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DEVELOPING A WORKFLOW TO EVALUATE MEDICATIONS FOR REPURPOSING USING HEALTH CLAIMS DATA: APPLICATION TO SUBSTANCE USE DISORDERS

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DEVELOPING A WORKFLOW TO EVALUATE MEDICATIONS FOR REPURPOSING USING HEALTH CLAIMS DATA: APPLICATION TO SUBSTANCE USE DISORDERS

THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
College of Pharmacy
at the University of Kentucky

By

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2019

ABSTRACT OF THESIS

DEVELOPING A WORKFLOW TO EVALUATE MEDICATIONS FOR REPURPOSING USING HEALTH CLAIMS DATA: APPLICATION TO SUBSTANCE USE DISORDERS

Healthcare big data are a growing source of real-world data with which to identify and validate medications with repurposing potential. Previously, we developed a claims-based workflow to evaluate medications with potential to treat stimulant use disorders. In order to test the workflow, the framework was applied in the context of opioid use disorders (OUDs), for which there are medications with known efficacy. Using the Truven Marketscan Commercial Claims Database, a nested case-control analysis was conducted to determine the association between OUD medications (buprenorphine, naltrexone) and remission. Cases were defined as enrollees with a remission diagnosis and matched (1:4) to controls (individuals without remission) using incidence density sampling, with age group, sex, region, and index year as additional matching variables. After adjusting for behavioral health visits, polysubstance use disorders, and psychiatric disorders using conditional logistic regression, the odds of OUD medication exposure were 3.8 (99% confidence interval: 3.0 – 4.9) times higher in cases than controls. Evaluation of angiotensin converting enzyme inhibitors (e.g. lisinopril) as a negative control revealed no significant association between the medication and remission. This work demonstrates the feasibility of using administrative health claims data to evaluate the effectiveness of medications to treat substance use disorders.

KEYWORDS: Medication repurposing, health claims, substance use disorders

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Date

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I am immensely grateful to my family who cheers me on from a distance. Lastly, I would thank to my husband, Danny, for unwavering support. I can't be me without you.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1. INTRODUCTION

1.1 MEDICATION REPURPOSING

Drug repurposing, a complementary approach to *de novo* drug discovery[1], is the process of identifying novel indications for existing medications. Medication repurposing offers several advantages over *de novo* drug discovery in that it is more cost effective and the medication can be brought to market more rapidly to treat the additional disease since it will have already been approved by regulatory agencies[1]. Generally, identification of a biological target is a prerequisite for *de novo* drug discovery, which can be conceived of as a translational approach (molecular target → clinic) to therapeutic discoveries. Similarly, many systematic approaches to drug repurposing (e.g. computational screening of genetic and chemical libraries) are best suited to medical conditions for which biological mechanism(s) of disease are known[2]. However, conditions with complex underlying etiology, such as neuropsychiatric and substance use disorders, represent challenges that call for reverse-translational approaches[3].

In response to limitations of the translational approach to drug development, researchers have developed strategies to implement reverse-translational drug repurposing. One such strategy is to match diseases based on phenotype similarity and then map those relationships to known molecular disease pathways[4–6]. Xu and colleagues[7] recently applied this approach to glioblastoma subtypes exhibiting distinct molecular and clinical phenotypes to prioritize medications likely to be most effective for a given subtype. A related approach is to match diseases based on common Food and Drug Administration (FDA)-approved medications and predict novel drug uses based on shared treatment profiles[8]. Ultimately, reverse-translational medication repurposing is a promising strategy and can be particularly effective when the etiology of a disorder is complex and a biological target is not readily apparent, as in the case with substance use disorders.

1.2 REVERSE-TRANSLATIONAL MEDICATION REPURPOSING WORKFLOW

The growing volume, access, and quality of healthcare data provides a valuable resource for engaging in drug repurposing from a reverse-translational perspective. Healthcare data are available in a variety of forms including health claims, electronic health records, images, and even social media[9]. Administrative health claims data are one source of healthcare data that provide a longitudinal source of information from inpatient and outpatient services, including demographics, diagnoses, procedures, and prescriptions. As such, health claims data are a good source of real-world health data to use for exploratory analyses to identify medications with potential for repurposing.

Figure 1 displays data processing workflow we previously developed for using health claims data to evaluate medications for repurposing[10]. The first step in the process is to identify the sample of interest, which will likely be accomplished using diagnosis codes. Once the sample of interest has been identified, the next step is to identify candidate medications for evaluation. This can be accomplished through a data-driven strategy (e.g. hypothesis generation via data mining) or using *a priori* knowledge. Prescription medications are labeled using National Drug Codes, which can be aggregated into therapeutic classes and Generic Product Indicators using resources like the Medi-Span® data dictionary[11]. Using the Generic Product Indicator (GPI), characterizing prescriptions within a sample can be done at the level of root classification (e.g. antidepressants), medication subclass (e.g. norepinephrine-dopamine reuptake inhibitors), or specific medications (e.g. bupropion). In describing medication characteristics, it is advisable to provide a measure of adherence and duration that the medication is prescribed to the sample. Once the sample has been identified and medication(s) selected, the workflow takes on characteristics of a retrospective pharmacoepidemiologic study. Claims data provide an open cohort, so it is necessary to define an index date relative to some characteristic of each individual as a proxy for the study start date. The index date is important for defining a baseline period during which sample characteristics can be determined and exclusion criteria can be applied. Exposure for the retrospective analysis will be a

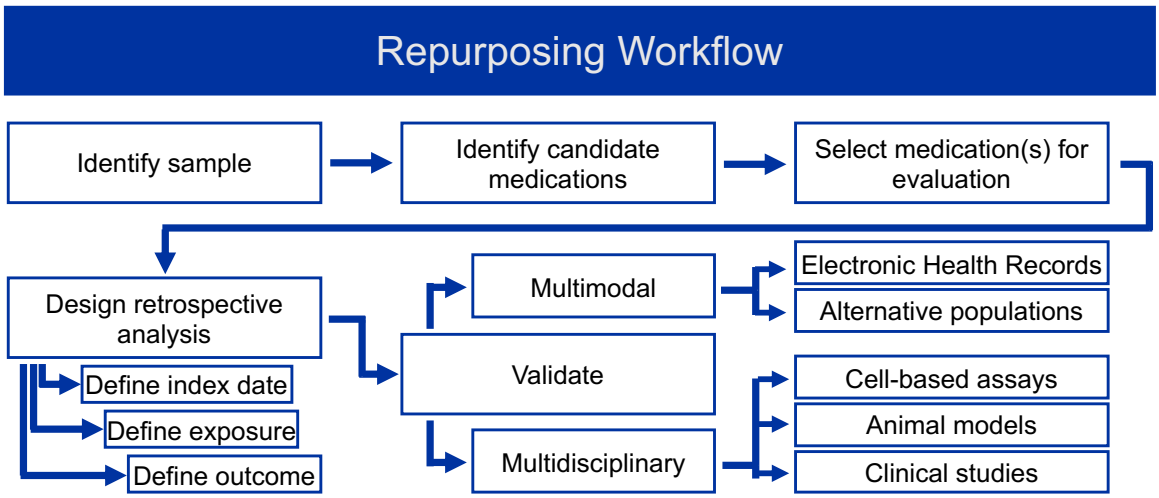

Figure 1. Workflow for reverse-translational medication repurposing using health claims data. Reverse translational medication repurposing begins with sample and candidate medications identification, followed by selection of medications for retrospective analysis. Findings should then be validated in a broader multimodal and multidisciplinary context.

medication or combinations of medications prescribed to an individual, while the outcome may vary considerably depending on the medical condition of interest. The outcome may be determined from diagnosis or procedure codes, or it could be feature(s) aggregated over a period of time, such as healthcare utilization and expenditures. Clearly defined temporal parameters for exposures and outcomes are necessary when designing the retrospective analysis. For most studies, defining exposure should follow the new-user design[12], wherein the exposure group includes new medication users who have no evidence of a prescription for some period of time (e.g. 6 months) prior to the index date. Similarly, when choosing an outcome, it is important to be mindful of temporal logistics. Specifically, the outcome must occur after initiation of the medication and fall within a time-frame that is consistent with the medication's putative therapeutic effect based on clinical understanding of the disease. Once the retrospective analysis specifications have been determined, statistical analyses should be implemented according to the outcome. If the retrospective analysis identifies a beneficial health outcome of a medication, plans should be made to validate the findings from both a multimodal and multidisciplinary perspective. Initially, the analysis should be repeated using alternate data sources representing different types of information

(e.g. electronic health records) or populations (e.g. commercially-insured vs. Medicaid). Subsequently, the findings can be pursued in a multidisciplinary context to understand how the medication is working (mechanism of action) using cell-based assays, recapitulate the finding in animal models, and ultimately test the therapy in human clinical trials.

