EXECUTIVE SUMMARY

Background: In September 2013, the FDA issued a letter to sponsors of approved ER/LA opioid analgesic NDAs, requiring postmarketing studies to assess the risks of misuse, abuse, addiction, overdose, and death.[a] It was ultimately determined that ten observational studies would be necessary to answer these questions (Studies #3033-1 through #3033-10, previously # 2065-1 through # 2065-4).

The subject of this review, PMR #3033-10, specifically, requires "a*n observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.*" When applied to drugs with potential for abuse, the term "doctor/pharmacy shopping" refers to a patient's practice of seeking prescriptions from multiple prescribers without their coordination or knowledge. At present, there is no standard definition of doctor/pharmacy shopping, and its relation to misuse, abuse, and/or addiction has not been well characterized. However, there is no ideal "gold" standard against which to measure the performance of doctor/pharmacy shopping metrics. Therefore, the Opioid PMR Consortium (OPC) is conducting three complementary studies, PMR #3033-8, #3033-9, and #3033-10, that evaluate these metrics in different settings and compare against different measures of misuse, abuse, and addiction— respectively, an administrative claims-based algorithm, patient self-report, and potentially aberrant behaviors documented in the medical record.

The amended Final Study Report for PMR #3033-10, submitted March 14, 2018 is the subject of this review. **The purpose of this review is twofold: (1) to determine whether this study fulfills PMR #3033-10, and (2) to interpret the findings of the study as they relate to doctor/pharmacy shopping outcomes metrics as a measure of possible misuse, abuse, and/or addiction.**

Methods: This study was a retrospective analysis of prescription opioid dispensing history and review of linked medical records, using the HealthCore Integrated Research Database (HIRD). The study population included adult patients with at least two opioid dispensings; at least one opioid must have been dispensed in 2012 with an additional one within the following 18 months. Patients were excluded if their charts could not be obtained, or if they had a known history of substance abuse identified through the administrative claims data. A four-category doctor/pharmacy shopping classification scheme based on that developed in PMR #3033-8 was evaluated in relation to behaviors suggestive of misuse, diversion, abuse, and/or addiction documented in the medical record. Behavior outcomes were defined as having at least one, two, and three behaviors documented, or having at least one behavior in either of two behavior clusters derived using cluster analysis. One cluster included behaviors that explicitly referenced abuse, misuse, and addiction; the other cluster included behaviors that suggested excessive healthcare utilization. The doctor-shopping models, both with and without covariates, were also evaluated for their ability to predict the behavior outcomes and to discriminate between those with and without potentially aberrant behavior outcomes.

Results: Overall, 78% of eligible opioid users in the HIRD showed no shopping, 11% minimal shopping, 8% moderate shopping, and 4% severe shopping. Compared to those in the no shopping group, those with higher levels of possible shopping behavior were younger and female, had higher levels of healthcare utilization, general pain complaints, and psychiatric comorbidity,

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[a] https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf

and a higher total number of opioid dispensings.

Compared to the no shopping category, only the severe doctor/pharmacy shopping category (>4 opioid prescribers and >2 pharmacies during an 18-month period) was significantly associated with having at least one, two, or three behaviors (AORs 2.4, 3.3, 6.3, respectively) or having a behavior in either cluster (AORs 4.1 and 2.1) identified in the medical record. Although a gradient was observed for mild and moderate shopping categories, being in these categories was not significantly associated with any of the potentially aberrant behavior outcomes.

Across all outcomes, the adjusted model consisting of the doctor/pharmacy shopping category and covariates performed modestly better than the covariate-only model in predicting the outcome, suggesting that the inclusion of doctor/pharmacy shopping category does contribute significant explanatory information to modeling the probability of identifying a potentially aberrant behavior in the medical record, after accounting for the number of opioid dispensings, other healthcare utilization measures, and sociodemographic information.

For the shopping-only and shopping-and-covariates models to predict each of the five outcomes, a cut-off value was selected to maximize the sum of sensitivity and specificity of classifying the outcome. Sensitivity ranged from 0.41 to 0.73, specificity ranged from 0.61 to 0.77, positive predictive value (PPV) ranged from 0.19 to 0.64, and negative predictive value (NPV) ranged from 0.59 to 0.96.

