



Title	Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain
Authors(s)	Klimas, Jan, Gorfinkel, Lauren, Fairbairn, Nadia, et al.
Publication date	2019-05-03
Publication information	Klimas, Jan, Lauren Gorfinkel, Nadia Fairbairn, and et al. "Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain." American Medical Association (AMA), May 3, 2019. https://doi.org/10.1001/jamanetworkopen.2019.3365 .
Publisher	American Medical Association (AMA)
Item record/more information	http://hdl.handle.net/10197/10570
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Publisher's version (DOI)	10.1001/jamanetworkopen.2019.3365

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**Strategies to identify patient risks of prescription opioid addiction when initiating opioids
for pain: A systematic review**

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Running head: Risk for Prescription Opioid Use Disorder

Word Count: 3285

Tables: 3

Online supplementary material: 1

Revised: 15 Mar. 19

KEY POINTS.

Question: How to identify patients with pain among whom prescription opioids can be safely prescribed.

Findings: A systematic review found that a history of opioid or non-opioid use disorder, a mental health diagnosis and concomitant prescription of certain psychiatric medications may be associated with an increased risk of prescription opioid addiction. However, only the absence of a mood disorder appeared useful for identifying lower risk patients and assessment tools incorporating combinations of patient characteristics and risk factors were not useful.

Meaning: There are few valid ways to identify patients who can be safely prescribed opioid analgesics.

ABSTRACT

Importance: Although prescription opioid use disorder is associated with substantial harms, strategies to identify patients with pain among whom prescription opioids can be safely prescribed have not been systematically reviewed.

Objective: To review the evidence examining predictors and screening tools for identifying adult patients at high versus low risk of developing symptoms of prescription opioid addiction when initiating prescription opioids for pain.

Data Sources: MEDLINE and EMBASE (1946 – November 2018) were searched for articles investigating risks of prescription opioid addiction.

Study Selection: Original studies that were included compared symptoms, signs, risk factors and screening tools among patients who developed prescription opioid addiction and who did not.

Data Extraction and Synthesis: Two investigators independently assessed quality to exclude biased or unreliable study designs and extracted data from higher quality studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Accuracy Studies (PRISMA-DTA) reporting guideline was followed.

Main Outcomes and Measures: Likelihood ratios (LR) for risk factors and screening tools were calculated.

Results: Of 1287 identified studies, six high quality articles were included in the qualitative synthesis and four were included in the quantitative synthesis. A history of opioid (LR range, 17 - 22) or non-opioid use disorder (LR range, 4.2–17), as well as certain mental health diagnoses (e.g., personality disorder, LR 27, [95% CI, 18-41]), and concomitant prescription of certain psychiatric medications (e.g., atypical antipsychotics, LR 17, [95% CI, 15-18]) may be useful for identifying high-risk patients. Among individual findings, only the absence of a mood disorder (negative LR, 0.5 [95% CI 0.45-0.52]) appeared useful for identifying lower risk patients. Despite their widespread use, most screening tools involving combinations of questions were based on low quality studies or, when diagnostic performance was assessed among quality studies, demonstrated poor performance in helping to identify high risk or low risk patients.

Conclusions and Relevance: While a history of substance use disorder, certain mental health diagnoses and prescription of certain concomitant psychiatric medications appeared useful for identifying higher risk patients, few quality studies were available and no symptoms, signs or screening tools were particularly useful for identifying those at lower risk.

Word count: 349

Keywords: opioid use disorder, risk assessment, pain, systematic review

INTRODUCTION

Recently, prescription opioids have been detected in up to 77% of opioid-related overdose fatalities, and the health, social and economic costs associated with opioid use disorder (OUD) continue to rise.^{1,3} Importantly, the quantities of opioids prescribed in different regions have been strongly associated with higher rates of subsequent opioid overdose.⁴ Nevertheless, despite the well-recognized harms of prescription opioids, recent data suggest that the number of opioid prescriptions is remaining stable and while U.S. has seen a fall in the national opioid prescribing rate, in 2017, prescribing rates continued to remain very high in most U.S. jurisdictions.^{5,6}

