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Characteristics of Chronic Pain Patients Who Take Opioids and Persistently Report High Pain Intensity

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Abstract

Background and Objectives—The use of self-report questionnaires to detect characteristics of altered central pain processing, as seen in centralized pain disorders such as fibromyalgia, allow for the epidemiological studies of pain patients. Here, we assessed the relationship between reporting high levels of pain while taking opioids and the presence of characteristics associated with centralized pain.

Methods—We evaluated 582 patients taking opioid medications using validated measures of clinical pain, neuropathic pain symptoms, mood, and functioning. A multivariate linear regression model was used to assess the association between levels of pain while taking opioids and presenting with characteristics consistent with having centralized pain.

Results—We found that 49% of patients taking opioids continued to report severe pain (7/10). In multivariate analysis, factors associated with having higher levels of pain in opioid users included higher fibromyalgia survey scores ($P = 0.001$), more neuropathic pain symptoms ($P < 0.001$), and higher levels of depression ($P = 0.002$). While only 3.2% were given a primary diagnosis of fibromyalgia by their physician, 40.8% met American College of Rheumatology survey criteria for fibromyalgia.

Conclusions—Our findings suggest that patients with persistently high pain scores despite opioid therapy are more likely than those with lower levels of pain to present with characteristics associated with having centralized pain. This study cannot determine whether these characteristics were present before (fibromyalgia-like patient) or after the initiation of opioids (opioid-induced hyperalgesia). Regardless, patients with a centralized pain phenotype are thought to be less responsive to opioids and may merit alternative approaches.

INTRODUCTION

Estimates suggest that more than 100 million Americans live with chronic pain.¹ As a result, there has been a substantial increase in the prescription of opioids for nonmalignant pain, with some studies suggesting an increase of more than 100% in the past decade, along with a concomitant increase in opioid abuse and accidental overdose.² Despite the increase in opioid prescriptions, few studies support a favorable risk-benefit ratio for their long-term use

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in patients with chronic nonmalignant pain.³ Nonetheless, as many as 90% of the patients who present to pain centers for treatment are already taking opioids.⁴ Thus, a common problem in clinical practice is the chronic pain patient who has been maintained on opioids but who continues to experience persistent pain. Unfortunately, there is a dearth of information regarding the characteristics of patients with severe pain despite taking opioids.

Centralized pain syndromes are conditions caused by damage to or malfunction of the central nervous system. Fibromyalgia is the centralized pain disorder that has been the best studied.^{5,6} As described in a review by Clifford Woolf, beyond fibromyalgia, there are a number of disorders in which a portion of the cohort demonstrates features of centralized pain, including chronic low back pain, temporomandibular disorders, osteoarthritis, rheumatoid arthritis, dental pain, and chronic headache. The multiple overlapping conditions are bound by a common pathophysiological mechanism of altered central pain processing,⁷ although the specific mechanisms can vary.

It is important to identify centralized pain disorders, in part because patients with centralized pain may have an impaired response to opioids. Patients who have disorders of central pain processing such as fibromyalgia are thought to be less responsive to opioid therapy due to decreased opioid binding potential,^{8,9} which may result from increased endogenous opioid production.¹⁰ Hence, identifying centralized pain characteristics (phenotype) may help explain the lack of response to opioids in other patient populations. In addition, there is a growing body of preclinical and clinical evidence that patients taking opioids can develop increased pain, which has been termed opioid-induced hyperalgesia (OIH).¹¹ OIH represents another disorder of altered central pain processing.

Unfortunately, there are no diagnostic criteria for identifying the presence of centralized pain. However, the prototypical centralized pain disorder of fibromyalgia is commonly associated with several characteristics such as pain that is more widespread and neuropathic in nature, decreased functional status, comorbid symptoms (fatigue, sleep disturbances, trouble thinking, trouble remembering), and elevated levels of depression and anxiety.^{5-7,12} Although not intended to diagnose patients with fibromyalgia or centralized pain, validated self-report questionnaires can be used in an epidemiological fashion to detect patients with phenotypic differences associated with altered central pain processing.¹³

The primary objective of this study was to assess the relationship between reporting high levels of pain while currently taking opioids and the presence of characteristics associated with centralized pain. We hypothesized that patients with persistently high pain despite opioid therapy would be more likely to present with characteristics consistent with having centralized pain than those reporting lower levels of pain.

