SIGNIFICANCE

Mortality and morbidity related to suicidal behavior and opioid use disorder (OUD) have increased significantly over the past decade. In the US, suicide and self-harm account for over 48,000 deaths and almost 500,000 emergency department visits annually[1]. Opioid overdoses account for over 47,000 deaths annually as well as approximately 100,000 hospitalizations and 200,000 emergency department visits[2, 3].

These two public health crises are intertwined at multiple levels[4, 5]:

- People with a range of mental health conditions are at high risk for both suicidal behavior[6] and OUD[4, 5]:
- Opioid use[7] and OUD[8] increase risk of developing a mood or anxiety disorder.
- Chronic pain is associated with increased risk of mood or anxiety disorder[9] and suicidal behavior[10].
- The boundary between unintentional and intentional opioid overdose is indistinct[4].
- Shared social and environmental factors increase risk of OUD and suicidal behavior[5].
- Withdrawal from or forced tapering of opioids may increase risk of suicidal behavior[11].

Reflecting these bi-directional relationships, risk of suicidal ideation and behavior is markedly increased in people with OUD, with highest risk for more severe outcomes[12, 13]. Compared to the general population, people with OUD are approximately 50% more likely to report suicidal ideation, twice as likely to report attempting suicide, and several times more likely to die by suicide[14].

Medications for OUD, especially buprenorphine, have the potential to decrease illicit opioid use and reduce the multiple negative consequences of OUD, including fatal and nonfatal overdose, criminal justice involvement, infectious complications, and misuse of other substances[15].

In addition, buprenorphine may also have specific effects on suicide risk. Several small randomized trials of buprenorphine treatment in treatment-resistant depression (with or without co-occurring OUD) suggest that buprenorphine may reduce depressive symptoms and suicidal ideation[16-19].

These data suggest that increased use of buprenorphine in people with OUD, especially among those at increased risk for suicide, could significantly reduce suicidal behavior, acting via multiple pathways:

- Direct effects on depressive symptoms and suicidal ideation
- Indirect effects via avoidance of repeated episodes of opioid withdrawal
- Indirect effects via improved functioning and reduced exposure to social or environmental insults

No conceivable randomized trial, however, would be large enough to assess effects of buprenorphine on suicidal behavior. Consequently, we propose a large observational study to evaluate the effects of initiating buprenorphine treatment on subsequent suicidal behavior among people with documented OUD, including those with and without co-occurring mental health conditions or other risk factors for suicidal behavior.

The proposed new research will take advantage of a range of previous research by MHRN investigators as well as research in MHRN health systems by the Health Systems Node of the NIDA Clinical Trials Network. Relevant prior research includes:

- Methods and tools to assess mental health diagnoses and treatments using health system records[6, 20-24]
- Use of health records data to assess OUD diagnoses and treatments[25-31]
- Population-based ascertainment of suicidal behavior[6, 20-22, 32]
- Development of machine learning models to predict suicidal behavior[6, 23]
- Methods for causal inference from observational designs[33, 34]

INNOVATION

No previous research has examined the effect of buprenorphine (or other treatments for OUD) on suicidal behavior. In addition, this work will take advantage of newly available tools and methods, including:

- Standard assessments of depression, suicidal ideation, and substance use in MHRN health systems
- Translation of risk prediction models to use for causal inference regarding therapeutics
- Use of real-world health system data to evaluate off-target therapeutic effects

APPROACH

Overview

We propose to use population-based data from four large MHRN health systems to examine the effect of initiating buprenorphine treatment for OUD on risk of suicidal behavior over the following 90 days.

Settings

The four health systems contributing to this research serve a combined population of approximately 11.5 million patients. Each health system provides comprehensive health services, including mental health specialty care, specialty care for substance use disorders, outpatient general medical care, emergency department care, and inpatient care. As integrated health systems providing both direct care and insurance coverage, these health systems have access to comprehensive data regarding care provided by internal providers or facilities (via electronic health records) and care provided externally (via insurance claims). In each health system, patients served are representative of the service area population. As shown in the table below, patients include large numbers enrolled via Medicare or Medicaid and large numbers from traditionally under-represented racial and ethnic groups.