<u>Interpretation and Conclusions</u>: **This study met its stated objectives and fulfills PMR #3033-10.** Although the study was not able to validate a doctor-pharmacy shopping classification scheme against a gold-standard measure of clinically-confirmed misuse, abuse, and/or addiction, it provided some valuable insights on the value of doctor-pharmacy shopping metrics. Being in the most extreme shopping category (>4 opioid prescribers and >2 pharmacies during an 18-month period) was significantly associated with having behaviors in the medical record potentially related to misuse, abuse, and/or addiction. However, neither alone nor in combination with other patient and prescription characteristics, did shopping category discriminate well between patients with and without these behaviors. In particular, the positive predictive value was low, indicating that a high proportion of patients who would be identified as "severe doctor shoppers" using this definition do not have any evidence of aberrant behaviors in their medical record. Therefore, although claims-based evidence of use of multiple prescribers and pharmacies may be one factor possibly indicating an elevated risk of misuse, abuse, and/or addiction, it should not be used as a proxy outcome for abuse, misuse, diversion, and/or addiction, as it is likely to misclassify a high proportion of patients. As expected, the study had multiple limitations—including, importantly, the exclusion of individuals with claims for substance use disorders and the limited ability to detect misuse, abuse, and addiction in the medical record— and it will be most useful when findings are interpreted together with those of its complementary doctor/pharmacy-shopping studies, PMR 3033-8 and 3033-9.

1 INTRODUCTION

1.1 BACKGROUND AND REGULATORY HISTORY

The first extended-release/long-acting (ER/LA) opioid analgesic was approved by the FDA in 1987. Since this time, multiple additional NDAs have been approved. Based on a review of the literature, the Food and Drug Administration (FDA) concluded that more data are needed regarding the serious risks of misuse, abuse, addiction, overdose, and death associated with the long-term use of extended release/long acting (ER/LA) opioid analgesics. Thus, in September 2013, the FDA issued a letter to sponsors of approved ER/LA opioid analgesic NDAs, requiring

five postmarking studies to assess these risks—four observational studies and one randomized trial.[b] It was ultimately determined that ten observational studies and one trial would be necessary to answer the questions posed in the original five post-marketing requirements (PMRs), and in February 2016, the original four PMRs were released and a new letter sent re-issuing the PMRs as ten observational studies and one trial.[c] The ten observational studies are labeled Study #3033-1 through #3033-10 (Previously # 2065-1 through # 2065-4).

PMR #3033-10, specifically, requires "a*n observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.*" When the applied to drugs with potential for abuse, the term "doctor/pharmacy shopping" refers to a patient's practice of seeking prescriptions from multiple prescribers without their coordination or knowledge. At present, there is no single standard definition of doctor/pharmacy shopping, or a model that adequately describes doctor/pharmacy shopping and its relation to misuse, abuse, and/or addiction. Furthermore, there is not an ideal "gold" standard against which to measure the performance of doctor/pharmacy shopping metrics. Therefore, the Opioid PMR Consortium (OPC) is conducting three complementary studies, PMR #3033-8, #3033-9, and #3033-10, that evaluate these metrics in different settings and comparing against different measures of misuse, abuse, and addiction—respectively, an administrative claims-based algorithm, patient self-report, and potentially aberrant behaviors documented in the medical record. The overarching objective of these three studies is to define and validate possible doctor/pharmacy shopping metrics as measures indicative of misuse, diversion,[d] abuse, and/or addiction.

On June 22, 2017 the OPC submitted the Final Study Report of Observational Study #3033-10, conducted to fulfill PMR #3033-10. In response to a November 6, 2017 FDA Information Request, the OPC submitted an amended Final Study Report for this study on March 14, 2018. This amended report is the subject of this review. **The purpose of this review is twofold: (1) to determine whether this study fulfills PMR #3033-10, and (2) to interpret the findings of the study as they relate to doctor/pharmacy shopping outcomes metrics as a measure of possible misuse, abuse, and/or addiction.**

1.2   REVIEW METHODS AND MATERIALS

The subject of this review is the amended Final Study Report for "Observational Study #3033-10 (formerly #2065-4C): Retrospective cohort study to evaluate the relation between doctor/pharmacy shopping and outcomes suggestive of misuse, diversion, abuse and/or addiction by medical record review," submitted to FDA on March 14, 2018.