METHODS

As part of standard clinical care at the University of Michigan Back & Pain Center (Department of Anesthesiology), all new patients complete an intake packet that includes routine medical information along with a battery of validated self-report measures. Institutional Review Board (University of Michigan, Ann Arbor, MI) approval was obtained prior to implementation of the intake packet. A cover letter stated that information from the questionnaires could be used for research purposes, and a waiver of informed consent was obtained. Patients were asked specifically about demographics, pain, physical function, psychological factors, medication use, and previous pain therapies.

All pen-and-paper data collected for clinical and research use were entered into the Assessment of Pain Outcomes Longitudinal Electronic Data Capture System (APOLO EDC).¹⁴ Patients from this dataset have been used in reports describing chronic pain and

smoking,¹⁵ pain in childhood¹⁶ and the presence of fibromyalgia in patients with spine pain.¹² For the current study, patients 18 years of age and older presenting from November 2010 to March 2012 who were currently taking opioids were included.

Current opioid use

Opioid use was assessed using a comprehensive checklist of opioid medications (generic names, brand names, and free text) that also queried whether the use was current or previous. A patient was classified as a current opioid user if he checked “yes” to current use for at least one of the opioids listed in the new patient form.

Pain severity

A continuous measure of pain severity was assessed using the mean from the 4 pain severity items from the Brief Pain Inventory (BPI).¹⁷ Patients were queried about their worst, least, average, and current pain (0 = no pain; 10 = pain as bad as you can imagine).

Centralized pain phenotype

Several validated self-report measures were used to evaluate the phenotypic characteristics of patients taking opioids. The American College of Rheumatology (ACR) survey criteria for fibromyalgia were used to measure features consistent with centralized pain, including widespread body pain and comorbid symptoms. The updated ACR survey criteria were introduced in 2010¹⁸ and provisionally accepted by the ACR in 2011 and, unlike the 1990 criteria, do not require a tender point examination.¹⁹ Whereas a clinical diagnosis of fibromyalgia still requires a clinical examination and sometimes laboratory testing to rule out other explanations for the pain, the measure has been proposed by experts to be used in an epidemiological fashion to detect pain that is likely due in part to altered central pain processing.⁷ The Widespread Pain Index (WPI) was scored using the Michigan Body Map²⁰ to calculate the number of 19 painful body areas comprising the ACR survey criteria (score 0-19).¹⁸ The Symptom Severity (SS) scale is a measure of comorbid symptoms (eg, trouble thinking, fatigue) and was used to assess the second aspect of the criteria.¹⁸ Survey criteria for a dichotomous categorization of fibromyalgia are WPI ≥ 7 and SS ≥ 5 or WPI = 3-6 and SS ≥ 9. Using these cutoffs, patients can be classified into 1 of 2 groups: patients who meet the ACR survey criteria for fibromyalgia and those who do not. The WPI and the SS scales can also be combined to provide a continuous measure of fibromyalgia symptoms (0-31) that can be thought of as centralized pain severity.¹³ The 9-item PainDETECT was used to assess the presence and severity of neuropathic pain symptoms. Studies have demonstrated correlations between high neuropathic pain description on the PainDETECT and widespread pain.²¹ Scores range from [-1] to 38, and total scores greater than or equal to 19 suggest a neuropathic component is likely.

Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS). The HADS consists of two 7-item subscales that measure symptoms of depression and anxiety. Scores range from 0 to 21 for each scale with higher scores indicative of greater levels of symptoms of depression and anxiety.²² Lastly, functional status was assessed using the 10-item PROMIS Function Short Form 1 with higher scores representing higher functionality.²³

The primary clinical diagnosis assigned by the physician caring for the patient was obtained from the hospital administrative database. Given the unreliable nature of secondary diagnoses, only primary diagnoses were included. Particular attention was given to the fibromyalgia diagnosis (729.1) to determine whether any of the patients were assigned the categorical diagnosis by their treating physician.

Statistical Analysis—Missing data for the validated measures were handled as described by instrument authors and detailed in our previous publication.¹⁴ For a more clinically meaningful assessment of pain severity, patients were divided into groups according to tertiles based on the distribution of the BPI scores for univariate comparisons of the phenotypic measures assessed. Univariate analysis was done using regression models with differences between the 3 pain groups expressed by a categorical variable included in the model as a covariate. Between-group analysis was adjusted for multi-comparisons using the Holm method. A separate regression model was used for each variable being analyzed dependent on the scale of that variable. Linear regression was used with continuous variables, logistic regression with binary variables, multinomial logit model with nominal variables, and proportional odds model with ordinal variables. Predictors of high pain severity were assessed using multivariate linear regression models with BPI pain severity as a continuous response. Variable selection was done by backward elimination using the Akaike Information Criterion (AIC) and the model-based likelihood ratio test.

