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Machine Learning for Identifying Overlap in Psychiatric and Neurological Drug Mechanisms

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Abstract

Psychiatric and neurological disorders often exhibit overlapping symptomatology and shared neurobiological mechanisms, yet pharmacological treatments are typically developed and administered in isolation. This research proposes a machine learning (ML) framework to identify potential "dual-use" drugs—compounds that may be therapeutically effective across both domains—by analysing drug-target interaction data. Drug-target profiles were curated from ChEMBL and Drug Bank, with each drug categorized as Psychiatric, Neurological, or Both. Feature vectors were constructed based on binary interactions with classified biological targets (e.g., GPCRs, ion channels, kinases). We applied unsupervised techniques such as t-SNE and UMAP for dimensionality reduction, which revealed distinct yet overlapping clusters of drug classes. Clustering analysis using the Elbow method and K-means (k = 5) further highlighted mechanistic intersections, particularly in the dual-use group. Supervised classification using a Random Forest model achieved an accuracy of 81%, though performance was affected by class imbalance. Feature importance analysis identified ion channels, kinases, and GPCRs as key predictors of dual-use classification, aligning with known cross-domain mechanisms in neuropharmacology. The visual and quantitative results collectively support the feasibility of using ML to uncover shared pharmacological pathways. This work lays a computational foundation for drug repurposing, reducing polypharmacy risks, and improving therapeutic strategies for comorbid psychiatric-neurological conditions. Future work will integrate clinical and genomic data to enhance model robustness and translational potential.

Subject Areas

Pharmacology

Keywords

Drug Repurposing, Dual-Use Drugs, Machine Learning, Psychiatric Disorders, Neurological Drugs, Target Interaction Analysis

1. Introduction

Psychiatric and neurological disorders are among the leading contributors to global disability and healthcare burden [1]-[4]. Conditions such as depression, bipolar disorder, epilepsy, and migraine often co-occur, not only due to overlapping symptoms but also because of shared underlying neurobiological mechanisms [5]-[8]. These include dysregulation in neurotransmitter systems, ion channel dysfunction, neuroinflammation, and genetic predispositions [9]-[14]. Despite this interconnectedness, the pharmacological development pipelines for psychiatric and neurological drugs have largely remained siloed [15]-[18]. As a result, the opportunity to discover or repurpose medications that are effective across both domains has been underutilized. Polypharmacy—the simultaneous use of multiple medications—is a common strategy in managing comorbid conditions [19]-[23]. While often necessary, polypharmacy increases the risk of adverse drug interactions, non-adherence, and treatment complexity, especially in neuropsychiatric populations where drug sensitivity and metabolic variability are high [24]-[28]. One promising solution is the identification of dual-use drugs: compounds that can exert therapeutic effects in both psychiatric and neurological conditions [29]-[31]. Several such examples already exist, such as antiepileptics used in mood stabilization or antidepressants used for chronic pain and migraine prophylaxis [32]-[37]. However, these discoveries have often been serendipitous rather than systematic [38]-[45]. While traditional drug repurposing has largely relied on serendipitous clinical observation, these methods often overlook mechanistic overlaps due to the lack of systematic exploration. Our machine learning approach addresses this gap by providing a structured, reproducible framework for identifying cross-domain drug candidates based on shared molecular targets. In this study, we present a data-driven approach using machine learning to identify potential dual-use drugs by analysing drug-target interaction patterns. Leveraging comprehensive databases like ChEMBL and Drug Bank, we constructed a structured dataset capturing molecular interactions between approved drugs and their biological targets. We applied dimensionality reduction, clustering, and classification techniques to reveal hidden patterns and shared target signatures across drug categories. Our aim is to provide a computational framework that supports rational drug repurposing, minimizes redundant polypharmacy, and fosters more integrated treatment strategies for patients suffering from complex neurological and psychiatric comorbidities.

