REVIEW

ADDICTION   SSA

Prevalence of problematic pharmaceutical opioid use in patients with chronic non-cancer pain: A systematic review and meta-analysis

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Abstract

Background and aims: Chronic non-cancer pain (CNCP) is one of the most common causes of disability globally. Opioid prescribing to treat CNCP remains widespread, despite limited evidence of long-term clinical benefit and evidence of harm such as problematic pharmaceutical opioid use (POU) and overdose. The study aimed to measure the prevalence of POU in CNCP patients treated with opioid analgesics.

Method: A comprehensive systematic literature review and meta-analysis was undertaken using MEDLINE, Embase and PsycINFO databases from inception to 27 January 2021. We included studies from all settings with participants aged ≥ 12 with non-cancer pain of ≥ 3 months duration, treated with opioid analgesics. We excluded case–control studies, as they cannot be used to generate prevalence estimates. POU was defined using four categories: dependence and opioid use disorder (D&OUD), signs and symptoms of D&OUD (S&S), aberrant behaviour (AB) and at risk of D&OUD. We used a random-effects multi-level meta-analytical model. We evaluated inconsistency using the I^2 statistic and explored heterogeneity using subgroup analyses and meta-regressions.

Results: A total of 148 studies were included with > 4.3 million participants; 1% of studies were classified as high risk of bias. The pooled prevalence was 9.3% [95% confidence interval (CI) = 5.7–14.8%; I^2 = 99.9%] for D&OUD, 29.6% (95% CI = 22.1–38.3%, I^2 = 99.3%) for S&S and 22% (95% CI = 17.4–27.3%, I^2 = 99.8%) for AB. The prevalence of those at risk of D&OUD was 12.4% (95% CI = 4.3–30.7%, I^2 = 99.6%). Prevalence was affected by study setting, study design and diagnostic tool. Due to the high heterogeneity, the findings should be interpreted with caution.

Conclusions: Problematic pharmaceutical opioid use appears to be common in chronic pain patients treated with opioid analgesics, with nearly one in 10 experiencing dependence and opioid use disorder, one in three showing signs and symptoms of dependence and opioid use disorder and one in five showing aberrant behaviour.

KEYWORDS
Meta-analysis, opioid analgesics, opioid dependence, opioid use disorder, prevalence, systematic review

INTRODUCTION

Chronic non-cancer pain (CNCP), defined as pain which is not cancer-related and which lasts for longer than 3 months, is one of the most common causes of disability globally [1]. Population-based studies have reported that almost one in five US adults and as many as one in two UK adults suffer with the condition, which is often managed in primary care settings [2, 3]. Despite limited evidence of long-term clinical benefit of opioids for CNCP and guidelines advising against their use for many pain conditions [4, 5], opioid analgesics continue to be widely prescribed (almost 31% of CNCP patients are prescribed opioids world-wide) [6]. In UK primary care patients, large increases in opioid prescriptions were observed from 2006 to 2017, including a five-fold increase in codeine prescriptions and a 30-fold increase in oxycodone prescriptions [7]. Nearly 6 million adults in England were dispensed an opioid pain medicine from 2017 to 2018 [8].

Long-term opioid prescribing has been associated with many harms, including accidental and fatal prescription opioid overdose, problematic pharmaceutical opioid use (POU) and transition to illicit use [9–11]. In the United States, overdose deaths caused by prescription opioid analgesics, illicit opioids such as heroin and synthetic opioids such as fentanyl contribute to a 'triple wave epidemic' which has been described as an opioid 'crisis' and declared as a public health emergency by the US Department of Health and Human Services [12, 13]. There is increasing concern in the United Kingdom regarding opioid use due to the widespread prescribing of opioids for CNCP and the increase in opioid-related fatalities [14]. Nearly 50% of all fatal overdoses included opioids (illicit heroin and morphine), and opioid-related hospitalizations increased by almost 50% in the decade from 2008 to 2018 [14]. A study comparing opioid use and related adverse effects among 19 European countries and the United States found that the United Kingdom had the highest consumption of prescription opioids, with the highest rates of opioid-related hospital admissions and overdose deaths observed in Scotland [15]. As there is less evidence that widespread opioid prescribing in the United Kingdom has directly led to addiction or been implicated in deaths, caution has been expressed about referring to the United Kingdom situation as an opioid 'epidemic' [16]. However, the Scottish Government declared opioid-related deaths as a public health emergency in 2021 [17]. Clinicians and policymakers need to have accurate estimates showing that the prevalence of POU in CNCP as POU, including opioid dependence and opioid use disorder, is associated with significant harms to individuals, families and society and is a huge public health burden [18]. An appreciation of the size of the problem is important to motivate and implement prevention strategies. These may include preventing initial exposure to opioids by use of other pain management interventions, clinician and patient education regarding opioids and caution with initiating opioid prescribing, screening and monitoring for opioid use disorders to enable early identification of individuals with POU and use of effective OUD treatment such as medications and behavioural therapy [19]. Other preventive strategies may focus on harm reduction such as the use of naloxone to prevent overdose deaths [18, 19].

Previous systematic reviews and meta-analyses aimed at estimating the prevalence of POU in CNCP patients have significant limitations [10, 20–25]. A major limitation is the inconsistency in defining POU with the use of multiple definitions and terminology (such as misuse, abuse, addiction, dependence, opioid use disorder, problematic use and aberrant behaviour). Although some of these terms (dependence, opioid use disorder, abuse) have been precisely defined in publications such as the Diagnostic and Statistical Manual (DSM) of Mental Disorders and the International Classification of Diseases (ICD), there is variation in how POU is classified throughout DSM and ICD editions [26, 27]. Other POU terms (misuse, addiction, problematic use, aberrant behaviour) are more imprecisely defined. Additional limitations include the small number of studies included in reviews and the lack of robustness of data aggregation using disparate and inconsistent POU definitions. This has resulted in huge variation in the reported prevalence rates for POU in CNCP, with rates ranging from almost negligible to more than 80% [10, 20–25]. A more accurate estimate of prevalence of POU in CNCP patients is required, as this is important for clinicians and policymakers to gauge the true extent of the problem, inform prescribing decisions and take appropriate action, including developing and implementing effective interventions to prevent and manage POU. In this review we aim to more robustly estimate the prevalence of POU in CNCP patients treated with opioid analgesics.

METHODS

Search strategy and selection criteria

In this systematic review and meta-analysis, inclusion criteria were adults and children aged ≥ 12 years and patients with a diagnosis of CNCP (defined as non-cancer pain of 3 months' duration or longer) who were prescribed or treated with prescription opioid analgesics. Studies in mostly or wholly paediatric populations (mean age < 18 years or small numbers of adult participants) or which focused solely upon use of illicit opioids and non-medical use of opioid analgesics were excluded. A comprehensive range of study designs was included as follows: cohort studies, longitudinal studies, cross-sectional studies (surveys), registry-based studies (e.g. claims data), incidence studies, retrospective chart reviews and other types of studies such as studies validating screening instruments and intervention studies which also measured POU, such as drug dependence/misuse or drug abuse liability. Case–control studies were excluded as the study design precludes the estimation of incidence or prevalence rates. Data were collected from a range of different settings, including primary care, pain clinics and other outpatient clinics, emergency departments, prescription databases, patient registries and toxicology databases. We included studies if they reported any POU, which was described in various ways in the literature, as follows: aberrant behaviour [28], abuse [29], addiction [30], substance dependence [29, 31, 32], misuse [30] and substance use disorder [33] (Supporting information, Table S1).

Electronic databases, including MEDLINE, Embase and PsycINFO via Ovid platform, were searched from their respective inception dates to 27 January 2021, with no language restrictions. Cited reference searches of selected and key articles were also searched to identify further papers for inclusion. The search strategy is provided in the Supporting information, Appendix, pp. 4–11.

For each study, two independent reviewers carried out a title and abstract screen based on the inclusion and exclusion criteria. Reviewers met to discuss and resolve any discrepancies which arose

TABLE 1 Definitions of the four problematic pharmaceutical opioid use (POU) categories used in this analysis.

