

# Evaluation by Survival Analysis of Cold Pain Tolerance in Patients with Fibromyalgia and Opioid Use

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**Purpose:** The cold pressor test (CPT) is a clinical pain research method used to measure cold pain tolerance. During this test, participants immerse an extremity (ie, hand or foot) into cold water for as long as tolerable. The duration of the test (traditionally up to an experimentally imposed cut-off at 2 minutes) indicates the amount of cold pain tolerance by the participant. Prior research studies have investigated cold pain tolerance in patients with chronic pain. However, few of these studies have used survival analysis, which allows for proper handling of data censoring and is therefore, an optimal statistical method for CPT data analysis. The goal of the present study was to use survival analysis to evaluate cold pain tolerance in patients with fibromyalgia. Furthermore, we aimed to model relationships between psychological and clinical variables as well as opioid medication use and cold pain tolerance.

**Patients and Methods:** A total of 85 patients with fibromyalgia (42 who were taking opioids) and 47 healthy pain-free controls provided CPT and questionnaire data (collected across 2 study sites) for a case-control study. We used survival analysis using Cox regression to evaluate group differences (patients vs controls) in cold pain tolerance and to evaluate cold pain tolerance relationships with psychological, clinical, and medication use.

**Results:** As compared to healthy controls, patients with fibromyalgia exhibited significantly lower CPT survival (HR = 2.17, 95% CI: [1.42, 3.31],  $p = 0.00035$ ). As indicated by Cox regression models, the significant group difference in CPT survival did not relate to our selected psychological and clinical measures ( $p > 0.05$ ). The groups of non-opioid-taking patients and healthy controls showed consistent CPT survival across study sites. However, patients taking opioid pain medications showed differences in CPT survival across study sites.

**Conclusion:** By using survival analysis, an optimal method for time-to-event pain measures such as the CPT, we confirmed previously identified reductions in cold pain tolerance in patients with fibromyalgia. While our selected psychological and clinical measures were not significantly associated with cold pain tolerance, our data suggest that opioid medication use may impart greater cold pain tolerance in some patients.

**Keywords:** chronic pain, opiate, cold pressor test, hyperalgesia

## Plain Language Summary

In clinical settings, cold pain tolerance is often measured using the Cold Pressor Test (CPT). For this test, participants place their hand or foot in cold water for as long as they can tolerate. The CPT is useful for studying chronic pain conditions, such as fibromyalgia, which impacts many individuals worldwide. Even though many researchers have used the CPT, a recent publication pointed out that most published studies using the CPT have used calculations that were not ideal for the data. In this analysis, researchers used survival analysis, a semiparametric method more suitable for CPT data, to study cold pain tolerance in women with fibromyalgia compared to women with no pain conditions. CPT data and psychological measures (for example, depression and anxiety scores) were collected from two separate studies to form a total group of 85 people with fibromyalgia and 47 people with no chronic pain. They reported the below conclusions:

- Similar to prior study results, women with fibromyalgia show lower tolerance to cold pain compared to pain-free women.

- The difference in cold pain tolerance between women with fibromyalgia and pain-free women cannot be entirely explained by differences in the included psychological factors (like anxiety and depression).
- Being prescribed an opioid pain medication for fibromyalgia may have different effects on tolerance to cold pain, depending on the patient. Data for this study were collected from patients who were at 2 different US locations. For the patients who were taking opioids, the group of patients at one of these locations showed greater cold pain tolerance compared to healthy controls, while the other group of patients who were taking opioids (at the other study location) did not. More research is needed to understand what these results mean.

## Introduction

Chronic pain is highly prevalent across all demographics, is a major contributor to the current opioid epidemic, and imparts a major burden on society.<sup>1</sup> As one method to clinically assess chronic pain, the cold pressor test (CPT) provides a way to measure cold pain tolerance. Broadly, both clinical practice and pain research use the CPT to measure pain tolerance across healthy individuals and chronic pain patient populations.<sup>2</sup> While complex and interacting multi-system processes in the body driving chronic pain remain unclear, CPT-measured pain tolerance may provide useful insights into underlying mechanisms (eg, psychological and clinical drivers of pain sensitization) among individual patients and to characterize unique types and stages of chronic pain.

While many prior studies include CPT data, to date, most of these studies have used parametric statistical analysis which for time-to-event data does not involve proper handling of censoring. Censoring implies that not all data points (ie, survival times) are observed, and it must be accounted for during statistical inference.<sup>3</sup> Despite censored data being more suitably analyzed by survival analysis, published studies of pain tolerance in patients with chronic pain have rarely used survival analysis methods to analyze CPT data.<sup>4</sup> For example, such studies have used CPT data to study pain tolerance in adults with irritable bowel syndrome (IBS),<sup>5</sup> to study psychological and genetic predictors of pain tolerance in healthy subjects,<sup>6</sup> and to measure opioid-induced hyperalgesia (OIH) in opioid-dependent patients.<sup>7</sup> However, these specific studies of pain tolerance represent a notable few involving survival analysis. Meanwhile, regarding pain tolerance in the fibromyalgia patient population, to our knowledge, no studies have reported CPT data as analyzed using survival analysis methods.

CPT data are “censored time-to-event data” which are appropriately analyzed by regression models. Of these models, the Cox proportional-hazards model is the most common. The Cox proportional-hazards model is a semiparametric model that uses a set of time-independent explanatory variables for prediction of risk.<sup>8</sup> In the case of pain tolerance data collected using the CPT, the data are analyzed using the hazard function  $h(t)$  which represents an individual’s risk of removing their hand from the cold water at some time  $t$ . Survival analysis uses the hazard ratio (HR) to assess the individual risk experienced at any given time and provides a quantified value comparing survival probability between two groups.

In both healthy individuals and patients with chronic pain, such as fibromyalgia, pain tolerance may be affected by numerous health and psychological factors. Prior literature indicates that, compared to healthy individuals, **patients with fibromyalgia demonstrate less cold pain tolerance**.<sup>9–11</sup> Differences in cold pain tolerance relate to changes in activity within brain sensorimotor, attentional, and executive control networks, as well as subcortical/brainstem areas,<sup>12–15</sup> and such findings suggest that cold pain tolerance is modulated by cognitive and psychological processes. For example, in pain-free individuals and individuals with chronic pain, state anxiety, representing a major psychological factor, relates to greater pain sensitivity.<sup>16–19</sup> Additionally, in patients with fibromyalgia, greater clinical pain intensity relates to both greater number of pain areas across the body and increased negative affective states.<sup>20</sup> Moreover, pain intensity is related to positive and negative affect<sup>21,22</sup> and affect balance.<sup>23</sup>

In addition to influences by psychological factors, the use of opioid medications may influence levels of pain tolerance. Opioid medication prescribed as long-term treatment for chronic pain poses risks of addiction, overdose, and opioid-induced hyperalgesia (ie, increased pain response when taking opioids).<sup>24,25</sup> Concurrent with mechanisms of opioid-induced hyperalgesia, greater sensitivity and lower tolerance to cold stimuli have been observed in patients with opioid dependence<sup>7,26</sup> as well as in patients with fibromyalgia.<sup>27</sup>

The present case-control study aimed to provide an analysis of CPT-evaluated cold pain tolerance in patients with fibromyalgia with enhanced rigor and reliability by using both survival analysis statistical methods. We compared CPT survival and psychological/clinical correlates in patients with fibromyalgia vs a healthy control group. We hypothesized

that compared to healthy pain-free controls, patients with fibromyalgia would demonstrate less cold pain tolerance (ie, higher CPT survival hazard). We additionally hypothesized that in patients with fibromyalgia, factors of state anxiety, negative affect, number of pain areas in the body, and opioid use would be related to less pain tolerance. Lastly, we explored additional psychological and clinical factors and their relationship to cold pain tolerance in patients with fibromyalgia.

