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Withdrawal symptoms predict prescription opioid dependence in chronic pain patients

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ABSTRACT

Background: The last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes substantial changes for prescription opioid-use disorder (POUD). After its removal as a criterion, the goal of this study was to estimate the prevalence of withdrawal symptoms in long-term users of prescription opioids and its association with the new DSM-5 POUD classification.

Methods: Data were collected from 215 long-term consumers of opioid medication who were chronic non-cancer pain patients. Participants completed sociodemographic, Adjective Rating Scale for Withdrawal (ARSW), opioid treatment characteristics, POUD criteria (DSM-5), and pain intensity measurements.

Results: 26.6% of the participants were classified with moderate to severe POUD. Higher intensity of withdrawal symptoms was found in patients with moderate/severe POUD, younger age, and higher pain intensity ($p < .01$). Anxiolytics ($p < .01$) and antidepressants use ($p < .05$) and percentage of smokers ($p < .05$) were significantly higher in patients with severe withdrawal. Logistic regression analyses suggested moderate [odds ratio (OR) = 3.25] and severe (OR = 10.52) withdrawal as the strongest predictor of POUD. Age, anxiolytics use, and smoking were also associated with POUD, but multilevel analysis showed that these variables do not moderate the association between withdrawal intensity and POUD.

Conclusion: Escalation of withdrawal intensity during opioid treatment can be used to identify patients with POUD. Further studies are needed to assess the clinical implications of these findings during long-term opioid therapy for chronic pain.

1. Introduction

The use of prescription opioids for the treatment of chronic pain has increased worldwide (Cooper et al., 2017; Fischer et al., 2014; Helmerhorst et al., 2017; Kaye et al., 2017). However, the long-term use of these medications has been pointed out as a risk factor for opioid analgesics misuse (Chou et al., 2015; Dowell et al., 2016; Edlund et al., 2014). The fifth revision of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013) included several changes to the diagnostic criteria for prescription opioid-use disorder (POUD). As recommended by the DSM-5 working group (Hasin et al., 2013), abuse and dependence symptoms have been combined into a single disorder graded by severity, and the legal problems criterion has been replaced with craving. However, the removal of withdrawal symptoms and tolerance criteria for those taking opioids under appropriate medical supervision (e.g., chronic pain patients) is perhaps the most substantial change. The reason for excluding these symptoms is their consideration as normal neurophysiological adaptations that appear in response to chronic opioid exposure (Boscarino et al., 2015; Hasin et al., 2013; Volkow and McLellan, 2016), which has generated considerable debate concerning the controversial conceptualization of addictive behavior as a biological and brain disease (Becoña, 2016; Hall et al., 2015; Hammer et al., 2013; Robinson and Adinoff, 2016; Volkow and McLellan, 2016).

Despite these changes, it could be interesting to assess the relationship of withdrawal symptoms reported by chronic non-cancer pain (CNCP) patients under long-term opioid treatment, with the construct of opioid addiction proposed in DSM 5. For this reason, the aim of the present study is to examine the association of these symptoms with the new DSM 5 opioid-use disorder classification and its predictive power for the severity classification of POUD.

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2. Material and methods

2.1. Participants

The sample included 215 patients with chronic non-cancer pain (CNCP) from the Pain Unit of a general university hospital. Participants were recruited between September 2014 and January 2017. Inclusion criteria were as follows: (a) being older than 18 years and (b) having used opioid analgesics for at least 90 days, which is considered long-term opioid therapy (Chou et al., 2015; Dowell et al., 2016). The exclusion criteria were: (a) presenting mental severe pathologies (e.g., psychosis or dementia), (b) having a diagnosis of cancer, or (c) being unable to be properly evaluated.

2.2. Measures

The following patient demographic and clinical characteristics were assessed: age, gender, diagnosis, current pharmacological treatment (type and dosage in milligrams of opioids consumed, time in treatment with prescription opioids, adjuvant medications for treating pain), and concomitant substance use. For comparison purpose, each opioid dose prescribed was converted to parenteral morphine equivalent dose (MED) using the American Pain Society guidelines (2016). If multiple opioids were used, the total MED per day was calculated by adding the morphine-equivalents doses of each opioid prescribed.

