



Psychological factors associated with the adherence to analgesic treatment in patients with chronic pain: systematic review of the literature

Factores psicológicos asociados a la adherencia al tratamiento analgésico en pacientes con dolor crónico: revisión sistemática de la literatura

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ABSTRACT

Introduction: The lack of adherence is frequent in chronic pain (CP) patients and the influence of psychological factors may play a relevant role. The aim of this study was to analyze the psychological factors related to the adherence to analgesic treatment in patients with CP.

Methodology: A systematic review was carried out, including original articles published in English and Spanish between June-2009 and June-2019 included in Pubmed, Scopus, Web of Science and PsycINFO. Articles with cross-sectional and longitudinal design were included, carried out in a population >18 years with chronic non-oncological pain (CNOP) and that analyzed any psychological variable in relation to adherence to analgesic treatment. The search terms were "adherence", "compliance", "misuse", "analgesic", "chronic pain" and "psychology". The quality of the articles included was analysed through the Critical Appraisal Checklist for Analytical Cross-sectional studies of Joanna Briggs Institute for cross-sectional studies and the Newcastle-Ottawa Quality Assessment Form for Cohort Studies for the longitudinal studies.

RESUMEN

Introducción: La falta de adherencia terapéutica es frecuente en pacientes con dolor crónico y la influencia de factores psicológicos sobre ella puede ser relevante. El objetivo del estudio es analizar los factores psicológicos relacionados con la adherencia al tratamiento analgésico en paciente con DC.

Metodología: Se realizó una revisión sistemática donde se incluyeron artículos originales publicados en inglés y castellano entre junio de 2009 y junio de 2019 incluidos en Pubmed, Scopus, Web of Science y PsycINFO. Se incluyeron artículos con diseño transversal y longitudinal, llevados a cabo en una población > 18 años con dolor crónico no oncológico (DCNO) y que analizaban cualquier variable psicológica en relación con la adherencia al tratamiento analgésico. Los términos de búsqueda fueron "adherence", "compliance", "misuse", "analgesic", "chronic pain" y "psychology". La calidad de los artículos incluidos se analizó mediante la *Critical Appraisal Checklist for Analytical Cross-sectional studies* de Joanna Briggs Institute para los estudios transversales y *Newcastle-Ottawa Quality Assessment Form for Cohort Studies* para los longitudinales.

Results: A total of 1184 articles were initially identified, and 14 were finally selected. Depression was the most studied variable, being included in 11 articles, followed by anxiety, that appeared in 6. Both depression and anxiety were repeatedly associated with lower adherence to analgesic treatment, and the same was true in two of the articles that measured jointly the relationship of anxiety and depression on analgesic adherence (high negative affect 39.1 % vs. low negative affect 8.3 %, $p = 0.013$). Active coping strategies were found to be associated with underuse (OR = 1.132, 95 % CI: 1.027-1.249, $p = 0.013$) and poor coping strategies were associated with opioid misuse ($p = 0.01$). The association between catastrophizing and analgesic adherence was addressed in 5 articles, and although it was found that catastrophizing was related to low adherence ($r = 0.45$, $p = 0.01$), this result was no longer significant when evaluated alongside anxiety and depression.

Conclusion: The identification and control of psychological factors in patients suffering from CP is necessary, as it could serve to improve adherence to analgesic treatment in these patients.

Key words: Chronic pain, systematic review, adherence, psychological factors, analgesic.

Resultados: Se identificaron 1184 artículos, de los cuales 14 fueron finalmente seleccionados. La depresión fue la variable más estudiada, incluida en 11 artículos, seguida de la ansiedad, que apareció en 6. Tanto la depresión como la ansiedad se asociaron de manera constante y significativa con una menor adherencia al tratamiento analgésico, y lo mismo fue cierto en dos de los artículos que miden conjuntamente la relación de ansiedad y depresión en la adherencia analgésica (efecto negativo alto 39,1 % vs. efecto negativo bajo 8,3 %, $p = 0,013$). Se encontró que las estrategias de afrontamiento activas se asociaban con infrauso (OR = 1,132, IC 95 %: 1,027-1,249, $p = 0,013$) y las pobres estrategias de afrontamiento se relacionaron con un mal uso de los opioides ($p = 0,01$). La asociación entre catastrofismo y adherencia analgésica se abordaba en 5 artículos, y aunque se encontró que el catastrofismo se relacionaba con una baja adherencia ($r = 0,45$, $p < 0,01$), este resultado dejó de ser significativo cuando se evaluaba junto a la ansiedad y a la depresión.

Conclusiones: La identificación y control de los factores psicológicos en los enfermos que sufren DC es necesario, ya que podría servir para mejorar la adherencia al tratamiento analgésico en estos pacientes.

Palabras clave: Dolor crónico, revisión sistemática, adherencia, factores psicológicos, analgésicos.

INTRODUCTION

Chronic pain (CP) is a health problem affecting approximately 19 % of the adult population in Europe (1), and 16.6 % of the population in Spain (2). CP has implications that go beyond the physical distress of the patient, affecting the psychological and social spheres, causing a decrease in quality of life (3-5). In addition, CP has important consequences for work activity because CP has been linked to a decrease in the productivity of working hours (6-8).

