Predicting Stimulant and Opioid Co-Prescribing Among Members Initiating Opioid Therapy Using a Machine Learning Model

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BACKGROUND

- Rates of central nervous system stimulant prescribing continue to rise, yet the drivers behind stimulant prescribing following initial opioid exposure remain poorly understood.[1]
- In patients with concurrent opioid and stimulant use, stimulants were positively associated with escalated opioid doses, influencing the opioid dose trajectories per mean daily morphine milligram equivalent (MME).
- Studies have shown that prescription stimulant use, even without misuse, is positively associated with opioid misuse among other substance use.[2,3]
- Patients who used both opioids and stimulants had more than twice the hazard of fatal overdose compared to patients who only used opioids, with this risk increasing over time.[4]

OBJECTIVE

- To apply a machine learning model to identify risk factors most strongly associated with stimulant prescribing among members initiating opioid therapy.

METHODS

DATA SOURCE

- A retrospective cohort analysis was conducted using administrative claims data from 4/1/2024 to 3/31/2025

STUDY POPULATION

- **Inclusion criteria**
  - Opioid-naïve at the start of the index period based on the absence of opioid claims in the 108 days prior to the index date (4/1/2024)
  - No evidence of cancer prior to starting a new opioid prescription
  - Eligible for plan coverage 1 year before and after the index date (4/1/2024)
  - One or more factors indicating a higher risk for co-prescribing (see factors in Figure 2) at the start of the index period (4/1/2024)
- **Exclusion criteria**
  - History of a documented cancer diagnosis, sickle cell disease diagnosis, cancer drug claim, or prescriber who is an oncologist or hematologist
  - History of receiving hospice or palliative care or resided in a long-term care facility

STATISTICAL ANALYSIS

A gradient boosting model (XGBoost) was used to predict stimulant prescribing as the primary outcome, defined as a claim for a stimulant medication during the study period following the first opioid claim.

- The dataset was split into training (80%) and testing subsets (20%). Model performance was evaluated using the average precision and area under the Receiver Operator Characteristic Curve (auROC).
- **Factors used to predict stimulant prescribing included:**
  - Member average daily MME
  - Count of member opioid prescriptions
  - Claims for potentiator medications (muscle relaxants, nonbenzodiazepine sedative hypnotics, gabapentin, and pregabalin)
  - Claims for opioid or potentiator medications from ≥ 3 different prescribers
  - Member age over 45 years old
  - Claims for antidepressant medications
  - Opioid or potentiator medications from ≥ 3 different pharmacies
  - Claims for antipsychotic medications
  - Concurrent opioid and benzodiazepine prescriptions
  - No gap in therapy (GIT) ≥ 32 days over the 12-month period for opioid prescriptions
  - Substance use disorder (SUD) or opioid use disorder (OUD) diagnosis based on ICD-10 codes
  - Alcohol use disorder (AUD) diagnosis based on ICD-10 codes

FIGURE 1: STUDY DESIGN: APRIL 1, 2024 TO MARCH 31, 2025

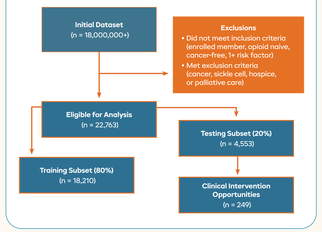


TABLE 1: POPULATION DEMOGRAPHICS (N = 22,763)

Gender	
Females (%)	13,547 (59.51)
Males (%)	9,216 (40.49)
Age (years)	
< 55 (%)	9,664 (42.45)
55-64 (%)	5,599 (24.60)
65-74 (%)	3,842 (16.88)
≥ 75 (%)	3,658 (16.07)
Opioid Naive Members	
Members who remained opioid naive throughout index period (%)	7,067 (31.05)
Risk Factors	
Member Average MME (SD)	9 ±16
Average Opioid Prescription Count (SD)	1 ±2
Potentiator Claims (%)	12,112 (53.21)
Opioid/Potentiator Claims from ≥ 3 Prescribers (%)	914 (4.02)
Age > 45 (%)	16,597 (72.91)
Antidepressant Claims (%)	7,843 (34.46)
Opioid/Potentiator Claims from ≥ 3 Pharmacies (%)	4,429 (19.46)
Antipsychotic Claims (%)	1,057 (4.64)
Opioid/Benzo Concurrent Use (%)	2,171 (9.54)
No GIT (%)	14,153 (62.18)
SUD/OUD (%)	13 (0.06)
AUD (%)	4 (0.02)

RESULTS

FIGURE 2: RISK FACTORS RANKED BY XGBOOST MODEL

XGBoost identified **average daily MME as the most important risk factor** in predicting stimulant prescribing following an opioid claim. Other highly ranked risk factors included potentiator medication use, member age over 45, antidepressant or antipsychotic use, and having multiple prescribers for potentiator medications.

