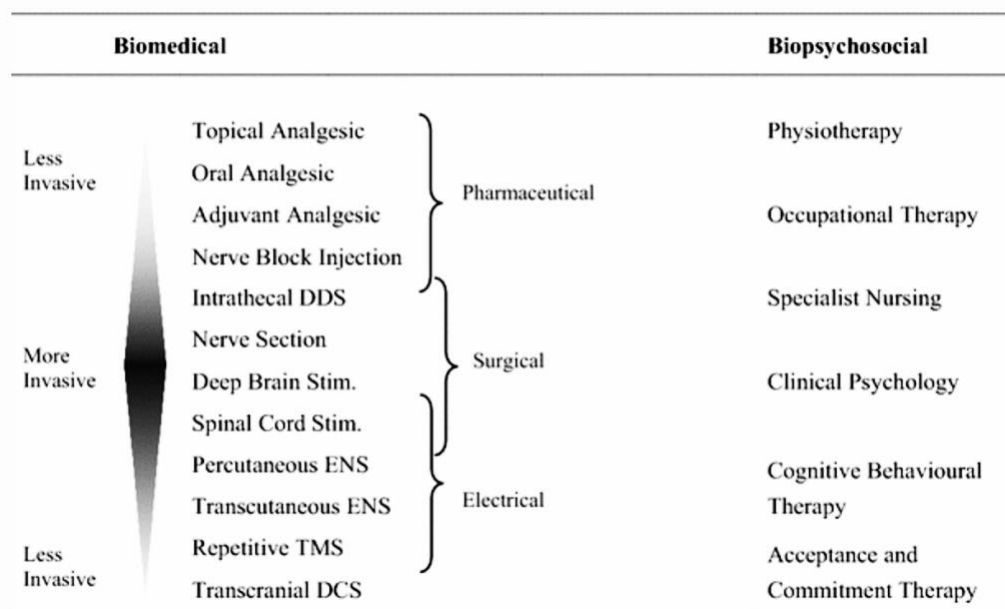
Pharmacological treatment has been at the center of chronic pain management since the late 1990’s, when pain was dubbed the “fifth vital sign” and the notion of assessment and treatment of pain as a patient right gained widespread acceptance (Tompkins et al., 2017). Analgesic medications

administered orally are typically a first-line approach, beginning with non-steroidal anti-inflammatory drugs (NSAIDs), which are supported by strong evidence in the treatment of chronic lower back pain and reduce the production of inflammatory chemicals in addition to providing relief from pain (Hooten & Cohen, 2015; Hylands-White et al., 2017). Medications considered to be weak opioid analgesics – such as codeine, dihydrocodeine, tramadol, and tapentadol – may be considered as a next step, followed by strong opioid medications, which have the benefit of greater potency with the increased risk of more severe side effects (Hooten & Cohen, 2015; Hylands-White et al., 2017; Sarzi-Puttini et al., 2012). Opioids can work similarly to endorphins, or endogenous opioids that reduce pain by attenuating the transmission of nociceptive signals in the central nervous system, and have been demonstrated to be effective in treating chronic lower back pain unresponsive to non-opioid therapies (Deyo et al., 2015; Hooten & Cohen, 2015; Hylands-White et al., 2017). However, tolerance to the effects of opioid medications can develop rapidly, even inducing pain sensitivity, while evidence for their long-term efficacy remains limited, particularly when compared with non-opioid analgesic medications (Deyo et al., 2015; Hooten & Cohen, 2015; Hylands-White et al., 2017; Koes et al., 2006). Additionally, one of the major risks associated with opioid therapy is the development of opioid use disorder and possible opioid overdose, which has contributed to an ongoing public health crisis (Volkow & Collins, 2017). Adjuvant medications, such as muscle relaxants, various classes of antidepressants, and gabapentinoids have

also demonstrated some efficacy in the treatment of chronic pain and may be prescribed along with or in some cases in place of oral analgesic medications (Hooten & Cohen, 2015).

Non-pharmacological treatments for chronic pain include medical procedures and non-invasive interventions that employ physical, psychological, or multidisciplinary modalities. Invasive procedures, which are typically reserved for cases resistant to analgesics due to their high cost and risk profile, include spinal injections, surgery, neurostimulation, and intrathecal drug delivery (Hooten & Cohen, 2015; Hylands-White et al., 2017; Koes et al., 2006; Sarzi-Puttini et al., 2012). Though these types of treatments have become more widely available over the past decade, increased use has not led to a significant reduction in disability rates, given studies demonstrating conflicting efficacy (Hooten & Cohen, 2015; Hylands-White et al., 2017). Complementary and alternative non-pharmacological approaches that address biopsychosocial factors related to pain such as massage, yoga, and psychological therapies are supported by robust evidence (Hooten & Cohen, 2015; Koes et al., 2006; Skelly et al., 2018). Interventions such as exercise, acupuncture, and spinal manipulation have also been associated with improvements in pain and physical functioning (Hooten & Cohen, 2015; Koes et al., 2006; Skelly et al., 2018). Psychological-based interventions such as cognitive behavioral therapy (CBT) – which addresses negative pain-related thoughts, feelings, and behaviors – and mindfulness meditation (MM) training – which encourages non-judgmental awareness of

bodily sensations and pain-related cognitions – have been associated with improvements in emotional functioning and pain acceptance in individuals with chronic pain (Henschke et al., 2010; Hooten & Cohen, 2015; Kabat-Zinn, 2005). These non-pharmacological treatments have been explicitly prioritized by CDC guidelines in recent years, and evidence suggests that integrating these treatments into standard medical care may be associated with favorable outcomes (Dowell et al., 2016; Hooten & Cohen, 2015). Overall, there is strong evidence for the efficacy of multidisciplinary treatment programs for chronic lower back pain, and some studies have suggested that outcomes may be further improved by matching patients to a particular treatment type (Koes et al., 2006; Skelly et al., 2018).



**Fig. 2. Treatment approaches for chronic pain management.** A diagram of biological and biopsychosocial treatments for chronic pain. *DDS* drug delivery system, *Stim.* Stimulation, *ENS* electrical nerve stimulation, *TMS* transcranial magnetic stimulation, *DCS* direct current stimulation (Hylands-White et al., 2017).