Among the interventions recommended to treat CP, those based on a multidisciplinary approach are increasingly used, including non-pharmacological treatments with physical, cognitive-behavioral therapies, exercises, and relaxation therapies, among others (9,10). Despite this, pharmacological treatment is essential for CP control, although the patient's response to these treatments is often not optimal (11). Some epidemiological studies have shown that between 50 and 70 % of patients with CP take pain relievers to treat pain, and that 4 % use opioids (6,12,13). However, a high percentage of them report severe or unbearable pain (48.9 %) (2).

The lack of adherence to analgesic treatment in patients with chronic non-cancer CP (CNCP) ranges from 8 to 53 %, which could explain, in part, the lack of control of pain reported by the patients (12).

Factors such as being older than 60 years, being a woman, being of a non-Caucasian race, the presence of comorbidities and the high level of stress have been related to the low compliance that a patient with CP has of the analgesic treatment prescribed by his doctor (1,14-16). It has also been shown that the presence of mood disorders and anxiety can condition the low adherence to treatment found in these patients (4). However, the relationship of other psychological factors with treatment adherence in these patients has received little attention, although it seems reasonable to think that they could influence treatment adherence and consequently the response to the treatments of the patients (17,18).

Because of the above, in the present study we aim to identify the psychological factors related to adherence or misuse of analgesic treatment in patients with CNCP through a systematic review of the scientific literature published in recent years.

METHODOLOGY

Design of the study

A systematic review of the literature was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (19). The study protocol was registered in the International Prospective

Register of Systematic Reviews (PROSPERO) with reference number: CRD42020139675.

Search strategy

An exhaustive search of the original articles included in the PubMed, Scopus, Web of Science and PsycINFO databases was performed between June 2009 and June 2019, with a transversal and longitudinal observational design. Articles published in English were included that included patients with CNCP, with a duration of more than 3 months, as defined by the International Association for the Study of Pain (IASP) [20]. The keywords and search strategies were: (((adherence AND analgesic) OR (compliance AND analgesic) OR (misuse AND analgesic) OR "treatment adherence and compliance"[Mesh]) AND "chronic pain" AND "psychology") AND "last 10 years" [PDat] AND Humans[Mesh]) en PubMed y (TITLE-ABS-KEY (adherence AND analgesic) OR TITLE-ABS-KEY (compliance AND analgesic) OR TITLE-ABS-KEY (misuse AND analgesic) OR TITLE-ABS-KEY (treatment AND adherence AND compliance) AND TITLE-ABS-KEY (chronic AND pain) AND TITLE-ABS KEY (psychology)) AND PUBYEAR > 2008 AND (LIMIT-TO (LANGUAGE , "English")) in Scopus y (((adherence AND analgesic) OR (compliance AND analgesic) OR (misuse AND analgesic) OR ("treatment adherence and compliance") AND "chronic pain" AND "psychology")) in Web of Science y PsycINFO.

Eligibility criteria

We included studies performed in a population > 18 years with CNCP, which aimed to analyze the relationship between the lack of adherence understood as the lack of compliance with the recommendations or prescription provided by the physician (misuse or low adherence to the analgesic treatment) and any psychological variables. Within the studies, it was taken into account that the variables were directly related to the patient and not to the interaction of patients with the physician, family member or their support network. Studies focusing on the abuse of these drugs not including psychological variables, studies based on patients with cancer pain, review articles, meta-analyses, or short articles were excluded.

Study selection

Two authors reviewed the title and abstract of all articles. Duplicate studies were removed using the Mendeley Desktop 1.19.4 tool. Pre-selected studies were analyzed in depth and also their list of references to identify those that could be included in the present review. The quality of eligible cross-sectional studies was assessed using the Critical Appraisal Checklist for Analytical Cross-sectional studies of Joanna Briggs Institute [21], which includes a checklist containing 8 items. The scores used in the study conducted by Ortega et al. were taken into account for the classification of the included studies. [22], being considered a high-quality

article (low risk of bias) when it met at least 5 of the items in this list; studies not meeting this criterion were considered of low quality (Annex 1).

The quality of longitudinal studies was assessed using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies tool [23]. This tool evaluates the quality of studies through 8 items grouped into three categories: Selection, comparability, and outcome. Each article can have a maximum of 9 asterisks, and they were considered high quality when they had at least 6 asterisks (22,24) (Annex 1).

RESULTS

A total of 1184 potential articles were found in the search. After the selection process, 14 articles meeting the inclusion criteria were selected (Figure 1).

Quality of studies

All articles included in the review met at least 5 checklist criteria in cross-sectional studies [17,25-33] (Table I) and at least 8 criteria in longitudinal studies [34-37] (Table II), indicating good quality.

