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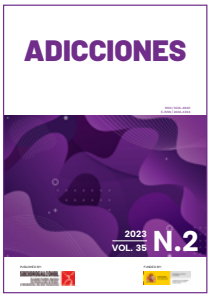

REVIEW

Systematic review on the clinical management of chronic pain and comorbid opioid use disorder

Revisión sistemática sobre el manejo clínico del dolor crónico y el trastorno por uso de opioides simultáneo

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Abstract

The crisis caused by prescribed opioids and their related side effects are a public health problem worldwide. Most of these are prescribed for coping with chronic pain. The coexistence of opioid use disorder (OUD) in patients with chronic pain represents a complex challenge due to the need for managing both pain and OUD. The aim of this systematic review is to evaluate the efficacy of feasible treatments for this population with OUD and comorbid chronic pain for both conditions. A systematic database search has been performed using Cochrane Library, MEDLINE, PsycINFO and ClinicalTrials.gov in compliance with PRISMA guidelines. Eligible articles addressed the outcomes in chronic pain patients with comorbid opioid use disorder after treatment interventions were applied. Of 593 identified articles, nine were eligible for qualitative review (n = 7 pharmacological interventions; n = 2 psychological interventions). Methadone, buprenorphine, cognitive-behavioral and mindfulness showed promising results, but data were inconclusive (<2 RCT with low risk of bias). It is unclear whether the opioid agonist treatment should be maintained or tapered and which drug should be prescribed for the opioid substitution therapy (methadone or buprenorphine/naloxone). Mindfulness and cognitive behavioral therapy have a discrete effect on improving negative affect but not pain. The therapeutic approach might be individualized under a shared decision-making basis.

Key words: opioid use disorder, chronic pain, methadone, buprenorphine, cognitive behavioral therapy

Resumen

La crisis causada por los opioides recetados y sus efectos secundarios relacionados son un problema de salud pública en todo el mundo. La mayoría de estos medicamentos se recetan para el afrontamiento del dolor crónico. La coexistencia del trastorno por uso de opioides (TUO) en pacientes con dolor crónico representa un desafío complejo debido a la necesidad de controlar tanto el dolor como el TUO. El objetivo de esta revisión sistemática es evaluar la eficacia de los tratamientos posibles para dicha población con TUO y dolor crónico. Se ha realizado una revisión sistemática usando las bases de datos Cochrane Library, MEDLINE, PsycINFO y ClinicalTrials.gov, conforme a las pautas PRISMA. Los artículos elegibles abordaron los resultados en pacientes con dolor crónico y diagnóstico comórbido de TUO, después de aplicar una intervención. De 593 artículos identificados, nueve eran elegibles para la revisión cualitativa (n = 7 intervenciones farmacológicas; n = 2 intervenciones psicológicas). La metadona, la buprenorfina, la terapia cognitivo-conductual y el mindfulness mostraron resultados prometedores, pero los datos no eran concluyentes (<2 ECA con bajo riesgo de sesgo). No está claro si el tratamiento con agonistas opioides debe mantenerse o disminuirse y qué fármaco debe prescribirse para la terapia de sustitución de opioides (metadona o buprenorfina/naloxona). El mindfulness y la terapia cognitivo-conductual tienen un efecto discreto en la mejora del afecto negativo, pero no del dolor. El enfoque terapéutico podría individualizarse sobre la base de una toma de decisiones conjunta.

Palabras clave: trastorno por uso de opioides, dolor crónico, metadona, buprenorfina, terapia cognitivo-conductual

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Chronic pain (defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [International Association for the Study of Pain, 2020]) affects 25.3 million adults (11.2%) in America (Nahin, 2015). World Health Organization adds to the definition the length of symptom ("persists or recurs for longer than 3 months" [World Health Organization, 2019]). Between 5 and 8 million patients use opioids for chronic pain (National Institutes of Health, 2014). Opioid prescriptions for chronic non-cancer pain (CNCP) have increased drastically since 1999, especially in United States, country that consumes 80% of the global manufactured opioids (Brown & Sloan, 2017). Parallel to the increase of prescriptions, the rates of opioid use disorders (OUD) and overdoses have also increased (in 2015, drug overdoses deaths involving opioids were 33,091, 63% of overall drug overdose deaths) (Rudd, Seth, David & Scholl, 2016).

Whereas the usefulness of opioids for acute and cancer-related pain is well known (Wiffen, Wee, Derry, Bell & Moore, 2017), efficacy of opioids in CNCP is nowadays highly controverted. Long-term efficacy in controlling pain has failed to be demonstrated (Chou et al., 2015) and many patients discontinue long-term opioid therapy due to insufficient pain relief or adverse events (Noble et al., 2010). Regarding these adverse effects related to long-term opioid therapy in patients with CNCP the rate of opioid misuse has been estimated between 21% and 29% and the rate of opioid addiction between 8% and 12% (Vowles et al., 2015). Moreover, the absolute event rate for any adverse event with opioids is 78% whereas the absolute event rate of any serious event is 7.5% (Els et al., 2017). Guidelines regarding prescription of opioids and chronic pain (Busse et al., 2017; Dowell, Haegerich & Chou, 2016) discourage its use and, given the case, prescription must be the lowest effective dose (preferably ≤50 Morphine Milligram Equivalent Doses, MED) (Busse et al., 2017; Dowell et al., 2016). In patients with high opioid doses (≥90 MED/day), a tapering strategy is recommended, especially in those who have not reached enough pain relief (Busse et al., 2017; Dowell et al., 2016).

The Centers for Disease Control and Prevention (CDC) 2016's Guideline for Prescribing Opioids for Chronic Pain (Dowell et al., 2016) states in its 12th recommendation that "Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder". The rationale is that tapering or discontinuing opioid medications could result in enhanced pain and craving with consequent use of illicit drugs and potential harms to the patient. On the other hand, continuing with opioid medication may increase tolerance, cause hyperalgesia, strengthen addiction and provoke a potentially harmful use. Maintenance of this equilibrium represents a big challenge.