1.3 APPLICATION OF WORKFLOW TO STIMULANT USE DISORDERS

In the initial development of the framework, the reverse-translational medication repurposing workflow was applied to stimulant use disorders. Using the Truven MarketScan Commercial Claims Database, individuals (18-64 years) with a cocaine or amphetamine use disorder diagnosis were identified based on *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) codes. Notably, the diagnostic codes for methamphetamine use disorder are categorized under 'amphetamine' abuse and dependence, so the term amphetamine(s) is used to describe this sample. However, epidemiological findings from the Treatment Episode Dataset suggest that most (94%) individuals in the amphetamines category represent individuals using methamphetamine[13]. Having identified 82,137 and 110,015 individuals with amphetamine and cocaine use disorder, respectively, the next step was to identify candidate medications. To do so, pharmacy claims were screened for the most commonly prescribed medications to individuals in our sample. Bupropion (i.e. Wellbutrin®, Zyban®), which is a norepinephrine-dopamine reuptake inhibitor and nicotinic acetylcholine receptor antagonist that is prescribed for depression and smoking cessation, was the most commonly prescribed medication among individuals with a stimulant use disorder. Since bupropion also has potential as an indirect agonist replacement therapy for stimulant use disorders[14], it was selected to be evaluated for potential to treat stimulant use disorders. The outcome of interest was an ICD-9-CM diagnosis of remission. Using a retrospective cohort analysis, we found that filling a prescription of bupropion within 30 days of first documented stimulant use disorder diagnosis increased odds of a subsequent remission diagnosis by 2.1 times (99% confidence interval: 1.09-3.89) in individuals with an amphetamine

use disorder, but not those with a cocaine use disorder. The finding that bupropion was associated with remission only among individuals with amphetamine use disorder (and not cocaine) was consistent with the preponderance of evidence from clinical studies[14], bolstering credibility for the validity of the workflow.

1.4 OPIOID USE DISORDER TEST CASE

Since there are no FDA-approved pharmacotherapies to treat stimulant use disorders, there is no benchmark (i.e. positive control) against which to test the findings from administrative data. In order to further develop the medication repurposing workflow for application to substance use disorders, the purpose of this study was to establish the feasibility of using administrative health claims data to assess the real-world effectiveness of medications used to treat substance use disorders. Unlike the case for stimulant use disorders, there are medications with FDA-approval to treat opioid use disorder (OUD). Specifically, buprenorphine products and naltrexone are identifiable in pharmacy claims data and are FDA-approved to treat OUD. Buprenorphine significantly increases treatment retention and negative urine samples, and reduces opioid craving in randomized controlled trials of individuals with OUD[15,16]. When patients adhere to treatment (≥ 80%), naltrexone increases retention and abstinence by nearly 3-fold versus placebo or no pharmacological treatment[17]. To establish the groundwork for future studies on stimulant use disorders, we evaluated the effectiveness of medications known to treat OUD in the context of our medication repurposing workflow.

CHAPTER 2. METHODS

2.1 DATA SOURCE

Data were obtained from individuals enrolled in the Truven Marketscan Commercial Claims Database between January 1, 2009 and December 31, 2016. The Truven database is a

collection of inpatient, outpatient, professional, and pharmacy health claims from commercially-insured individuals and their spouses and dependents, which represented about 120 million lives during the observation period[18].

2.2 COHORT

Individuals with an ICD-9-CM or ICD-10-CM diagnosis of OUD (Appendix A) were eligible to be included in the cohort. The ICD-9-CM codes used to identify OUD were a conservative selection based on previous research[19,20] that did not include poisonings or remission codes. Corresponding ICD-10-CM codes that included the terms 'abuse' or 'dependence' were also included. A previous validation study of ICD-9-CM diagnostic codes for substance use disorder revealed that these codes have high specificity (92-99%), but only moderate sensitivity (54-78%)[21].

2.3 STUDY DESIGN

The index month was defined as the month during which the first OUD diagnosis was observed (Figure 2). Baseline measures were evaluated during the six months prior to and including the index month. In order to be included in the final cohort, enrollees must have been between the ages of 18 to 64 years during the index month, had six months of eligibility prior to the index month (baseline), prescription drug and mental health insurance coverage at baseline, and valid enrollment information. Of the 562,850 Truven enrollees with an OUD diagnosis, 312,214 had at least six months of eligibility in the dataset prior to the index date with valid enrollment information. A further 153,022 met all inclusion criteria, such that they were between the ages of 18 and 64, had prescription and mental health insurance coverage, and no observable remission diagnosis or OUD medication exposure during the baseline period (Figure 3).

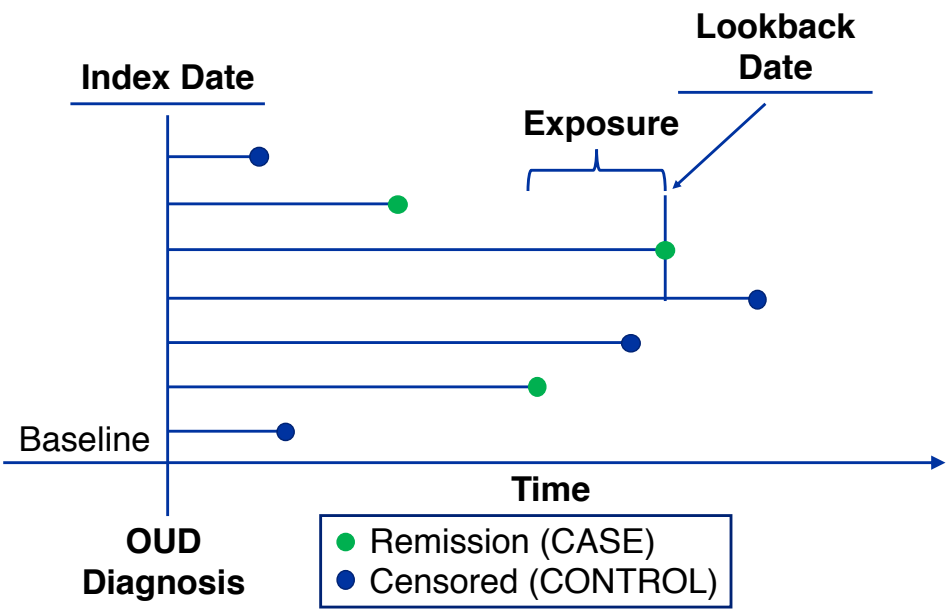

Figure 2. Nested case-control study design using incidence density sampling. Each enrollees' index date was defined as the first observed opioid use disorder (OUD) diagnosis. Baseline covariates were measured in the 6 months prior to the index date. Enrollees were then followed until they received a remission diagnosis (green dot; case) or until they were censored (blue dot; controls, i.e. enrollees without remission). Cases were matched with controls for time at risk. Medication exposure was determined in the up to 6 months leading up to the lookback date.