General characteristics of the selected studies

Of the 14 studies (Table III), 3 had been conducted in the general population [26,28,33], 7 in patients treated in pain clinics [17,27,30,31,34,36,37], in 3 studies the results came from patients included in health record databases [25,29,35] and in 1 study the patients had been recruited in different health centers or centers for the elderly [32]. Of the 14 articles, 4 included patients with CP of specific cause (musculoskeletal pain, spinal pain, chronic low back pain, and headache) [17,33,34,37] and the remainder did not specify the cause of CP. Only 3 of the 13 articles [25,32,33] specified the age group of the population included (Table III) and only 2 articles indicated the response rates which were 57 % and 80.7 % [25,27].

The psychological factors most frequently analyzed in the studies were depression [17,25,27-32,34,36,37], anxiety [27-30,32,35], depression and anxiety measured together [26,33], coping strategies [28,35] and catastrophizing [17,29,30,34,36] (Table III).

Ways to assess adherence, misuse, or low compliance

Adherence, including misuse or low compliance to analgesic treatment, was measured in different ways: Through interviews [28,29,32,35,37], with The Current Opioid Misuse Measure (COMM) [27,30], Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) [17,33,36], Pain Medication Questionnaire (PMQ) [25], urine and blood tests [31], and other assessment tools specified in Table II. Patients were found to be non-adherent, misused, or underuse

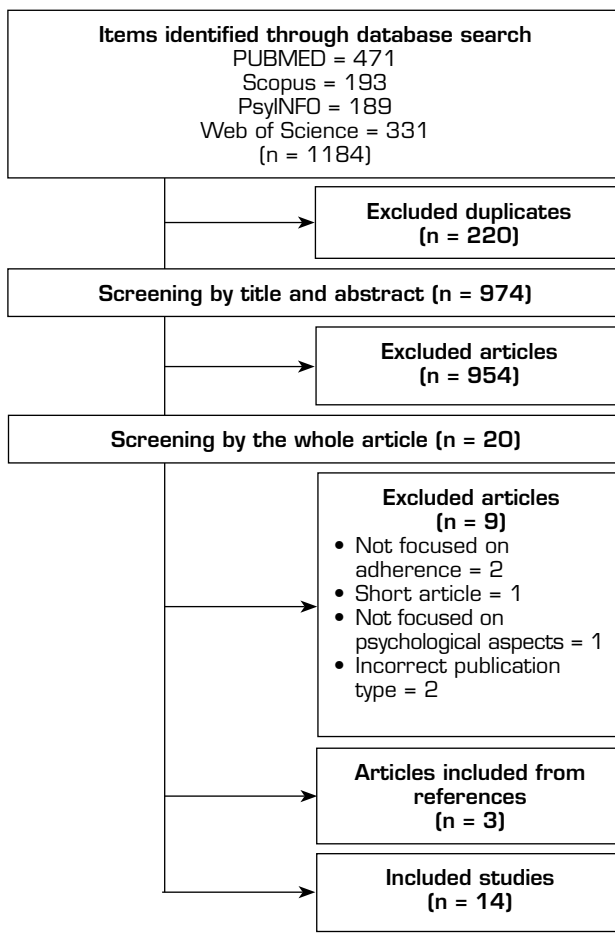


Fig. 1. Flow chart.

when they did not take analgesic drugs as prescribed by their physician (Table III).

Relationship between depression and adherence to treatment

The relationship between depression and adherence to analgesic treatment was analyzed in 11 out of the 14 articles [17,25,27-32,34,36,37]. Of these, in the 9 using different scales, the presence of depression was found to be related to lower adherence or misuse of these drugs [17,25,27,28,30-32,36,37] (Table III). In one of the previously mentioned studies [27], patients were more likely to abuse opioids among people with moderate depression (adjusted OR = 4; 95 % CI = 1.1-14.58), moderate-severe depression (adjusted OR = 8.56; 95 % CI = 2.19-33.37), and severe depression (adjusted OR = 23.5; CI 95 % = 5.12-107.81). However, in 2 other studies using the Anxiety and Depression Scale (HADS) and the Patient-Reported Outcomes Measurement Information System (PROMIS) no relationship was found between these two variables [29,34] (Table III).

Relationship between anxiety and adherence to treatment

The relationship between anxiety and adherence to treatment was analyzed in 6 articles, and one of them found [30] that a high score on the Beck Anxiety Inventory (BAI) scale, that is, a higher level of anxiety, was associated with low adherence ($r = 0.54$, $p < 0.001$).

Furthermore, in a study using Generalized Anxiety Disorder scale (GAD-7) [35], comparing the group with problems due to the use of substances and the group with problems of multiple comorbidity vs. group of poor physical functioning, in both cases they were found to be as-

TABLE I
RISK OF BIAS FROM INCLUDED CROSS-SECTIONAL STUDIES (N = 10)

	<i>Inclusion</i>	<i>Setting</i>	<i>Valid and reliable exposure</i>	<i>Objective</i>	<i>Confounding factors</i>	<i>Strategies for confounding factors</i>	<i>Valid and reliable outcomes</i>	<i>Appropriate statistical analysis</i>	<i>Number of "yes"</i>
Park and Lavin, 2010	1	1	1	1	1	0	1	1	7
Martel et al., 2013	1	1	1	1	1	0	1	1	7
Skinner et al., 2012	1	1	1	1	1	0	1	1	7
Feingold et al., 2018	1	1	1	0	1	0	1	1	6
Broekmans et al., 2010	1	1	1	0	1	0	1	1	6
Hah et al., 2017	1	0	1	0	1	0	1	1	5
Arteta et al., 2015	1	0	1	1	1	0	1	1	6
Kipping et al., 2014	1	0	1	1	1	0	1	1	6
Wasan et al., 2015	1	1	1	1	1	0	1	1	7
Chang, 2018	1	1	1	1	1	0	1	1	7