Prescription opioid withdrawal was assessed using the Adjective Rating Scale for Withdrawal (Amass et al., 2000), which is made up of 16 Likert-type items, ranging from 0 (not at all) to 9 (severe), that assess severity of opioid withdrawal symptoms (e.g., painful joints, runny nose, nausea, or irritability). Patients were asked to rate the severity of the symptoms only if experienced between doses or when the patient skips or miss a dose. The ARSW showed unifactorial structure, invariance across gender, and excellent internal consistency (Cronbach's alpha = 0.85) in the validation performed with CNCP patients under long-term treatment with opioids (Coloma-Carmona et al., 2018) as well as with patients in treatment with buprenorphine/naloxone (Barbosa-Leiker et al., 2014).

Prescription opioid-use disorder was assessed with 9 binary items (yes/no) that include all abuse and dependence symptoms of DSM-IV-TR (American Psychiatric Association, 2002) excluding tolerance, withdrawal, and legal problems. For a better drug-craving measure, the presence of this symptom during the last 24 h was assessed with Weiss' craving scale (Weiss et al., 1995), which has been also used in previous studies to assess craving for prescription opioids among chronic pain patients (Martel et al., 2016; Wasan et al., 2012). POUD severity was graded by no or few symptoms (0–1 symptoms), mild (2–3 symptoms), moderate (4–5 symptoms), and severe (6 or more symptoms) according to DSM-5 severity indicator (American Psychiatric Association, 2013).

Due to the similarity of withdrawal and chronic pain symptoms, pain intensity was also assessed using the Spanish version of the Brief Pain Inventory (Badia et al., 2003). Level of pain (score range: 0–40) was calculated by adding the scores of the visual analog scales' items of each factor (worst, least, average and current pain).

2.3. Procedure

Data were collected during consultation hours of the Pain Unit. A signed informed consent was requested before assessment, and the instruments were individually applied by trained psychologists in a 30-minute interview. No compensation was paid for participation. The study was reviewed and approved by the Committee of Research and Ethics of the Miguel Hernández University and of the hospital.

2.4. Data analysis

Data analyses were carried out with SPSS 23.0. All the analyses were performed at a confidence level of 95%. Descriptive and bivariate analysis were performed using chi-square as the contrast statistic for the non-continuous variables and independent *t*-test for continuous variables with normal distribution and variance homogeneity. One-way ANOVA and post-hoc tests were used for non-continuous variables with more than 2 categories. Cohen's *d*, Cramer's *phi*, and eta squared effect sizes were also calculated. Binary logistic regression was used to assess association between POUD (outcome variable) and withdrawal severity (predictor variable). Any variable that showed significant differences between levels of withdrawal intensity was included in the model to control for potential confounders and possible interaction effects of the predictors. The analyses were performed using the hierarchical method, and continuous variables were mean-centered.

3. Results

3.1. Sample characteristics

Individuals who did not complete the entire evaluation or did not understand the questions (due to neurological problems or being under effect of drugs) were excluded (n = 8), resulting in a study sample size of 207. Sample characteristics are presented in Table 1. Mean age was 59.00 ± 14.32 years (range 25–94), and 66.3% (n = 138) were female. Main reasons for seeking treatment were back pain (57.5%, n = 119), leg pain (15.9%, n = 33), and neck and shoulder pain (11.6%, n = 24). Average time in treatment with opioid medication was 2.42 ± 2.92 years, and the mean morphine-equivalent dose was 37.20 ± 47.20 mg per day.

Regarding the use of adjuvant medications for treating pain, anxiolytics were identified as the most prescribed drugs (46.9%, n = 97). Antidepressants (18.8%; n = 39), antiepileptic drugs (14%, n = 29), and hypnotics (7.7%, n = 17) were also used but less frequently. In addition, alcohol was the substance consumed the most during the last month (41.4%, n = 85), followed by tobacco (28%, n = 58) and cannabis (2.9%, n = 6).