2.4 INCIDENCE DENSITY SAMPLING

Cases were identified from the final cohort if they had a remission diagnosis (Appendix B) following their index month. Of the final cohort, 3,902 received a remission diagnosis following the index date and were classified as cases. This left 149,120 potential controls (enrollees without a remission diagnosis) to use for matching. Controls were selected from the eligible sample and matched 4:1 with cases using incidence density sampling[22]. Incidence density sampling requires that controls be 'at risk' for the same period of time as cases without having received a remission diagnosis (Figure 2). As such, the lookback date was defined as the month of remission for cases and as the month in which controls had been at risk for the same period of time as their matched case (i.e. control index month + time at risk of matched case). Additional matching variables included baseline age group, sex, region, and year of first diagnosis (i.e. index

year). All but four cases were matched with four controls, resulting in 3,898 cases and 15,592 controls (Figure 3).

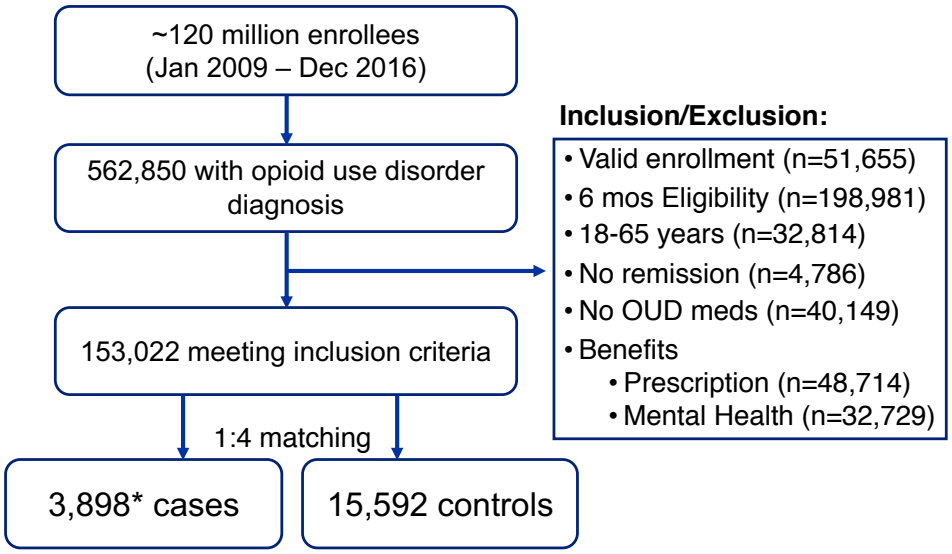

Figure 3. Inclusion diagram for opioid use disorder cohort and nested case-control analysis. Of the 562,850 enrollees with an opioid use disorder (OUD) diagnosis, 153,022 met all inclusion criteria to be included in the cohort. From that cohort, 3,898 (2.5%) cases (i.e. enrollees with remission) were identified and matched (1:4) with controls (n=15,592; enrollees without remission) on baseline age group, sex, region, and index year. *Four cases were not matched to controls. Jan: January; Dec: December; Mos: Months.

2.5 EXPOSURE

Exposure was defined as any OUD medication (i.e., buprenorphine, buprenorphine-naloxone, and naltrexone) prescription compared to no OUD medication prescription. Prescriptions for OUD medications were identified from pharmacy claims using Medi-Span®'s GPIs (Appendix C). As a proxy for adherence, proportion of days covered (PDC) was calculated as a sum of the non-overlapping days' supply during the lookback period divided by the number of days during that period multiplied by 100. Exposure was then defined as a dichotomous variable indicating presence (1) or absence (0) of at least 80% PDC during the lookback period. For this analysis, only pharmacy claims were used, thus provider-administered medications that would show up as procedure codes are excluded. Moreover, as this is a claims-

based identification of OUD medication, methadone was not captured in the measure of OUD medication exposure because it is not dispensed at pharmacies for this indication.

2.6 NEGATIVE CONTROL

Association of angiotensin converting enzyme (ACE) inhibitors with OUD remission was evaluated as a negative control using the same framework as that for OUD medications as there is no direct evidence to suggest that ACE inhibitors would treat OUD. The cohort was created identically to that for the primary analysis with the exception that individuals were excluded on the basis of ACE inhibitor exposure at baseline rather than OUD medication exposure. ACE inhibitors were identified using the GPI 4-digit code (3610x; Appendix D). There were 178,186 in the final cohort, of whom 6,137 were identified as cases leaving 172,049 potential controls. After incidence density sampling, 6,134 cases were matched 4:1 with controls (n=24,536) for time at risk, age group, sex, region, and index year. Statistical analyses were identical to those implemented for the analysis of OUD medication and remission.

2.7 COVARIATES

Age, sex, region, and insurance type were determined from enrollment data at baseline. Age was then categorized into an ordinal variable with four levels as follows: 18-26, 27-35, 36-50, and 51-64 years. Behavioral health visits were defined as the presence of a service category on a given claim (Appendix E). Polysubstance use was a binary variable indicating the presence (1) or absence (0) of diagnoses for cocaine, amphetamine, alcohol, cannabis, tobacco, <u>or</u> other (hallucinogens, sedatives, inhalants, barbiturates) use disorder during the lookback period (Appendix F). The presence of concurrent psychiatric disorders was determined using clinical classification software (CCS) codes indicating mood disorders (657), anxiety disorders (651), adjustment disorders (650), and attention-deficit, conduct, and disruptive behavior

disorders (652) during the lookback period[23]. For analysis, psychiatric disorders were aggregated into a single binary variable indicating the presence (1) or absence (0) of CCS codes for any of the psychiatric disorders listed.

2.8 STATISTICAL ANALYSIS

Descriptive statistics were used to characterize the matched sample, testing for group differences with chi-square tests of independence. Conditional logistic regression was used to evaluate the association between OUD medication exposure and OUD remission. Adjusted models included behavioral health visits, polysubstance use disorders, and psychiatric disorders separately and combined. The fully adjusted model included behavioral health visits, polysubstance use disorders, and psychiatric disorders as covariates. Due to the large sample size, alpha was set at 0.01 for all analyses. All matching and statistical analyses were implemented using SAS version 9.4.

CHAPTER 3. RESULTS

3.1 DEMOGRAPHICS

There were 153,022 enrollees meeting inclusion criteria for the OUD cohort (Table 1). The cohort was primarily male (52.6%), on employer-sponsored health insurance (71.1% vs. health plan), from the south region (44.4%), and without a behavioral health visit at baseline (67%). The age distribution was similar between all age groups except 27-35 years, which only represented 13.8% of the cohort. Mood (37.2%) and anxiety disorders (31.4%) were present in about a third of the cohort at baseline. Moreover, alcohol (14.4%) and cannabis use disorders (8.3%) were the most frequent co-occurring substance use disorders at baseline, consistent with epidemiological research of polysubstance use[24].

Table 1. Characteristics of opioid use disorder cohort and matched cases and controls. There were 153,022 enrollees meeting inclusion criteria from which 3,898 cases (i.e. enrollees with remission diagnosis) were identified and matched 1:4 with controls (i.e. no remission) for time at risk, age group, sex, region, and index year. All values represent number with column percentages. P-value represents difference between cases and controls.

