LEVERAGING MACHINE LEARNING FRAMEWORK TO PREDICT BUPRENORPHINE/NALOXONE TREATMENT DISCONTINUATION

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ABSTRACT

Opioid use disorder (OUD) is a growing public health concern in the United States, causing nearly 130 deaths every day. The negative economic health burden attributed to OUD is substantial that exceeds roughly $56 billion annually. Buprenorphine/naloxone is an evidence-based and cost-effective opioid agonist therapy most commonly prescribed for treating OUD. Retaining in the treatment for long-term treatment with better continuity is proven to produce better treatment outcome in terms of reduced relapse rate and abstinence. However, premature discontinuation from the buprenorphine/naloxone treatment often times leads to unfavorable and negative health outcomes such as higher rate of relapse and increased risk of other substance use disorder. Hence, there exists a critical need to proactively identify individuals who are at risk of discontinuing buprenorphine/naloxone treatment prematurely. Till date, there has been little in-depth research that focuses on predicting buprenorphine/naloxone treatment discontinuation. To that end, in this study, we propose a framework leveraging state-of-the-art machine learning algorithms to predict premature treatment discontinuation, in particular for naïve patients on buprenorphine/naloxone treatment. We used All Payer Claims Data (APCD), a database that records pharmacy claims for state’s commercially insured population. We designed a retrospective longitudinal study to investigate the buprenorphine refill pattern for those naïve patients. In addition, we identified several patient-level demographic and prescriber-level characteristics to be used as features in the predictive models. We then implemented several binary classification algorithms including logistic regression, decision tree, random forest, neural network, boosted trees classifier, support vector machine, naïve Bayes and soft voting ensemble models to predict treatment discontinuation. Models are compared on the basis of accuracy, precision, recall and area under receiving operating characteristics curve (C-statistics). Results showed that random forest model outperforms other models with a high C-statistics of 82.16% and a recall score of 93.75%. Features having significant importance on predicting treatment discontinuation were identified from feature importance plots. Stratification of new patient records based on their discontinuation risk level was done using Youden index to optimize the threshold on predicted propensities. This study has the potential to help clinicians improve existing treatment guidelines in order to reduce the premature discontinuation from buprenorphine/naloxone treatment.
1. Introduction
Over the past two decades, there has been an overwhelming surge in the demand, use and dispense of prescription opioids, for the purpose of pain medication, but has unfortunately engendered some unintended consequences such as abuse and deaths due to overdose [1, 2]. Addiction to opioids have become the leading cause of deaths in the United States followed by deaths due to suicides and motor vehicle crashes [3]. In spite of stringent laws to prohibit the use and sale of illicit drugs, there have been limited efforts to monitor the dispensing and sale of physician prescribed drugs and the associated health risks that affect the quality of life of an individual [4]. While a carefully planned opioid treatment can provide temporary relief to patients with chronic non cancer pain (CNCP), the long-term effects of these drugs still remain questionable [5].

Buprenorphine/naloxone, a drug combination acts as a partial agonist against the harmful side effects associated with an opioid, without compromising the pain relieving properties [6]. Several studies have supported the relatively benign properties of buprenorphine/naloxone as a healthier treatment alternative to conventional opioids [7-10], especially for patients having a past history of opioid or other substance use disorder and having little to no withdrawal symptoms upon discontinuation [11]. However, early discontinuation from the buprenorphine/naloxone can often times lead to undesirable outcomes such as relapse, increased chances of acquiring medication from illicit sources and doctor shopping [12]. Thus, we realized that there hasn’t been any significant in-depth research to study the underlying causes of premature discontinuation of buprenorphine/naloxone treatment.

In recent years, the application of big-data analytics and machine learning in the healthcare field has proven beneficial for physicians in accurate diagnosis and prediction of diseases and has also enabled health policy makers in reducing overall annual cost of healthcare [13]. Thus, we aim to create analytics driven framework that can accurately predict the likelihood of an opioid naïve individual to continue or discontinue his/ her buprenorphine/naloxone treatment. For this purpose, we tested several machine learning algorithms with the potential to efficiently handle complexed, imbalanced datasets, and provide information about the factors that motivate the incidence of premature
discontinuation of an opioid naïve individual to buprenorphine/naloxone treatment. Further, the predicted class propensities of the best fitted model were used to stratify the level of discontinuation risk (High, medium or low) associated with each patient. This risk stratification approach can be a useful tool for healthcare professionals to make an informed decision with respect to each subgroup.