	Definition
Dependence and Opioid Use Disorder	This category includes Dependence and Opioid Use Disorder (D&OUD) identified among study participants using Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Disease (ICD) diagnostic criteria/codes for opioid dependence or opioid use disorder as follows: Substance Use Disorder/Opioid Use Disorder Please see Supporting information, Table S1 for the definition of substance use disorder in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [33] Substance Dependence/Opioid Dependence There are multiple definitions of dependence which vary across different editions of the DSM and ICD as follows: DSM-III. A, Either pathological use or impairment in social or occupational functioning; B, either tolerance or withdrawal DSM-III-R. A, 3 of 9 symptoms; symptoms have equal weight; B, duration of symptoms for at least 1 month of symptoms occurred repeatedly over a longer period of time. Symptoms include: • Taking substance in larger amount or over longer period than intended • Persistent desire of unsuccessful efforts to cut down or control use • Spending a great deal of time to get or use the substance, or recover from its after-effects • Frequent intoxication or withdrawal when expected to fulfil major obligations • Giving up activities for substance use • Continuing to use despite problems • Tolerance • Withdrawal • Using substance to relieve or avoid withdrawal symptoms DSM-IV: Dependence is defined as the presence of three or more of the following criteria in a 12-month period: tolerance; withdrawal; increasing use over time; persistent or unsuccessful attempts to reduce use; preoccupation or excessive time spent on use or recovery from use; negative impact on social, occupational or recreational activity and continued use despite evidence of it causing psychological or physical problems ICD-10: Dependence is defined as a cluster of physiological, behavioural and cognitive phenomena that develop after repeated substance use and that typically include a strong desire to take the drug; difficulties in controlling its use; persisting in its use despite harmful consequences; increased tolerance and sometimes a physical withdrawal state ICD-11: Please see Supporting information, Table S1 for the definition of substance/opioid dependence using the ICD-11 diagnostic criteria [32]
Signs and symptoms of D&OUD	In this category, multiple behaviours indicative of D&OUD are shown by study participants without specific use of DSM or ICD diagnostic codes to identify D&OUD. It is differentiated from the category of aberrant behaviour (see below) by the clear presence of behaviours such as craving, tolerance, withdrawal or a loss of control over use (for example continued use despite psychological or physical harm or use which takes priority over usual obligations) Diagnostic tools or methods of assessment included clinical judgement, self-assessment with questionnaires, structured interviews (including adapted questions of the World Health Organization's Composite International Diagnostic Interview (WHO CIDI), use of the abuse index, Current Opioid Misuse Measure (COMM), Portenoy's criteria, Prescribed Opioids Difficulties Scale (PODS), Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), Prescription Drug Use Questionnaire (PDUQ), Drug Misuse Index (DMI).
Aberrant behaviour	In this category, study participants show one or more examples of aberrant behaviour, such as inappropriate drug-seeking behaviour, seeking early refills, repeated dose escalations, frequently lost prescriptions, seeking drugs from multiple providers and positive or inappropriate urinalysis/urine drug screens These behaviours do not meet threshold for dependence or opioid use disorder (for example there is the absence of craving, tolerance, withdrawal, ongoing use despite physical harm or exacerbation of psychological problems) Diagnostic tools or methods of assessment included clinical judgement, structured interview, self-report, UDT, Pain Medication Questionnaire (PMQ), Aberrant Drug Behaviour Index (ADBI), Chabal criteria, insurance claims, questionnaires, Prescription Opioid Misuse Index (POMI), Screener and Opioid Assessment for Patients with Pain (SOAPP) and the revised version (SOAPP-R), dose escalation, opioid misuse score.
At risk of D&OUD	In this category study participants exhibit characteristics which may increase their risk of developing opioid dependence or opioid use disorder in the future, however, they do not show aberrant behaviour or meet criteria for dependence or opioid use disorder Diagnostic tools included clinical judgement, structured interviews and questionnaires including the Opioid Risk Tool (ORT).

at team meetings. A full text review of the studies retained at this stage was undertaken by two independent reviewers.

The protocol for this study is registered in the PROSPERO database (CRD42019132364). The systematic review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [34].

Data extraction

Data from the included studies were extracted by the team of reviewers onto a standardized data extraction form. All extracted data

were checked by an independent reviewer to ensure the accuracy of data extraction. Queries were noted, discussed and resolved at team meetings.

The following data were extracted: title, authors, year of publication, study design, study location, setting, overall sample size, population studied, type and duration of CNCP, sample demographics, treatment duration, type of prescribed opioids, authors' classification of POU, measurement or diagnostic tools and methods of assessment used to establish POU (see Lawrence *et al.* (2017) for a detailed review of validated measurement tools [35] and the next section for definitions and categorization), prevalence rate of problematic opioid use and the numerators and denominators used to calculate

Identification of studies via databases and other sources

Identification

Records identified from databases:
MEDLINE (2736); PsycINFO (1174); Embase (4042); Ovid XS (OUD) (482)
n = 8434

Other sources: *n* = 13

Total, *n* = **8447**

→ Duplicate records removed before screening:
n = **2586**

Screening

Records screened *n* = **5861**

→ Records excluded *n* = **5278**

Eligibility

Full-text articles assessed for eligibility
n = **583**

→ Full-text articles excluded, *n* = **349**

  Ineligible population (179)
  Ineligible outcome (65)
  Ineligible publication type (59)
  Ineligible study design (11)
  Multiple reasons (35)

+ Secondary articles, *n* = **39**
+ Awaiting classification, *n* = **47**

Included

Studies included in qualitative synthesis
n = **148**

Studies included in quantitative synthesis (meta-analysis)
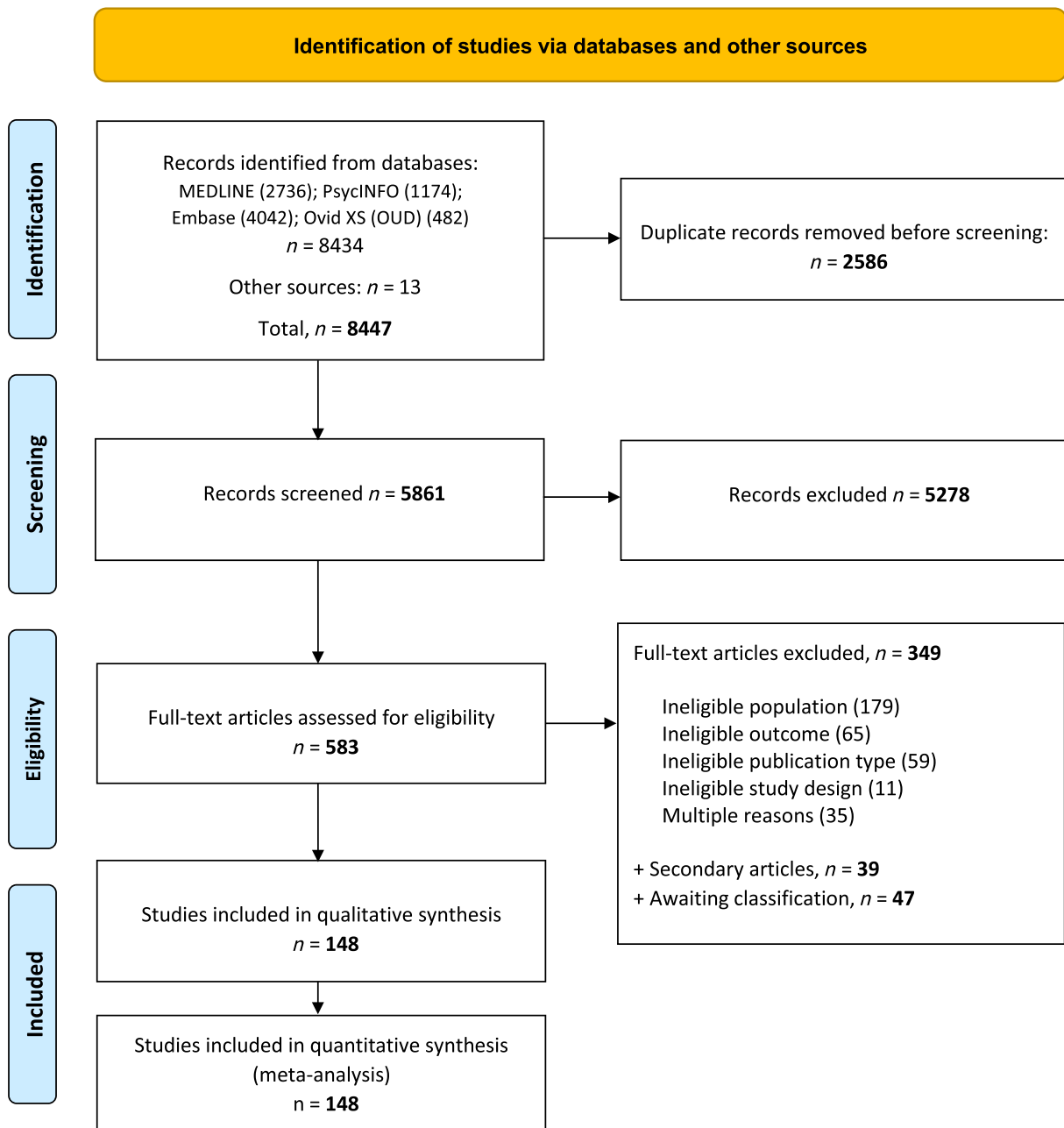n = **148**

FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) flow diagram for study records.

prevalence estimates. We contacted authors of studies for further clarification or to obtain non-published data.