Characteristics	Total Cohort (n=153022)	Controls (n=15592)	Cases (n=3898)	p-value
Sex				1
Male	80459 (52.6)	9040 (58)	2260 (58)	
Female	72563 (47.4)	6552 (42)	1638 (42)	
Age Group				1
18-26	39131 (25.6)	7372 (47.3)	1843 (47.3)	
27-35	21051 (13.8)	2308 (14.8)	577 (14.8)	
36-50	46252 (30.2)	3560 (22.8)	890 (22.8)	
≥ 50	46588 (30.5)	2352 (15.1)	588 (15.1)	
Region				1
Northeast	29508 (19.3)	3888 (24.9)	972 (24.9)	
North Central	29328 (19.2)	3500 (22.5)	875 (22.5)	
South	67913 (44.4)	4360 (28)	1090 (28)	
West	25369 (16.6)	3800 (24.4)	950 (24.4)	
Unknown	904 (0.6)	44 (0.3)	11 (0.3)	
Behavioral health visits				<.0001
No	102538 (67)	10115 (64.9)	1765 (45.3)	
Yes	50484 (33)	5477 (35.1)	2133 (54.7)	
Insurance Type				0.0299
Employer	108761 (71.1)	12024 (77.1)	2942 (75.5)	
Health plan	44261 (28.9)	3568 (22.9)	956 (24.5)	
Employee Relationship				0.0543
Employee	72380 (47.3)	5337 (34.2)	1259 (32.3)	
Spouse	46608 (30.5)	3580 (23)	943 (24.2)	
Child/other	34034 (22.2)	6675 (42.8)	1696 (43.5)	
Substance Use Disorders				
Alcohol	22050 (14.4)	1778 (11.4)	722 (18.5)	<.0001
Cannabis	12735 (8.3)	1284 (8.2)	473 (12.1)	<.0001
Tobacco	5243 (3.4)	347 (2.2)	159 (4.1)	<.0001
Amphetamines	4232 (2.8)	481 (3.1)	182 (4.7)	<.0001
Cocaine	5856 (3.8)	541 (3.5)	231 (5.9)	<.0001
Psychiatric Disorders				
Mood Disorders	56888 (37.2)	4633 (29.7)	1705 (43.7)	<.0001
Anxiety Disorders	48036 (31.4)	3580 (23)	1416 (36.3)	<.0001
Attention-deficit disorders	10390 (6.8)	935 (6)	289 (7.4)	0.0011
Adjustment Disorders	8476 (5.5)	563 (3.6)	239 (6.1)	<.0001

3.2 MATCHED DEMOGRAPHICS

The sample was matched on baseline sex, age group, and region, so the distribution of these characteristics was identical between cases and controls (Table 1). Compared to controls, a higher proportion of cases (54.7%) had concurrent behavioral health visits than controls (35.1%).

Notably, cases were more likely to have concurrent diagnoses of psychiatric and substance use disorders than controls.

3.3 OUD MEDICATION EXPOSURE

OUD medication exposure during the lookback period was more common in cases than controls, such that 6.4% of cases were exposed (i.e. met threshold PDC) compared to 1.7% of controls (Figure 4). In the unadjusted analysis, the odds of OUD medication exposure were 4.1 times greater for cases than controls (Table 2). The adjusted odds ratio for OUD medication exposure after adjusting for behavioral health visits, polysubstance use disorders, and psychiatric disorders was 3.8 times greater for cases than controls. Stated differently, this suggests that there was a 280% increase in the likelihood of OUD medication exposure among cases relative to controls. With an unadjusted Experimental Event Rate of 48.5% (i.e. remission among OUD medication exposed) and a Control Event Rate of 19.2% (i.e. remission among OUD medication non-exposed), the Number Needed to Treat is 3.4. Specifically, 3.4 individuals need to be treated in order for 1 to experience remission.

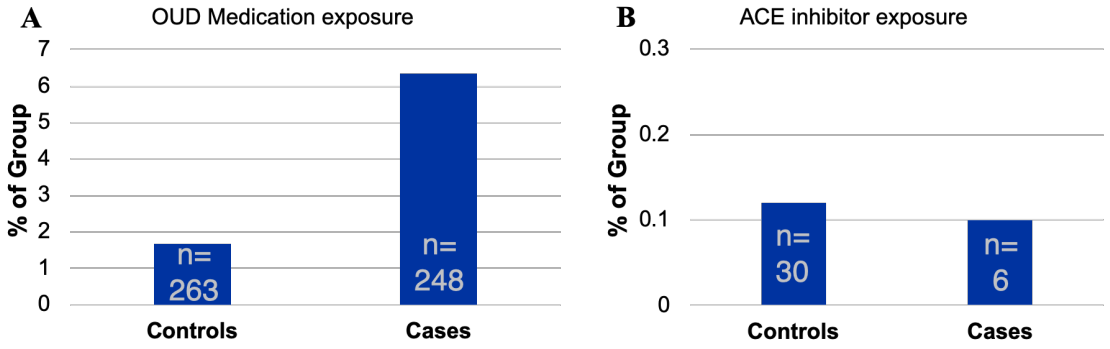

Figure 4. Proportion of cases and controls with medication exposure. (**A**) Of the 15,592 controls (i.e. no remission), 263 (1.7%) had exposure to opioid use disorder (OUD) medications prior to the lookback date. Among 3,898 cases (i.e. enrollees with remission diagnosis), 248 (6.4%) had prior exposure to OUD medications. (**B**) Although there were far fewer new-users of angiotensin converting enzyme (ACE) inhibitors (different x-axis), the proportion of exposed did not differ between cases and controls.

3.4 NEGATIVE CONTROL

Cases were no more likely than controls to have ACE inhibitor exposure during the lookback period. Adjusted and unadjusted analyses indicated that the odds of ACE inhibitor exposure were not significantly different from 1 (Table 2).

Table 2. Conditional logistic regression analyses of opioid use disorder medications or angiotensin converting enzyme inhibitors with remission. The odds of opioid use disorder (OUD) medication exposure were consistently 3.7 to 4.1 times higher in cases (i.e. enrollees with remission) than controls (i.e. enrollees without remission) in matched unadjusted and adjusted models. In contrast, there was no evidence to suggest that angiotensin converting enzyme (ACE) inhibitors were significantly associated with remission.

	OUD Medications			**ACE Inhibitors**		
	OR	99% CI	p-value	OR	99% CI	p-value
Unadjusted	4.1	3.3, 5.3	<0.001	0.8	0.25, 2.5	0.6179
Adjusted						
Behavioral Health Visits	3.7	2.9, 4.8	<0.001	0.89	0.29, 2.8	0.7982
Polysubstance Use Disorders	4.1	3.2, 5.3	<0.001	0.83	0.26, 2.6	0.6740
Psychiatric Disorders	4.0	3.1, 5.1	<0.001	0.82	0.26, 2.6	0.6614
Fully	3.8	3.0, 4.9	<0.001	0.90	0.28, 2.9	0.8208

OR:Odds Ratio; CI: confidence interval

Fully adjusted includes behavioral health visits, polysubstance use disorders, and psychiatric disorders

CHAPTER 4. DISCUSSION

4.1 GENERAL

This work demonstrates the feasibility of using administrative health claims data to evaluate the effectiveness of medications used to treat substance use disorders. Moreover, this work lays the foundation for computational repurposing strategies[25] to be applied using administrative claims data, especially in the context of substance use disorders. In this test case, we evaluated the association of a remission diagnosis with previous exposure to medications known to treat OUD that are available by prescription[15–17]. As expected from randomized control trials, this nested case control analysis found consistent increases in the odds of exposure to OUD medications among individuals who had remission (cases) compared to controls. Importantly, these findings support the use of remission diagnoses as a proxy for medication effectiveness in the context of substance use disorders. Although it would be compelling to test the workflow in

the context of a physiological disease (e.g. insulin for diabetes) to ascertain reasonable effect sizes, the treatment of behavioral disorders is vastly different from physiological diseases and diagnostic codes for most diseases do not indicate the absence of a condition. Ultimately, the goal of this research is to generalize this approach to other substance use disorders for which there are no FDA-approved pharmacotherapies (e.g. stimulant use disorders). These findings suggest that this is a viable approach for such pursuits and establishes the framework for using health claims data for computational repurposing, which is the use of automated workflows to generate candidate medication leads for repurposing.

