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Review article

Iatrogenic opioid use disorder, chronic pain and psychiatric comorbidity: A systematic review

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ABSTRACT

Objective: A systematic review of the literature on the risks of developing iatrogenic opioid use disorders in chronic pain patients with psychiatric comorbidity.
Methods: We conducted literature searches on Pubmed with key subjects: “chronic pain”, “psychiatry”, “opioids” and “opioid use disorder” and for original, English written articles published from 2000 until the first of September 2017. Final selection of the articles for review was made in a consensus between three reviewers.
Results: Longitudinal studies showed a significant association between psychiatric comorbidity, especially depression and anxiety disorders and the development of problematic opioid use, more severe opioid craving and poor opioid treatment outcome (analgesia and side effects) in chronic pain patients. Cross-sectional studies showed a similar association between psychiatric disorders and problematic opioid use, where studies in specialized pain settings showed a higher prevalence of psychiatric disorders, compared to non-specialized settings.
Conclusions: This systematic review showed a significant association between psychiatric comorbidity, especially depression and anxiety disorders and the development of problematic opioid use in chronic pain patients. We therefore recommend psychiatric screening in chronic pain management. Chronic pain patients with comorbid psychiatric disorders need a multidisciplinary approach and monitoring opioid use is warranted in these patients.

1. Introduction

The worldwide increase in prescription opioid use has been associated with an increased prevalence of opioid use disorders and a rise in opioid overdoses and opioid-related deaths. Opioids have an important role in treatment of pain, particularly in patients with acute and cancer-related pain [1]. Studies show an ongoing increase in opioid prescriptions, both in the United States (US) and Europe [2–4]. For instance in 1991 76 million opioid prescriptions were dispensed by US pharmacies and 207 million in 2013 [5]. In parallel there has been an increase in the prevalence of opioid use disorders, opioid-overdose and opioid-related deaths. In 2016 11.5 million people misused prescription opioids in the US [6] and 116 people died every day from opioid-related drug overdoses [7]. The costs of the opioid crisis were estimated at $504.0 billion in 2015 in the US [8]. Though the last couple of years the number of opioid prescriptions in the US has decreased slightly, there is an continuing rise of opioid-related mortality [9,10].

Patients with chronic non-cancer pain (CNCP) are at specific risk to develop opioid use disorders [11]. Of all pain patients with a new opioid use episode, 5.3% continued opioids after 1 year [12]. However, evidence for effectiveness of prolonged opioid treatment is lacking [13]. In two meta-analyses, the estimated prevalence of CNCP patients using prescribed opioids non-medically is 48% to 60% [14,15]. With a prevalence of chronic pain of around 19% in Europe, this has become a major public health concern [16].

Within the population of chronic pain patients, those with comorbid psychiatric symptoms are particularly at risk for developing opioid use disorders [17]. Depression and anxiety in chronic pain patients are associated with more persistent pain [18,19], lower quality of life [18,20,21], higher opioid doses and prolonged prescription of opioids [22–25]. In addition, there is evidence that particularly depressive, anxiety and substance use disorders (SUD) are associated with increased use of prescribed opioids in the general population [26,27].

Importantly, most clinical trials that investigate the effects of opioids in chronic pain patients, exclude patients with psychiatric comorbidity [13]. Moreover, guidelines from American Association for pain include limited direction for the specific treatment of chronic pain patients with psychiatric comorbidity. Similarly, the guidelines for prescribing opioids for chronic pain by the Center for Disease Control and Prevention [28] have no recommendations regarding psychiatric

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screening (www.cdc.gov). The only, non-systematic, review about this topic also highlights the relationship between psychiatric disorders and opioid problematic prescription use in chronic pain patients [29]. The objective of this review is to add to this previous review, by applying a systematic approach and add literature 'published between 2000 and 2017' on the risks of iatrogenic opioid use disorders in chronic pain patients with psychiatric comorbidity. We will specifically address the question which (combination of) psychiatric disorders are most associated with problematic opioid use in CNCP patients, since the largest increase of opioid prescriptions is in that group [2,30]. Where possible, suggestions for clinical practice are provided.

2. Materials and methods

2.1. Design and literature search

For this systematic literature review, the electronic database PubMed was searched for original, English written articles published from 2000 until the first of September 2017 using the following search strategy:

(((((((non-malignant chronic pain) OR non cancer pain) OR long term pain) OR analgesics) OR chronic pain[MeSH Terms]) AND opioid analgesics[MeSH Terms])) AND (((psychopathology) OR psychiatric disorder) OR mental disorder[MeSH Terms])) AND (((((opioid misuse) OR opioid abuse) OR aberrant drug behavior) OR illicit drug use) AND opioid related disorders[MeSH Terms]).

2.2. Selection criteria

Inclusion criteria were: study population of patients with CNCP (defined as pain persisting for at least 3 months, not primarily caused by cancer; [31]), intervention with opioid treatment, opioid use and problematic opioid use, preferably defined as opioid use disorder conform according to Diagnostic and Statistical Manual of Mental Disorders (DSM) III/IV/5 or International Statistical Classification of Diseases and Related Health Problems (ICD)-9/10 criteria and systematic assessment of psychiatric symptoms. First, titles of all identified articles were screened for the inclusion criteria (SR). Next, abstracts of the selected articles were screened using the same criteria, by two reviewers (SR and MB) independently. Final selection of articles for review was made in a consensus meeting with a third reviewer (AS). See Fig. 1 for a flow chart of the selection process.

2.3. Data abstraction and quality assessment

From each study we collected the following information: title, year published, study design, population, sample size, outcome measures, main results, limitations and conclusions. The PRISMA guidelines for scientific reading were used to assess quality of the selected articles [32]. This includes for example selection of study population, data collection process, risk of bias (e.g. selection bias) and other limitations.

3. Results

3.1. Search results

The Pubmed search using the search terms described above yielded 2893 original articles (see Fig. 1 for study selection). After excluding non-human studies, and those not written in English, 1109 articles remained. After screening these titles for relevance to our review objective thirty-two articles remained and following subsequent screening of abstracts twenty-two articles remained. Two reviewers (SR, MB) were in full agreement in both selection steps. After reading the twenty-two articles, another eight articles were excluded, because they were not related to the review objective. Finally we included fourteen articles four on longitudinal studies (Table 1) and ten on cross-sectional studies, (Table 2).

3.2. Study results

3.2.1. Longitudinal association between psychiatric disorders and problematic opioid use

Of the four publications on longitudinal studies two reported on the same sample [41,42]. The three samples sizes were 55 [33], 46,256 [41,42] and 59,077 [34], with a total of 105,388 participants. Ages ranged from 13 to > 65 years, 43% were men, with follow-up time from 5.5 to 60 months. The three samples included chronic pain patients from a general population sample [34,41, > 42] and patients from specialized pain centres [33]. All studies took place in the US, and applied validated instruments to reliably assess psychiatric symptoms and problematic opioid use. Psychiatric morbidity was assessed with structured clinical interviews (diagnoses) and self-report questionnaires [33] or with ICD-9 from administrative (claims) data (not further specified) for opioid misuse and psychiatric diagnoses, for instance anxiety, adjustment or mood disorders [34,41,42]. In one study also Urine Toxicology Screens (UTS) were used [33].