We extracted the definitions of POU reported by the study authors. We used similar methodology to Vowles et al. (2015), and extracted and recorded prevalence rates for POU to one decimal place [25]. Where a study reported multiple rates for a single POU outcome we recorded all estimates. If prevalence rates were not explicitly reported within the manuscripts, we calculated the rates manually.

Data analysis

We defined four categories of POU as follows: (i) dependence and opioid use disorder (D&OUD) identified using diagnostic codes, (ii) signs and symptoms of D&OUD, (iii) aberrant behaviour and (iv) at risk of D&OUD (Table 1). Four reviewers were involved in categorizing POU outcomes. Reviewers dealt with disagreements regarding categorization of POU outcomes via multiple discussions until consensus was reached. Details of the definitions used by study authors for each outcome and their subsequent categorizations are provided in the Supporting information, Appendix, pp. 31–86.

We assessed risk of bias using 10 items addressing four domains of bias (selection bias, non-response bias, measurement bias and analysis bias) by Hoy et al. (2012) [36], plus a summary risk of bias assessment (the rater's subjective judgement based on responses to the preceding items). Items were scored as 'yes' (low risk) or 'no' (high risk) and the summary risk of bias was assessed as 'low', 'moderate' or 'high' based on whether further research was very unlikely (low), likely (moderate) or very likely (high) to have an important impact on our confidence in the estimate and to change it.

As some studies reported multiple prevalence results for the same outcome, we followed a strategy by López-López et al. (2018) using a convergent and integrative approach to meta-analysis [37]. Specifically, we used a multi-level meta-analytical model described by Konstantopoulos (2011) [38], which included random effects at both study and measurement levels. As some studies reported multiple prevalence results within the same pools of participants using different measurement tools or criteria, we assumed prevalence estimates within studies are correlated and incorporated this within the model. Prevalence results were logit-transformed before applying the synthesis model, and then back-transformed and reported in percentages for ease of interpretation. We applied cluster-robust inference methods to minimize potential misspecification of the model [39, 40]. The I^2 statistic was used to quantify inconsistency [41]. We calculated the overall I^2 statistic using the between- and within-cluster heterogeneities proposed by Nakagawa & Santos (2012) [42]. To aid the

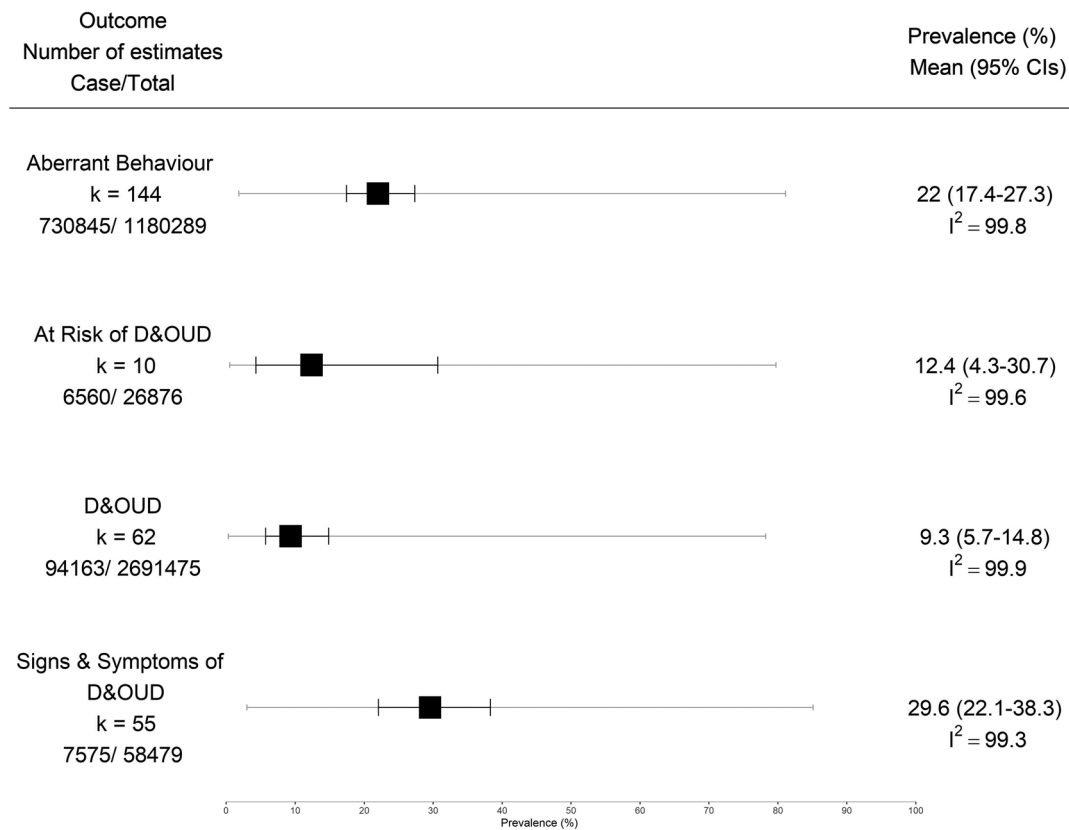| Outcome Number of estimates Case/Total	Prevalence (%) Mean (95% CIs)
Aberrant Behaviour k = 144 730845/ 1180289	22 (17.4-27.3) $I^2 = 99.8$
At Risk of D&OUD k = 10 6560/ 26876	12.4 (4.3-30.7) $I^2 = 99.6$
D&OUD k = 62 94163/ 2691475	9.3 (5.7-14.8) $I^2 = 99.9$
Signs & Symptoms of D&OUD k = 55 7575/ 58479	29.6 (22.1-38.3) $I^2 = 99.3$

FIGURE 2 Prevalence of all problematic opioid use outcomes. Squares represent mean pooled prevalence estimates and error bars represent 95% confidence intervals. Grey bar across the square and error bars shows 95% prediction intervals.