Methadone is a synthetic μ-opioid agonist with a long half-life (5-55h) approved as analgesic and treatment of opioid use disorder. It is also an NMDA-receptor antagonist, meaning that it is useful for chronic neuropathic pain. Nevertheless, due to its complex non-linear pharmacokinetics, its potential serious adverse effects including cardiac events (QT prolongation, *torsade de pointes*, arrhythmias…), risk of overdose and minor events like sedation, constipation, nausea or dizziness, must be strictly monitored. Additionally, methadone's analgesic effects last 4-6h requiring multiple daily doses (Heinzerling, 2019). Buprenorphine is a μ-opioid partial agonist also approved as analgesic and treatment for opioid use disorder. It is usually combined with naloxone to deter intravenous use. Although oral absorption of naloxone is very low, it causes withdrawal symptoms if injected. It is also a κ-opioid receptor antagonist and may be able to reduce hyperalgesia. As a partial opioid agonist, it has ceiling effects and, therefore, a better safety profile compared to complete agonists like methadone (Heinzerling, 2019). Despite its safer profile, methadone retains longer in treatment patients with opioid use disorder than buprenorphine (Mattick, Breen, Kimber & Davoli, 2014). Psychological therapies are one of the main cornerstones of addiction treatments (Kampman & Jarvis, 2015). For example, cognitive behavioral therapy (CBT) has proven to be effective in substance use disorders (Dutra et al., 2008), to cope with chronic pain (Williams, Eccleston & Morley, 2012), even in patients with CNCP and substance use disorder (Ilgen et al., 2016). Research also supports the use of mindfulness-based interventions (MBIs) such as Mindfulness-Based Relapse Prevention (MBPR) (Bowen, Chawla & Marlatt, 2011), Mindfulness-Oriented Recovery Enhancement (MORE) (Garland et al., 2014), and Mindfulness-Based Addiction Treatment (MBAT) (Vidrine et al., 2016) for treating addictive behaviors (Garland & Howard, 2018; Li, Howard, Garland, McGoverns & Lazar, 2017), and has obtained higher rates of abstinence among people who use heroin (Chen et al., 2019). Mindfulness has also been found useful for reducing pain attentional bias in CNCP patients (Garland & Howard, 2013), and has reduced pain severity and desire for opioids in CNCP patients at risk of OUD (Garland et al., 2014).

Unfortunately, evidence of CDC 12th statement is extrapolated from studies regarding general OUD or OUD for prescribed opioids but none specifically for OUD in CNCP. The outcomes of these studies regarding pain relief do not specifically focus on this population. The aim of this work is to collect and analyze the most updated and based-on-evidence data on clinical management of both opioid use disorder and comorbid chronic pain in those patients suffering from both conditions, whether the proposed

therapies are pharmacological or non-pharmacological and focusing on those outcomes related to these two simultaneous conditions.

Methods

Data sources and search strategy

This study has been done following PRISMA's guidelines (Moher, Liberati, Tetzlaff & Altman, 2009). A previous protocol has been registered in PROSPERO (CRD42020198672). To write this systematic review, the investigators have searched articles related to CNCP and comorbid OUD focused on its clinical management, based on evidence. The combination of used terms, in English, is displayed in Figure 1. The chosen databases to perform the search were Cochrane Library, PsycINFO, MEDLINE and ClinicalTrials.gov because they are some of the most used databases and have a high acceptance (Murdoch University, 2021).

The search included articles from the date of inception of the databases to December 2019 and the search and selection process were performed from January 2020 to March 2020. The writing of the review was done between April and May 2020. Two investigators designed the search strategy, one investigator conduct the initial search and selection under the supervision of two other investigators and three investigators participated into the final process of selecting those articles to be included in the review. As only one investigator performed the initial search and selection, no inter-judge reliability could be assessed. The search was restricted to 1) human studies and 2) completed studies.

Inclusion and exclusion criteria

Methadone and buprenorphine are the only approved therapies for treating both coexistent conditions. With respect to the literature regarding the effectiveness of psychological interventions for treating chronic pain and increasing abstinence in OUD or reducing prescribed opioids, there is some preliminary evidence that CBT and mindfulness therapy may be useful but findings to date are mixed (Eccleston et al., 2017). On the other hand, naltrexone has not been included because, even though an analgesic effect has been described recently, the mechanism remains uncertain and its indication nowadays is only for treating OUD (and alcohol use disorders), not both conditions of interest at the same time.

Publications were eligible for inclusion if they were: (1) metanalysis or systematic reviews with a pharmacological or psychological intervention for treating comorbid CNCP and OUD; (2) randomized, controlled and/or double-blind clinical trials (RCT) with a pharmacological or psychological intervention for treating CNCP and comorbid OUD; (3) nonrandomized and observational studies examining the outcomes of patients treated with a pharmacological and/or psychological intervention for CNCP and comorbid OUD. Studies were excluded if they were: non-English nor Spanish written, without published results, narrative reviews, case reports, letters, editorials and animal or laboratory studies.

Regarding the PICO questions, investigators only were willing to include those articles that all their population had a diagnose for both CNCP and OUD, independently of the setting, the sex, age or other demographic characteristics; an active intervention (and comparator in RCT) had to be applied in those participants either pharmacological, methadone or buprenorphine/naloxone, or non-pharmacological, CBT or mindfulness; the primary and secondary outcomes had to be related with evolution of CNCP and/or evolution of the OUD after the intended intervention, as the purpose of the review is to assess the development of both conditions after the intervention. To consult the PICO questions and the rest of the included studies' characteristics, lector is referred to consult Tables 1, 2 and 3.

From a total of 593 articles meeting the search criteria, 7 duplicates were detected with Mendeley Reference Manager® software and were removed. 586 records were screened at the title and abstract and 30 full-text studies were assessed for eligibility. The systematic review flow diagram of this article is represented in Figure 2.

Assessment of methodological quality

The assessment of methodological quality has been focused on those studies with an RCT basis, as their level of evidence is higher. To do so, authors have assessed the methodological quality using the Rob 2 Cochrane risk of bias tool (Sterne et al., 2019).