### ***Sex Differences in Chronic Pain***

Interest in sex-specific differences in the experience of pain and prevalence of chronic pain conditions has increased over the past decade (Keefe et al., 2004), with studies suggesting a number of complex and often multifactorial physiological and anatomical mechanisms that may account for observed difference. Women, for example, are more likely to experience pain as a result of disease or medical procedures, and to develop chronic pain conditions such as fibromyalgia, osteoarthritis, or low back pain (Keefe et al., 2004; Templeton, 2020). They also report greater pain sensitivity across various patient populations as well as in healthy controls, and pain in more areas of the body that is described as more severe compared to their male counterparts (Racine et al., 2012b; Sorge & Strath, 2018; Templeton, 2020). A variety of biological factors have been implicated in this observation, which can generally be ascribed to differences in anatomy, gonadal hormone production, immune-mediated inflammatory responses, and nervous system activation (Sorge & Strath, 2018; Templeton, 2020). While the terms “sex” and “gender” have often been used interchangeably, for the purposes of this research, the former is meant to refer to a dichotomous concept that reflects biological differences between men and women largely based on their respective reproductive organs, with the latter referencing a more complex and continuous designation that reflects a broad range of psychological and sociocultural characteristics typically ascribed to each sex (Racine et al., 2012b).

Several biological and physiological factors have been implicated in observed sex differences in pain between males and females. One that has received much attention is the role of gonadal hormones produced by the male testes and female ovaries. Though research findings have not been conclusive, some studies have suggested that testosterone may exert an antinociceptive or protective effect while estrogen exerts a pronociceptive effect (Bartley & Fillingim, 2013; Lund & Lundeberg, 2008). The role of these hormones in pain modulation is further supported by the distribution of sex hormone receptors in areas of the nervous system associated with nociceptive processing, and observations that the hormonal cyclicity of women contributes to variations in pain sensitivity during different phases of the menstrual cycle (Bartley & Fillingim, 2013; Mogil, 2012). Given that sex hormones affect the development and function the immune system, and that various immune cells play an important role in pain processing, immunological mechanisms are also believed to underlie observed sex differences in clinical and experimental pain (Rosen et al., 2017). Females tend to mount a more robust immune response than their male counterparts, particularly in terms of adaptive immunity, and recent research has suggested that the influence of sex hormones on various pathways of the immune system may predispose women to the development and maintenance of chronic inflammatory and neuropathic pain (Doyle & Murphy, 2017; Rosen et al., 2017). Additional evidence suggests that gonadal hormones may influence the endogenous opioid system, contributing to differences in activation of mu-opioid

receptors and cortical activity during the processing of pain-related stimuli that may also help to account for sex-based differences in the experience of pain (Bartley & Fillingim, 2013; Lund & Lundeborg, 2008).

Various theories may help to explain differences in pain between sexes as a function of psychological factors. Sex differences in psychological states or certain patterns of ideation that are believed to modulate the experience of pain – such as anxiety, negative affect, catastrophizing, self-efficacy, somatic awareness, and coping – may contribute significantly to sex differences in pain, and in some cases were found to be entirely responsible for observed differences in pain between sexes (Bartley & Fillingim, 2013; Mogil, 2012; Wiesenfeld-Hallin, 2005). Coping strategies, for example, have been found to differ significantly between males and females (Bartley & Fillingim, 2013). Problem-focused techniques and distraction tend to be most effective and widely utilized amongst males, while females rely upon a wider range of strategies including emotion-focused techniques, attentional focus, cognitive reinterpretation of pain sensations, social support and positive self-statements (Bartley & Fillingim, 2013; Fillingim et al., 2009; Keogh & Eccleston, 2006; Racine et al., 2012b; Unruh et al., 1999). Additionally, women often report higher levels of pain-related catastrophizing, which may mediate sex differences in pain-related outcomes as well as in the interaction between pain intensity and opioid prescription (Bartley & Fillingim, 2013; Fillingim et al., 2009; Keogh & Eccleston, 2006; Sharifzadeh et al., 2017).

