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Adolescents and Young Adults with Sickle Cell Disease: Nociplastic Pain and Pain Catastrophizing as Predictors of Pain Interference and Opioid Consumption

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Abstract

Objectives: Some patients with sickle cell disease (SCD) have features of nociplastic pain. While research suggests that many patients with nociplastic pain consume more opioids due to opioid non-responsiveness, little is known about the impact of nociplastic pain and pain catastrophizing on opioid consumption and pain interference among adolescents and young adults (AYA) with SCD. The purpose of this study was to 1) characterize nociplastic pain and pain catastrophizing among AYA with SCD, and 2) determine whether these characterizations are associated with subsequent opioid consumption and pain interference one-month after characterization.

Methods: Participants completed surveys characterizing nociplastic pain and catastrophizing at a routine clinic visit (baseline). Thereafter, participants received weekly text messages which included pain interference and opioid consumption surveys. Multi-predictor two-part models were used to evaluate the predictive relationships between baseline characterizations and subsequent pain interference, and opioid consumption.

Results: Forty-eight AYA aged 14–35 completed baseline measures. Twenty-five percent of participants had scores suggestive of nociplastic pain. Greater nociplastic pain features significantly increased the odds of consuming opioids (OR 1.2) and having greater interference from pain (OR 1.46). Regression analyses found that greater baseline nociplastic pain characteristics were significantly associated with opioid consumption (β .13) and pain interference (β .061); whereas higher pain catastrophizing scores predicted less opioid consumption (β −.03) and less pain interference (β −0.0007).

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Discussion: In this sample of AYA with SCD, features of nociplastic pain predicted higher subsequent opioid consumption and pain interference. Being aware of nociplastic pain features in patients with SCD may better guide individualized pain management.

Keywords

sickle cell disease; nociplastic pain; pain catastrophizing

Introduction

Acute pain, or vaso-occlusive pain crisis, is the most common reason for health service utilization among Adolescent and Young Adults (AYA) with sickle cell disease (SCD).[1,2] Unfortunately, currently available pharmacological and non-pharmacological interventions have only limited benefits in managing daily SCD pain.[3,4] Research among other pain populations (e.g., rheumatoid disorders, back/spinal pain, chronic pain associated with hepatitis C) has identified two clinical characteristics: (a) features of nociplastic pain and (b) pain catastrophizing as being important mediators/moderators of the pain experience and treatment responsiveness.[5–9] To date, these characteristics have been understudied in SCD populations.

Nociplastic pain refers to augmented central nervous system processing of nociception that can occur even with minimal or no tissue damage or without evidence for disease or lesion of the somatosensory system.[10] Patients with nociplastic pain often present clinically with widespread pain, increased pain sensitivity, reduced physical function, and opioid non-responsiveness.[5,6] A growing body of literature suggests that a subset of patients with SCD have widespread pain and impaired pain processing manifested as decreased thermal and mechanical pain thresholds.[11–16] Further, patients with these clinical manifestations have increased pain intensity, pain severity, functional disability, and pain catastrophizing.[11,17]

Opioid non-responsiveness is a lack of pain relief or an increased pain intensity after opioid use, which may lead to increased opioid consumption.[18–21] Empirical evidence suggests that patients with SCD who receive chronic opioid therapy often present with nociplastic pain features including increased hyperalgesia, temperature sensitivity, and reduced function.[22] Currently, the presence of nociplastic pain is rarely taken into account when prescribing analgesics for SCD; but it could be increasing risk without the associated benefit of pain relief.

In addition to opioid non-responsiveness, a growing body of literature describes patterns and personal factors that are linked to opioid use and misuse among patients with chronic or nociplastic pain.[7,8,23,24] Several studies have found associations between pain catastrophizing and opioid misuse among patients with chronic pain.[7,8,23,24] Catastrophizing occurs when an individual has irrational thoughts about their pain, including rumination, magnification, and helplessness.[25] Pain catastrophizing is often described as an exaggerated, negative cognitive-affective response to current or anticipated pain and has been associated with increased pain sensitivity and severity among patients with SCD.[26,27] However, literature evaluating the relationship between pain catastrophizing and opioid use within the SCD population is sparse.[22,28]

Empirical evidence suggests that less than 1% of deaths due to opioid pain relievers in non-cancer disorders occurred among patients with SCD.[29] Despite minimal addiction and opioid overdose rates, clinicians often perceive that patients with SCD are at an increased risk for opioid abuse, misuse, and addiction.[30] Stigmatization in SCD may be present due to high opioid dosages and false racial perceptions.[31,32]