TABLE II
ASSESSMENT OF THE QUALITY OF THE INCLUDED LONGITUDINAL STUDIES (N = 4)

	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Number of asterisks
Wong et al., 2015	A*	A*	A*	A*	A* / B*	B*	B	B*	8
Peacock et al., 2016	A*	A*	B*	A*	A* / B*	B*	B	B*	8
Jamison et al., 2009	B*	A*	A*	A*	A* / B*	B*	B	B*	8
Bernadette et al., 2011	B*	A*	C	A*	A* / B*	B*	B	C	6

sociated with an increased risk of being non-adherent to opioid therapy (adjusted OR = 2.59, 95 % CI: 1.69-3.99, $p < 0.001$, and adjusted OR = 3.32, 95 % CI: 2.29-4.81, $p < 0.001$, respectively) (Table III). In contrast, two other studies using PROMIS (29) and the Hamilton Anxiety Rating Scale (HAM-A) (32) found no significant relationship between anxiety and opioid misuse.

In the remaining 2 studies, higher scores on the Hospital Depression and Anxiety Scale (HADS) (higher levels of depression and anxiety) were shown to increase the risk of non-adherence (28) when comparing adherent participants versus participants overusing analgesics (anxiety, $p = 0.045$; depression, $p = 0.007$). The other study (27) evaluating anxiety using The Generalized Anxiety (GAD-7) showed that as scores on this scale increased ($B = 0.47$, $p < 0.001$), opioid misuse increased. In addition, in this study, among patients with severe depression, opioid misuse was 75.3 % in those with severe anxiety and 50 % in those with mild or moderate anxiety (27) (Table III).

Depression and anxiety measured together (negative affect) and adherence to treatment

Two of the articles included in the review measured depression and anxiety together. In one of them (26), it was observed that patients who used opioids only when they felt pain (symptomatic use) had worse mental health than patients who had a pattern of scheduled use of these drugs (they were not taken exactly as directed by their doctor, but it was always taken at the same time: Mean = 30.5; standard error (EE) = 1.5; scheduled use: Mean = 22.8; EE = 1.9). In addition, the other study (33) found that subjects with higher scores in the HADS scale had a higher risk of opioid misuse compared to the group with low score (39.1 vs. 8.3 %, $p = 0.013$) (Table III).

Relationship between coping strategies and adherence to treatment

The relationship between coping and adherence to analgesics was analyzed in only 2 studies, showing that people with more active coping strategies were at increased risk of non-adherence to analgesics due to underuse (OR = 1.132, 95 % CI: 1.027-1.249,

$p = 0.013$). However, patients with a more passive coping strategy tended to show a lack of adherence due to drug overuse compared with patients with adherent behaviors (mean = 33.4 standard deviation (SD): 5.00 vs. mean = 31.6 SD: 6.6, $p = 0.095$) (28). Although evaluated on a different scale, another study (35) also found that patients with poor coping strategies were more likely to be non-adherent (Table III). It was also shown that these patients were highly likely to have a borderline personality disorder and little social support (35).

Relationship between catastrophizing and adherence to treatment

We identified 5 studies analyzing the relationship between catastrophizing and adherence to analgesic treatment. In 3 of them, it was found that when the levels of catastrophizing measured with *The Pain Catastrophizing Scale (PCS)* were high, the risk of non-adherence or misuse of opioids was higher (17,29,36) (Table III). However, another study using the same tool found no relationship between catastrophizing and non-adherence (34).

Of the 5 studies analyzed, the study measuring catastrophizing with The Catastrophizing Subscale (CSQ-CAT) (30) found that catastrophizing was associated with an increased risk of opioid misuse ($r = 0.45$, $p < 0.001$), although this result was not significant when evaluated alongside anxiety and depression.

DISCUSSION

The lack of adherence to analgesic treatment in patients with CNCP has been described above. However, studies analyzing psychological factors associated with analgesic adherence in these patients are scarce, and the results are inconsistent.

Among the results obtained in the review, depression is the variable that has been most studied in its association with analgesic adherence in patients with CNCP, being found in 8 out of the 14 articles included in this review that depression is a risk factor for low adherence. Similarly, the relationship between anxiety and adherence was analyzed in 6 studies, showing in two studies that its presence was associated with lack of adherence specifically with opioid treatment (30,35).

