








## PSYCHOLOGY, PSYCHIATRY, & BRAIN NEUROSCIENCE SECTION

# Mood and Anxiety Symptoms in Persons Taking Prescription Opioids: A Systematic Review with Meta-Analyses of Longitudinal Studies

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### Abstract

**Objective.** To review evidence from longitudinal studies on the association between prescription opioid use and common mood and anxiety symptoms. **Design.** We conducted a systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. **Methods.** We searched PubMed, Embase, and PsycINFO for search terms related to opioids AND (depression OR bipolar OR anxiety OR post-traumatic stress disorder [PTSD]). Findings were summarized narratively, and random-effects meta-analyses were used to pool effect sizes. **Results.** We identified 10,290 records and found 10 articles that met our inclusion criteria. Incidence studies showed that people who used prescription opioids had an elevated risk of any mood outcome (adjusted effect size [aES] = 1.80 [95% confidence interval = 1.40–2.30]) and of an anxiety outcome (aES = 1.40 [1.20–1.80]) compared with those who did not use prescription opioids. Associations with depression were small and not significant after adjustment for potential confounders (aES = 1.18 [0.98–1.41]). However, some studies reported an increased risk of depressive symptoms after increased (aES = 1.58 [1.30–1.93]) or prolonged opioid use (aES = 1.49 [1.19–1.86]). **Conclusions.** Mental health should be considered when opioids are prescribed because some patients could be vulnerable to adverse mental health outcomes.

**Key Words:** Opioid-Related Disorders; Mood Disorders; Bipolar Disorder; Depression; Anxiety Disorders; Trauma and Stressor-Related Disorders

### Introduction

Prescription opioids are considered essential medicines to treat acute and cancer pain, but they can be highly addictive [1]. Over the past two decades, the

prescription of opioids for the management of chronic non-cancer pain has increased [2], contributing to more than 16 million people meeting criteria for opioid use disorder globally [3].

Evidence that opioids are effective in the management of chronic non-cancer pain is limited [4, 5], but the unintended adverse consequences of their use—dependence and unintentional overdose—are well documented [6, 7]. Emerging epidemiological evidence suggests a link between prescription opioid use and negative mental health consequences, such as anxiety and depression [8]. Mood disorders can be triggered by the use of, misuse of, or withdrawal from other substances [9], with a notably high co-occurrence of depression and alcohol use disorder [10]. Patients with existing mental health disorders are already more likely to be prescribed opioids. Approximately half (51%) of all prescription opioids in the United States are prescribed to the 16% of the adult population with depression and anxiety [11]. There is also emerging evidence that people with preexisting mental health issues are less responsive to nonpharmacological approaches to pain treatment and are therefore more likely to be prescribed opioids [12, 13]. The relationship between chronic pain and mental health is complex, as both conditions contribute to each other [14]. The relationship between mental health outcomes and opioid use may be similarly complex and bidirectional.

To date, the evidence for the relationship between opioid use and mental health has focused on the extra-medical use of prescribed opioids, as indicated by behaviors such as the diversion of or tampering with medication and requesting an increased dose, *inter alia*. Extra-medical opioid use increases the risk of opioid use disorder [15], in addition to the increased prevalence of depression and anxiety in individuals using nonprescription medical opioids [16]. Those at higher risk of extra-medical opioid use include men, young people, and those with a lifetime history of substance use or mental disorders [17]. A recent review found relationships between any opioid misuse—extra-medical use of prescription opioids, as well as the use of illicit substances, such as heroin—and anxiety and depression [18]. Mental disorders are well-identified risk factors for problem opioid use, but less is known about the risks of developing these common mental disorders after the initiation of opioid use [19]. The evidence for a causal role of opioid initiation in the development of a mental health disorder is based predominately on nonhuman animal studies [20]. The evidence from longitudinal studies of the onset of mental health problems in humans after the initiation of prescription opioid use has not been comprehensively examined.

Mental disorders are an increasing burden on public health systems, and they can compound the distress of individuals who are using prescription opioids for pain conditions [21]. Therefore, it is critical to understand the impact that prescription opioid use could have on mental health. We reviewed longitudinal studies that examined the incidence and prevalence of mood and anxiety symptoms after the use of prescription opioids.

## Methods

### Protocol and Eligibility Criteria

The review was conducted as part of a registered protocol (PROSPERO ascension CRD42019128510; see [Supplementary Data S1](#)) following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see [Supplementary Data S2](#)). Articles in any language were eligible for inclusion.

We included longitudinal epidemiological studies with observational, quantitative data and excluded experiments, clinical trials, crossover studies, qualitative studies, case studies, commentaries, guidelines, editorials, presentations, scale development studies, psychometric studies, or validity studies. Reviews were used for secondary reference searches.

We included studies of cohorts and patients or subsamples (e.g., trauma or veteran samples) who were prescribed opioids and compared them with cohorts that were not using opioids or were prescribed and using lower opioid dosages.

Samples of fewer than 30 participants were excluded because they were unlikely to produce stable prevalence estimates. Patients in opioid agonist treatment (including methadone, buprenorphine, and others) were excluded because their prescribed opioids could be for treatment (e.g., methadone samples) of opioid use disorders. There were no exclusion criteria for the type of pain, condition, or injury of the samples. We excluded studies that examined only nonprescribed opioid use specifically (studies of heroin as the exposure variable), but we included studies that examined opioids as a broad group (that could include prescribed opioids) to allow more studies to be included.

Studies were included if the individual or combined diagnoses fell within the depression, anxiety, bipolar, or post-traumatic stress disorder (PTSD) diagnoses or subtypes, with symptoms assessed with a validated screening tool or with a *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or *International Classification of Diseases* (ICD) diagnosis. Finally, we excluded studies that did not report mental health outcomes after opioid use. We prioritized studies that reported on the incidence of the common mood and anxiety outcomes after prescription opioid use. However, because of the scarcity of data, we also included studies that reported the prevalence of mood and anxiety symptoms in samples that included those with and without mental disorders at baseline and examined whether they adjusted for baseline mood and anxiety levels. That is, we included two types of studies: 1) Studies were included if the samples did not have a mental disorder at baseline to examine incidence at follow-up; and 2) in studies that included a mix of individuals with and without a mental disorder at baseline, they were included to examine the prevalence of common mood and anxiety symptoms at follow-up and

were evaluated on the basis of whether the follow-up analysis adjusted for baseline mental disorders.

