Identifying Opioid and Illicit Drug Use from Adverse Event Reported Outcomes Using Machine Learning

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Abstract

Earlier identification of opioid and illicit drug use may be used as a powerful tool for better guiding treatment strategies as well as appropriate triage of suspected illicit drug overdose patients. In this study, a machine learning model was used to distinguish patient drug use based solely on reported physiological events. For training and testing sets, data were derived from AEOLUS, a database of curated adverse drug reports based on the US Food and Drug Administration (FDA) Adverse Event Reporting System. Google's TensorFlow library was used to build, train, and test the linear regression model. The positive results of this study suggest that machine learning approaches can be used to identify drugs based on reported outcomes.

Introduction

Toxicology screening with patient urine and blood samples has become a standard of care for patients suspected of illicit or opioid drug use [1]. Absent essential information about whether illicit or opioid drugs are involved in the manifestation of symptoms can lead to challenges in developing strategies for patient treatment. Improvements in rapidly identifying illicit drugs and opioids based on presentation of symptoms have the potential to change practice patterns, especially in acute care environments. The steady increase in drug overdose deaths since the 2000s[2] therefore calls for improved drug screening methods in the clinical setting. In emergency situations, rapid detection of exact prescription or illicit drug use can be crucial for

determining proper care delivery.

The availability of drug adverse event reporting provides an opportunity to build predictive models for detection of drug use. This study uses data from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), a database containing quarterly reports on adverse event and medication error reports submitted to FDA [3]. In the FAERS dataset, combinations of drugs are reported with combinations of resulting adverse outcomes [3], providing information linking drugs with certain physiological effects. Combined with current machine learning techniques, this information can be used to create algorithms correlating certain physiological factors with known drug outcomes. These correlations can then be used to construct predictive algorithms that determine drug use.

Machine learning involves the use of data to create predictive models that can learn and improve without the aid of explicit programming. Two steps are involved in the creation of a machine learning algorithm: (1) training and (2) testing. Training involves performing statistics iteratively on a set of data until the predictions made by the model reach a certain level of accuracy. Afterwards, testing is done to further improve the model and determine the final accuracy. Machine learning techniques have been used previously in clinical settings to improve viral testing [4], graft failure prediction [5], and clinical decision making for breast cancer drug therapies[6]. Given the breadth of clinical data available, machine learning provides techniques to standardize and improve clinical care.

In this study, machine learning techniques were used to explore the potential to identify opioid and illicit drug intake based on electronically captured FAERS data. Opioids and illicit drugs were tested specifically given the rise in illicit drug and opioid overdose cases nationwide[7], making drug detection increasingly important in the clinical setting. Utilizing

machine learning tools provided for by TensorFlow[8], Google's machine learning library, the goal of this study was to explore the potential to develop a predictive modeling system that does not require full patient history and makes classifications based on a patient's current physiological state. Specific focus of this study was on four commonly prescribed opioids: (1) oxycodone; (2) hydrocodone; (3) fentanyl; and (4) morphine and three commonly abused drugs: (1) cocaine; (2) heroine; and (3) methamphetamine. The promising findings suggest that the machine learning approach employed in this study can indeed be used to rapidly identify individuals who may be at high risk of illicit or opioid drug use.

Materials and Methods

FAERS

The FDA Adverse Event Reporting System (FAERS) is a database containing information on adverse event and medication error reports submitted to the FDA [3]. Event reports are submitted quarterly by health professionals and consumers and evaluated by clinical reviewers in the Center for Drug Evaluation and Research. Information is presented as reports stating all drugs taken by patients followed by all outcomes presented. No causal links are recorded between product and outcome. Using FAERS for mining drug-effect associations has been an active area of research and multiple data mining algorithms have been created for this purpose [9-11]. To date, there has been no reported use of predictive machine learning models for determining possible drugs based upon given events.