TABLE III
CHARACTERISTICS OF THE STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Author, year	Aim	Population (age)	Variables and instruments	Results	Clarifications
Arteta et al., 2015	To investigate whether anxiety and depression mediate the relationship between pain catastrophism and the risk of opioid abuse prescribed in patients with CP.	n = 215 patients M age = 46.22 SD = 10.03	Anxiety: BAI Depression: BDI-II Catastrophizing: CSQ-CAT of CSQ Opioid misuse: COMM	Anxiety ($r = 0.54, p < 0.001$) depression ($r = 0.61, p < 0.001$) and catastrophizing ($r = 0.45, p < 0.001$) were associated with misuse of prescription opioids However, when anxiety and depression were analyzed together with catastrophizing, the effect of catastrophizing was no longer significant	
Bernadette et al., 2011	To examine race-related differences in adherence to preventive medication in headache patients and identify factors that predict adherence to medication in Caucasian and African American headache patients	Longitudinal study <i>First measure:</i> - n = 173 caucasian - n = 112 african americans <i>Segunda medida (6 meses):</i> - n = 79 caucasian - n = 32 african americans >18 años	Adherence to medication: Self-reported follow-up diary Major depressive disorder: PRIME-MD	Patients with major depressive disorder were less likely to adhere to preventive analgesic medication for headache (OR = 1.02, 95 % CI = 1.01-1.05, $p = 0.03$)	
Broekmans et al., 2010	To examine the determinants of lack of adherence, overuse, and lack of use of opioids in patients with CNCP with a focus on factors related to the five categories of determinants of non-adherence to medication, as proposed by WHO (health care, socioeconomic factors related to the system, condition, treatment and patient)	n = 265 patients > 18 years	Adherence to medication: Self-reported interview Anxiety and depression: HADS Coping Strategy: VPMI	Patients who were underusing opioids used more active coping strategies (OR = 1.132, 95 % CI = 1.027-1.249, $p = 0.013$) Patients who had overuse of their medication had higher scores on the anxiety subscales (m = 10 SD 8-12.2 vs. m = 9 SD: 5-12, $p = 0.045$) and depression (m = 10 SD: 8-13.25 vs. m = 8 SD: 5-11, $p = 0.007$) and a tendency to use passive coping strategies compared to adherent patients (m = 33.4 SD: 5.00 vs. m = 31.6 SD: 6.6, $p = 0.095$)	
Chang et al., 2018	To describe the prevalence of prescription opioid misuse and identify factors associated with misuse in adults with CP aging 50 years or more	n = 130 > 50 years	Depression: GDS Anxiety: HAM-A Prescription opioid use: TLFB	he likelihood of opioid misuse is 5.7 times (OR 5.723 CI 95 %: 1.851-17.690, $p = 0.002$) higher for people with moderate depression than for a person with mild depression Anxiety was not associated with opioid abuse	

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TABLE III (CONT.)
CHARACTERISTICS OF THE STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

<i>Author, year</i>	<i>Aim</i>	<i>Population (age)</i>	<i>Variables and instruments</i>	<i>Results</i>	<i>Clarifications</i>
Feingold et al., 2018	To explore the association between the severity of depression and opioid misuse rates among patients with CP	n = 265 patients > 18 years with CNCP	Opioid misuse: COMM Comorbid depression: PHQ-9 Comorbid anxiety: GAD-7	The prevalence of opioid abuse among participants with depression was 45.7 %, compared with 7.6 % for participants without depression. Among participants with mild, moderate, moderately severe and severe depression , opioid abuse was 9.8 %, 22.5 %, 42.2 %, and 75.2 %, respectively. Significantly higher probabilities of opioid abuse among people with moderate depression (adjusted OR = 4; 95 % CI = 1.1-14.58), moderate-severe (adjusted OR = 8.56; 95 % CI = 2.19 a 33.37) and severe (adjusted OR = 23.5; 95 % CI = 5.12 to 107.81), but not among those with mild depression (adjusted OR = 1.55; 95 % CI = 0.41 to 5.8) Among participants with severe depression , opioid misuse was 75.3 % among those with severe anxiety and 50 % among those with mild or moderate anxiety Higher levels of anxiety were associated with higher rates of opioid abuse (B = 0.47, $p < 0.001$).	
Hah et al., 2017	Examine demographic, psychosocial characteristics, pain-specific behavioral factors, substance abuse history, sleep, and indicators of general physical function as predictors of opioid misuse in patients suffering from CP	41 adult patients with CP with opioid misuse M age = 44.4; SD = 14.2	Depression and anxiety: PROMIS Catastrophic pain: PCS Misuse of prescription opioids: Defined as 1) take an opioid in a different way or dose than prescribed, or 2) take the opioid from another person prescribed to do so	Patients who showed misuse of prescription opioids showed higher levels of anxiety (OR 1.05 95 % CI: 1.02-1.09, $p = 0.005$) and depression (OR 1.05, 95 % CI: 1.01-1.08, $p = 0.007$) and catastrophizing (OR 1.04, 95 % CI: 1.01-1.06, $p = 0.008$)	
Jamison et al., 2009	To examine differences over time in a series of measures between patients with CP who were classified as high or low risk of opioid misuse based on the scores in <i>The Screener and Opioid Assessment for Pain Patients</i> (SOAPP)	Longitudinal study n = 110 patients > 18 years experiencing pain for more than 3 months	Predict low adherence among patients with CP for opioid therapy: SOAPP Catastrophizing: PCS Depression: CESD-10	At baseline, subjects in the high SOAPP group reported more pain ($p < 0.05$) higher levels of catastrophizing ($p < 0.05$) and depression ($p < 0.05$) compared with the low SOAPP group	