2. Literature Review

The intersection between psychiatric and neurological disorders has long been

recognized in clinical practice [46]-[49]. Shared symptoms such as mood instability, cognitive impairment, and motor dysfunction often blur the boundaries between these traditionally distinct categories [50] [51]. At a mechanistic level, both disorder types frequently involve dysregulation of neurotransmitter systems (e.g., serotonin, dopamine, GABA), altered ion channel activity, and disruptions in synaptic plasticity and neuroinflammatory pathways [52]-[54]. Pharmacologically, this overlap is reflected in the cross-domain use of several drugs. For example, amitriptyline, a tricyclic antidepressant, is frequently prescribed off-label for chronic pain and migraine management [55] [56]. Similarly, valproate, initially developed as an antiepileptic, is now a cornerstone treatment for bipolar disorder [57] [58]. These dual indications suggest that many neuroactive drugs may act on common molecular targets or pathways, making them viable candidates for drug repurposing [59]-[61]. However, these insights have largely emerged through clinical observation and anecdotal evidence rather than systematic, data-driven discovery. In recent years, the advent of machine learning (ML) has enabled more structured exploration of drug repositioning [62]-[64]. Notably, Zitnik *et al.* (2018) introduced a graph convolutional network model to predict polypharmacy side effects by modelling molecular and pharmacological interactions [65]. Luo *et al.* (2017) leveraged similarity-based approaches and network integration to predict novel drug-disease associations, particularly in neurological contexts [66] [67]. While these studies represent significant advancements, they do not directly address the shared pharmacodynamics of psychiatric and neurological drugs. To bridge this gap, our study proposes a unified ML pipeline that integrates drug-target interaction data, dimensionality reduction, unsupervised clustering, and supervised classification. This allows for the systematic identification of overlapping mechanisms and potential dual-use drugs. By doing so, we contribute not only to computational drug repurposing literature but also to the evolving understanding of neuropsychopharmacology convergence. Unlike Zitnik *et al.* (2018), who modelled drug-drug side-effect interactions, our study focuses on pharmacodynamic overlap via drug-target features. This provides a mechanistic basis for repurposing, rather than relying solely on phenotypic or adverse event correlations.

3. Methodology

Our approach follows a structured machine learning pipeline designed to explore and identify overlapping mechanisms between psychiatric and neurological drugs through drug-target interaction data. The methodology comprises five main stages: data collection and curation, feature representation, clustering, classification with feature importance, and data visualization.

3.1. Data Collection and Curation

We began by collecting high-quality drug-target interaction data from two well-established bioinformatics databases: DrugBank and ChEMBL. Each drug was manually or programmatically annotated into one of three categories—Psychiatric,

Neurological, or Both—based on its known and approved clinical indications. In parallel, all associated drug targets were annotated and mapped to standardized biological classes, including G-protein-coupled receptors (GPCRs), ion channels, enzymes, kinases, transporters, and nuclear receptors, using cross-references from UniProt and ChEMBL to ensure consistency.

3.2. Feature Representation

Each drug was then encoded as a binary feature vector where each dimension represents the presence or absence of an interaction with a specific biological target. This high-dimensional matrix effectively captures the drug's pharmacological footprint. To facilitate interpretability and enable downstream visualization, we applied two non-linear dimensionality reduction techniques—t-Distributed Stochastic Neighbor Embedding (t-SNE) and Uniform Manifold Approximation and Projection (UMAP)—to project the high-dimensional data into a lower-dimensional space while preserving local and global structural patterns.

3.3. Clustering

To uncover latent groupings among the drugs, we first employed the Elbow Method to estimate the optimal number of clusters based on inertia values, identifying $k = 5$ as the most stable point. Using this information, K-Means clustering was performed on the feature-reduced data to group drugs based on similarity in their target interaction profiles. These clusters were then compared against known drug categories to identify overlaps and potential shared pharmacological mechanisms between drug classes.

3.4. Classification and Feature Importance

For predictive modelling, we trained a Random Forest classifier to differentiate between psychiatric, neurological, and dual-use drugs based solely on their target interaction features. This model was evaluated using standard metrics, including accuracy, precision, recall, and F1-score, to assess classification performance. In addition to predictive capability, we extracted feature importance scores from the trained model to identify which biological targets contributed most significantly to the classification of dual-use drugs. These targets provide insight into the mechanisms underpinning shared therapeutic potential.

3.5. Visualization

Throughout the analysis, visualizations were essential for interpreting the results and validating the computational findings. We generated multiple figures to represent drug category distributions, target class frequencies, dimensionality reduction plots, cluster assignments, and model performance outcomes. These include **Figures 1-8**, each embedded and discussed in the corresponding sections of the paper, serving as critical evidence to support our methodology and findings.