Forest plot: Dependence & Opioid Use Disorder

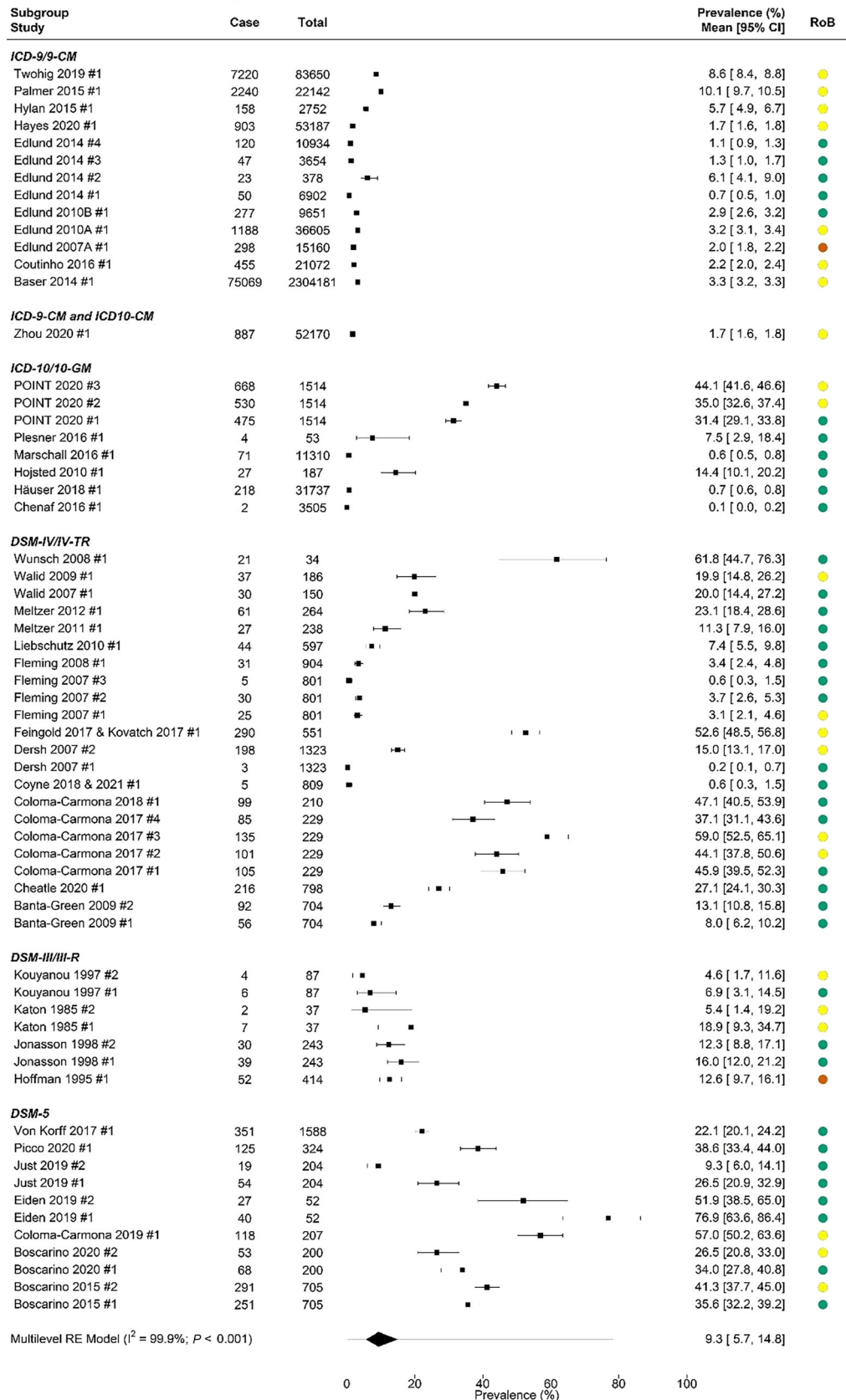| Subgroup / Study	Case	Total	Prevalence (%) Mean [95% CI]	RoB
ICD-9/9-CM				
Twohig 2019 #1	7220	83650	8.6 [8.4, 8.8]	yellow
Palmer 2015 #1	2240	22142	10.1 [9.7, 10.5]	yellow
Hylan 2015 #1	158	2752	5.7 [4.9, 6.7]	yellow
Hayes 2020 #1	903	53187	1.7 [1.6, 1.8]	yellow
Edlund 2014 #4	120	10934	1.1 [0.9, 1.3]	green
Edlund 2014 #3	47	3654	1.3 [1.0, 1.7]	green
Edlund 2014 #2	23	378	6.1 [4.1, 9.0]	green
Edlund 2014 #1	50	6902	0.7 [0.5, 1.0]	green
Edlund 2010B #1	277	9651	2.9 [2.6, 3.2]	green
Edlund 2010A #1	1188	36605	3.2 [3.1, 3.4]	green
Edlund 2007A #1	298	15160	2.0 [1.8, 2.2]	red
Coutinho 2016 #1	455	21072	2.2 [2.0, 2.4]	green
Baser 2014 #1	75069	2304181	3.3 [3.2, 3.3]	yellow
ICD-9-CM and ICD10-CM				
Zhou 2020 #1	887	52170	1.7 [1.6, 1.8]	yellow
ICD-10/10-GM				
POINT 2020 #3	668	1514	44.1 [41.6, 46.6]	yellow
POINT 2020 #2	530	1514	35.0 [32.6, 37.4]	yellow
POINT 2020 #1	475	1514	31.4 [29.1, 33.8]	green
Plesner 2016 #1	4	53	7.5 [2.9, 18.4]	green
Marschall 2016 #1	71	11310	0.6 [0.5, 0.8]	green
Hojsted 2010 #1	27	187	14.4 [10.1, 20.2]	green
Häuser 2018 #1	218	31737	0.7 [0.6, 0.8]	green
Chenaf 2016 #1	2	3505	0.1 [0.0, 0.2]	green
DSM-IV/IV-TR				
Wunsch 2008 #1	21	34	61.8 [44.7, 76.3]	green
Walid 2009 #1	37	186	19.9 [14.8, 26.2]	yellow
Walid 2007 #1	30	150	20.0 [14.4, 27.2]	green
Meltzer 2012 #1	61	264	23.1 [18.4, 28.6]	green
Meltzer 2011 #1	27	238	11.3 [7.9, 16.0]	green
Liebschutz 2010 #1	44	597	7.4 [5.5, 9.8]	green
Fleming 2008 #1	31	904	3.4 [2.4, 4.8]	green
Fleming 2007 #3	5	801	0.6 [0.3, 1.5]	green
Fleming 2007 #2	30	801	3.7 [2.6, 5.3]	green
Fleming 2007 #1	25	801	3.1 [2.1, 4.6]	yellow
Feingold 2017 & Kovatch 2017 #1	290	551	52.6 [48.5, 56.8]	yellow
Dersh 2007 #2	198	1323	15.0 [13.1, 17.0]	yellow
Dersh 2007 #1	3	1323	0.2 [0.1, 0.7]	green
Coyne 2018 & 2021 #1	5	809	0.6 [0.3, 1.5]	green
Coloma-Carmona 2018 #1	99	210	47.1 [40.5, 53.9]	green
Coloma-Carmona 2017 #4	85	229	37.1 [31.1, 43.6]	green
Coloma-Carmona 2017 #3	135	229	59.0 [52.5, 65.1]	yellow
Coloma-Carmona 2017 #2	101	229	44.1 [37.8, 50.6]	green
Coloma-Carmona 2017 #1	105	229	45.9 [39.5, 52.3]	green
Cheatle 2020 #1	216	798	27.1 [24.1, 30.3]	green
Banta-Green 2009 #2	92	704	13.1 [10.8, 15.8]	green
Banta-Green 2009 #1	56	704	8.0 [6.2, 10.2]	green
DSM-III/III-R				
Kouyanou 1997 #2	4	87	4.6 [1.7, 11.6]	yellow
Kouyanou 1997 #1	6	87	6.9 [3.1, 14.5]	green
Katon 1985 #2	2	37	5.4 [1.4, 19.2]	yellow
Katon 1985 #1	7	37	18.9 [9.3, 34.7]	yellow
Jonasson 1998 #2	30	243	12.3 [8.8, 17.1]	green
Jonasson 1998 #1	39	243	16.0 [12.0, 21.2]	green
Hoffman 1995 #1	52	414	12.6 [9.7, 16.1]	red
DSM-5				
Von Korff 2017 #1	351	1588	22.1 [20.1, 24.2]	green
Picco 2020 #1	125	324	38.6 [33.4, 44.0]	green
Just 2019 #2	19	204	9.3 [6.0, 14.1]	green
Just 2019 #1	54	204	26.5 [20.9, 32.9]	green
Eiden 2019 #2	27	52	51.9 [38.5, 65.0]	green
Eiden 2019 #1	40	52	76.9 [63.6, 86.4]	green
Coloma-Carmona 2019 #1	118	207	57.0 [50.2, 63.6]	yellow
Boscarino 2020 #2	53	200	26.5 [20.8, 33.0]	yellow
Boscarino 2020 #1	68	200	34.0 [27.8, 40.8]	green
Boscarino 2015 #2	291	705	41.3 [37.7, 45.0]	yellow
Boscarino 2015 #1	251	705	35.6 [32.2, 39.2]	green
Multilevel RE Model (I^2 = 99.9%; P < 0.001)			9.3 [5.7, 14.8]	