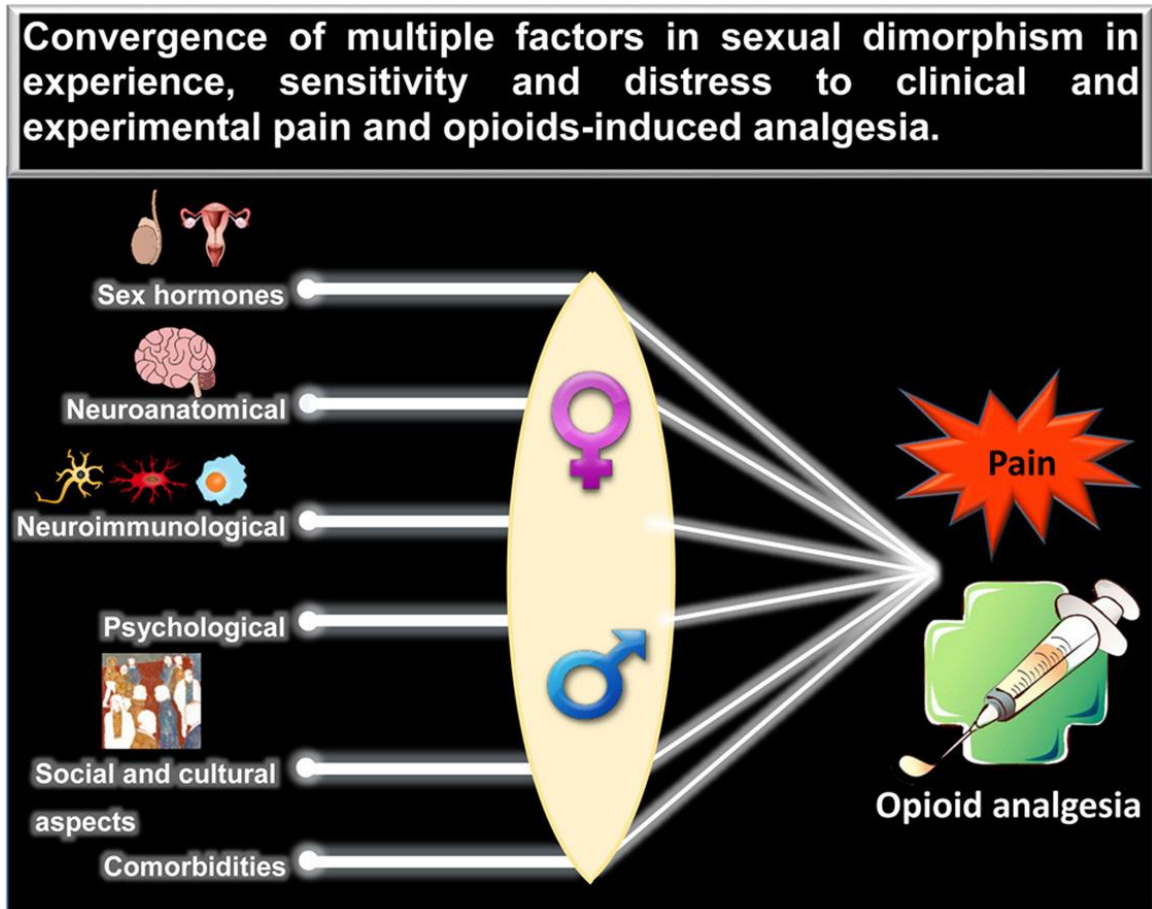
Women also report lower levels of perceived self-efficacy, which refers to the belief that one can successfully perform a behavior required to generate a successful outcome or desired goal (Bartley & Fillingim, 2013; Racine et al., 2012b). Greater levels of self-efficacy have been linked to lower levels of pain, pain sensitivity, and other pain-related physical symptoms (Bartley & Fillingim, 2013; Racine et al., 2012). Higher pain sensitivity amongst women may be driven by increased levels of hypervigilance (more focus and attention given to threatening situations) and bodily monitoring, along with a higher prevalence of psychological conditions such as anxiety and depression (Wiesenfeld-Hallin, 2005). Psychological factors contributing to sex differences in pain perception and pain expression are likely mediated by social factors such as stereotypes and beliefs or expectations regarding sex-specific roles and the nature of femininity or masculinity. This sociocultural element may lead to biased reporting of pain, with females at liberty to express pain behaviors and males being discouraged from doing so (Bartley & Fillingim, 2013; Mogil, 2012).

The physiological and psychological sex differences that affect the perception of and response to pain may also be significant in the context of opioid therapy. Although research into the association between sex and opioid efficacy has yielded inconclusive results (Doyle & Murphy, 2017; Niesters et al., 2010), key differences in drug binding and activation of the endogenous analgesic system have been reported (Wiesenfeld-Hallin, 2005). Compared to their male counterparts, women are more likely to obtain prescription opioid

medication and to experience opioid related side effects (Fillingim et al., 2005; Serdarevic et al., 2017). Studies have also suggested that women across all age groups are at a greater risk for opioid abuse, with an annual percentage increase in the death rate from prescription opioid-related overdose significantly outpacing that of men (Koons et al., 2018; Templeton, 2020). This corresponds to a striking increase in the incidence of neonatal opioid withdrawal syndrome over the past decade (Templeton, 2020). Psychiatric comorbidity and experiences of trauma may play an important role in this disparity, given the increased prevalence of gender-based violence and sexual abuse in women (Koons et al., 2018). Indeed, amongst individuals with opioid use disorder, psychiatric comorbidity was found to be more common, as well as more severe, in women and adolescent girls relative to their male peers (Bagley et al., 2020; Koons et al., 2018; McHugh et al., 2013).

In addition to being at a greater risk for pain syndromes and more responsive to painful stimuli, women report on their pain, seek out healthcare providers, and are targeted by pharmaceutical advertising more frequently than men (Koons et al., 2018; Mazure & Fiellin, 2018). Studies using virtual human technology have demonstrated that healthcare providers and trainees may use female sex as a cue for greater pain intensity, pain unpleasantness, and indication for opioid medication treatment when evaluating patients presenting with pain (Hirsh et al., 2009; Wandner et al., 2010). This is notable, given that

women with opioid use disorders are more likely than men to have first obtained opioids via prescription from a healthcare provider (McHugh et al., 2013).



**Figure 3. Convergence of multiple factors in sexual dimorphism in experience, sensitivity and distress to clinical and experimental pain and opioids-induced analgesia.** An illustration of the various factors that contribute to sex-based differences in pain and analgesia (Nasser & Afify, 2019).

## **SPECIFIC AIMS**

Previous studies have identified a variety of biological, psychological, and social factors that contribute to sex differences in the experience of pain and which may have an impact on opioid therapy for chronic pain management. However, the influence of these sex-specific factors and the way in which they interact amongst individuals suffering from chronic lower back pain who are taking a moderate to high dose of daily opioid medication remains unclear. The purpose of this study was to elucidate sex-specific differences within this population in order to expand the existing literature and to help inform more individualized clinical care.

## METHODS

### *Participants and Study Design*

The current study uses baseline data collected between 2017 and 2020 as part of a large multi-site clinical research trial comparing the effectiveness of mindfulness meditation (MM) to Cognitive Behavioral Therapy (CBT) in adults with opioid-treated chronic lower back pain (PCORI OPD-1601-33860; [clinicaltrials.gov/ct2/show/NCT03115359](https://clinicaltrials.gov/ct2/show/NCT03115359)). After providing informed consent, participants completed a series of baseline questionnaires assessing their pain, psychological status, medication use, and demographic information. Participants subsequently underwent quantitative sensory testing (QST) assessments of pain sensitivity and pain modulation, as described below. All procedures were approved by the Institutional Review Board of the University of Wisconsin-Madison, in conjunction with the Partners Healthcare Institutional Review Board.