## Material and Methods

### Participants

The study included female patient and control participants who each participated in one of the two separate studies during which data were collected. Two different research teams collected data independently at different times and locations. For Study 1 which was conducted at Stanford University, the first research team collected CPT data from 35 patients and 17 controls, who were recruited from the regions surrounding Palo Alto, CA, between 2015 and 2018. Results from analyses of other non-CPT-related data collected from Study 1 have been reported previously.<sup>28–30</sup> For Study 2 which was conducted at Duke University, the second research team collected data from 50 patients and 30 controls, who were recruited from the regions surrounding Durham, NC, between 2019 and 2021 (see Table 1 for demographic information).

**Table 1** Participant Demographics

		Patients	Controls
Total participants		85	47
Right handed		79	44
Self-identified race	Asian	3	10
	White/Caucasian	67	33
	Black/African American	9	2
	Other	6	2
Hispanic or Latinx ethnicity		9	2
Education level	Advanced degree	10	21
	College/university	67	26
	High school	7	0
Employment status	Full-time	27	29
	Part-time	18	6
	Unemployed	39	12
Age	Median	48	45
	IQR	[40, 56]	[36, 56]
	Mann–Whitney p-value	0.529	
Body mass index	Median	28.3	23.6
	IQR	[24.9, 33.3]	[21.7, 28.9]
	Mann–Whitney p-value	<0.001	

**Notes:** One control participant did not indicate handedness, and one patient did not provide education or employment information. The race category labeled “other” includes participants of Hispanic or Latinx ethnicity.

In Study 1 (Stanford University data collection site), all fibromyalgia patients met the modified American College of Rheumatology (ACR) 2011 criteria for fibromyalgia [widespread pain index (WPI)  $\geq 7$  + symptom severity (SS)  $\geq 5$ , or WPI 3–6 + SS  $\geq 9$ ; symptoms present at a similar level for at least 3 months; no disorder that would otherwise explain the pain].<sup>31</sup> In Study 2 (Duke University data collection site), fibromyalgia patients met the revised ACR 2016 criteria which includes a slight change in WPI criteria (range 4–6).<sup>32</sup> Additional eligibility criteria required all fibromyalgia patients to have pain in all four quadrants of the body, have an average pain score over the past month of at least 2 on a 0–10 verbal scale, have no MRI contraindications, and not be pregnant or nursing. Healthy control eligibility criteria required individuals to have no history of chronic pain, not be pregnant or nursing, have no MRI contraindications, not be taking pain- or mood-altering medications at the time of the study, and have no depression or anxiety disorder. In total, 85 fibromyalgia patients and 47 healthy participants signed written informed consent indicating their willingness to participate in the study, understanding of all study procedures, and acknowledgement that they could withdraw from the study at any time. We conducted all study procedures in accordance with the Declaration of Helsinki, and all study procedures were approved by the Stanford University Institutional Review Board for Study 1 and the Duke University Institutional Review Board for Study 2. We conducted analysis for this study under a data use agreement that was established allowing the data collected at Stanford to be analyzed by the research team at Duke University (K.T.M. was the PI for both Study 1 and Study 2). We pre-registered data analysis plans including hypotheses and exploratory analyses, which were published on the Open Science Framework (OSF) website at: DOI: 10.17605/OSF.IO/H2KGW.

## Medication Usage

In addition to the fibromyalgia eligibility criteria (described above), we enrolled patients with fibromyalgia into “opioid-taking” or “non-opioid” groups based on medication use criteria. Out of the 85 total patients with fibromyalgia, 43 patients were enrolled into the “non-opioid” (ie, opioid-naïve) group. The eligibility criteria for the non-opioid group required that the patients had never taken opioids for a period greater than 30 days, had not taken any opioids within the 90 days before study participation, and were not taking opioid medications as part of their pain treatment at the time of their study participation (of the 43 non-opioid patients, 17 patients were from Study 1 and 26 patients were from Study 2). The remaining 42 patients with fibromyalgia (out of the total 85 patients) were using prescribed opioid medications as part of their ongoing pain treatment at the time of the study. For enrollment into the opioid-taking patient group, these 42 patients met eligibility criteria that required them to have been taking opioid medications for at least 90 days prior to the study and at the time of their participation in the study (of the 42 opioid-taking patients, 18 patients were from Study 1 and 24 patients were from Study 2). For the opioid-taking patients, we recorded additional information about opioid medication dosage and duration of use, and all participants continued their medication use as prescribed during their participation in the study (see Table 2).

## Study Procedures

### Sample Size Calculation

We determined the total required sample size of the combined (Study 1 + Study 2) dataset based on the data collected in Study 1. Using the powerSurvEpi package in R, we calculated a sample size for Cox regression based on the hazard ratio (HR) between the fibromyalgia group and the healthy control group in the CPT data from Study 1 (HR = 2.83). To obtain a minimum power of 0.80 at the 0.05 alpha level for a targeted HR of 2.0 in the combined (Study 1 + Study 2) dataset, we determined that the combined dataset should have a minimum healthy control sample size of 39 (expecting 28 uncensored events; ie, time <120 seconds) and a minimum fibromyalgia sample size of 79 (expecting 73 uncensored events). Thus, the final combined study sample used in the analysis contained sufficient counts of healthy control ( $n = 47$ ) and fibromyalgia ( $n = 85$ ) participants.

### Cold Pressor Test Procedures

We conducted the cold pressor test in different facilities and by different experimenters in Study 1 and Study 2, with slight variations in protocol. In Study 1 (data collection site at Stanford University), we individually tailored the initial temperature of the cold water to each participant’s sensitivity. Specifically, we determined and used the temperature associated with each participant’s pain intensity rating of 3 on a 0–10 visual analog scale (VAS, anchors of “no pain” and “worst pain imaginable”).<sup>33</sup> To determine the individually tailored cold water temperatures for each participant, patients and healthy controls each