AEOLUS

From the community efforts of the Observational Health Data Science and Informatics (OHDSI) initiative, the FAERS and LAERS (Legacy Adverse Event Reporting System, which

contains adverse event reports before 2012) datasets were reprocessed, cleaned, and standardized to form the Adverse Event Open Learning through Universal Standard (AEOLUS) database[15]. Single missing value imputation was first performed followed by case de-duplication. Every case was then given a primaryid or isr number, which indicate FAERS or LAERS cases respectively. Linked to each case are reported outcomes, given in OHDSI outcome concepts, and associated drugs, standardized to RxNorm Concept Unique Identifiers. Data are organized in AEOLUS into seven different MySQL tables, two of which were used in this study: one listing case ids with reported outcome concept ids and another listing case ids with standard drug concept ids. There were a total of 4245 distinct drug IDs and 17,710 distinct outcome IDs.

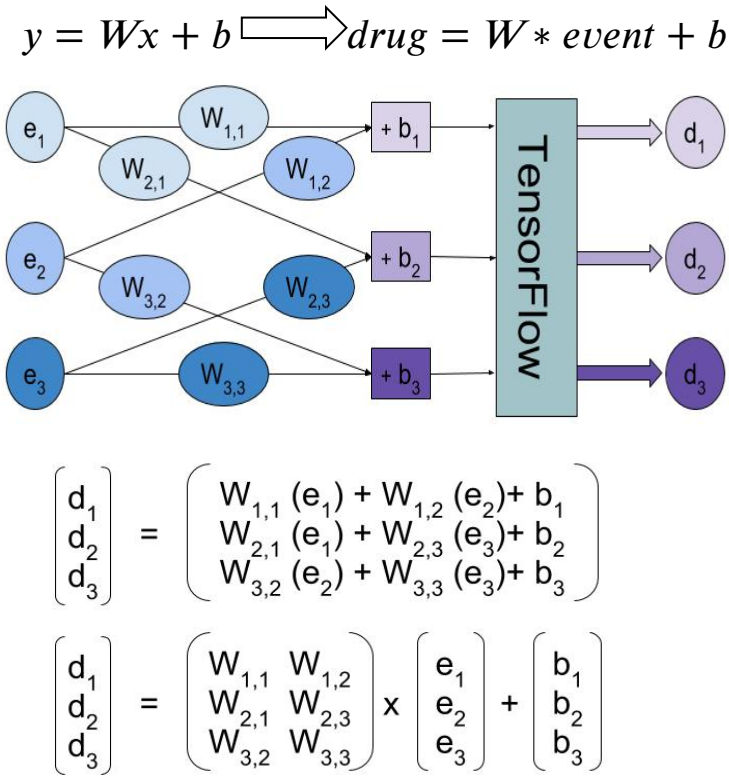

Figure 1: Overview of linear regression model employed by TensorFlow. e_n represents event n and d_m represents drug m. $W_{m,n}$ represents the weight multiplied to event n for drug m and b_m represents the bias for drug m. The bottom half of the figure shows the resulting matrix multiplication.

Machine Learning Model

A linear regression model, similar to that employed with the Mixed National Institute of Standards and Technology (MNIST), was used for training and testing. MNIST is a large database of handwritten digits that have been subjected to various machine learning methods to identify systems or approaches that achieve near-human performance. The model follows a y=Wx+b equation (Figure 1), with drugs as the dependent variable and physiological events as the independent variable. The linear model also accounted for biases (b) and contained a matrix for weights (W). The drugs and outcomes were given Boolean 0 or 1 values depending on if the drug or outcome was present in the tested case (Figure 2). For example, following Figure 1, e_1 would be a Boolean for the presence of event A and would be 0 or 1 depending on if event A was present in the test case. d_1 would be a Boolean for the presence of drug B and would be 0 or 1 depending on if drug B was present in the test case. $W_{1,1}$ is the weight multiplied to e_1 for the calculation of the probability d_1 was present (Figure 1). In this study, this was implemented using TensorFlow, which is Google's open-source software for deep neural networks, and provides a platform for accurate, large-scale machine learning research [8]. In TensorFlow, the data are vectorized into tensors and used to construct a data-flow graph. The graph is altered as more training data are deployed, adjusting the weights of the neural network with each iteration. In this study, TensorFlow was used to follow this machine learning model, iteratively adjusting weights and biases using softmax regression and loss functions.