All four longitudinal studies found significant associations between psychiatric comorbidity at baseline measurement and problematic opioid use at follow-up, after adjusting for socio-demographic and clinical (pain) covariates. Particularly, depression and anxiety disorders were associated with problematic opioid use. Wasan et al. [33] assessed problematic opioid use prospectively in a sample of low back pain patients (n = 55) in specialized treatment facilities, who started opioid treatment. Mean age of low Negative Affect (NA) group was 55 years and in high NA group 49 years. At baseline the following psychiatric questionnaires were assessed; the DSM-IV Axis I diagnosis and Hospital Anxiety and Depression Scale; high NA > 8, moderate NA > 6 < 8 and low NA < 6. After two and four months a Drug Misuse Index (DMI) was calculated, based on Current Opioid Misuse Measure (COMM), Addiction Behavior Checklist and UTS. The most common psychiatric co-morbidities were major depression (31%), dysthymia (20%), post-traumatic stress disorder (9%), adjustment disorder (9%), and generalized anxiety disorder (7%). High NA was associated with poor opioid treatment outcomes. The high NA group showed higher rates of opioid misuse (39.1% versus 8.3%, p = 0.013) and more craving for opioids (p = 0.041). High NA was also associated with nearly 50% less improvement in pain, and more and intense opioid side effects. Analyses were adjusted for baseline pain level and opioid use. One limitation of this study was the use of self-reports. Moreover, analgesia from opioids was lower in high NA group, but these participants may still have felt that the therapy was beneficial to them because of possible non-analgesic opioid effects and may have wished it to continue.

Richardson (2012) [34] studied opioid use in youth (13–24 years of age) with a new episode of CNCP, using a large population sample of insurance claims from the Health Core Integrated Research Database (n = 59,077), with 18 months follow-up. At follow-up, those with a pre-existing mental health diagnosis had a 2.4-fold increased risk of receiving chronic opioids versus no opioids (OR: 2.36, 1.73–3.23), and a 1.8-fold increased risk of chronic opioid prescriptions versus short-term incidental opioids (OR: 1.83, 1.34–2.50), compared to those without a mental health diagnosis (after adjustment for age, gender, socio-demographics, chronic disease status and type of pain condition). In the chronic opioid prescription group 17% had a mental health (mainly anxiety and major depressive disorders) or substance use diagnosis, compared to 11% in the non-chronic use group and 8% in the non-user group. Main limitation was the use of administrative data (ICD-09, not further specified).

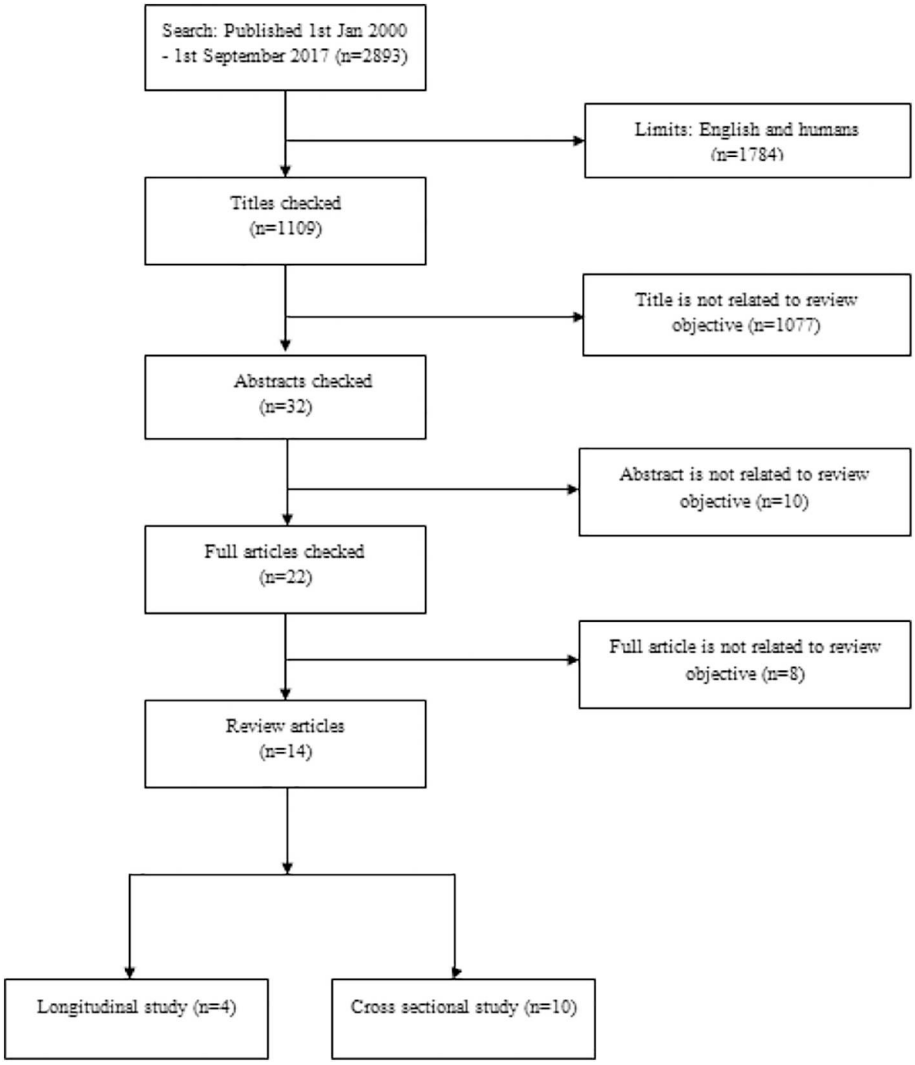

Fig. 1. Flow chart outlining the selection procedure of research articles used in this review.

Two studies used claims data from two disparate adult populations [41,42], one national commercially insured population (Health Core-HC, n = 36,605), and one state-based publicly insured population (Arkansas Medicaid-AM, n = 9,651). In both samples 3% of patients had claims based on opioid abuse/dependence. The HC sample showed that between 2000 and 2005, rates of chronic opioid use increased by 35% among individuals with a mental health or SUD, versus 28% among individuals without these disorders. In the AM sample chronic opioid use increased with 55% among individuals with a mental health or SUD versus 40% among those without, over a five-years period. The average daily dose of opioids in milligram morphine equivalents (MME) was generally between 50 and 55 mg. The average daily dose increased (< 10%) between 2000 and 2005 in HC, and decreased (< 10%) in AM [41].

In their second analysis of the same datasets, Edlund et al. [42] analyzed predictors of an opioid abuse/dependence diagnosis. In the HC sample predictors identified were being diagnosed with one mental health disorder (OR = 1.73, 95%CI = 1.49–2.01), two mental health disorders (OR = 2.08, 95%CI = 1.69–2.55), and a substance abuse diagnosis (OR = 5.55, 95%CI = 4.06–7.58). In the AM sample the same predictors were identified: diagnosed with one mental health disorder (OR = 1.17, 95%CI = 0.85–1.61), with two mental health disorders (OR = 1.70, 95%CI = 1.21–2.39), and a substance abuse diagnosis (OR = 5.50, 95%CI = 2.94–10.30). Although psychiatric disorders were more common than SUDs, effects of the latter were stronger. The median daily dosages were 32 MME and 35 MME in HC and AM respectively. Higher daily dosages were associated with post-index opioid abuse/dependence. A limitation of these two studies was the use of administrative data (ICD-09, not further specified).