This study demonstrates the ability of the application of the repurposing workflow to health claims data to recapitulate small randomized controlled trials of the effect of medications used to treat OUD. Moreover, to demonstrate the specificity of the approach, the association between ACE inhibitors and OUD remission was assessed. As expected, there was no association between exposure to ACE inhibitors and OUD remission. ACE inhibitors are prescribed for hypertension and work by inhibiting the production of angiotensin II, which is a hormone that increases vasoconstriction. As yet, there is no direct evidence to suggest that ACE inhibitors would be associated with outcomes of OUD. However, there is evidence that ACE inhibitors have central actions, including increasing dopamine in the striatum[26–28]. Some studies have also demonstrated that ACE inhibitors can alter the subjective effects of other drugs of abuse like methamphetamine, but these tended to be cardiovascular in nature rather than psychological (i.e., drug-liking and high)[29,30]. Future work will evaluate alternate medications as negative controls to further substantiate the specificity of the approach to appropriately rule out medications with no known treatment effect.

4.2 LIMITATIONS & FUTURE DIRECTIONS

One of the primary limitations of the workflow is in using remission as the outcome, as remission diagnoses are rare. About 2.5% of the final cohort had a remission diagnosis,

substantially limiting the sample of individuals with the outcome of interest. Based on medical coding guidelines and conversations with clinicians, a diagnosis of remission is up to the discretion of the provider, in part, because there are no biomarkers for substance use disorders. As such, many individuals who are in fact in remission are likely to be misclassified as not having remission. The rare coding and uncertainty regarding remission diagnoses as beneficial outcomes are likely to be the primary limitations in the application of this medication repurposing workflow moving forward. As such, it will be necessary to determine alternative outcomes that are more frequently observed in administrative data that can be used as outcomes (emergency department visits, healthcare expenditures, and healthcare utilization)[31].

The use of administrative pharmacy claims data to measure medication exposure presents some limitations. Specific to OUD medications is that methadone for OUD was not available in claims data as it is provided by Opioid Treatment Programs, which in 2015 provided methadone to 356,843 clients[32]. As such, it is possible that individuals being treated for OUD with methadone were misclassified as having no treatment since this could not be measured with the available data. However, after matching for age, sex, region, and year, it is unlikely that there would be systematic differences between cases and controls in methadone exposure. A more general limitation of using pharmacy claims to measure medication exposure is that filling a prescription does not guarantee that an individual took the medication. For this reason, in the primary analysis OUD medication exposure was defined as having greater than or equal to 80% PDC[33].

A further limitation of this study has to do with generalizability. The study was conducted using individuals with commercial health insurance, and as such, the findings may not be representative of individuals with OUD. Although nearly 50% of the United States has commercial health insurance[18], individuals with substance use disorders are generally overrepresented in the uninsured category. Specifically, between 2007 and 2013, 24% of individuals with substance use disorders were uninsured[34]. Moreover, due to the limited

availability of sociocultural variables in this administrative dataset, there is the potential for unmeasured confounders. Ultimately, expanded or linked datasets will be valuable to account for sociodemographic confounders as this medication repurposing workflow continues to be developed. It will also be valuable to replicate these findings in an alternative data source, such as using Medicaid claims where the prevalence of substance use disorders is more than double that of some commercial populations[19].

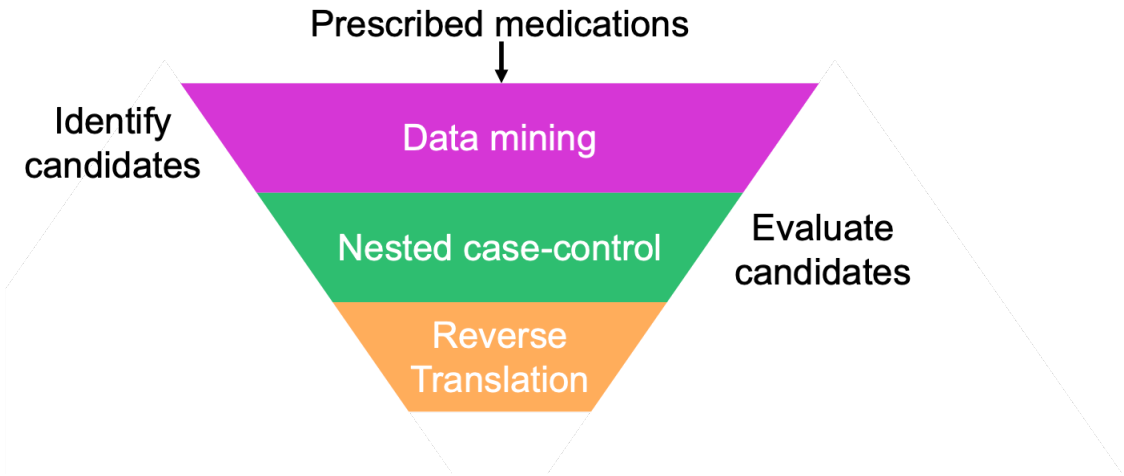

Figure 5. Reverse-translational repurposing pipeline. Similar to the *de novo* drug discovery pipeline, the claims-based reverse-translational repurposing pipeline would start with many candidates (individual and combination medications) identified through data mining. Those candidates generated through data mining would then be evaluated using the nested case control analysis described here. Candidates that passed the nested case-control screen would then go on to further reverse-translational analysis, which could include preclinical or cell-based assays. Importantly, this reverse-translational pipeline could have the potential to identify novel mechanisms of treatment for stimulant use disorders.

4.3 CONCLUSIONS

The findings presented here demonstrate the feasibility of using administrative health claims data to evaluate the effectiveness of medications to treat substance use disorders. Notably, using remission as an outcome appears to serve as a proxy for medication effectiveness, at least in the context of OUDs. These findings also provide an effect size benchmark for future studies in evaluating the effectiveness of other medications to treat substance use disorders. Importantly, this work lays the foundation for future work to leverage the power of healthcare big data to

combine data mining and pharmacoepidemiologic strategies to advance medications discoveries for substance use disorders. Similar to the *de novo* drug discovery pipeline, the vision for the reverse-translational medication repurposing pipeline is to discover many candidate medications and systematically screen them for potential to be repurposed (Figure 5). Specifically, applying data mining to health claims data can discover medications (i.e. identify targets) that frequently co-occur among individuals who have remission. These individual or combination medications can then be further screened using the nested case-control analysis presented here. Medications generated and validated using this pipeline can then be subject to further reverse-translation using preclinical or cell-based assays. Notably, this approach could identify novel mechanisms of treatment for stimulant use disorders based on the reverse-translational analyses. The next steps will be to apply the repurposing workflow back to stimulant use disorders by first generating candidate medications and combinations using data mining that will then be evaluated using a retrospective analysis (Figure 1). This data-driven repurposing approach has the potential to inform research along the translational-science spectrum, ranging from in vitro assays to animal models to clinical trials (Figure 6), ultimately advancing medications discoveries for substance use disorders.

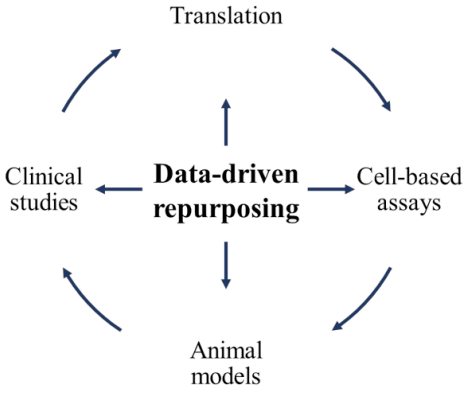

Figure 6. Integration of data-driven repurposing into translational science cycle. The goal of the repurposing workflow is to complement the broad spectrum of approaches to medications development.