In summary, the relationships among nociplastic pain, pain catastrophizing, opioid consumption, and pain interference have not been well investigated. To address this gap, we used a prospective, longitudinal study design and aimed to 1) describe the incidence and severity nociplastic pain features as well as pain catastrophizing in a clinic sample of AYA with SCD, and 2) to determine whether nociplastic pain features and pain catastrophizing predict weekly opioid consumption, and pain interference in the month following baseline phenotyping. The overarching hypothesis of this study was that baseline nociplastic pain and pain catastrophizing in adolescents and young adults with SCD would predict increased average daily opioid consumption (MME) and increased weekly pain interference in the subsequent month.

Methods

Sample and Setting

Adolescents and young adults with SCD were recruited between 8/2019 and 12/2020 from the Pediatric and Adult Comprehensive Sickle Cell Clinics at Mott Children's Hospital and Michigan Medicine. Patients were eligible for the study if they were between the ages of 14 and 35 and could speak and read English. Data collection required the use of a smartphone and therefore patients were excluded from the study if they did not have access to this technology. To investigate the risk factors that might be linked to opioid misuse, patients were recruited regardless of current opioid use patterns. The study was approved by the University of Michigan Institutional Review Board.

Recruitment

Potentially eligible patients *(n*=114) were pre-screened via chart review. Before attempting to consent a patient to the study, the PI or trained research assistant discussed the patient's eligibility with a clinic provider. Further, patient eligibility was confirmed using a checklist outlining each element of the inclusion and exclusion criteria. Fifty-seven patients were excluded due to exclusion criteria (*n*=14), transfer of care or clinic discharge (*n*=30), or failure to appear to clinic appointments (*n*=13). Nine patients declined participation in the study. The remaining patients (*N*=48) were recruited.

Data Collection

The PI or trained research assistant discussed study procedures, obtained informed consent, and collected baseline data with all study participants during their outpatient clinic appointment. Two participants who did not have an upcoming outpatient appointment met with the PI or trained research assistant outside of clinic to provide informed consent and complete baseline data.

To address the study aims, participants completed electronic Qualtrics™ surveys about demographic characteristics, nociplastic pain, pain catastrophizing, opioid consumption, and pain interference. The survey order was randomized via the randomizer element within Qualtrics™. Following survey completion, the PI or research assistant taught participants how to download the GeoPain @ Home mobile application (app) on their personal cell phone. Participants were taught how to use the app, and then completed their baseline data.

After baseline, participants were instructed to complete the body map in the GeoPain @ Home app every day for 30 days. A daily reminder function was enabled within the app so that participants received a notification every day to fill out the body map. To collect longitudinal pain interference and opioid consumption information, participants received a Qualtrics™ SMS text message containing a link to the pain interference and opioid consumption surveys every Friday during the 30-day study period (four times total).

Measures

Demographic Survey.—Participants self-reported their age, gender, education level, and sickle cell genotype within the baseline demographic survey. Sickle cell genotype was confirmed by the PI or research assistant via the electronic health record (EHR).

Nociplastic pain features.—The “Fibromyalgia score” from the ACR 2011 Fibromyalgia Survey Criteria was used to evaluate the degree of nociplastic pain.[33] Fibromyalgia (FM) is considered a prototypic nociplastic pain condition. Repeated assessments for the presence of FM have been linked to experimental pain sensitivity and altered brain structure and function (i.e., neurobiological indices of nociplastic pain).[10,34,35] For the assessment of nociplastic pain, the American College of Rheumatology 2011 Fibromyalgia (FM) Survey Score is more accurately represented by a continuum where even sub-diagnostic scores are positively correlated with symptoms and poorer treatment response across a variety of pain conditions.[20,36–38] Higher scores on this measure have been associated with replicable patterns of pain-promoting brain activity on functional neuroimaging and quantitative sensory testing, even when the index pain condition differs.[39,40]

The ACR 2011 FM Survey Criteria contains two subscales: 1) the Widespread Pain Index (WPI) (19 items) evaluating the presence or absence of pain over the last 7 days in 19 different body regions, and 2) the Symptom Severity Scale (SSS) (6 items) evaluating the severity and presence of six comorbid symptoms. Scores from the WPI and the SSS are summed to create a total survey score ranging from 0–3. Empirical evidence supports the measure’s internal consistency reliability (α=0.71), validity (content and convergent), and responsiveness.[33,41,42] Further, evaluations of the ACR 2011 FM Survey Criteria’s sensitivity and specificity support total survey scores ≥ 13 are indicative of a probable FM diagnosis, or those with nociplastic pain features.[18,43]

