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Opioid-Induced Hyperalgesia in Community-Dwelling Adults with Chronic Pain

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Keywords

heat pain perception; opioid; hyperalgesia

1. Introduction

Opioid-induced hyperalgesia (OIH) refers to alterations in pain perception following exposure to opioids. Although this phenomena has been observed in preclinical investigations [5, 38, 40] and in experimental pain studies involving humans [1, 36, 54], the potential hyperalgesic effects of long-term opioid use on pain perception in adults with chronic pain have not been widely reported [21]. Thus, an important knowledge gap exists regarding the occurrence of OIH in samples of community-dwelling adults with chronic pain receiving long-term opioid therapy.

Heat pain (HP) perception refers to a group of quantitative sensory tests (QST) used to quantify thermal sensory perception in humans [49]. One approach for conducting QST is based on the method levels where the intensity of a range of randomly delivered magnitudes, or levels, of heat stimuli are rated on an 11-point numerical rating scale (0 = no pain, 10 = most intense pain) by the subject [19]. The QST method of levels is appropriate for use in clinical studies [14, 15], and has been used to investigate the associations between HP perception and morphine equivalent dose in adults with chronic pain using greater than 30 mg morphine equivalents daily [28]. However, the associations between HP perception and long-term exposure to any morphine equivalent dose could provide important information about the potential hyperalgesic effects of opioids in routine clinical practice. Therefore, the primary aim of this study was to determine the associations between opioid use and HP perception in a sample of community-dwelling adults with chronic pain consecutively admitted to an outpatient interdisciplinary pain treatment (IPT) program.

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The research was conducted at the Mayo Pain Rehabilitation Center and the Translational Research Unit for Chronic and Acute Pain, Mayo Clinic, Rochester, MN.

Conflict of Interest Statement

The authors have no financial conflict of interests to report.

2. Methods

2.1. Participants

All data were collected prospectively as an integral part of the IPT program. Written consent was provided by all patients for use of their medical records for research purposes, and the study protocol was approved by the Mayo Foundation Institutional Review Board. Individuals eligible for study inclusion included all patients consecutively admitted to the Mayo Comprehensive Pain Rehabilitation Center from March 2009 to March 2010. Inclusion criteria included admission to the IPT program, an admitting diagnosis of fibromyalgia, low back pain, generalized myofascial pain or chronic headache, persistent non-cancer pain greater than 3 months duration, and age ≥ 18 years. The specified diagnostic categories were chosen because they encompass 62% to 75% of all patients admitted to the IPT program [10, 27, 31], which ensured an adequate number of patients would be available in each group to investigate the potential associations between opioid use and pain diagnosis. Exclusion criteria included the presence of a major medical (e.g., severe cardiac or pulmonary disease), surgical (e.g., spine or intraabdominal surgery within 6 months of admission) or psychiatric disorder (e.g., schizophrenia, dementia) that precluded full participation in the 3-week IPT program. During this time period, 187 consecutively admitted patients met inclusion criteria and were successfully recruited for study participation. Of these patients, 85 were currently using prescription opioids, and 102 were not using opioids. The opioid status was confirmed by urine drug screening at admission.

2.2. Study setting

The clinical setting of the outpatient IPT program has been previously described [52]. In brief, patients attend the outpatient pain treatment program 8 hours daily for 3 consecutive weeks excluding weekends. A cognitive behavioral model served as the basis for treatment, and the primary treatment goal was restoration of physical and emotional functioning. Patients were involved in daily physical and occupational therapy, and all patients attended daily educational group sessions related to management of depressive symptoms, relaxation training, stress management, activity moderation, and elimination of pain behaviors.

2.3. Demographic and clinical characteristics

Baseline demographic and clinical characteristics were collected at admission including age, sex, pain duration, marital status, years of education, employment status, primary pain site, and smoking status.

2.4. Determination of morphine equivalent dose

The daily opioid dose of each patient was determined for the past 30 days upon admission by self-report and review of pharmacy records, as previously described [11]. The daily opioid dose was converted to daily morphine equivalents using an equianalgesic conversion software program [12] used at our outpatient treatment center [11, 32].