Appendix A: Diagnostic codes to identify opioid use disorder

ICD codes	Version	LABEL
304	ICD-9-CM	Opioid type dependence unsp use
304.01	ICD-9-CM	Opioid dependence continuous
304.02	ICD-9-CM	Opioid dependence episodic
304.7	ICD-9-CM	Opioid/Oth dependence unsp
304.71	ICD-9-CM	Opioid/Oth dependence continuous
304.72	ICD-9-CM	Opioid/Oth dependence episodic
305.5	ICD-9-CM	Nondep opioid abuse unsp use
305.51	ICD-9-CM	Nondep opioid abuse continuous use
305.52	ICD-9-CM	Nondep opioid abuse episodic use
F11.10	ICD-10-CM	Opioid abuse, uncomplicated
F11.120	ICD-10-CM	Opioid abuse with intoxication, uncomplicated
F11.121	ICD-10-CM	Opioid abuse with intoxication delirium
F11.122	ICD-10-CM	Opioid abuse with intoxication with perceptual disturbance
F11.129	ICD-10-CM	Opioid abuse with intoxication, unspecified
F11.14	ICD-10-CM	Opioid abuse with opioid-induced mood disorder
F11.150	ICD-10-CM	Opioid abuse with opioid-induced psychotic disorder with delusions
F11.151	ICD-10-CM	Opioid abuse with opioid-induced psychotic disorder with hallucinations
F11.159	ICD-10-CM	Opioid abuse with opioid-induced psychotic disorder, unspecified
F11.181	ICD-10-CM	Opioid abuse with opioid-induced sexual dysfunction
F11.182	ICD-10-CM	Opioid abuse with opioid-induced sleep disorder
F11.188	ICD-10-CM	Opioid abuse with other opioid-induced disorder
F11.19	ICD-10-CM	Opioid abuse with unspecified opioid-induced disorder
F11.20	ICD-10-CM	Opioid dependence, uncomplicated
F11.220	ICD-10-CM	Opioid dependence with intoxication, uncomplicated
F11.221	ICD-10-CM	Opioid dependence with intoxication delirium
F11.222	ICD-10-CM	Opioid dependence with intoxication with perceptual disturbance
F11.229	ICD-10-CM	Opioid dependence with intoxication, unspecified
F11.23	ICD-10-CM	Opioid dependence with withdrawal
F11.24	ICD-10-CM	Opioid dependence with opioid-induced mood disorder
F11.250	ICD-10-CM	Opioid dependence with opioid-induced psychotic disorder with delusions
F11.251	ICD-10-CM	Opioid dependence with opioid-induced psychotic disorder with hallucinations
F11.259	ICD-10-CM	Opioid dependence with opioid-induced psychotic disorder, unspecified
F11.281	ICD-10-CM	Opioid dependence with opioid-induced sexual dysfunction
F11.282	ICD-10-CM	Opioid dependence with opioid-induced sleep disorder
F11.288	ICD-10-CM	Opioid dependence with other opioid-induced disorder
F11.29	ICD-10-CM	Opioid dependence with unspecified opioid-induced disorder
F11.1	ICD-10-CM	Opioid abuse
F11.12	ICD-10-CM	Opioid abuse with intoxication
F11.15	ICD-10-CM	Opioid abuse with opioid-induced psychotic disorder
F11.18	ICD-10-CM	Opioid abuse with other opioid-induced disorder
F11.2	ICD-10-CM	Opioid dependence
F11.22	ICD-10-CM	Opioid dependence with intoxication
F11.25	ICD-10-CM	Opioid dependence with opiod-induced psychotic disorder
F11.28	ICD-10-CM	Opioid dependence with other opioid-induced disorder

Appendix B: Diagnostic codes to identify remission

ICD codes	Version	LABEL
304.03	ICD-9-CM	Opioid type dependence remiss
304.73	ICD-9-CM	Opioid/oth dependence remiss
305.53	ICD-9-CM	Nondep opioid abuse remiss
F11.11	ICD-10-CM	Opioid abuse, in remission
F11.21	ICD-10-CM	Opioid dependence, in remission

Appendix C: Medi-span® codes to identify opioid use disorder medications

Medi-Span GPI	LABEL
65200010200715	Buprenorphine HCl-Naloxone HCl SL Tab 1.4-0.36 MG (Base Eq)
65200010208240	Buprenorphine HCl-Naloxone HCl SL Film 8-2 MG (Base Equiv)
65200010200760	Buprenorphine HCl-Naloxone HCl SL Tab 11.4-2.9 MG (Base Eq)
65200010208280	Buprenorphine-Naloxone Buccal Film 6.3-1 MG (Base Equiv)
65200010208260	Buprenorphine-Naloxone Buccal Film 2.1-0.3 MG (Base Equiv)
65200010200732	Buprenorphine HCl-Naloxone HCl SL Tab 5.7-1.4 MG (Base Eq)
65200010200745	Buprenorphine HCl-Naloxone HCl SL Tab 8.6-2.1 MG (Base Eq)
65200010208270	Buprenorphine-Naloxone Buccal Film 4.2-0.7 MG (Base Equiv)
65200010208220	Buprenorphine HCl-Naloxone HCl SL Film 2-0.5 MG (Base Equiv)
65200010200740	Buprenorphine HCl-Naloxone HCl SL Tab 8-2 MG (Base Equiv)
65200010208250	Buprenorphine HCl-Naloxone HCl SL Film 12-3 MG (Base Equiv)
65200010200720	Buprenorphine HCl-Naloxone HCl SL Tab 2-0.5 MG (Base Equiv)
65200010200725	Buprenorphine HCl-Naloxone HCl SL Tab 2.9-0.71 MG (Base Eq)
65200010208230	Buprenorphine HCl-Naloxone HCl SL Film 4-1 MG (Base Equiv)
65200010102320	Buprenorphine HCl Subdermal Implant 74.2 MG (Base Equiv)
65200010100760	Buprenorphine HCl SL Tab 2 MG (Base Equiv)
65200010100780	Buprenorphine HCl SL Tab 8 MG (Base Equiv)
93400030001920	Naltrexone For IM Extended Release Susp 380 MG
93400030100305	Naltrexone HCl Tab 50 MG

Appendix D: Angiotensin converting enzyme inhibitors

Medi-Span GPI	LABEL
3610x	Accupril, Aceon, Altace, Benazepril HCl, Capoten, Captopril, Enalapril Maleate, Enalaprilat, Epaned, Fosinopril Sodium, Lisinopril, Lotensin, Mavik, Moexipril HCl, Monopril, Perindopril Erbumine, Prinivil, Qbrelis, Quinapril HCl, Ramipril, THSC Captopril, THSC, Lisinopril, Trandolapril, Univasc, Vasotec, Zestril

Appendix E: Service category codes to identify behavioral health visits

Service Category	LABEL
31118	Substance Abuse Facility IP Behavioral Health Therapy
31418	Substance Abuse Facility OP Behavioral Health Therapy
31518	Substance Abuse Physician OP Behavioral Health Therapy
31618	Substance Abuse Professional OP Behavioral Health Therapy
30218	Mental Health Physician IP Behavioral Health Therapy
30118	Mental Health Facility IP Behavioral Health Therapy
30418	Mental Health Facility OP Behavioral Health Therapy
30518	Mental Health Physician OP Behavioral Health Therapy
30618	Mental Health Professional OP Behavioral Health Therapy
31218	Substance Abuse Physician IP Behavioral Health Therapy
31318	Substance Abuse Professional IP Behavioral Health Therapy
30318	Mental Health Professional IP Behavioral Health Therapy