Participants from the Boston metropolitan area were recruited via public advertisements, direct referrals by study-affiliated physicians, and targeted mailings to individuals identified through electronic health record databases at Brigham and Women's Hospital. Participants were included if they were at least 21 years of age, experienced low back pain on a daily basis for 3 months or longer, rated their pain as a 3 or greater on a 0-10-point scale, scored a 21 or above – indicating at least moderate disability – on the Oswestry Disability Index, and reported daily prescription opioid medication use for back pain equal to 15mg of morphine equivalent dose (MED) or more. Potential participants were

excluded if they reported that their back pain was concentrated outside of the low back (lumbar area or sciatic joint), were unwilling or unable to participate in the group therapy sessions and data collection activities, had previously received formal training in MM or CBT, did not speak English fluently – as groups were conducted only in English – or had been diagnosed with an exclusionary mental health disorder. Individuals with schizophrenia, schizoaffective or other delusional disorders, bipolar disorder with manic episodes, or borderline personality disorder were excluded due to challenges related to group participation. Incarcerated adults, pregnant women, and adults who were unable to provide informed consent were also excluded from the study.

### ***Self-Report Measures***

#### **Brief Pain Inventory**

The Brief Pain Inventory (BPI) provides a rapid assessment of the patient pain experience by addressing an individual's pain as well as its impact on daily functioning (Cleeland & Ryan, 1994). To assess pain severity, participants were asked to rate their pain on a scale of 0 (no pain) to 10 (pain as bad as you can imagine) at its worst in the past week, at its least in the past week, on average, and at the time of survey completion. To assess pain interference, participants were asked to indicate the degree to which their pain has interfered with their general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life during the past week, on a scale of 0 (does not

interfere) to 10 (completely interferes). Scores on the four pain severity items and seven pain interference items were averaged to determine a composite score for each. The BPI is valid and reliable in assessing cLBP (Keller et al., 2004; Tan et al., 2004) and has been studied in various populations with non-cancer pain.

### Oswestry Disability Index

The Oswestry Disability Index (ODI) is a valid and vigorous measure used to assess functional disability due to low back pain (Fairbank et al., 1980; Fairbank & Pynsent, 2000). The survey comprises ten items covering the topics of pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life and traveling. For each item, participants selected one of six statements corresponding to scores of 0 (least disability) through 5 (greatest disability) that most closely aligned with his or her ability. Item scores were summed, divided by the total possible score, and multiplied by 100 to determine an aggregate score reflecting the percent of disability. (The sex life section was designated “if applicable” and the total possible score was reduced by 5 if participants chose to leave this item unanswered). The ODI is reliable and responsive to change in evaluating the effectiveness of treatment for cLBP (Chapman et al., 2011; Davidson & Keating, 2002).

### Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a reliable measure for detecting and assessing the symptom severity of depression and anxiety disorders in outpatient populations (Bjelland et al., 2002; Zigmond & Snaith, 1983). The 14-item measure intermingles 7 items corresponding to an anxiety subscale (HADS-A) and 7 items corresponding to a depression subscale (HADS-D). Participants rated each item on a Likert scale ranging from 0 (absence) to 3 (extreme presence), with a total possible score of 21 for each subscale (Bond et al., 2019). Greater negative affect, as indicated by higher scores on the HADS, has been associated with poorer outcomes in opioid-treated individuals with chronic pain (Jamison et al., 2013; Martel et al., 2014).

#### Mindful Attention Awareness Scale

The Mindful Attention Awareness Scale (MAAS) is a 15-item measure designed to assess dispositional mindfulness, or a receptive state of mind characterized by non-judgmental attention to and awareness of events occurring in the present (Brown & Ryan, 2003; Carlson & Brown, 2005). Participants were asked to indicate the frequency with which they have the experience described in each item using a 6-point Likert scale ranging from 1 (almost always) to 6 (almost never). The sum of all 15 items was computed to determine the final score, with higher scores corresponding to higher levels of mindfulness.

#### Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) is a 13-item measure that assesses catastrophizing in terms of three components, namely rumination, magnification and helplessness (Osman et al., 1997; Sullivan et al., 1995). Participants were asked to indicate the degree to which they experience certain thoughts and feelings indicative of catastrophizing in response to pain, on a scale from 0 (not at all) to 4 (all the time). Item scores were summed to determine an aggregate score of pain catastrophizing. The PCS is a valid and reliable assessment in individuals with chronic lower back pain (Van Damme et al., 2002).

#### Chronic Pain Acceptance Questionnaire - Revised

The revised version of the Chronic Pain Acceptance Questionnaire (CPAQ-R) is a 20-item measure that assesses acceptance of chronic pain in terms of an individual's engagement in daily activities irrespective of pain and willingness to experience pain rather than trying to avoid it (McCracken et al., 2004). Participants rated the statement in each item using a 7-point Likert scale ranging from 0 (never true) to 6 (always true), with higher scores indicating greater pain-related acceptance. Item scores were summed to determine an aggregate score of chronic pain acceptance.

#### Current Opioid Misuse Measure

The Current Opioid Misuse Measure (COMM) is a 17-item measure developed to provide a brief assessment of aberrant drug-related behaviors in

chronic pain patients on long-term opioid therapy (Butler et al., 2007).

Participants were asked to rate the frequency with which they experienced situations indicative of medication misuse over the past 30 days, on a 5-point Likert scale ranging from 0 (never) to 4 (very often). Item scores were summed to determine an aggregate score of opioid misuse. Unlike measures that predict misuse behaviors by assessing patient characteristics, the COMM helps to identify active misuse with strong reliability and predictive validity (Butler et al., 2010).

#### Timeline Follow-Back

The Timeline Follow-Back (TLFB) is a reliable calendar-based method of evaluating daily patterns and frequencies of drug or alcohol use during a given period of time (Fals-Stewart et al., 2000; Sobell & Sobell, 1992). To complete the survey, participants were provided with a visual calendar indicating the 14-day period of interest and asked to list the names and dosages of any opioid medications taken within that timeframe. Research coordinators were able to provide assistance in the case of any uncertainty regarding a particular medication's opioid classification. Participants then provided retrospective estimates of their opioid medication use for each day, beginning with the day prior to survey completion and working backwards. All reported opioids were converted to converted to a morphine equivalent dose using standard conversion factors (see Appendix). Medication use for each day was summed, and the mean was computed to determine the average daily (morphine equivalent) opioid

dose in mg/day. Participants were also encouraged to include information regarding medication from current prescriptions, previous prescriptions, as well as other sources in order to accurately capture the full extent of opioid medication use.

### ***Quantitative Sensory Testing***

Participants underwent a brief battery of quantitative sensory tests to assess pain sensitivity and pain modulation. These standardized psychophysical assessments have been recommended for clinical phenotyping, and can provide novel information with respect to an individual's somatosensory functioning (Attall et al., 2011; Backonja et al., 2013).