### Search Strategy

We focused on depression, bipolar, anxiety, and PTSD because a pilot search identified that there was more literature on prescription opioid use and these common mental health problems. The database searches were conducted in PubMed, Embase, and PsycINFO in October 2018 and then were updated in October 2020. We restricted our results to studies published after 2010 to capture more recent data. We searched for (opioids search terms) AND ((depression search terms) OR (bipolar search terms) OR (anxiety search terms) OR (post-traumatic stress disorder [PTSD] search terms)) using a title or abstract search and database-specific searchers (PubMed: Medical Subject Heading [MeSH] terms, EMBASE: Emtree terms; PsycINFO Index terms; see [Supplementary Data S3](#)). The search was limited to human studies. Our search strategy was supplemented by a manual search in Google Scholar and a secondary reference search of reviews identified on similar topics.

### Study Selection

Duplicates were removed to facilitate the screening of titles. Then, abstracts and full texts were screened against the inclusion criteria (see [Figure 1](#) for screening flow; see [Supplementary Data S4](#) for inclusion and exclusion criteria). Screening at the abstract and full-text stages was undertaken independently by two researchers. Discrepancies were resolved by discussion and clarification of the inclusion and exclusion criteria.

### Data Extraction

For each of the included studies, we extracted the study characteristics and settings (e.g., population survey or hospital setting), measurements and definitions of the opioid use (e.g., dose, any use, use disorder), and mental health outcomes of interest and how they were assessed. We extracted the unadjusted and adjusted effect sizes reported and the key findings.

Definitions of opioid use across the included studies were variable and at times ambiguous. We provide top-down categorizations of type of opioid use in our synthesis as three categories: 1) presumed opioid use as prescribed (POP), 2) nonmedical prescription opioid use (NMPOU), and 3) undefined or potential nonmedical prescribed opioid use (UD).

### Synthesis of Results

Random-effects meta-analyses were conducted on the mood and anxiety outcomes reported in the studies through the use of the *metafor* package in StatsNotebook (<https://statsnotebook.io/>; Brisbane, Australia) for R (R Foundation for Statistical Computing; Vienna, Austria). We presented estimates by the common mood and

anxiety outcome groups that the studies reported on. These included 1) any mood outcomes (as a composite group as reported by the original studies), 2) bipolar outcomes, 3) depressive outcomes, 4) dysthymia, 5) any anxiety outcomes, 6) PTSD, 7) panic disorder, 8) social anxiety, and 9) generalized anxiety.

If there was only one study that reported on a specific outcome, the estimates were included only in our summary table, with a note that the estimate was from one study. If a study reported multiple estimates for various levels of prescription opioids exposure against the same reference or comparison group, multilevel meta-analyses were conducted to adjust for the nested nature of the data and to overcome effect size dependency. Where there were multiple studies that reported on a specific outcome, funnel plots were used to examine the effect estimates of the individual studies against the standard error to assess potential publication bias. Plots that are not symmetrical inverted funnels would indicate the presence of bias.

We analyzed studies that reported on the incidence and prevalence of the common mood and anxiety outcomes after exposure to the prescription opioid use categories in separate analyses; the use categories were the exposure variables in our meta-analysis. Unadjusted and adjusted estimates and estimates of opioid use as the exposure were reported separately from estimates of opioid use disorders as the exposure variable. Input data for the effect sizes included the odds ratios or hazard ratios.

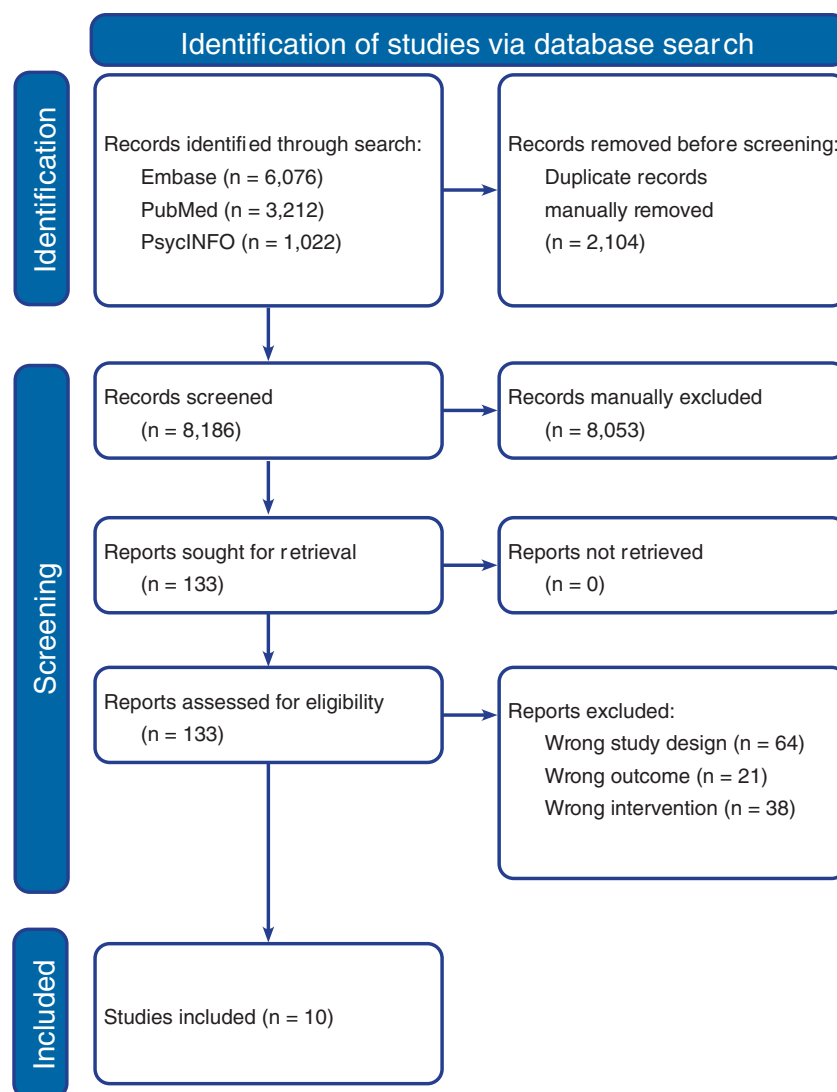
We planned to conduct subgroup meta-analyses by the definition and levels of prescription opioids exposure and by the instruments used to measure symptomatic mood and anxiety outcomes. We also planned to conduct meta-regression analyses by study-level sociodemographic factors. However, because of the small number of studies for each of the mood and anxiety outcomes, we were unable to conduct subgroup or meta-regression analyses. We summarized these findings by narrative review.