The key contributions of this research include:

1. Development of a predictive analytics framework using machine learning to accurately classify adherent and non-adherent population. Using this model we investigate the most influential demographic and clinical features that strongly affect discontinuation to buprenorphine/naloxone treatment. Identification of these features and based on their importance with respect to each other can help physicians and healthcare researchers to develop new models and data collection strategies so as to reduce the premature discontinuation of treatment.

2. Using the best classification algorithm that stratifies patients into ‘low’, ‘medium’ and ‘high’ risk categories by using an optimized threshold on the predicted class propensities calculated using the Youden index. Segregation of patient records into various risk groups, can motivate healthcare providers to improve treatment adherence of high risk groups either by a timely and structured follow-up or by adjusting their medication course. Through this, physicians can formulate targeted interventional strategies for patients that fall in the high risk category.
2. Review of current literature

2.1 Application of machine learning in healthcare analytics
Numerous research studies have demonstrated the advantages of using machine learning over traditional statistical tools to build robust predictive models that utilize large scale datasets in healthcare domains. As a tangible outcome, their work have proven to be beneficial in several application areas such as risk prediction in patients with coronary heart and cardiovascular diseases [14-16], prediction of hospital readmission rates [17, 18], predicting survivability of cancer patients [15, 19-22], identification of factors that are key contributors to clinical depression and other mental health disorders [23-27], etc.

2.2 The use of predictive analytics in opioid crisis
Recent studies have been focused on developing machine learning models to predict risks associated with overdose and misuse of opioids along with some actionable insights to mitigate the rising epidemic [28-32]. For example, one of the research papers reported the high statistical significance between opioid overdose and substance use disorder. It was further reported that this significance differed based on gender groups and concluded the fact that male groups with a prior history of substance use disorder are more likely to overdose an opioid [33]. Another study with similar results highlighted the strong correlation between substance abuse and opioid overdose, using logistic regression as a base model [34]. By deploying Cox-proportional Hazard Model, a study was able to identify patients based on their risk factors, to filter out the most ‘vulnerable’ population that qualifies for opioid disorder treatment using buprenorphine/naloxone formulation [35].

2.3 Predicting medication adherence using machine learning
As per one definition, adherence or medication compliance is the degree of alignment of patients to the treatment prescribed by their respective physicians [36]. Non-compliance to the prescribed treatment has several consequences when it comes to long-term therapy and the cost incurred by various health service providers [37]. A large proportion of selected
articles have discussed about various strategies to reduce the treatment drop-out rates. For example, one research article makes use of a combined classification model to predict treatment adherence among patients diagnosed with heart failure, after comparing several tree based, Bayesian and probabilistic models, based on their C-statistics [38]. Similar studies have proposed a web-based framework to collect patient data from various sources such as hospitals and pharmacies and utilizes tree-based algorithms to predict medication adherence among patients suffering from hypertension and other generic diseases [39, 40]. One article made use of survival analysis as a statistical tool to predict the risk of medication non-adherence among patients diagnosed with breast cancer [41]. There are also a few published articles that propose different methods to monitor adherence in opioid related treatment [12, 42]. Similar studies have also identified the key contributing factors to the non-adherence to their opioid treatment [43, 44]. Only one article discussed impact of substance use disorder on the non-compliance to buprenorphine/naloxone treatment [45].

To sum up, the following limitations in the articles cited in this section have been identified as a potential gap in the current literature:

1. Persistent use of conventionally pre-selected predictors governing patient characteristics.
2. Lack of relevant articles that makes use of advanced machine learning algorithms that can predict buprenorphine/naloxone treatment discontinuation.

Identifying limitations like these, opens up a horizon of ideas to conduct research in a way to bring novelty in existing techniques and maximize predictive ability.
3. Model development
This section discusses on the design of an analytics-driven framework to identify factors contributing to buprenorphine/naloxone treatment discontinuation. We realized that mere examination of patients’ individual characteristics such as age, gender and other demographic factors may not be sufficient to provide enough information for our defined objective as they do not trace a patient’s treatment right from one’s first prescription till the first discontinuation episode. In order to capture this information gap, we realized the need to incorporate additional clinical characteristics associated with the provider prescribing buprenorphine/naloxone to that patient, such as prescription volume, total number of unique providers visited by the patient, provider specialty, etc.