Prevalence (%) axis: 0 20 40 60 80 100

FIGURE 3 Forest plot of Dependence and Opioid Use Disorder. Squares represent mean prevalence estimates and error bars represent 95% confidence intervals of each result from studies. Diamond shows the mean pooled estimate and the 95% confidence intervals. Grey bar across the diamond shows 95% prediction intervals. Risk of bias (ROB); red: high, yellow: moderate, green: low.
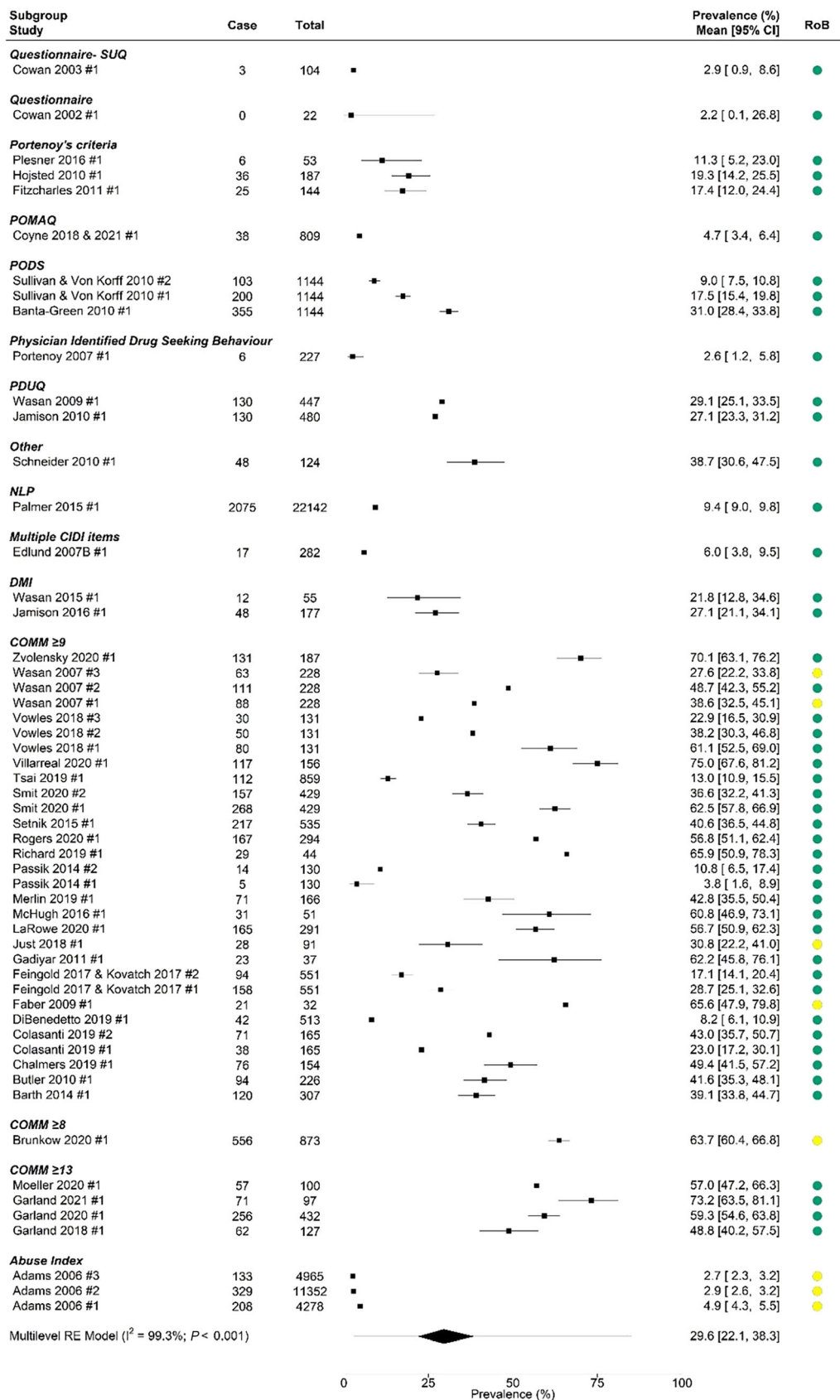
Forest plot: Signs and Symptoms

Subgroup Study	Case	Total	Prevalence (%) Mean [95% CI]	RoB
Questionnaire- SUQ				
Cowan 2003 #1	3	104	2.9 [0.9, 8.6]	●
Questionnaire				
Cowan 2002 #1	0	22	2.2 [0.1, 26.8]	●
Portenoy's criteria				
Plesner 2016 #1	6	53	11.3 [5.2, 23.0]	●
Hojsted 2010 #1	36	187	19.3 [14.2, 25.5]	●
Fitzcharles 2011 #1	25	144	17.4 [12.0, 24.4]	●
POMAQ				
Coyne 2018 & 2021 #1	38	809	4.7 [3.4, 6.4]	●
PODS				
Sullivan & Von Korff 2010 #2	103	1144	9.0 [7.5, 10.8]	●
Sullivan & Von Korff 2010 #1	200	1144	17.5 [15.4, 19.8]	●
Banta-Green 2010 #1	355	1144	31.0 [28.4, 33.8]	●
Physician Identified Drug Seeking Behaviour				
Portenoy 2007 #1	6	227	2.6 [1.2, 5.8]	●
PDUQ				
Wasan 2009 #1	130	447	29.1 [25.1, 33.5]	●
Jamison 2010 #1	130	480	27.1 [23.3, 31.2]	●
Other				
Schneider 2010 #1	48	124	38.7 [30.6, 47.5]	●
NLP				
Palmer 2015 #1	2075	22142	9.4 [9.0, 9.8]	●
Multiple CIDI items				
Edlund 2007B #1	17	282	6.0 [3.8, 9.5]	●
DMI				
Wasan 2015 #1	12	55	21.8 [12.8, 34.6]	●
Jamison 2016 #1	48	177	27.1 [21.1, 34.1]	●
COMM ≥9				
Zvolensky 2020 #1	131	187	70.1 [63.1, 76.2]	●
Wasan 2007 #3	63	228	27.6 [22.2, 33.8]	●
Wasan 2007 #2	111	228	48.7 [42.3, 55.2]	●
Wasan 2007 #1	88	228	38.6 [32.5, 45.1]	●
Vowles 2018 #3	30	131	22.9 [16.5, 30.9]	●
Vowles 2018 #2	50	131	38.2 [30.3, 46.8]	●
Vowles 2018 #1	80	131	61.1 [52.5, 69.0]	●
Villarreal 2020 #1	117	156	75.0 [67.6, 81.2]	●
Tsai 2019 #1	112	859	13.0 [10.9, 15.5]	●
Smit 2020 #2	157	429	36.6 [32.2, 41.3]	●
Smit 2020 #1	268	429	62.5 [57.8, 66.9]	●
Setnik 2015 #1	217	535	40.6 [36.5, 44.8]	●
Rogers 2020 #1	167	294	56.8 [51.1, 62.4]	●
Richard 2019 #1	29	44	65.9 [50.9, 78.3]	●
Passik 2014 #2	14	130	10.8 [6.5, 17.4]	●
Passik 2014 #1	5	130	3.8 [1.6, 8.9]	●
Merlin 2019 #1	71	166	42.8 [35.5, 50.4]	●
McHugh 2016 #1	31	51	60.8 [46.9, 73.1]	●
LaRowe 2020 #1	165	291	56.7 [50.9, 62.3]	●
Just 2018 #1	28	91	30.8 [22.2, 41.0]	●
Gadiyar 2011 #1	23	37	62.2 [45.8, 76.1]	●
Feingold 2017 & Kovatch 2017 #2	94	551	17.1 [14.1, 20.4]	●
Feingold 2017 & Kovatch 2017 #1	158	551	28.7 [25.1, 32.6]	●
Faber 2009 #1	21	32	65.6 [47.9, 79.8]	●
DiBenedetto 2019 #1	42	513	8.2 [6.1, 10.9]	●
Colasanti 2019 #2	71	165	43.0 [35.7, 50.7]	●
Colasanti 2019 #1	38	165	23.0 [17.2, 30.1]	●
Chalmers 2019 #1	76	154	49.4 [41.5, 57.2]	●
Butler 2010 #1	94	226	41.6 [35.3, 48.1]	●
Barth 2014 #1	120	307	39.1 [33.8, 44.7]	●
COMM ≥8				
Brunkow 2020 #1	556	873	63.7 [60.4, 66.8]	●
COMM ≥13				
Moeller 2020 #1	57	100	57.0 [47.2, 66.3]	●
Garland 2021 #1	71	97	73.2 [63.5, 81.1]	●
Garland 2020 #1	256	432	59.3 [54.6, 63.8]	●
Garland 2018 #1	62	127	48.8 [40.2, 57.5]	●
Abuse Index				
Adams 2006 #3	133	4965	2.7 [2.3, 3.2]	●
Adams 2006 #2	329	11352	2.9 [2.6, 3.2]	●
Adams 2006 #1	208	4278	4.9 [4.3, 5.5]	●
Multilevel RE Model (I^2 = 99.3%; P< 0.001)			29.6 [22.1, 38.3]	