Risks of biases were assessed with the Newcastle Ottawa Quality Assessment Scale for cohort studies (see [Supplementary Data S6](#)). Quality assessment was conducted by one reviewer and checked for accuracy by a second reviewer. Discrepancies were resolved by discussion.

## Results

### Study Selection

The database search identified 10,290 records, from which 8,186 unique records were screened by title and abstract. Of these, 8,053 titles/abstracts were excluded (see [Figure 1](#)) in line with our inclusion and exclusion criteria (see [Supplementary Data S4](#)) Potential studies identified from the supplementary search had already been identified from the database search. From the 133



**Figure 1.** PRISMA flowchart of search results and inclusion of studies.

records screened in full, 10 articles met our inclusion criteria.

### Study Characteristics

Most studies were from the United States ( $n = 8$ ; see [Table 1](#)). The U.S. studies included longitudinal population household surveys [22, 23], analyses of the Veterans Health Administration samples [24–27], chart reviews of hospital records [27], outpatient studies of primary care clinics [28], and studies of trauma surgery inpatient services [29]. Studies from non-U.S. locations included one hospital burn unit study from South Korea [30] and a genome-wide association study of UK and Denmark data [31].

### Quality Assessment

The included studies were of high quality (average score = 81%; see [Supplementary Data S7](#)). Across all the studies, full scores were given for sample selection methods and the assessment of the exposure and outcome variables because we excluded studies with

inadequate methods. All studies either included samples that were free of the mood or anxiety outcomes at baseline or adjusted for mood and anxiety at baseline when assessing the longitudinal relationship between prescription opioid use and mental health outcomes. At a minimum, all studies adjusted for key potential confounding variables (e.g., age, sex, the severity of injury in patient studies), with half also adjusting for other substance use and other mental health comorbidities (see [Supplementary Data S7](#)). The studies scored low on sample representativeness, with only three studies representative of the population or using general medical records [22, 23, 31]. The other studies included specific patient groups or war veterans—key groups in the U.S. population who use prescription opioids.

### Narrative Review

[Table 1](#) summarizes the methods and findings of the included incident, prevalence, and symptoms studies, listed in alphabetical order of the first authors' last names.

**Table 1.** Study characteristics and summary of findings in studies of incidence, prevalence, and symptoms of mood and anxiety

First Author and Year, Location	Sample Setting and Characteristics	Prescription Opioid Use Measure	Mental Health Outcome Measure	Effect Size	Effect Key (+, -, ns)	Main Finding
Incident studies Martins 2012, USA	Longitudinal population household survey with two waves (2001–2005; 3-year FU); N = 34,653, 42% male, mean age = 50	Nonmedical prescription opioid use vs no non-medical prescription opioid use <sup>NMPOU</sup>	Incident mood disorders	OR = 2.10 [1.60–2.80], aOR = 1.80 [1.40–2.30]	+	Lifetime nonmedical prescription opioid use at wave 1 predicted mood disorders at wave 2.
				OR = 1.70 [1.30–2.10], aOR = 1.40 [1.10–1.80]	+	
				OR = 2.00 [1.30–3.10], aOR = 1.50 [0.90–2.50]	+	
				OR = 2.00 [1.40–3.00], aOR = 1.60 [1.00–2.40]	+	
				ns	ns	
				ns	ns	
Salas 2017, USA	Veterans Health Administration data (2000–2012; 2-year FU); N = 7,051, 96% male, mean age = 56	Decrease vs stable MED <sup>UD</sup>	Incident depression	HR = 0.91 [0.76–1.09], aHR = 0.91 [0.76–1.09]	ns	Incidence rates were 14.1/1,000 PY (person-years) in stable rate, 13.0/1,000 PY in decreasing, 19.3/1,000 PY in slowly increasing, and 27.5/1,000 PY in rapidly increasing dose. Compared with stable rate, risk of NOD increased incrementally for slow (HR = 1.22; 95% confidence interval: 1.05–1.42) and rapid (HR = 1.58; 95% confidence interval: 1.30–1.93) rate of dose increase. Faster rates of MED escalation contribute to NOD, independent of maximum dose, pain, and total opioid duration.
				HR = 1.40 [1.20–1.62], aHR = 1.22 [1.05–1.42]	+	
				HR = 2.00 [1.66–2.42], aHR = 1.58 [1.30–1.93]	+	
				ns	ns	
Scherrer 2014, USA	Retrospective chart review of Veterans Affairs chart database (1999–2007; FU variable); N = 49,770, 96% male, mean age = 55	90–180 days vs 1–89 days duration of opioid use POP	Incident depression, ICD-9-CM code	HR = 1.25 [1.06–1.47], aHR = 1.24 [1.05–1.46]	+	Compared with patients using opioids for 1–89 days, the risk of diagnosed depression was significantly greater in patients who used for 90–180 days (HR = 1.25; 95% CI: 1.06–1.47) or >180 days (HR = 1.53; 95% CI: 1.33–1.76).
				HR = 1.53 [1.33–1.76], aHR = 1.51 [1.31–1.74]	+	

(continued)