Of the 207 patients, 26.6% (n = 55) were classified as having moderate (9.7%, n = 20) to severe (16.9%, n = 35) symptoms of POUD. On the contrary, most participants had no or few symptoms (43%, n = 89) and mild symptoms of POUD (30.4%, n = 63).

Table 1
Sample characteristics (N = 207).

	Total sample (N = 207)
Demographics	
%(n) Male	33.70 (69)
%(n) Female	66.30 (138)
Mean ± SD age (years)	59.00 ± 14.32
POUD Severity	
%(n) Not moderate/severe	70.4 (152)
%(n) Moderate/severe	26.6 (55)
Pain variables	
Mean ± SD BPI intensity score	23.76 ± 6.28
Opioid treatment characteristics	
Mean ± SD duration (years)	2.42 ± 2.92
Mean ± SD daily MED (mg)	37.20 ± 47.20
Mean ± SD opioids prescribed	1.32 ± 0.55
Adjuvant medications for treating pain	
% (n) Anxiolytics	46.9 (97)
% (n) Antidepressants	18.8 (39)
% (n) Antiepileptic drugs	14 (29)
% (n) Hypnotics	7.7 (17)
Concomitant substance use (last month)	
% (n) Alcohol	41.4 (85)
% (n) Tobacco	28 (58)
% (n) Cannabis	2.9 (6)

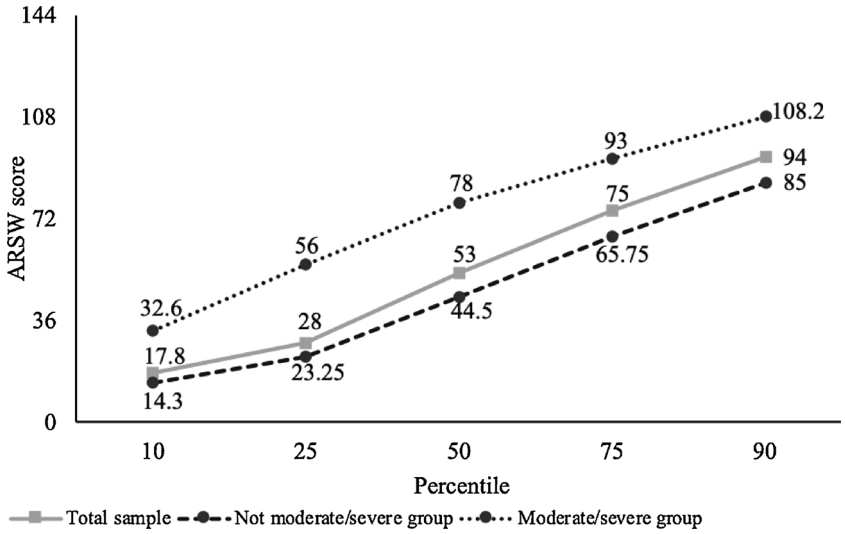

Fig. 1. Percentile distribution of the ARSW scores (ranged between 0 and 144) of the total sample and stratified by opioid-use disorder severity.

3.2. Prevalence and percentile distribution of withdrawal symptoms

As in previous research (Boscarino et al., 2015), the number of POUD symptoms score was dichotomized as moderate/severe and not moderate/severe. In comparison with the not moderate/severe group (see Fig. 1), the percentile distribution of the ARSW scores showed higher values of withdrawal symptoms among patients with moderate/severe POUD (50^{th} percentile: 44.5 vs. 78; 90^{th} percentile: 85 vs. 108.2).