Conditions Tested

This study focused on evaluating the ability to develop a prediction model using TensorFlow for effectiveness in classifying based on drug class, identifying the presence of specific drugs, and distinguishing between individual drugs. For drug class, opioids were chosen

given the rising opioid epidemic [7] and four commonly prescribed opioids were specifically analyzed: (1) oxycodone; (2) hydrocodone; (3) fentanyl; and (4) morphine. For individual drug identification, three of the most common illicit drugs reported in AEOLUS were used: (1) cocaine, (2) methamphetamine, and (3) heroin. Evaluation of the model thus came from three tested conditions: (1) classification of opioid versus non-opioid; (2) prediction of illicit drug presence versus absence; (3) identification between different illicit drugs.

Developing Outcome and Drug Arrays

Arrays of Outcomes and Drugs were generated based on cases reported in AEOLUS. For identifying opioids, the total set of outcomes considered was narrowed down to the 35 outcomes with the highest numbers of cases. In other words, each drug-associated outcome was required to occur in a certain number of cases for each drug, and only the 35 outcomes with the highest number of cases were selected for the final outcome array (Table 1). For illicit drugs, the 20 outcomes with the highest number of cases for each illicit drug were used given the smaller number of total outcomes for illicit drugs (Table 2).

Given some of the outcomes coded in the AEOLUS dataset were non-physiological, another round of testing was performed removing all non-physiological outcomes and all cases containing only non-physiological outcomes for the illicit drugs. The twenty highest physiological outcomes with the highest number of cases were used for the outcome arrays. The differences in outcome are shown in Table 3.

A total of 5000 cases were used as training and test cases for each condition tested except for the between drug comparisons, which utilized 2000 cases each. For the conditions using 5000 cases, eighty percent of the cases were randomly assigned to the training set and twenty percent were assigned to the testing set. For the drug comparisons, fifty percent of cases were randomly

assigned to the training set and fifty percent were assigned to the testing set. All specific outcomes and drugs were organized from each reported case into the Boolean Drug and Outcome arrays. The final set of training and testing outcome arrays were concatenated into two arrays with dimensions Tx4000 and Tx1000 respectively or Tx1000 and Tx1000 respectively where T depends on the number of outcomes tested in each case. Similarly, the training and testing drug arrays were concatenated into two arrays with dimensions 1x4000 and 1x1000 or 1x1000 and 1x1000.

Table 1 35 Outcomes with the highest number of cases for opioid classification

Outcome	Outcome Code	Number of cases
PAIN IN EXTREMITY	36516959	6128
FATIGUE	35809076	16091
ARTHRALGIA	36516812	22152
ASTHENIA	35809072	29948
DEATH	35809059	264244
ABDOMINAL PAIN	35708154	36210
HEADACHE	36718132	45104
COMPLETED SUICIDE	36919230	50462
RENAL FAILURE	37019318	218245
PNEUMONIA	36110597	57750
HYPERHIDROSIS	35809134	223394
DIZZINESS	35205025	65865
BACK PAIN	36516951	72851
SOMNOLENCE	36718321	80160

PAIN	35809243	99102
INJURY	36211303	233584
CHEST PAIN	35205185	239270
DEHYDRATION	36416606	244572
MALAISE	35809079	105524
ANXIETY	36918858	114380
WEIGHT DECREASED	36315380	120121
ANAEMIA	35104074	249940
HYPOTENSION	37622449	229200
NAUSEA	35708202	138003
PYREXIA	35809054	144935
INSOMNIA	36718555	151124
DIARRHOEA	35708093	160394
VOMITING	35708208	173710
DYSPNOEA	35205038	184787
CONFUSIONAL STATE	36718301	191037
RENAL FAILURE ACUTE	37019319	254098
CARDIAC ARREST	35204966	195884
CONSTIPATION	35708100	202342
RESPIRATORY ARREST	37219893	206227
DEPRESSION	36918942	214085