3.2.2. Cross-sectional association between psychiatric disorders and problematic opioid use

Ten studies had a cross-sectional design (see Table 2), with a total of 4,785 participants (38% men) with sample sizes ranging from 40 [43] to 1,883 participants [24]. Baseline age ranged from 18 to > 70 years. Chronic pain patients were identified either in non-specialized settings like primary care or emergency rooms [24,35,36,44], or in specialized pain clinics [25,37–40,43]. All studies took place in the US and a variety of validated assessment tools were used.

The studies in the non-specialist settings including patients with chronic pain, who were on opioids, described a high prevalence of psychiatric co-morbidity, predominantly mood- and anxiety disorders. Merrill et al. [24] showed that among pain patients on long-term opioid treatment in general practice, higher opioid doses were associated with higher levels of depression symptoms and higher risk for self-reported clinical depression. Over 60% of patients receiving a daily morphine equivalent > 120 mg were clinically depressed, a 2.6-fold higher risk (95% CI 1.5–4.4) than patients on low doses. Most important limitations of this study were use of self-reports, the cross-sectional design and a response rate of 60%.

Table 1
Longitudinal studies in this systematic review.

Author(s)	Study design	Study population	Operationalization: chronic pain, opioid use, psychiatric disorders	Results	Quality assessment
1. Wasan et al, 2015	Longitudinal (6.5 months follow-up)	55 chronic low back pain patients in specialized pain settings	**Chronic pain**: Pain < 6 months. **Opioid use**: Week 1–3: opioid titration treatment; week 4–20 continuation phase, week 21–24: opioid tapering. **Psychiatric disorders**: Exclusion; active SUD[a], history SUD, active suicidality or psychosis at baseline. • SUD: Baseline: SOAPP(−R)[b] and DSM-IV[c]. Continuation phase (2 + 4 months): DMI score[d]. • Psychiatric disorders: Baseline: DSM- IV Axis I diagnosis and HADS[e].	Psychiatric disorder 100%, current major depression 31%, dysthymia 20%, history SUD 16%, adjustment disorder and PTSD 9%, generalized anxiety disorder 7%, panic, bipolar disorder and OCD 4%. Low NA[f] n = 24, moderate NA n = 7 and high NA n = 24. High NA: ↑ risk opioid misuse (39.1 vs. 8,3%, P = 0.013) and ↑ craving opioids vs. low NA (P = 0.041). High NA: ↑ pain, ↑ catastrophizing and ↑ neuroticism, correlated with HADS (PCC: 0.58 and 0.66, P < 0.01 for both).	**Power**: Sample size calculations on power of 0.80 is n = 20. n = 24 in high vs. n = 24 in low NA group. **Publication bias**: Unknown, study supported by the National Institute of Drug Abuse of the National Institute of Health grant K 23, DA020682, authors declare no competing interests. **Selection bias**: Patients from specialized pain clinics, may not be generalized to patients in other settings. Probably more chronic use and maybe more psychiatric psychopathology in this group, overestimation? Only patients with access to healthcare, an underestimation? **Attrition bias**: Flow-chart clearly describes study flow. Total drop out 25%. No significance differences in average age, gender distribution, average baseline pain level and duration of pain between drop-outs and analyzed patients. **Assessment method**: A psychiatrist administered a structured interview (not further specified) to determine any DSM IV diagnosis. HADS and SOAPP are structured self-reports. Chance of underreported opioid SUD/MH[g] because of social desirability?
2. Richardson et al, 2012	Longitudinal (18 months follow-up)	59,077 adolescents (13–24 years) with a new episode of CNCP[h] in general population sample	**Chronic pain**: Duration not specified. **Opioid use**: > 90 days of opioids within 6-month period with no gap in use of > 30 days in the 18 months following the first qualifying pain. **Psychiatric disorders**: 6 months prior first pain diagnosis. • SUD: ICD-9-CM[i]. • Psychiatric disorders: ICD-9-CM.	Chronic opioid use: 321 patients (0.5%), opioid SUD 0.6%, any SUD 2.8%, anxiety 8.1%, bipolar 2.2%, major depression 5.9%, any MH 15.6%. Some opioid use: 16,172 patients (27.4%). 17.1% of chronic opioid use had a MH or SUD vs. 10.6% non-chronic users vs. 8.2% non-users. Patients with MH: 2.4 × ↑ risk receiving chronic opioids vs. no opioids (OR 2.36, CI 1.73–3.23) and a 1.8 × ↑ likelihood receiving chronic opioids vs. some opioids (OR 1.83, CI 1.34–2.50). Predictive: male, older age, community (white, low education).	**Power**: No sample size calculation, n = 59,077 appears appropriate. **Publication bias**: Unknown, study supported by grants from Alcohol and Drug Abuse Institute at the University of Washington and from National Institute on Drug Abuse (NIDA R01 DA022560-01). **Selection bias**: Patients between 13 and 24 years, may not necessary national representative for adult population. Younger age may be associated with less chronic use, underestimation? Patients with access to healthcare, an underestimation? Overestimation because only patients with most problems report in healthcare? **Attrition bias:** Unknown. **Assessment method**: Administrative data. **N**on-structured ICD-09 software were used to identify mental health problems and SUD (not further specified). Underestimation opioid SUD/MH? Chance of underestimation because possible stigmatization/social desirability?

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Table 1 (*continued*)

Author(s)	Study design	Study population	Operationalization: chronic pain, opioid use, psychiatric disorders	Results	Quality assessment
3. Edlund et al 2010, trends…	Longitudinal (between 2000 and 2005)	HealthCore (HC): 36,605 + Arkansas Medicaid (AM): 9,651 patients with CNCP on chronic opioid prescription in general population sample	**Chronic pain**: Duration not specified. **Opioid use**: ≥ 90 days' continuous use of opioids during calendar year. Psychiatric disorders: • SUD: ICD-09 CM. • Psychiatric disorders: ICD-09 CM.	HC: Any MH/SUD 10.1% to 14.9% in AM: 23.7% to 35.1%. HC: Chronic opioid use ↑ by 34.9% among individuals with MH/SUD vs. 27.8% without MH/SUD. AM: Chronic opioid use ↑ by 55.4% among individuals with MH/SUD vs. 39.8% without MH/SUD.	**Power**: No sample size calculation, n = 36,605 + 9,651 appears appropriate. **Publication bias**: Unknown, study supported by NIH grant DA022560-01. **Selection bias**: May not be a national representative sample (diverse sources). AM serves a disadvantaged and vulnerable population, region with highest opioid use in country. Overestimation SUD/MH? HC fully insured (pharmacy coverage) overestimation SUD/MH? Only patients with access to healthcare, an underestimation? Overestimation because only patients with most problems report in healthcare? **Attrition bias**: Total missing < 1.5%. **Assessment method**: Administrative data; ICD-09 using validated grouping software developed by the Agency for Healthcare Research and Quality (not further specified). Underestimation opioid SUD/MH? Underestimation because possible stigmatization/social desirability? **Others**: Outliers > 0.5%. Not verified whether CNCP was chronic. Unknown whether opioids were for the CNCP.
4. Edlund et al 2010, risks…	Longitudinal[j] (5.5–54 months follow-up)	HC 36,605 + AM 9,651 patients with CNCP on chronic opioid prescription in general population sample	**Chronic pain**: Duration not specified. **Opioid use**: ≥ 90 days' continuous use of opioids within a 6 month period during study period. Psychiatric disorders: • SUD: opioid SUD and non-opioid SUD: ICD-09 (CM) (pre and post index). • Psychiatric disorders: ICD-09 CM (adjustment, anxiety, mood, personality and miscellaneous disorders (no MH, 1 MH, 2 + MHs).	Opioid SUD (post index): HC 3.2%, AM 2.9%, 4×↑ vs. pre-index. • HC: 1 MH 6.1% and > 2 MHs 10.9%. • AM: 1 MH 3.7% and > 2 MHs 7.6%. Predictors: • Psychiatric comorbidity: 1 MH (HC: OR 1.73, CI 1.49–2.01. AM: OR 1.17, CI 0.85–1.61), 2 MH (HC: OR 2.08, CI 1.69–2.55. AM: OR 1.70, CI 1.21–2.39) • Pre-index substance abuse diagnosis (HC: OR 5.55, CI 4.06–7.58. AM: OR 5.50, CI 2.94–10.30) • Age < 50 year, back or neck pain, higher dosage and longer prescription Non opioid SUD: HC 4.4% and AM 13.8%. Predictors: headache, prior SUD in history, high opioid dosage and long prescription.	**Power**: No sample size calculation, n = 36,605 + 9,651, appears appropriate. **Publication bias:** Unknown. **Selection bias**: May not be a national representative sample (diverse sources). AM serves a disadvantaged and vulnerable population, region with highest opioid use in country. Overestimation SUD/MH? HC fully insured (pharmacy coverage) overestimation SUD/MH? Patients with access to healthcare, an underestimation? Overestimation because only patients with most problems report in healthcare? **Attrition bias**: No drop-outs, all patients were eligible. **Assessment method**: Administrative data; ICD-09 using validated grouping software developed by the Agency for Healthcare Research and Quality (not further specified). Underestimation opioid SUD/MH? Underestimation because possible stigmatization/social desirability?