	# Patients or Members	# Insured by		# by Race/Ethnicity			EHR Data Since
		Medicare	Medicaid	Black	Asian	Hispanic	
Henry Ford Health	1,234,911	253,178	245,516	282,456	32,492	41,532	2012
KP Northern Cal	4,477,759	710,699	282,722	268,667	744,014	766,609	2004
KP Southern Cal	4,907,940	522,236	413,267	355,324	433,941	1,584,620	2004
KP Washington	817,429	116,438	13,408	19,906	40,670	21,912	2005
TOTAL	11,438,039	1,602,551	954,913	926,353	1,251,117	2,414,673	

Data Resources

Research centers at each participating health system maintain comprehensive research data warehouses following the Health Care Systems Research Network Virtual Data Warehouse model[35]. At each site, original data sources (electronic health records, insurance claims, pharmacy dispensings, etc.) are transformed to a common format and file structure, allowing efficient and accurate use of standard programs to conduct multi-site research. Specific data tables relevant to this proposed work include:

- Enrollment – includes dates and source of coverage for current and past periods of health plan enrollment (used to assess completeness of capture for services in external facilities)
- Utilization – includes dates, diagnosis codes, procedure codes, specialty/department codes for all inpatient and outpatient services, including telephone and online encounters - including codes for OUD treatments administered in outpatient settings and medication assisted treatment facilities
- Pharmacy – includes dates, drug identifiers (NDC, RxNorm), quantity, days supply, and formulary status for all filled outpatient prescriptions – including medications for OUD and pain management
- Patient-reported outcomes – Includes item-level data for standard questionnaires administered at outpatient visits, during inpatient encounters, or online - including PHQ-9 depression questionnaires[36-38], Columbia Suicide Severity Rating Scales[39], AUDIT-C alcohol questionnaires, and drug use screens.
- Cause of death – Includes detailed cause of death data via routine linkage to state vital statistics data

Sample

Outpatient visits between 1/1/2012 and 12/31/2019 with a recorded diagnosis of OUD will be eligible for inclusion in the buprenorphine treatment group or untreated control group, subject to the following limitations or exclusions:

- Age >=16 on day of visit
- Enrolled in participating health system on day of visit and for the prior 12 months

- No filled prescription for buprenorphine or other medication for treatment of OUD (extended release naltrexone, methadone) in the prior 12 months

Any eligible visit followed by a filled outpatient prescription for buprenorphine formulations used to treat OUD within 7 days will be included in the treatment group.

Any eligible visit NOT followed by a filled prescription for buprenorphine or other medication for OUD within 90 days will be eligible for inclusion in the comparison group.

This sampling strategy would allow multiple visits per person to be eligible and allow separate visits by a single individual to be included in both the treatment and comparison groups. We discuss below our analytic strategy to account for this clustering.

Outcome

The primary study outcome will be suicidal behavior (suicide death, non-fatal suicide attempt, or other deliberate self-harm diagnosis) over 90 days following the index visit. Secondary analyses will consider 30- and 180-day periods.

Suicide deaths will be ascertained from cause-of-death data tables in each site's research data warehouse (originally sourced from state mortality data). Following methods used in previous MHRN research[6, 20-22] primary analyses will include deaths coded as either due to self-inflicted injury or poisoning (ICD10 codes X60-X84) or due to injury or poisoning with undetermined intent (Y10-Y34). Secondary analyses will exclude deaths coded as due to undetermined intent (expected to contribute approximately 5% of the events in an at-risk population based on prior MHRN research).

Non-fatal suicide attempts and other deliberate self-harm will be ascertained from research data warehouse encounter diagnosis tables, including diagnoses from ambulatory encounters, emergency department encounters, and inpatient encounters. Previous MHRN research[6, 22, 32, 40] has included injuries and poisonings coded as either due to self-harm or due to undetermined intent (with undetermined intent events contributing approximately 20% of the total). Research now underway is examining full-text records from encounters with diagnoses in three "borderline" categories:

- injuries and poisonings coded as having undetermined intent
- injuries with plausible consequence of self-harm (e.g. wrist or forearm laceration) and no coding of intent
- injuries with plausible consequence of self-harm coded as accidental

Each of these "borderline" groups will be included or excluded from our final specification of suicide attempt or deliberate self-harm depending on confirmation rates observed in this ongoing research.

Treatment Exposure

Duration of continuous exposure to buprenorphine in the treatment group will be assessed using pharmacy dispensing and insurance claims records for the 90 days following the index visit. These calculations will presume that all dispensed medication was consumed and will allow gaps of up to 25% of "day supply" in determining continuous exposure.

Pharmacy dispensing and insurance claims data will also be used to identify use of other medications for OUD (extended-release naltrexone methadone) during the 90 days following the index visit.

At the KP Washington site, linkage to state Prescription Monitoring Program data will allow assessment of medication treatment for OUD from external providers or facilities not captured by health system records.