Pain Catastrophizing Scale.—The 13-item Likert-type Pain Catastrophizing Scale (PCS) assesses thoughts and feelings about pain.[44] Total PCS scores range from 0 to 52 with higher scores indicative of greater catastrophic thinking about pain. The PCS has demonstrated strong internal consistency reliability (α= 0.93), convergent and discriminant

validity, and structural validity based on confirmatory factor analysis results among young adults.[45]

PROMIS® Short Form v1.0 – Pain Interference 4a.—The 8-item PROMIS® Pain Interference Short Form assesses the self-reported consequences of pain on social, cognitive, emotional, physical, and recreational activities over the previous 7 days using a 5-point Likert scale.[46] Raw scores range from 8 to 40, with higher scores indicating more activity interference due to pain.[46] Previous psychometric testing of the PROMIS® Pain Interference Short Form supports the measure's internal consistency reliability (α= 0.90 to 0.99), test-retest reliability (ICC 0.83 to 0.95), and sensitivity in adolescents and adults with nociplastic pain features.[46–48]

Opioid Consumption.—Through the Qualtrics™ Opioid Consumption survey, participants self-reported which, if any, opioids they were taking, and the average number of pills taken per day in the previous seven days. The average number of pills per day was converted into average daily MME using the Oregon Pain Guidance Opioid Conversion Calculator (2017). The conversion calculator considers the total dose (mg) of each opioid consumed per day in its MME calculations. Participants completed the Opioid Consumption survey at baseline and each of the subsequent 4 Fridays.

GeoPain @ Home Mobile Application.—Daily pain intensity was included as a covariate within our predictive models. Participants reported daily pain intensity using a color scale from 0 to 10 within the GeoPain™ @ Home interactive body map (MoxyTech Inc., MI). This commercial app is a derivative of a mobile app developed at the University of Michigan to optimize data collection among patients with migraines, dental pain, and cancer pain.[49,50] Empirical evidence supports the convergent validity and sensitivity of app in patients with nociplastic pain features.[49,50]

After selecting their pain intensity, participants shaded the corresponding body area. If varying pain intensity was reported in different body regions, all intensity scores were averaged to derive an overall body map pain intensity score. Participants were instructed to complete a body map daily throughout the 30-day study period. Daily pain intensity scores were aggregated into an average weekly pain intensity score. Thus, each participant had one baseline pain intensity score and four average weekly pain intensity scores. Average weekly pain scores were calculated only using days with data available.

Statistical Analyses

Electronic survey and mobile application data were exported from Qualtrics™ and the GeoPain @ Home internet server and analyzed using Stata software.[51] Descriptive statistics (e.g. means, frequencies, 95% confidence intervals, and standard deviations) were calculated for all variables and covariates including demographic characteristics, pain catastrophizing, nociplastic pain, pain intensity, opioid consumption MME, and pain interference. For all PROMIS® Pain Interference SF scores, the raw total scores were converted to T-scores (mean=50, standard deviation=10) using the PROMIS® Health Measures Scoring Service

(PROMIS® Cooperative Group. Unpublished manual for the Patient Reported Outcomes Measurement Information System (PROMIS®) (Version 1.1.v 9)).

The Oregon Pain Guidance Opioid Conversion Calculator (2017) was used to convert opioid use into average daily MME based on Opioid Consumption Surveys and corresponding EHR dosages. We excluded one opioid consumption diary based on suspected entry error (700 MME). Six participants reported using opioids from lapsed prescriptions. In these instances, average daily opioid consumption MME was calculated from the discontinued prescriptions. Further, three participants with no EHR prescription history reported taking codeine. Since it is possible that these participants were prescribed opioids from outside institutions, we utilized standard adult dosages of codeine/acetaminophen (30/300mg) from Chronic Pain Clinical Practice Guidelines to calculate average daily opioid consumption MME for these three participants.[52]

To evaluate the predictive relationships among nociplastic pain, pain catastrophizing, and our two outcome variables, pain interference and opioid consumption, we ran a series of multi-predictor two-part models for mixed discrete-continuous outcomes. Outcome variables were measured repeatedly over time permitting us to incorporate potential variability within subject in the statistical models and increasing precision of measured outcomes given the repeated measures. Although the analysis was not focusing on change over time, given no intervention, the analytic approach was able to incorporate all available data using standard error adjustments for the nesting of observations within subjects (i.e. cluster-adjusted standard errors). Table 1 shows more detail on how many observations per subject were available for analysis.