**Table 2 Medications**

	<b>Patients</b>	<b>Controls</b>
Opioids	42	0
Hydrocodone/acetaminophen	16	
Tramadol	15	
Oxycodone/acetaminophen	4	
Morphine	3	
Codeine/acetaminophen	2	
Tapentadol	2	
Hydrocodone	1	
Oxycodone	1	
Methadone	1	
Hydromorphone	1	
NSAID	37	2
Acetaminophen	30	0
GABA analogue (eg, gabapentin)	28	1
Muscle relaxant (eg, cyclobenzaprine)	27	0
SNRI (eg, duloxetine)	26	0
Benzodiazepine	16	0
Antiepileptic (eg, topiramate)	15	0
SSRI (eg, fluoxetine)	14	2
Triptans (eg, sumatriptan)	13	0
SARI (eg, trazodone)	10	0
NDRI (eg, methylphenidate, bupropion)	10	0
Ondansetron	7	0
Other anxiolytic (eg, buspirone)	6	0
Benzodiazepine-like (eg, eszopiclone, zolpidem)	5	1
Medical cannabis	5	1
Tricyclic antidepressant (eg, amitriptyline)	5	0
Antipsychotic (eg, lurasidone, prochlorperazine)	4	0
Low-dose naloxone	3	0
Topical lidocaine patch	1	0

**Notes:** One control participant with premenstrual symptoms (2 days per month) reported taking gabapentin (100 mg/day, 2 days per month) and fluoxetine (40 mg/day), one control participant reported taking naproxen for menstrual cramps as needed, and another control participant reported taking celecoxib (200 mg) 3 weeks prior to the study visit due to a sports-related ankle injury. One control participant reported taking zolpidem for sleep, and another control participant reported taking cannabidiol oil (0.5 mg/day) for better rest.

**Abbreviations:** NSAID, nonsteroidal anti-inflammatory drug; GABA, gamma-aminobutyric acid; SNRI, serotonin and noradrenergic reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitor; NDRI, norepinephrine–dopamine reuptake inhibitor.

participated in a brief cold water immersion test of the left hand, which lasted up to 30 seconds in duration (5 minute inter-test interval) and was repeated up to 2 times as necessary at different temperatures. The cold water temperature evoking a pain intensity rating of VAS = 3 was used in the subsequent CPT assessment. In Study 2 (data collection site at Duke University), we standardized the temperature of the cold water used in the CPT for all participants to 5°C. Other than the individualized vs standardized temperatures described above, both studies involved the same CPT set up and procedures. To set up the CPT assessment, we filled a large plastic container with ice water, adjusted the temperature, removed any remaining ice, and recorded the final pre-test temperature of the water. Then, participants submerged their right hand in the cold water (with no remaining ice) for as long as tolerable (up to a 2-minute cut-off time to ensure patient safety and validity of the test). The CPT assessment began (and we started a digital timer) when the participant first immersed their hand into the water, and for the test, we allowed the participant to keep her hand in for up to a maximum of 2 minutes. The 2-minute cut-off is typically used in CPT studies to avoid changes in body temperature and other sources of experimental variability that may occur with longer durations of the test.<sup>2,4</sup> After the CPT assessment, each participant rated their pain intensity and pain unpleasantness associated with the cold water experience on a 0–10 VAS sliding scale.

### Psychological and Clinical Questionnaires

In addition to providing demographic and medication information, all subjects completed the following set of questionnaires: Beck Depression Inventory (BDI),<sup>34</sup> Behavioral Inhibition System/Behavioral Approach System (BIS/BAS),<sup>35</sup> Positive and Negative Affect Schedule (PANAS),<sup>36</sup> Profile of Mood States (POMS),<sup>37</sup> State-Trait Anxiety Inventory (STAI-State, STAI-Trait),<sup>38</sup> Brief Pain Inventory (BPI),<sup>39</sup> Fibromyalgia Assessment Status (FAS),<sup>40</sup> and Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue.<sup>41</sup>

### Statistical Analyses

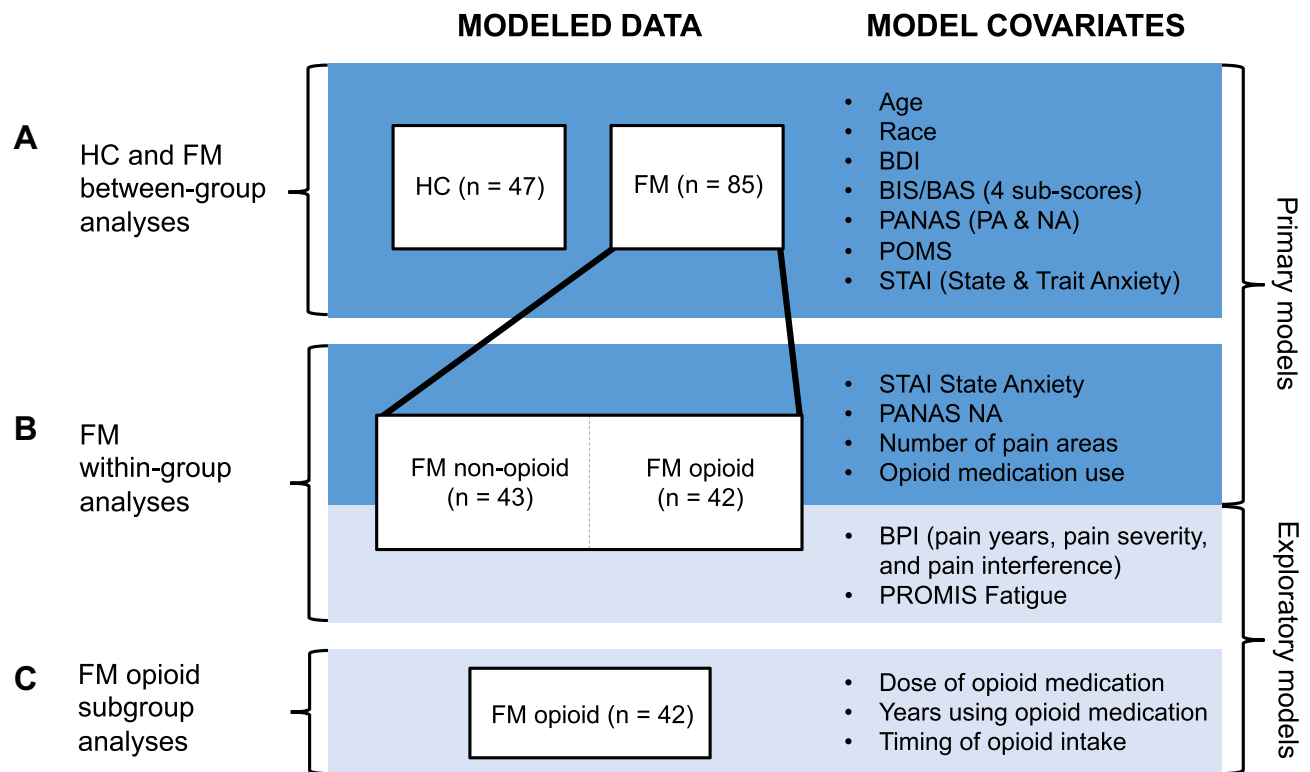
We stored questionnaire data in secure REDCap databases and manually entered (by double data confirmatory entry) CPT data from case report forms into digital spreadsheets prior to analysis. We pre-registered all analyses in the OSF registry (DOI: 10.17605/OSF.IO/H2KGW) and conducted the analyses in R version 3.6.0.