As the ARSW scores follow a normal distribution, the range of withdrawal symptoms were also equally stratified into three severity groups: 0–36 (mild intensity: $\leq 33^{rd}$ percentile), 37–68 (moderate intensity: 33^{rd} to 66^{th} percentile), and 69–144 (severe intensity: $\geq 66^{th}$ percentile). As expected, withdrawal symptoms also appear in patients without moderate/severe POUD (see Table 1). However, a significantly higher percentage of patients with moderate and severe withdrawal was observed among those also classified with moderate/severe POUD ($p < .01$).

3.3. Comparison of patient characteristics by level of withdrawal intensity

A comparison of patient characteristics by level of withdrawal intensity is presented in Table 2. One-way ANOVAs showed there were significant differences in age and pain intensity between groups of withdrawal intensity ($p < .01$). Post-hoc tests revealed that mean age of patients who reported severe withdrawal was significantly lower than mean age of those with mild withdrawal. In addition, pain intensity significantly increased with withdrawal intensity across the three groups. The prescription of anxiolytics ($p < .01$) and antidepressants ($p < .05$), as well as the use of tobacco during the last month ($p < .05$), was significantly higher in patients with severe withdrawal compared to those with mild withdrawal intensity. No differences in total daily MEDs, duration of treatment, or number of opioids used were found between groups of withdrawal intensity ($p > .05$).

3.4. Association of withdrawal symptoms with opioid-use disorder

The hierarchical binary regression was performed using the POUD variable as the outcome. Three models were created by first adding withdrawal intensity as the predictor variable then adding the variables significantly associated with withdrawal (pain intensity, age, use of anxiolytics and antidepressants, and smoking) and finally including two-way interaction terms between the control variables and withdrawal.

Withdrawal intensity had a significant high predictive power for POUD. Concretely, moderate and severe withdrawal symptoms offered odds ratios (*OR*) of 3.25 (CI95%: 1.18–8.98, $p = .023$) and 10.52 (CI95%: 4.03–27.49, $p < .001$), respectively. The association of severe withdrawal intensity and POUD was also significant ($OR = 7.14$, CI95%: 2.36–21.59, $p < .001$) when simultaneously adding pain, age, anxiolytics, antidepressants, and smoking to the regression model. Pain intensity was not significantly associated with POUD ($OR = 0.98$, CI95%: 0.92–1.05; $p = .578$), nicotine use ($OR = 0.83$, CI95%: 0.36–1.88; $p = 0.647$), or antidepressants use ($OR = 1.41$, CI95%: 0.59–3.37; $p = 0.440$), which suggests that adding them as control variables will not improve the ability of the model to predict the disorder (Table 3).

Finally, neither of the two-way interactions terms between level of withdrawal intensity and the covariates were significant ($p > .05$). These results indicate that age and anxiolytics use did not moderate the relationship between withdrawal intensity and the opioid-use disorder, suggesting an independent association of the predictor and control variables with the outcome. Since interaction terms were not significant, only main effects are presented in Table 3.

4. Discussion

The main goal of this study was to examine the relationship between withdrawal symptoms and the new DSM-5 opioid-use disorder criteria. In order to do so, a sample of chronic pain patients under long-term opioid therapy was asked to report the severity of 16 withdrawal symptoms experienced when skipping or missing an opioid dose using the Adjective Rating Scale for Withdrawal (Amass et al., 2000).

Our study points to a 26.6% rate of moderate to severe POUD, similar to the rates found by other authors (Dunn et al., 2017). While withdrawal symptoms appear also in patients with few or mild POUD (Ballantyne, 2007; Fields, 2011; Ling et al., 2011; Shurman et al., 2010), significant higher values of withdrawal intensity were found among patients with a moderate and severe disorder. Logistic regression analyses suggest that withdrawal intensity is the strongest predictor of POUD, with an increased likelihood of having moderate/severe POUD in patients who experience moderate (OR = 3.25) and severe (OR = 10.52) withdrawal when skipping or missing a dose.

Some patient and treatment characteristics were found to have a significant relationship with opioid withdrawal intensity. As in previous research, no gender differences were found (Back et al., 2011), but withdrawal symptoms were higher in younger patients, which is a risk

Table 2
Differences in participant characteristics between levels of withdrawal intensity (N = 207).