Two-part models simultaneously use a logit model to predict the probability of a binary zero versus a prve outcome, and an ordinary least squares regression model to predict the positive outcome.[53] Since pain interference scores range from 8–40, with a score of 8 representing no pain interference, we rescaled the total scores with a range from 0–32. Using two-part models for our analyses allowed us to include all pain interference and opioid consumption data, including zero values. We evaluated the centrality and dispersion of pain interference and opioid consumption data with and without zero values. The distribution of each dependent variable was right skewed even when analyzing positive values. For this reason, we used ordinary least squares (OLS) linear regression models with logged non-zero dependent variables to predict the positive values within each two-part model. Since both our dependent variables were logged, we used a nonparametric method—Duan's smearing retransformation—to produce interpretable fitted values of the two-part models.[54]Consistent with Duan (1983), we used nonparametric bootstrapping to re-estimate the model and re-compute the standard errors and confidence intervals.[53,54]

Age and sex were two demographic covariates included in the models. Additionally, to account for the effect of pain intensity on pain interference and opioid consumption, we included longitudinal pain intensity scores as a covariate within each model. Three participants were unable to download the GeoPain @ Home mobile app to their personal cell phone to provide baseline and longitudinal pain intensity data. Thus, baseline pain intensity

scores were reported by 45 participants. A total of 162 baseline and average weekly pain intensity scores were used in the predictive analyses.

This study was a secondary analysis of a larger study which was powered for 75 participants. Due to sample saturation and limited resources, 48 participants were recruited. All results of this study emphasize effect magnitude and variation, augmented by p values for statistical significance.[55]

Results

Forty-eight AYA with SCD were included in this analysis. Their demographic information and characteristics are presented in Table 2.

Descriptive Statistics of Baseline Characteristics

Baseline nociplastic pain, pain catastrophizing, pain intensity, pain interference, and opioid consumption descriptive statistics are provided in Table 3. As shown, average nociplastic pain features score was 8.96, however, 12 participants (25%) had a nociplastic pain score ≥ 13 which is indicative of a probable FM diagnosis, a prototypical nociplastic pain condition.[18,43] Pain catastrophizing was fairly low in this sample with 36 participants (75%) having scores ≤ 25. At baseline, 22 participants reported no opioid use.

Descriptive Statistics of Longitudinal Variables

Longitudinal daily opioid consumption MME and pain interference are also provided in Table 3. Pain Interference scores were about 0.5 standard deviations higher than the PROMIS® normative sample mean.

Forty-five participants were able to download GeoPain @ Home application. After baseline, 35 participants provided pain intensity data throughout the 30-day study period. Throughout the 30 days, participants completed an average of 16.22 (SD=12.37) pain diaries. Twenty-five participants (42%) completed more than 15 pain diaries. As described in Table 3, average weekly pain intensity scores ($\bar{X}$=2.77) were relatively low throughout the 30-day study period.

Opioid Consumption and Pain Interference Model Results

Table 4 provides the results of the two-part models that evaluated the predictive relationships among nociplastic pain, pain catastrophizing, and the outcome variables (average daily opioid consumption MME and pain interference). Stronger features of nociplastic pain increased the odds of consuming opioids (Odds Ratio [OR] 1.2; 95% Confidence Interval [CI] 1.04 – 1.38) and having pain interference (OR 1.46; CI 1.21 – 1.76). In participants who consumed opioids (n=30), features of nociplastic pain predicted higher opioid consumption (β .13; CI 0.08 – 0.19). In the subset of patients with pain interference scores > 0 (n=40), baseline nociplastic pain scores were positively and significantly predictive of longitudinal pain interference (β .06; CI 0.02 – 0.21). Pain catastrophizing scores did not significantly increase the odds of consuming opioids (OR 0.99; CI 0.94 – 1.05). In those who consumed opioids (n=30), pain catastrophizing scores significantly predicted less opioid consumption

(β −.03; CI −0.06 to −0.01). However, higher pain catastrophizing scores significantly increased the odds of having pain interference (OR 1.05; CI 1.01 – 1.1). Moreover, pain catastrophizing scores significantly predicted longitudinal pain interference in participants who had pain interference scores > 0 (n=40).