2.5. Measures

2.5.1. Heat pain perception—HP perception was assessed one day following admission to the IPT program using the automated Computer Aided Sensory Evaluator IV (CASE IV; WR Electronics, Stillwater, MN) system [18-20] as previously described [28, 29]. The CASE IV system delivered discrete magnitudes of heat stimuli units, termed “just noticeable difference” (JND), interspersed with null stimuli in random order through a 10 cm² thermode applied to the skin. The testing sequence used involved 25 discrete levels of heat stimuli (range 1 to 25) [16]. The baseline temperature was of 34° C (level 1), and the levels of heat stimuli increased exponentially to a temperature of 48° C (level 21). For levels 22, 23 and 24, the temperature of the thermode was raised to 48° C for 1.5, 5, and 10 seconds, respectively. At level 25, the temperature was raised to 49° C for 10 seconds. After each stimulus, including all null stimuli, subjects were asked to grade pain intensity using an 11-point scale, where 0 denoted no pain and 10 represented the most intense possible pain. The test was considered completed when either the subject rated the intensity of a heat stimulus 5, or the maximum stimulus level had been delivered. A quadratic regression equation was then fitted to the pain ratings, from which HP 0.5, HP 5 and HP 5-0.5 were calculated by the CASE IV software program (WR TestWorks, version 2.0) [17, 41]. Heat pain 0.5 represents the midpoint between a nonpainful stimulus and the smallest stimulus magnitude necessary to elicit a pain sensation (threshold), HP 5 represents the stimulus magnitude necessary to elicit an intermediately intense pain rating of 5, and HP 5-0.5 represents the slope of a regression line fitted to the curve connecting HP 5 and HP 0.5.

The raw sensory data, in units of JND, were adjusted by the CASE IV computer program for age, sex, height, weight, body surface area, body mass index, and body region of testing [15, 17, 41], and converted to a standardized unit termed normal deviate (ND). The means and standard deviations used to standardize the raw sensory data were derived from a population of normal individuals (N = 330) without neurological disease [15]. A ND value of 0 corresponds to the 50th percentile and has a standard deviation of 1 [15, 17, 41]. Thus, a ND < 0 suggests a trend toward increased hyperalgesia (ND = -2.33 is the 1st percentile), whereas a ND > 0 represents a trend toward reduced pain sensitivity (ND = 2.33 is the 99th percentile). Normative values of HP perception are available for numerous body regions including the hands [19].

The thermode was placed on the dorsum of the nondominant hand for easy accessibility and QST was performed in a purpose designated, climate controlled room. All patients using opioids were on stable dosages at the time of testing. Subjects were masked to the magnitude of the heat stimulus. The entire test algorithm required less than 5 minutes to complete, as previously reported [28, 29].

2.5.2. Pain severity—Pain severity was assessed using the pain severity subscale of the Multidimensional Pain Inventory (MPI) [35]. Three specific questions were used to assess pain severity: 1) “Rate the level of your pain at the present moment”; 2) “On the average, how severe has your pain been during the last week”; and 3) “How much suffering do you experience because of your pain.” Raw scores were converted to standardized *t*-scores with

a normative value of 50 (range 0–100) and a SD of 10 [48]. This self-report questionnaire has proven reliability and construct validity [3].

2.5.3. Depressive symptoms—The Center for Epidemiologic Studies Depression (CES-D) scale was used to measure the severity of depressive symptoms [44]. The 20-item self-administered questionnaire has established reliability and validity [23, 60]. Total scores range from 0 to 60, where higher scores indicate greater levels of depression.

2.5.4. Pain catastrophizing—The Pain Catastrophizing Scale (PCS) is a 13-item self-administered questionnaire that assesses negative emotions associated with actual or anticipated pain experiences [50]. Scores range from 0 to 52, and higher scores indicate greater levels of pain catastrophizing.