3.1 Data preprocessing and feature selection
The data required for our analysis was obtained from the All Payer Claim Database (APCD) [46] provided by the Center for Health Information and Analysis (CHIA). This data consists of a wealth of information about a patient’s pharmacy claim, insurance status, days of medicine supplied, ZIP code and the National Provider Identification (NPI) code of the prescribing physician from the years 2013 to 2017. From this database, we extracted all claims associated with buprenorphine/naloxone dispenses. In order to declare a patient as being naïve to any previous buprenorphine/naloxone claim we further filtered the claims such that no patient has any claim in the year 2013 i.e. precedes our study period from 2014 to 2017. Finally, we incorporate corresponding provider characteristics and demographic features were obtained by merging the databases obtained from National Plan and Provider Enumeration System (NPPES) and Area Health Resource Files (AHRF), respectively. This detailed merging procedure to prepare the final analytical file has been aptly demonstrated in Figure 1.
3.2 Data cleaning and imputing missing data

Patient age (continuous variable): From the data we observed several records with missing age values. This problem was addressed by imputing the missing ages with the any one of measure of central tendency such as the mean or median age of the age column. For this, first we observe the overall skewness of all the ages. If the distribution of the data is skewed towards the right, the mean value takes precedence over the median and vice versa in case the skewness is towards the left.

Healthcare taxonomy codes (categorical variable): In the NPPES database, a physician’s area of specialty has been coded into several alphanumeric taxonomy codes. To facilitate better interpretability of results, these codes have been replaced with their actual description which makes the data more understandable.
3.3 Model development

Based on our objective to precisely classify a naïve individual as to whether he or she adheres or not to their treatment plan, we can frame our problem as a binary classification problem. Realizing the absence of a predefined target variable, we traced the entire cohort of patients along a 24-month study period. Patients with a continuous presence in the defined timeframe were labeled as ‘0’ or continuing patients, while the rest were labeled as ‘1’ or discontinuing patients. The final analytical file consists of 22 predictor variables and one target variable.

For our pre-defined purpose of predicting discontinuing patients and stratifying their risk levels based on predicted propensities of belonging to the class of interest, we first segmented 70% of the analytical file into a training set to build the model and test the model on the remainder 30% of the data. The imbalance in the training data was eliminated using Synthetic Minority Oversampling Technique (SMOTE) [47] to obtain an exact 50:50 balance between the classes. We then developed and tuned 5 of the most commonly used classification algorithms: Logistic Regression, Decision Trees, Random Forest, Neural Networks, Boosted Trees Classifier, Support Vector Machines and Naïve Bayes Classifier. According to previously published literature, these algorithms have been proven to yield the best classification results [48-50]. In addition we combined all the above algorithms as an ensemble classifier that uses a ‘soft’ voting estimation to classify records based on predicted class propensities at a default threshold. The performance of each algorithm on the test data was then compared based on several evaluation metrics such as accuracy, precision, recall and area under the receiver operating characteristics curve (C-statistics).

The sensitivity and specificity of the best performing algorithm was balanced using an optimized threshold as measured by the Youden index [51]. Based on the observed distribution of all patients’ propensity to discontinue a buprenorphine/naloxone treatment, the records in the test data were stratified into 3 risk groups: High risk (the top 10 percentile of predicted propensities), Medium risk (records with propensities between the optimized threshold and the 90th percentile) and Low risk (records with predicted propensities below the optimized threshold). This model was also used to compare the importance of all features that were used during the training step.
4. Results

4.1 Evaluation of model performance

<table>
<thead>
<tr>
<th>Model</th>
<th>Modification</th>
<th>Accuracy</th>
<th>Precision</th>
<th>Recall</th>
<th>C-statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logistic Regression</td>
<td>Base model</td>
<td>0.8587</td>
<td>0.8662</td>
<td>0.9888</td>
<td>0.832</td>
</tr>
<tr>
<td></td>
<td>Oversampling</td>
<td>0.8047</td>
<td>0.9</td>
<td>0.8675</td>
<td>0.7998</td>
</tr>
<tr>
<td>Decision Tree</td>
<td>Base model</td>
<td>0.7848</td>
<td>0.8825</td>
<td>0.8619</td>
<td>0.6192</td>
</tr>
<tr>
<td></td>
<td>Oversampling</td>
<td>0.7097</td>
<td>0.9164</td>
<td>0.726</td>
<td>0.7122</td>
</tr>
<tr>
<td>Random Forest</td>
<td>Base model</td>
<td>0.8362</td>
<td>0.875</td>
<td>0.9428</td>
<td>0.7788</td>
</tr>
<tr>
<td></td>
<td>Oversampling</td>
<td>0.8477</td>
<td>0.89</td>
<td>0.9375</td>
<td>0.8216</td>
</tr>
<tr>
<td>Neural Network</td>
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<td>0.8401</td>
<td>0.8901</td>
<td>0.9292</td>
<td>0.8197</td>
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<tr>
<td></td>
<td>Oversampling</td>
<td>0.7643</td>
<td>0.9083</td>
<td>0.8051</td>
<td>0.7673</td>
</tr>
<tr>
<td>Boosted Trees Classifier</td>
<td>Base model</td>
<td>0.8536</td>
<td>0.8684</td>
<td>0.9783</td>
<td>0.8314</td>
</tr>
<tr>
<td></td>
<td>Oversampling</td>
<td>0.7328</td>
<td>0.9169</td>
<td>0.7555</td>
<td>0.7863</td>
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<tr>
<td>Support Vector Machines</td>
<td>Base model</td>
<td>0.8599</td>
<td>0.8659</td>
<td>0.9911</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Oversampling</td>
<td>0.8003</td>
<td>0.8909</td>
<td>0.8728</td>
<td>0.7739</td>
</tr>
<tr>
<td>Bernoulli Naïve Bayes</td>
<td>Base model</td>
<td>0.7854</td>
<td>0.8129</td>
<td>0.9963</td>
<td>0.7778</td>
</tr>
<tr>
<td></td>
<td>Oversampling</td>
<td>0.7052</td>
<td>0.9367</td>
<td>0.702</td>
<td>0.7843</td>
</tr>
<tr>
<td>Soft Voting Ensemble</td>
<td>Base model</td>
<td>0.7845</td>
<td>0.8947</td>
<td>0.9022</td>
<td>0.7246</td>
</tr>
<tr>
<td></td>
<td>Oversampling</td>
<td>0.7874</td>
<td>0.9131</td>
<td>0.8299</td>
<td>0.7967</td>
</tr>
</tbody>
</table>