Prevalence (%) — 0, 25, 50, 75, 100

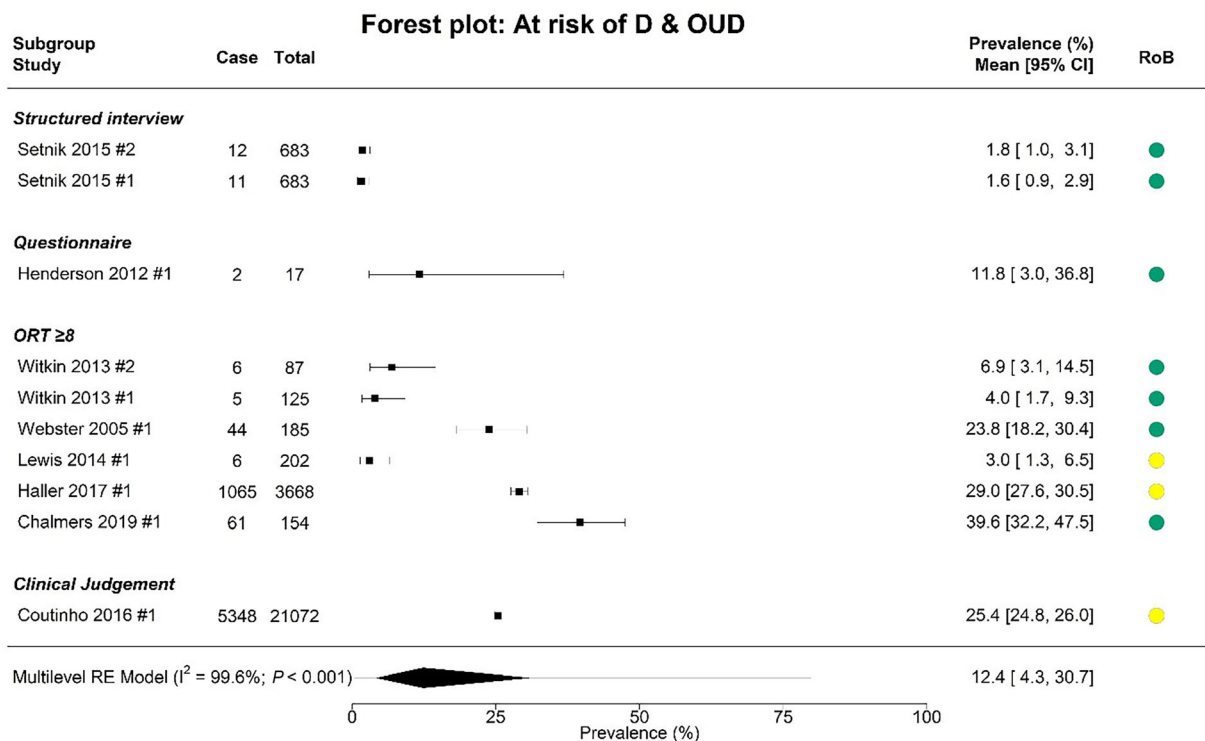**FIGURE 4** Forest plot of signs and symptoms of Dependence and Opioid Use Disorder. Squares represent mean prevalence estimates and error bars represent 95% confidence intervals of each result from studies. Diamond shows the mean pooled estimate and the 95% confidence intervals. Grey bar across the diamond shows 95% prediction intervals. Risk of bias (ROB); red: high, yellow: moderate, green: low.

interpretation of heterogeneity we also present prediction intervals [43] and between-study variances in the forest plots. All models were fitted using restricted maximum likelihood estimation. The detailed statistical model is presented in the Supporting information, Appendix, p. 30.

We carried out subgroup analyses and evaluated potential sources of heterogeneity between studies by adding potential moderators as fixed effects to the multi-level model. We used meta-regression models to examine the influence of potential moderators (mean age, sex (proportion female), ethnicity (proportion white), publication year, study design (cohort, cross-sectional, interventional, retrospective chart review, other), study location (Asia, Australasia, Europe, Middle East, North America, multiple), setting (pain clinic, primary care, registry/database, secondary and tertiary care, emergency department, mixed setting), duration of pain [short (< 1 year), medium (1–4 years), long (> 4 years)], diagnostic criteria/method of assessment and overall risk of bias (low, moderate, high) on the size of the mean prevalence. We also analysed subordinate components of the risk of bias according to Migliavaca *et al.* (2020) in binary (yes/no) categories as follows: appropriate definition of condition, appropriate sampling, appropriate measurements, appropriate response rate, appropriate follow-up length, appropriate data collection and appropriate statistics [44].

Sensitivity analyses were carried out by altering the assumption of interdependency between prevalence results within studies and using Freeman–Tukey double arcsine transformation. Sensitivity analyses were not conducted on risk of bias due to the very low number of studies rated as having high risk of bias. All analyses were carried out in R statistical computing software, version 4.3.0 using the *metafor*, *clubSandwich* and *ggplot2* packages [45–47].

RESULTS

Figure 1 provides the flow-chart for our screening process. We identified 8447 records from database searching and other sources. A total of 5861 records were screened for inclusion; 5278 were excluded at title and abstract stage (due to reasons such as wrong study design-treatment studies, acute postoperative studies, opinion pieces, general surveys, single case reports), with 583 reviewed at full text. A total of 148 studies (reported in 148 publications) were included in the final review [48–195], in the Supporting information, Appendix, pp. 12–21. Four publications reported data for more than one study [89, 134, 162, 173], while data from three studies were reported in multiple publications [83, 84, 96, 129, 137, 139, 140]. Our searches also retrieved multiple publications associated with the Pain and Opioids in Treatment (POINT) cohort study [26, 27, 65, 196–200]. For the POINT study, we used data obtained directly from study authors in our analyses.

Study characteristics are reported by study in the Supporting information, Appendix, Table S2. Most studies had a cohort or cross-sectional study design (66 and 57 studies, respectively). There were six interventional studies. Most studies (115/148) were conducted in

the United States, with 24 in Europe (including five in the United Kingdom, three in France and four each for Spain and Germany), two in Australia and seven in other countries. Fifty-four studies were carried out in pain clinics, 28 in primary care and there were 23 registry/database studies.

Overall, 4 301 910 participants were included, with study size ranging from 15 to 2 304 181. There was variability in the reporting of demographic data, with 75% reporting mean or median data for age, 93% reporting sex and 51% reporting participants' ethnicity; 69% of studies provided information on the type of pain, 76% on the duration of pain and 56% on specific prescription opioids used.

One hundred and nine (74%) studies were classified as low risk of bias, with 25% considered to be at moderate risk of bias and 1% classified as high risk of bias. Most studies classified as moderate or high risk of bias did not have a sample representative of the national population, did not use an acceptable case definition, did not use a study instrument shown to have validity and reliability and did not report an appropriate length of the prevalence period for the parameter of interest (duration of chronic pain).

The frequency tables of reported prevalence results and studies are presented in the Supporting information, Appendix, p. 87, Tables S7–S10. A summary forest plot of the prevalence estimates by outcome using the logit transformation is shown in Figure 2. Forest plots for each POU outcome by study and overall risk of bias assessment and including prediction intervals are reported in Figures 3–6.

Forty-three studies reported D&OUD (62 prevalence estimates, sample size n = 2 691 475). The pooled prevalence of D&OUD was 9.3% [95% confidence interval (CI) = 5.7–14.8; I^2 99.9%; Figure 3]. Diagnostic tool (method of assessment) was a strong predictor of prevalence (Supporting information, Appendix, pp. 99–100, Table S19). Subgroup analyses by ICD or DSM diagnostic tool (Supporting information, Appendix, p. 108, Figure S14) showed the lowest DOUD prevalence rates when ICD-9 and ICD-10 codes were used; these were 3% (95% CI = 1.7–5.3; I^2 97.2%) and 2.4% (95% CI = 0.2–26.3; I^2 99.7%), respectively. Higher prevalence rates were observed using DSM-III (9.9%, 95% CI = 4.6–19.8; I^2 94.9%), DSM-IV (13.1%, 95% CI = 5.5–28.2; I^2 99.4%) and DSM-5 (36.7%, 95% CI = 21.0–55.9; I^2 97.6%). In addition to the method of assessment used, we found significant differences in the prevalence of DOUD according to study setting, study design and two components of the risk of bias assessment—appropriate response rate and appropriate data collection. The highest prevalence rates were seen in pain clinics (29.2%, 95% CI = 13.1–53.0; I^2 98.9%) and mixed settings (31.0%, 95% CI = 7.2–72.4; I^2 98.4%) and the lowest observed in registry/database studies (1.9%, 95% CI = 1.0–3.5; I^2 98.8%). Studies which were assessed as not having an appropriate response rate on the risk of bias tool reported higher prevalence than those with an appropriate response rate (Supporting information, Appendix, p. 109, Figure S15); the converse was seen for those studies which reported appropriate data collection versus those that did not (Supporting information, Appendix, p. 110, Figure S16).