2.6. Statistical plan

2.6.1. Sample size—In a previous study, univariable and multiple variable linear regression analyses demonstrated a significant association between ND values of HP 5-0.5 and morphine equivalent dose [28]. The mean ND value and standard deviation (SD) of HP 5-0.5 in this previous study was 0.29 (SD = 1.14). For purposes of the current study, a group difference (opioid versus nonopioid) of half this SD ($1.14/2 = .57$) would yield an effect-size correlation of $r = 0.22$ (Cohen's $d = 0.5$). A Cohen's d value of this magnitude represents a medium-size clinical effect [9]. Therefore, assuming a SD of 1.14, an effect size of $r = 0.22$, and a 2-sided significance level of 0.05, 187 patients would provide greater than 95% probability of detecting a between group difference of 0.57 ND units in HP 5-0.5. The sample size calculations were performed using the methods described by Dupont et al. [13] and Hsieh et al. [33].

2.6.2. Data analyses—Demographics and clinical characteristics were summarized for the opioid and nonopioid groups. Continuous variables were compared using unpaired t -tests, and categorical variables were compared using chi-square tests. For all HP parameters, 1-sample Kolmogorov-Smirnov tests were performed to determine the normal distribution of the data. Nonparametric tests (Mann-Whitney U Test) were used to assess the effect of opioid use on HP perception. Measures of HP perception significantly associated with an effect of opioid use (HP 5-05) were subjected to univariable regression analyses. In the univariable analysis of JND (nonstandardized) values of HP 5-0.5 (dependent variable), independent variables included opioid use and baseline demographic and clinical characteristics including age, sex, body mass index (BMI), pain duration, work status, pain diagnosis, pain severity, depression, and pain catastrophizing. These patient characteristics were included because, 1) they have been previously shown to influence pain perception in humans [4, 15, 22, 24, 29, 59], or 2) a significant group difference was identified for a particular characteristic (e.g., age, employment status, pain diagnosis). A similar univariable analysis was performed using ND (standardized) values of HP 5-0.5 as the dependent variable; the use of ND values in this manner has been previously described [15, 28, 29, 46, 47]. In this univariable analysis, independent variables included opioid use and patient characteristics including work status, pain diagnosis, pain severity, depression, and pain catastrophizing. However, because ND values have been adjusted for anthropometric

characteristics known to influence pain perception including age, sex, and BMI [15, 17, 41], these factors were not included as independent variables. Separate multiple variable linear regression analyses were then performed for both JND and ND values of HP 5-0.5 using the described independent variables. The level of significance for all tests was set at $P < 0.05$, and all analyses were completed using SPSS (IBM, Inc., Chicago, IL, Version 21.0).

3. Results

3.1. Sample characteristics

Table 1 contains a summary of the demographic and clinical characteristics. The majority of patients in both groups were Caucasian females with a mean pain duration of approximately 10 years. The mean daily morphine equivalent dose was 88 mg (standard deviation 92), and the median dose was 60 mg (25th to 75th interquartile range 30 to 120). The morphine equivalent dose ranged from 5 mg to 472 mg. The age of the opioid group was significantly greater than the nonopioid group, and a significantly greater proportion of the nonopioid group was currently working. Additionally, a greater proportion of the opioid group had a diagnosis of low back pain and generalized pain, and a greater proportion of the nonopioid group had a diagnosis of fibromyalgia and headache. No significant group differences in pain severity, depression or pain catastrophizing were observed. Figure 1 depicts the distribution of JND and ND values of HP 0.5, HP 5 and HP 5-0.5. The JND values of HP 0.5 and HP 5 were normally distributed, and the ND values of HP 5-0.5 were normally distributed (1-sample Kolmogorov-Smirnov tests $P > .05$).