This section focuses on the comparison of the various classification algorithms based on their performance on the test data. Selection of the best model depends on the ability of the model to accurately classify as many discontinuing patients in the test sample as possible. Misclassifying a continuing patient as discontinuing is of least concern to our study. This is because misclassifying a record as discontinuing patient may prompt a provider to be extra cautious before prescribing buprenorphine/naloxone. But misclassifying a discontinuing patient as continuing may cause that patient to diverge away from his/ her treatment plan and obtain pain medication drugs from another provider or from alternate illicit sources, thus causing a serious case of medical negligence. Therefore,
metrics like accuracy and precision alone cannot be considered entirely reliable in selecting the best model. Thus we choose to opt for the algorithm having the highest recall and C-statistics of the best classification model. The summary of model performance on the test data is shown in Table 1 above. As we can observe from the Figures 2 and 3, the Random Forest classification algorithm (Recall=0.9375; C-statistics=0.8216), clearly outperforms all other algorithms in predicting buprenorphine/naloxone treatment discontinuation.

![Figure 2. Comparing recall score of each model](image2)

![Figure 3. Comparison of ROC curves](image3)
The above models are further compared based on their area under precision-recall curve (AUPC) Figure 4. Here too, the Random Forest model has a comparatively larger spread of its AUPC based on a higher recall score compared to other algorithms.

**Figure 4. Comparison of Precision-Recall curves**

### 4.2 Risk stratification using predicted propensities

Using the Random Forest classification algorithm and threshold for class propensities so as to balance the sensitivity and specificity was calculated by the Youden index. Based on an individual’s likelihood to discontinue an ongoing buprenorphine/ naloxone treatment, 10.02% of the patient records in the test data were stratified as the group with a ‘high’ risk of treatment discontinuation, followed by 52.54% and 37.44% of ‘medium’ and ‘low’ risk categories respectively (Table 2).
Table 2. Random Forest performance across all risk groups

<table>
<thead>
<tr>
<th>Evaluation Metric</th>
<th>Stratified risk groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (37.44%)</td>
</tr>
<tr>
<td>Total Count, %</td>
<td>583</td>
</tr>
<tr>
<td>Average class propensity, range</td>
<td>0.56 (0.38-0.69)</td>
</tr>
<tr>
<td>Total continuing,%</td>
<td>185 (31.73%)</td>
</tr>
<tr>
<td>Total discontinuing,%</td>
<td>398 (68.27%)</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>72.86%</td>
</tr>
<tr>
<td>PPV, %</td>
<td>74.94%</td>
</tr>
</tbody>
</table>

Based on the high sensitivity and PPV values across medium and high risk groups, the Random Forest algorithm was able to perfectly stratify the records in test data. The importance of each feature used during the model training process, with respect to its target variable, can be observed in Figure 5. The proportion of days covered during 2 years of buprenorphine treatment (or PDC), patient insurance type (HMO, PPO or other), patient gender (Male or Female), provider experience level and demographic

![Figure 5. Feature importance based on Random Forest classifier](image-url)
characteristics such as median household income of each patient emerge as some of the top most important features in predicting treatment non-adherence.