While there is great variability in the estimates,^{7,8} a substantial proportion of persons prescribed opioids for chronic pain may subsequently develop OUD. As such, the optimal mechanism for prevention remains with the promotion of safer prescribing by health care professionals. The need for safer prescribing is also acknowledged in the recent U.S. Centers for Disease Control and Prevention pain guidelines that highlight the importance of carefully screening patients to identify those that are high risk of OUD.⁹ However, patient characteristics and screening tools currently in use for predicting risk of prescription opioid addiction have not been critically assessed for diagnostic performance in a systematic review. Therefore, this review describes the incidence of prescription OUD and diagnostic accuracy of strategies used for identifying patients at high versus low risk of prescription OUD being prescribed opioids for pain.

METHODS

To identify relevant articles that examined risk factors for opioid addiction as defined by study authors, MEDLINE and EMBASE from 1946 to November 2018 were systematically searched.

Search terms included *opioid-related disorders*, MESH term *substance related disorders*, *pain*, *analgesics*, and terms previously found to be useful for retrieving diagnostic studies.¹⁰ To be eligible for the present review, we also restricted to studies of opioid naïve patients newly starting opioid medications for pain and excluded studies assessing for a diagnosis of OUD among patients already on opioid-based medications. We also undertook a quality review of identified studies. Specifically, studies that evaluated prescription characteristics, patient characteristics (including a previous diagnosis of either a substance use disorder or mental health disorder), and screening tools assessing symptoms of prescription opioid addiction in the context of pain management (see tools characteristics in eTable2), were considered, so long as they met a pre-defined quality threshold (≥ 3) based on a five-level Hierarchy of Evidence rating scale by Simel and Drummond.¹¹ In accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-DTA), and Standards for Reporting Diagnostic Accuracy (STARD), sources of bias for each study were also evaluated with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) Tool.¹²⁻¹⁵

Data Synthesis and Analysis The population incidence of prescription OUD after opioid prescription was estimated by collating data on opioid “dependence” and “abuse” from previous reviews on the topic (including a Cochrane Collaboration review).^{7,8,16} In brief, data on the incidence of prescription OUD in opioid-naïve patients being prescribed opioids for pain was extracted from the studies that met the eligibility requirement for this review (search was not intended to assess incidence of prescription OUD, see details in eAppendix 1). Here, summary incidence was calculated using a random effects estimate from the included studies and performed via a Comprehensive Meta-analysis (version 3) software.¹⁷

For illustrative purposes, where possible, data were extracted and used to calculate likelihood ratios (LR), sensitivity and specificity for each individual risk factor identified for the development of prescription OUD. Full details of the search strategy, search results, study quality review and calculation of diagnostic accuracy estimates are available in supplemental online material (see eAppendix 1). Contingency tables (2x2) were constructed to estimate the likelihood ratios (LR), sensitivity, and specificity for each risk factor or screening tool. Data were entered into Microsoft Excel spreadsheets predesigned to calculate the sensitivity, specificity, LRs, and their 95% CIs. When a symptom, sign or risk factor was assessed in only one high quality study, the LR and 95% confidence interval (CI) were reported. When a symptom, sign or risk factor was assessed in two studies, the range of LRs was reported. If a symptom, sign or risk factor was considered in three or more studies, the protocol sought to pool the LR data using separate univariate random-effects meta-analysis. $LR \geq 2.5$ or ≤ 0.5 was considered as potentially clinically useful.