3.2. Associations between opioid use and JND values of HP 5-0.5

Table 2 contains the mean JND values of HP 0.5, HP 5, and HP 5-0.5. An effect of opioid use was observed for JND values of HP 5-0.5, where values of the opioid group were significantly lower (more hyperalgesic) compared to the nonopioid group. In univariable linear regression analysis (Table 3), current opioid use (independent variable) was significantly associated with lower JND values of HP 5-0.5 (dependent variable) where opioid use was associated with a 1.07 reduction in JND values. Compared to low back pain, a diagnosis of fibromyalgia or generalized pain was significantly associated with greater (less hyperalgesic) JND values of HP 5-0.5. In multiple variable linear regression analysis adjusted for age, sex, BMI, work status, pain diagnosis, pain duration, pain severity, depression, and pain catastrophizing, the association between opioid use and HP 5-0.5 retained significance (Table 3). Other significant factors in this multiple variable model included a diagnosis of generalized pain where patients with this diagnosis had significantly greater (less hyperalgesic) JND values of HP 5-0.5 compared to patients with low back pain.

3.4. Associations between opioid use and ND values of HP 5-0.5

Table 2 contains the mean ND values of HP 0.5, HP 5, and HP 5-0.5. An effect of opioid use was observed for ND values of HP 5-0.5, where values of the opioid group were significantly lower (more hyperalgesic) compared to the nonopioid group. In univariable linear regression analysis (Table 4), current opioid use was significantly associated with lower ND values of HP 5-0.5 where opioid use was associated with a 0.55 reduction in ND values. Additionally, not currently working was significantly associated with lower ND

values, and a diagnosis of generalized pain (compared to low back pain) was associated with greater ND values of HP 5-0.5. In multiple variable linear regression analysis adjusted for work status, pain diagnosis, pain duration, pain severity, depression, and pain catastrophizing, the association between opioid use and HP 5-0.5 retained significance (Table 4). Other significant factors in this multiple variable model included a diagnosis of generalized pain where patients with this diagnosis had significantly greater (less hyperalgesic) ND values of HP 5-0.5 compared to patients with low back pain.

4. DISCUSSION

The main finding of this study involving a sample of community-dwelling adults with chronic pain was the significant association between opioid use and lower, or more hyperalgesic, values of HP 5-0.5. More specifically, in the univariable linear regression analyses, opioid use was associated with a 1.07 JND and .55 ND reduction (more hyperalgesic) in HP 5-0.5. In the multiple variable models adjusted for clinical characteristics known to influence HP perception, opioid use was associated with a .93 JND and .51 ND reduction in HP 5-0.5.

The HP 5-0.5 parameter is a measure of the slope of the line connecting HP 5 and HP 0.5. As the slope of the line increases (becomes steeper), values of HP 5-0.5 decrease (become more negative) indicating progressively worsening hyperalgesia. This parameter of HP perception has been shown to be an indicator of hyperalgesia in patients with diabetic peripheral neuropathy and in patients undergoing opioid tapering [14, 28]. Further examination of the summary values of HP perception (Table 2) show that the mean values of HP 0.5, which is a measure of HP threshold, were similar for the opioid and nonopioid groups. However, the mean values of HP 5, which is an intermediate measure of HP tolerance, differed between the two groups; the mean values of the opioid group were less (more negative) than the mean values of the nonopioid group. Thus, the HP 5 values of the opioid group were shifted to the left which increased the slope of the line connecting HP 5 and HP 0.5. The leftward shift of HP 5 resulted in significantly lower (more hyperalgesic) values of HP 5-0.5 in the opioid group compared to the nonopioid group. These observations suggest that a HP parameter that takes into account the relationship between HP threshold and tolerance may be a more sensitive measure of hyperalgesia than either HP threshold or HP tolerance alone.

The evidence supporting OIH in adults with chronic pain receiving long-term opioids is mixed [21]. For example, hyperalgesic changes to cold pressor pain threshold and tolerance were observed in patients with chronic pain following use of oral morphine and methadone [7, 25]. Despite hyperalgesic changes to cold pressor pain, no significant hyperalgesic effects were observed for HP, mechanical pain, or electrical pain thresholds and tolerances [7, 25]. Hyperalgesic changes in HP perception were observed in patients with chronic radicular low back pain and in a separate cohort comprised predominately of patients with chronic low back pain, but no significant changes in cold pressor pain were observed [6, 51]. In studies that utilized more advanced approaches to assess pain perception, hyperalgesic responses to the diffuse noxious inhibitory control paradigm (otherwise termed conditioned pain modulation) and temporal summation of the second pain were observed between

chronic pain patients receiving long-term opioid therapy compared to chronic pain patients not using opioids [6, 45].