RESULTS

Participants

Of the 1208 new patients evaluated over the study period, 582 (48.2%) reported that they were currently taking opioids and had a valid BPI pain score and were thus included in the analysis. The majority of patients taking opioids were female (57.7%; $n = 336$). The mean age for participants was 49.11 years old ($SD = 14.39$) and 86.4% ($n = 503$) were Caucasian. Of the participants in this study, 53.6% ($n = 312$) were married and 29.4% ($n = 171$) reported having a college degree or higher.

Pain severity and a centralized pain phenotype

While only 18 (3.2%) of the 566 patients with primary diagnostic code data available had been assigned a primary diagnosis of fibromyalgia by their treating physician during their new patient evaluation (Table 1), the ACR survey criteria for fibromyalgia were met by 40.8% of all new patients taking opioids. Among patients currently taking opioids, 49.1% rated their pain as 7 or greater on the BPI pain severity subscale. The mean BPI pain severity score was 6.8 ($SD 1.7$). Based on their BPI pain severity scores, patients were divided into tertiles: Group 1 Lowest Pain group ≤ 6 , Group 2 Middle Pain group > 6 and < 7.5 , and Group 3 Highest Pain group > 7.5 . A series of univariate regression analyses with Holm-adjusted between-group comparisons were conducted for each variable in Table 2. Group differences resulting from these analyses are depicted in Table 2 for demographic variables and a number of characteristics associated with pain that is phenotypically more centralized in nature including meeting ACR survey criteria (dichotomous measure), fibromyalgia survey score (continuous measure), neuropathic pain symptoms, symptoms of depression and anxiety, and reduced physical functioning.

Comparisons between the 3 pain severity groups revealed that 50.3% of patients in the highest group and 46.1% in the middle pain group met ACR survey criteria for fibromyalgia, compared with 27.8% in lowest pain group ($P < 0.001$). Patients with the highest pain severity (Group 3) reported higher fibromyalgia survey scores, more neuropathic pain, higher depression and anxiety symptoms, and reduced physical functioning compared to the lowest pain and middle pain groups. Additionally, the middle pain group (Group 2) reported higher levels of fibromyalgia symptoms, more neuropathic pain, more symptoms of depression and anxiety, and reduced physical functioning compared with the lowest pain group (Group 1).

Gender, age, race, marital status, education, fibromyalgia survey score, ACR fibromyalgia positive status, neuropathic pain symptoms, HADS scores, and physical function (PROMIS) variables were included in the multivariate analysis. Table 3 shows the best multivariate model for the continuous BPI measure of pain severity as a response, resulting from backward variable selection. In summary, higher scoring pain patients tended to be non-Caucasian, unmarried and have lower levels of education, while also having higher fibromyalgia survey scores, more neuropathic pain symptoms, and higher depressive symptoms. Contrary to our expectations, anxiety ($\beta = 0.021$; $P = 0.283$) and physical functioning ($\beta = -0.012$; $P = 0.331$), while highly significant in the univariate analysis, were not significant in the full model for pain severity prior to best model selection (not shown). Their effect was well explained by the other variables included in the model.

DISCUSSION

In this study of new patients evaluated in an academic tertiary care pain clinic, we found that almost half (49.1%) of patients taking opioids continued to report severe pain (scores ≥ 7). As hypothesized, the multivariate linear regression model showed that independent predictors of higher pain scores included higher fibromyalgia survey scores, more neuropathic pain symptoms, and higher depressive symptoms (Table 3). These are features that have been classically demonstrated in patients with altered central pain processing.^{6,7,9,12} When patients were segmented into 3 groups based on pain severity scores, we found that 50.3% of patients with the highest pain scores (Group 3) and 46.1% of patients with middle pain scores (Group 2) met survey criteria for fibromyalgia, compared with only 27.8% in the lowest pain score group (Group 1; Table 2). The characteristics (phenotype) of the high pain opioid group in this study suggest the need for an alternative treatment approach, as opioids are less likely to be helpful in a centralized pain population.^{8,10}