1) < chronic pain >
2) AND < opiate > OR < opioid > OR < narcotic >
3) AND < addiction > OR < misuse > OR < disorder > OR < aberrant behavior > OR < abuse > OR < dependence >
4) AND < methadone > OR < buprenorphine > OR < cognitive behavioral therapy > OR < mindfulness >

Figure 1. **Combination of terms used to perform the literature search, in title, abstract and/or keywords.**

Table 1. *Summary of the pharmacological observational descriptive studies.*

Author, year	Participants' characteristics				Setting	Intervention	Primary Outcome	Other outcomes	Results
	OUD diagnosis	CNCP diagnosis	Number of participants (mean age)	% Male					
Rhodin et al. 2006	DSM-IV	Pain physician assessment and medical records.	n = 60 (43)	51.6	Outpatient methadone maintenance program in Sweden.	Oral MTD (mean dose 99.5mg, range 10-350mg) to treat OUD and CNCP in a pilot program (average treatment duration 38.3 months, range 1-94 months).	Evaluation of analgesia.	Evaluation of side effects, quality of life and identification of risk factors related to OUD in CNCP population.	For patients with a correct follow-up (48/60, 80%), 75% reported "good" pain relief and 25% "moderate". Most patients reported an improvement in their quality of life (mean 50.8, range 0-100). Common side effects were sedation, loss of energy, increase in weight, insomnia, sweating, weakness, sexual dysfunction and anorexia (>40%). Previous story of addiction or mental disorder was found as the main risk factor to develop OUD.
Pade et al. 2012	DSM-IV	Physical examination and medical records.	n = 143 (52)	93	Primary care setting for military veteran population in New Mexico, USA.	Sublingual BUP/NLX (mean dose of BUP 16mg, range 6-28mg).	Evaluation of analgesia compared to baseline.	Relapse during the 6 first months and retention on BUP/NLX treatment.	BUP/NLX decreased significantly ($p<0.001$) pain (mean 5.6; 95% CI 5.4 -5.8) compared to baseline (mean 6.39; 95% CI 6.2 - 6.6). 65% of the patients remained abstinent and on treatment for 6 months. 42% remained on BUP/NLX more than 6 months, 13% greater than one year and 3.5% more than 18 months.
Streltzer et al. 2015	DSM-IV	Pain clinic assessment and medical records.	n = 43 (50)	70	Outpatient psychiatric pain clinic in Hawaii, USA.	Sublingual BUP/NLX (median dose 8mg, range 0.25-32mg; median treatment duration 19 months, range 1-85 months).	Analysis of the evolution of patients through treatment course.	Differences between patients who had and had not a previous history of drugs and/or alcohol abuse regarding positive non-physiological pain (Waddell test [Waddell, McCulloch & Kummel, 1980]), more-than-one pain location, smoking habit, prescription of BNZ and rates of maintenance in treatment or detoxification.	During treatment, 10 patients returned to prescription opioids, drop out or were transferred to a licensed opioid treatment program (23%); 19 patients maintained treatment (44%); 3 patients successfully detoxed (7%); 3 patients transferred care (7%); 6 patients were lost to follow-up (14%); 2 patients died (4.7%), 1 from overdose. 35 patients (74%) remained in treatment more than 6 months. No significant differences were found between patients with and without previous history of alcohol/drugs abuse in positive non-physiological pain (100% vs. 72%), more than one pain location (53% vs. 61%), smoking habit (67% vs. 47%), prescription of BNZ (53% vs. 36%), and rate of maintenance in treatment or detoxification (47% vs. 54%).
Worley et al. 2017	DSM-IV	Patient self-report pain ≥3months and confirmation through medical screening.	n = 125 (no mean age specified).	52	Community clinics affiliated with a national clinical trial network (POATS) in 10 USA cities.	Tapering BUP/NLX (maximum range doses 8-32mg) for 4 weeks, continued by 8 weeks of follow-up.	Correlation between pain volatility during the tapering phase with the risk of relapse (assessed by self-referred use and urine drug screen).	Correlation between baseline pain and the degree of improvement in analgesia with the risk of relapse (assessed by self-referred use and urine drug screen).	Volatility of pain was found significantly correlated with positive drug screening (OR: 2.43; 95%CI 1.03-5.76; p = .04) and self-referred drug use (IRR: 1.66; 95%CI 1.20-2.58; p = .009). A lower degree of pain improvement was found significantly correlated with positive drug screening (2.38; 95%CI 1.13-5.02; p = .02) and self-referred drug use (IRR: 1.4; 95%CI 1.02-1.97; p = .04). Baseline pain was not significantly correlated with positive drug screening (OR: 1.13; p = .44) nor self-referred drug use (IRR: 1.16; p = .42).

Note. BNZ: benzodiazepines; BUP/NLX: buprenorphine/naloxone; CNCP: chronic non-cancerous pain; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association, 1993); IRR: incidence-rate ratio; MTD: methadone; OR: odds ratio; OUD: opioid use disorder; POATS: Prescription Opioid Addiction Treatment Study (Weiss et al., 2011); USA: United States of America.

Table 2. *Summary of the pharmacological open-label, controlled, randomized clinical trials.*