RESULTS

Incidence of opioid use disorder in pain management

Research to date has found that the incidence of symptoms of prescription OUD varies widely in reviews of studies of opioid-prescribed patients, which report that between 0.10% to 34% develop prescription OUD symptoms following an opioid prescription.^{7,8,16} This review found that the incidence of prescription OUD symptoms in quality (level ≥ 3) studies varied with the patient population, care setting and criteria for diagnosis. For instance, prescription OUD symptoms were higher in studies of chronic pain management programs, which involved direct clinical follow-up and screening of all patients, than in database studies that relied on diagnostic codes in administrative datasets (e.g., International Classification of Disorders - ICD criteria, or

ICD-CM – clinical modification criteria, or Diagnostic and Statistical Manual - DSM). In two prospective observational studies of patients in chronic pain management programs that used in-person assessments for all patients and employed non-ICD or non-DSM explicit criteria (e.g., aberrant behaviors, evidence of illicit substances or abnormal findings such as presence of a nonprescribed opioid), the reported incidence of these indicators was 34% (standard error = 4.9%)¹⁸ and 28% (standard error = 4.3%),¹⁹ respectively. In contrast, the incidence of prescription OUD symptoms was dramatically lower in the two included large database studies that relied on physician-reported ICD-9-CM diagnoses to assess opioid abuse and dependence. In these studies, the reported incidence of these diagnoses was 0.10% (standard error [SE] = 1.90)²⁰ among commercially-insured persons who received an initial opioid prescription (and who received an opioid abuse / dependence diagnosis within two years of filling the opioid prescription [OUDs], vs. those who did not receive such a diagnosis within two years [non-OUDs]), and 3.2% (SE = 0.083) among recipients of chronic opioid therapy,²¹ respectively. When subjected to a meta-analysis, across three studies (one study's data was missing) of patients prescribed opioids for pain, the incidence of prescription OUD was 2.5% (95% CI, 0.15-30%, I²=99%).^{18,20,21} The heterogeneity was created by two very large analyses of insurance databases with low incidence (0.10%²⁰ and 3.2%²¹), that dominated the results of a small prospective cohort study of patients with chronic pain referred to a psychology practice (incidence 34%).¹⁸ While further research is required, these findings suggest that incidence studies relying on conventional physician reporting that is based on overall judgment (i.e., a coded diagnosis from an encounter form), and incomplete surveillance, may substantially underestimate the incidence of prescription OUD.

Risk factors for prescription opioid addiction

Of 1287 identified citations that were screened, 102 were identified as being eligible for full text review, 96 of which were excluded for either not meeting the pre-defined study quality threshold or other reasons (see eFigure 1). Overall, six high quality articles were included in the qualitative (narrative) synthesis and four were included in the quantitative synthesis. Two studies reported on risk factors (eTable 1) and two studies reported on risk prediction tools (see details in eTable 2). The four high quality studies, included in the quantitative synthesis, were all retrospective studies that overall included 2,888,346 patients with 4470 cases that met the authors' definitions of prescription opioid addiction.¹⁸⁻²¹ Three of the four high-quality studies, which were included in the quantitative synthesis, examined chronic pain^{18,19,21} while one study²⁰ included patients “who had at least one opioid prescription claim,” and 58.83% of whom also had a diagnosis of chronic pain disorder (as per ICD-9; Bryan Cochran, Ph.D., email communication, March 7, 2019).

Among included studies that met the quality threshold (see quality assessment in eAppendix 3 and eTable 4), a history of any pain disorder (LR 23, [95% CI, 18-29]) was associated with increased risk of prescription opioid addiction (Table 1).^{20,21} Furthermore, personality disorder (LR 27, [95% CI, 18-41]),²⁰ somatoform disorder (LR 12, [95% CI, 7.18-18]),²⁰ psychotic disorder (LR 11, [95% CI, 8.5-14]),²⁰ and non-opioid substance use disorder (LR range 4.2-17)^{20,21} were associated with the greatest likelihood of subsequent symptoms of prescription opioid addiction (eTable 5-6). Using a conservative estimate of pretest probability of 2.5% prescription OUD, patients with a personality disorder, somatoform disorder, or psychotic disorder would have an elevated post-test probability of 41%, 24%, and 22% respectively of developing OUD. While mood and any anxiety disorder also had modest LRs (6, [95% CI, 5.8-6.2]; and 5.3, [95% CI, 5-5.6], respectively), only the absence of a mood disorder (negative LR 0.5, [95% CI, 0.45-0.52]) appeared to meaningfully reduce the likelihood of prescription opioid addiction.²⁰ In one study,

having a previous history of OUD was associated with an increased risk for the subsequent development of prescription OUD following opioid prescribing for chronic pain management (LR range 17-22).²¹ Among two included studies, men (LR range 1.1-1.4) were not obviously more likely than women to develop prescription OUD.^{20,21}