Appendix F: Diagnostic codes to identify polysubstance use disorders

Substance	ICD-9-CM and ICD-10-CM codes
Amphetamine	304.40, 304.41, 304.42, 305.70, 305.71, 305.72, F15.10, F15.120, F15.121, F15.122, F15.129, F15.14, F15.150, F15.151, F15.159, F15.180, F15.181, F15.182, F15.188, F15.19, F15.20, F15.220, F15.221, F15.222, F15.229, F15.23, F15.24, F15.250, F15.251, F15.259, F15.280, F15.281, F15.282, F15.288, F15.29, F15.90, F15.920, F15.921, F15.922, F15.929, F15.93, F15.94, F15.950, F15.951, F15.959, F15.980, F15.981, F15.982, F15.988, F15.99
Cocaine	304.20, 304.21, 304.22, 305.60, 305.61, 305.62, F14.10, F14.120, F14.121, F14.122, F14.129, F14.14, F14.150, F14.151, F14.159, F14.180, F14.181, F14.182, F14.188, F14.19, F14.20, F14.220, F14.221, F14.222, F14.229, F14.23, F14.24, F14.250, F14.251, F14.259, F14.280, F14.281, F14.282, F14.288, F14.29, F14.90, F14.920, F14.921, F14.922, F14.929, F14.94, F14.950, F14.951, F14.959, F14.980, F14.981, F14.982, F14.988, F14.99
Cannabis	304.30, 304.31, 304.32, 305.20, 305.21, 305.22, F12.10, F12.120, F12.121, F12.122, F12.129, F12.150, F12.151, F12.159, F12.180, F12.188, F12.19, F12.20, F12.220, F12.221, F12.222, F12.229, F12.250, F12.251, F12.259, F12.280, F12.288, F12.29, F12.90, F12.920, F12.921, F12.922, F12.929, F12.950, F12.951, F12.959, F12.980, F12.988, F12.99
Alcohol	303.90, 303.91, 303.92, 305.00, 305.01, 305.02, F10.10, F10.120, F10.121, F10.129, F10.14, F10.150, F10.151, F10.159, F10.180, F10.181, F10.182, F10.188, F10.19, F10.20, F10.220, F10.221, F10.229, F10.230, F10.231, F10.232, F10.239, F10.24, F10.250, F10.251, F10.259, F10.26, F10.27, F10.280, F10.281, F10.282, F10.288, F10.29, F10.920, F10.921, F10.929, F10.94, F10.950, F10.951, F10.959, F10.96, F10.97, F10.980, F10.981, F10.982
Tobacco	305.1, 305.10, 305.11, 305.12, F17.200, F17.203, F17.208, F17.209, F17.210, F17.213, F17.218, F17.219, F17.220, F17.223, F17.228, F17.229, F17.290, F17.293, F17.298, F17.299, Z72.0
Other (Barbiturates, Hallucinogens, Inhalants, Sedatives)	304.10, 304.11, 304.12, 305.40, 305.41, 305.42, 304.50, 304.51, 304.52, 305.30, 305.31, 305.32, F13.10, F13.120, F13.121, F13.129, F13.14, F13.150, F13.151, F13.159, F13.180, F13.181, F13.182, F13.188, F13.19, F13.20, F13.220, F13.221, F13.229, F13.230, F13.231, F13.232, F13.239, F13.24, F13.250, F13.251, F13.259, F13.26, F13.27, F13.280, F13.281, F13.282, F13.288, F13.29, F13.90, F13.920, F13.921, F13.929, F13.930, F13.931, F13.932, F13.939, F13.94, F13.950, F13.951, F13.959, F13.96, F13.97, F13.980, F13.981, F13.982, F13.988, F13.99, F16.10, F16.120, F16.121, F16.122, F16.129, F16.14, F16.150, F16.151, F16.159, F16.180, F16.183, F16.188, F16.19, F16.20, F16.220, F16.221, F16.229, F16.24, F16.250, F16.251, F16.259, F16.280, F16.283, F16.288, F16.29, F16.90, F16.920, F16.921, F16.929, F16.94, F16.950, F16.951, F16.959, F16.980, F16.983, F16.988, F16.99, F18.10, F18.120, F18.121, F18.129, F18.14, F18.150, F18.151, F18.159, F18.17, F18.180, F18.188, F18.19, F18.20, F18.220, F18.221, F18.229, F18.24, F18.250, F18.251, F18.259, F18.27, F18.280, F18.288, F18.29, F18.90, F18.920, F18.921, F18.929, F18.94, F18.950, F18.951, F18.959, F18.97, F18.980, F18.988, F18.99

BIBLIOGRAPHY

1. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. *Nat Rev Drug Discov*. 2004;3(8):673-683.

2. Li J, Zheng S, Chen B, Butte AJ, Swamidass SJ, Lu Z. A survey of current trends in computational drug repositioning. *Brief Bioinform*. 2016;17(1):2-12.

3. Lee H-M, Kim Y. Drug Repurposing Is a New Opportunity for Developing Drugs against Neuropsychiatric Disorders. *Schizophr Res Treat*. 2016;2016:6378137.

4. Hoehndorf R, Oellrich A, Rebholz-Schuhmann D, Schofield PN, Gkoutos GV. Linking PharmGKB to phenotype studies and animal models of disease for drug repurposing. *Pac Symp Biocomput*. 2012:388-399.

5. Xu R, Wang Q. Large-scale extraction of accurate drug-disease treatment pairs from biomedical literature for drug repurposing. *BMC Bioinformatics*. 2013;14:181.

6. Xu R, Li L, Wang Q. Towards building a disease-phenotype knowledge base: extracting disease-manifestation relationship from literature. *Bioinformatics*. 2013;29(17):2186-2194.

7. Chen Y, Xu R. Drug repurposing for glioblastoma based on molecular subtypes. *J Biomed Inform*. 2016;64:131-138.

8. Chiang AP, Butte AJ. Systematic evaluation of drug-disease relationships to identify leads for novel drug uses. *Clin Pharmacol Ther*. 2009;86(5):507-510.

9. Raghupathi W, Raghupathi V. Big data analytics in healthcare: promise and potential. *Health Inf Sci Syst*. 2014;2:3.

10. Hankosky ER, Bush HM, Dwoskin LP, et al. Retrospective analysis of health claims to evaluate pharmacotherapies with potential for repurposing: Association of bupropion and stimulant use disorder remission. *AMIA Annu Symp Proc*.;2018:1292-1299.

11. Dickstein C, Gehring R. *Administrative Healthcare Data: A Guide to Its Origin, Content, and Application Using SAS®*. Cary, NC: SAS Institute Inc; 2014.

12. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-920.

13. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Treatment Episode Data Set (TEDS): 2005-2015. National Admissions to Substance Abuse Treatment Services. BHSIS Series S-91, HHS Publication No. (SMA) 17-5037. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2017.

14. Stoops WW, Rush CR. Agonist replacement for stimulant dependence: a review of clinical research. *Curr Pharm Des*. 2013;19(40):7026-7035.

15. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet Lond Engl*. 2003;361(9358):662-668.

16. Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003;349(10):949-958.

17. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev*. 2011;(4):CD001333.

18. Hansen L. *The Truven Health MarketScan Databases for Life Sciences Researchers*. https://truvenhealth.com/Portals/0/Assets/2017-MarketScan-Databases-Life-Sciences-Researchers-WP.pdf.

19. Davenport S, Matthews K. *Opioid Use Disorderin the United States: Diagnosed Prevalence by Payer, Age, Sex, And State*.; 2018. http://www.milliman.com/uploadedFiles/insight/2018/Opioid_Use_Disorder_Prevalence.pdf.

20. Cochran G, Gordon AJ, Lo-Ciganic W-H, et al. An Examination of Claims-based Predictors of Overdose from a Large Medicaid Program. *Med Care*. 2017;55(3):291-298.

21. Kim HM, Smith EG, Stano CM, et al. Validation of key behaviourally based mental health diagnoses in administrative data: suicide attempt, alcohol abuse, illicit drug abuse and tobacco use. *BMC Health Serv Res*. 2012;12:18.

22. Desai RJ, Glynn RJ, Wang S, Gagne JJ. Performance of Disease Risk Score Matching in Nested Case-Control Studies: A Simulation Study. *Am J Epidemiol*. 2016;183(10):949-957.