We will determine whether the objectives outlined in the final, approved study protocol have been met and the planned analyses have been conducted, thereby fulfilling the PMR. We will also summarize and interpret the findings of the study using fundamental principles of epidemiology.

2   REVIEW RESULTS

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[b] https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf

[c] https://www fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM484415.pdf

[d] The OPC included diversion as an outcome of interest in this study. Although FDA agreed to its inclusion as an exploratory outcome, the focus of this review will be the safety outcomes explicitly required as part of the PMR: misuse, abuse, and addiction.

2.1   STUDY OVERVIEW

	Study
1.1 Objectives/Aims/Scope	To assess whether the percentage of patients with behaviors suggestive of misuse, diversion, abuse and/or addiction described in the medical record increased across increasing categories of possible doctor/pharmacy shopping behavior.
1.2.1 Design	
1.2.1.1 Type/setting	Retrospective analysis of prescription opioid dispensing history and review of linked medical records
1.2.1.2 Data Source	HealthCore Integrated Research Database^{SM} [HIRD]
1.2.1.3 Time Period	2012-2014
1.2.1.4 Criterion (Selection) Standards	Adult patients with at least two opioid dispensings; at least one opioid must have been dispensed in 2012 with an additional one within the following 18 months. Patients must have had continuous enrollment in a health plan included in the HIRD for at least six months prior to and for at least 18 months following the date of the first IR or ER/LA opioid dispensing. Patients were excluded if their charts could not be obtained, or if they had a known history of substance abuse identified through the administrative claims data.
1.2.3 Exposure/Intervention	Category of possible doctor/pharmacy shopping: 1. No shopping behavior • 1 prescriber OR • 1 pharmacy OR • 2 prescribers AND 2 pharmacies 2. Minimal shopping behavior • 2 prescribers AND >2 pharmacies OR • 3 or 4 prescribers AND 2 pharmacies 3. Moderate shopping behavior • 3 or 4 prescribers AND >2 pharmacies OR • >4 prescribers AND 2 pharmacies 4. Severe shopping behavior • >4 prescribers AND >2 pharmacies
1.2.4 Outcome(s)	Five primary outcomes: • Two are clusters of behaviors that represent two latent underlying factors among the behaviors suggestive of

	misuse, diversion, abuse, and/or addition. Clusters are derived using factor analysis, or cluster analysis. One cluster included behaviors that explicitly referenced abuse, misuse, and addiction; the other cluster included behaviors that suggested excessive healthcare utilization. • The other three primary outcomes include having documented in the medical record at least one, at least two, and at least three of the behaviors suggestive of misuse, diversion, abuse, and/or addition.

1.2.5 Covariates	• Age in years
	• Gender
	• Geographic region of residence
	• Type of opioids used
	    ○ Immediate release (IR) only
	    ○ ER/LA only
	    ○ Both IR and ER/LA
	• Number of total opioid dispensings
	• Number of distinct prescribers identified
	• Number of distinct pharmacies identified
	• Duration of opioid use
	• Opioid dose
	• Individual psychiatric comorbidities and number
	• Individual pain diagnoses and number
	• Use of other medications with abuse potential
	• Types of healthcare facilities where the patient sought care
	• Number of office visits