Table 1. continued

First Author and Year, Location	Sample Setting and Characteristics	Prescription Opioid Use Measure	Mental Health Outcome Measure	Effect Size	Effect Key (+, -, ns)	Main Finding
Scherrer 2016, USA	Chart review of hospital records: Veterans Health Affairs (VHA); 2002–2017, FU variable; N = 70,997, 94% male, mean age = 55	31–90 days vs 1–30 days duration of opioid use <sup>POP</sup>	Incident depression diagnosis, ICD-9-CM codes	HR = 1.23 [1.16–1.31], aHR = 1.18 [1.10–1.25]	+	Across three hospital databases, longer duration of opioid use was consistently associated with higher risk of incident depression. Findings of opioid dose on depression were mixed, with positive effects observed in people who used a higher dose of >100 mg/day, but were not statistically significant.
		>90 days vs 1–30 days duration of opioid use <sup>POP</sup>		HR = 1.31 [1.22–1.40], aHR = 1.35 [1.26–1.44]	+	
		51–100 mg/day vs 1–50 mg/day of opioid dose <sup>POP</sup>		HR = 1.20 [1.10–1.31], aHR = 1.02 [0.93–1.12]	+	
		>100 mg/day vs 1–50 mg/day of opioid dose <sup>POP</sup>		HR = 1.74 [1.49–2.04], aHR = 1.14 [0.94–1.39]	+	
		31–90 days vs 1–30 days duration of opioid use <sup>POP</sup>		HR = 1.22 [0.97–1.52], aHR = 1.29 [1.03–1.62]	ns	
		>90 days vs 1–30 days duration of opioid use <sup>POP</sup>		HR = 2.26 [1.63–3.14], aHR = 1.88 [1.27–2.78]	+	
		51–100 mg/day vs 1–50 mg/day of opioid dose <sup>POP</sup>		HR = 0.78 [0.60–1.03], aHR = 0.94 [0.72–1.21]	ns	
		>100 mg/day vs 1–50 mg/day of opioid dose <sup>POP</sup>		HR = 1.15 [0.72–1.86], aHR = 0.71 [0.40–1.28]	ns	
		31–90 days vs 1–30 days duration of opioid use <sup>POP</sup>		HR = 1.39 [1.22–1.59], aHR = 1.33 [1.16–1.52]	+	
		>90 days vs 1–30 days duration of opioid use <sup>POP</sup>		HR = 1.90 [1.62–2.24], aHR = 2.05 [1.75–2.40]	+	
Scherrer 2016, USA	Chart review of hospital records: Henry Ford Health System (2005–2017, FU variable); N = 22,981, 40% male, mean age = 48	51–100 mg/day vs 1–50 mg/day of opioid dose <sup>POP</sup>	Incident depression diagnosis, ICD-9-CM codes	HR = 0.93 [0.83–1.06], aHR = 0.98 [0.86–1.10]	ns	
		>100 mg/day vs 1–50 mg/day of opioid dose <sup>POP</sup>		HR = 1.13 [0.84–1.53], aHR = 1.24 [0.92–1.65]	ns	

(continued)

Table 1. continued

First Author and Year, Location	Sample Setting and Characteristics	Prescription Opioid Use Measure	Mental Health Outcome Measure	Effect Size	Effect Key (+, -, ns)	Main Finding
<b>Prevalence studies</b>						
Rossof 2020, UK and Denmark	UK Biobank Genome-Wide Association studies (GWAS; 2007–2020); N = 143,265 cases, 46% male, mean age = 56.5. Cross-sectional, no FU.	Opioid use (e.g., morphine, oxycodone, codeine, fentanyl, pethidine, and tramadol) <sup>UD</sup>	Major depression / major depressive disorder	OR = 1.14 [1.06–1.22], aOR = 1.14 [1.04–1.25]	+	In this two-sample Mendelian randomization study using genetic instruments for common pain medications, the genetic liability for prescription opioid use was associated with increased risk of major depression and anxiety and stress-related disorders.
	Danish Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) cohort (GWAS; 2012–2018); N = 31,885, 44% male, median age = 19. Cross-sectional, no FU.		Anxiety and stress-related disorders, Statistical Classification of Diseases and Related Health Problems 10-R	OR = 1.24 [1.07–1.44], aOR = 1.30 [1.08–1.56]	+	
Schepis 2013, USA	Longitudinal population household survey with two waves (2001–2005; 3-year FU); N = 34,653, 48% male, mean age = 50	Weekly or daily use of nonmedical prescription opioids vs monthly or less frequent use <sup>NMPOU</sup>	Depressive disorders, NIAAA Interview Schedule-IV Bipolar disorders, NIAAA Interview Schedule-IV Anxiety disorders, NIAAA Interview Schedule-IV	aOR = 1.95 [1.07–3.54]	+	Weekly/daily use predicted depression, bipolar, and anxiety.
Scherrer 2015, USA	Patients recruited from outpatient primary care clinics (2008–	≤50 mg MED vs no use of average daily MED <sup>POP</sup>	Depression, Patient Health Questionnaire (PHQ-2)	aOR = 2.12 [1.52–2.96]  aOR = 1.72 [1.28–2.30]	+	After adjustment for covariates, an increase to >50 mg in opioid MED from non-use increased patients' probability of depression over time (OR = 2.65 [95% CI = 1.17–5.98]).

(continued)

Table 1. continued

First Author and Year, Location	Sample Setting and Characteristics	Prescription Opioid Use Measure	Mental Health Outcome Measure	Effect Size	Effect Key (+, -, ns)	Main Finding
<b>Symptoms studies</b> Hong 2016, South Korea	2011; 1-year minimum FU, up to 2-year FU; N = 355, 28% male, mean age = 46. Hospital Burn Unit (2014; 2-week FU); N = 43, 74% male, mean age = 47	>50 mg MED vs no use of average daily MED POP	Depressive symptom scores, Hamilton Depression Scale (HAM-D) scores, Clinician-Administered PTSD Scale (CAPS)	OR = 3.32 [1.43–7.69], aOR = 2.65 [1.17–5.98]	+ +	Opioid doses were positively correlated with depressive symptom at follow-up (aR = 0.33, P = 0.03) but not PTSD symptoms (aR = 0.21, p = 0.20), with adjustment for age and severity of injuries.
Ruggles 2017, USA	Veterans Health Administration data (2003–2004; 2-year FU); N = 5,479, 97% male, mean age = 51	Opioid use (heroin, morphine, codeine, opium, and prescription opioids/painkillers) UD	Depressive symptoms, Patient Health Questionnaire (PHQ-9 score ≥ 8)	aOR = 1.24, P < 0.05	+	Opioid use status at preceding survey predicted current depression.
Trevino 2013, USA	Patients recruited from trauma surgery inpatient service; N = 80, 55% male, mean age = 48; 4-month FU.	Opioid use vs no opioid use UD	Depression, HADS Anxiety, HADS PTSD, PCL-C	P < 0.05 P < 0.05 ns	+ + ns	Statistically significant differences were observed between those using narcotics at 4 months on outcomes of depression and anxiety but not PTSD.