Certain opioid prescription characteristics may be also associated with an increased risk of developing OUD. Specifically, a new prescription for any opioid for ≥ 30 days appeared to place patients at greater risk for prescription OUD when compared to those patients receiving supply of opioids for < 30 days (LR range 3.5-4.9).²¹ This finding was consistent whether the opioids were prescribed alone, or in tandem with schedule II short-acting opioids, or prescribed in tandem with opioids of other schedule. When patients get to opioid dose above 120 milligrams morphine equivalents per day (LR range 3.2-3.4), they have a higher risk of subsequent prescription OUD.²¹ Though the presence of any concomitant psychiatric medication, such as anxiolytics (LR 7.3, [95% CI, 6.5-8.3]), appeared to place patients at greater risk of developing prescription OUD, as shown in Table 1, atypical antipsychotics appeared to be associated with the highest risk (LR 17, [95% CI, 15-18]).

Receiving an opioid for < 30 days (negative LR range 0.95-0.96) and when patients do not get to an opioid dose above 120 milligrams morphine equivalents per day (negative LR range 0.85-0.85; the LR range is derived from two separate databases described in this study) did not lower the risk of prescription OUD.²⁰ Similarly, the absence of concomitant psychiatric medications (negative LRs from 0.59-0.93) was not particularly useful for lowering the risk of prescription OUD (Table 1 and eTable 7).²⁰

Risk Assessment Tools

While this review identified 31 studies that have evaluated risk assessment tools for prescription OUD, only two studies (which examined five individual tools) met criteria to be defined as high-quality and thus were included (Table 2).^{18,19} Further, despite risk assessment tools becoming a widespread aspect of the prescribing of opioids in some pain management settings,²² their ability to identify high versus low risk patients was limited. Among the tools evaluated through high quality studies, the Pain Medication Questionnaire (PMQ) (cut-off score ≥ 30), appeared most promising though its ability to differentiate high risk from low risk patients was overall poor (Table 2). Among the PMQ validation sample, having ≥ 30 positive answers modestly increased the likelihood of symptoms of prescription OUD (LR 2.6, [95% CI, 1.4-4.8]). However, having < 30 positive answers had marginal utility for identifying those least likely to develop prescription OUD (negative LR 0.75, [95% CI, 0.60-0.94]). In addition to its limited ability to discern high from low risk patients, and the fact that the PMQ is only useful for patients who have had pain treated in the past, the tool may be cumbersome, requiring approximately 10 minutes to administer. Similarly, no scale proved useful for assessing patients newly presenting with chronic or acute pain. Nevertheless, the PMQ is different from other scales because it assesses patient agreement with statements about their beliefs concerning past pain relief and behaviors in addressing pain, rather than traditional risk factors – such as prior substance use disorders or comorbid conditions. Examples of questions include items such as: “*In the past, I have had some difficulty getting the medication I need from my doctor(s)*”; or “*At times, I take pain medication when I feel anxious and sad, or when I need help sleeping.*”

Other risk assessment tools we evaluated, several of which are in common use, addressed traditional risk factors (such as personal and family history of substance “abuse” or psychological

illness). These included the Opioid Risk Tool (LR 1.5, [95% CI, 0.76-2.9]), Brief Risk Questionnaire (LR 1.2, [95% CI, 0.96-1.6]), Brief Risk Interview (LR 1.2, [95% CI, 0.96-1.6]), and Screener and Opioid Assessment for Patients with Pain (LR 1.2, [95% CI, 0.94-1.4]) (see tools' characteristics in Table 3 and eTable 2).^{18,19} Further, when their ability to discern high versus low risk patients was critically assessed using 95% confidence intervals of likelihood ratios, none of these risk assessment tools appeared useful (Table 2).