1.2.6 Sample Size	A stratified random sample of patients was selected for medical record review; the number of patients in each of the four categories of doctor/pharmacy shopping, based on pre-specified power calculations, was as follows: • No shopping behavior: 115 patients • Minimal shopping behavior: 139 patients • Moderate shopping behavior: 147 patients • Severe shopping behavior: 189 patients
1.2.7 Statistical Analyses	Descriptive statistics: the number and percentage of patients in each category having any of the five outcomes. For each of the outcomes, the association with possible doctor/pharmacy shopping category status was examined using

	logistic regression, computing crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) to compare the following possible doctor/pharmacy shopping categories: • Minimal versus no shopping • Moderate versus no shopping • Severe versus no shopping In addition to crude and adjusted models, a covariates-only model was constructed for each outcome and compared to the full model to evaluate the additional contribution of doctor/pharmacy shopping to the model. The receiver operating characteristic (ROC) curve of the unadjusted model (i.e., logistic model including doctor/pharmacy shopping only) and full model were calculated, identifying the point on the ROC curve that maximized the sum of sensitivity and specificity. Performance metrics of the unadjusted and the full models (sensitivity, specificity, positive predictive value, and negative predictive value to discriminate patients with each outcome) were calculated based on this cut-off point.
1.2.8 Study Results	Overall, 78% of eligible opioid users in the HIRD showed no shopping, 11% minimal shopping, 8% moderate shopping, and 4% severe shopping. Only the severe doctor/pharmacy shopping category was significantly associated with having at least one, two, or three behaviors (Adjusted ORs 2.4, 3.3, 6.3, respectively) or having a behavior in either cluster (Adjusted ORs 4.1 and 2.1). A gradient was observed for mild and moderate shopping categories, but being in these categories was not significantly associated with any of the potentially aberrant behavior outcomes. Across all outcomes, the adjusted model consisting of the doctor/pharmacy shopping category and covariates performed modestly better than the covariate only model in predicting the outcome, suggesting that the inclusion of doctor/pharmacy shopping category does contribute significant explanatory information to modeling the probability of detecting a potentially aberrant behavior, after accounting for the number of opioid dispensings, other healthcare utilization measures, and sociodemographic information. Using a cut-off point that maximized the sum of sensitivity and specificity and the performance of the shopping-only (unadjusted) and shopping-and-covariates (adjusted) models in predicting each of the five outcomes, sensitivity ranged from 0.41 to 0.73, specificity ranged from 0.61 to 0.77, positive predictive value (PPV) ranged from 0.19 to 0.64, and negative predictive value (NPV) ranged from 0.59 to 0.96.

	Within the severe shopping category, 56% had evidence in the medical record that the prescriber was aware of at least one other prescriber.
1.2.9. Conclusions	Being in the most extreme doctor/pharmacy shopping category (>4 opioid prescribers and >2 pharmacies during an 18-month period) was significantly associated with having behaviors in the medical record potentially related to misuse, abuse, and/or addiction. However, neither alone or in combination with other patient and prescription characteristics, did shopping category discriminate well between patients with and without these behaviors.

2.2   STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

The overarching objective of PMR studies #3033-8, #3033-9, and #3033-10 was to define and validate possible doctor/pharmacy shopping as outcomes suggestive of misuse, diversion, abuse, and/or addiction.

The objective of Study #3033-10 was to assess whether the percentage of patients with behaviors suggestive of misuse, diversion, abuse, and/or addiction described in the medical record increased across pre-specified increasing categories of possible doctor/pharmacy shopping behavior.

2.3   STUDY METHODS

2.3.1   Design & Setting

2.3.1.1   Study Type

This was a retrospective analysis of prescription opioid dispensing history linked to review of medical records.

2.3.1.2   Data Source, Setting & Time Period

The study was conducted in the HealthCore Integrated Research Database (HIRD), a large administrative insurance and health plan database with longitudinal medical and pharmacy claims. For the subset of patients who are "fully insured," meaning that risk for patient insurance costs is held by the health plan contributing data to the HIRD rather than by an employer group for which only administrative services are offered by the contributing health plan, the HIRD can be linked to inpatient and outpatient medical records from healthcare providers who submit claims captured in the data source. As of July 2014, the database contained approximately 36.1 million lives with medical and pharmacy eligibility, of which 8.5 million were currently active.