Author, year	Participants' characteristics				Setting	Intervention	Active comparator	Primary Outcome	Other outcomes	Results
	OUD diagnosis	CNCP diagnosis	Number of participants (mean age)	% Male						
Blondell et al. 2010	DSM-IV	Multi-disciplinary pain assessment and medical records.	n = 12 (45)	50	Outpatient clinics of a tertiary-care teaching hospital in New York State, USA.	3 sublingual tablets* of 2/0.5mg of BUP/NLX (steady dose) per day for 6 months.	3 sublingual tablets* of 2/0.5mg of BUP/NLX per day for one month, 2 for one month,1 for two months and none for two months (tapering dose).	Treatment retention at the completion of each protocol.	Number of days of licit or illicit drug use or alcohol determined by participant self-report or positive urine toxicology; initiation of and engagement in behavioral therapy or medical counseling.	5 out of 6 participants in the "steady dose" group completed the protocol compared to none out of 6 in the "tapering dose" group, which was found significant (p = .015), with a RR** of 0.1667 (95% CI 0.0278 – 0.9975; p = .0497). As none of the patients in the active comparator arm completed the protocol, secondary outcomes were not analyzed.
Neumann et al. 2013	DSM-IV-TR and DAST>4	Pain related to spine or large joint confirmed by diagnostic imaging and medical records.	n = 54 (38.3)	53.7	Outpatient primary care center in New York State, USA.	Sublingual BUP/NLX tablets 4/1-16/4mg (average dose14.93/3.73mg) per day divided 2-4 times daily for 6 months.	Oral MTD tablets20-60mg (average dose 29.09mg) per day divided 2-4 times daily for 6 months.	Self-reported analgesia at 6 months compared to the initial visit.	Treatment retention; self-reported functioning; self-reported drug and alcohol use.	The mean percent change of pain from baseline between BUP/NLX group (87.4, SD = 33.4) and MTD group (88.6, SD = 24.5) was not significant (p = .918); follow-up effect was revealed (p = .043) and across both treatments' participants reported less pain (mean = 5.5, SD = 1.9) than baseline (mean = 6.3, SD = 1.2) with a 12.75% reduction in pain at medium effect size (Cohen's d = 0.52). 26 participants (48.1%) completed the protocol, 13 in each arm, with no significant differences (p = .77). The mean percent change of functioning from baseline between BUP/NLX group (121.9, SD = 63.9) and MTD group (113.8, SD = 62.5) was not significant (p = .787). 5 participants in the BUP/NLX group referred use of opioids compared to none in the MTD group, which was found significant (p = .039). In BUP/NLX group 4 participants reported alcohol use compared to 2 in the MTD group, with no significant difference (p = .645).
Neumann et al. 2019 ***	DSM-IV-TR and DAST >4	Failed back surgery confirmed by physical examination or diagnostic imaging.	n = 19 (41.1)	31.6	Outpatient primary care center in New York State, USA.	Sublingual BUP/NLX tablets8/2-16/4mg per day divided 2-4 times daily for 6 months.	Oral MTD tablets 30-60mg per day divided 3-4 times daily for 6 months.	Self-reported analgesia.	Self-reported functioning; illicit drug use; depression; craving.	The mean pain severity among completers (10, 6 in MTD and 4 in BUP/NLX), measured by a VAS at 6 months was 71.8 (SD = 20.9) in the BUP/NLX group compared to 36.3 (SD = 22.4) in the MTD group, which showed no significant difference (p = .097). Functioning, measured by VAS, in the MTD group was 31.7 (SD = 25.1) compared to 71.3 (SD = 16.0) in the BUP/NLX group, which showed no significant differences (p = .088). Among completers, 1 participant in each arm had a positive urine test for opioids at the end of the protocol compared to 3 in BUP/NLX group and 4 in the MTD group at baseline. Depression, assessed with the BDI, scored 17.0 (SD = 18.2) in the MTD group compared to 15.3 (SD = 14.2) in the BUP/NLX, which showed no significant differences (p = .895). The mean measurement for craving among completers measured by a VAS at 6 months was 11.7 (SD = 18.1) in the MTD group compared to 27.2 (SD = 31.7) in the BUP/NLX group, with no significant difference (p = .348).

Note. BDI: Beck Depression Inventory (Beck, Ward, Mendelson, Mock & Erbaugh, 1961); BUP/NLX: buprenorphine/naloxone; CNCP: chronic non-cancerous pain; DAST: Drug Abuse Screening Test (Skinner, 1982); DSM-IV(-TR): Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association, 1993) Text Revision (American Psychiatric Association, 2000); MTD: methadone; OUD: opioid use disorder; SD: standard derivation; USA: United States of America; VAS: visual analogue scale.

* Initial doses could be adjusted based on individual's response.

** RR was calculated by the reviewers with www.medcalc.org/calc/relative_risk.php.

*** Results have been extracted from those published in the protocol (National Library of Medicine US, 2019) when the original paper has provided them across both treatments instead of single treatments.

Table 3. *Summary of the non-pharmacological open-label, controlled, randomized clinical trials.*

Author, year	Participants' characteristics				Setting	Intervention	Active comparator	Primary Outcome	Other outcomes	Results
	OUD diagnosis	CNCP diagnosis	Number of participants (mean age)	% Male						
Barry et al. 2019*	DSM-IV-TR	Self-referred moderate-to-severe low back pain (≥4 NRS) over 6 months.	n = 40 (38.1)	62.5	Outpatient pain clinic in Connecticut, USA.	CBT (one 30-45 minutes weekly session) for 12 weeks.	MDC (four 15-20 minutes sessions) for 12 weeks.	Rates of abstinence compared to baseline; significant reductions in pain interference (≥2 points) from baseline.	Maximum consecutive weeks of abstinence; rates of significant reduction (≥2 points) in pain intensity from baseline.	The proportion of abstinent patients is significantly higher compared to baseline in the CBT group compared to MDC [Wald $\chi 2$ (1) = 5.47; p = .019]. No significant difference (≥2 points) was found in pain interference from baseline between CBT (42.9%) and MDC (42.1%) [$\chi 2$ (1,N) =40 = 0.002, p = .962]. The mean consecutive weeks of abstinence in the CBT group was 6.1 (SD = 4.2) and 3.9 (SD = 3.3), which was not significant (p = .06). Pain intensity from baseline in the CBT group was 14.3% and 15.8% in the MDT group, which was not found significant [$\chi 2$ (1,N) =40 = 0.018, p = .894].
Garland et al. 2019 **	Being in MMT for 3 months	CNCP ≥8 in Gracely Box Scale (Gracely & Kwilosz, 1988) for 2 months or longer.	n = 30 (50.4)	50	Outpatient methadone clinic in New Jersey, USA.	MORE in 8 sessions of group therapy intervention, 2 hours each week (participants were asked to practice 15 minutes of mindfulness every day).	MMT.	Craving.	Pain intensity; pain unpleasantness; stress; positive affect.	The MORE group reported 44% less craving than the MMT group, which was significant (Group X Time B= -0.019, SE= 0.005, p <.001). Pain intensity was not significant (p > .1). The MORE group reported 13% less pain unpleasantness than the MMT group, which was significant (Group X Time B= -0.007, SE = 0.003, p = .025). The MORE group reported 26% less stress than the MMT group, which was significant (Group X Time B= -0.014, SE= 0.004, p = .003). The MORE group reported 22% greater affect than the MMT group, which was significant (Group X Time B= -0.01, SE= 0.004, p = .017).