Because the CPT relies on time-to-event data, we fit the data with Cox proportional-hazards models which predict participants' CPT survival hazard from their group status (patient or control), demographic information, behavioral and psychological measures, and medication information. Prior to analysis, we assessed variables for greater than 5% missingness to determine whether data imputation would be required. We did not impute missing values for variables with less than 5% missingness. All models used in this analysis contained an adjustment variable for starting temperature and a binary variable indicating Study (Study 1 or Study 2) to control for any systematic differences between trials. Nested Cox models were compared using the likelihood ratio test (LRT), and non-nested Cox models were compared using the `plrtest` function in R (created by Thomas Hielscher) which implements a partial LRT suited for non-nested Cox models.<sup>42</sup>

We first compared cold pain tolerance between patients (ie, combined opioid-taking and non-opioid patients) and healthy control groups using a Cox model to predict CPT hazard from fibromyalgia group status. To investigate the effect of demographic and psychological/clinical measures on the relationship between fibromyalgia and CPT hazard, we built a multivariate Cox model by selecting up to 4 additional covariates to add to the model (ie, in addition to group status) (Figure 1A). We selected the 4 additional covariates based on preliminary significance with CPT hazard (described below) from an array of a priori identified possible covariates, including age, body mass index (BMI), race (White, Asian, Black, other), BDI score, BAS reward responsiveness, BAS drive, BAS fun-seeking, BIS score, PANAS positive affect, PANAS negative affect, POMS total mood disturbance, STAI state anxiety, and STAI trait anxiety. We first individually modeled the CPT hazard function given by each covariate (including an adjustment variable for starting temperature and a binary variable for Study), and then we selected up to 4 of the most significant variables with coefficient  $p < 0.2$ . We tested these variables for high correlation (continuous variables: Pearson  $r > 0.7$ , categorical variables:  $\chi^2$  test  $p < 0.01$ ), and we included in the model only the most significant variable of any group of highly correlated variables.

We hypothesized that state anxiety, negative affect, number of pain areas in the body, and opioid medication use would be correlated with decreased pain tolerance in patients with fibromyalgia. To test these hypotheses within the





**Figure 1** Diagram of statistical models.

**Notes:** The primary hypotheses were first tested (A) across all participants [both healthy control (HC) and fibromyalgia (FM) groups] and (B) within the fibromyalgia group. Exploratory tests were then conducted (B) within the fibromyalgia group as well as (C) within the opioid-taking subgroup. All tests were conducted using Cox proportional hazards models.

**Abbreviations:** BDI, Beck Depression Inventory; BIS/BAS, Behavioral Inhibition System/Behavioral Activation System; PANAS, Positive and Negative Affect Schedule; POMS, Profile of Mood States; STAI, State-Trait Anxiety Inventory; BPI, Brief Pain Inventory; PROMIS, Patient-Reported Outcome Measurement Information System.

patient group, we modeled CPT hazard with each of STAI state anxiety, PANAS negative affect, FAS pain areas, and a binary variable indicating opioid medication use (Figure 1B).

Due to the non-normality of the data, we used the Mann–Whitney *U*-test to conduct all group comparisons of the psychological/clinical variables. We confirmed proportional hazards for all models using the `cox.zph` function in R, and we identified observations with deviance residuals greater than 2.5 or less than −2.5 as possible outliers.

## Exploratory Analyses

To validate the multivariate model and address the possibility of correlated groups of covariates in the model, we also used Lasso regression to identify variables predictive of CPT hazard. The Lasso approach tends to select one predictor out of a group of correlated predictors and discard the rest, and it can be more accurate than stepwise selection.<sup>43</sup>

In addition to state anxiety, negative affect, number of body areas with pain, and opioid medication use, we also explored other factors potentially predictive of CPT survival within the patient group using Cox models. These exploratory variables included the covariates tested in the primary analysis as well as patients' number of years with pain (BPI), average pain intensity (BPI), average pain interference (BPI), and PROMIS Fatigue score (Figure 1B). Because the study (ie, data collection site) effect on CPT survival was significant, we also separately analyzed Study 1 and Study 2 to evaluate CPT relationships with clinical/psychological variables. Additionally, compared to Study 1 we observed a stronger relationship between opioid medication use and CPT survival in Study 2. We sought to determine the factors that might account for this between-study difference. We hypothesized that such factors might include opioid dosage, duration of opioid use, or timing of last intake (ie, the opioid half-life range during which the CPT test was performed, calculated based on the time of the last opioid dose and the drug-specific half-life). Given this, we conducted a sub-analysis of the opioid-taking fibromyalgia group by testing for study differences in these three additional factors (opioid dose, opioid duration, and opioid intake timing), and we tested these factors as separate predictors of CPT

survival (Figure 1C). Lastly, we conducted a post-hoc sensitivity analysis of opioid medication effects by re-evaluating the primary results on the dataset including only non-opioid-taking patients and healthy controls.

## Results

### Participant Demographics and Medication Use

We analyzed data from a total of 85 patients and 47 controls (see Table 1 for demographic information). Forty-three out of the 85 fibromyalgia participants were not taking opioid medications and were taking over-the-counter pain medications. The remaining 49% (n = 42) of the fibromyalgia patients were taking opioid pain medications. The opioid-taking sub-group had a median daily morphine equivalent dose (MED) of 20 mg morphine and a median opioid-taking duration of 5 years. Of the patients with fibromyalgia, 59% (n = 50) were taking anti-depressants, 26% (n = 22) were taking benzodiazepines or benzodiazepine-like medications, and 56% (n = 48) were taking muscle relaxants or anti-seizure medications. The number of patient and healthy control participants (from both Study 1 and Study 2) taking each medication type is shown in Table 2.

### Psychological and Clinical Measures

Less than 5% of the questionnaire responses were missing from the data (Supplementary Figure 1). Among the patient group, participants reported number of body areas (FAS) with pain ranged from 3 (the minimum criteria) to 19 (maximum). The median pain severity was 5.8/10 and median pain interference was 6.4/10 (BPI). The patient vs healthy control groups showed significant differences in CPT time, STAI trait anxiety, STAI state anxiety, PANAS positive affect, PANAS negative affect, BAS fun-seeking, BIS score, POMS total mood disturbance, and BDI score (Table 3).

**Table 3** Clinical and Psychological Measures Between Groups

	Patients			Controls			Mann–Whitney p-value
	N	Median	IQR	N	Median	IQR	
CPT time	85	23.12	[12.00, 41.00]	47	38.62	[23.425, 120.00]	<0.001
BDI depression	84	16.00	[11.00, 24.00]	47	1.00	[0.00, 3.00]	<0.001
BAS reward responsiveness	81	17.00	[15.00, 18.40]	46	17.00	[15.40, 18.00]	0.707
BAS drive	81	11.00	[9.00, 13.00]	46	11.10	[9.25, 13.00]	0.356
BAS fun-seeking	81	10.40	[9.00, 12.00]	46	12.00	[10.55, 13.00]	0.003
BIS behavioral inhibition	81	22.00	[19.00, 24.00]	46	18.70	[16.20, 21.60]	<0.001
PANAS positive affect	85	25.00	[19.00, 31.00]	47	35.00	[32.00, 40.50]	<0.001
PANAS Negative affect	85	20.00	[16.00, 26.00]	47	12.00	[11.00, 15.00]	<0.001
POMS total mood disturbance	85	18.00	[9.00, 36.00]	47	−4.00	[−8.00, 2.00]	<0.001
STAI state anxiety	85	41.00	[35.00, 47.00]	46	26.00	[22.00, 32.00]	<0.001
STAI trait anxiety	81	45.00	[40.00, 54.00]	47	31.00	[25.50, 36.00]	<0.001
BPI pain years	82	10.00	[5.00, 15.00]				
BPI pain severity	85	5.75	[4.75, 6.50]				
BPI pain interference	83	6.43	[5.214, 7.50]				
FAS total pain areas	85	13.00	[9.00, 16.00]				
PROMIS fatigue	84	66.05	[63.90, 72.32]				

**Notes:** Participant counts for each measure differ from the total number of participants because some participants did not complete all questionnaires. Data are presented for descriptive purposes only; therefore, the Mann–Whitney p-values shown are not corrected for multiple comparisons.