	Mild withdrawal (n = 73)	Moderate withdrawal (n = 65)	Severe withdrawal (n = 69)	Statistic (*p*)	ES
Demographics					
% (n) Female	23.2 (48)	21.3 (44)	21.7 (45)	χ^2 = 0.101 (.951)	Φ = 0.02
Mean ± SD age (years)	63.04 ± 14.08[a]	59.45 ± 13.8[a,b]	54.38 ± 13.97[b]	F = 6.877 (.001)**	η^2 = 0.06
POUD Severity					
% (n) Not moderate/severe	44.1 (67)[a]	32.9 (50)[b]	23 (35)[c]	χ^2 = 31.239 (.001)**	Φ = 0.38
% (n) Moderate/severe	10.9 (6)[a]	27.3 (15)[b]	61.8 (34)[c]		
Pain intensity					
Mean ± SD BPI score	21.18 ± 6.04[a]	23.88 ± 5.92[b]	26.33 ± 5.84[c]	F = 13.294 (.001)**	η^2 = 0.12
Opioid treatment characteristics					
Mean ± SD duration (years)	1.95 ± 2.15	2.58 ± 3.54	2.77 ± 2.97	F = 1.562 (.212)	η^2 = 0.02
Mean ± SD daily MED (mg)	28.38 ± 29.05	36.14 ± 47.33	47.69 ± 59.80	F = 2.986 (.053)	η^2 = 0.03
Mean ± SD opioids prescribed	1.26 ± 0.53	1.29 ± 0.45	1.42 ± 0.62	F = 1.626 (.199)	η^2 = 0.02
Adjuvant medications for treating pain					
% (n) Anxiolytics	27.4 (20)[a]	55.4 (36)[b]	59.4 (41)[b]	χ^2 = 17.373 (.001)**	Φ = 0.19
% (n) Antidepressants	9.6 (7)[a]	20 (13)[a,b]	27.5 (19)[b]	χ^2 = 7.555 (.023)*	Φ = 0.19
% (n) Antiepileptic drugs	13.7 (10)	13.8 (9)	14.5 (10)	χ^2 = 0.021 (.990)	Φ = 0.01
% (n) Hypnotics	6.8 (5)	9.2(6)	8.7 (6)	χ^2 = 0.291 (.865)	Φ = 0.04
Concomitant substance use (last month)					
% (n) Alcohol	40.3 (29)	44.6 (29)	39.1 (27)	χ^2 = 0.460 (.795)	Φ = 0.05
% (n) Tobacco	19.4 (29)[a]	26.2 (17)[a,b]	39.1 (27)[b]	χ^2 = 6.938 (.031)*	Φ = 0.18
% (n) Cannabis	1.4 (1)	3.1 (2)	4.3 (3)	χ^2 = 1.100 (.577)	Φ = 0.07

N: number, ES: effect size, BPI: Brief Pain Inventory, MED: morphine-equivalent dose, MG: milligrams.
Values with same superscript (a,b,c) are not significantly different ($p > .05$) by ANOVA post-hoc test.
*$p < .05$, **$p < .01$.

Table 3
Binary logistic regression models for testing the association between prescription opioid-use disorder and withdrawal symptoms (N = 207).

	Unadjusted Model		Adjusted Model with confounders	
Variables	*OR* [95% CI]	*p*	*OR* [95% CI]	*p*
Withdrawal (ref. = mild)				
Moderate	3.25 [1.18-8.98]*	.023*	2.32 [0.77-6.98]	.133
Severe	10.52 [4.03-27.49]**	.001**	7.14 [2.36-21.59]**	.001**
Control variables				
Age	—		0.95 [.92-.98]**	.001**
Pain intensity	—		0.98 [.92-1.05]	.578
Anxiolytics	—		3.00 [1.36-6.64]**	.007**
Antidepressants	—		1.41 [0.59-3.37]	.440
Tobacco	—		0.83 [0.36-1.88]	.647

OR = odds ratio, CI: confidence interval.
*$p < .05$; **$p < .01$.

factor for opioid analgesics misuse (Boscarino et al., 2015, 2011; Cochran et al., 2014; Han et al., 2013; Liebschutz et al., 2010; Manchikanti et al., 2012; Voon et al., 2017).