Note. BUP/NLX: buprenorphine-naloxone; CBT: cognitive behavioral therapy; CNCP: chronic non-cancerous pain; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision (American Psychiatric Association, 2000); MDC: methadone drug counseling; MMT: methadone maintenance treatment; MORE: Mindfulness-Oriented Recovery Enhancement; MTD: methadone; NRS: numerical rating scale; SD: standard derivation; SE: standard error; USA: United States of America.

*This is a pilot study which its focus of interest are feasibility and acceptability. The outcomes are those considered as preliminary efficacy outcomes.
**The results are obtained from a ecological momentary assessment of a uncompleted clinical trial.

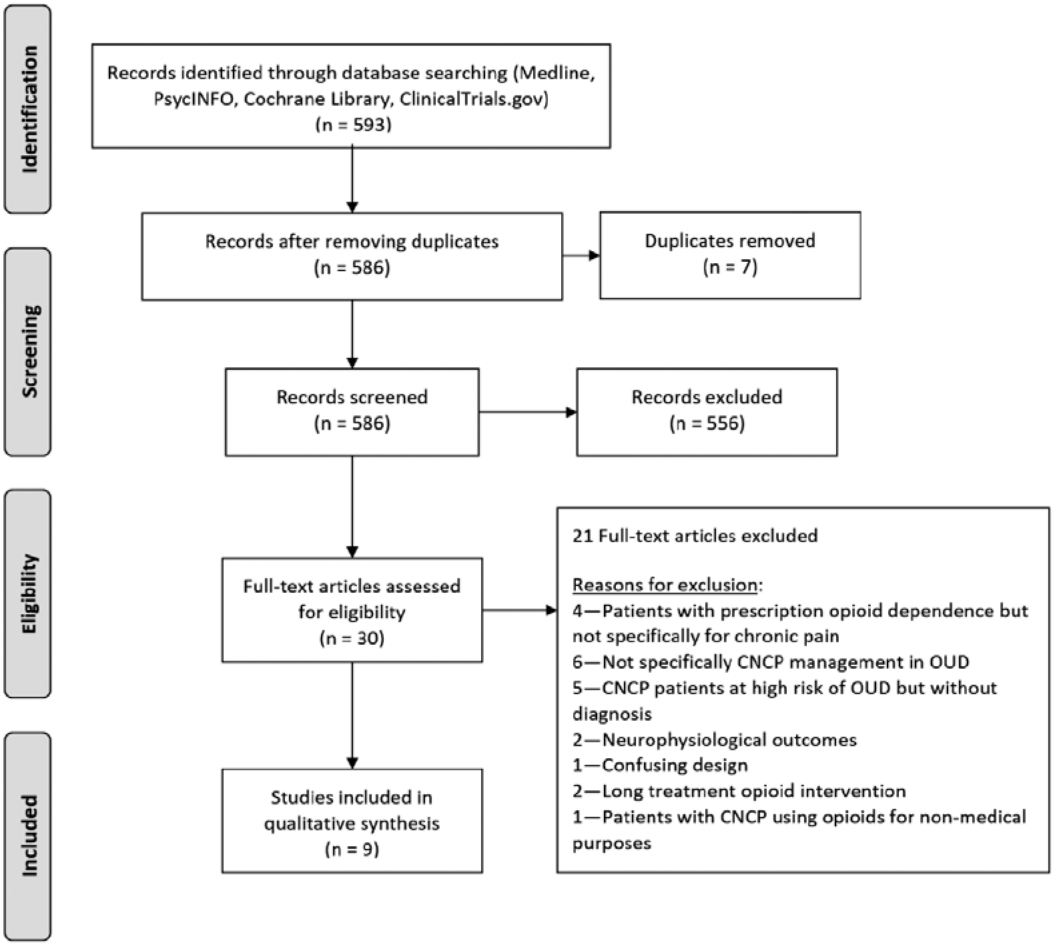

Figure 2. **Flow diagram of the literature search, inclusion process and reasons for exclusion after full-text assessment.**

Results

Nine studies were finally included in the qualitative synthesis. Five studies were RCTs and four were observational studies. The results of the studies have been organized according to whether the treatments are pharmacological or psychological. After full-text extraction, significant methodological differences among studies were noted, inhibiting the possibility of pooling the results of the outcomes to perform a quantitative analysis.

Pharmacological treatments

Methadone was studied in 1 observational study and 2 RCTs. The observational study reported that pain relief was "good" in 75% of participants and "moderate" in 25% (Rhodin, Grönbladh, Nilsson & Gordh, 2006). The 2 RCTs comparing effectiveness of methadone with buprenorphine/naloxone did not show significant differences in terms of analgesia and relapse (Neumann, Blondell, Hoopsick & Homish, 2019; Neumann et al., 2013).

Buprenorphine/naloxone was studied in 3 observational studies and 3 RCTs. 1 observational study reported a significant analgesic effect compared to baseline and a rate of abstinence for 6 months and retention on treatment of 65% (Pade, Cardon, Hoffman & Geppert, 2012) whereas 1 observational study reported a 74% of retention on treatment at 6 months (Streltzer, Davidson & Goebert, 2015). 1 observational study found a positive correlation during treatment with buprenorphine between a higher volatility of pain or a poorer improvement of it and opioid relapse (Worley, Heinzerling, Shoptaw & Ling, 2017). 1 RCT compared tapering doses with steady doses of buprenorphine/naloxone, reporting a relative risk of 0.17 (calculated for this systematic review) of not completing the treatment when doses were steady instead of tapered (Blondell et al., 2010). As previously noted, 2 RCT compared methadone with buprenorphine/naloxone. None of them could demonstrate significant differences between these treatments with regard to analgesia and rate of relapse (Neumann et al., 2013, 2019).