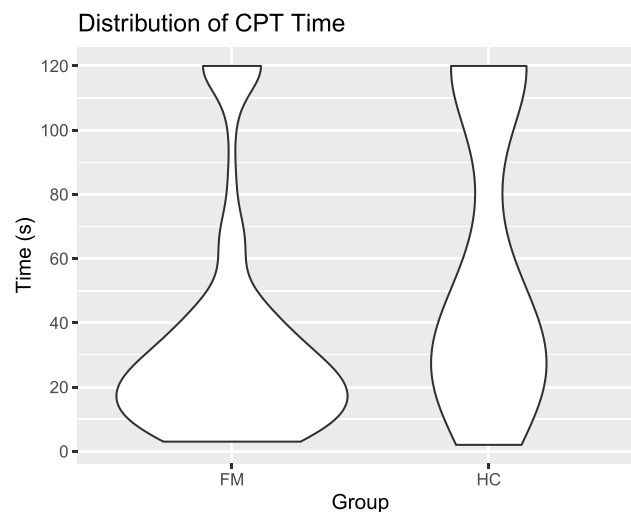
**Abbreviations:** BDI, Beck Depression Inventory; BAS, Behavioral Activation System; BIS, Behavioral Inhibition System; PANAS, Positive and Negative Affect Schedule; POMS, Profile of Mood States; STAI, State-Trait Anxiety Inventory; BPI, Brief Pain Inventory; FAS, Fibromyalgia Assessment Status; PROMIS, Patient-Reported Outcome Measurement Information System; IQR, interquartile range.



## Group Comparison of CPT Survival

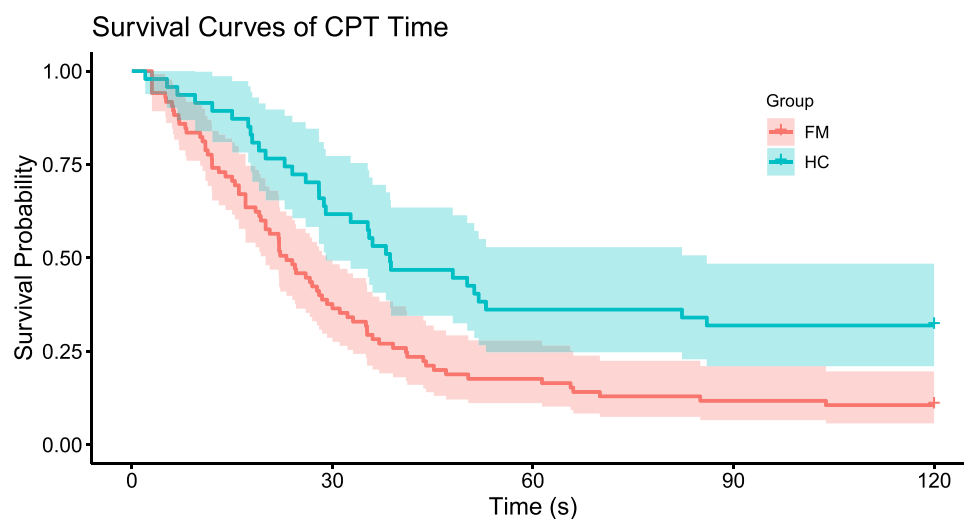
The distributions of CPT time by group are shown in [Figure 2](#) (Mann–Whitney  $p = 0.00080$ ). When including adjustment variables for Study 1 vs Study 2 and CPT starting temperature, patients with fibromyalgia had significantly lower CPT survival probability compared to controls (HR = 2.17, 95% CI [1.42, 3.31],  $p = 0.00035$ ) ([Figure 3](#)). The starting temperature of the CPT was not significantly different across studies (Mann–Whitney = 0.39, median = 5.0°C, IQR = [4.7, 5.2]).

Regarding study-specific effects, between the fibromyalgia participants in Study 1 vs Study 2, CPT time was significantly different ( $p = 0.00079$ ). Overall, the patients in Study 2 demonstrated a higher proportion of censored CPT times (16%) compared to the patients in Study 1 (3%). In contrast, healthy controls showed no significant differences in CPT time between studies. The proportion of censored times in Study 1 and Study 2 were 29% and 33%, respectively.



**Figure 2** Distribution of CPT time by group.

**Notes:** Distributions of raw CPT times from the fibromyalgia (FM) and healthy control (HC) groups are shown. The control group contained a larger proportion of censored times (CPT cut-off at 120 seconds) compared to the fibromyalgia group.



**Figure 3** Kaplan–Meier curves of CPT assessment results by group.

**Notes:** Kaplan–Meier curves with 95% confidence intervals show the difference in CPT survival probability over time between the fibromyalgia (FM) group and healthy control (HC) group. The  $p$ -value shown is for the group effect in the Cox regression model of CPT survival time with adjustments for starting temperature and study effect. Time-to-event data was censored at 120 seconds, and proportional hazards criteria were met for Cox regression.

Results from the single-variable Cox models of CPT hazard, which each included a psychological/clinical variable, showed that none were significantly associated with CPT survival ( $p > 0.05$ ) after accounting for starting temperature, study differences, and group status. However, both variables of Study 1 and fibromyalgia group status were significantly associated with greater hazard in each of these models. The multivariate Cox model included the variable for patient group status ( $HR = 1.99$ ,  $p = 0.0020$ ), selected variables which included BAS fun-seeking ( $HR = 0.94$ ,  $p = 0.28$ ), BAS drive ( $HR = 0.97$ ,  $p = 0.50$ ), and “other” race ( $HR = 1.78$ ,  $p = 0.15$ ), as well as an indicator variable for Study 2 and an adjustment variable for starting temperature (exact, measured before the CPT assessment). High collinearity was not detected between any covariates. The multivariate model did not improve the fit for the CPT data compared to the simpler model with no psychological predictors (LRT:  $p = 0.16$ ).