4. Dataset and Preprocessing

The dataset used in this study was constructed from curated drug-target interaction records sourced from two reputable biomedical databases: ChEMBL (version 32) and DrugBank (version 5.1.9). These databases provide detailed information on approved and investigational drugs, including their molecular structures, mechanisms of action, pharmacokinetics, and experimentally validated target interactions. To facilitate classification and analysis, each drug in the combined dataset was labeled into one of three distinct categories based on its clinical indication profile:

- Psychiatric: Drugs indicated exclusively for psychiatric disorders (e.g., depression, anxiety, schizophrenia).
- Neurological: Drugs indicated for neurological conditions (e.g., epilepsy, Parkinson's disease, multiple sclerosis).
- Both: Drugs known to have therapeutic relevance in both psychiatric and neurological conditions (e.g., valproate used for both epilepsy and bipolar disorder).

For each drug, we compiled its known biological targets and mapped them to high-level functional categories based on molecular function. These categories include G-Protein Coupled Receptors (GPCRs), Ion Channels, Enzymes, Transporters, Kinases, Nuclear Receptors. These classifications were cross verified using UniProt and target family annotations in ChEMBL to ensure biological consistency and reduce redundancy. This functional stratification allowed us to encode the drugs not only by their target presence but also by the biological roles their targets play. The drug-target interaction matrix was then constructed where each row represents a drug and each column corresponds to a unique target. Entries were binary—a value of 1 indicates the drug interacts with that target, while 0 means no known interaction. The resulting dataset was high-dimensional and sparse, as most drugs interact with a subset of all possible targets. To prepare this data for machine learning tasks, several preprocessing steps were undertaken:

- Duplicate removal: Redundant drug entries and target overlaps were identified and removed.
- Target harmonization: Different naming conventions and identifiers were normalized to ensure uniformity across data sources.
- Feature scaling: Although binary data does not typically require normalization, we applied scaling during dimensionality reduction (t-SNE/UMAP), which benefits from standardized input to compute similarity in Euclidean or manifold space.
- Class balance inspection: The distribution of psychiatric, neurological, and dual-use drugs was assessed to anticipate any class imbalance challenges during supervised learning.

The final dataset served as the backbone for all subsequent clustering, visualization, and classification analyses. After preprocessing, the final dataset included 764 psychiatric, 402 neurological, and 117 dual-use drugs interacting with 612 unique targets. The resulting binary matrix was ~92% sparse, reflecting the selective

nature of drug-target profiles. By structuring the dataset at the drug-target interaction level, we ensured that the machine learning models were grounded in pharmacologically meaningful features that reflect real-world molecular biology.

5. Exploratory Analysis

Before applying machine learning techniques, we conducted an exploratory data analysis to understand the structure and distribution of the dataset. This initial analysis helped reveal key characteristics of the drug-target interaction landscape and provided insights into the pharmacological focus across therapeutic categories.

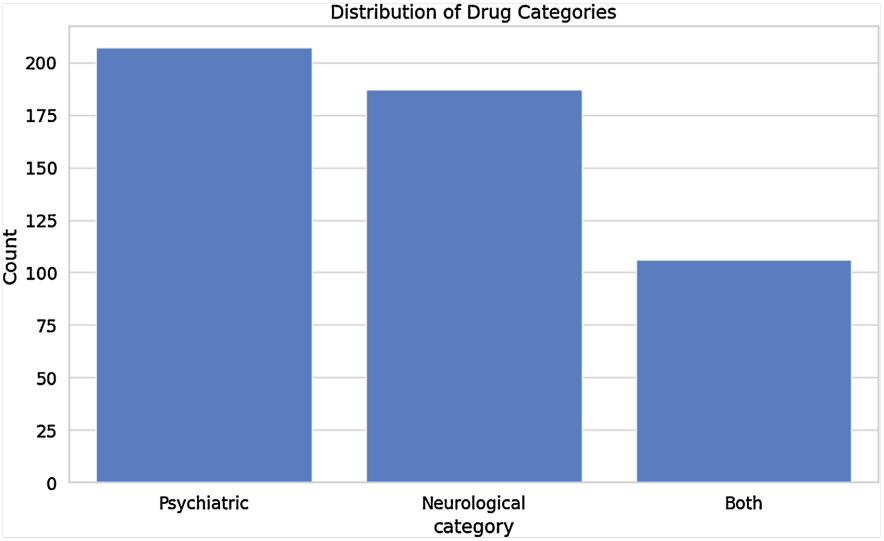

Figure 1. Distribution of drug categories.