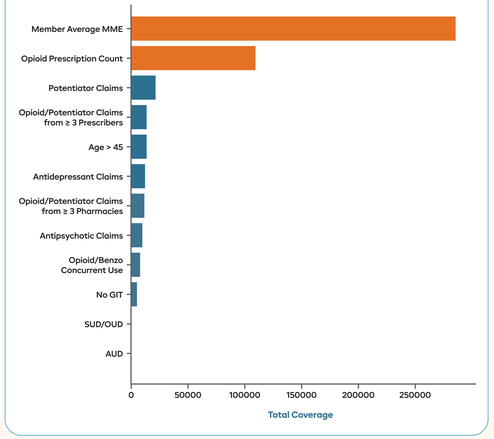


FIGURE 3: CONFUSION MATRIX OF TESTING DATA SUBSET

Among the testing subset (n=4,553), 87 members (true positive) and 162 members (false negative) identified by the model represent the 249 members who would benefit from additional clinical review by a pharmacist and intervention as appropriate. The 249 members identified by the model proceeded to manual review by a pharmacy professional and **216 of the 249 members (86.7%) were appropriately identified as high risk with concordance between the model and clinical expertise.**

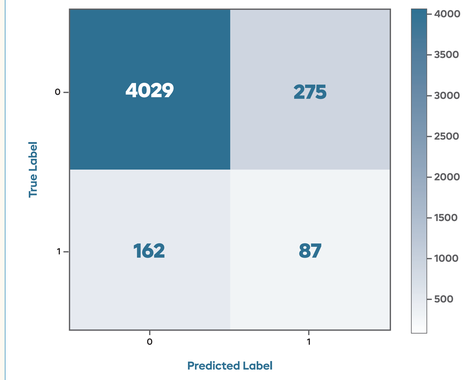


FIGURE 4: RECEIVER OPERATING CHARACTERISTIC (ROC) CURVE CAPTURING MODEL SENSITIVITY

This ROC curve graphically represents the performance of our binary classification model, with the true positive rate (sensitivity) plotted against the false positive rate (1-specificity). The curve being closer to the top left corner indicates better model performance in identifying members who would benefit from clinical intervention. The model achieved an **average precision of 0.60, F1 score of 0.62, and an auROC of 0.83** on the testing subset.

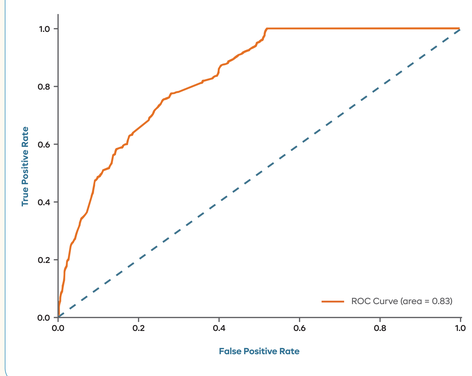
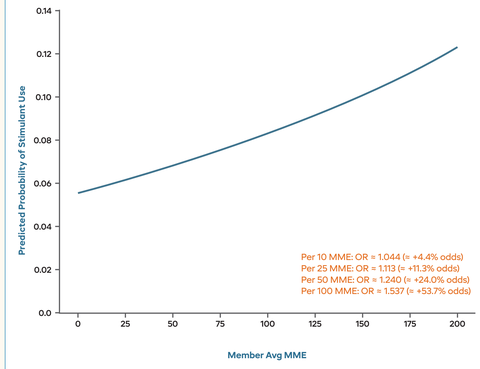


FIGURE 5: ELEVATED MME LEVELS ARE ASSOCIATED WITH GREATER PROBABILITY OF STIMULANT USE (LOGISTIC REGRESSION)

Risk of stimulant co-prescribing increases sharply with higher opioid exposure, **doubling between 0 and 200 MME.**



CONCLUSIONS

- Higher opioid dosing, measured by average daily MME, was the most significant predictor of stimulant co-prescribing (XGBoost), increasing member risk for opioid dose escalation and overdose (logistic regression).
- Members identified as high risk by the model underwent manual clinical review by a pharmacy professional, with 86.7% of identified members validated as high risk via manual review.
- The influence of additional risk factors, including psychiatric comorbidities and polypharmacy, indicates a need for targeted utilization management strategies and clinical interventions.
- Combining higher opioid doses with stimulant prescribing may elevate the risk of misuse, diversion, and adverse outcomes, underscoring the need for careful monitoring and risk mitigation strategies.

LIMITATIONS

- Retrospective claims data lacks crucial clinical context as it does not capture written clinical rationales related to member medication prescribing, relies on appropriate billing codes, and may underestimate use if medications were obtained through alternate means.
- Demographic data available for members was limited and potentially incomplete, overlooking additional social determinants of health that could aid the model in predicting stimulant prescribing.
- No causal relationship may be concluded from this study.

FUTURE DIRECTIONS

- Application of this model in practice would enable members to receive individualized clinical interventions earlier, with PBMs leveraging established provider outreach means to ensure safe opioid and stimulant co-prescribing and allow for the opportunity to support clinicians in developing tailored MME taper plans or alternative interventions.
- Efficient identification of higher risk members is warranted to minimize administrative burdens associated with manual risk screenings, and machine learning can enable higher-impact outreach to members and providers with greater risk stratification accuracy compared to traditional manual review methods.
- With machine learning-based clinical services becoming available, clients can access a live repository of data to optimize member screening abilities, with such data captured in a dashboard tool for client reference and benchmarking.

DISCLOSURE

This research was conducted by Navitus Health Solutions of Madison, WI, without external funding.

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