Variable selection with Lasso regression revealed similar results: the binary variables for patient group status ( $HR = 1.71$ ,  $p = 0.048$ ) and Study 2 ( $HR = 0.61$ ,  $p = 0.017$ ) were significant covariates selected by Lasso (10-fold cross-validation using Harrell’s C-index, and coefficients were extracted at the value of  $\lambda$  giving the minimum mean cross-validation error). The Lasso model also selected BAS fun-seeking, BIS score, “other” race, and STAI state anxiety, but these were not significant predictors of CPT survival. The Lasso-selected Cox model was neither a significant improvement upon the p-value-selected multivariate Cox model (partial LRT:  $p = 0.82$ ) nor upon the original simple Cox model with no psychological/clinical predictors (LRT:  $p = 0.23$ ).

## Psychological and Clinical Predictors of CPT Survival in Fibromyalgia Patients

Within the patient group, STAI state anxiety, PANAS negative affect, number of pain areas, and opioid medication use were all not significantly associated with CPT survival probability ( $p > 0.0125$ ). Other exploratory variables, including BAS fun-seeking ( $HR = 0.86$ ,  $p = 0.014$ ) and BAS drive ( $HR = 0.89$ ,  $p = 0.021$ ), indicated trends for stronger relationships (ie, larger effect sizes, but note these were not corrected for multiple comparisons) with CPT survival in fibromyalgia patients (but not in healthy controls). We report Cox regression statistics within the fibromyalgia patient group ( $n = 85$ ) for covariates selected for a priori tests (opioid medication use, PANAS negative affect, number of pain areas, and STAI state anxiety) as well as exploratory covariates (BAS fun-seeking and BAS drive) in [Table 4](#) and [Supplementary Table S1](#).

The CPT survival rate in Study 2 patients was greater compared to Study 1 patients ( $HR = 0.48$ , 95% CI [0.30, 0.77],  $p = 0.0026$ ) even when accounting for CPT starting temperature [Note: This study difference in CPT survival was absent in the healthy control group ( $HR = 0.83$ ,  $p = 0.62$ )]. Because we observed significant between-study CPT differences in the patient group, the effects of covariates on CPT survival are also reported by the study in [Table 4](#). No demographic,

**Table 4** CPT Covariates in Patients: Cox Regression HRs and P-values Stratified by Study

Variable		Combined Study 1 + Study 2 (n = 85)			Study 1 (n = 35)			Study 2 (n = 50)		
		HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
A priori	Opioid medication use	0.684	[0.433, 1.081]	0.104	0.877	[0.444, 1.731]	0.705	0.509	[0.265, 0.974]	0.041
	PANAS negative affect	0.982	[0.952, 1.014]	0.266	0.979	[0.934, 1.027]	0.382	0.987	[0.947, 1.029]	0.537
	FAS number of pain areas	1.033	[0.974, 1.096]	0.275	1.072	[0.97, 1.185]	0.173	1.011	[0.941, 1.085]	0.771
	STAI state anxiety	1.003	[0.983, 1.024]	0.742	1.011	[0.972, 1.051]	0.593	1.001	[0.977, 1.025]	0.937
Exploratory	BAS fun-seeking	0.856	[0.757, 0.969]	0.014	0.856	[0.697, 1.051]	0.137	0.867	[0.744, 1.009]	0.066
	BAS drive	0.888	[0.803, 0.983]	0.021	0.907	[0.768, 1.073]	0.255	0.878	[0.773, 0.998]	0.047

**Notes:** Models differ in number of data points ( $\pm 4$ ) due to participants with incomplete questionnaire responses. Each model with combined data included an adjustment variable for starting temperature and an indicator variable for Study 2. Each model with only Study 1 ( $n = 35$ ) or only Study 2 ( $n = 50$ ) data included an adjustment variable for starting temperature (exact, measured before CPT assessment). For HR estimates without adjustment variables, see [Supplementary Table S1](#). For all covariates not shown, similar HRs were observed across both studies. For the 4 priori variables, P-value  $< 0.0125$  was required for significance. Results for exploratory variables are uncorrected and reported here for descriptive purposes only and represent trend associations. The separate results for Study 1 and Study 2 are shown for descriptive purposes only and are uncorrected for multiple comparisons.

**Abbreviations:** HR, hazard ratio; CI, confidence interval; PANAS, Positive and Negative Affect Schedule; FAS, Fibromyalgia Assessment Status; STAI, State-Trait Anxiety Inventory; BAS, Behavioral Activation System.

psychological, or clinical variables were significant predictors of CPT survival in the patient group of either study after correction for multiple comparisons, and most variables showed consistent effects (direction and magnitude) between studies. The use of opioid medication was associated with greater CPT survival in Study 2 (HR = 0.51, 95% CI [0.27, 0.97],  $p = 0.041$ ) but not in Study 1 (HR = 0.88,  $p = 0.71$ ), and no interaction effect was detected between study and opioid medication use ( $p = 0.26$ ).

## Between-Study Variability in the Opioid-Taking Patient Subgroup

As noted above, the data showed a positive trend (non-significant) between opioid medication use and CPT survival among fibromyalgia patients in Study 2 (Table 4). The direction of this effect was independent of any demographic, psychological, or clinical differences between the opioid-taking patients of Study 2 and their non-opioid-taking counterparts (Supplementary Table S2); for instance, the positive trend between opioid medication use and CPT survival was preserved even when analyses were stratified by age group or patients' number of years with pain.

CPT times did not differ significantly between studies for the subgroup of patients with fibromyalgia who were not taking opioids ( $p = 0.11$ ) nor for the healthy control group ( $p = 0.52$ ). However, in the subgroup analysis of opioid-taking patients, these patients demonstrated significantly different CPT times in Study 1 vs Study 2 ( $p = 0.0028$ ). Meanwhile, neither the duration of opioid medication use ( $p = 0.97$ ), nor the daily opioid dose ( $p = 0.96$ ), nor the distribution of intake timing ( $\chi^2$  test  $p = 0.091$ ) significantly differed between studies (Table 5). The demographic, psychological, and clinical profiles of the opioid-taking subgroups were also consistent between studies.

## Post-Hoc Sensitivity Analysis of Opioid Medication Relationships

When assessing study differences in CPT survival within each group/subgroup separately, Study 2 showed a stronger association with higher CPT survival probability in opioid-taking patients (HR = 0.40,  $p = 0.013$ ) compared to non-opioid patients (HR = 0.60,  $p = 0.12$ ) and healthy controls (HR = 0.83,  $p = 0.62$ ). Due to this additional between-study variation present in the subgroup of opioid-taking patients compared to the rest of the sample (Figure 4), we conducted a separate analysis with the opioid-taking subgroup removed in order to identify any changes in the group and study effects on CPT survival. In Table 6 and Supplementary Table S3, we report the Cox regression statistics for group effect for all fibromyalgia patients ( $n = 85$ ) vs healthy controls ( $n = 47$ ) (top row, also refer to Figure 3), and for comparison to non-opioid-taking fibromyalgia patients ( $n = 43$ ) vs healthy controls (bottom row). After removing the opioid-taking subgroup, the group effect between the non-opioid patient subgroup with healthy controls increased (HR = 2.70,  $p = 0.000054$ ), and the Cox model indicated that the study effect was no longer significant (HR = 0.67,  $p = 0.11$ ).