Furthermore, higher use of anxiolytics and antidepressants was found in the group with a greater severity of withdrawal, which also had a higher percentage of smokers. These findings are consistent with previous studies showing that, although combined drug therapy is widely used for the treatment of chronic pain (Barry et al., 2015; Chaparro et al., 2012; Holbech et al., 2017; Mao et al., 2011; Zin and Ismail, 2017), polypharmacy is associated with greater adverse interactions, overdose risk, and opioid misuse (Dunn et al., 2017; Giummarra et al., 2015; Quinn et al., 2017; Schatman and Ziegler, 2017; Turner and Liang, 2015; Webster, 2017). In addition, other authors had also reported that smoking increases the likelihood of prescription opioid-use disorder (Jamison et al., 2011; Webster, 2017; Young-Wolff et al., 2017; Zale et al., 2015).

Moreover, withdrawal seems to increase with average pain intensity. It could be that, due to the similarity, patients may not differentiate between chronic pain and withdrawal symptomatology. However, the lack of association between patient's pain intensity and POUD found in the regression model suggest that both are experienced as two different phenomena (Dunn et al., 2015; Karasz et al., 2004; Rosenblum et al., 2008), and the ARSW is a reliable measure of withdrawal in chronic pain patients (Coloma-Carmona et al., 2018). In addition, the hierarchical analysis showed that none of these patient and treatment characteristics moderate the association of withdrawal intensity and POUD, indicating that withdrawal intensity, age, and anxiolytics use were independently associated with POUD.

These findings have important clinical and research implications for the area of treatment of chronic pain. Despite the fact that withdrawal is no longer included as a criterion for opioid-use disorder when occurring under proper medical supervision, high levels of withdrawal intensity during opioid treatment seem to be a useful indicator to identify patients with POUD. Since patients sometimes did not recognize or identify an inappropriate use of the treatment (Carballo et al., 2016), the characteristics of the ARSW (self-report, rapid, and non-invasive) make it a useful and clinically feasible screening tool that allow POUD to be identified without directly asking the central question. In this sense, the escalation in withdrawal intensity can be used, before deeper assessment, as an indicator to reassess treatment plans in order to reduce potential risk of POUD (Carballo et al., 2016; Chang and Compton, 2013; Morgan et al., 2013).

This study presents certain limitations. The representativeness of the sample could be improved by using a random selection method. The study also presents inherent limitations of the use of self-reports, such as bias of social desirability, which was reduced using single face-to-face interviews and voluntary participation in the study.

However, there are also some strengths to be considered. This is one of the few studies that use the new DSM-5 criteria to assess opioid-use disorder. Furthermore, we used a validated craving measure, reducing a possible underestimation or overestimation of the data. To our knowledge, this is also the first study that assess the association between withdrawal symptoms and the DSM-5 opioid-use disorder criteria and that uses a validated tool to assess prescription opioid withdrawal in chronic pain population (Coloma-Carmona et al., 2018).

Further longitudinal studies with larger samples are needed in which the ARSW is repeatedly apply to assess its effectiveness in the control and reduction of POUD during long-term opioid therapy for chronic pain.

Contributors

All authors contributed to the design of the study. A. Coloma-Carmona participated in data collection, conducted the statistical analysis and participated in the writing of the whole manuscript. J.L. Carballo participated in the conception and design of the study and participated in the writing of the results and discussion section of the manuscript. J. Rodríguez-Marín participated in the interpretation of data and in the writing of the introduction and methods section. A. Pérez-Carbonell participated in data collection and in the writing of the introduction and discussion section. All authors approved the final version of the manuscript.

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Conflict of interest

No conflict declared.

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