Pain sensitivity was first assessed using a digital pressure algometer (Somedic; Sollentuna, Sweden) to determine participants' mechanical pain thresholds. Force was applied at a steadily increasing rate of 30 kPA/s until the subject indicated that the pressure sensation was "first perceived as painful." These pressure pain thresholds (PPTs) were determined bilaterally at the trapezius muscle, lower back, and thumb, with two trials performed on each side of the body. Next, weighted probes ranging from 64-256mN were used to assess mechanical temporal summation. A train of 10 pinprick stimuli was applied at a rate of 1 per second to the skin on the dorsum of the right middle finger between the two interphalangeal joints. The lowest-force probe that produced pain rated as 20 or greater on a 0-100 scale was used in this step. Participants provided

pain ratings for the 1<sup>st</sup>, 5<sup>th</sup>, and 10<sup>th</sup> stimuli, and temporal summation was determined by calculating the difference in pain intensity ratings between the 10<sup>th</sup> and 1<sup>st</sup> stimuli.

Conditioned pain modulation (CPM) was assessed using a series of cold pressor tasks, involving immersion of the dominant hand in a bath of circulating cold water at a constant temperature of 4°C. Participants were asked to immerse their hand in the water for up to 20 seconds, at which point the PPT was assessed on the contralateral trapezius muscle. After a 2-minute break, this procedure was repeated a second time, completing one full trial. Two trials were performed, and CPM was calculated as a ratio of the PPT during the cold pressor task relative to the baseline PPT. Participants were also asked to rate any lingering cold pain at 15 and 30 seconds following withdrawal of the hand from the cold water bath. A final cold pressor task was carried out in which the participant immersed the dominant hand in the cold water until either pain tolerance was reached or three minutes had elapsed.

### ***Data Analysis***

Differences between sexes were compared using a series of independent t-tests for continuous variables and chi-square analyses for categorical variables. The relationship between pain intensity with clinical outcomes, measures of pain sensitivity, and measures of pain modulation in the male and female participant groups were examined using Pearson correlations. Given that pain interference

was the only significant predictor of pain intensity common to both sexes, additional analysis was carried out to determine whether this factor played a similar role in both males and females. Thus, the correlation between pain intensity and pain interference was further explored using linear regression and Fisher's z-transformation analysis. Finally, multiple regression analysis was conducted to determine a predictive model for pain intensity in males and females. Only variables that were significantly associated with pain intensity in males, females, or both groups were included in the model.

## RESULTS

### *Participant Characteristics*

The sample consisted of 175 participants, including 99 females and 76 males with an average age of 58 years and 60 years, respectively (see Table 1). All participants suffered from moderate to severe chronic low back pain being treated with 15 mg/day of morphine-equivalent opioid dose or greater for a duration of at least three months. There were no significant differences between the groups with respect to age, race, ethnicity, education level, employment status or smoking history; additional information is presented in Table 1.

**Table 1. Participant Characteristics**

Characteristics	Female (n=99)	Male (n=76)	t or X <sup>2</sup> statistic
Age, mean (SD)	58.2 (10.1)	60.4 (10.9)	-1.3
Race, n (%)			7.9
American Indian or Alaska Native	2 (2)	0 (0)	
Asian	0 (0)	0 (0)	
Black or African American	25 (25)	12 (16)	
Native Hawaiian or Pacific Islander	0 (0)	0 (0)	
White	56 (57)	57 (75)	
More than one race	8 (8)	3 (4)	
Other	4 (4)	1 (<1)	
Unknown	4 (4)	3 (4)	
Ethnicity, n (%)			0.9
Hispanic or Latino	4 (4)	4 (5)	
Not Hispanic or Latino	77 (78)	62 (82)	
Unknown	18 (18)	10 (13)	
Education, n (%)			10.7
No High School Diploma	8 (8)	4 (5)	
High School Graduate or GED	11 (11)	15 (20)	
Some College, No Degree	22 (22)	20 (26)	
Occupational/Technical/Vocational Program	4 (4)	9 (12)	
Associate Degree	12 (12)	6 (8)	

Bachelor's Degree	29 (29)	12 (16)	
Graduate or Professional Degree	11 (11)	9 (12)	
Unknown	2 (2)	1 (1)	
<hr/>			
Employment, n (%)			4.4
Working	10 (10)	6 (8)	
Unemployed	8 (8)	6 (8)	
Sick Leave or Maternity Leave	0 (0)	1 (1)	
Disabled, Due to Back Pain	37 (37)	29 (38)	
Disabled, Not Due to Back Pain	19 (19)	9 (12)	
Retired	16 (16)	16 (21)	
Student	3 (3)	2 (3)	
Other	5 (5)	5 (7)	
Unknown	1 (1)	2 (3)	
<hr/>			
Smoking History, n (%)			0.4
Never Smoked	38 (38)	29 (38)	
Current Smoker	18 (18)	16 (21)	
Former Smoker	40 (40)	28 (37)	
Unknown	3 (3)	3 (4)	
<hr/>			
**p<.01			
*p<.05			
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### ***Sex Differences in Clinical Outcomes***

There were no differences in anxiety, depression, mindfulness, catastrophizing, or chronic pain acceptance scores between men and women (Table 2). Compared to male participants, females expressed greater pain intensity ( $t_{172}=2.37, p<0.05$ ), as well as higher levels of pain interference ( $t_{168}=2.80, p<0.01$ ). Pain disability and opioid misuse did not differ between the two groups. However, male participants reported a higher average dose of daily opioid medication compared to their female counterparts ( $t_{74.6}=-3.28, p<0.01$ ).