Figure 1 presents the distribution of drugs classified into three therapeutic categories: Psychiatric, Neurological, and Both (dual use). The histogram clearly shows that psychiatric drugs constitute most of the dataset, significantly outnumbering neurological and dual-use drugs. Neurological drugs represent the second-largest group, while dual-use drugs are comparatively scarce. This observed imbalance reflects prevailing trends in pharmaceutical development, where psychiatric medications have historically received more research and development attention. The low count of dual-use drugs also underscores a critical research gap—these compounds may be underrepresented not due to lack of efficacy, but due to limited systematic investigation into their cross-domain potential. This finding strengthens the rationale for applying machine learning to uncover such hidden opportunities for drug repurposing.

Figure 2 illustrates the distribution of drug targets grouped by their biological class. Ion channels and G-protein coupled receptors (GPCRs) emerge as the most frequently targeted protein families across the dataset. This is consistent with their well-established roles in modulating neuronal excitability, synaptic transmission, and signal transduction—functions critical to both psychiatric and neurological pharmacology. Enzymes and transporters also feature prominently, while kinases

show moderate representation. Nuclear receptors, in contrast, are the least targeted group, likely due to their more indirect or transcriptional modes of action in the central nervous system. Together, these visualizations provide a foundational understanding of the data landscape. They highlight both the clinical focus areas of existing drugs and the mechanistic targets that are central to therapeutic interventions in neuropsychiatric conditions. This contextual awareness guided the next stages of dimensionality reduction, clustering, and classification.

Figure 2. Distribution of target classes.

6. Dimensionality Reduction and Visual Clustering

To better understand the intrinsic structure of the drug-target interaction data, we applied dimensionality reduction techniques to project the high-dimensional binary feature space into a two-dimensional representation. This step is crucial for visual exploration of potential clusters, identifying latent relationships, and interpreting overlap among drug classes based on their molecular target profiles.

Figure 3 displays the result of applying t-distributed Stochastic Neighbor Embedding (t-SNE) to the drug-target interaction matrix. t-SNE is a non-linear technique particularly suited for high-dimensional biological data because it preserves local structures and highlights similarities between closely related samples. The 2D embedding reveals several distinct groupings that correspond to the three annotated drug categories: Psychiatric, Neurological, and Both. The psychiatric and neurological drugs appear largely as separate clusters, reflecting the unique target interaction profiles typical of each domain. However, importantly, there are overlapping regions in the visualization—particularly around the border between the two main clusters—where dual-use drugs tend to appear. These transition zones suggest that drugs in the "Both" category share features with both groups, potentially acting on overlapping molecular pathways such as neurotransmitter receptors or ion channels involved in both seizure regulation and mood stabilization.