Table 2 20 Outcomes with the highest number of cases for each illicit drug

Cocaine	Heroin	Methamphetamine
DRUG DEPENDENCE	EXPOSURE VIA INGESTION	EXPOSURE VIA INGESTION
MULTIPLE DRUG OVERDOSE INTENTION	MULTIPLE DRUG OVERDOSE	PULMONARY ARTERIAL HYPERTENSION
POISONING	POISONING	POISONING
COMPLETED SUICIDE	COMPLETED SUICIDE	COMPLETED SUICIDE
DRUG ABUSER	DRUG ABUSER	DRUG ABUSER
INTENTIONAL DRUG MISUSE	INTENTIONAL DRUG MISUSE	INTENTIONAL DRUG MISUSE
POLYSUBSTANCE ABUSE	POLYSUBSTANCE ABUSE	DRUG INTERACTION
CARDIO-RESPIRATORY ARREST	CARDIO-RESPIRATORY ARREST	CARDIO-RESPIRATORY ARREST
OVERDOSE	OVERDOSE	OVERDOSE
TOXICITY TO VARIOUS AGENTS	TOXICITY TO VARIOUS AGENTS	TOXICITY TO VARIOUS AGENTS
SUBSTANCE ABUSE	SUBSTANCE ABUSE	SUBSTANCE ABUSE
DRUG TOXICITY	DRUG WITHDRAWAL SYNDROME	DRUG TOXICITY
AGITATION	DRUG WITHDRAWAL SYNDROME NEONATAL	INTENTIONAL MISUSE
DRUG ABUSE	DRUG ABUSE	DRUG ABUSE
CARDIAC ARREST	CARDIAC ARREST	CARDIAC ARREST
AGGRESSION	DRUG DEPENDENCE	CARDIOMYOPATHY
RESPIRATORY ARREST	RESPIRATORY ARREST	RESPIRATORY ARREST
DRUG SCREEN POSITIVE	PULMONARY OEDEMA	PULMONARY OEDEMA
DEATH	DEATH	DEATH
COMA	UNRESPONSIVE TO STIMULI	UNRESPONSIVE TO STIMULI

Table 3 20 Physiological Outcomes with the highest number of cases for each illicit drug

Cocaine	Heroin	Methamphetamine
CONVULSION	EXPOSURE VIA INGESTION	EXPOSURE VIA INGESTION
BLOOD CREATINE PHOSPHOKINASE INCREASED	EUPHORIC MOOD	PULMONARY ARTERIAL HYPERTENSION
TACHYCARDIA	SOMNOLENCE	SEROTONIN SYNDROME
COMPLETED SUICIDE	COMPLETED SUICIDE	PNEUMONIA
SOMNOLENCE	CONVULSION	RESPIRATORY DEPRESSION
DEPRESSION	DEPRESSION	DEPRESSION
SUICIDE ATTEMPT	SUICIDE ATTEMPT	SUICIDE ATTEMPT
CARDIO-RESPIRATORY ARREST	CARDIO-RESPIRATORY ARREST	CARDIO-RESPIRATORY ARREST
SUICIDAL IDEATION	NYSTAGMU	MULTI-ORGAN FAILURE
VOMITING	VOMITING	VOMITING
NAUSEA	DEVELOPMENTAL DELAY	NAUSEA
DRUG WITHDRAWAL SYNDROME	DRUG WITHDRAWAL SYNDROME	HYPOTENSION
AGITATION	DRUG WITHDRAWAL SYNDROME NEONATAL	AGGRESSION
HYPOTENSION	LOSS OF CONSCIOUSNESS	LOSS OF CONSCIOUSNESS
CARDIAC ARREST	CARDIAC ARREST	CARDIAC ARREST
AGGRESSION	COMA	CARDIOMYOPATHY
RESPIRATORY ARREST	RESPIRATORY ARREST	RESPIRATORY ARREST
LOSS OF CONSCIOUSNESS	PULMONARY OEDEMA	PULMONARY OEDEMA
DEATH	DEATH	DEATH
COMA	UNRESPONSIVE TO STIMULI	UNRESPONSIVE TO STIMULI