The first recorded dispensing of an IR or ER/LA opioid in 2012 defined the index date. The baseline period included all data prior to the index date, and had a minimum duration of six months per the study inclusion criteria. The follow-up period during which the investigators assessed possible doctor/pharmacy shopping behavior included the first 18 months following the index date. For patients with a presumed death event prior to 18 months after the index date, the follow-up period consisted of the time between the index date and the claims-identified presumed

	disorder		month but does not return).
Excessive phone calls requesting opioids	Characteristic associated with opioid misuse status in retrospective medical record review study. Aberrant Drug Behavior criteria used in Prescription Opioid Therapy Questionnaire	Cheatle, 2013 [3] Chabal, 1997 [5] Jamison, 2010 [6]	Medical record indicates one or more of the following: • Phone calls requesting opioids. Number of phone calls identified will be recorded. • Notes indicating that the office believes that the number of contacts pertaining to the patient seeking opioids is excessive.
Excessive visits requesting opioids	Committee of the Seattle Veterans Affairs Medical Center consensus item validated in a pain clinic setting.	Chabal, 1997 [5]	Medical record indicates one or more of the following: • Visits where the patient requested opioids. Number of visits identified will be recorded. • Notes indicating that the office believes that the number of visits related to the patient seeking opioids is excessive.
Requested refills instead of clinic visit	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Characteristic associated with substance use disorder	Webster, 2005 [1] Fleming, 2007 [4]	Medical record indicates one or more of the following: • At least one instance where the patient asked for a refill instead of a visit. • At least one attempt to obtain a refill without a visit in phone log or administrative notes.

Reported lost or stolen prescriptions	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Characteristic associated with opioid misuse status in retrospective medical record review study. Aberrant Drug Behavior criteria used in Prescription Opioid Therapy Questionnaire	Webster, 2005 [1] Cheatle, 2013 [3] Jamison, 2010 [6]	Medical record indicates one or more of the following. Each will be recorded separately. • Patient states that the prescription for opioids was lost, misplaced, or inadvertently destroyed (e.g., spilled, thrown away, etc). • Patient states that the prescription for opioids was retrieved from the pharmacy by someone not authorized by the patient. • Patient states that the prescription for opioids was stolen either from the pharmacy or from the patient. • Patient reported never receiving filled prescriptions (e.g. mail order prescription).

Loses medications more than once	Item from a validated questionnaire that was positively associated with addiction status. Aberrant Drug Behavior criteria used in validation of the Opioid Risk Tool. Committee of the Seattle Veterans Affairs Medical Center consensus item validated in a pain clinic setting.	Compton, 1998 [7] Witkin, 2013 [2] Chabal, 1997 [5]	Provide a count of the number of instances where the patient's opioid prescription was lost, misplaced or inadvertently destroyed.
Requested early refills more than once from same provider	Item from a validated questionnaire that was positively associated with addiction status. Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Characteristic associated with substance use disorder	Compton, 1998 [7] Webster, 2005 [1] Fleming, 2007 [4]	Provide a count of the number of instances where the patient requested an early refill.

Was discharged from practice because of egregious aberrant behavior or placed on a watch list	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Aberrant Drug Behavior criteria used in validation of the Opioid Risk Tool.	Webster, 2005 [1] Witkin, 2013 [2]	Medical record indicates one or more of the following: • Practice has discontinued care of the patient due to violation of a Patient-Prescriber Agreement for their opioid medication; • Patient is under probation with the practice or dismissed due to suspected abuse, misuse, addiction or diversion of their opioid analgesics; • Patient is under probation with the practice or dismissed due to abusive behavior towards staff; • Patient is under probation with the practice or dismissed due to other behaviors where an explicit mention of opioids is noted in the medical record. • Engaged in violent or confrontational behavior that let to termination of care by the pain physician.
Resisted therapy changes/alternative	Aberrant behavior indicating abuse of	Webster, 2005 [1]	Medical record indicates one or more of the following. Each will be captured separately.