[a] Substance use disorder.
[b] Screener and Opioid Assessment for Patients with Pain.
[c] Diagnostic and Statistical Manual of Mental Disorder.
[d] Drug Misuse Index; composite COMM (Current Opioid Misuse Measure) ABC (Addiction Behavior Checklist) and UTS (Urine Toxicology Screen).
[e] Hospital Anxiety and Depression Scale.
[f] Negative Affect.
[g] Mental Health disorder.
[h] Chronic Non-Cancer Pain.
[i] International Classification of Diseases, Ninth Revision (Clinical Modification). Index date: 1st day of opioid prescription. Pre and post index date: 12 months ± index date.
[j] Index date: 1st day of opioid prescription. Pre and post index date: 12 months ± index date.

Table 2
Cross sectional studies in this systematic review.

Author(s)	Study design	Study population	Operationalization: chronic pain, opioid use, psychiatric disorders	Results	Quality assessment
5. Merrill et al, 2012	Cross sectional	1,883 patients with CNCP and using opioids in a non-specialized pain setting (from CONSORT study[a])	**Chronic pain**: Duration not specified. **Opioid use**: ≥10 opioid prescriptions and/or received ≥120 days' supply in a 1-year period prior to the sample selection date, with ≥90 days between 1st and last opioid dispensing that year. Using opioids every day in 2 weeks prior interview were included. Psychiatric disorders: ● SUD: PODS[b]. ● Psychiatric disorders: PHQ[c] (depression).	Major depression 61.4% receiving 120+ mg daily (MME[d]) vs. low dose (< 20 mg daily) 26.8% (95% CI 1.5–4.4). Higher opioid doses reported ↑ levels of depression: Patients with ↑ dose opioid were younger vs. low dose ($P < 0.0001$). ↑ Dose control concerns to prescribed opioids ($P < 0.0001$).	**Power**: No sample size calculation, n = 1,883 appears appropriate. **Publication bias:** Unknown. **Selection bias**: Patients with access to healthcare, an underestimation? Overestimation because only patients with most problems report in healthcare? **Attrition bias**: n = 3,790 approached, 185 ineligible (no further information), n = 2,163 interviews completed for a response rate of 60%. 87% of n = 2163 included in analyzes. Response rate higher for patients over age of 65, overestimation? Gender differences were small (not further specified) in response rate. Response rate increased with higher average daily dose, overestimation? **Assessment method**: PODS and PHQ are structured self-reports, underestimation because possible stigmatization/social desirability? **Others**: Patients received money and gift card after participation (small amount).
6. Banta-green et al, 2009	Cross sectional	704 pain patients with chronic opioid use in a non-specialized pain setting (integrated group practice)	**Chronic pain**: Pain ≥3 months. **Opioid use**: Chronic opioid use in the 12 months prior interview; filling ≥10 opioid prescriptions in 12 months period or filling a prescription for at least a 120 days' supply of opioids and ≥6 opioid prescriptions during 12 months period. Psychiatric disorders: ● SUD: DSM IV (CIDI[e] and PDUQ[f]), ASSIST[g]. ● Psychiatric disorders: PHQ for anxiety and PHQ-2 for depression.	Opioid dependence 13%, opioid abuse 8%. Depression 21%, anxiety 15%. Three classes: 1) Typical group (82%); had persistent, moderate mental health and pain symptoms. 2) Addictive behavior group (12%); elevated mental health symptoms and opioid problems, but pain similar to the typical group. 3) Pain dysfunction class (6%); significant higher pain interference as well as elevated mental health and opioid problems. Prescribed average daily dose of opioids: 3 × ↑ for those in 2 atypical groups. Addictive vs. typical group: younger and male, ↑ treatment for depression.	**Power**: No sample size calculation, n = 704 appears appropriate. **Publication bias:** Unknown. **Selection bias**: In non-specialized integrated group practice. Appears a national representative sample for chronic pain patients. Patients with access to healthcare, an underestimation? Overestimation because only patients with most problems report in healthcare? **Attrition bias**: n = 778 interviews conducted with response rate of 57%. Most common reasons of eligible patients: being physically or mentally unable to participate in phone interview, having a non-working phone number and using opioids medicines for reasons other than pain. Among those who met eligibility criteria, a lack of participation in the study was most commonly due to active refusal, reasons for refusal were not documented. Non-responders may be more sick, underestimation? Non-responders are more likely to be younger, overestimation male and have a higher opioid dose, underestimation? **Assessment method**: CIDI is a structured interview conducted by certified CIDI trainers who reviewed and approved tapes of practice interviews. ASSIST, PDUQ and PHQ(2) are structured interviews. Underestimation because possible stigmatization/social desirability? **Others**: Patients received money after participation (small amount).
7. Wilsey et al, 2008	Cross sectional	113 chronic pain patients visiting an emergency department or urgent case	**Chronic pain**: Pain > 3 months. **Opioid use**: Taking opioids for pain and seeking a refill.	High SOAPP 81%. Current or history of SUD 74%, high BDI 79%. Anxiety 53% trait anxiety and 57% state anxiety. Past substance abuse 76%, abusing	**Power**: No sample size calculation, n = 113 appears appropriate. **Publication bias**: Unknown, funding by the

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Table 2 (*continued*)