The individual outcome and drug arrays were of dimensions Tx1 and 1x1, respectively. The arrays were composed of 0s and 1s and made on a case-by-case basis. For each case, the drug and outcome dictionaries were duplicated and values for present drugs and outcomes were changed to 1. Figure 2 graphically depicts the entire process of going from the drug and outcome information associated with each case to the final drug and outcome arrays.

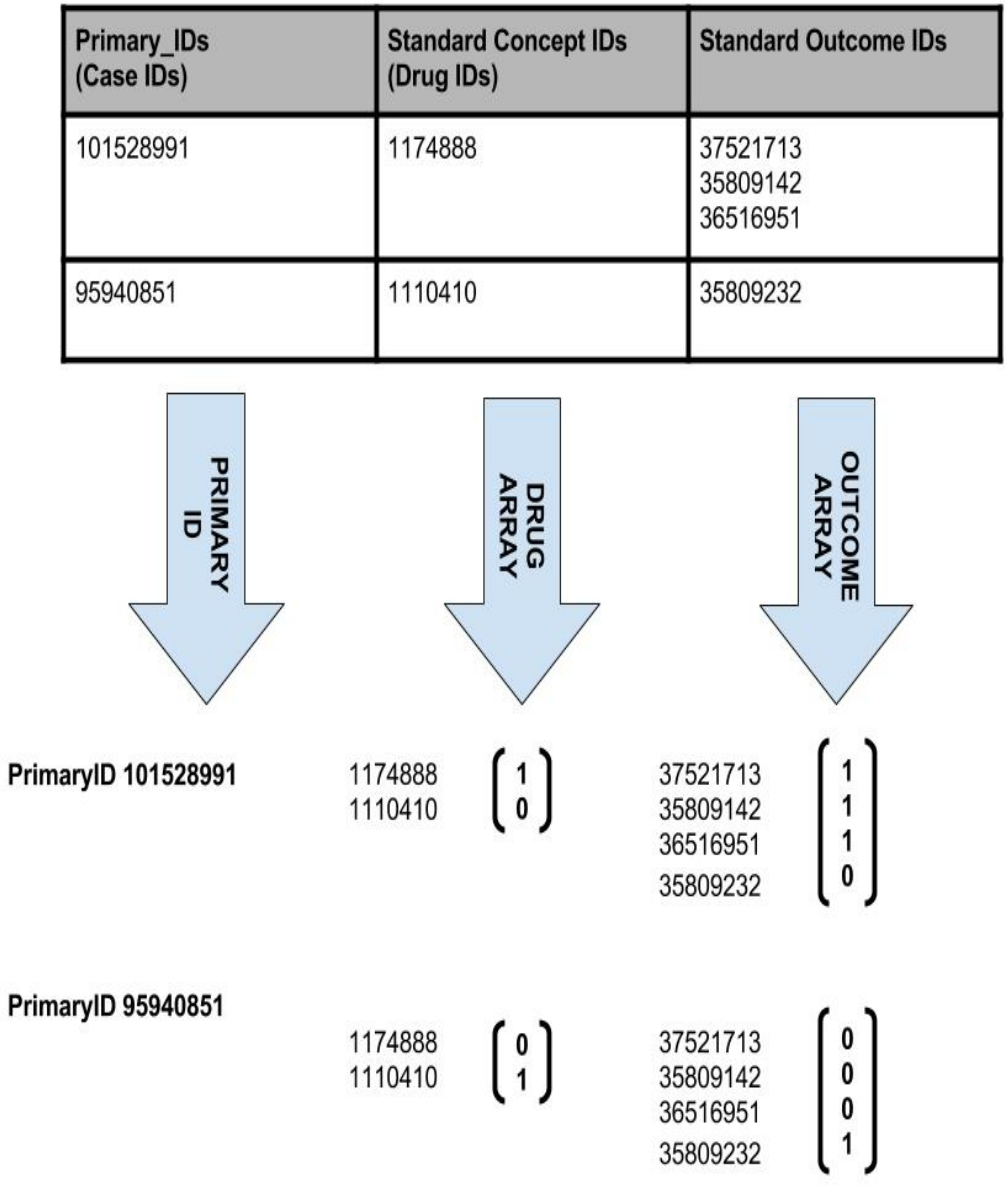

Figure 2 AEOLUS element extraction and creation of the drug and outcome arrays

Training and Testing

For each condition with 5000 total cases, 4000 cases were used as a training set. For each condition with 2000 total cases, 1000 cases were used as a training set. The weight matrix, with dimensions 1xT, and bias were adjusted with every iteration during training based on a loss function. 1000 cases were tested for each condition with TensorFlow and accuracy was determined at every step based on the differences between the given and predicted outcome arrays. Every case resulted in a 0 or 1 accuracy measurement, with 0 meaning the model predicted inaccurately and 1 meaning the model predicted accurately. The final accuracy measurements were based on these individual 0 or 1 accuracy measurements.

Results

Based on the analysis of outcomes reported in AEOLUS, the TensorFlow machine learning approach implemented in this study was able to identify cases associated with illicit drug use but was not successful in classifying opioids. The general profile of the outcomes for the opioids revealed that each of the opioids analyzed in this study share about seventy to eighty percent of the reported outcomes with the other opioids analyzed in this study (Table 4). This suggested validity in our ability to group all four drugs into one class. The general profile of the outcomes for illicit drugs revealed that each of the illicit drugs analyzed in this study share about half the reported outcomes with other drugs analyzed in this study (Table 5). This suggested some characteristics related to outcomes upon which a machine learning approach can be used to predict use of the drug.

Table 4 Overlap between outcomes reported as adverse events for three illicit drugs