1 of the 2 RCTs that compared methadone with buprenorphine/naloxone, pointed out that, even though there were no significant differences, across both treatments

Supporting materials

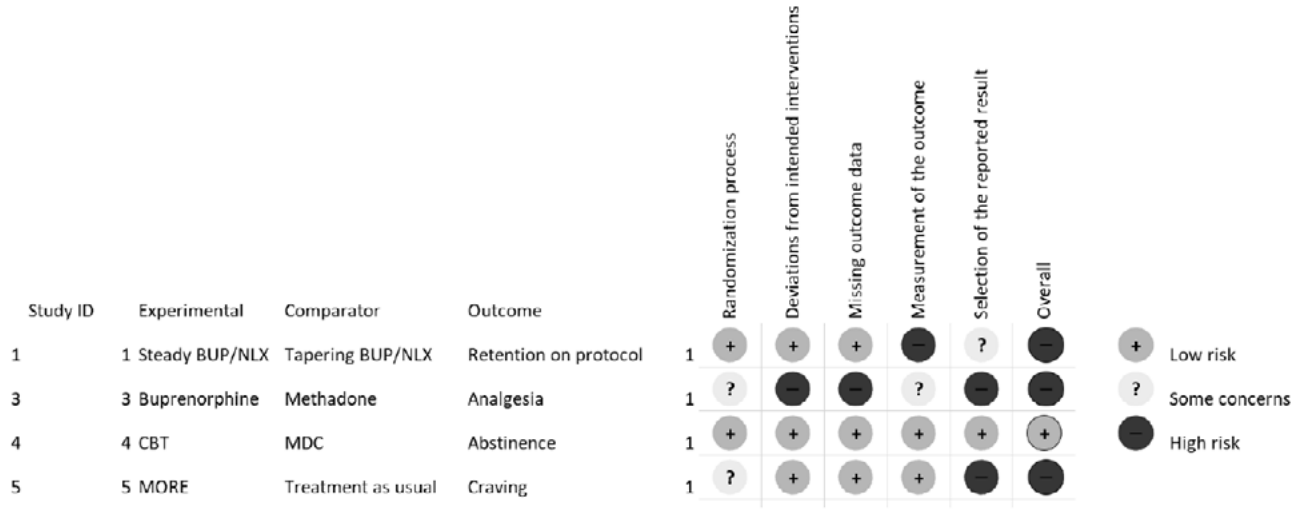

Figure 3. **Rob2 risk of bias panel for included randomized clinical trials (intention-to-treat analysis).**

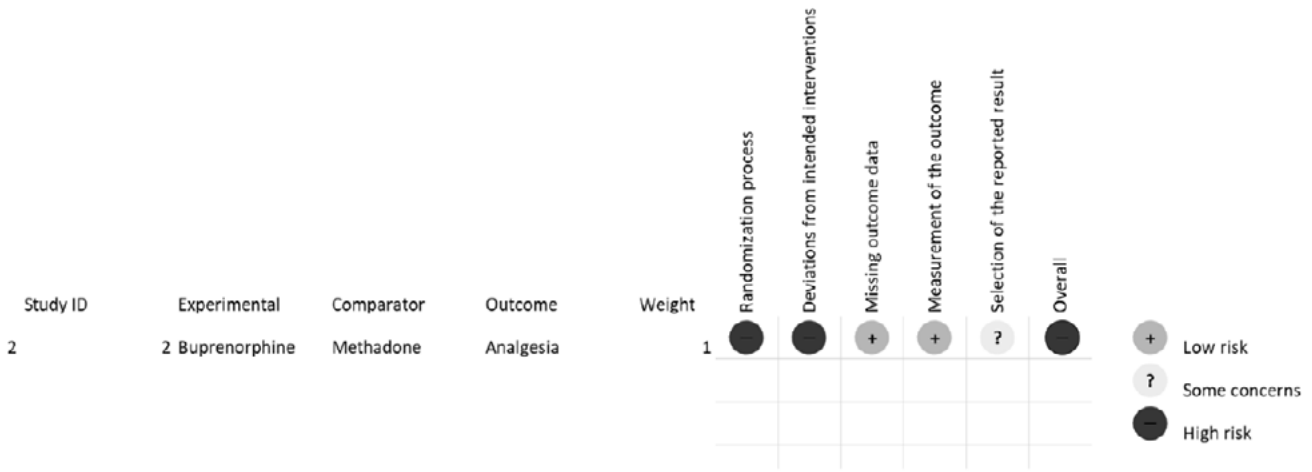

Figure 4. **Rob2 risk of bias panel for included randomized clinical trials (per-protocol analysis).**

there was a reduction of pain from baseline of 12.75% (Cohen's d 0.52) (Neumann et al., 2013).

Further details of the included studies are summarized in Table 1 for the observational studies and in Table 2 for the RCTs.

Psychological treatments

CBT was studied in 1 RCT (a pilot study, which its main outcomes were acceptability and feasibility, not efficacy). It reported a significant higher proportion of abstinence in patients undergoing CBT (Wald χ^2 (1) = 5.47, p = .019). Number of maximum consecutive weeks of abstinence from nonmedical opioid use was higher for patients assigned to CBT than for patients assigned to control group (mean 6.1 [SD 4.2] and 3.9 [SD 3.3]), respectively, Cohen's d 0.58, calculated for this systematic review). On the other hand, no significant differences were found in terms of analgesia (Barry et al., 2019).

Mindfulness was studied in 1 ecological momentary assessment of an RCT (not yet completed). It reported a significant reduction of craving and stress and a significant increase of the positive affect (Group X Time B = -0.019, SE = 0.005, p < .001). Nevertheless, no significant differences were found related to analgesia (Garland, Hanley, Kline & Cooperman, 2019).

Further details of these studies are summarized in Table 3.