## Discussion

To our knowledge, we present the first survival analysis and Cox regression modeling of CPT data in patients with fibromyalgia vs healthy controls. Our study analyzed data across combined datasets and evaluated cold pain tolerance differences in patients with fibromyalgia who take opioids vs those who do not take opioids. We conducted this analysis to respond to the need to re-evaluate the statistical methods used in clinical pain tolerance research.<sup>4</sup> Most previous analyses of CPT data have used parametric methods to form conclusions about cold pain tolerance. However, such approaches do not account for censored data (eg, CPT time), which are almost always not normally distributed and cannot be effectively normalized with data transformations.<sup>4</sup> By considering survival probability instead of time, survival analysis allows us to conduct inference with the censored data points despite not having observed their true values. Furthermore, multivariate methods (as opposed to single-variable comparisons) are needed to more accurately model the complex, interacting processes involved in pain tolerance. In this study, we analyzed CPT data with the Cox proportional-hazards model, a semiparametric model which is widely used in various disciplines to analyze right-censored, time-to-event data with covariates. By comparing patients with fibromyalgia vs healthy controls, we observed group differences in cold pain tolerance which were significant. While the effects of psychological and clinical variables appeared limited, among patients with fibromyalgia who take opioids, our data suggest that **opioid medication use may influence cold pain tolerance for a proportion of patients**.

**Table 5** Comparison of CPT Time and Opioid Dose, Duration, and Timing Across Studies

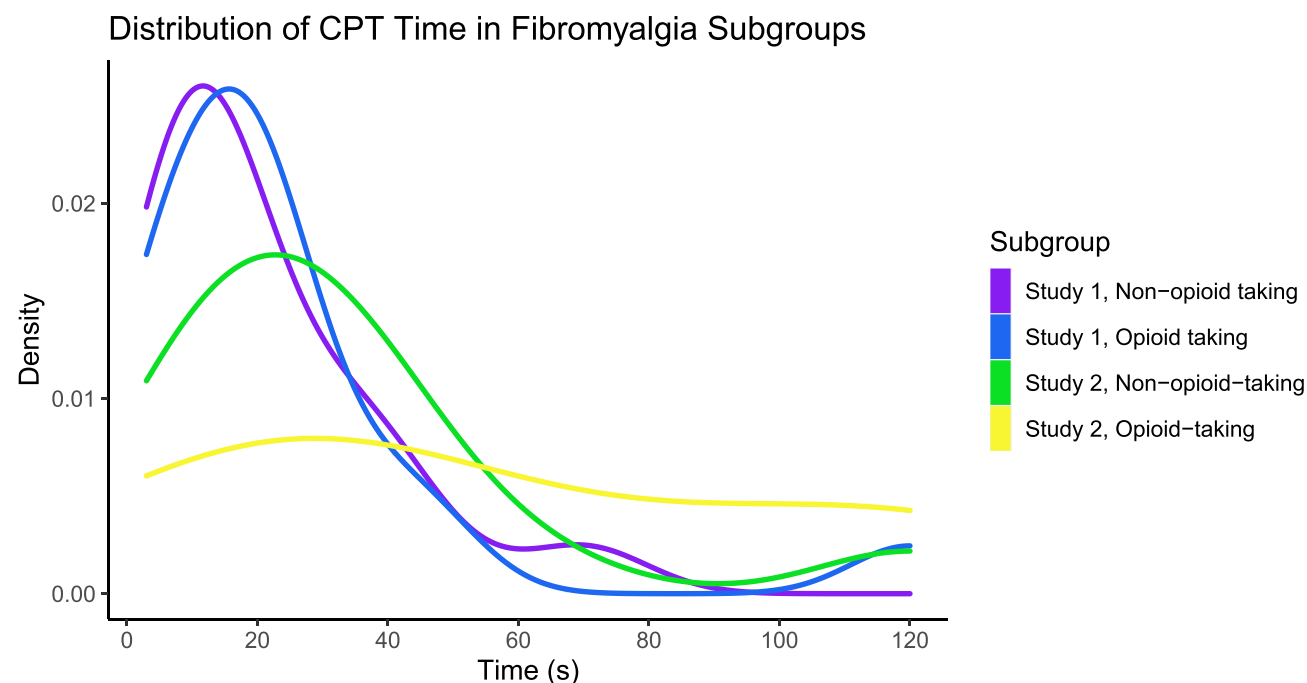
		Study 1	Study 2	P-value
<b>CPT time</b>	FM non-opioid N	17	26	0.115
	FM non-opioid median	13.00	25.58	
	FM non-opioid IQR	[11.00, 28.00]	[13.13, 39.89]	
	FM opioid N	18	24	0.003
	FM opioid median	17.00	33.71	
	FM opioid IQR	[9.50, 25.50]	[22.03, 107.87]	
	HC N	17	30	0.521
	HC median	29.00	44.45	
	HC IQR	[20.00, 120.00]	[28.16, 120.00]	
<b>Opioid daily MED (mg)</b>	N	18	22	0.956
	Median	17.50	20	
	IQR	[7.88, 39.38]	[5.00, 30.00]	
	Minimum	1.00	5.00	
	Maximum	75.00	90.00	
<b>Opioid duration (years)</b>	N	18	21	0.966
	Median	4.25	5.00	
	IQR	[0.88, 10.00]	[3.00, 7.00]	
	Minimum	0.25	0.08	
	Maximum	40.00	15.00	
<b>Opioid timing (N)</b>	<1 half-life	4	5	0.091
	1–2 half-lives	6	1	
	2–3 half-lives	2	5	
	>3 half-lives	6	12	

**Notes:** Two patients from Study 2 did not report their opioid medication dosage, 3 patients from Study 2 did not report their duration of opioid medication use, and 1 patient from Study 2 did not report the time of their last opioid intake. Mann–Whitney p-values are reported for all comparisons except for opioid timing, where the Chi-squared p-value is reported.

**Abbreviations:** FM, fibromyalgia; HC, healthy control; IQR, interquartile range; MED, morphine equivalent dose; mg, milligrams; N, number of subjects.

## Reduced CPT Survival in Fibromyalgia and Potential Contributors

In alignment with previous pain tolerance data in patients with fibromyalgia,<sup>9–11</sup> our data demonstrate that patients with fibromyalgia have lower rates of survival in the CPT assessment. Under both p-value-based and Lasso regression variable selection methods, fibromyalgia status was the most significant predictor of CPT survival probability even when accounting for psychological measures including anxiety, depression, and negative affect. This suggests that fibromyalgia may impair cold pain tolerance in ways beyond such psychological processes alone; for example, cold pain tolerance may be altered in conjunction with underlying neurobiological mechanisms. In this study, we did not evaluate neuropathic measures of chronic pain that may be potentially related to pain tolerance. Meanwhile, it is important to note that pain sensitivity in fibromyalgia may be attributed to biological alterations spanning both peripheral and central nervous systems.<sup>44,45</sup> Among different patients, fibromyalgia can be characterized by varying amounts of peripheral nociceptor pathologies<sup>46,47</sup> and central alterations such as altered descending control of pain and central sensitization.<sup>48,49</sup> The



**Figure 4** Distributions of patient CPT times by study and opioid medication use.

**Notes:** CPT times of fibromyalgia patients in Study 1 and Study 2 are shown by subgroups (opioid-taking vs non-opioid-taking). The distribution of CPT times for opioid-taking patients in Study 2 is shown to be more uniform compared to the right-skewed distributions of CPT times in all other fibromyalgia subgroups.

sensation of cold pain, specifically, is mediated by transient receptor potential melastatin 8 (TRPM8), and alterations to this receptor may account for cold hyperalgesia in a variety of chronic pain conditions, including fibromyalgia.<sup>50,51</sup> Nerve fiber diameter, collected via skin biopsy, has also been shown to be reduced in some fibromyalgia patients.<sup>52</sup> In future studies of cold pain tolerance, measures of neuropathic pain should be collected in both patients and healthy controls to complement data collected via questionnaires.