**Table 2. Independent t-tests for Clinical Outcomes**

Outcome	Group	Mean	Std. Deviation	t	d
Anxiety	Female	9.82	3.08	0.72	0.11
	Male	9.49	2.73		
Depression	Female	9.02	2.26	-1.44	0.23
	Male	9.51	1.98		
Mindfulness	Female	55.13	26.53	-1.65	0.26
	Male	61.55	22.82		
Catastrophizing	Female	22.84	13.11	1.09	0.17
	Male	20.66	12.25		
Chronic Pain Acceptance	Female	61.69	15.18	-0.46	0.07
	Male	62.76	14.05		
Pain Intensity	Female	6.79	1.55	2.37*	0.36
	Male	6.24	1.47		
Pain Interference	Female	7.00	1.76	2.80**	0.43
	Male	6.21	1.93		
Disability	Female	51.97	17.36	1.45	0.25
	Male	47.88	15.13		
Opioid Misuse	Female	8.78	6.84	-0.62	0.09
	Male	9.44	7.07		
Opioid Dose (mg/day)	Female	46.51	50.14	-3.28**	0.57
	Male	118.55	172.10		

\*\*p<.01  
\*p<.05

***Sex Differences in Pain Sensitivity***

There were significant sex-based differences in pain sensitivity across a number of QST modalities. Compared to males, females reported lower pain thresholds in response to mechanical pressure applied to the trapezius ( $t_{71.5}=-4.82$ ,  $p<.01$ ), the lower back ( $t_{74.4}=-3.31$ ,  $p<.01$ ), and the thumb ( $t_{81.3}=-4.21$ ,  $p<.01$ ). Additionally, females provided higher pain intensity ratings for mechanical punctate probes of various forces ( $t_{113.1}=2.17$ ,  $p<.05$ ) and reported

greater painful aftersensations following administration of the pin prick stimuli ( $t_{100.8}=2.13$ ,  $p<.05$ ), suggesting differences in hyperalgesia. Both male and female participants demonstrated temporal summation of mechanical punctate pain, but there were no group differences in the pain ratings provided for the 1<sup>st</sup>, 5<sup>th</sup>, and 10<sup>th</sup> sequential stimuli or in the overall temporal summation of the probes (Table 3).

**Table 3. Independent t-tests for QST Outcomes**

Outcome	Group	Mean	Std. Deviation	t	d
Pressure Pain Threshold - Trapezius	Female	234.75	108.49	-4.82**	0.92
	Male	382.06	198.05		
Pressure Pain Threshold - Low Back	Female	222.82	119.75	-3.31**	0.63
	Male	330.20	207.33		
Pressure Pain Threshold - Thumb	Female	230.64	104.06	-4.21**	0.80
	Male	335.97	155.50		
Mean Pain Rating 64-256mN Probes	Female	12.91	16.65	2.17*	0.38
	Male	7.78	9.13		
1 <sup>st</sup> Stimulus Pain Rating	Female	14.64	15.79	0.84	0.15
	Male	12.20	15.75		
5 <sup>th</sup> Stimulus Pain Rating	Female	26.35	22.58	1.64	0.31
	Male	19.97	18.51		
10 <sup>th</sup> Stimulus Pain Rating	Female	34.59	28.00	1.62	0.30
	Male	26.67	23.97		
Temporal Summation of Probes	Female	20.36	20.07	1.68	0.31
	Male	14.47	17.24		
Painful Probe Aftersensations	Female	6.34	13.29	2.13*	0.37
	Male	2.52	5.82		

\*\*p<.01

\*p<.05

### ***Sex Differences in Pain Modulation***

Female participants reported a lower baseline pain threshold ( $t_{65.9}=-4.09$ ,  $p<.01$ ) as well as a lower conditioned pain response ( $t_{76.3}=-4.08$ ,  $p<.01$ )

compared to males. However, there were no group differences in the cold pain rating, time to withdraw, maximum cold pain rating, or painful cold aftersensations. Similarly, no differences in conditioned pain modulation between male and female participants were observed (Table 4).

**Table 4. Independent t-tests for CPM Outcomes**

Outcome	Group	Mean	Std. Deviation	t	d
Baseline Pain Threshold	Female	216.30	114.54	-4.09**	0.79
	Male	362.28	233.35		
Cold Pain Rating	Female	60.60	28.94	-0.59	0.11
	Male	63.86	30.19		
Time to Withdraw	Female	16.33	4.54	0.49	0.09
	Male	15.88	5.37		
Conditioned Pain Response	Female	306.69	155.91	-4.08**	0.79
	Male	465.14	238.22		
Maximum Cold Pain Rating	Female	68.60	27.48	0.12	0.02
	Male	67.96	30.45		
Painful Cold Aftersensations	Female	18.56	23.71	1.70	0.31
	Male	12.16	17.25		
Conditioned Pain Modulation	Female	90.39	96.15	-0.55	0.10
	Male	100.14	93.20		

\*\*p<.01

\*p<.05

### ***Predictors of Pain Intensity by Sex***

Results of Pearson correlations indicated differing associations between pain intensity and the remaining clinical and experimental outcomes in male and female participant groups. In female participants, greater pain intensity was associated with greater catastrophizing ( $r=.318$ ;  $p<0.01$ ), higher levels of pain interference ( $r=.334$ ;  $p<0.01$ ), and a greater maximum cold pain rating ( $r=.238$ ;  $p<0.05$ ). In male participants, greater pain intensity was associated with higher