FU = follow-up; N = sample size; + = increased risk; - = reduced risk; ns = not significant; a = adjusted; R = regression coefficient; HADS = Hospital Anxiety and Depression Scale; MED = morphine equivalent dose; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NOD = new onset depression; PCL-C = PTSD Check-List-Civilian.

Prescription opioid use measure categories notations: POP = presumed opioid use as prescribed, NMPOU = nonmedical prescription opioid use, UD = undefined or potential nonmedical prescribed opioid use.



### Incidence Studies

We identified four studies that investigated the incidence of mood and anxiety outcomes after prescription opioids exposure [22, 25–27].

Martins and colleagues analyzed data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) that studied 34,653 adults in the United States to examine the longitudinal association between nonmedical prescription opioid use and mood and anxiety disorders [22]. The NESARC is a longitudinal household population survey that collected the first wave in 2001–2002 and the second wave in 2004–2005. In the study, nonmedical prescription opioid use was defined as using a prescription opioid “without a prescription, in greater amounts, more often, or longer than prescribed, or for a reason other than a doctor said you should use them.” Prescription opioid use disorders were assessed by the Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS)-IV to assess lifetime abuse and dependence according to DSM-IV criteria. They found that nonmedical prescription opioid use was associated with incident mood disorders (odds ratio [OR] = 2.10 [95% CI = 1.60–2.80], adjusted odds ratio [aOR] = 1.80 [1.40–2.30]) and incident anxiety disorders (OR = 1.70 [1.30–2.10], aOR = 1.40 [1.10–1.80]) [22]. Opioid abuse or dependence was associated with incident mood disorders (OR = 2.00 [1.30–3.10], aOR = 1.50 [0.90–2.50]) and incident anxiety disorders (OR = 2.00 [1.40–3.00], aOR = 1.60 [1.00–2.40]) in the unadjusted model [22]. However, the results were no longer significant in an adjusted model that controlled for demographics, comorbid mood/anxiety disorders, and other substance use [22].

Salas and colleagues examined the effects of changes in levels of prescription opioid use (undefined or potentially nonmedical) in a Veterans Health Administration sample on incident depression in a 2-year follow-up [25]. The Veterans Health Administration samples were predominantly male with a mean age of 55 years. Risks of incident depression did not significantly differ between people whose milligram morphine equivalent dose decreased and people whose opioid dose did not change (hazard ratio [HR] = 0.91 [0.76–1.09], adjusted hazard ratio [aHR] = 0.91 [0.76–1.09]) [25]. Those whose opioid dose increased had higher risks of incident depression (slow increase: HR = 1.40 [1.20–1.62], aHR = 1.22 [1.05–1.42]; a more rapid increase: HR = 2.00 [1.66–2.42], aHR = 1.58 [1.30–1.93]) than did those who received a stable opioid dose [25]. Faster rates of dose escalation predicted a new onset of depression, independently of maximum opioid dose, pain, and total duration of opioid use [25].

Scherrer and colleagues analyzed the Veterans Affairs records in 1999–2007 to examine the incidence of depression as a function of the duration of as-prescribed opioid use [26]. They found that the adjusted risk of

diagnosed depression was significantly greater in patients who used for 90–180 days (HR = 1.24 [1.05–1.46]) or >180 days (HR = 1.51 [1.31–1.74]) than in patients who used opioids as prescribed for only 1–89 days [26].

In a subsequent study, Scherrer, Salas, and colleagues [27] examined the relationship between mental health and the duration and dose of opioids used as prescribed in three independent samples, namely, the Veterans Health Affairs, the Baylor Scott & White Health hospital records, and the Henry Ford Health System hospital records. Patients given 51–100 mg/day (compared with 1–50 mg/day) of opioids did not have a significantly higher risk of an incident depression diagnosis (aHR = 1.02 [0.93–1.12]), but those given >100 mg/day did (aHR = 1.14 [0.94–1.39]) in the Veterans Health Affairs dataset (94% men, mean age = 55 years). However, opioid dosage levels were not significantly associated with incident depression in the chart review study of Baylor Scott & White Health (38% men, mean age = 45 years) or Henry Ford Health System (40% men, mean age = 48 years) hospital records. In all three datasets, a longer duration of opioid use was associated with an increased incidence of depression. Compared with patients who used for 1–30 days, the adjusted risks were 1.18 (1.10–1.25), 1.29 (1.03–1.62), and 1.33 (1.16–1.52) in patients who used for 31–90 days, and 1.35 (1.26–1.44), 1.88 (1.27–2.78), and 2.05 (1.75–2.40) in those who used for >90 days, in the Veterans Health Affairs, Baylor Scott & White Health, and Henry Ford Health System charts, respectively [27].

The incidence studies reported positive associations between longer duration of opioid use and incident depression, reported mixed findings on the dosage of opioids, and highlighted a lack of data on anxiety.

### Prevalence Studies

We identified three longitudinal studies of the effects of prescription opioids exposure on the prevalence of mood and anxiety symptoms at follow-up [23, 28, 31].