Covariates or Confounders

A diverse array of demographic and clinical characteristics recorded prior to or at the index visit will be used to develop propensity scores and/or disease risk scores as described below. As described below, inclusion or exclusion of specific covariates will be determined by variable selection or other machine learning methods. The range of potential covariates considered will include:

- Demographic characteristics – age, sex, race, ethnicity, neighborhood socioeconomic status

- Co-occurring substance use disorders, mental health conditions, and general medical conditions – indicated by receipt of specific groups of diagnoses used in our previous research[6, 23]
- Intensity of prior outpatient mental health and substance use disorder treatment – indicated by specific procedure and diagnosis codes used in our previous research[6, 23]
- Prior acute-care (inpatient and emergency department) treatment of mental health and substance use disorders – indicated by specific procedure and diagnosis codes used in our previous research[6, 23]
- Prior use of medications for treatment of mental health and substance use disorders – indicated by specific classes of NDC/RxNorm codes used in our previous research[6, 23, 29, 41]
- Prior and index visit responses to depression (PHQ-9) and suicide risk (Columbia) questionnaires
- Duration and dose of prior prescribed opioid use using methods from our previous research[25-27, 29]
- Concomitant treatments for chronic pain (physical therapy, acupuncture, etc.)

We will consider diagnosis, prescription, and utilization data for up to five years prior to the index visit. Work in progress will inform how time patterns of predictors are represented in the new work proposed here.

Analytic Strategy

Analyses will compare odds of suicidal behavior in the treatment and comparison groups over 90 days following an index visit. Primary analyses will consider only intent to treat, including all visits followed by buprenorphine initiation within 7 days in the treatment group regardless of duration of subsequent treatment. Secondary analyses may limit the treatment group to visits followed by at least 30, 60, or 90 days of continuous treatment. Additional secondary analyses may exclude from the treatment and comparison groups any visits followed by alternative medications for opioid use disorder (methadone, extended-release naltrexone) within 90 days.

While the comparison group will be limited to visits at which buprenorphine treatment could have been initiated, we must expect that patient characteristics associated with risk of suicidal behavior may influence either clinicians' decisions to recommend buprenorphine treatment or patients' acceptance of such a recommendation. A variety of analytic methods are available to account for this potential confounding by indication. Selection of the optimal method will depend on patterns of treatment utilization and patterns of covariates/predictors observed in our data, but we propose to consider three analytic options – two propensity-score approaches and one disease risk-score approach:

- Propensity-score matching using machine learning-derived propensity scores – propensity score matching can be an effective way of estimating treatment effects in settings where confounding by indication is present[42]. Propensity-score matching estimates the effect of treatment on the treated, that is propensity score matching aims to estimate the reduction in the suicide attempt among those people who received the treatment that is *due* to the treatment. Other approaches estimate the average treatment effect, which is the effect of the treatment if *everyone* were to receive it. When confounding by indication is present, it is unlikely that everyone would ever receive the treatment, thus the average treatment effect is not of scientific interest. Propensity score matching provides an accessible approach to estimating the treatment effect of interest in this setting.
- Propensity-score weighting using machine learning-derived propensity scores – While propensity score matching is straightforward to explain, it can be challenging to implement especially in large populations. Finding appropriate matches for all treated subjects is often computationally challenging especially in large sample sizes. Recently, weighting estimators have been developed that approximate matching estimators[43, 44] and estimate the average treatment effect on the treated. These weighting approaches combine the flexibility and ease of implementation of weighting approaches, but reduce confounding by indication by focusing on comparing treatments on a population of individuals who have the potential to receive both treatments in real-world settings, that is on the population for which the propensity score distributions overlap[43]. We will implement propensity score variable selection approaches designed to increase the statistical efficiency of inverse probability of treatment weighted estimators and develop analogous variable selection techniques for weighting estimators designed to approximate matching estimators[33].

- Disease risk score adjustment using machine learning-derived suicide risk prediction scores – The alternative disease risk score[45-47] method may have advantages in the evaluation of new treatments where the number of people already exposed to the treatment of interest is not large enough to build robust propensity score models. This approach will most directly take advantage of prediction models developed by MHRN investigators.