Forty-four studies reported signs and symptoms of D&OUD (55 prevalence estimates, sample size n = 58 479). The pooled

FIGURE 5 Forest plot of aberrant behaviour. Squares represent mean prevalence estimates and error bars represent 95% confidence intervals of each result from studies. Diamond shows the mean pooled estimate and the 95% confidence intervals. Grey bar across the diamond shows 95% prediction intervals. Risk of bias (ROB); red: high, yellow: moderate, green: low.

prevalence of signs and symptoms of D&OUD was 29.6% (95% CI = 22.1–38.3; I^2 99.3%; Figure 4). The method of assessment or diagnostic tool used strongly influenced prevalence rates; the highest rates were seen with the three different cut-offs using the COMM tool (Supporting information, Appendix, p. 113, Figure S20). Study setting, publication year and the appropriate measurements component of the risk of bias assessment also contributed significantly to the observed heterogeneity in the prevalence of signs and symptoms of DOUD (Supporting information, Appendix, Table S20). The highest rates were seen in on-line settings, emergency departments and in primary care (Supporting information, Appendix, p. 112, Figure S19). Low rates were observed in other settings and where the setting was not specified. Studies with higher scores on the risk of bias assessment related to appropriate measurements reported higher prevalence estimates than those with a lower score (Supporting information, Appendix, p. 114, Figure S21).

Seventy-nine studies reported aberrant behaviour (144 prevalence estimates, n = 1 180 289). The pooled prevalence of aberrant behaviour was 22% (95% CI = 17.4–27.3; I^2 99.8%; Figure 4). We found some evidence of a significant difference in prevalence of aberrant behaviour according to study design and diagnostic tool (Supporting information, Appendix, pp. 103–104, Table S21), albeit weaker than for DOUD and signs and symptoms of DOUD. The highest rates were reported in cross-sectional studies (Supporting information, Appendix, p. 115, Figure S22) and those using the Screener and Opioid Assessment for Patients with Pain (SOAPP) tool (cut-off ≥ 7) and the Pain Medication Questionnaire (PMQ) (≥ 22), in the Supporting information, Appendix, p. 116, Figure S23. There was also some evidence for a significant effect of two components of the risk of bias assessment (Supporting information, Appendix, pp. 117–118, Figures S24 and S25), appropriate sampling (highest prevalence reported for those studies which scored the lowest on the checklist, in the Supporting information, Appendix, Figure S24) and appropriate follow-up length (highest prevalence for those studies which did not have an appropriate follow-up length, in the Supporting information, Appendix, Figure S25).

Eight studies assessed the prevalence for at-risk of D&OUD (10 prevalence, estimates, n = 26 876). The pooled prevalence was 12.4% (95% CI = 4.3–30.7; I^2 99.6%; Figure 5). We did not find any evidence for a significant difference in the prevalence of at-risk of D&OUD for any of the potential moderators investigated (Supporting information, Appendix, pp. 105–106, Table S22).

Sensitivity analyses using different transformation models (Supporting information, Appendix, pp. 93–94, Tables S15–S18) showed an impact of these on the results of the meta-analyses. As the differences in the prevalence estimates were minimal across the two transformation methods, the differences are likely to be explained by differences in the sampling variances for the different transformations, leading to different heterogeneity variance estimates and therefore different study weights in the meta-analysis (Supporting information, Appendix, pp. 95–96, Figures S5–S8). In contrast, the interdependency assumption had little impact on the pooled prevalence estimates (Supporting information, Appendix, pp. 97–98, Figures S9–S12).

DISCUSSION

Principal findings

The prevalence of POU is high with almost one in 10 people identified as D&OUD using diagnostic criteria or at risk of D&OUD, one in three showing S&S of D&OUD and one in five showing aberrant behaviour. However, there was considerable heterogeneity between studies across outcomes and variation in relation to classification and measurement of outcomes. Several moderators, including diagnostic tool (or method of assessment), study setting and specific items on the risk of bias tool, were found to be associated with the pooled prevalence estimates. The evidence was predominantly from North American studies and high-income countries, and we did not detect consistent differences by study location.

Strengths and weaknesses

A major strength of this study is the comprehensive search for studies, which resulted in the inclusion of 148 studies and more than 4.3 million patients in the final review. The largest previous review, by Vowles et al. (2015) [25], included 38 studies and a little over 1 million participants [10, 20–25]. There was huge variability in studies reporting POU due to the interchangeable use of terms such as abuse, dependence, addiction and misuse by study authors and the lack of

consistency in the definitions of POU identified using the same measurement tool. Unlike Vowles et al. (2015), who re-categorized study outcomes as misuse, abuse and addiction, most of the previous reviews summarized results based on study authors' definitions. Therefore, the second main strength of this study is our attempt to address this variability by categorizing POU more robustly. Thirdly, we carried out subgroup analyses and meta-regression for multiple factors, including the measurement or diagnostic tool used to identify POU, to explore some of the observed heterogeneity.

There are several limitations. A single study (Baser et al., 2014) [56], contributed to 54% of the entire sample. Few studies were reported from lower- and middle-income countries, with no data available from Africa, South America or the Caribbean. This may explain the lack of geographical differences found among the studies. Another limitation is the lack of clear evidence on the generalizability of the prevalence estimates and the extent to which they can be extrapolated to other populations. Fourthly, although we carried out random-effects meta-analyses to capture uncertainty resulting from heterogeneity among studies, our pooled analyses showed extremely high inconsistency (shown by I^2) and heterogeneity (shown by prediction intervals within the forest plots). This variability among studies may limit the generalizability and reliability of the findings and further underscores the need for caution when interpreting the results. The high levels of inconsistency persisted within subgroups even when the same method of assessment was used. Our exploration of heterogeneity using meta-regression and subgroup analyses found significant evidence that moderators such as study

FIGURE 6 Forest plot of at risk of Dependence and Opioid Use Disorder (D&OUD). Squares represent mean prevalence estimates and error bars represent 95% confidence intervals of each result from studies. Diamond shows the mean pooled estimate and the 95% confidence intervals. Grey bar across the diamond shows 95% prediction intervals. Risk of bias (ROB); red: high, yellow: moderate, green: low.

TABLE 2 Comparison of findings throughout systematic reviews of studies reporting problematic opioid use outcomes in chronic non-cancer pain patients.

	Current study	Noble et al. 2008	Morasco et al. 2011	Minozzi et al. 2013	Chou et al. 2015	Vowles et al. 2015	Higgins et al. 2018
Population	Patients with chronic non-cancer pain prescribed opioids	Patients with chronic non-cancer pain treated with opioids for ≥ 6 months	Patients with chronic non-cancer pain	Patients receiving treatment with strong opioids for acute or chronic pain due to any physical condition	Patients with chronic pain receiving long-term opioid therapy ≥ 3 months	Patients with chronic non-cancer pain using opioids orally	Patients with pain who were exposed to opioid analgesic therapy
Abuse	Not reported	0.43%. Two studies included. Abuse not clearly defined, based on study authors' reporting. Lack of clarity and inconsistency of reporting of abuse	Not reported	Not reported	0.6–8%. Varied measurement of outcome. Three studies	8%. Varied measurement of outcome. One study	4.7% (range = 0.2–34.2%)*. Clinical diagnosis of opioid dependence or abuse disorder, established in studies by the use of DSM or ICD criteria or clinician assessment. 12 studies
Addiction	Not reported	0.042%. Seven studies included. Addiction not clearly defined, based on study authors' reporting. Lack of clarity and inconsistency in reporting of addiction	Not reported	Not reported	2–14%. Varied measurement of outcome. Seven studies	8–12%. (95% CI = 3–17%). Varied measurement. 12 studies	Not reported
Dependence[†]	9.3%. D&OUD defined using diagnostic codes (95% CI = 5.7–14.8%) 29.6%. S&S of D&OUD (95% CI = 22.1–38.3%)	Not reported	Not reported	Median = 4.5% (range = 0–31%) Median = 0.5% (range = 0–24%)* 17 studies included, 15 studies included only patients with non-cancer pain. 14 studies included only adult patients with choric pain. DSM-IV or ICD-10 categories used to define dependence	3–26%. Varied measurement of outcome. Three studies	Not reported	4.7% (range = 0.2–34.2%)* Clinical diagnosis of opioid dependence or abuse disorder, established in studies by the use of DSM or ICD criteria or clinician assessment. 12 studies