Rossoff et al. [31] conducted a Mendelian randomization study to assess whether there was a causal association between undefined and potentially nonmedical opioid use and anxiety and depression disorders. They used genomic data from the UK Biobank 2007–2020 (N = 143,265 cases, 46% men, mean age = 56.5 years) and the Danish Lundbeck Foundation Initiative for Integrative Psychiatric Research cohort 2012–2018 (N = 31,885, 44% male, median age = 19 years). Their analysis found that the genetic liability for opioid use was associated with an increased risk of depression (aOR = 1.14 [1.04–1.25]) and anxiety and stress-related disorders (aOR = 1.30 [1.08–1.56]), even after accounting for the use of non-opioid pain medications. Bidirectional analysis further showed that genetic liability for major depressive disorder, but not anxiety and stress-related disorders, was also associated with

increased prescription opioid use risk (aOR = 1.18 [1.08–1.30]). This study provided genetic evidence for a causal relationship between prescription opioid use and depression and anxiety disorders. There appear to be a bidirectional causal relationship between opioid use and depression and a monodirectional relationship of opioid use on anxiety.

Schepis and colleagues examined the effects of the frequency of nonmedical prescription opioid use on the prevalence of mental health outcomes in NESARC participants [23]. They compared the prevalence of mental disorders at follow-up between people who engaged in weekly or daily use of nonmedical prescription opioids and people who used opioids monthly or less frequently. They found that weekly/daily use predicted higher odds of depressive (aOR = 1.95 [1.07–3.54]), bipolar (aOR = 2.12 [1.52–2.96]), and anxiety disorders (aOR = 1.72 [1.28–2.30]). These associations remained significant after adjustment for sex, race/ethnicity, age, marital status, employment/student status, education level, household income, region of the United States, personality disorder, and axis I comorbidities.

The influence of opioid dose was investigated in a smaller study by Scherrer, Salas, and colleagues [28] that sampled outpatients (N = 355, 28% men, mean age = 46 years) of primary care clinics using opioids as prescribed. The authors found that compared with those receiving no prescription opioids, a lower dose ( $\leq 50$  mg of milligram morphine equivalent dose) was not statistically associated with having depressive symptoms after adjustment for potential confounders (aOR = 1.08 [0.65–1.79]), whereas a higher dose ( $> 50$  mg of milligram morphine equivalent dose) significantly increased the odds of having depressive symptoms (aOR = 2.65 [1.17–5.98]).

The prevalence studies generally found a positive association between opioid use and common mood and anxiety disorders.

### Symptom Studies

We identified three studies that investigated the levels of mood and anxiety symptoms after prescription opioids exposure [24, 29, 30].

PTSD symptoms were examined in a South Korean study by Hong and colleagues [30], who sampled patients from a hospital burns unit, comprising 74% men (mean age = 47 years). Dose of as-prescribed opioid (morphine and fentanyl) use was not significantly correlated with PTSD symptoms at follow-up. In the case of depression, however, opioid doses were positively correlated with depressive symptoms at follow-up ( $R = 0.33$ ,  $P = 0.03$ ) after adjustment for age and severity of injuries [30].

Ruggles and colleagues conducted a 2-year follow-up study of a Veterans Health Administration sample and reported a positive association between baseline undefined or potentially nonmedical prescription opioid use

and later depressive symptoms measured by the Patient Health Questionnaire (aOR = 1.24,  $P < 0.05$ ) [24].

Trevino and colleagues studied opioid use in patients from a trauma surgery inpatient service (55% men, mean age = 48 years) [29]. They found significant differences between individuals using undefined or potentially non-medical prescription opioids and those not taking opioids at 4 months on levels of depression and anxiety but not PTSD symptoms [29].

These symptom studies were consistent in their observations that opioid use was associated with higher levels of depressive symptoms [24, 29, 30].

### Meta-Analytic Results

A summary of unadjusted and adjusted estimates of mental health effects after opioid use and opioid use disorder are presented in Table 2 (data available in Supplementary Data S4). Any opioid use had significant longitudinal associations with the incidence of any mood disorder as reported by the original studies (adjusted effect size [aES] = 1.8 [1.40–2.30]) and any anxiety disorder as reported by the original studies (aES = 1.70 [1.30–2.10]). These positive relationships were found in both the unadjusted and adjusted meta-analyses, though these findings were based on only one study. Unadjusted estimates showed a positive association between opioid use and incidence of depression (effect size [ES] = 1.24 [1.00–1.53]), but the effect size was small, and the pooled adjusted estimates were not statistically significant (aES = 1.10 [0.89–1.36]).

Opioid use was also positively associated with the prevalence of bipolar disorder (aES = 2.09 [1.56–2.80]), any anxiety disorder (aES = 1.42 [1.22–1.65]), and generalized anxiety disorder (aES = 1.50 [1.10–2.10]). Opioid use was positively associated with depression in unadjusted estimates (ES = 1.24 [1.03–1.49]) but not in the adjusted estimates (aES = 1.14 [0.95–1.37]). Within studies, the sample sizes of people with an opioid use disorder were often small. Incidence outcomes were only for any mood disorders and any anxiety disorders. A significant adjusted association was found in opioid use disorder and any anxiety disorder (aES = 1.6 [1.00–2.40]). Summary results of prevalent mental disorders among those with an opioid use disorder were bipolar disorder (aES = 2.60 [1.00–6.80]), depressive disorder (aES = 1.60 [1.00–2.60]), any anxiety disorder (aES = 1.60 [1.00–2.40]), and generalized anxiety disorder (aES = 1.60 [1.00–2.50]). PTSD was excluded from the summary estimates because of a lack of data.