Author(s)	Study design	Study population	Operationalization: chronic pain, opioid use, psychiatric disorders	Results	Quality assessment
		centre with opioids (non- specialized pain setting)	Psychiatric disorders: • SUD: based on SOAPP. • Psychiatric disorders: BDI[h], STAI[i], PDQ-4[j] and SCID[k].	alcohol 15% and abusing other substance 28%. History of alcoholism 41% and remote history of substance abuse 60%. Panic attacks 12% and PTSD 34%. Personality disorder 18%. Panic disorder, trait anxiety and personality disorder explained 38% of variance of SOAPP.	Mayday Fund and Grant Number UL1 RR024146 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. **Selection bias**: Patients visiting an ED or UC, may not be a national representative sample. ED/UC more serious cases, maybe more SUD/psychiatry overestimation? Patients with access to healthcare, an underestimation? **Attrition bias:** Unknown. **Assessment method:** BDI, SOAPP, STAI and PDQ are structured self-reports, underestimation because possible stigmatization/social desirability? SCID is a structured interview by a clinical psychologist. **Others**: Patients received money after participation (small amount).
8. Fleming et al, 2008	Cross sectional	904 chronic pain patients receiving opioid therapy from their primary care physician (non-specialized pain settings)	**Chronic pain**: Duration not specified (from chronic pain study; average 16 years). **Opioid use**: Taking daily or intermittent opioids in the previous 6-months (average 6.4 years). Psychiatric disorders: • SUD: DSM IV (Substance Dependence Severity Scale; last 30 days). • Psychiatric disorders: ASI[l].	Opioid SUD 3.4%, any SUD 9.6%. Hospitalized for psychiatric disorders 24.7%, in mental health counseling 60%. Depression 34.3%, anxiety 36.6%, serious attempt to end their life 20.6%. ASI score > 0.49 21.8%. Patients ≥4 aberrant behaviors (see methods of article) have more likely an current SUD (OR 10.14: 3.72–27.64) and high ASI-score (OR 2.38, 1.65–3.44) vs. ≤3 behaviors. Patients ≥4 aberrant behaviors ↑ likely male gender (OR 2.08: 1.48–2.92) and older age (OR 0.69, 0.59–0.81) compared to ≤3 behaviors. Low dose opioids (< 20 mg per day) were no more likely to predict aberrant behaviors than high dose use (> 100 mg).	**Power**: No sample size calculation, n = 904 appears appropriate. **Publication bias**: Unknown, study supported by NIDS grant R01DA013686-02, no other sources of funding. **Selection bias**: Appears a national representative sample for patients receiving opioids for chronic pain from primary care physicians. Patients with access to healthcare, an underestimation? Overestimation because only patients with most problems report in healthcare? **Attrition bias**: n = 1009 final sample. n = 916 taking daily or intermittent opioids in previous 6 months. n = 904 had completed data. Response rate 78%, non-responders may be more sick, underestimation? Excluded patients were significantly older than included patients (52.5 vs. 48.3), no other significant differences between included vs. excluded patients. More younger ages included, underestimation? **Assessment method**: SDSS is a semi-structured interview. ASI is a structured interview. Underestimation because stigmatization/social desirability? **Others**: Patients received money after participation (small amount).
9. Martel et al, 2014	Cross sectional	82 chronic musculoskeletal pain patients with prescribed opioids in a specialized pain setting	**Chronic pain**: Chronic back or neck pain > 6 months. **Opioid use**: Prescribed opioid medication > 6 months. **Psychiatric disorders**: Exclusion active SUD past year (by Mini International Neuropsychiatric Interview) and DSM IV diagnosis of any psychotic disorder.	Anxiety (r = 0.31, P < 0.01) and depression (r-0,25, P < 0.05) associated with opioid misuse (COMMs). Correlation NA and COMM (r = 0.29, P < 0.01). Anxiety (r = 0.30 P < 0.01) and depression (r = 0.21, P < 0.05) associated with opioid craving. Correlation pain intensity and NA (r = 0.34, P < 0.01) and correlation pain intensity and COMM's (r = 0.21, P = 0.05). Correlation NA and	**Power**: No sample size calculation, n = 82 appears appropriate. **Publication bias**: Unknown, study supported in part by an investigator-initiated grant form Endo Pharmaceuticals, Chadd Ford, Pennsylvania, and grants R2 1DA024298 and K23 DA020682 from the National Institute on Drug Abuse (NIDA) of the National Institute of Health, Bethesda, MD and Arthritis Foundation. Authors have no financial

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Table 2 (*continued*)

Author(s)	Study design	Study population	Operationalization: chronic pain, opioid use, psychiatric disorders	Results	Quality assessment
			• SUD: COMM[m] and SOAPP. • Psychiatric disorders: Self-reports NA and craving (Visual Analogue Scale)	craving (r = 0.27, P < 0.05) and craving and COMM's (r = 0.43 P < 0.01). Indirect effect craving (95% BC CI). Sobel *Z*-test (Z = 2.1, P < 0.05).	interests in results and no conflict of interests. **Selection bias**: Patients from tertiary pain center with relative high doses of opioids. May not be generalized to patients in other settings. More chronic use and maybe more psychiatry, overestimation? Patients with access to healthcare, an underestimation? **Attrition bias**: Patients included in study were part of a larger study in which patients were enrolled in a RCT of a behavioral intervention designed to improve prescription opioid compliance, however the study populations do not match each other. **Assessment method**: MINI is a structured interview, administrated and scored by a trained research assistant. COMM and SOAPP are structured self-reports. NA and craving (VAS) are also self-reports, underestimation because possible stigmatization/social desirability? **Others**: Patients received money after participation (small amount). Use of convenience sample.
10. Martel et al, 2013	Cross sectional	115 patients with chronic musculoskeletal pain in a specialized pain setting	**Chronic pain**: Pain > 6 months. **Opioid use**: Reported whether or not they were currently taking any opioids. Psychiatric disorders: • SUD: Exclusion. • Psychiatric disorders: SOAPP-R, PASS[n], BDI and PCS[o].	Men 52.1% taking opioids and women 46.3% taking opioids (p = 0.54). After controlling for the PASS, contribution PCS to prediction SOAPP-R (Z = 2.1, p < 0.05) but decreased from 21% (beta = 0.47) to 5% (beta 0.31). After controlling for the BDI, contribution PCS to prediction SOAPP-R (Z = 1.4, NS) but decreased from 21% (beta = 0.47) to 10% (beta 0.39).	**Power**: No sample size calculation, n = 115 appears appropriate. **Publication bias**: Unknown, funding was provides by National Institute of Health and had no further role in this manuscript. Authors have no financial interest in results and no conflict of interest. **Selection bias**: Patients from specialized pain clinic, may not be generalized to patients in other settings. More chronic use and more psychiatry, overestimation? Patients with access to healthcare, an underestimation? **Attrition bias:** Unknown. **Assessment method**: SOAPP, PASS, PCS and the BDI are structured self-reports, underestimation because possible stigmatization/social desirability?
11. Proctor et al, 2013	Cross sectional	216 consecutive pain patients in specialized pain setting (independent neurodiagnostic clinic)	**Chronic pain**: Duration not specified. **Opioid use**: Prescribed opioids for chronic pain 70.7% Psychiatric disorders: • SUD: Self report DSM-IV and verified by addiction expert certified[p] (no specific opioids). • Psychiatric disorders: CAAPE[q] derived from DSM-IV.	SUD 1.9% (alcohol dependence and abuse). 0% any other SUD (e.g. opioid use disorders). Major depression 44.4%, manic episode 3.2%, PTSD 29.2%, OCD and panic attacks 9.3%. 1 Axis I disorder 23.2%, 2 axis I disorders 17.6%, > 2 axis I disorders 8.3%. Axis II: OCPD 62.5%, other personality disorder 5.0%, > 1 personality disorders: 6.1%. Totally ≥1 axis I disorder 49.1%. Alcohol dependence 0.5%, alcohol abuse 1.4%.	**Power**: No sample size calculation, n = 216 appears appropriate. **Publication bias:** Unknown. **Selection bias**: Patients from specialized pain clinic, may not be generalized to patients in other settings. More chronic use and maybe more psychiatry, overestimation? Patients with access to healthcare, an underestimation? **Attrition bias**: Unknown. **Assessment method**: DSM IV and CAAPE are structured self-reports, underestimation because possible stigmatization/social desirability?
12. Haller et al, 2010	Cross sectional	40 chronic pain patients in specialized pain setting with opioid abuse or dependence	**Chronic pain**: Pain > 6 months (pain diagnosis by pain expert). **Opioid use**: Daily use of opioids.	Opioid abuse 28.9%, dependence 71.1%. Mood disorders: lifetime 85%, current 57.5%. Lifetime psychiatric diagnosis 92.5%, severe mental illness	**Power**: No sample size calculation, n = 40 appears appropriate. **Publication bias:** Unknown.