TABLE 2 (Continued)

	Current study	Noble et al. 2008	Morasco et al. 2011	Minozzi et al. 2013	Chou et al. 2015	Vowles et al. 2015	Higgins et al. 2018
Substance use disorder[†]	9.3%- D&OUD diagnostic codes (95% CI = 5.7–14.8%) 29.6%. S&S of D&OUD (95% CI = 22.1–38.3%)	Not reported	3–43% (current). Four studies included- prescribed opioids. SUD defined using investigators' operational definitions for categorization and included positive urine screens for illicit substances, self-reported history of SUD, medical record documentation of SUD status, responses on validated self-report measures as well as structured clinical interviews or diagnostic interviews	Not reported	Not reported	Not reported	4.7% (range = 0.2–34.2%)*. Clinical diagnosis of opioid dependence or abuse disorder, established in studies by the use of DSM or ICD criteria or clinician assessment. 12 studies
Misuse	Not reported	Not reported	Not reported	Not reported	8–16%, varied measurement of outcome. Seven studies	21–29% (95% CI = 13–38%). Varied measurement of outcome. 29 studies	Not reported

Abbreviation: SUD = Substance Use Disorder.

*Incidence rates are reported instead of prevalence rates. [†]In our analysis substance dependence is combined with Opioid Use Disorder. Rates for Dependence and Opioid Use Disorder (D&OUD) identified using diagnostic criteria and signs and symptoms (S&S) of D&OUD are included.

design, study setting and diagnostic tool/method of assessment impacted upon prevalence estimates. The heterogeneity caused by diagnostic tool may be explained by the variations in the definitions used by different DSM and ICD editions. For example, whereas the DSM-IV defined dependence and abuse as separate POU outcomes, DSM-5 combined these two definitions into a single classification of opioid use disorder [201]. Additionally, the definition for dependence in DSM-IV differed from the ICD definitions for dependence [202]. Study setting was also an important moderator; the lowest prevalence of D&OUD was observed in registry/database settings, with the highest prevalence observed in pain clinics, on-line and in mixed settings. With the exception of three studies [65, 116, 160], most of the studies reporting D&OUD using ICD codes were also registry/database studies; therefore, it is possible that the lower prevalence for D&OUD reported using ICD codes may be due to under-reporting or under-diagnosis of

patients based on clinical notes or algorithms in registry/database studies compared with active identification in other settings.

A fifth limitation is the inclusion of studies which considered aberrant behaviours of study participants as POU, despite issues with how some included studies used and conceptualized this term. Although aberrant behaviours may indicate a problematic relationship with prescription opioids, other contextual factors may influence the likelihood of these behaviours. For example, missed clinic visits, no-shows or no follow-up may be associated with other social issues or disability, and not reflect POU. Whereas an inappropriately positive urine drug test for the presence of other opioids may indicate problem use, a negative test may indicate medication non-adherence or diversion. Other aberrant behaviours, such as early refills or multiple prescriptions, may be indicative of inadequate pain control. Despite these shortcomings, we felt that it was still important to include a

prevalence estimate of aberrant drug-related behaviours to aid understanding of the extent of the problem of POU in this cohort of patients.

A final limitation is the inclusion of a category of POU for those at risk of D&OUD. Studies which used a high score (≥ 8) on the Opioid Risk Tool (ORT) to define POU, and which were originally classified as misuse by study authors, were included in this category. However, it is likely to be a very weak indicator of actual POU or D&OUD.

Comparison to other studies

It is important to compare our findings with the results of previous reviews. Voon et al. (2017) [24] carried out a review of reviews to synthesize evidence from previous systematic reviews [5, 10, 22, 23, 25, 203] on the epidemiology of chronic pain and prescription opioid misuse [abuse, addiction, dependence, misuse and substance use disorder (SUD)]. The results of this review updated with our study findings are presented in Table 2, together with the findings of other reviews which reported other POU outcomes not analysed in this review (abuse, addiction, misuse). Estimates were not reported from Kalso et al. (2004) due to small sample sizes and short duration of follow-up [5]. Findings from Higgins et al. (2018) [20] are also included in the table, although their results are not directly comparable with the other reviews as incidence rates were reported. Our pooled prevalence for dependence was within the ranges reported by Minozzi et al. (2013) [22] and Chou et al. (2015). Only one other study reported SUD (Morasco et al. 2011) [23]. The authors reported a range of 3–48% However, the review is not directly comparable to ours due to variations in the method of assessment. The authors relied upon the operational definitions that the study investigators used to categorize SUD and did not re-classify POU outcomes. Their SUD category included self-reported history of SUD, documentation from medical records of SUD and positive urine drug screens for illicit substances (which we considered to be aberrant behaviour), in addition to validated self-report measures and structured clinical or diagnostic interviews.

CONCLUSIONS AND FUTURE RESEARCH

Our study has strengthened the evidence base regarding the commonality of POU in CNCP patients treated with opioids. However, it was also impacted by limitations of the evidence base, such as the heterogeneity of study methods, study settings and diagnostic tools used to identify POU and the lack of consistency and precision in POU definitions. Better reporting of study descriptors is needed, particularly with respect to ethnicity, type of prescription opioids used and the presence of other comorbid conditions, such as mental health issues, and problematic use of other medicines associated with dependence, such as benzodiazepines or gabapentinoids. There is an opportunity for high-quality studies using well-defined outcomes to be carried out in different settings and populations to provide better estimates. However, despite the problems identified with the literature,

there is enough evidence describing the extent of the problem for clinicians and policymakers to take appropriate action.

Current clinical guidance for the management of CNCP varies by geographical setting. In the UK, National Institute for Health and Care Excellence (NICE) guidance does not recommend the initiation of opioids to manage chronic pain in those aged 16 years and over, yet it is clearly happening [204]. In the United States, the new Centers for Disease Control and Prevention (CDC) guideline offers a more flexible approach to managing chronic pain with opioids, although they advise clinicians to use caution when prescribing opioids at any dosage and to consider the risk/benefit of opioids if they are considering increasing the dosage [205]. European clinical practice recommendations allow the use of opioids for chronic non-cancer pain, particularly where non-opioid treatments have been ineffective, contraindicated or not tolerated [206]. Better approaches are urgently needed to prevent and manage POU in CNCP. These may include the promotion of best practice in opioid prescribing, education of patients and prescribers regarding opioid-related harms, improving access to appropriate pain management, early screening and identification of POU and use of strategies for tapering or reducing opioids together with alternative pain management strategies to mitigate the risk of patients replacing with non-prescribed opioids and pharmacological and non-pharmacological treatment of POU.

AUTHOR CONTRIBUTIONS

Kyla Thomas: Conceptualization (lead); data curation (equal); formal analysis (equal); funding acquisition (lead); methodology (lead); writing—original draft (lead); writing—review and editing (lead). **Michael N Dalili:** Conceptualization (supporting); data curation (equal); formal analysis (equal); project administration (lead); writing—original draft (supporting); writing—review and editing (equal). **Hung-Yuan Cheng:** Data curation (supporting); formal analysis (lead); writing—review and editing (equal). **Sarah Dawson:** Data curation (supporting); writing—review and editing (supporting). **Nick Donnelly:** Data curation (supporting); writing—review and editing (equal). **Julian Higgins:** Methodology (supporting); writing—review and editing (supporting). **Matthew Hickman:** Conceptualization (supporting); methodology (supporting); writing—review and editing (supporting).

DECLARATION OF INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: K.T. reports financial support from the National Institute for Health and Care Research (NIHR) for this study.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon request.

ETHICS STATEMENT

Ethical approval for this evidence synthesis was not required.

DATA SHARING

Data are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.