Table 3 shows the summary results of the association between opioid dose and duration of use with depression. A slow increase of opioid dose (aES = 1.22 [1.05–1.42]), a rapid increase of opioid dose (aES = 1.58 [1.3–1.93]), a duration of use of more than 30 days (aES = 1.38 [1.16–1.63]), and a duration of use of 90 days or more

**Table 2.** Pooled estimates of the association of prescription opioid use, and opioid use disorder, with diagnosed mood and anxiety outcomes

	Unadjusted				Adjusted			
	n <sup>†</sup>	ES	Lower	Upper	n	ES	Lower	Upper
<b>Exposure: any opioid use</b>								
<b>Incidence</b>								
Mood outcomes								
Any mood outcomes	1	2.10*	1.60	2.80	1	1.80*	1.40	2.30
Bipolar	0	—	—	—	0	—	—	—
Depression	8	1.24	1.00	1.53	8	1.10	0.89	1.36
Dysthymia	0	—	—	—	0	—	—	—
Anxiety outcomes								
Any anxiety	1	1.70*	1.30	2.10	1	1.40*	1.10	1.80
PTSD	0	—	—	—	0	—	—	—
Panic disorder	0	—	—	—	0	—	—	—
Social anxiety disorder	0	—	—	—	0	—	—	—
Generalized anxiety	0	—	—	—	0	—	—	—
<b>Prevalence<sup>†</sup></b>								
Mood outcomes								
Any mood outcomes	1	2.10*	1.60	2.80	1	1.80*	1.40	2.30
Bipolar	1	2.00*	1.10	3.60	2	2.09*	1.56	2.80
Depression	10	1.24*	1.03	1.49	11	1.14	0.95	1.37
Dysthymia	1	1.40	0.90	2.40	1	1.00	0.60	1.70
Anxiety outcomes								
Any anxiety	2	1.43*	1.05	1.95	3	1.42*	1.22	1.65
PTSD	0	—	—	—	1	1.23	0.90	1.57
Panic disorder	1	1.60*	1.10	2.40	1	1.30	0.90	2.00
Social anxiety disorder	1	1.70*	1.10	2.50	1	1.10	0.70	1.70
Generalized anxiety	1	2.10*	1.60	2.80	1	1.50*	1.10	2.10
<b>Exposure: opioid use disorder</b>								
<b>Incidence</b>								
Mood outcomes								
Any mood outcomes	1	2.00*	1.30	3.10	1	1.50	0.90	2.50
Bipolar	0	—	—	—	0	—	—	—
Depression	0	—	—	—	0	—	—	—
Dysthymia	0	—	—	—	0	—	—	—
Anxiety outcomes								
Any anxiety	1	2.00*	1.40	3.00	1	1.60	1.00	2.40
PTSD	0	—	—	—	0	—	—	—
Panic disorder	0	—	—	—	0	—	—	—
Social anxiety disorder	0	—	—	—	0	—	—	—
Generalized anxiety	0	—	—	—	0	—	—	—
<b>Prevalence<sup>†</sup></b>								
Mood outcomes								
Any mood outcomes	1	2.00*	1.30	3.10	1	1.50	0.90	2.50
Bipolar	1	2.50	1.00	5.90	1	2.60	1.00	6.80
Depression	1	2.10*	1.30	3.30	1	1.60	1.00	2.60
Dysthymia	0	—	—	—	0	—	—	—
Anxiety outcomes								
Any anxiety	1	2.00*	1.40	3.00	1	1.60	1.00	2.40
PTSD	0	—	—	—	0	—	—	—
Panic disorder	1	2.30*	1.20	4.10	1	1.80	0.90	3.40
Social anxiety disorder	1	1.80	1.00	3.30	1	1.20	0.60	2.40
Generalized anxiety	1	2.50*	1.60	3.90	1	1.60	1.00	2.50

n = number of estimates included in the meta-analysis.

Any opioid use does not include opioid disorder. Any mood and any anxiety are not the composite of other specific diagnosis.

\*Significant at  $P < 0.05$ .

<sup>†</sup>Inclusive of incident studies.

<sup>‡</sup>Data available in [Supplementary Data S4](#).

**Table 3.** Pooled estimates of the association of opioid use dose and duration with depression outcomes

Opioid dose	Unadjusted				Adjusted			
	n <sup>‡</sup>	ES	Lower	Upper	n	ES	Lower	Upper
<b>Incident depression</b>								
Dose increase (ref: stable dose)								
Slow increase	1	1.40*	1.20	1.62	1	1.22*	1.05	1.42
Rapid increase	1	2.00*	1.66	2.42	1	1.58*	1.30	1.93
Dose amount								
51–100 mg/day vs 1–50 mg/day	3	1.01	0.75	1.36	3	0.99	0.74	1.33
>100 mg/day vs 1–50 mg/day	3	1.40	0.90	2.17	3	1.09	0.70	1.68
Duration of use								
>30 days	8	1.38*	1.17	1.64	8	1.38*	1.16	1.63
≥90 days	5	1.47*	1.18	1.84	5	1.49*	1.19	1.86
<b>Depressive symptoms</b>								
Dose amount (ref: no use)								
Low dose	1	1.99*	1.19	3.31	1	1.08	0.65	1.79
High dose	1	3.32*	1.43	7.69	2	1.63	0.86	3.08

\*Significant at  $P < 0.05$ .

<sup>‡</sup>Data available in [Supplementary Data S4](#).

(aES = 1.49 [1.19–1.86]) were longitudinally associated with depressive disorder.

The summary estimates make clear that the data are sparse for all the opioid exposure and mood and anxiety symptom outcomes analyzed. Depression after opioid use had the best data, and it was the only outcome that was meaningful to examine in funnel plots. These were approximately symmetrical, and the tests for funnel plot asymmetry were not statistically significant ([Supplementary Data S4](#)).

## Discussion

We systematically reviewed and meta-analyzed longitudinal evidence on the impact of prescription opioid use on mental health. Although the evidence was limited, the incidence and prevalence of mood and anxiety disorders and symptoms increased after the initiation of opioid use or during longer durations of prescription opioid use.

Mental health disorders are widely accepted as risk factors for opioid use and opioid use disorders, but our review suggests that opioid use (particularly over long periods of time and in increasing doses) might also increase the risks of developing depressive, bipolar, and anxiety disorders.