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TABLE III (CONT.)
CHARACTERISTICS OF THE STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Author, year	Aim	Population (age)	Variables and instruments	Results	Clarifications
Kipping et al., 2014	To investigate the reliability of patients' reports regarding their current use of pain medications	n = 243 patients treated in pain clinic, of whom 100 were pre-surgical patients > 18 years	Compliance: urine and blood tests Degree of depression: ADS	High depression scores in ADS predict non-adherence to treatment (OR = 2.12, 95 % CI: 1.18-3.80), $p < 0.05$)	
Martel et al., 2013	To examine variables that could be the basis of the association between catastrophizing and the risk of misusing prescription opioids in patients with CP	n = 115 patients with musculoskeletal pain over 6 months M age men = 46.0; SD = 11.6 M age women = 48.3; SD = 10.3	Risk of misuse of prescription opioids: SOAPP-R Catastrophizing: PCS Anxiety: PASS Depressive symptoms: BDI	Catastrophizing ($r = 0.45$, $p < 0.01$), anxiety ($r = 0.44$, $p < 0.01$) and depression ($r = 0.34$, $p < 0.01$) were associated with an increased risk of prescription opioid misuse The results also showed that catastrophizing and the risk of opioid misuse was partly mediated by patients' anxiety levels ($Z = 2.1$, $p < 0.05$) Catastrophizing is an important "single" predictor of opioid misuse risk, even when monitoring patients' anxiety and depression levels ($B = 0.30$, $p < 0.05$)	
Park et al., 2010	To determine the correlation between opioid misuse and physical disability, alcohol abuse, depressive symptoms, spirituality, social support, and social networking among community-dwelling older adults (65 years or older) with CP	n = 163 subjects > 65 years with CP treated with opioids	Misuse of opioids: PMQ Depressive symptoms: CESD-10	Higher levels of depressive symptoms were significantly associated with an increased risk of opioid misuse ($B = 0.366$, $t = 2.278$, $p = 0.024$)	
Peacock et al., 2016	1. To identify subgroups of people with non-cancer pain based on their risk factors for non-adherent opioid treatment 2. To compare the demographic profile, pain, treatment, and access to health services of these subgroups 3. To assess whether belonging to the defined subgroup predicted non-adherence at the time of recruitment and prospectively for 3 months	Longitudinal study n = 1.514 > 18 years with CP > 3 months taking opioids for CP for > 6 weeks	Affective disorder: PHQ-9 GAD-7 of PHQ-9 ≥ 10 Coping strategies: PSEQ Opioid adherence: Participants were asked to report whether they had 10 behaviors identified in the literature as risk factors associated with non-adherence to opioids in the previous 3 months	Four groups were identified: 1) Poor physical functioning group (27 %) ($n = 402$) 2) Poor coping and physical functioning group ($n = 533$) (35 %) 3) Substance use problems group ($n = 207$) (14 %) 4) Multiple comorbidity problems group ($n = 372$) (25 %) The last 2 groups had an increased risk of requesting higher doses of opioids, drug misuse, dose accumulation, and alteration of the recommended dose, compared with the physical malfunction group Group with substance use problems vs. poor physical functioning group (adjusted OR 2.59 (1.69-3.99), $p < 0.001$) and group with multiple comorbidity problems vs. poor physical functioning group (adjusted OR 3.32 (2.29-4.81), $p < 0.001$) showed a higher risk of reporting one or more non-adherent behaviors	Description of groups at risk of non-adherence: 3) Substance use problems group: High probability of personal history of substance abuse; more likely to be younger and have suffered child abuse 4) Multiple comorbidity problems group: high probability of personal history of substance abuse and experience of child abuse, high probability of affective disorder, borderline personality disorder and family history of substance abuse, and a high probability of reporting physical malfunction, poor coping strategies , and low social support