Using these analytic methods, we will address the following specific questions:

1) Main effect: Among people with recognized OUD, how does initiation of buprenorphine treatment affect risk of suicidal behavior over the following 90 days compared to risk among otherwise similar people with OUD not initiating buprenorphine treatment? – Using the modeling strategies above, we will first estimate the relative odds of suicide attempt over 90 days among patients initiating buprenorphine treatment vs. otherwise comparable patients not so treated. As described above, primary analyses will be according to intent-to-treat with secondary analyses considering duration of subsequent treatment.
2) Heterogeneity of effect: Does any effect of initiating buprenorphine vary according to:
    a. Means or mechanism of suicidal behavior (opioid overdose vs. other overdose vs. non-overdose self-harm)? – Additional analyses will examine overall effect of buprenorphine initiation on three specific subgroups of outcomes: fatal or non-fatal self-harm due to any opioid poisoning/overdose, fatal or non-fatal self-harm due to any poisoning/overdose not including opioids, and fatal or non-fatal self-harm not involving poisoning or overdose.
    b. Presence/absence of co-occurring mental health condition or severe mental illness? – Additional analyses will examine overall effect of buprenorphine initiation stratified by presence/absence of severe mental illness diagnosis (schizophrenia, schizoaffective disorder, bipolar disorder) and stratified by presence/absence of a broader range of mental health diagnoses (schizophrenia, schizoaffective disorder, bipolar disorder, unipolar depression, anxiety disorder)
3) Specificity of effect: Are effects observed for buprenorphine also observed for alternative medications for treatment of OUD (e.g. naltrexone)? – Sample size permitting, additional analyses will use the methods described above to estimate the relative odds of suicide attempt over 90 days among patients initiating buprenorphine treatment vs. otherwise comparable patients initiating treatment for OUD with naltrexone.

Sample Size/Statistical Power

Based on research by Dr. Boudreau and colleagues in 5 MHRN health systems (manuscript under review) we estimate the prevalence of diagnosed OUD among adult health system members/patients to be approximately 0.6% and the rate of buprenorphine use among those with OUD diagnoses to be approximately 16%. Applying those rates to the member/patient populations aged 16 or older in participating health systems (approximately 9 million), we estimate an eligible population of approximately 55,000 people with diagnosed OUD and 8,700 using buprenorphine.

While analyses will include multiple encounters per person and may include a comparison sample two or three times as large as the treatment group, we conservatively estimate statistical power assuming a single observation per person and equal sizes of treatment and comparison groups. We assume a 90-day risk of self-harm or suicide attempt among people with OUD of 4%. Under those assumptions and conducting power calculations for a comparison of proportions from independent samples, 8,700 OUD patients treated with buprenorphine and an equally sized comparison group would have greater than 80% power (2-sided alpha level of 0.05) to detect a decrease in 90-day risk from 4% to 3.2% (relative odds of 0.8)

Limitations

We should acknowledge several potential limitations of the methods we propose, including:

- Inaccurate or incomplete ascertainment of suicide attempts or self-harm – Our previous work[6, 32] supports the high positive predictive value of our computable phenotype for suicide attempt or self-harm, and work in progress will further refine that phenotype. Nevertheless, we must acknowledge that some people experiencing self-harm will not present for medical care. Consequently, our results will only apply to medically attended self-harm (i.e. serious enough to come to medical attention).

- Incomplete ascertainment of OUD treatment – Given stigma associated with OUD, some people receiving OUD treatment may seek care outside of participating health systems and pay for care out-of-pocket. As described above, we will use prescription monitoring program data from one study site to evaluate the magnitude of this misclassification.
- Residual confounding by indication – While we propose state-of-the are methods to account for potential confounding by indication, we must acknowledge that we cannot rule out residual confounding. As discussed above, however, a true randomized trial to assess this question is probably not feasible.
- Multiple pathways for therapeutic effect – As discussed above, buprenorphine may reduce risk of suicidal behavior through a variety of direct and indirect pathways. The data available to us will not allow us to distinguish between these different mechanisms, but secondary analyses regarding naltrexone may help distinguish specific effects of buprenorphine from general effects on OUD.

Potential Impact

Findings of this work should directly influence clinical and policy decisions regarding use of buprenorphine treatment in people with OUD at risk for suicidal behavior, especially people with co-occurring mental health conditions.

In addition, this work may inform future research regarding effects of opioid agonists on suicidal behavior, including development of new pharmacotherapies.

Dissemination and Implementation

As always, all tools and technical materials (e.g. sampling programs, specifications of analytic variables, analytic code, detailed results regarding model performance, etc.) will be immediately placed in the public domain and distributed by our public GitHub code repository. As with our previous and ongoing work, we will continue to collaborate closely with MHRN health systems regarding rapid implementation of research findings and will provide technical support to a wide range of stakeholders, including health systems, electronic health records vendors, regulators, other researchers, NIH scientists, and other research funders.