DISCUSSION

Recently published estimates suggest that more than one third of U.S. civilian, non-institutionalized adults used prescription opioids in 2015.¹ However, despite the public health emergency related to prescription opioid addiction, this review demonstrated that there are few quality studies available to help health care professionals and that estimates of the incidence of prescription opioid addiction in quality (level ≥ 3) studies have likely been under-estimated.^{18,19}

Among single high-quality studies, having a previous history of a substance use disorder (opioid or non-opioid), or mental health diagnosis (e.g., personality disorder, somatoform disorder, psychotic disorder, or anxiety disorder) was associated with a substantial increase in the likelihood of developing a prescription OUD. Furthermore, certain opioid prescription characteristics, including a duration of ≥ 30 days and a daily dose >120 mg morphine equivalents and concurrent prescriptions of atypical antipsychotics, were associated with an increase in the likelihood of developing a prescription OUD. However, few of these findings have been replicated in more than one study. Quality replication studies are needed. Furthermore, only absence of mood disorder produced negative likelihood ratios that modestly lowered risk for prescription OUD whereas none of the other findings were useful for identifying lower risk patients. Finally, despite risk

assessment tools becoming a widespread aspect of the prescribing of opioids in pain management care environments,²² they appeared to be of little value for identifying high- or low-risk patients.

While not relevant to the assessments of most individual characteristics or medication characteristics, one explanation for the poor performance of risk prediction tools may be that the act of screening may change patient behavior and/or decision-making by physicians, lowering the overall incidence rate of prescription OUD.²³ In other words, risk prediction tools may have low apparent diagnostic accuracy because assessment process itself lowers the incidence of prescription OUD in high risk patients. For instance, since the PMQ has a series of questions that can be used to discuss the dangers of opioid addiction, the tool itself may increase patient awareness and encourage patients to limit opioid use. This may not be relevant to high quality studies where risk assessment and prescribing behavior were independent.^{20,21} While this explanation requires further investigation, from an evidence-based medicine perspective, the findings of this review nevertheless suggest that health care professionals do not have good tools to identify patients at high or low risk for the development of a prescription OUD, among whom prescription opioids can be safely prescribed.

While these findings are disheartening given the urgent need to identify more effective strategies to manage chronic pain patients, they are well-aligned with the evolving literature regarding risk of prescription OUD among individuals prescribed opioid medications for pain management, and the discordance between this literature and common prescribing behaviors in North America. For instance, while recent reports have demonstrated that physician perception of the low risk of prescription opioids may be based on flawed or limited studies,²⁴ more rigorous reviews have highlighted the risks of prescription opioids and the limited evidence of benefit.^{25,26} For instance, the systematic review for the Pathways to Prevention Workshop, which was

sponsored by the U.S. National Institutes of Health, highlighted questions about the clinical effectiveness of prescription opioids in the chronic pain context and reported a dose-dependent risk for serious harms of long-term opioid therapy for chronic pain.²⁷ More recently, the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial found treatment with prescription opioids to be not superior to treatment with non-opioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain.²⁸ Together with the lack of diagnostic value of the tools in widespread use for identifying high or low risk patients, as identified in our review, this evolving literature on the limitations and harms of prescription opioids highlight the need to reconsider the common prescription of opioids for minor acute pain conditions and chronic pain.^{25,26}