These disparate findings could be due, in part, to 1) the use of nonstandardized values of pain perception, 2) lower dosages of opioids, and 3) the confounding effects of opioid tolerance. First, the testing protocols for QST, including the method of levels as used herein, have been validated [18-20, 46] and have good reproducibility over time [43, 46, 57]. However, standardized normative values adjusted for individual differences in anthropometric characteristics known to influence pain perception [15, 46] were not used in the aforementioned studies of OIH in patients with chronic pain. The use of standardized values has been recommended in order to mitigate within-group and between-group variation in raw sensory data [2, 17, 41, 46, 47, 56]. Second, OIH has been associated with exposure to greater opioid dosages [28, 34]. In some, but not all previous studies of OIH in chronic pain patients, the opioid dosages were small to moderate which could partially explain some of the observed variation between the different studies. For example, the mean daily oral hydromorphone dose in the Suzan et al. [51] study was 11.6 ± 4.8 mg, and the median daily oral morphine doses in the Chu et al. [7] and Ram et al. [45] studies were 75 mg (range 30 mg to 120 mg) and 45 mg (range 3 mg to 1110 mg), respectively. Third, it can be difficult to distinguish between OIH and opioid tolerance because both entities are characterized, in part, by inadequate analgesia and a reduction in the observed clinical responsiveness to opioids. In a randomized, placebo-controlled trial of sustained release morphine for chronic low back pain, patients allocated to receive morphine developed opioid tolerance but not OIH following 1 month of oral therapy at a moderate dose (mean daily dose, 78.3 ± 37.5 mg) [8].

The findings of this and other studies have important implications for future research. Although the QST method of levels has not been widely used to assess pain perception in adults with chronic pain, we have previously reported several key associations between the parameters of HP perception and important features of chronic pain including pain severity, morphine equivalent dose, and genetic factors known to influence pain perception. First, in a prospective study of adults with chronic pain, lower ND values of HP 0.5 were significantly associated with greater pain severity scores in a multivariable model adjusted for morphine equivalent dose, pain duration, and pain diagnosis [29]. Second, in a prospective study of adults with chronic pain undergoing medically directed opioid tapering, lower (more hyperalgesic) ND values of HP 5-0.5 were associated with greater morphine equivalent dose in a multivariable model adjusted for pain severity, pain duration, and pain diagnosis [28]. Furthermore, tapering of greater morphine equivalent dosages was associated with lower values of HP 5-0.5 in a multivariable model adjusted for pain severity, pain duration, pain diagnosis, symptoms of opioid withdrawal, and time between completion of the opioid taper and performance of the final QST [28]. Third, in a sample of 277 adults with chronic pain, ND values of HP 0.5 were greater among individuals with the intermediate expressing triallelic serotonin transporter gene linked polymorphic region (5-HTTLPR) genotype compared to individuals with the high expressing 5-HTTLPR genotype in a multivariable model adjusted for sex [26]. This is relevant because alterations in the expression of the serotonin transporter gene have been shown to influence HP perception in both preclinical [42, 55] and clinical studies [37, 39, 53]. The findings from the current study extend the

observations from our previous work and suggest that the QST method of levels may be appropriate for, 1) investigating the potential hyperalgesic changes in opioid naïve individuals with chronic pain initiating long-term opioid therapy, and 2) investigating the potential genetic underpinnings that may influence hyperalgesia in adults receiving long-term opioids.