Table 5 provides the average marginal effects for each independent variable on average daily MME and pain interference for the combined two-part models. The marginal effects of nociplastic pain and pain catastrophizing on average daily MME were significant at the 5% level. The marginal effect of nociplastic pain on average daily MME is depicted in Figure 1. As nociplastic pain scores increased, opioid consumption increased by 4.06 MME while controlling for age, sex, pain intensity, and pain catastrophizing. As pain catastrophizing scores increased, opioid consumption decreased by −0.77 MME while controlling for age, sex, pain intensity, and nociplastic pain.

Nociplastic pain had a significant marginal effect of 1.05 on pain interference (Figure 2): as nociplastic pain scores increased, pain interference scores also increased by 1.05. Pain catastrophizing did not have significant average marginal effect on pain interference.

Discussion

While any given individual with SCD can have varying degrees of nociplastic pain, in this study 25% of the AYA participants had sufficient characteristics of nociplastic pain to suggest a comorbid diagnosis of fibromyalgia. This percentage is comparable with other research studies that have evaluated nociplastic pain among patients with SCD.[11,12,15,16] Further, this study found significant and positive predictive relationships between nociplastic pain and two primary outcomes: opioid consumption and pain interference. The positive relationship found between nociplastic pain and increased opioid consumption is supported in earlier studies.[18,20]

To our knowledge, our study is the first to evaluate features of nociplastic pain among AYA patients with SCD using a patient-reported outcome (PRO) measure, the continuous score from the ACR 2011 FM Survey Criteria. Compared to the more time-consuming approach of quantitative sensory testing (QST), administering this PRO measure in clinical or research settings is convenient and feasible. Further, empirical evidence supports the sensitivity and specificity of the survey to differentiate those with and without nociplastic pain.[33] Thus, the ACR 2011 Fibromyalgia Survey Criteria could be useful in clinical settings to identify patients who may be at increased risk for consuming more opioids without benefit and having more pain interference. Ultimately, measuring nociplastic pain in the clinical setting may facilitate individualized pain management, including referrals to specialists (e.g., integrative health practitioners, palliative care providers) and the use of effective non-pharmacologic pain management approaches.[3–6]

The findings of our study may also have implications for non-pharmacological pain management approaches for SCD-associated pain.[3,4] In our study, nociplastic pain was significantly predictive of opioid consumption and pain that interferes with social, emotional, and physical functioning. To our knowledge, only six randomized control trials

(RCTs) conducted among patients with SCD have tested the efficacy of non-pharmacologic interventions, including yoga, massage, relaxation, healing touch, and Cognitive Behavioral Therapy (CBT).[14,15,56–60]All five RCTs had either no or minimal effect on daily SCD pain. This warrants further research into examining non-pharmacologic interventions with an individualized multimodal approach.[14]

Despite the established benefit of CBT in other nociplastic pain populations, two non-pharmacologic RCTs investigating the efficacy of CBT-based interventions in patients with SCD found either no or minimal effects in reducing pain.[56,59] Given not all individuals with SCD also exhibited features of nociplastic pain, it is possible that those with such features would be more likely to respond positively to cognitive and behaviorally oriented treatments. Future intervention studies are needed to evaluate the effectiveness of CBT among patients with SCD with nociplastic pain overlay.

Baseline pain catastrophizing scores were relatively low in our sample. Average PCS scores were 16.23, whereas previous literature reported much higher mean PCS scores ($\bar{X}$= 28.5–29) among patients with SCD.[26] In contrast to our hypothesis, pain catastrophizing significantly predicted less opioid use. These findings conflict with research supporting a predictive relationship between pain catastrophizing and increased opioid consumption in SCD populations.[7,9,28] These conflicting findings may be explained by the overall low pain catastrophizing scores within our sample, as previously described. Total PCS scores can range from 0–52. In our sample, 75% had total PCS scores ≤ 25.

Low mean pain catastrophizing in our study may be explained by recall bias, or an inability to accurately remember previous events.[61] The PCS asks respondents to recall their thoughts about pain from a previous painful event.[44] Empirical evidence suggests that emotional processes may bias the ability to recall past negative events.[61–63] Further, the ability to recall a past painful event may have been confounded by relatively low pain intensity scores within our sample. Many participants within our sample reported either no or minimal daily pain throughout the study period. These participants may have had difficulty accurately recalling a previous painful event and responding to the questions within the PCS. In summary, low mean pain catastrophizing due to recall bias may have limited the ability of our statistical model to accurately predict the relationships among pain catastrophizing, opioid consumption, and pain interference.