23. Elixhauser A, Steiner C, Palmer L. *Healthcare Cost and Utilization Project – HCUP A Federal-State-Industry Partnership in Health Data*.; 2015. https://www.hcup-us.ahrq.gov/toolssoftware/ccs/CCSUsersGuide.pdf.

24. Brecht M-L, Huang D, Evans E, Hser Y-I. Polydrug use and implications for longitudinal research: ten-year trajectories for heroin, cocaine, and methamphetamine users. *Drug Alcohol Depend*. 2008;96(3):193-201.

25. Hurle MR, Yang L, Xie Q, Rajpal DK, Sanseau P, Agarwal P. Computational drug repositioning: from data to therapeutics. *Clin Pharmacol Ther*. 2013;93(4):335-341.

26. Jenkins TA, Mendelsohn FA, Chai SY. Angiotensin-converting enzyme modulates dopamine turnover in the striatum. *J Neurochem*. 1997;68(3):1304-1311.

27. Jenkins TA, Wong JY, Howells DW, Mendelsohn FA, Chai SY. Effect of chronic angiotensin-converting enzyme inhibition on striatal dopamine content in the MPTP-treated mouse. *J Neurochem*. 1999;73(1):214-219.

28. Wincewicz D, Braszko JJ. Validation of Brain Angiotensin System Blockade as a Novel Drug Target in Pharmacological Treatment of Neuropsychiatric Disorders. *Pharmacopsychiatry*. 2017;50(6):233-247.

29. Newton TF, De La Garza R, Grasing K. The angiotensin-converting enzyme inhibitor perindopril treatment alters cardiovascular and subjective effects of methamphetamine in humans. *Psychiatry Res*. 2010;179(1):96-100.

30. Verrico CD, Haile CN, De La Garza R, Grasing K, Kosten TR, Newton TF. Subjective and Cardiovascular Effects of Intravenous Methamphetamine during Perindopril Maintenance: A Randomized, Double-Blind, Placebo-Controlled Human Laboratory Study. *Int J Neuropsychopharmacol*. 2016;19(7).

31. Lundgren L, Chassler D, Ben-Ami L, Purington T, Schilling R. Factors associated with emergency room use among injection drug users of African-American, Hispanic and White-European background. *Am J Addict*. 2005;14(3):268-280.

32. Alderks CE. *Trends in the use of methadone, buprenorphine, and extended-release naltrexone at substance abuse treatment facilities: 2003-2015 (UPDATE)*. Rockville, MD.: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration

33. Bagalman E, Yu-Isenberg KS, Durden E, Crivera C, Dirani R, Bunn WB. Indirect costs associated with nonadherence to treatment for bipolar disorder. *J Occup Environ Med*. 2010;52(5):478-485.

34. Mark TL. The Effect of the Affordable Care Act on Uninsured Rates Among Individuals With Mental and Substance Use Disorders. *Psychiatr Serv.* 2019;70(4):343.

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BOOK CHAPTERS

1. **Hankosky ER** & Gulley JM (2016) Adolescent exposure to amphetamines and vulnerability to addiction. The Neuropathology of Drug Addictions and Substance Misuse (ed. Preedy, V), 292-299. London, Academic Press.

2. Dwoskin LP, **Hankosky ER**, Glaser PEA, Bardo MT. Methamphetamine. 2nd Edition. *Addiction Science: Science and Practice*. Ed BA Johnson, Springer Science.

PEER-REVIEWED PUBLICATIONS

1. Rosenkranz JA, **Venheim ER**, & Padival M (2010) Chronic stress causes amygdala hyperexcitability in rodents. *Biological Psychiatry*, 67: 1128-36.

2. Atchley D, **Hankosky ER**, Gasparotto K, & Rosenkranz JA (2012) Pharmacological enhancement of calcium-activated potassium channel function reduces the effects of repeated stress on fear memory. *Behavioural Brain Research*, 232: 37-43.

3. **Hankosky ER** & Gulley JM (2013) Performance on an impulse control task is altered in adult rats exposed to amphetamine during adolescence. *Developmental Psychobiology*, 55: 733-744.

4. **Hankosky ER**, Kofsky NM, & Gulley JM (2013) Age-dependent effects of amphetamine exposure on attentional set-shifting. *Behavioral Brain Research*, 252: 117-125.

5. Kougias DG, Nolan SO, Koss WA, Kim T, **Hankosky ER**, Gulley JM, & Juraska JM (2016) Beta-hydroxy-beta-methylbutyrate (HMB) ameliorates aging effects in the dendritic tree of pyramidal neurons in the medial prefrontal cortex of both male and female rats. *Neurobiology of Aging*, 40: 78-85.

6. Kang S, Paul K, **Hankosky ER**, Cox CL, & Gulley JM (2016) D1 receptor-mediated inhibition of medial prefrontal cortex neurons is disrupted in adult rats exposed to amphetamine in adolescence. *Neuroscience*, 324: 40-49.

7. **Hankosky ER**, Sherrill LK, Ruvola LA, Haake RM, Kim T, Hammerslag LR, Kougias DG, Juraska JM, & Gulley JM (2016) Effects of β-hydroxy-β-methyl butyrate (HMB) on working memory and cognitive flexibility in an animal model of aging. *Nutritional Neuroscience,* 20: 379-387.

8. Kougias DG, **Hankosky ER**, Gulley JM, Juraska JM (2017) Beta-hydroxy-beta-methylbutyrate (HMB) ameliorates age-related deficits in water maze performance, especially in male rats. *Physiology and Behavior*, 170: 93-99.

9. **Hankosky ER**, Westbrook SR, Haake RM, Marinelli M, & Gulley JM (2017) Reduced sensitivity to reinforcement in adolescent compared to adult Sprague-Dawley rats of both sexes. *Psychopharmacology*, 235: 861-871.

10. **Hankosky ER**, Joolakanti SR, Nickell JR, Janganati V, Dwoskin LP, Crooks PA (2017) Fluoroethoxy-1,4-diphenethyl piperidine and piperazine derivatives: Potent and selective inhibitors of [^{3}H]dopamine uptake at the vesicular monoamine transporter-2. *Bioorganic and Medicinal Chemistry Letters,* 27: 5467-5472.

11. Westbrook SR, **Hankosky ER**, Dwyer MR, Gulley JM (2018) Age and sex differences in behavioral flexibility, sensitivity to reward value, and risky decision-making. *Behavioral Neuroscience*, 132: 75-87.

12. Cui L, Zeng N, Kim M, Mueller R, **Hankosky ER**, Redline S, Zhang GQ (2018) X-search: an open access interface for cross-cohort exploration of the National Sleep Research Resource. *BMC Medical Informatics and Decision Making*, 18: 99.

13. **Hankosky ER**, Westbrook SR, Haake RM, Willing J, Raetzman LT, Juraska JM, Gulley JM (2018) Age- and sex-dependent effects of methamphetamine on cognitive flexibility and 5-HT_{2C} receptor localization in the orbitofrontal cortex of Sprague-Dawley rats. *Behavioral Brain Research*, 349: 16-24.

14. Freeman PR, **Hankosky ER**, Lofwall MR, Talbert JC (2018) The changing landscape of naloxone availability in the United States, 2011 – 2017. *Drug and Alcohol Dependence,* 191: 361-364.

15. Fouladvand S, **Hankosky ER**, Henderson D, Bush HM, Chen J, Dwoskin LP, Freeman PR, Kantak K, Talbert JC, Tao S, Zhang GQ (2018) Predicting substance use disorder using long-term ADHD medication records in Truven. *Health Informatics Journal*, DOI 10.1109/ICHI-W.2018.00014.

16. **Hankosky ER**, Bush HM, Dwoskin LP, Daniel R. Harris, Darren W. Henderson, Zhang GQ, Freeman PR, Talbert JC. (2018) Retrospective analysis of health claims data to evaluate pharmacotherapies with potential for repurposing: Association of bupropion and stimulant use disorder remission. *AMIA Annu Symp Proc:* 1292-1299.