While prior reviews have attempted to describe risk factors or opioid risk screening tools that can be used to classify patients into high- versus low-risk categories, none have conducted rigorous quality assessments, or used likelihood ratios as a strategy to assess the diagnostic utility of screening for risk factors or screening tools.^{16,22,29-31} Recently, an earlier similar review¹⁶ on this topic has been updated,^{32,33} but our review used more systematic approach and quality assessment of reviewed studies. Specifically, our study quality assessment resulted in the exclusion of the majority of studies included in earlier reviews on this topic.^{7,16} Nevertheless, the present review's limitations highlight the gaps that exist in the literature in this area. For instance, the identified heterogeneity among the included studies due to patient population, care setting and criteria for diagnosis, as described above. In fact, the diagnosis of prescription opioid addiction in the context of chronic pain can be challenging,³⁴ and studies included in this review used varying definitions (e.g., DSM-4, DSM-5, ICD-9, etc.) for the diagnosis of prescription opioid addiction. Because its definition has not been consistent in the pain literature, we considered a wide definition of

prescription opioid addiction based on the definitions employed by study authors (see definitions in eTable 8). Although the low incidence of OUD found in the large cohort studies^{20,21} might suggest that patients with an OUD diagnosis in those studies were more likely to have severe OUD, this explanation requires further investigation.

While it would be hoped that individual patient characteristics and risk screening tools might prove useful, when subjected to critical review, only a few individual patient characteristics (often identified in only one un-replicated study) helped identify high-risk patients and no individual patient characteristics, other than a possible benefit of the absence of mood disorder, or screening tools appeared particularly useful for safely identifying lower risk patients. Instead, most screening tools, including the commonly used Opioid Risk Tool,^{35,36} were based on lower quality studies or, when test performance was assessed by calculating likelihood ratios, demonstrated poor diagnostic performance.

CONCLUSION

This review found that a history of opioid or non-opioid substance use disorder, as well as concomitant prescription of certain psychiatric medications, prolonged duration of opioid prescriptions (greater than 30 days), higher daily opioid doses and a history of certain mental health disorders may be useful for identifying high-risk patients, whereas only the absence of mood disorder was useful for identifying lower risk patients. The review also found that most screening tools are from low quality studies and that no screening tool was particularly useful for identifying patients among whom opioids can be safely prescribed. Further, few high quality studies exist that can inform clinicians and policymakers on how to manage this difficult and important public health problem. These findings, alongside persistently high rates of opioid prescribing and the literature demonstrating the overall harms and limited benefits of prescription opioids in many pain

conditions,²⁵⁻²⁸ suggest that prescribers should be better aware of the major diagnostic limitations of assessing patient characteristics and using screening tools when seeking to identify patients who may be safely prescribed opioid medications.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Financial Disclosures: None declared.

Funding/Support: This research was undertaken, in part, thanks to funding from an operating grant from Canadian Institutes of Health Research (397968); from the Canada Research Chairs program through a Tier 1 Canada Research Chair in Inner City Medicine which supports Dr. Evan Wood. A European Commission grant (701698) supports Dr. Klimas. Drs. Nolan and Fairbairn are supported by the Michael Smith Foundation for Health Research. Dr. Simel receives honoraria for contributions to JAMAEvidence.com. His work was supported by the Durham Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT), (CIN 13-410) at the Durham VA Health Care System. Funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Role of the Sponsor: The granting agency funded the salaries of research staff in addition to investigators salary awards, as reported under Funding/Support.

Acknowledgments: The lead author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Lauren Gorfinkel and Jan Klimas wrote the first draft of the manuscript, based on an outline developed by Jan Klimas and Evan Wood. All co-authors contributed to the revision process. We thank the following colleagues: Dean Gustini, MLit (Library of the University of British Columbia), Loai Al-Barquoni, MD, PhD (Bond University, Australia) and Ahmed Adam, MPH (BCCSU), for research and administrative assistance that was compensated or conducted as part of their regular paid positions with their respective organizations.

Table 1. Risk factors that predict Prescription Opioid Use Disorder among opioid naïve patients initiating prescription opioids.