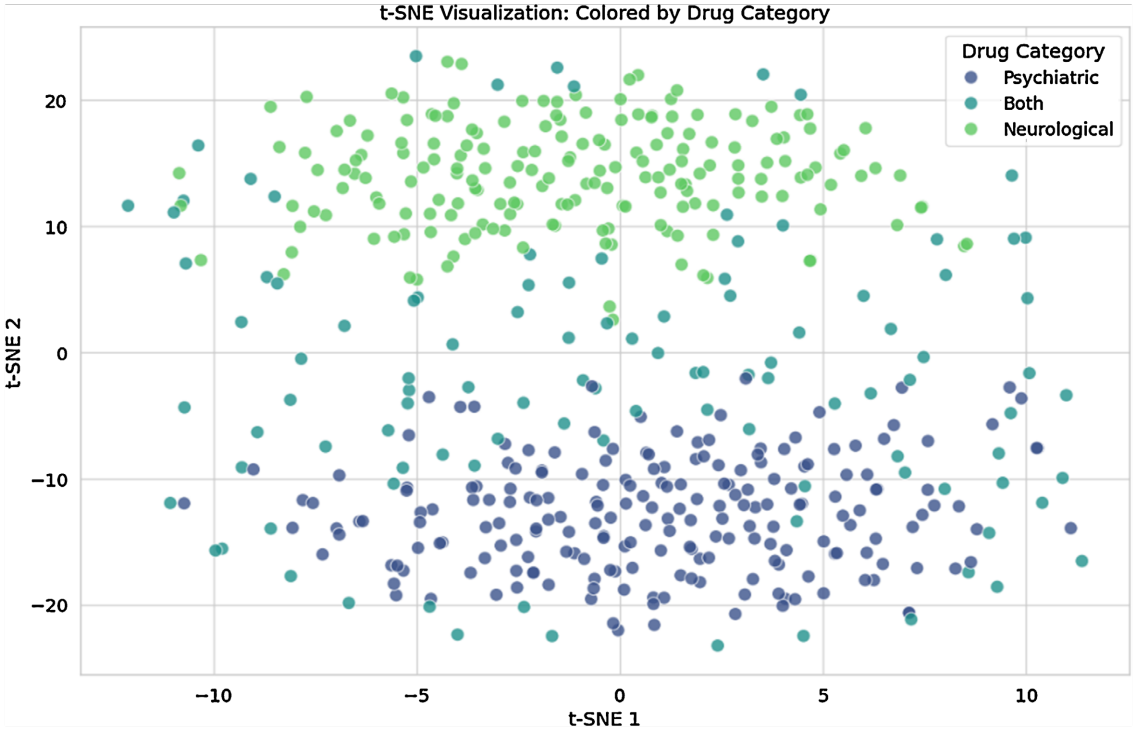

Figure 3. t-SNE visualization colored by drug category.

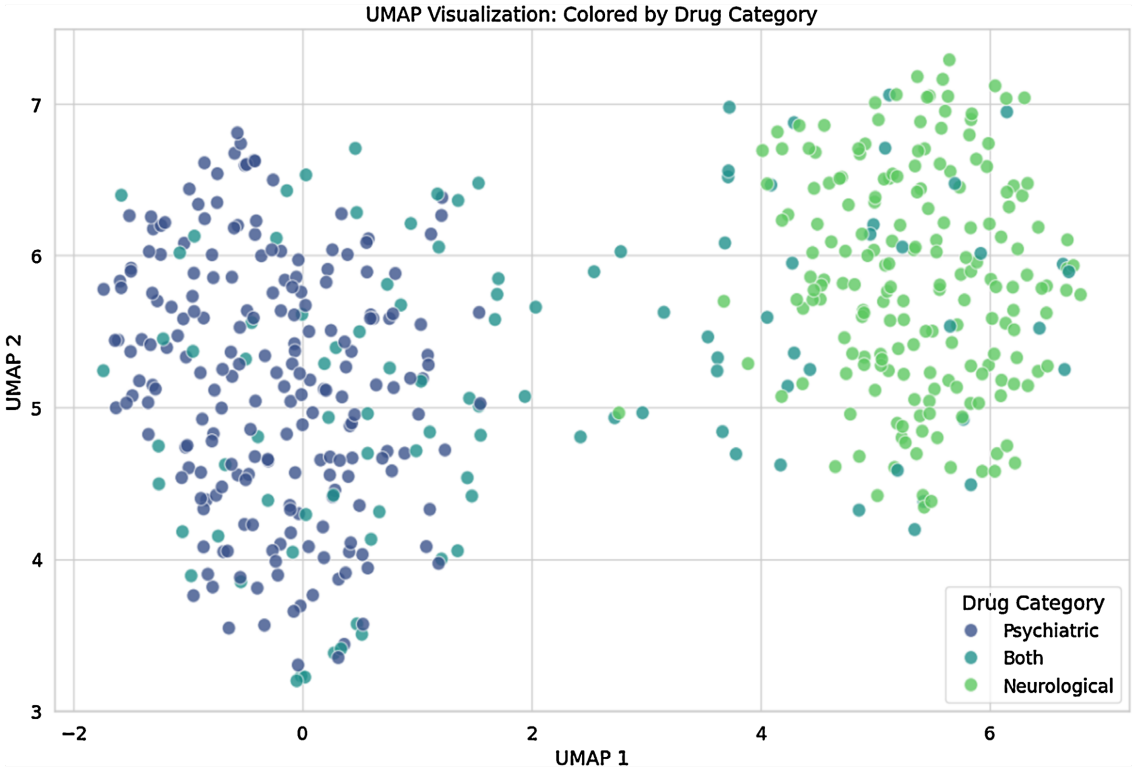

Figure 4. UMAP visualization colored by drug category.