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TABLE III
CHARACTERISTICS OF THE STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Author, year	Aim	Population (age)	Variables and instruments	Results	Clarifications
Skinner et al., (2012)	To explore the relationship between opioid use patterns, pain severity, and pain-related mental health in patients with CP who received opioids	n = 157 pain over 6 months > 60 years	Measure of misuse of prescription drugs: PDUQ Anxiety and depression: NAs	Symptomatic opioid use was associated with worse pain-related mental health (m = 30.5; EE = 1.5). In contrast, opioid use in a programmed pattern was associated with improved pain-related mental health (m = 22.8; EE = 1.9)	Usage patterns: <ul style="list-style-type: none"> - Symptom use: Medicines are taken when there is pain and if it does not hurt, do not take it - Strategic use: Need to take medicines when there is a need to be active - Scheduled use: Use of medication according to the time of the day - Non-use: Non-use is a conscious choice based on other preferences to manage their painful condition
Wasan et al., 2015	To confirm the hypothesis that in the treatment of chronic low back pain (CLBP), patients with high negative affect (NA) would have decreased opioid analgesia and had higher rates of opioid misuse compared with patients with CLBP with low NA	n = 72 subjects with NA aged 21 to 75 years and CLBP for at least 6 months	Levels of NA symptoms: Total HADS (combined depression and anxiety): Each subject was assigned a level (low, moderate, or high) based on the combined scores of the depression and anxiety subscales. High NA was defined as more than > 8 points on the depression and anxiety subscales, low NA was less than < 6 on each subscale, and moderate NA was 6-8 Opioid abuse risk: SOAPP Catastrophizing: PCS Neuroticism: Neuroticism Subscale of the NEO Personality Inventory	The high NA group had a significantly higher rate of opioid misuse (39.1 % vs. 8.3%, $p = 0.013$) and significantly more opioid cravings than the low NA group (SOAPP item 11, revised, $p = 0.041$)	The high NA group also had significantly higher scores of pain catastrophizing ($r = 0.58$; $p \leq 0.01$) and neuroticism ($r = 0.66$; $p \leq 0.01$), which correlated significantly with total HADS scores
Wong et al., 2015	To examine the relationships between treatment adherence, pain treatment satisfaction, disability, and quality of life (QoL) in a sample of patients with CP	Longitudinal study n = 178 patients 18 years	Medical Adherence: PCRS Depression: HADS-D Depression subscale Catastrophic pain: PCS	There was no relationship between depression and adherence to treatment, or between catastrophizing and adherence	PCRS assesses adherence with recommendations in ten areas: Treatment medications, discontinuation of medications, use of assistance devices, physical therapy exercises, other home treatments, follow-up appointments and referrals to other healthcare professionals, surgical interventions, alternative medicine treatments, and other treatment recommendations

Mean: M*; standard deviation: SD*; standard error: S.E.

Patient Health Questionnaire-9 (PHQ-9): 9 items, rated on a scale (0 = nothing to 3 = almost every day). Total scores: 5 (mild depression), 10 (moderate depression), 15 (severe moderate depression), and 20 (severe depression). *Generalised Anxiety Disorder - 7 (GAD-7):* Total scores of 5, 10, and 15 represent mild, moderate, and severe levels of anxiety, respectively. Score ≥ 10 indicates generalized anxiety. *Primary Care Evaluation of Mental Disorders (PRIME-MD):* Pain Self-Efficacy Questionnaire (PSEQ): ≤ 30 . *The Beck Anxiety Inventory (BAI):* Score between 0 and 21, higher levels of anxiety at higher scores. *The Beck Depression Inventory II (BDI-II):* The score between 0 and 21, the higher the score, the higher the depressive symptoms. *Catastrophizing subscale (CSQ-CAT) of The Coping Skill Questionnaire (CSQ):* The Current Opioid Misuse Measure (COMM): 17 items categorizing responses from 0 (never) to 4 (very often). *Pain Medication Questionnaire (PMQ):* 26 items. Higher score indicates increased risk of opioid misuse. *The Center for Epidemiologic Studies Depression Scale-10 (CESD-10):* 10 items. Score > 10 (cut-off point). *The Participant Compliance Reporting Scale (PCRS):* Pain Catastrophizing Scale (PCS): 13 items. It examines three components: Rumination, increase, and impotence. *PROMIS:* 22 items. *Screening and Opioid Assessment for Patients With Pain-Revised (SOAPP-R):* 24 items that rank from 0 (never) to 4 (very often). *Pain Anxiety Symptoms Scale (PASS):* 20 items. *Likert scale:* from 0 (never) to 5 (always). *Hospital Depression and Anxiety Scale (HADS):* Depression subscale of 7 items and anxiety subscale of 7 items. Total score between 0 and 21 for each subscale. Higher scores indicate more symptoms. *The Vanderbilt Pain Management Inventory (VPMI):* Consists of an active coping subscale (7 items, range: 7-35) and a subscale of passive coping (11 items, range 11-55). Higher scores indicate more frequent use of coping strategies. *Prescription Drug Use Questionnaire (PDUQ):* 42 items. *Negative Affect Subscale (NAs):* 5 items measuring.

In line with these results, Broekmans et al. [28] show a lack of adherence due to overuse when scores on the HADS scale are high, and Feingold et al. [27] show that anxiety is a higher risk factor for opioid misuse when it occurs concomitantly with depression. These results are relevant if we consider that anxiety and depression occur frequently in conjunction [38], and it has been described that there is a two-way relationship between both processes that could affect treatment adherence in patients with CP [39].

Moreover, the diversity of the results observed in the studies, which could be explained by the variety of methods used to evaluate depression and anxiety and the different way of measuring adherence, should be noted as a remarkable result. Timmerman et al. [11] highlighted these limitations in the various studies analyzed in their review, and they noted the difficulty that this causes in the interpretation of the results.

One fact frequently observed in the studies is the consideration of adherence as a dichotomous variable (adherence *versus* non-adherence), without delving in specific aspects included in this construct despite it has been shown that adherence follows a complex pattern of behavior that is difficult to evaluate from a binary response [40]. Similarly, the differentiation between intentional or unintentional adherence suggested by other authors [41] was considered only in one of the studies included in the review [28], which constitutes an added limitation in the proper assessment of adherence.