Finding	Author, year	Studies, Reference[#]	Sensitivity (95% CI)	Specificity (95% CI)	LR positive (95% CI)	LR negative (95% CI)
Risk Factors^a						
<u>Mental Health History</u>						
Any personality disorder	Cochran, 2014	1 ²⁰	0.08 (0.05-0.12)	1.0 (1.0-1.0)	27 (18-41)	0.99 (0.99-1.0)
Any pain disorder	Cochran, 2014	1 ²⁰	0.02 (0.02-0.03)	1.0 (1.0-1.0)	23 (18-29)	0.98 (0.98-0.99)
Past opioid use disorder (OUD) ^b	Edlund, 2010	1 ²¹	0.07-0.09 (range)	1.0-1.0 (range)	17-22 (range)	0.91-0.93 (range)
Somatoform disorders	Cochran, 2014	1 ²⁰	0.08 (0.05-0.11)	1.0 (1.0-1.0)	12 (7.8-18)	0.99 (0.99-1.0)
Psychotic disorders	Cochran, 2014	1 ²⁰	0.19 (0.15-0.25)	1.0 (1.0-1.0)	11 (8.5-14)	0.98 (0.98-0.99)
Any mood disorder	Cochran, 2014	1 ²⁰	0.55 (0.53-0.56)	0.91 (0.91-0.91)	6.0 (5.8-6.2)	0.50 (0.45-0.52)
Any anxiety disorder	Cochran, 2014	1 ²⁰	0.29 (0.27-0.31)	0.95 (0.95-0.95)	5.3 (5-5.6)	0.75 (0.74-0.77)
Past substance-use disorder, other than opioid	Cochran, 2014; Edlund, 2010 ^b	2 ^{20,21}	0.14-0.58 (range)	0.95-0.98 (range)	4.2-17 (range)	0.44-0.88 (range)
<u>Demographics</u>						
Gender (male)	Cochran, 2014; Edlund, 2010 ^b	2 ^{20,21}	0.33-0.60 (range)	0.56-0.72 (range)	1.1-1.4 (range)	0.72-0.96 (range)
Prescription characteristics						
<u>Concomitant medication:</u>						
- Atypical antipsychotic	Cochran, 2014	1 ²⁰	0.24 (0.22-0.25)	0.10 (0.10-0.10)	17 (15-18)	0.77 (0.76-0.79)
- Anxiolytics ^c	Cochran, 2014	1 ²⁰	0.08 (0.07-0.09)	0.99 (0.99-0.99)	7.3 (6.5-8.3)	0.93 (0.92-0.94)
- Tricyclics	Cochran, 2014	1 ²⁰	0.40 (0.38-0.06)	0.92 (0.92-0.92)	5.1 (4.8-5.3)	0.66 (0.64-0.68)

Table 1. Risk factors that predict Prescription Opioid Use Disorder among opioid naïve patients initiating prescription opioids.

Finding	Author, year	Studies, Reference[#]	Sensitivity (95% CI)	Specificity (95% CI)	LR positive (95% CI)	LR negative (95% CI)
- Anticonvulsant	Cochran, 2014	1 ²⁰	0.34 (0.32-0.35)	0.93 (0.93-0.93)	5.0 (4.8-5.3)	0.71 (0.69-0.73)
- Other antidepressants	Cochran, 2014	1 ²⁰	0.45 (0.44-0.47)	0.88 (0.88-0.88)	3.8 (3.7-4.0)	0.62 (0.60-0.64)
- Benzodiazepine	Cochran, 2014	1 ²⁰	0.53 (0.51-0.54)	0.81 (0.81-0.81)	2.7 (2.6-2.8)	0.59 (0.58-0.61)
Any opioid, i.e. all schedule types ^{b,d}	Edlund, 2010	1 ²¹	0.05-0.06 (range)	0.99-0.99 (range)	3.5-4.9 (range)	0.95-0.96 (range)
Opioid dose >120mg/day ^b	Edlund, 2010	1 ²¹	0.20-0.21 (range)	0.94-0.94 (range)	3.2-3.4 (range)	0.85-0.85 (range)

LR= Likelihood Ratio; ^aLR≥2.5 or an LR<0.5 was considered as potentially clinically useful and only select risk factors are reported in this table. See eTable 7 for the full list of eligible risk factors and calculated LR.

^bThe LR range is derived from two separate databases described in this study.²¹

^cBupirone Hydrochloride, Bryan Cochran, Ph.D., email communication, March 8, 2019.