This study has limitations. First, the majority of study participants were Caucasian women residing in the United States, and only 5% were from minority populations. This is consistent with the referral pattern of our pain treatment program [27, 30]. Thus, the risk of referral bias cannot be excluded, and the associations between HP perception and opioid use may not be fully applicable to other populations of adults with chronic pain. However, as previously reported [26-29], the clinical characteristics of the cohort were similar to a random sample of community-dwelling adults with chronic pain derived from the catchment area of our pain treatment program [58]. Second, the study cohort was limited to individuals diagnosed with fibromyalgia, low back pain, generalized myofascial pain, or chronic headache. Patients with a diagnosis of generalized myofascial pain were significantly less hyperalgesic compared to patients with low back pain. This observation suggests that the baseline pain diagnosis may influence the expression of OIH; therefore, the study findings may not be readily generalized to other diagnostic subgroups of adults with chronic pain. Third, although patients were on stable dosages of opioids and the opioid status of all patients were confirmed by urine toxicology screening, a formal assessment of opioid withdrawal symptoms was not performed. Despite the small risk of unrecognized opioid withdrawal actually occurring in our cohort, this is an important consideration because opioid withdrawal could have potentially influenced our study observations. Fourth, data related to the duration of opioid therapy were not available. This is important because the potential effects of the duration of opioid use have not been fully investigated. Finally, the study findings may have been influenced by unrecognized clinical factors among individuals who have the resources and are willing to participate in a 3-week IPR program.

The observations from this study suggest that long-term opioid use is associated with hyperalgesia. Specifically, opioid use was associated with a one-half SD reduction in a standardized parameter of HP perception in a multivariable model adjusted for clinical factors known to influence pain perception in humans. Appropriately designed longitudinal trials (e.g., case control, interrupted time series, N-of-1) that involve opioid naïve patients initiating opioid therapy are needed to fully investigate the long-term effects of opioid use on pain perception in adults with chronic pain. As previously suggested [28], the QST method of levels and, in particular, the HP 5-0.5 parameter could expand the methodological approaches available for investigating the effects of opioids on pain perception in humans.

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Figure 1. Distribution of HP 0.5 (A), HP 5 (B) and HP 5-0.5 (C) in units of just noticeable difference (JND) and normal deviates (ND). The JND values of HP 0.5 and HP 5 were normally distributed, and the ND values of HP 5-0.5 were normally distributed (1-sample Kolmogorov-Smirnov test $P > .05$).

Table 1

Demographic and clinical characteristics.

Characteristic	Group		<i>P</i> -value *
	Opioid (n=85)	Nonopioid (n=102)	
Age, years, mean $\pm$ SD	48.3 $\pm$ 13.6	43.2 $\pm$ 12.7	.009
Sex, No. female (%)	60 (70)	74 (72)	.767
Ethnicity, No. (%)			.167
Caucasian	82 (97)	95 (93)	
African American	0	2 (2)	
Hispanic	1 (1)	3 (3)	
Other	2 (2)	2 (2)	
Education, years, mean $\pm$ SD	14.9 $\pm$ 2.4	15.1 $\pm$ 3.1	.772
Currently working for wages, No. (%)	16 (19)	34 (33)	.021
Currently married, No. (%)	62 (73)	62 (61)	.080
Pain duration, years, mean $\pm$ SD	10.4 $\pm$ 8.7	9.8 $\pm$ 8.0	.656
BMI (kg/m ²), mean $\pm$ SD	29.4 $\pm$ 7.0	29.6 $\pm$ 6.1	.892
Currently smoking, No. (%)	12 (14)	18 (18)	.513
Primary pain diagnosis, No. (%)			.001
Fibromyalgia	25 (29)	35 (34)	
Low back pain	36 (42)	26 (25)	
Headache	4 (5)	24 (24)	
Generalized pain	20 (24)	17 (17)	
Morphine equivalent dose, mg/day, mean $\pm$ SD	0	88 $\pm$ 92	
MPI pain severity	51.9 $\pm$ 6.3	50.3 $\pm$ 7.4	.116
CES-D	30.2 $\pm$ 11.9	28.8 $\pm$ 13.9	.468
PCS	28.2 $\pm$ 9.9	26.7 $\pm$ 12.5	.359

MPI, Multidimensional Pain Inventory; CES-D, Centers for Epidemiologic Studies Depression scale; PSC, Pain Catastrophizing Scale; SD, standard deviation

* *t* tests for continuous variables, chi-square test for categorical variables

Table 2Mean values ($\pm$ SD) of HP perception.