therapy	opioids used in validation of the Opioid Risk Tool. Characteristic associated with opioid misuse status in retrospective medical record review study. Aberrant Drug Behavior criteria used in Prescription Opioid Therapy Questionnaire	Cheatle, 2013 [3] Jamison, 2010 [6]	• Patient insisted on a particular formulation of opioid analgesic; ◦ Insists on a specific product name; ◦ Insists on non-abuse deterrent formulations; • Patient insisted on opioid therapy versus alternative pain management forms; • Patient was not compliant with non-opioid pain medication or therapy (e.g., did not follow up on physical therapy referral); • Patient resisted change in opioid product; • Patient resisted change to opioid dose; • Patient resisted change from opioid to non-opioid pain medication. • Reports a bad past experience or no relief by non-opioid or alternative products offered.
Patient has persistent/non-modifiable pain	Characteristic associated with substance use disorders.	Larson, 2007 [8] Liebschutz, 2010 [9] Potter, 2008 [10] Cheatle, 2014 [3]	Medical record indicates one or more of the following: • Pain scores or other markers of patient-reported pain do not change with treatment, time of day, or other factors. • Patient reports that nothing decreases their pain.
Multiple causes of pain are reported	Characteristic evaluated as a marker of abuse in a retrospective medical record review study.	Cheatle, 2014 [3]	Medical record indicates one or more of the following: • More than one painful condition; or • Multiple pain complaints requiring opioids (different pain sites/new injuries).

Third party required to manage patient's medications	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record indicates one or more of the following: • Patient is under the care of a conservator; • Patient is enrolled in a drug treatment program that manages their pain medication; • Pain medication is dispensed to the patient only through a third party (nurse, primary care aid, etc).
Sold prescription	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record indicates that patient sold a prescription/medication or solicited assistance in selling a prescription/medication, either by the patient's own admission, by the statement of a personal contact of the patient, or through records of legal action taken against the patient.
Inappropriate dose, source or route used			

Obtains opioids from a non-medical source	Item from a validated questionnaire that was positively associated with addiction status. Committee of the Seattle Veterans Affairs Medical Center consensus item validated in a pain clinic setting.	Compton, 1998 [7] Chabal, 1997 [5]	Medical record indicates that patient purchased opioids from a non-medical source (e.g., drug dealer, friend), either by the patient's own admission, by the statement of a personal contact of the patient, or through records of legal action taken against the patient.
Forged prescription	Item from a validated questionnaire that was positively associated with addiction status. Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Compton, 1998 [7] Webster, 2005 [1]	Medical record indicates that patient forged a prescription or solicited assistance in forging a prescription, either by the patient's own admission, by the statement of a personal contact of the patient, or through records of legal action taken against the patient.
Injected drug	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record indicates that patient injected opioids, either by the patient's own admission, by the statement of a personal contact of the patient.
Used additional opioids than those prescribed	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record indicates that patient acquired and used an opioid medication not prescribed by this healthcare provider, either by the patient's own admission or by the statement of a personal contact of the patient.

Unauthorized dose escalation	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Aberrant Drug Behavior criteria used in validation of the Opioid Risk Tool. Aberrant Drug Behavior criteria used in Prescription Opioid Therapy Questionnaire	Webster, 2005 [1] Witkin, 2013 [2] Jamison, 2010 [6]	Medical record indicates that patient has used more opioid than was prescribed, either by the patient's own admission or by the statement of a personal contact of the patient.
Emergency Room (ER) visits to get opioids	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Item from a validated	Webster, 2005 [1] Compton, 1998 [7] Cheatle, 2013 [3]	Medical record indicates: • Provide a count of the number of ER visits recorded where the patient requested treatment for pain. • Provide a count of the number of ER visits recorded where the patient requested

	questionnaire that was positively associated with addiction status. Characteristic evaluated (but not associated with misuse) in retrospective medical record review study. Committee of the Seattle Veterans Affairs Medical Center consensus item validated in a pain clinic setting. Aberrant Drug Behavior criteria used in Prescription Opioid Therapy Questionnaire	Chabal, 1997[5] Jamison, 2010 [6]	opioids. • Provide a count of the number of ER visits recorded where the patient requested opioids and there was reference to a primary care provider or pain specialist referring the patient to the ER.
Save/hoard unused medication	Item from a validated questionnaire that was positively associated with addiction status. Characteristic associated with substance use disorder.	Compton, 1998 [7] Fleming, 2007 [4]	Medical record indicates that patient has saved or hoarded unused opioid medications that were prescribed, either by the patient's own admission or by the statement of a personal contact of the patient.