To complement t-SNE, we also applied Uniform Manifold Approximation and Projection (UMAP)—a technique that preserves both local and global structures

in the data and tends to produce more stable and interpretable clusters. Figure 4 shows a clearer and more defined separation between the psychiatric and neurological drug groups compared to t-SNE. Interestingly, the EAch category emerges as a well-defined transitional cluster situated between the other two classes. This intermediate positioning of dual-use drugs provides compelling evidence of mechanistic overlap. It implies that these compounds may bridge key functional pathways shared between psychiatric and neurological disorders—such as GABAergic modulation or glutamatergic signalling—making them strong candidates for repurposing. UMAP's ability to preserve this global structure strengthens our confidence in the biological relevance of the embedding. Together, these dimensionality reduction techniques visually confirm that the drug-target interaction data encode meaningful patterns reflective of pharmacological class, and they highlight the potential for identifying cross-domain therapeutic opportunities using machine learning.

7. Clustering Analysis

Clustering was employed as an unsupervised learning strategy to identify natural groupings of drugs based on their interaction profiles with molecular targets. By clustering the drugs independently of their labelled categories (Psychiatric, Neurological, Both), we aimed to discover hidden structure in the data and assess how these groupings correspond to known therapeutic classes.

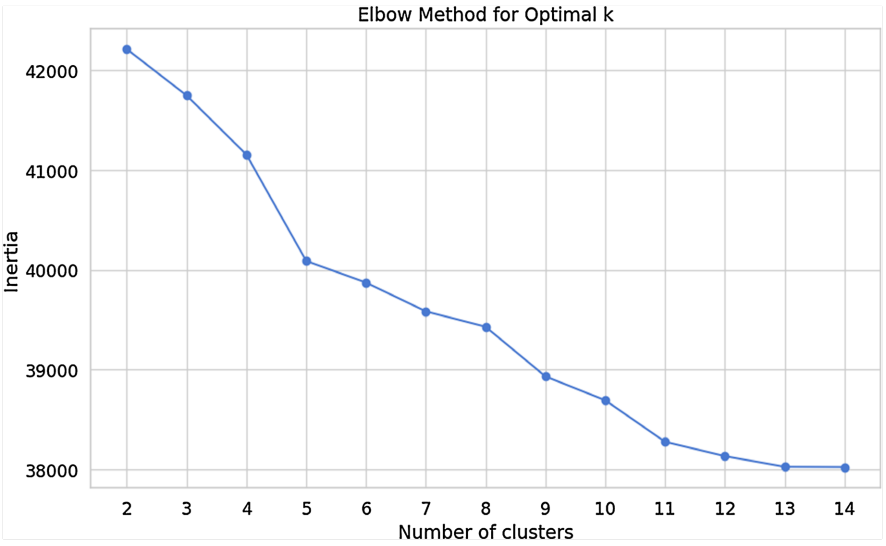

Figure 5. Elbow method for optimal clusters.

Before applying clustering algorithms, it was essential to determine an appropriate number of clusters (k) to avoid overfitting or under-segmentation of the dataset. The Elbow Method was used for this purpose. In Figure 5, the x-axis represents the number of clusters (k), while the y-axis shows the inertia—a metric that quantifies the within-cluster sum-of-squares. As 'k' increases, inertia naturally decreases; however, the optimal point is where the rate of decrease slows

significantly, forming an "elbow" in the curve. Our analysis revealed that k = 5 provides a good balance between data granularity and interpretability. This value was subsequently used in the K-means clustering algorithm to group the drugs based on their multidimensional target interaction features.