One of the challenges in pain management is what to do with patients who are taking opioids but continue to report significant pain. Once progression of the disease has been ruled out, the clinician is faced with a differential diagnosis that includes (1) pain disorders that are potentially resistant to opioid therapy (eg, fibromyalgia and conditions with a similar pathophysiology),^{8,9} (2) opioid tolerance,¹¹ (3) opioid-induced hyperalgesia,¹¹ or (4) a combination of issues. Distinguishing between these processes can be difficult because all encompass the common feature of a patient taking opioids who continues to report persistently high pain. Altered central pain processing is thought to be less responsive to opioid therapy and, of potentially greater concern, opioid therapy may potentially worsen pain symptoms in some individuals. In regard to responsiveness, fibromyalgia has been associated with lower endogenous opioid receptor binding availability⁸ and higher levels of cerebrospinal fluid opioids,¹⁰ suggesting that the endogenous opioid system is already activated in centralized pain. This may explain the anecdotal sense that opioids are ineffective in patients who have developed centralized pain as a result of their primary pain disorder.²⁴ Opioid tolerance is a normal physiologic response to opioids that involves desensitization of the anti-nociceptive pathways. Proposed mechanisms for opioid tolerance²⁵ do not include central sensitization to nociceptive input.²⁶ In contrast, opioid-induced hyperalgesia involves the activation of pronociceptive pathways by exogenous opioids that results in central sensitization to pain.²⁶ The result is an increase in pain sensitivity with the potential to exacerbate pre-existing pain.¹¹ Thus, the mechanisms for opioid-induced hyperalgesia and other centralized pain states can be quite similar since they both appear to involve neuroplastic changes in the central nervous system leading to sensitization of pronociceptive pathways. Hence, the present study cannot differentiate patients with a pre-opioid therapy centralized pain state from those that have developed OIH.

Despite a similar clinical presentation, these are distinct concepts that merit entirely different treatment algorithms. For example, a patient who has developed tolerance to opioids should, in theory, be treated with higher doses of opioids.¹¹ On the other hand, a patient who developed centralized pain as a result of the primary pain condition itself, or after starting opioids (OIH), may benefit from minimizing or weaning off of opioids and using non-opioid medications such as antidepressants and anticonvulsants.^{9,11} While definitive statements cannot be made, the results of the current study have potentially interesting clinical implications for managing patients on opioids who continue to report a high level of pain. The findings suggest that when we take into account pain severity, the patients who continue to report high pain (which may be clinically indicative that the opioids are not helping with pain management) are more likely to have a centralized pain. Although these results cannot distinguish between tolerance, pain disorders that are potentially resistant to opioid therapy (eg, fibromyalgia and other centralized pain conditions), and OIH, they do suggest the need to further explore the relationship between altered central pain processing and the effectiveness of opioids.

Pain severity using a 0 to 10 scale is the most common means for assessing patients' pain complaints, which was the rationale for group separation and the analytical approach. With regards to generating hypotheses about pain management for patients taking opioids who continue to report high pain, the univariate findings (Table 2) from the current study have potentially useful practical applications. For example, patients with the highest pain severity (7.5 or above on the BPI severity scale) who have characteristics of centralized pain may be less likely to have opioid tolerance. These results suggest that patients on opioids, who continue to report severe pain, are a heterogeneous group and that there could be clinical utility in differentiating between patients. In most clinics, physicians and patients do not want to work through large numbers of questionnaires as occurs in our clinic. These data support our contention that additional questionnaires may only be necessary in patients with persistently high pain scores to assist in identifying those with a more centralized pain phenotype, which could ultimately affect the management plan. Although additional research is needed, there is mechanistic rationale for the treatment of patients with altered central pain processing in a manner similar to that of fibromyalgia. This would include medications like gabapentinoids, tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors rather than opioids.

Limitations

This study has several limitations. First, these cross-sectional data do not allow for a causal assessment of the responsiveness to opioids, but instead suggest that certain characteristics are associated with patients taking opioids who report high levels of pain. Second, because there is no opioid naïve group, it is important to use caution when interpreting these results. It is certainly possible that the association between high pain and having characteristics associated with centralized pain is related to the effect (or lack of effect) of opioids; alternatively, the high pain may be due to more severe disease or a function of another process not accounted for in this study. Third, neither the duration nor the dose of opioids was measured and this could contribute to pain report in a number of ways. For example, patients who have recently initiated opioids could be on a low dose that is not sufficient to address their pain. Conversely, more long-term and/or high dose opioid users could be experiencing OIH. Lastly, these data are from a single center and may not be generalizable to other populations.

Conclusions

The current study used brief, validated scales in a clinical setting and found that patients taking opioids who still have higher pain scores despite opioid therapy are more likely to

present with features of centralized pain regardless of their primary pain disorder than patients with lower pain scores. Although self-report measures cannot differentiate the etiology of the centralized pain process, which may be a product of the initial pain problem (eg, centralized pain or fibromyalgia-like state), OIH, or a combination of both processes, they provide a reference for understanding potential differences in underlying pain processes. Therefore, further studies are needed to identify phenotypic characteristics associated with these patients, as well as quantitative sensory testing to aid in the diagnosis of the pain mechanism and, ultimately, the best treatment strategies for these patients.