Solicited opioids from other providers	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Committee of the Seattle Veterans Affairs Medical Center consensus item validated in a pain clinic setting.	Webster, 2005 [1] Chabal, 1997 [5]	Medical record indicates that patient has sought opioids from another provider, either by the patient's own admission, by the statement of a personal contact of the patient, or by records of communication between healthcare providers (discharge summary copied in the medical record, specialist visit notes, etc).
Explicit reference to abuse, misuse or addiction			
Abused prescribed drug	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record contains reference to opioid abuse, including: • Illegal use of the drug; • Use of more drug than prescribed for non-medicinal reasons; • Use of quantities or routes (e.g., injection, snorting) of the drug meant to enhance intoxication; • Explicit reference to "abuse"

Physician believes patient is addicted	Item from a validated questionnaire that was positively associated with addiction status.	Compton, 1998 [7]	Medical record states that either • The physician suspects opioid addiction • The physician has referred the patient for addiction treatment services • Physician describes impaired control over drug use, compulsive use, continued use despite harm, and craving
Patient believes patient is addicted	Item from a validated questionnaire that was positively associated with addiction status.	Compton, 1998 [7]	Medical record states that either • The patient suspects opioid addiction, and has shared this with the physician or staff • Patient reports impaired control over drug use, compulsive use, continued use despite harm, and craving
Family believes patient is addicted	Item from a validated questionnaire that was positively associated with addiction status.	Compton, 1998 [7]	Medical record states that either • The family suspects opioid addiction, and this has been shared via telephone or other communication • The family suspects opioid addiction as relayed to the healthcare provider by the patient. • Contacts report impaired control over drug use, compulsive use, continued use despite harm, and craving

Use opioids for purpose other than pain	Item from a validated questionnaire that was positively associated with addiction status. Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Characteristic associated with substance use disorder.	Compton, 1998 [7] Webster, 2005 [1] Fleming, 2007 [4]	Medical record indicates any of the following. <u>Each will be recorded separately.</u> • The patient requested/wanted opioids for anxiety; • The patient requested/wanted opioids for depression; • The patient requested/wanted opioids for sleep disturbances; • The patient was seeking euphoria or intoxication from opioids; or • The patient used opioids for a purpose other than pain.
Risk factors			
Spouse/significant other has a drug abuse problem	Item from a validated questionnaire that was positively associated with addiction status.	Compton, 1998 [7]	Medical record indicates: • The patient's spouse/significant other has a suspected or confirmed drug abuse problem; • The patient's spouse/significant other is seeking treatment for drug abuse.

Concurrent or history of substance abuse	Medical record review study showing that abuse history was associated with aberrant drug behavior.	Michna, 2004 [11]	Medical record indicates: • References to substance abuse either by the patient's own admission, by the statement of a personal contact of the patient, or by records of communication between healthcare providers • Physician recommendation for substance abuse treatment programs • Patient is enrolled in a substance abuse treatment program • Please record current substance abuse and history of substance abuse separately.
Concurrent or history of abuse of alcohol	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Item from a validated questionnaire that was positively associated with addiction status. Medical record review study showing that abuse history was associated with aberrant drug behavior.	Webster, 2005 [1] Compton, 1998 [7] Michna, 2004 [11]	Medical record indicates: • References to alcohol abuse either by the patient's own admission, by the statement of a personal contact of the patient, or by records of communication between healthcare providers • Physician recommendation for alcohol abuse treatment programs • Treatment with products used off-label for alcohol abuse (topiramate, etc) with explicit reference that the medication is given for alcohol abuse • Current alcohol abuse and history of alcohol abuse will be recorded separately.

Use of alcohol for pain management	Characteristic associated with substance use disorder.	Fleming, 2007 [4]	Medical record indicates one or more of the following. Each will be captured separately. • Patient used alcohol because of pain; or • Patient used alcohol and opioids together.

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