HP Parameter	Opioid (n=85)	Nonopioid (n=102)	<i>P</i> -value*
HP 0.5			
JND	18.76 $\pm$ 2.76	18.42 $\pm$ 3.48	.689
ND	-.64 $\pm$ 1.26	-.64 $\pm$ 1.46	.726
HP 5			
JND	22.09 $\pm$ 2.74	22.82 $\pm$ 3.49	.092
ND	-.85 $\pm$ 1.53	-.40 $\pm$ 1.65	.068
HP 5-0.5			
JND	3.33 $\pm$ 2.07	4.40 $\pm$ 2.72	.004
ND	-.16 $\pm$ 1.28	.39 $\pm$ 1.28	.005

SD, standard deviation; JND, just noticeable difference; ND, normal deviates

* Mann-Whitney U test

Table 3

Univariable and multiple variable linear regression analyses with JND (nonstandardized) values of HP 5-0.5 as the dependent variable.

Independent Variables	Univariable Regression Coefficients			Multiple Variable Regression Coefficients [*]		
	B	95% CI	P value	B	95% CI	P value
Current opioid use	−1.07	−1.78 to −.36	.003	−.93	−1.70 to −.16	.019
Age	−.02	−.05 to .01	.119	−.02	−.04 to 0.16	.344
Female sex	.33	−.47 to 1.13	.415	.07	−.78 to .92	.874
Body mass index (kg/m ²)	.03	−.03 to .08	.316	.04	−.02 to .09	.236
Pain duration (years)	−.02	−.06 to .02	.367	0.0	−.05 to .05	.997
Currently working	−.40	−1.22 to .41	.332	−.33	−1.16 to .50	.438
Pain diagnosis						
-Low back pain		0.00			0.00	
-Fibromyalgia	.93	.05 to 1.81	.039	.74	−.20 to 1.69	.122
-Generalized	1.13	.12 to 2.14	.029	1.1	.04 to 2.10	.042
- Headache	1.09	−.02 to 2.20	.055	.36	−.84 to 1.55	.557
Pain severity	.01	−.04 to .06	.658	.01	−.05 to .07	.669
Depression	.02	−.01 to .05	.109	.02	−.02 to .06	.292
Pain catastrophizing	.01	−.02 to .05	.387	< .01	−.04 to .04	.963

JND, just noticeable difference; CI, confidence interval; pain severity, Multidimensional Pain Inventory pain severity subscale; depression, Centers for Epidemiologic Studies Depression scale; pain catastrophizing, Pain Catastrophizing Scale

* adjusted for all other factors listed in the table

Table 4

Univariable and multiple variable linear regression analyses with ND (standardized) values of HP 5-0.5 as the dependent variable.

Independent Variables	Univariable Regression Coefficient			Multiple Variable Regression Coefficient [*]		
	B	95% CI	P value	B	95% CI	P value
Current opioid use	-.55	-.92 to -.18	.004	-.50	-.89 to -.11	.013
Pain duration (years)	-.02	-.04 to <-.01	.022	-.01	-.04 to .01	.272
Currently working	-.43	-.85 to -.01	.049	-.40	-.82 to .03	.066
Pain diagnosis						
-Low back pain		0.00			0.00	
-Fibromyalgia	.38	-.08 to .84	.106	.32	-.14 to .78	.174
-Generalized	.59	.06 to 1.12	.030	.60	.07 to 1.12	.027
- Headache	.45	-.13 to 1.03	.129	.10	-.50 to .71	.737
Pain severity	.01	-.02 to .03	.639	.01	-.02 to .04	.586
Depression	.01	-.01 to .02	.148	.01	-.01 to .03	.280
Pain catastrophizing	.01	-.01 to .02	.418	<-.01	-.02 to .02	.958

ND, normal deviate; CI, confidence interval; pain severity, Multidimensional Pain Inventory pain severity subscale; depression, Centers for Epidemiologic Studies Depression scale; pain catastrophizing, Pain Catastrophizing Scale

* adjusted for all other factors listed in the table