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Table 1

Primary diagnostic category within each pain severity group in patients taking opioids

Primary diagnostic category	Lowest group (< 6 on BPI)	Middle Group (6 and 7.5 on BPI)	Highest group (> 7.5 on BPI)
Spine pain	45.3	51.1	53.0
Musculoskeletal pain	20.3	19.1	13.0
Peripheral nerve pain	8.9	3.4	10.3
Central nervous system	5.4	6.7	8.6
Fibromyalgia	2.5	2.5	4.9
Centralized pain syndrome	0.5	0.6	0.0
Abdominal pain	4.9	4.5	2.7
Facial pain	4.9	6.2	1.1
Headache	2.0	1.7	0.5
Genitourinary pain	1.0	2.8	1.1
Pelvic pain	2.5	0.0	0.5
Miscellaneous pain	2.0	1.7	0.0
Total N	203	178	185

Scores are percentages

Total N =566 due to missing data on primary diagnostic code variable

Table 2

Univariate between group differences for demographic and key study variables based on pain severity.

	Group 1 Lowest pain (BPI 6)	Group 2 Middle pain (BPI >6 and 7.5)	Group 3 Highest pain (BPI > 7.5)	Overall 1 vs. 2 vs. 3 (p value)	1 vs. 2 (p value)	1 vs. 3 (p value)	2 vs. 3 (p value)
DEMOGRAPHICS							
Gender (% female)	53%	62%	59%	0.16	0.07	0.20	0.58
Age	51.1 (15.1)	47.6 (13.5)	48.3 (14.2)	0.03	0.02	0.05	0.62
Ethnicity (% white)	95.2 %	85.5%	83.2%	<0.001	<0.001	<0.001	0.54
Marital status (% married)	63.6%	54.2%	45.4%	0.001	0.06	<0.001	0.09
Education (% college)	40.7%	29.4%	18.5%	<0.001	0.02	<0.001	<0.001
PAIN, AFFECT AND FUNCTION							
ACR Survey Criteria (% positive)	27.8%	46.1%	50.3%	<0.001	<0.001	<0.001	0.44
Fibromyalgia Survey Score	10.7 (4.51)	13.5 (5.55)	14.7 (5.92)	<0.001	<0.001	<0.001	0.04
Neuropathic pain symptoms	15.8 (7.18)	20.4 (7.95)	23.7 (8.49)	<0.001	<0.001	<0.001	<0.001
Depressive symptoms	8.5 (3.97)	9.74 (4.26)	11.3 (4.62)	<0.001	0.004	<0.001	<0.001
Anxiety symptoms	7.76 (3.93)	9.14 (4.46)	10.7 (4.72)	<0.001	0.002	<0.001	<0.001
Physical functioning	31.2 (7.73)	29.2 (7.16)	26.1 (7.76)	<0.001	0.01	<0.001	<0.001

The cohort was divided into tertiles based on the distribution of pain severity as measured by the Brief Pain Inventory (BPI). Separate regression models were conducted for each covariate. Model selection based on the variable type (see Methods section), and corrections made for multiple comparisons. P values represent the overall group result followed by the individual between group analyses. The American College of Rheumatology (ACR) survey criteria for fibromyalgia was analyzed in two ways: 1) percentage of patients meeting previously described cut points for survey criteria; 2) continuous score for the measure (0-31). Other measures of pain, affect and physical functioning were analyzed as continuous scores.

Table 3

Multivariate Regression Model Predicting Pain Severity.

	Estimate (regression coefficient)	SE	Test Statistic	P value
(Intercept)	5.286	0.323	16.356	< 0.001
Race (Caucasian)	−0.549	0.219	−2.509	0.012
Marital status (married)	−0.354	0.136	−2.600	0.010
College graduate	−0.433	0.146	−2.964	0.003
Fibromyalgia survey score	0.045	0.014	3.312	0.001
Neuropathic pain symptoms	0.059	0.009	6.807	<0.001
Depressive symptoms	0.050	0.016	3.052	0.002

Caucasian race, being married and educational level of college graduate or higher were each independently associated with a lower pain severity, while higher fibromyalgia survey scores, more neuropathic pain descriptors and higher depressive symptoms were each independently predictive of higher pain severity. SE = standard error.