In the Figure 6 below we can observe the distribution of provider volume with respect to each of the risk groups. A provider can belong to any of the three categories depending on the annual patient count, i.e. the average number of patients treated under a provider’s supervision per year: high volume (treated more than 199 patients per year), medium volume (treated 51 to 199 patients per year) and low volume (treated less than 50 patients per year). We observe that patients under the treatment of high volume providers are comparatively at a higher risk of buprenorphine/naloxone treatment discontinuation than the patients who visit medium and low volume providers.

![Figure 6. Risk groups based on provider annual patient volume](image)
5. Discussion

Through this study, we made an effort to identify the factors that greatly contribute to premature discontinuation of buprenorphine/naloxone treatment. Using the All Payer Claims Dataset, we created an analytical file consisting of a cohort of opioid naïve individuals. This analytical file was then merged with the NPPES and AHRF datasets to obtain corresponding physician and demographic characteristics. Finally we tested state-of-the-art machine learning algorithms and selected the model having strong predictive ability to classify discontinuing patients. We observed that Random Forest classifier with a high recall score and C-statistic performed better than other algorithms most of which were based on traditional statistical techniques. This means that a single decision tree, linear model or simple Bayesian techniques may not be sufficient enough to make accurate prediction. Random Forest classifier instead makes use of a large cluster of decision trees to obtain higher predictive ability, which asserts the fact that there are multiple decision criterions that must have influenced a naïve opioid user to discontinue his/her treatment. We then deploy this Random Forest to segment the records in the test data into 3 risk groups, namely high, medium and low based on the predicted propensity of belonging to the class of interest (Here, discontinuation). This stratification of risk subgroups, can be an important tool for healthcare providers and policy makers to develop targeted interventional plans depending on specific subgroup as it has been proven to be beneficial in previous research [50]. In this study, we do not base our assumption of the best model using a single evaluation metric. Instead we focus on making an informed judgement to select the best model based on recall score and C-statistics, which was found to be the highest for Random Forest. The high value of PPV across the stratified risk groups as seen in Table 1, further strengthens our decision to deploy Random Forest as a predictive model in classifying adherent and non-adherent patients.

While some aspects in the feature importance plot in Figure 5 seem to remain consistent with extant research [29, 52-54] such as the impact of PDC in regards to treatment adherence, an important revelation can be found from the bar-plot in in Figure 6. We see that patients under the treatment of providers who have a higher annual patient count are at a higher risk of discontinuing treatment as compared to other risk groups. What was initially perceived as counterintuitive results, one possible explanation is that providers
having a high patient volume might have to attend patients who have a worse history of opioid or substance abuse, as compared to patients in medium and low risk groups who visits providers having low and medium volume of annual patient count. Second, realizing past history of abuse of these patients, high volume providers may find it challenging to maintain a consistent follow-up with their patients in order to prevent them from diverging off-track from their medication course. This might be different in case of providers having lower annual patient volume as they are able to maintain a better follow-up and stable medication course that can make their patients to adhere to their buprenorphine/naloxone treatment for a longer duration than patients stratified in the high-risk category. Thus, we believe that providers with a high annual patient count must be extra cautious when prescribing buprenorphine/naloxone to their patients to prevent premature discontinuation and ensure a longer treatment adherence.

6. Limitations and directions for further research
In this study we found several limitations that must have possibly impaired our research scope. Firstly, the data that we used for our analysis fails to capture information about prior history of misuse or drug overdose especially from non-medical sources. Second, had there been more information regarding the clinical history of these patients such as the reason for admission, vitals diagnosis, associated hospital settings, mortality information, etc. could have enabled better selection of cohort. Last, the available data primarily records pharmacy claims from the state of Massachusetts. The study results may possibly differ across other states provided we have a large scale database and improved strategies of data collection which can be considered as a part of a future research avenue.

7. Conclusion
This paper demonstrates the potential of machine learning algorithms, as an efficient tool to predict discontinuation of buprenorphine/naloxone treatment, which to the best of our information, is one of the first study of its kind. In order to have unbiased predictions with respect to any algorithm we oversample the training dataset to have a fair balance between
the classes. As a proposed framework and on the basis of superior performance metrics, we make use of Random Forest algorithm having a high recall score and C-statistic to make the best predictions in classifying naïve opioid users as continuing or discontinuing treatment. Further, we use the same algorithm to stratify a patient record in to one of the three risk levels based on the predicted class propensity which serve as an essential tool not just from a clinical but also from a health policy point of view. This study, by making use of an analytics driven approach, can further motivate clinicians and researchers to explore new areas of research in regards to pain medication and treatment adherence using machine learning and not just traditional statistical approaches.

REFERENCES