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Table 2 (*continued*)

Author(s)	Study design	Study population	Operationalization: chronic pain, opioid use, psychiatric disorders	Results	Quality assessment
			Psychiatric disorders: • SUD: DSM-IV. • Psychiatric disorders: SCID-CV.	55%, current psychiatric diagnosis 67.5%; 1 current diagnose 30%, ≥2 current diagnosis 37.5%. Double depression[r] 22.5%. Lifetime alcohol 52.5%. Other non-opioid SUD 42.5%, ≥2 lifetime non-opioid SUD 32.5%.	**Selection bias**: Patients from specialized pain clinic, may not be generalized to patients in other settings. More chronic use and maybe more psychiatry, overestimation? Patients with access to healthcare, an underestimation? **Attrition bias**: n = 72 included, n = 46 (passed telephone prescreening, signed informed consent and began baseline evaluation). n = 6 failed complete baseline. No information about potential difference between included vs. excluded patients. Underestimation because possible stigmatization/social desirability? **Assessment method**: DSM-IV and SCID-CV are structured interviews.
13. Wasan et al, 2007	Cross sectional	228 patients prescribed opioids for CNCP in 3 specialized pain settings	**Chronic pain**: Duration not specified. **Opioid use**: Prescribed opioids for CNCP. Psychiatric disorders: • SUD: Baseline SOAPP (≤8). Follow up: COMM, POTQ[s], 5 + 6 months UTS. Misuse/Abuse: DMI score[t]. • Psychiatric disorders: Follow-up: PDUQ[u] (only 5 different psychiatric questions).	Opioid SUD 38.6%. High psych[v] (n = 125 = 55%), low psych (n = 103 = 45%). High psych vs. low psych: ↑ SOAPP, COMM and DMI score ($p < 0.001$); younger, taking opioids for longer time and ↑ drug misuse behavior. Psychiatric status 10% of variance SOAPP (r^2) = 0.095, which is high F ((1.206) = 21.4, $P < 0001$ beta = 0.31). Psychiatric status 13% of variance COMM score ($r^2 = 0.13$), F((1.212) = 32.6, $P < 0.001$ beta = 0.37).	**Power**: No sample size calculation, n = 228 appears appropriate. **Publication bias:** Unknown. **Selection bias**: Patients from specialized pain clinic, may not be generalized to patients in other settings. More chronic use and maybe more psychiatry, overestimation? **Attrition bias**: N = 56 excluded (20%) because missing data or data were lost to follow-up. Excluded patients were younger than included patients (45.6 vs. 50.5; $P < 0.01$), no other significant differences between included vs. excluded patients. More older ages in included group, more chronic opioid use, overestimation of the problem? **Assessment method**: SOAPP and COMM are structured self-reports, underestimation because possible stigmatization/social desirability (Study used the Marlow-Crown Social Desirability Scale-Short Form). POTQ and PDUQ are structured clinical interviews. **Others**: Patients received money after participation (small amount).
14. Manchikanti et al, 2007	Cross sectional	500 consecutive pain patients with stable doses opioids in a specialized pain setting (interventional pain management setting)	**Chronic pain**: Duration not specified (range 1–44 years, average 10.7 years). **Opioid use**: Stable opioid use in pain management. Psychiatric disorders: • SUD: *abuse* received controlled substances from any place/source other than prescribing physician. And/or escalation use of controlled substances (dose(s) and schedule). *Drug trafficking*: According to the legal determination as described by statute and in courts of law. *Past history of illicit drug use* based on report/history and/or information (medical report) • Psychiatric disorders: DSM-IV-TR.	"Doctor shopping" or "trafficking" opioids (abuse) 9%. Depression 59%, anxiety 64% and somatization disorder 30%. Illicit drug use 16%. Drugs abuse depressed patients vs. no depression (12% vs. 5% $P < 0.05$). Current illicit drug in women with depression vs. without (22% vs. 14%). Prescription drug abuse in women with depression vs. without (11% vs. 4%). Current illicit drug use highest in males with somatization disorder vs. without (22% vs. 9% $p < 0.05$). Current illicit drug more prevalent in depressed women vs. men (22% vs. 12%). Anxiety males vs. females (58% vs. 69%).	**Power**: No sample size calculation, n = 500 appears appropriate. **Publication bias**: Unknown, supported in part by funding from the Center for Clinical Bioethics and Division of Palliative Medicine, Georgetown University Medical Center and the Samueli Institute. **Selection bias**: Patients from specialized pain clinic, may not be generalized to patients in other settings. More chronic use and maybe more psychiatry, overestimation? Patients with access to healthcare, an underestimation? **Attrition bias**: n = 566. n = 66 refuse to participate (no further information). Non-responders may be more sick, underestimation? **Assessment method**: DSM-IV-TR based questionnaire, followed by a physician conducted

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Table 2 (*continued*)

Author(s)	Study design	Study population	Operationalization: chronic pain, opioid use, psychiatric disorders	Results	Quality assessment
					interview. Underestimation because possible stigmatization/social desirability?

[a] The CONsortium to Study Opioid Risks and Trends.
[b] Prescribed Opioid Difficulties Scale.
[c] Patients Health Questionnaire.
[d] Morphine Milligram Equivalent.
[e] Composite International Diagnostic Interview.
[f] Prescription Drug Use Questionnaire.
[g] Alcohol, Smoking and Substance Involvement Screening Test.
[h] Beck Depression Inventory.
[i] Spielberger State-Trait Anxiety Inventory.
[j] Personality Diagnostic Questionnaire, 4th Edition.
[k] Structured Clinical Interview for DSM (Clinical Version).
[l] Addiction Severity Index (0.5 = moderately severe psychiatric illness).
[m] Current Opioid Misuse Measure.
[n] Pain Anxiety Symptoms Scale.
[o] Pain Catastrophing Scale.
[p] By the American Society of Addiction Medicine.
[q] Comprehensive Assessment And Psychological Evaluation.
[r] Major depression and dysthymia.
[s] Prescription Opioid Therapy Questionnaire.
[t] DMI based on SOAPP, COMM, POTQ and UTS.
[u] Prescription Drug Use Questionnaire.
[v] ≥2 score on PDUQ.