Another explanation for these conflicting findings may lie in the way pain catastrophizing was measured. The PCS evaluates dispositional pain catastrophizing or the trait-like tendency of catastrophic thinking. Empirical evidence suggests that measuring situational pain catastrophizing, i.e., immediately following a painful event, may be more appropriate among patients who experience daily pain.[64,65] Prior research among patients with nociplastic pain compared measures of dispositional and situational pain catastrophizing and suggests that situational pain catastrophizing has a much stronger association with experimental pain responses.[64] Thus, the results of our predictive models may have supported our hypothesis had we measured situational catastrophizing at multiple time points throughout the study period.

Our research study has several limitations. First, low pain catastrophizing and potential recall bias during baseline survey completion may have limited our ability to accurately predict the relationships among pain catastrophizing, opioid consumption, and pain interference. Second, this is the first study to our knowledge to use the ACR 2011 FM Survey Criteria among the AYA SCD population. Although evidence supports the reliability and validity of the instrument among several nociplastic pain populations,[20,36–40] psychometric testing of the measure among the SCD population is warranted to support the reliability and validity of our findings. Our study is also limited by the discrepancies found in the self-reported opioid consumption data. One baseline self-reported opioid consumption diary was excluded from our analyses due to a suspected entry error of 700 MME. Also, several participants reported taking opioid prescriptions that were either discontinued or absent from the EHR. The discrepancies in self-reported opioid consumption may be suggestive of recall bias, which may have confounded our results. Third, our study only included patients from one academic medical center, limiting the generalizability of our findings to all patients with SCD. Fourth, our study was limited by recruitment and retention rates. Although the statistical modeling procedures used within this study were appropriate based on the distribution of our data, our findings should be interpreted with caution due to our small sample size. Further, many patients did not complete the weekly opioid consumption and pain interference surveys and daily pain diaries. As presented in Table 1, some participants did not complete opioid consumption or pain interference surveys after baseline. Daily pain diary completion rates were much lower. Eleven participants (24%) did not complete any pain diaries after baseline. Further, daily diary completion rates reduced over time. These missing data may have limited the precision of measured pain outcomes and reduced the representativeness of our sample. Evidence suggests that diversity and cultural bias training, increased community engagement, and modification of recruitment schedules and settings may enhance research recruitment and retention among African Americans.[66]

In conclusion, our findings did not support positive relationships among pain catastrophizing, opioid consumption, and pain interference in this sample of AYA with SCD. However, these findings should be interpreted with caution due to suspected recall bias and low variability of pain catastrophizing within our sample. Our study found that nociplastic pain was associated with increased opioid consumption. Clinicians may want to use nociplastic pain assessments to identify those who may be at increased risk for higher opioid use and having pain that interferes with social, emotional, and physical function. Ultimately, awareness of nociplastic pain may reduce ineffective opioid use, lead to implementation of cognitive behavioral therapies to reduce daily pain, and thereby improve functioning among patients with SCD.

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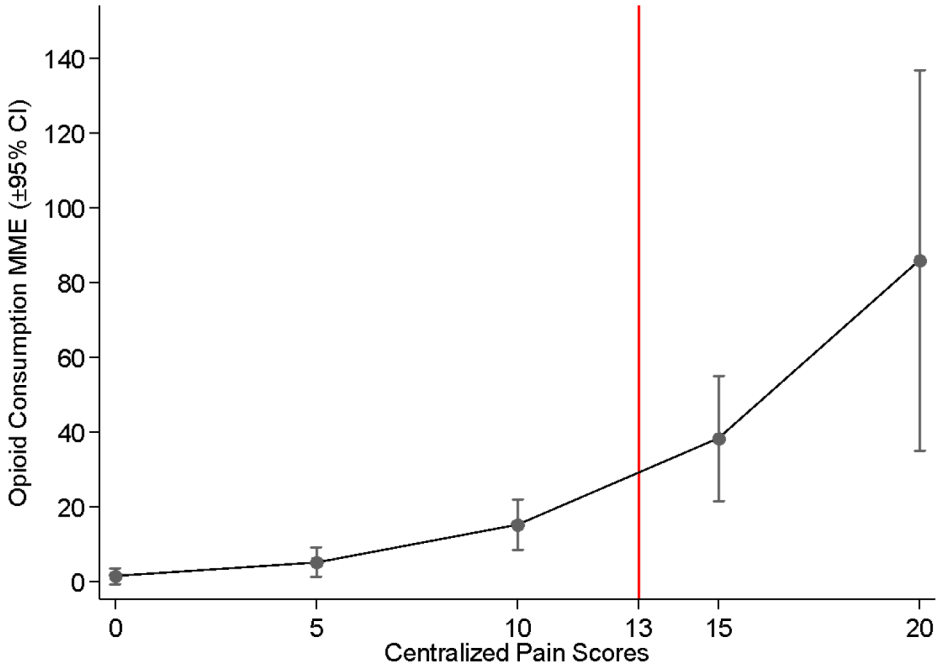