Mechanisms that might mediate the relationship between opioid use and poorer mental health could include stigma and isolation, declining physical health, and a general decline in quality of life [32, 33]. These mechanisms are prevalent in persons with chronic pain and persons who are opioid dependent. As the opioid system may be directly involved in the regulation of mood, the dysregulation of the endogenous opioid system as a consequence of opioid misuse could factor into the development, exacerbation, or maintenance of depression, anxiety, or other mood disorders [34–36]. Comorbid mental health and substance use disorders are major risk

factors for suicide and self-harm attempts [37], which occur at an almost eight times higher rate among people who use illicit opioids [38]. Lastly, work in animals and humans has shown that opioids inhibit the gonadal axis, with chronic use potentially resulting in hypogonadism [39]. Individuals with hypogonadism can suffer from sexual dysfunction and decreased libido, which are likely to have a striking impact on the development or exacerbation of mood and other mental health disorders.

Important treatment outcomes for patients with chronic pain who are prescribed opioids include pain relief, improved functional capacity, and improved quality of life [5, 40]. Monitoring mental health is particularly important when changes are made in opioid dosages or opioids have been used for prolonged periods because these can have negative impacts on patients' quality of life. Our review included mainly studies of patients who were prescribed opioids to treat a physical health condition involving pain, e.g., trauma, surgery, or burns. We did not examine the relationship between poor mental health and the use of opioid agonist therapy to treat opioid addiction. Generally, individuals who receive opioid agonist therapy for opioid use disorders experience significant improvements in mental health [41]. Further work is necessary to refine our understanding of the extent to which prescription opioid use increases the risk of mood and anxiety disorders and symptomatology. This will be key in allowing prescribers to weigh the costs and benefits of using opioids to treat chronic pain. Where opioid therapy is indicated, a multidisciplinary approach is warranted, in which mental health is closely monitored to minimize the increased risk of opioid overdose [42, 43].

One difficulty in interpreting our findings is the inability to disentangle pain from the observed associations between opiate use or escalation with anxiety and depression. This is because the studies that were

identified overwhelmingly consisted of individuals who were prescribed opiates as a treatment for physical pain. The experience and intensity of pain have independently been associated with the incidence of depression and anxiety [44], and the number of pain locations and increased duration of pain have been associated with the course of depressive and anxiety symptoms [45]. Pain is also the precursor for the prescription of opiates, with pain intensity a predictor of initial opioid prescribing for chronic pain in primary care settings and of the prevalence and incidence of prescription opioid use disorder [46, 47]. Given these independent associations, it is likely that the experience of pain and the characteristics of that experience (i.e., duration, intensity, location, and number of locations) could be contributing to the associations we observed between opiate use and mental health outcomes. Two avenues of future research could assist in untangling the interplay of pain, opioids, and mental health. One is the inclusion of non-opioid analgesics in the treatment of pain as a precursor for mental health. Rossoff and colleagues included participants receiving both opioid and non-opioid analgesics [31]. This would allow for the experience of pain to be decoupled from opioid use in understanding mental health. Indeed, the authors found a significant unique contribution of opioid use when the use of non-opioid analgesics was controlled. Another useful avenue for future research would be the biological circuits that underlie 1) the experience of pain; 2) the generation of emotion, which is dysregulated in anxiety and depression; and 3) the reward circuit, which is key to the development of addiction [48]. Animal models and human neural data could be used to delineate the unique and shared contribution of pain within this mosaic of relationships.

### Limitations

The present review has several key limitations. The lack of data prevented us from answering some of the a priori research questions in our protocol. For example, we did not have enough studies to conduct subgroup analyses by mental health assessment tools or a meta-regression of the effects of sociodemographic characteristics on the relationship between opioid use and mental health.

We had not included substance-induced mood disorders because we found a lack of existing literature that focused on them specifically.

We were unable to select variables to control for in the adjusted analysis because this depended on variables used in the original studies. Not all studies adjusted for other substance use. Persons prescribed opioids might be more likely to be dependent on other substances (e.g., alcohol), which can also be associated with increased mood and anxiety symptoms. Future studies that compare mood and anxiety outcomes after other substance use and poly-substance use are warranted.

We excluded studies that specified exposure to non-medicinal or nonprescription opioids (e.g., studies of heroin use). We included studies that specified prescription opioids and studies that examined opioid use broadly while including prescription opioids. Ideally, we would have excluded the latter, but the scarcity of research precluded us from focusing solely on prescription opioids. We conducted sensitivity analyses to exclude studies that examined opioid use as a broad group; for example, the Veterans Health Administration data analysis by Ruggles and colleagues [24] examined opioid use that could include heroin, morphine, codeine, opium, and prescription opioids/painkillers. The estimates of the associations were consistent after the exclusion of those studies. The association between different types of opioids used and these mood symptoms warrants further research.

There were limited data on the specific opioids that have been the subject of extra-medical use. We did not have enough data to compare the effects of different opioids. We also did not find enough data to examine the co-use of prescription opioids with other substances, e.g., the co-prescription of opioids and benzodiazepine, which has increased in the United States [49]. The effects of the co-use or substitution of cannabinoids for opioids also warrant future research.

The definition of opioid use across individual studies was variable and at times ambiguous. The literature would benefit from clearer reporting on the form of the opioid use in studies and an attempt at standardization of this terminology. We focused in this review on mood and anxiety disorders, but opioid use could be a factor in the development or exacerbation of other mental health disorders or more specific depressive or anxious symptomatology than gross diagnostic category. Future work that expands the scope of mental health disorders is warranted, as is work that takes a more fine-grained approach in, for example, understanding how opioid use influences symptoms such as flattened affect or anhedonia, which are features of depression.

Lastly, it is common for studies to create a composite diagnostic category such as “any anxiety disorder.” This has the benefit of providing more power to test theoretically associated diagnoses but runs the risk of inconsistency across studies where the individual diagnoses that comprise the composite category differ. Future work should better identify which diagnoses form a composite, and the establishment of agreed-upon theoretically driven composite categories is warranted.

### Conclusions

Mental health consequences need to be considered when opioids are prescribed. Although the evidence is limited, more frequent use, rapid opioid dose increases, and prolonged use of prescription opioids were associated with increased risks of mood and anxiety disorders. People who have developed an opioid use disorder while using



prescription opioids could be more vulnerable to developing mental health disorders, such as anxiety and depression.

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## Supplementary Data

[Supplementary Data](http://painmedicine.oxfordjournals.org) may be found online at <http://painmedicine.oxfordjournals.org>.

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