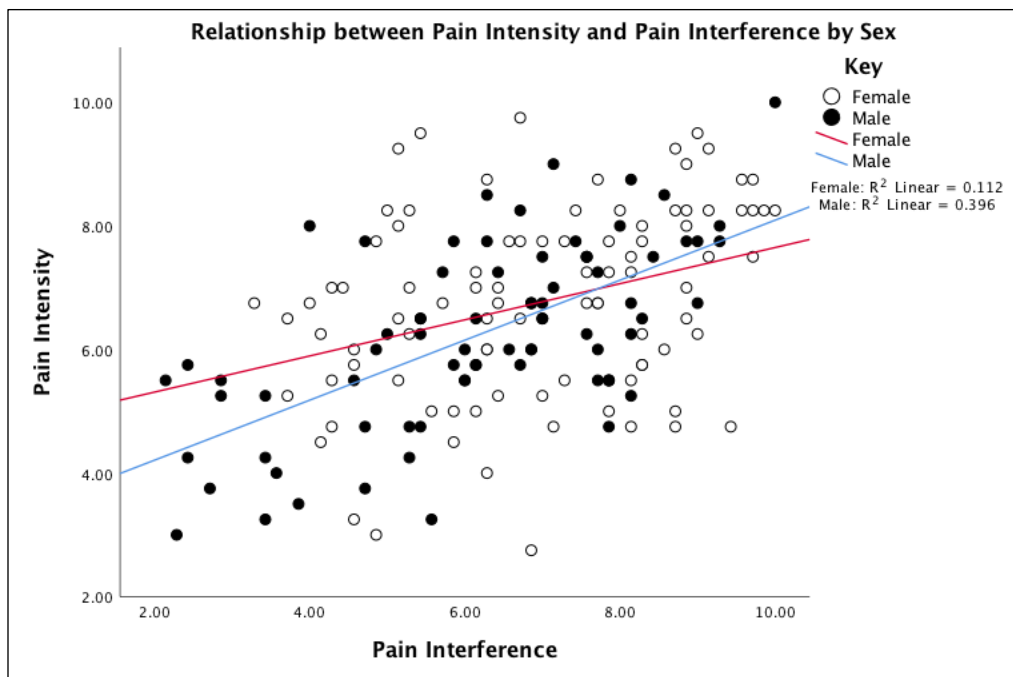
levels of pain interference ( $r=.629$ ;  $p<0.01$ ), greater disability ( $r=.436$ ;  $p<0.01$ ), less conditioned pain modulation ( $r=-.298$ ;  $p<0.05$ ), and lower pain intensity ratings for mechanical punctate probes of various forces ( $r=-.394$ ;  $p<0.01$ ) and the first sequential pin prick stimulus ( $r=-.292$ ;  $p<0.05$ ; see Table 5).

**Table 5. Pearson Correlations for Pain Intensity by Sex**

	Female	Male
Anxiety	0.137	0.130
Depression	0.190	-0.073
Mindfulness	-0.101	-0.134
Catastrophizing	0.318**	0.230
Chronic Pain Acceptance	-0.020	0.097
Pain Interference	0.334**	0.629**
Disability	0.186	0.436**
Opioid Misuse	0.120	0.080
Opioid Dose (mg/day)	-0.002	0.125
Pressure Pain Threshold - Trapezius	-0.143	0.119
Pressure Pain Threshold - Low Back	-0.034	-0.022
Pressure Pain Threshold - Thumb	0.146	0.178
Mean Pain Rating 64-256mN Probes	0.200	-0.394**
1 <sup>st</sup> Stimulus Pain Rating	-0.137	-0.292*
5 <sup>th</sup> Stimulus Pain Rating	0.012	-0.206
10 <sup>th</sup> Stimulus Pain Rating	-0.037	-0.203
Temporal Summation of Probes	0.048	-0.015
Painful Probe Aftersensations	0.071	-0.204
Baseline Pain Threshold	-0.203	0.210
Cold Pain Rating	0.201	-0.019
Time to Withdraw	0.031	-0.043
Conditioned Pain Response	-0.079	0.106
Maximum Cold Pain Rating	0.238*	-0.084
Painful Cold Aftersensations	0.177	-0.024
Conditioned Pain Modulation	0.115	-0.298*

Simple linear regression analysis was used to visualize the association between pain intensity and pain interference in males and females, and the

results of a Fisher Z-Transformation indicated that this correlation differed significantly between sexes ( $z=3.26$ ;  $p<0.01$ ). In other words, across the range of the pain intensity and pain interference scales, greater pain intensity was more strongly associated with higher levels of pain interference in male participants compared to females.



**Figure 4. Relationship between Pain Intensity and Pain Interference by Sex**

Significant variables from the Pearson correlations were used to create a regression model predicting pain intensity in the female and male participant groups. Pain intensity in female participants was significantly predicted by the regression equation  $F(7,40) = 2.267$ ,  $p<.05$ , with an  $R^2$  of 0.284. However, only pain interference and the 1<sup>st</sup> stimulus pain rating in in pain sensitivity testing

contributed significantly to the model (see Table 6). In male participants, the regression equation  $F(7,30) = 6.494$ ,  $p < .01$ ,  $R^2 = 0.602$  also significantly predicted pain intensity. In this case, pain interference and conditioned pain modulation were the only two variables that were significant predictors of pain intensity (see Table 6).

**Table 6. Linear Regression Analysis Results for Variables Predicting Pain Intensity**

	Females		
	<i>B</i>	<i>SE B</i>	$\beta$
Catastrophizing	-0.004	0.015	-0.040
Pain Interference	0.349	0.141	0.441*
Disability	-0.004	0.012	-0.050
Mean Pain Rating 64-256mN Probes	0.022	0.015	0.247
1 <sup>st</sup> Stimulus Pain Rating	-0.025	0.011	-0.320*
Maximum Cold Pain Rating	0.005	0.008	0.117
Conditioned Pain Modulation	-0.001	0.002	-0.081
Note: $R^2 = 0.284$ , $F = 2.267^*$			
	Males		
	<i>B</i>	<i>SE B</i>	$\beta$
Catastrophizing	-0.012	0.016	-0.100
Pain Interference	0.431	0.120	0.509**
Disability	0.011	0.013	0.111
Mean Pain Rating 64-256mN Probes	-0.041	0.024	-0.236
1 <sup>st</sup> Stimulus Pain Rating	-0.027	0.017	-0.219
Maximum Cold Pain Rating	0.002	0.006	0.032
Conditioned Pain Modulation	-0.005	0.002	-0.289*
Note: $R^2 = 0.60$ , $F = 6.49^{**}$			
** $p < .01$			
* $p < .05$			

## DISCUSSION

The current study examined the differences in pain-related clinical outcomes, pain sensitivity, and pain modulation between males and females with opioid-treated chronic lower back pain. Results indicated that women experience greater pain intensity and pain interference in addition to demonstrating increased pain sensitivity across various somatosensory measures compared to their male counterparts. While no sex differences in pain modulation were detected, the correlation between pain intensity and pain interference differed significantly between males and females, indicating that different mechanisms may underlie pain-related functional outcomes. Some studies have suggested that inflammatory markers such as the high-sensitivity C-reactive protein (hsCRP) could play a role in mediating this interaction and contributing to sex-specific differences in pain interference (Eslami et al., 2017).