## CPT Survival, Behavioral Activation System, and Reward Response

Overall, we did not observe clear relationships between CPT survival and the psychological and clinical questionnaire data collected. However, some relationships became more distinct when we performed survival analyses separately for fibromyalgia or healthy control groups. For instance, higher scores in BAS drive and BAS fun-seeking were slightly predictive of higher CPT survival among fibromyalgia patients, but not among healthy individuals. These results suggest that the psychological contributors to pain tolerance may differ between fibromyalgia patients and healthy individuals. For example, pain tolerance in fibromyalgia patients, compared to healthy controls, may be more susceptible to individuals' intrinsic drive to achieve goals (ie, BAS drive), and/or willingness to engage in unknown but possibly

**Table 6** Group Effect HRs from Sensitivity Analysis

Comparison	Combined Study 1 + Study 2 (n = 132)			Study 1 (n = 52)			Study 2 (n = 80)		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
All FM vs HC	2.169	[1.419, 3.315]	0.000348	3.020	[1.491, 6.116]	0.00215	1.803	[1.037, 3.136]	0.0368
FM non-opioid vs HC	2.695	[1.666, 4.361]	p < 0.0001	3.404	[1.522, 7.613]	0.00286	2.375	[1.291, 4.370]	0.00541

**Notes:** Each model with combined data included an adjustment variable for starting temperature and an indicator variable for Study 2. Each model with only Study 1 or only Study 2 data included an adjustment variable for starting temperature (exact, measured before CPT assessment). In the second row, opioid-taking patients from Study 1 (N = 18) and from Study 2 (N = 24) were excluded. For HR estimates without adjustment variables, see [Supplementary Table S3](#). P-values are reported for descriptive purposes and are not corrected for multiple comparisons.

**Abbreviations:** FM, fibromyalgia; HC, healthy control; HR, hazard ratio; CI, confidence interval.

rewarding activities (ie, BAS fun-seeking). Previous research has proposed the BIS-BAS model of chronic pain, suggesting that pain responses can be predicted by individual perceptions of reward and punishment.<sup>53</sup> Furthermore, prior neuroimaging research in patients with fibromyalgia has demonstrated that BAS drive is related to differences in regional brain response to anticipation of rewards<sup>28</sup> and avoidance of punishment.<sup>30</sup> Thus, alterations in recruited CNS activities ongoing during the CPT assessment may contribute to the observed differences in CPT survival between healthy controls and patients with fibromyalgia.

## Opioid Medication and CPT Survival

CPT survival times were significantly longer in opioid-taking patients compared to non-opioid-taking patients in one cohort of patients (Study 2), but not both. Furthermore, there was no evidence to suggest that these differences could be explained by patients' daily dose of opioid medication, duration of opioid medication use, or the timing of their last opioid intake. Meanwhile, in line with CPT survival relationships with BAS measures as described above, it is possible that changes in reward response in patients with fibromyalgia who take opioids<sup>30</sup> may relate to increased cold pain tolerance. Nonetheless, the observed inconsistencies across studies suggest that the relationship between opioid medication use and cold pain tolerance in fibromyalgia patients is tenuous, in that it may vary across patient cohorts and requires further investigation. Prior research has shown that individuals (with and without chronic pain) taking opioids demonstrate lower cold pain tolerance when measured prior to a scheduled opioid dose.<sup>54</sup> In another study, compared to non-opioid patients, opioid-taking patients with chronic pain had similar cold pain tolerance when measured within several hours after their morning analgesic dose.<sup>55</sup> The timing of opioid dose prior to CPT was variable in the present analysis, therefore, timing effects of opioids are unclear, yet given such prior evidence, opioid timing may be an important variable in assessing cold pain tolerance. Additionally, other studies in individuals with opioid use disorder (ie, opioid-addicted individuals without noted presence of chronic pain) have shown decreased opioid tolerance (by survival analysis) when individuals were tested at a time when opioids (eg, heroin and methadone) were present in their system.<sup>56</sup> Together, these prior research findings suggest potential differences in opioid effects on cold pain tolerance in patients with vs without chronic pain.

## Study Limitations

In this analysis, we combined two separate CPT studies to maximize statistical power. However, differences between the two studies significantly affected survival rates in the CPT. As compared to Study 1 which used individually tailored starting temperature, Study 2, in which the testing temperature was standardized to 5°C, was associated with lower CPT hazard when accounting for group status (ie, patient vs healthy control). Although the group effect was the most salient predictor of CPT survival in both studies (when each study was analyzed separately), the study effect in the combined analysis was nearly as notable as the group effect. Such significant differences in CPT survival between studies suggest limitations regarding the generalizability of CPT findings across different geographic/demographic cohorts and indicate that slight differences in CPT procedures (ie, starting water temperature) may influence the generalizability of results across studies.

Aside from our a priori modeled factors of opioid medication use, PANAS negative affect, number of pain areas, and STAI state anxiety, the within-group analyses for CPT survival relationships with clinical/psychological factors were exploratory and, as such, can only suggest trend relationships that may be relevant for future investigation. Additionally, we did not collect information on participants' vital signs (eg, blood pressure) which may be related to differences in pain perception.<sup>57</sup> Lastly, as described above, for patients who take opioids, timing of opioid intake prior to the CPT assessment was not controlled in these studies, yet opioid intake timing may be an important variable to consider in future investigations of opioid effects on cold pain tolerance.

## Conclusion

By using survival analysis to analyze time-to-event CPT data, we confirm previous findings that, compared to healthy individuals without chronic pain, individuals with fibromyalgia demonstrate less tolerance to cold pain as evoked by hand immersion into cold water. To further understand cold pain tolerance relationships to clinical/psychological factors in individuals with fibromyalgia, future investigations should include measures to evaluate the presence of peripheral



neuropathy and compare, in the same patients, results from the CPT and other tests of CNS-related pain processing function. Furthermore, as suggested by our results, **some fibromyalgia patients who take opioid medications may be associated with greater cold pain tolerance as compared to patients who do not take opioids**. In patients with fibromyalgia, cold pain tolerance may be related to differences in reward response and motivation, to regionally influenced variables such as prescribing practices and local geographic climate, and to timing of opioid intake. As such, to delineate contributions of these and other variables as well as effects of opioids on cold pain tolerance, future investigations using appropriate survival analysis methods of CPT data need to be conducted to study the intersecting realms of chronic pain and opioid use.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, K.T.M., upon reasonable request.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships, other than the described funding sources, that could be construed as a potential conflict of interest.

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