The relationship between coping strategies and lack of adherence to treatment has been analyzed in 2 of the articles in this review, showing that while active coping strategies are related to lack of adherence due to lack of use, passive strategies are related to lack of adherence due to overuse. In a newly published meta-analysis, Hagger and Orbell [42] note that when patients perceive the disease as controllable, they use more active coping strategies, whereas when they perceive it as uncontrollable, the strategies used are more passive. These results could explain ours and give more credibility to the hypothesis that patients using more active coping strategies and thinking that they can cope with CP without treatment may believe they do not need to take the medication. By contrast, patients perceiving their disease as uncontrollable and using more passive coping strategies may think that the pain will be more bearable if they take medication.

The results on the relationship between catastrophizing and adherence shown in the review are inconsistent, even when the tool used to assess catastrophizing is the same. Different authors have reported that catastrophizing can negatively skew the perceptions and experiences of the patients, creating types of passive behaviors, such as rumination or impotence, and play an important role in the CP experience [43,44]. It has been shown that patients who tend to experience pain with catastrophic vision are more vulnerable to the misuse of opioids because they may manifest unrealistic beliefs about pain and its consequences [45].

One fact also observed in our study is the lack of relationship between catastrophizing and misuse of opioids when this factor was evaluated together with anxiety and depression [33]. This result could be explained because anxiety and depression are strongly related to catastrophizing, both processes being able to have a mediating role

in the relationship between catastrophizing and the misuse of opioids, as Arteta et al. shows in their study [46].

The present study has some limitations, among which we noted the small number of articles meeting the inclusion criteria, which also only analyzed some psychological factors without considering other factors such as borderline personality disorder or neuroticism. It can also be a limitation that we did not specify all variables separately in the search strategy within the keywords instead of just the word "psychology". However, we believe that this more generic strategy would provide us with global information and in line with the objective of the study.

Another limitation is that derived from the diversity of scales used and the different methods for measuring adherence that difficult the analysis of the results. It is also necessary to point out that adherence or lack of adherence is not always the responsibility of the patient, but may also be due to variables associated with care processing and communication, so this aspect must also be studied.

As a strength of the study, we would like to point out that the results obtained are from the search performed in 4 databases and that the topic is novel and shows the need to analyze other psychological factors that may be important in adherence to treatment in patients with CNCP.

CONCLUSIONS

Little attention has been paid in the scientific literature to the relationship between adherence to analgesic treatment and psychological factors in patients with CNCP, and inconclusive results have also been found in studies addressing the issue. Despite this, there is some agreement showing that the presence of depression and/or anxiety are associated with the lack of analgesic adherence observed in patients. However, other factors such as coping, catastrophizing, or other factors with potential effect on adherence need to be better studied.

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CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest.

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ANNEX 1
TOOL USED TO EVALUATE THE QUALITY OF THE STUDY
AND THE RISK OF BIAS IN CROSS-SECTIONAL STUDIES

Joanna Briggs Institute Checklist for Analytical Cross-sectional studies

1. Were the criteria for inclusion in the sample clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was exposure measured in a valid and reliable way?
4. Were objective, standard criteria used for measurement of the condition?
5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

Tool used to evaluate the quality of the study of longitudinal studies

Newcastle Ottawa Scale for Cohort Studies

Selection

- 1) Representativeness of exposed cohort:
 - a) Truly representative of the _____ average (describe) in the community*.
 - b) Something representative of the _____ average in the community*.
 - c) Selected group of users, for example nurses, volunteers.
 - d) No description of cohort origin.
- 2) Selection from non-exposed cohort:
 - a) Extracted from the same community as the exposed cohort*.
 - b) Extracted from a different source.
 - c) Selected group of users, for example nurses, volunteers.
 - d) No description of the origin of the unexposed cohort.
- 3) Ascertainment of exposure:
 - a) Secure record (e.g. surgical record)*.
 - b) Structured interview*.
 - c) Written self-report.
 - d) No description.
- 4) Demonstration that outcome of interest was not present at the start of the study:
 - a) Yes*
 - b) No.

Comparability

- 5) Cohort comparability based on design or analysis controlled by confounders:
 - a) The study controls for age, sex and marital status*.
 - b) The study controls for other factors*.
 - c) Cohorts are not comparable based on controlled design or analysis for confounding factors.

Outcome

- 6) Assessment of outcome:
 - a) Independent blind assessment*.
 - b) Record Linkage*.
 - c) Self-report.
 - d) No description.
- 7) The follow-up was long enough for the results to occur:
 - a) Yes (≥ 5 years)*.
 - b) No.
- 8) Adequacy of cohort follow-up:
 - a) Complete follow-up: All subjects accounted for*.
 - b) Subjects lost to follow-up are unlikely to introduce bias (small number lost $\geq 80\%$ of follow-up, or description of those lost)*.
 - c) Follow-up rate $< 80\%$ and no description of those lost.
 - d) No declaration.

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