PROTOCOL

Association between opioid tapering and heroin use among people on chronic opioid therapy: a case control study

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VERSION 1/22/19

Background

Opioids have strong tolerance effects and are associated with physiologic dependence. As a result, exposure to decreases in dose may lead to increased pain and withdrawal. Tapered patients may therefore seek illicit opioids such as heroin or other drugs paradoxically increasing their risk for substance use disorder and overdose. It has been suggested that tapering policies are unintentionally contributing to increased overdoses due to heroin and illicitly manufactured fentanyl implying that overdose may, paradoxically, also be an adverse effect of tapering. It is unknown what kinds of tapering practices (i.e., sudden reduction or gradual overall decrease) could lead to these risks.

Aims and Hypotheses

Aim: To examine the association between opioid tapering and the incidence of heroin use and overdose among a population of individuals prescribed chronic opioid therapy.

Study Design

We will conduct a nested case control within a retrospective cohort study. The observation period will be 2006 through 2017. The cohort will consist of patients prescribed chronic opioid therapy, defined as ≥3 opioid dispensings of ≥10 average daily milligram morphine equivalents (MME) in a 90-day period. Patients are required to have at least 30 days enrollment after their index date. We will exclude buprenorphine-containing products and methadone dispensed in an addiction treatment center. We will use SAS text string search to locate use of heroin in the medical record. To confirm heroin use, electronic medical record review will be performed. Heroin use cases will be matched to up to 20 controls using risk set sampling, matched on demographic and descriptive variables. Patients will be followed until disenrollment, death or June 30, 2018.

Cases

Within the cohort of patients taking chronic opioid therapy, we will identify heroin use using a combination of ICD codes, an automated text string search to identify mention of heroin in the medical record, and manual chart review to confirm heroin use date.

Controls

We will use risk set sampling on the length of enrollment since entry into the cohort. Cases and controls are required to have at least the same amount of enrollment from the index dose to the index date.

Covariates

We will examine the following variables: age, gender, race/ethnicity, and insurance status; clinical diagnosis such as pain diagnoses, accidents and injuries, hepatitis C, mental health disorder diagnoses, alcohol use disorder and related conditions, length of time prescribed opioids, and tobacco or drug use documented in the social history or diagnosed as use disorder diagnoses. Also, utilization variables will

include outpatient, inpatient, and emergency department settings, surgical procedures, pharmacy dispensings.

Analyses

We will conduct a descriptive analysis comparing the demographic and clinical factors associated of the eligible cases of heroin use. We will analyze the cases and controls using conditional logistic regression to estimate matched odds ratios (mORs) and 95% confidence intervals (95% CIs). For the primary regression analysis, the dependent variable will beheroin use (yes/no) and the main exposure variable will be tapering status (yes/no). As a secondary analysis, we will compare the rate of tapering to the stable referent group. We will use the mORs estimated from the regression models to calculate the percentage attributable risk among individuals who were tapered and the attributable risk in the total population.

Role of the Funding Source

This study is supported by cooperative agreement U01 CE002791 through the Centers for Disease Control and Prevention. The funding source has scientific input in the design, conduct, or reporting of the study.

CHANGES TO THE PROTOCOL

Version 1/2/2020

Original Aim: To examine the association between opioid tapering and the incidence of heroin use and overdose among a population of individuals prescribed chronic opioid therapy.

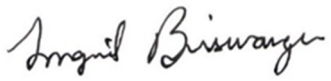
Outcome specification: We opted to examine opioid discontinuation of 45 or more days as the indicator of tapering. Tapering can either result in a discontinuation or a lowered dose. Identifying and categorizing tapering that resulted in a lowered dose but not a discontinuation into a meaningful outcome was found to be challenging using electronic dispensing data, as there was no consistent way to identify the start and end of the taper. This change was discussed with our CDC partner and approved in advance of our analysis.

Original Covariates

We will examine the following variables: age, gender, race/ethnicity, and insurance status; clinical diagnosis such as pain diagnoses, accidents and injuries, hepatitis C, mental health disorder diagnoses, alcohol use disorder and related conditions, length of time prescribed opioids, and tobacco or drug use documented in the social history or diagnosed as use disorder diagnoses. Also, utilization variables will include outpatient, inpatient, and emergency department settings, surgical procedures, pharmacy dispensings.

Covariates: We reduced the number of covariates given the number of cases that could be analyzed to reduce sparse data. We used the Charlson comorbidity score to collapse comorbidities into a single measure and to account for patients who may have high health care utilization. We also chose not adjust for drug use disorder because we suspected it may be part of the causal pathways and would therefore be inappropriate to adjust for.

Signed



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5/5/20

Date