Figure 1.

Predictive margins of nociplastic pain on average daily opioid consumption MME

Note. A score of 13 on the ACR 2011 Fibromyalgia Survey is indicative of probable FM diagnosis.

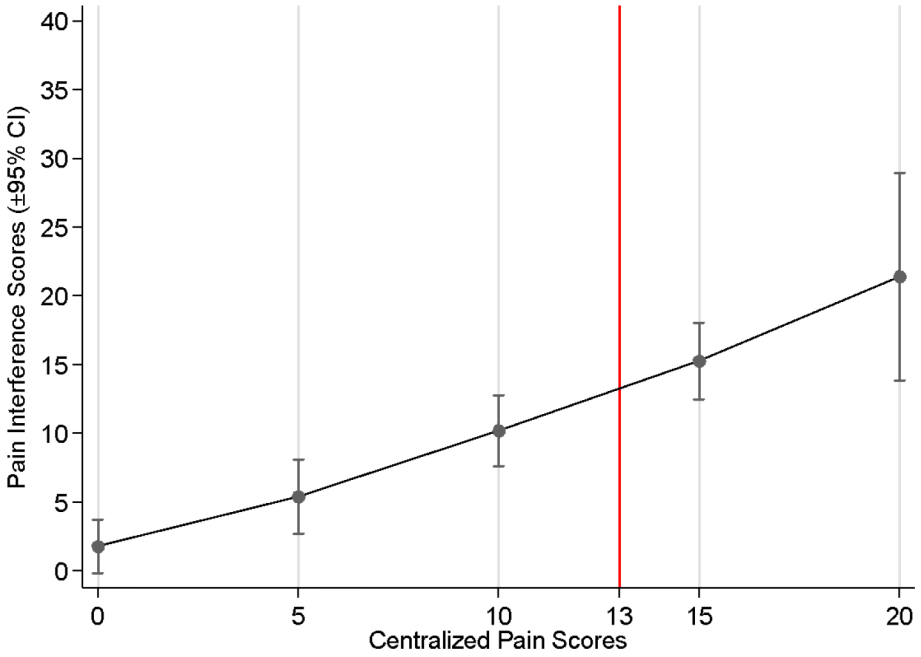

Figure 2.

Predictive margins of nociplastic pain on weekly pain interference

Note. A score of 13 on the ACR 2011 Fibromyalgia Survey is indicative of probable FM diagnosis.

Table 1.

Number of Observations Available per Subject for Outcomes; N=45 *

Number of Observations	Number of Subjects	% of Sample
Opioid Consumption MME		
One or more	11 +	24.4%
Two or more	7	15.5%
Three or more	7	15.5%
Four or more	19	42.2%
PROMIS® Pain Interference SF		
One or more	12	26.7%
Two or more	7	15.5%
Three or more	7	15.5%
Four or more	19	42.2%

Note. Obs=number of observations; MME= Morphine Milliequivalents; PROMIS®=Patient Reported Outcomes Measurement Information System; SF=Short Form

+ Outlier excluded

* Three participants were unable to download the GeoPain @ Home mobile app to provide baseline and longitudinal pain intensity data. Since pain intensity was included as a covariate in the models, the results above are reported using 45 participants.

Table 2.