^dPatients received at least 30 days supply of any opioid, i.e., Schedule III or IV AND short-acting schedule II AND long-acting schedule II opioids within a 6-month period.

Table 2. Risk of Prescription Opioid Use Disorder among opioid naïve patients initiating prescription opioids.

Finding	Author, year	Studies, Reference #	Sensitivity (95% CI)	Specificity (95% CI)	LR positive (95% CI)	LR negative (95% CI)
Composite measures/ instruments from included high quality studies^a						
Pain medication questionnaire (PMQ) ≥ 30	Jones, 2015	1 ¹⁸	0.35 (0.23-0.51)	0.86 (0.78-0.92)	2.6 (1.4-4.8)	0.75 (0.60-0.94)
Opioid Risk Tool (ORT) ≥ 8	Jones, 2015	1 ¹⁸	0.25 (0.14-0.40)	0.83 (0.74-0.90)	1.5 (0.76-2.9)	0.90 (0.75-1.1)
The Brief Risk Questionnaire (BRQ) ≥ 3	Jones, 2015	1 ¹⁸	0.73 (0.52-0.85)	0.40 (0.30-0.51)	1.2 (0.96-1.6)	0.67 (0.40-1.1)
The Brief Risk Interview (BRI) $\geq 1^b$	Jones, 2015	1 ¹⁸	0.69 (0.54-0.81)	0.45 (0.34-0.55)	1.2 (0.96-1.6)	0.70 (0.43-1.1)
Screening and Opioid Assessment for Patients with Pain (SOAPP) $\geq 8^c$	Akbik, 2006	1 ¹⁹	0.59 (0.49-0.68)	0.48 (0.42-0.55)	1.2 (0.94-1.4)	0.85 (0.65-1.1)

^a LR ≥ 2.5 or ≤ 0.5 was considered as potentially clinically useful and only select tools from higher quality studies are reported in this table. See eTable 2 for the full list of screening tools.

^b Positive test indicated by the presence of more ‘medium’, ‘medium high’, ‘high’ and ‘very high’ ratings (high risk) than ‘low’ and ‘low medium’ ratings (low risk) on 12 risk categories. The BRI > 1 was used in determining whether or not to prescribe patients opioids.

^c Total N = 397, but only 155/397 of the total participants had Urine Drug Screening information available. Moreover, only those patients who were suspected of “misusing” opioids underwent urine drug screening.

Table 3. Characteristics of opioid risk assessment tools from high quality studies included in quantitative synthesis.

Instrument ^a	Study	No. of Items	Scope	Response Format	Before or during opioid therapy	Score Range	Usual Cutpoint	Literacy Level	Administration or Completion Time, min	Quality score
PMQ	Jones 2015 ¹⁸	26	Specific to prescription opioids in chronic pain care	0="Never"/ "Disagree" to 4="4+ times" / "Agree"	During	0-104	<20.5: low risk 20.5-30.0: moderate 33.3-66.7: high	easy	~10 min	III
ORT	Jones 2015 ¹⁸	10	Specific to prescription opioids	Yes or No	Before	0-26	0-3: low 4-7: moderate ≥8: high	easy	<1 min	III
BRQ	Jones 2015 ¹⁸	12	Specific to prescription opioids for chronic pain	Yes or No and Rating Scales	During	0-24	≥3	easy	unclear	III
BRI	Jones 2015 ¹⁸	12	Specific to prescription opioids for chronic pain	Rating Scales from low- to very high risk	During	n/a	At least 1 area with the highest risk rating	easy	6-12 min	III
SOAPP	Akbik 2006 ¹⁹	14	Specific to prescription opioids in chronic pain care	0="Never" to 4="Very Often"	Before	0-56	≥8	easy	<8 min	III

^aSee eTable 2 for full list and description of all available screening tools. PMQ = Prescription Monitoring Questionnaire; ORT = Opioid Risk Tool; BRQ = Brief Risk Questionnaire; BRI = Brief Risk Interview; SOAPP = Screener and Opioid Assessment for Patients with Pain.

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