In the study of Banta-green et al. (2009) [44], using structured clinical interviews in a general practitioner setting, 21% of all patients with chronic opioid use (n = 704) had depression and 15% anxiety disorders. Based on latent class analyses, they described three distinct types of patient classes: a typical group (82%) experiencing persistent, moderate mental health and pain symptoms; an addictive behavior group (12%) with elevated mental health symptoms and opioid problems, but pain similar to the typical class; and a pain dysfunction group (6%) with significantly higher pain interference as well as elevated mental health and opioid problems. The prescribed average daily dose of opioids (derived from pharmacy data for the year prior to the interview) was three times higher for those in the two atypical groups, and these higher opioid doses were associated with opioid misuse. Furthermore, of the two atypical groups, the addictive behaviors group was more likely to have received treatment for a mood disorder compared with the pain dysfunction group, while there were no differences in the level of current depressive symptoms between these two groups. Main limitations of this study were the cross-sectional design and a response rate of 57%.

In the study of Wilsey et al. [35] among chronic pain patients taking opioids, who visited an emergency room, 79% of the patients had high self-reported levels of depression, using the Beck Depression Inventory (BDI-score ≥ 10). 53% of the patients had high levels of trait anxiety and 57% of the patients had state anxiety, using Spielberger State-Trait Anxiety Inventory (score ≥ 40). Lastly, 18% screened positive for a personality disorder, using the Personality Diagnostic Questionnaire, 4th edition (score ≥ 50). Using the Structured Clinical Interview for DSM-IV-R (SCID), psychiatric diagnoses were evaluated for SUD (74%), current panic attacks (12%) and a current post-traumatic stress disorder (34%). Panic attacks, trait anxiety and the presence of a personality disorder accounted for 38% of the variance in opioid abuse. They found no relationship between depression and opioid abuse. Important limitations were the cross-sectional design and the use of self-reports.

In the study of Fleming et al. [36] among chronic pain patients receiving opioid treatment from their general practitioner (n = 904), 34% had experienced serious depression and 37% anxiety over the last 30 days, as identified using a clinical interview. Moreover, 25% had previously been hospitalized for a psychiatric disorder, and 60% had participated in mental health counseling. Patients with four or more aberrant behaviors (assessed with a 12 aberrant drug behavior questionnaire) were more likely to have an opioid use disorder (OR 10.1 (3.7–27.6) or an untreated mental health problem, defined as Addiction Severity Scale composite score > 0.5 OR 2.4 (1.7–3.4). Most important limitations were the cross-sectional design and the lack of formal criteria for aberrant drug use behavior.

The studies in specialized pain settings showed higher percentages of psychiatric comorbidity, and similar associations between psychiatric comorbidity and problematic opioid use. Martel et al. [37] found that in chronic muscoskeletal pain patients on opioids (n = 82) self-reported anxiety ($r = 0.31$, $P < 0.01$) and depression ($r = 0.25$, $P < 0.05$), rated on a Visual Analogue Scale (VAS), correlated with prescribed opioid misuse severity. A bootstrapped multiple mediation analysis revealed that self-reported opioid craving over the past 24 h on a VAS (scale 0–100) mediated the association between NA and opioid misuse, as measured using the COMM. Self-reported pain intensity over the past 24 h did not show any relationship with opioid misuse. Limitations were the use of self-reports, use of a convenience sample and the cross-sectional design.

Higher levels of NA were also associated with higher risk of misuse among chronic muscoskeletal pain patients (n = 115) in the other study of Martel et al. [38], where they used the Screener and Opioid Assessment for patients with Pain-Revised (SOAPP-R). Patient's self-reported pain severity, pain sensitivity (i.e. low pain thresholds) as well as catastrophic thinking about pain were associated with higher risks for opioid misuse. Hierarchical multiple regression analysis showed evidence for a mediation effect of anxiety (assessed with the Pain Anxiety Symptoms Scale), and not of depression (assessed with the BDI) on the association between catastrophizing (assessed with the Pain Catastrophing Scale) and risk for opioid misuse. Main limitations of this study were the cross-sectional design, use of self-reports and exclusion of patients with SUD.

In the study of Proctor et al. [39], in a chronic neuropathic pain population (n = 216), substance abuse rates (according to DSM-IV-TR criteria, verified by an addictions expert) reported by patients were lower than those seen in the general population. In contrast, this study showed high rates of (clinician-rated) psychiatric disorders (DSM-IV-TR). Almost half of patients (49%) fulfilled criteria for at least one DSM-IV axis I disorder, mainly being major depressive disorder 44%, post-traumatic stress disorder 29%, and panic attacks 9%. Two thirds (67%) met criteria for a DSM-IV axis II disorder, predominantly obsessive-compulsive personality disorder (63%). Important limitations were the cross-sectional design and use of self-reports.

In the study of Haller et al. [43] among patients with chronic pain and an opioid use disorder, the vast majority had a lifetime psychiatric diagnosis (92.5%); and current psychiatric diagnosis (67.5%). The main psychiatric diagnoses, as assessed using structured clinical interviews, were lifetime mood disorders (85.0%); current mood disorders (57.5%), and other non-opioid SUDs (42.5%), the most common being alcohol-use disorder in remission. Main limitation in this study was the cross-sectional design.

Wasan et al. [25] measured problematic opioid use prospectively in a cohort of CNCP patients in treatment at specialized pain centres. Patients were classified in a low versus high psychiatric morbidity group, based on the Prescription Drug Use Questionnaire. At baseline the SOAPP-R was assessed and after a follow-up of 5–6 months, the COMM, Presciption Opioid Therapy Questionnaire (POTQ) and UTS were assessed. Based on the scores of the SOAPP-R, COMM, POTQ and UTS the DMI was calculated. The study showed that 38.6% of patients (n = 88) fulfilled criteria for high DMI. Those with high psychiatric morbidity (n = 125; 55%) had more aberrant opioid use behaviors, compared to those with low psychiatric comorbidity (SOAPP total score ≥ 8: $p < 0.001$; COMM total score ≥ 9: $p < 0.001$; DMI: $p < 0.001$), as well as more deviating UTS ($p \leq 0.01$). However, after adjusting for age, duration of opioid use and social desirability score the association with UTS became non-significant. Important limitations were the use of self-reports and a composite classification (DMI). Furthermore, the high psychiatric group had been taking opioids longer than the low psychiatric group and fifteen procent of the participants did not give a urine sample.

In the study of Manchikanti et al. [40], among pain patients stable on opioids, opioid abuse was higher in patients with self-reported depression (12%) than in those without (5%, $p \leq 0.05$). Opioid abuse was defined as either patients receiving opioids from anybody else than their prescribing physician, and/or when patients escalated the use of opioids beyond dose(s) and schedule prescribed. This effect was mainly driven by high opioid abuse rates among women with depression (22%), compared to women without depression (14%). Among men, opioid abuse was particularly high in those with somatization disorder (22%), compared to those without (9%, $p \leq 0.05$). Most important limitation of this study was the cross-sectional design.

4. Discussion

This systematic review aimed to unravel the relationship between psychiatric disorders and opioid use disorders in chronic pain patients [29]. Longitudinal studies showed a significant association between psychiatric comorbidity, especially depression and anxiety disorders and the development of problematic opioid use, more severe opioid craving and poor opioid treatment outcome (analgesia and side effects). Cross-sectional studies showed a similar association between psychiatric disorders and problematic opioid use, where studies in specialized pain settings showed a higher prevalence of psychiatric disorders,

compared to non-specialized settings. While most studies had cross-sectional designs, precluding conclusions regarding directionality of associations, the observed similar findings from longitudinal studies might suggest causality. In these studies, mostly based on chronic pain samples [33] and population samples from insurance claims [34,41,42], presence of psychiatric symptomatology at baseline was predictive of later problematic opioid use. Though the observed chronology suggests psychiatric symptomatology could contribute to an increased risk of opioid use disorders in these patients, it might also be that liabilities for both conditions play a role, for instance prior traumatic experiences [45–47] or genetic pleiotropy [47–49]. Different models of causality for observed comorbidities exist, like the liability, multiformity or causation models [50]. However, given the observational character of the studies presented here, no causal inferences can be made. Such causality can only be inferred from experimental designs, which seem not feasible in humans in this case.