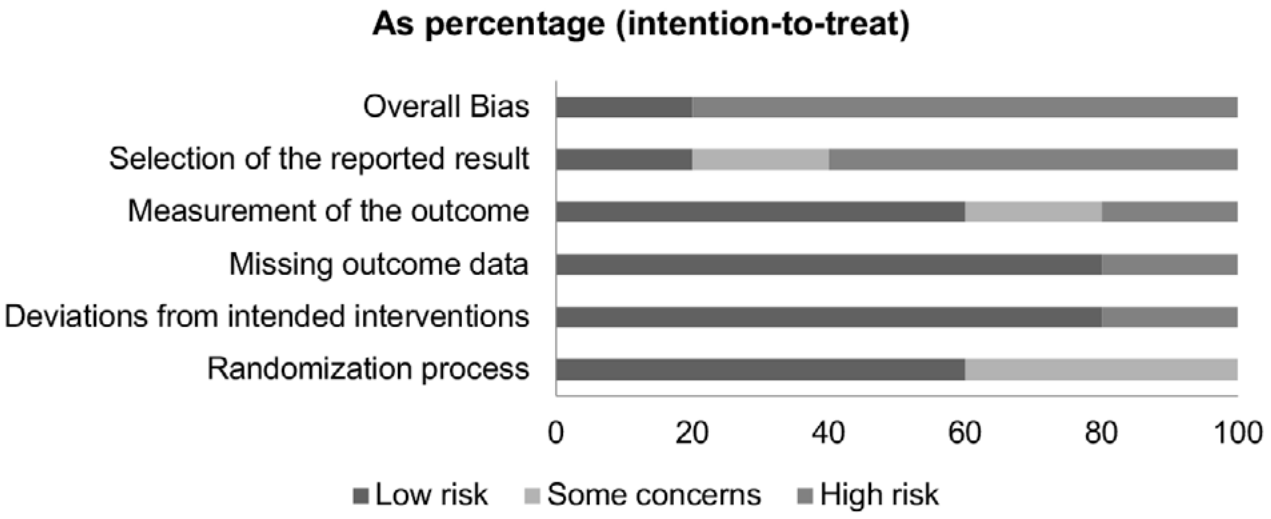

Figure 5. **Rob2 risk of bias panel for included randomized clinical trials (intention-to-treat analysis).**

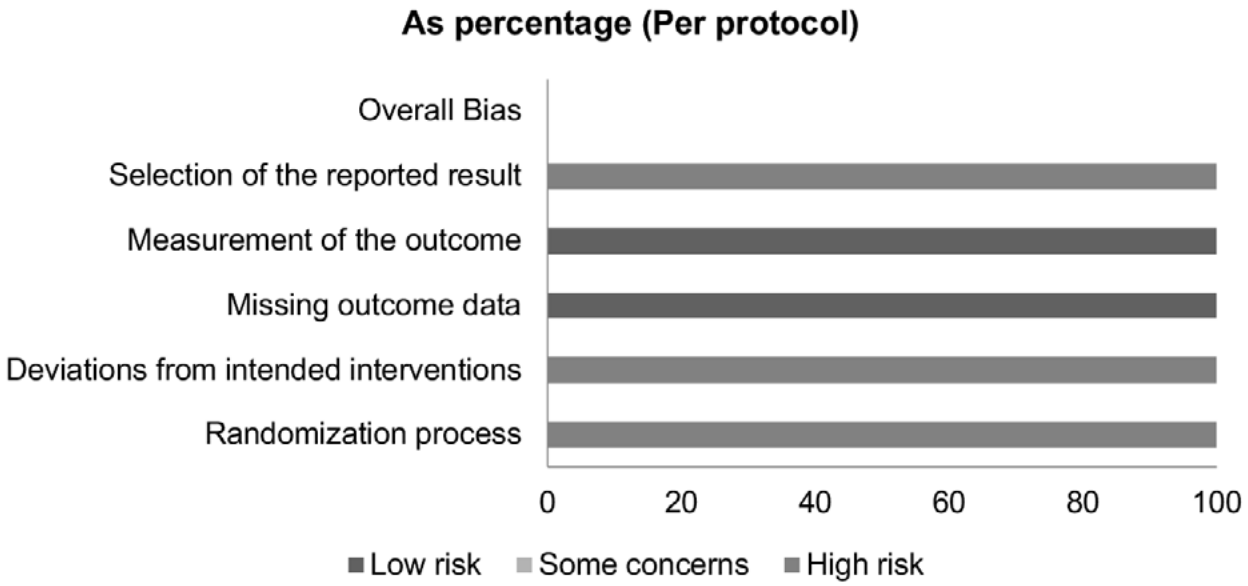

Figure 6. **Rob2 risk of bias panel for included randomized clinical trials (per-protocol analysis).**

Methodological quality assessment

Using the Rob 2 Cochrane tool (Sterne et al., 2019), 5 clinical trials were analyzed for their risk of bias (Figures 3-6).

3 pharmacological RCTs were assessed: 1 comparing steady doses of buprenorphine with tapering doses and 2 comparing buprenorphine's efficacy with methadone's. Buprenorphine was proven to be better when administered in steady doses but could not demonstrate superiority compared to methadone. However, all three studies showed an overall high risk of bias, mainly, due to substantial deviations from the protocol.

2 psychological RCTs were assessed: 1 study compared CBT and methadone counseling and 1 study compared mindfulness and methadone maintenance treatment. Both therapies reported significant higher abstinence rates and/or emotional improvement (craving, anxiety, stress) but did not demonstrate substantial differences in terms of analgesia. When assessed, only the CBT study had an overall low risk of bias, whereas the mindfulness study came up with a high risk of bias, showing a notable bias in the selection of the reported result. Despite the low risk of bias of the CBT trial, it should be borne in mind that it is a pilot study.

Discussion

After full-extraction and analysis of the studies, none of the proposed therapies (methadone, buprenorphine-naloxone, CBT and mindfulness) have demonstrated strong evidence for treating comorbid OUD and CNPC, in at least 2 RCT with low risk of bias including a control group (placebo, active comparator or treatment as usual).

Methadone and buprenorphine are useful in treating comorbid OUD and CNCP. However, this evidence is based on observational studies and three low quality RCTs. Methadone could not be assessed in the RCTs, as it was used as active comparator. On buprenorphine, maintenance strategy seems more useful than a decreasing-doses strategy towards discontinuation (Blondell et al., 2010), as pain aroused and increased the demand of painkillers. Buprenorphine could not demonstrate being more effective than methadone in two superiority RTCs (Neumann et al., 2013, 2019) neither for pain nor abstinence. However, when the groups were analyzed across both treatments, a significant improvement was found compared to baseline. With this insufficient evidence and the limitations of studies, no statement about efficacy or evaluation can be made about which treatment is preferred. It is clear that opioid substitution therapy is necessary for these patients but the assessment of efficacy should be studied in a double blind randomized basis with larger population; with a randomization that took into account the baseline pain intensity and prior use of opioids; primary outcomes defined as the change from baseline in opioid use (if relapse is the primary outcome) measured only by one method or change from baseline in pain intensity (if analgesia is the primary outcome) using standardized tools for measuring chronic pain (e.g., Brief Pain Inventory [Cleeland, 2009]).