Demographic Characteristics, N=48

Variable	N (%)
Age	
Mean (SD)	22.8 (5.9)
Range	14–35
Sex	
Female	27 (56.4)
Male	21 (43.8)
Race	
African American	47 (97.9)
More than one race	1 (2.1)
Ethnicity	
Not Hispanic or Latino	47 (97.9)
Unknown or do not wish to report	1 (2.1)
Education	
In middle school	1 (2.1)
In high school	11 (22.9)
Did not complete high school	3 (6.3)
Completed high school	4 (8.3)
Some college or technical training	16 (33.3)
University undergraduate degree	12 (25)
University post graduate degree	1 (2.1)
Sickle Cell Genotype	
HbSS	35 (72.9)
HbSC	10 (20.8)
HbSβ0	1 (2.1)
HbSβ+	2 (4.2)

Table 3.

Descriptive Statistics of Baseline and Longitudinal Variables

Variable	Obs	Baseline Obs	Mean	SD	Minimum	Maximum
Baseline Variables						
Pain Catastrophizing	48	48	16.23	13.36	0	50
ACR 2011 FM Survey Criteria	48	48	8.96	5.26	1	20
Opioid Consumption MME[+]	47	47	22.1	42.58	0	246
PROMIS® Pain Interference SF	48	48	55.56	10.91	41.6	75.6
Pain Intensity	48	48	3.41	2.57	0	9.71
Longitudinal Variables						
Opioid Consumption MME[+]	138	47	18.58	5.27	0	150
PROMIS® Pain Interference SF	139	48	54.45	1.28	40.7	77
Average Weekly Pain Intensity[a]	162	45	2.77	2.16	0	9.71

Note. SD=standard deviation; FM=Fibromyalgia; MME=Morphine Milliequivalents; PROMIS®=Patient Reported Outcomes Measurement Information System; SF=Short Form

[+]Outlier excluded (n=47)

[a]Three participants were unable to download the GeoPain @ Home mobile app to their personal cell phone to provide baseline and longitudinal pain intensity data

Table 4.

Two-part models of pain catastrophizing and nociplastic pain on outcome variables (average daily opioid consumption MME and weekly pain interference) N=45*

Variables	Opioid Consumption MME							
	Logit				OLS			
	Odds Ratio	*Standard Error*	*95% C.I.* [a]	*p-value*	*Coefficients*	*Standard Error*	*95% C.I.* [a]	*p-value*
Pain Catastrophizing	0.99	0.03	(0.94–1.05)	.776	−.03*	0.01	(−0.06 to −0.01)	.02
Nociplastic Pain	1.20*	0.09	(1.04–1.38)	.011	.13*	0.03	(0.08–0.19)	< .001
	Weekly Pain Interference							
	Logit				**OLS**			
	Odds Ratio	*Standard Error*	*95% C.I.* [a]	*p-value*	*Coefficients*	*Standard Error*	*95% C.I.* [a]	*p-value*
Pain Catastrophizing	1.05*	0.02	(1.01–1.10)	.026	−.0007	0.008	(−0.01 to 0.02)	.93
Nociplastic Pain	1.46*	0.14	(1.21–1.76)	< .001	.06*	0.02	(0.02–0.11)	.008

Note. MME= Morphine Milliequivalents; OLS= ordinary least squares; C.I..= confidence interval; OLS regression model was conditional non-zero outcome

[a]Shows the cluster-robust standard errors

*$p < .05$

*Three participants were unable to download the GeoPain @ Home mobile app to provide baseline and longitudinal pain intensity data. Since pain intensity was included as a covariate in the models, the results above are reported using 45 participants.

Table 5.

Average marginal effects for pain catastrophizing and nociplastic pain outcome variables (average daily opioid consumption MME and weekly pain interference) for combined two-part models) N=45 *

Variables	Observed Coefficients[a]	Std Error [b]	Z Value	p Value	95% C.I.[b]	
					Lower Limit	Upper Limit
Opioid Consumption Model						
Pain Catastrophizing	−.77	0.35	−2.24	.03	−1.45	−0.1
Nociplastic Pain	4.06	0.99	4.08	<.001	2.11	6.01
Pain Interference Model						
Pain Catastrophizing	.03	0.09	0.38	.70	−0.14	0.20
Nociplastic Pain	1.05	0.28	3.78	<.001	0.51	1.60

Note.

[a] Duan smearing retransformation was used to obtain fitted values

[b] Nonparametric bootstrapping was used to calculate standard errors and confidence intervals; Controlling for age, gender, and pain intensity

* Three participants were unable to download the GeoPain @ Home mobile app to provide baseline and longitudinal pain intensity data. Since pain intensity was included as a covariate in the models, the results above are reported using 45 participants.