	Oxycodone	Hydrocodone	Fentanyl	Morphine
Oxycodone	7639			
Hydrocodone	6253	7944		
Fentanyl	5894	5921	7253	
Morphine	6088	6053	5925	7449

Table 5 Overlap between outcomes reported as adverse events for three illicit drugs

	Cocaine	Methamphetamine	Heroin
Cocaine	1594		
Methamphetamine	743	1116	
Heroin	753	544	978

Table 6, 7, 8, and 9 summarize the statistics of the system to classify drug classes (Table 5), detect each drug (Table 6), detect each drug with only physiological outcomes (Table 7), and distinguish between drugs (Table 8) based on reported outcomes in AEOLUS. In total, 34,000 cases were used for training (4000 or 2000 for each condition) and 10,000 cases were tested (1000 for each condition).

Table 6 Summary of evaluation for opioid classification

Class	Sensitivity	Specificity	PPV	NPV
Opioids	0.507	0.468	0.463	0.511

Table 7 Summary of evaluation for three illicit drugs examined in this study

Drug	Sensitivity	Specificity	PPV	NPV
Cocaine	0.884	0.972	0.924	0.956
Methamphetamine	0.927	0.960	0.901	0.971
Heroin	0.928	0.983	0.955	0.972

Table 8 Summary of evaluation for three illicit drugs examined in this study after non-physiological outcomes removal

Drug	Sensitivity	Specificity	PPV	NPV
Cocaine	0.751	0.796	0.683	0.845
Methamphetamine	0.771	0.806	0.699	0.858
Heroin	0.405	0.868	0.597	0.752

Table 9 Summary of evaluation for ability to distinguish between the three illicit drugs

Comparison	Sensitivity	Specificity	PPV	NPV
Cocaine versus Heroin	0.751	0.336	0.579	0.526
Cocaine versus Methamphetamine	0.751	0.418	0.562	0.628
Heroin versus Methamphetamine	0.405	0.624	0.468	0.561

Discussion

In this study, a machine-learning model was developed for predicting opioid and illicit drug intake based on physiological outcomes as reported in public reporting adverse event systems. The algorithm was designed to predict whether an individual was using opioid and

illicit drugs based on a list of outcomes. It is important to note that the list of possible physiological events used in this study was limited to those that are reported to FDA. Outcomes that are not reported through FAERS are thus not currently incorporated into the model developed in this study. Nonetheless, the approach developed here provides a positive proof-of-concept that may be of clinical utility.