Regarding its pharmacodynamics, buprenorphine-naloxone would be a better option for its safety profile but for uncontrolled/severe pain with buprenorphine-naloxone, methadone should be considered in highly motivated patients (Neumann et al., 2019).

Regarding psychological interventions, two different interventions were studied with RCT design: CBT and mindfulness. Both studies claim to be the first of their type in these patients. In fact, one is a pilot study and the other is an ecological momentary assessment of an unfinished clinical trial. Results are positive towards managing negative emotions related to OUD and CNCP. However, none demonstrate greater improvement of pain than standard treatment (Barry et al., 2019; Garland et al., 2019). In addition, as pilot studies, the primary outcomes are feasibility and acceptance rather than actual OUD and CNCP outcomes, which reduces their reliability and precludes assessing the real efficacy. Moreover, only one study assessing the efficacy of CBT was considered to have a low risk of bias. Future studies should contemplate the same recommendations stated for the pharmacological studies except for the double-blind basis, in which it is not applicable. Additionally, the main outcomes should be related with efficacy, as feasibility and acceptance have already been demonstrated.

Only one literature review (Eilender, Ketchen, Maremmani, Saenger & Fareed, 2016) and one systematic review (Morasco et al., 2011) have been found on this topic. The systematic review tried to assess the efficacy of treatment for OUD and CNCP (among other questions regarding OUD and CNCP like epidemiological features or risk factors involved), reporting an average-low quality of evidence. However, when articles within the revision where analyzed, most of them did not accomplish having all the patients previously diagnosed with OUD and CNCP. Our current revision includes 8 articles that did not appear in the 2011 referred systematic review. This might be the first systematic review to include only studies in which their participants are already diagnosed with OUD and CNCP with a therapeutic intervention performed to treat both conditions.

We found a lack of terminology consensus. Terms like "addiction", "misuse", "abuse" or "dependence" are often used as synonyms. In part because criteria over opioid use disorder has changed from DSM-IV to DSM-V, text used as reference in psychiatry. DSM-IV used the terms "dependence" and "abuse" distinctly whereas DSM-V includes both under "opioid-related disorders". A series of questionnaires designed to identify opioid use disorders during long opioid treatment may be helpful to complement the diagnosis like the Current Opioid Misuse Measure, the Prescription Drug Use Questionnaire, the Pain Medication Questionnaire or the Prescription Opioid Misuse Index (Knisely, Wunsch, Cropsey & Campbell, 2008). The heterogeneity of these diagnostic tools does not facilitate obtaining strong conclusions. Moreover, other variables like quality of life or pain evolution should be considered.

Research seems to go towards preventing and diagnosing OUD in CNCP patients instead of treating them once OUD occurs. Tapering appears to be a valid option when OUD has not yet set up (Sullivan et al., 2017). Abuse deterrent formulations are an interesting preventive measure. They are designed so misusing opioids (snorting, injecting, crushing) would have no effect (Volkow & Thomas McLellan, 2016). Also, naltrexone, an opioid antagonist approved for treating opioid and/or alcohol use disorder, has recently demonstrated anti-inflammatory effects at low doses that would be useful in this population (Heinzerling, 2019). Nevertheless, none of these options have been approved for comorbid OUD and CNCP. Moreover, physicians, worried about this problem, are starting to get trained to be able to detect and evaluate patients with CNCP and problematic use of opioids (Butner et al., 2018).

This review has some limitations. Firstly, the strict criteria regarding the population (patients with both OUD

and CNCP) has caused a selection of very heterogenous studies with different proposed therapies and designs, making difficult to offer a strong assessment on the efficacy of every treatment. In addition, investigators are aware that only 9 studies included in the review do not offer strong conclusions on treating these patients because only articles that reported that all the participants had both OUD and CNPC and had an intervention applied for treating both conditions were admitted. For this reason, articles that studied CNCP and comorbid substance use disorder (but not specifically OUD), articles that focused on addiction to prescription opioids (but without a CNCP diagnose established) and articles including population on opioid treatment and at risk of misuse but without an actual OUD diagnosis, have been excluded. Secondly, due to this heterogeneity of the studies, it has not been possible to conduct a quantitative analysis. Thirdly, since the search process and selection were carried out from January 2020 to March 2020 and the articles were eligible until December 2019, no articles of 2020 and 2021 were included. For this same reason, latest PRISMA guidelines were not used, as they were yet not published during the making of this review. Fourthly, although the research and writing process was done by six investigators, only one investigator performed the initial selection of the articles. Despite being supervised the entire time, no inter-judge reliability or kappa factor could be assessed for this reason. However, in case of doubt, two investigators were consulted during the selection process. Fifthly, no truncation nor codification book were used to perform the search. Although it could have been useful, the PRISMA guideline that we followed did not require it.

Due to the lack of strong evidence, it is unclear whether the opioid agonist treatment should be maintained or tapered and which drug should be prescribed for the opioid substitution therapy (methadone or buprenorphine/naloxone). However, buprenorphine might be preferred for its safer profile. Mindfulness and cognitive behavioral therapy have shown a discrete effect on improving negative affect but not pain. Further research about treatment in these patients is urgently needed due to the synergic impact of these entities on morbimortality and their prevalence.

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Study has been registered in PROSPERO database (CRD42020198672).

Conflict of interests

López-Pelayo, H. received training grants (Exeltis, Pfizer, Esteve, Lundbeck). Dr. Gual received a grant from Novartis for a trial on cocaine that ended in April 2020. None of the previous conflicts of interest has relationship with this work. Other authors do not report any conflict of interest.

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Annex 1: Excluded articles after full-text revision

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