In accordance with the available literature, women reported greater pain intensity and pain interference compared to male participants. Females also demonstrated increased pain sensitivity compared to males during quantitative sensory testing. These findings lend further support to the theory that certain biological and psychological factors which are known to differ between men and women appear to mediate the individual experience of pain. Although no significant group differences were observed in terms of anxiety, depression, mindfulness, catastrophizing or pain acceptance, catastrophizing was only found

to be a significant predictor of pain intensity in the female participants. While prior studies have indicated that increased levels of catastrophizing amongst women may account for the greater prevalence of pain-related conditions and increased levels of pain intensity reported by women (Meints et al., 2019; Sharifzadeh et al., 2017), these results suggest that a given level of catastrophizing may also have a more pronounced impact on the experience of pain in women as compared to men.

The relationship between pain intensity and pain interference also helps to provide insight into the impact of chronic pain and possible mechanistic differences between males and females. Pain interference was associated with greater pain intensity in both females ( $r=.334$ ;  $p<0.01$ ) and males ( $r=0.629$ ;  $p<0.01$ ; see table 5). In male participants, the correlation between pain intensity and pain interference was sixty-three percent, contrasting with thirty-three percent in female participants. While results for both groups demonstrate that pain interference is a significant predictor of pain intensity, for male participants pain intensity accounts for sixty-three percent, or the majority of variation in pain interference. In other words, the major contributing factor to pain interference in males is simply the intensity of the pain itself. In comparison, pain intensity can be interpreted as accounting for only thirty-three percent of variation in pain interference for females, leaving sixty-seven percent attributable to other factors. Pain interference in females with chronic pain is mechanistically complex and likely driven by a number of physical and psychosocial factors, amongst which

the intensity of the pain itself plays a more limited role. Previous studies have suggested that pain-related catastrophizing, psychiatric disorders, and co-occurring drug abuse or dependence may play a unique role in contributing to pain interference amongst women (Barry et al., 2012; Meints et al., 2019).

Several limitations should be considered when interpreting these findings. Firstly, males and females were not equally represented within the sample, and the overall sample size of individuals from an urban geographic area may not be generalizable to other groups with chronic lower back pain. Secondly, racial and ethnic variability within the study sample was limited, with sixty-five percent of individuals identifying as white, and seventy-nine percent identifying as non-Hispanic. This is particularly significant given the substantial body of literature indicating that race and ethnicity can impact the experience and treatment of pain, particularly amongst racial and ethnic minority groups. Thirdly, limiting the sample to individuals taking a moderate-to-high daily dose of opioid medication, and reporting at least a moderate level of disability, may limit generalizability of the study results to patients with lower levels of functional impairment or those receiving lower doses of prescription opioid medication or no opioids at all. (In some cases, this may be the result of physician bias or limited access to healthcare, rather than a matter of choice or a desire to limit one's reliance upon opioid medications.)

An additional limitation that should be noted is the potential influence of a reporting bias amongst male participants. Several studies have suggested that male research subjects may be more likely to under-report clinical and experimental pain compared to females (Bartley & Fillingim, 2013; Mogil, 2012; Wiesenfeld-Hallin, 2005), which may have had an impact on the study results. Surveys were also administered in written format, which may impact result validity or have led to selection bias against individuals with limited health literacy. Additionally, individuals with substance use disorders (SUDs) are known to have high rates of chronic pain and opioid use, but thorough substance use histories were not collected as part of this research study, impacting our ability to explore SUD as a confounder or cofactor of pain relationships. Finally, because the data were not longitudinal in nature, there was no way to control for confounding factors at the individual level, such as those that may be linked to personality traits or one's specific medical, psychological, or social history.

In conclusion, this study lends further support to previous observations that women experience greater pain intensity, pain interference, and overall pain sensitivity as compared to their male counterparts. Furthermore, it provides additional insight into the role of catastrophizing and the link between pain intensity and pain interference within the context of sex differences in pain. These findings may help to inform a more personalized approach to clinical care that accounts for sex-specific factors that contribute to the individual experience of pain. For example, recent studies have suggested that multimodal treatment,

cognitive behavioral therapy, and acceptance and commitment therapy demonstrate strong evidence for the treatment of chronic non-cancer pain in adults with high levels of pain catastrophizing (Schütze et al., 2018). Additionally, this research draws attention to the need for evidence-based practices for the treatment of chronic pain in women, who are disproportionately afflicted by the condition yet often underrepresented in pain-related research (Racine et al., 2012a). Further investigation may also be warranted to determine how these sex-specific phenomena relate to gender identity, and whether these findings can be translated to non-gender-conforming individuals.

## APPENDIX

<b>Morphine Milligram Equivalent (MME) Conversion Factors</b>		
<b>Opioid medication (generic name)</b>	<b>Unit</b>	<b>MME Conversion Factor per Unit</b>
Buprenorphine patch (applied to skin) *	mcg/hr	12.6
Buprenorphine tablet or film (dissolve in mouth)	mg	30
Buprenorphine tablet or film (dissolve in mouth)	mcg	0.03
Butorphanol nasal solution	mg	7
Codeine	mg	0.15
Dihydrocodeine	mg	0.25
Fentanyl tablets, lozenges (dissolve in mouth)	mcg	0.13
Fentanyl oral spray or film (dissolves in mouth)	mcg; mcg/ml	0.18
Fentanyl nasal (nose) spray	mcg/ml	0.16
Fentanyl patch (applied to skin) **	mcg/hr	7.2
Hydrocodone	mg	1
Hydromorphone	mg	4
Levorphanol	mg	11
Meperidine	mg	0.1
Methadone		
(1-20)	mg	4
(21-40)	mg	8
(41-60)	mg	10
(>60)	mg	12
Morphine	mg	1
Nalbuphine	mg	1
Opium	mg	1
Oxycodone	mg	1.5
Oxymorphone	mg	3
Pentazocine	mg	0.37
Tapentadol	mg	0.4
Tramadol	mg	0.1
* MME conversion factor for daily dose = 1.8 (one patch lasts 7 days)		
** MME conversion factor for daily dose = 2.4 (one patch last 3 days)		

## **LIST OF JOURNAL ABBREVIATIONS**

BMJ	BMJ: British Medical Journal
JAMA	JAMA: The Journal of the American Medical Association
JBJS	The Journal of Bone and Joint Surgery

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## CURRICULUM VITAE