The system was created through data extraction from the AEOLUS database and TensorFlow's machine learning library. The AEOLUS database compiles quarterly FAERS reports and reprocessed the data to provide standardization and remove case duplication. All cases contained lists of present drugs and outcomes but did not directly link the two events. The AEOLUS dataset did include indications for primary and secondary suspects for each case, but these factors were not included owing to the self-learning nature of the machine learning algorithms. Additional features provided by AEOLUS include drug-outcome arrays providing statistics between each drug-outcome pairing, which could be utilized in future studies.

From the AEOLUS dataset, cases were chosen at random for training and testing sets. Boolean drug and outcome arrays were created for each case id with the condition being whether the drug or outcome was present or not. Utilizing solely Booleans, however, can lead to lower accuracies as the tested drugs were sometimes linked to unrelated outcomes owing to the prevalence of these outcomes generally within the training cases. As shown with the low specificity measurement for opioid classification, future expansion of this study into common prescription drug detection will be difficult given high prevalence of these drugs in large numbers of cases but no correlation to the outcomes presented.

TensorFlow software was utilized for all machine learning processes and the data was

modeled with a linear regression. This study used a simple softmax regression model and single layer convolution graphs. Next steps for accuracy improvement, however, will look more into multilayer convolution networks and use more sophisticated machine learning techniques provided by TensorFlow.

The proof-of-concept of this study demonstrated the potential of using machine learning techniques, such as those implemented in TensorFlow, to predict illicit drug use with reasonable accuracy. This approach could be used for detecting other significant events, such as detection of herbal or non-herbal supplement use. Herbal and non-herbal supplement use is not detected in routine drug screenings and depends solely on patients disclosing their use to providers. Studies have shown, however, that only around 33% of dietary and supplement users reveal their herbal and dietary supplement history to health care professionals [12-13]. Supplements, when combined with certain prescription drugs, can have adverse effects [14-15] and improper supplement use causes around 23,000 emergency department visits in the United States every year [16]. Thus the detection of patients' drug and supplement use is crucial to patient care. At the time of this study, there were no herbal or dietary supplements included in AEOLUS. Therefore, future work will include evaluation of the machine learning approach demonstrated in this study for supplement use detection after these data are included in AEOLUS.

There is a strong case to be made for using AEOLUS over FAERS, since drug and outcome information within AEOLUS are systematically encoded and mapped to accepted biomedical ontologies. This is a crucial step towards supporting the potential of developing robust machine learning approaches for prediction.

This study represents the first of its type where a machine learning approach is leveraged

to make use of publicly available outcome data associated with drug use prediction. Amidst the aforementioned limitations noted about using public data, the positive results of this study, especially with identifying illicit drugs, suggest that computational approaches can be used to identify instances where drug use may be involved with clinical cases. It is anticipated that the modeling approaches demonstrated in this study could be greatly enhanced by utilizing clinical data about patients who are associated with illicit drug use. This could include the incorporation of other data that may also impact risk of illicit drug use (e.g., sociodemographic features). The relative impact of additional such features compared to only reported outcome (which was the focus of this study) could inform development and implementation of systems in clinical contexts.

Conclusion

Machine learning techniques are powerful computational approaches for supporting predictive tasks that may be of clinical importance. In this study, TensorFlow is used to explore the potential of such approaches to predict illicit drug and opioid use. The generally positive findings of this feasibility study indicate that there is promise in harnessing reported outcome data for identifying clinically impactful drug use.

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