Future studies should shed more light on the chronology and the causal factors mediating the observed associations between psychiatric symptomatology, chronic pain, and opioid use disorders. There is a need for longitudinal studies to examine risk factors in these patients with chronic opioid use to find more evidence for causality and for further subtyping of patients at risk. For instance patients with chronic neuropathic pain report more frequent depression [51], possibly based on shared neuropathological mechanisms. Studies also need to further explore (treatable) psychological factors, like traumatic experiences that may contribute to the risk of aberrant opioid use. It could also be speculated that in at risk patients alternatives for full mu-opioid receptor agonists are preferred, like Non-Steroidal Anti-Inflammatory Drugs, partial mu-agonists opioids or kappa antagonists [52].

Furthermore, most studies indicate that mainly psychiatric symptoms of anxiety and depression drive the association between psychiatric symptomatology and opioid use disorders in chronic pain patients. This is in line with recent studies showing that mood and anxiety disorders predict opioid misuse among chronic pain patients [22]. Moreover, patients with more severe depression showed higher risks, suggesting a dose response relationship [23]. Similarly, anxiety sensitivity (defined as the fear of anxiety-related physical sensations) has been suggested as a factor contributing to elevated opioid misuse among patients with chronic pain [53]. It has to be acknowledged that depression and anxiety vary on a continuum from mild anxiety and depressive symptoms to full-blown psychiatric disorders, like major depression and panic disorder [24,33–35,37–41].

Psychiatric conditions characterized by depression and anxiety are sometimes considered stress-related disorders [54], suggesting potential shared stress-related mechanisms to be involved in pain perception, depression and anxiety and addiction liability. Several studies have indeed shown stress-dysregulation as a common pathway in pain perception, depression and anxiety disorders, and addiction. For example, it has been shown that individuals with high levels of depression or anxiety have lower pain thresholds with increased pain perception as a result [55]. Similarly, patients with pain and comorbid depression or anxiety were shown to be less sensitive to analgesic properties of opioids [33,56], suggesting a need for higher opioid dosing regimens, with subsequent increased risk for further dose escalation and development of problematic opioid use.

At a neurobiological level, disturbances in brain stress systems have repeatedly been shown in chronic pain, disorders of depression or anxiety (see reviews Boakye [57], Vinall [47] and Yalcin [59]) and addiction (see review Bart [52]). Shared neurobiological mechanisms include increased activation of corticotropin releasing factor, dynorphin and other stress-related neuropeptides (e.g. nociception and neuropeptide Y), the Hypothalamic-Pituitary-Adrenal axis, the noradrenergic stress pathway, and increased amygdala reactivity [47,57–59]. Also alterations in brain reward pathways have been suggested in all three conditions [60].

The observed associations between psychiatric symptomatology of depression and anxiety, and the risk of opioid use disorders in chronic pain patients emphasize the importance of identifying psychiatric comorbidity in chronic pain patients as early as possible. Several validated instruments for screening for psychiatric disorders are available for example Mini-International Neuropsychiatric Interview (MINI), which is a structured diagnostic screening tool [61] or self-report questionnaires like the Depression, Anxiety, Stress Scale (DASS) [62]. These are however not validated for chronic pain populations. The American Association for pain advises to screen for the risk of addiction with the SOAPP and monitoring with the COMM in patients with chronic pain, but not screening for psychiatric disorders. Similarly, the guidelines for prescribing opioids for chronic pain from the CDC (2017) have no recommendations regarding psychiatric screening (www.cdc.gov) [28]. The current findings, however do argue for screening for psychiatric disorders in chronic pain patients before starting opioids.

Once identified, patients with comorbid psychiatric disorders need a multidisciplinary approach. This includes thorough clinical assessment of psychiatric disorders, and subsequent treatment if necessary. Early detection and treatment might benefit these patients and reduce the risk of poor opioid treatment outcome, like opioid use disorder or inadequate analgesia [17,33,56]. There are currently no studies that evaluate treatment of psychiatric disorders in chronic pain patients. Interdisciplinary collaboration, including in clinical trials among patients with CNCP and psychiatric comorbidity, is key to further improve treatment options for this vulnerable population [63].

Finally, monitoring opioid use (dosage, tolerance, withdrawal and craving symptoms) in chronic pain patients is warranted, in order to pick up signals of aberrant opioid use behaviors in an early stage. This seems particularly relevant in those with psychiatric comorbidity. Available screening tools include the 'Universal precautions in pain medicine' [64], the SOAPP-R (prediction) [65] and COMM (monitoring) [66,67]. Despite the imminent risks associated with opioid use in CNCP patients, it is important to emphasize that opioids are very effective analgesics when used appropriately. Hence, opioids continue to play an important role in the treatment of pain.

The current findings should be interpreted baring some limitations of current literature in mind. Assessment of opioid misuse was mainly based on self-report. Self-report might be less reliable and lead to an underestimation of problematic opioid use [24,35,37,39]. However, some studies included objective measures of problematic opioid use, for instance quantitative biomarkers, showing similar findings as studies using self-report [25,33]. In addition, studies use different opioid use end-points, ranging from a formal DSM diagnosis of opioid use disorder to more loosely defined problematic opioid use or aberrant behavior. This may lead to differences in outcome. For example, Fleming et al. [36] showed that only 1% of subjects with 1–3 aberrant behaviors met DSM IV-TR criteria for current opioid dependence, compared to 9.9% of patients with four or more aberrant behaviors. The same applies to the assessment of psychiatric symptomatology. Some rely on self-report, others assess DSM diagnoses based on structured clinical interviews. This impedes comparison of results across studies, or a meta-analysis approach. Yet, it has to be acknowledged that despite these differences in outcome measures, the pattern of association between psychiatric symptoms (mainly depression and anxiety) and problematic opioid use is rather consistent. It also has to be noted that a minority of studies [24,37,38,44] only evaluated depression and anxiety instead of a broader spectrum of psychiatric diagnoses, which may overestimate the role of depression and anxiety disorders. Other studies that did include other psychiatric domains confirm the relevance of depression and anxiety disorders. All studies took place in the US, which raises the question whether conclusions can be generalized to other countries. Studies in US and Europe show an ongoing increase in opioid prescriptions, but also identify differences in the so-called opioid epidemic between these two continents [2,4]. Finally, most studies were performed in specialized pain settings. This suggests a risk of selection bias. However, the studies with the largest sample sizes were based on

population data, including insurance claims. These much larger studies revealed findings similar to those in smaller scale studies in specialized pain clinic settings, which makes an effect of selection bias less likely.

5. Conclusion

This systematic review showed a significant association between psychiatric comorbidity, especially depression and anxiety and the development of problematic opioid use, more severe opioid craving and poor opioid treatment outcome in chronic pain patients. Based on the current findings we recommend psychiatric screening and a multidisciplinary approach in management of chronic pain. Monitoring opioid use is warranted in these patients, particularly in those with psychiatric comorbidity. For instance using the 'Universal precautions in pain medicine', SOAPP-R or COMM.

Declarations of interests

There are no relevant conflicts of interests inside the submitted work to declare.

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Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2019.04.008.

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