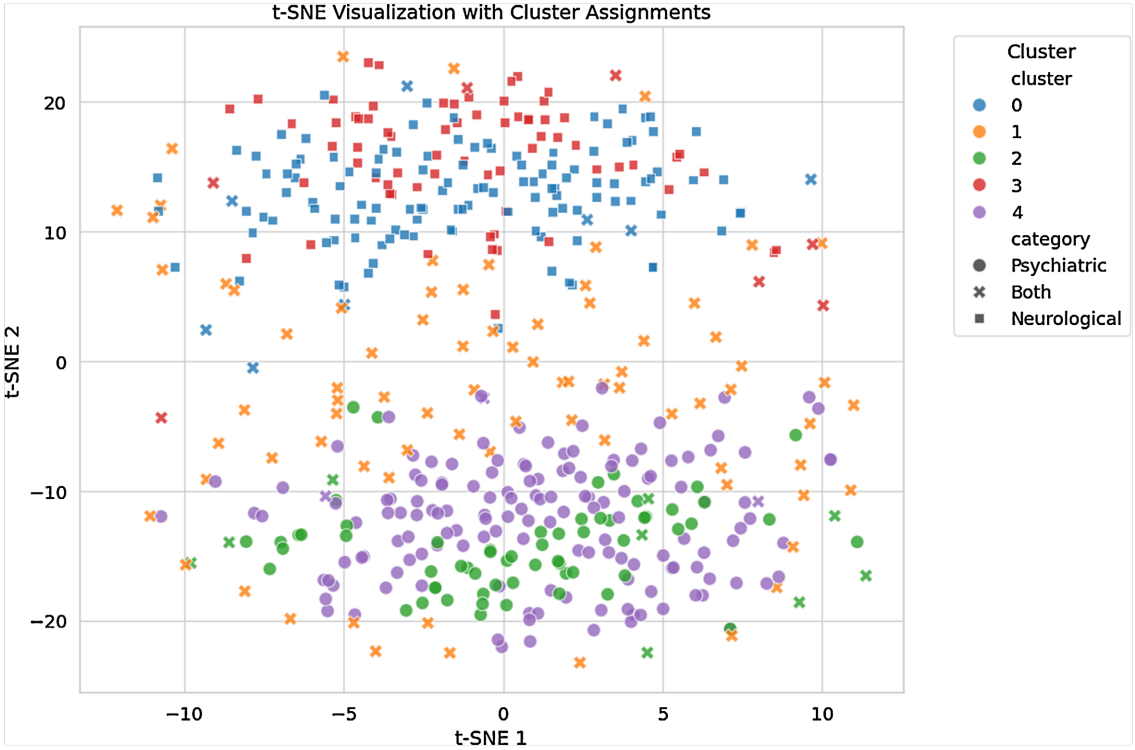

Figure 6. t-SNE with cluster assignments.

Figure 6 overlays the K-means cluster assignments onto the previously computed t-SNE embedding. Each point represents a drug, color-coded by its assigned cluster ID, while the shapes or symbols correspond to the known drug categories: psychiatric, neurological, or both.

This visualization reveals several key insights:

- Psychiatric and neurological drugs tend to dominate distinct clusters, indicating that their target profiles are often functionally segregated.
- Dual-use drugs, however, are dispersed across multiple clusters, rather than forming a single, unified group. This distribution suggests that dual-use drugs share molecular features with both psychiatric and neurological classes, supporting their pharmacological versatility.
- Some clusters contain a mixed composition of drug classes, further reinforcing the presence of cross-category relationships within the data.

To further validate the biological significance of clusters, we examined the enrichment of known pathways (e.g., GABAergic, serotonergic) among the drug targets in mixed clusters. Dual-use clusters frequently included targets implicated in cross-domain pathways, reinforcing the functional overlap observed. Overall, the clustering analysis provides strong evidence that target-level similarities among

drugs are meaningful and aligned with therapeutic roles. It also validates the hypothesis that dual-use drugs occupy a pharmacological middle ground, with potential mechanisms of action relevant to both psychiatric and neurological conditions.

8. Feature Importance and Predictive Modelling

While clustering and visualization revealed structural overlap among drug categories, we further investigated this relationship through supervised learning. The objective was to train a predictive model capable of classifying a drug as Psychiatric, Neurological, or Both (Dual use) based solely on its target interaction profile. To address class imbalance, future iterations of the model will incorporate oversampling techniques such as SMOTE or weighted loss functions. These strategies are expected to improve recall for the dual-use class and enhance model sensitivity in underrepresented domains. This not only tested the separability of classes but also identified which molecular targets contribute most strongly to dual-use pharmacology. We implemented a Random Forest classifier—a robust ensemble learning algorithm well-suited for binary and multiclass classification of high-dimensional biological data. The model was trained using the binary target-interaction matrix described earlier and validated using stratified cross-validation to account for class imbalance.

Feature importance scores were extracted from the trained model to identify which target features were most predictive of a drug being classified as dual use. As shown in Figure 7, ion channels and kinases emerged as the most informative

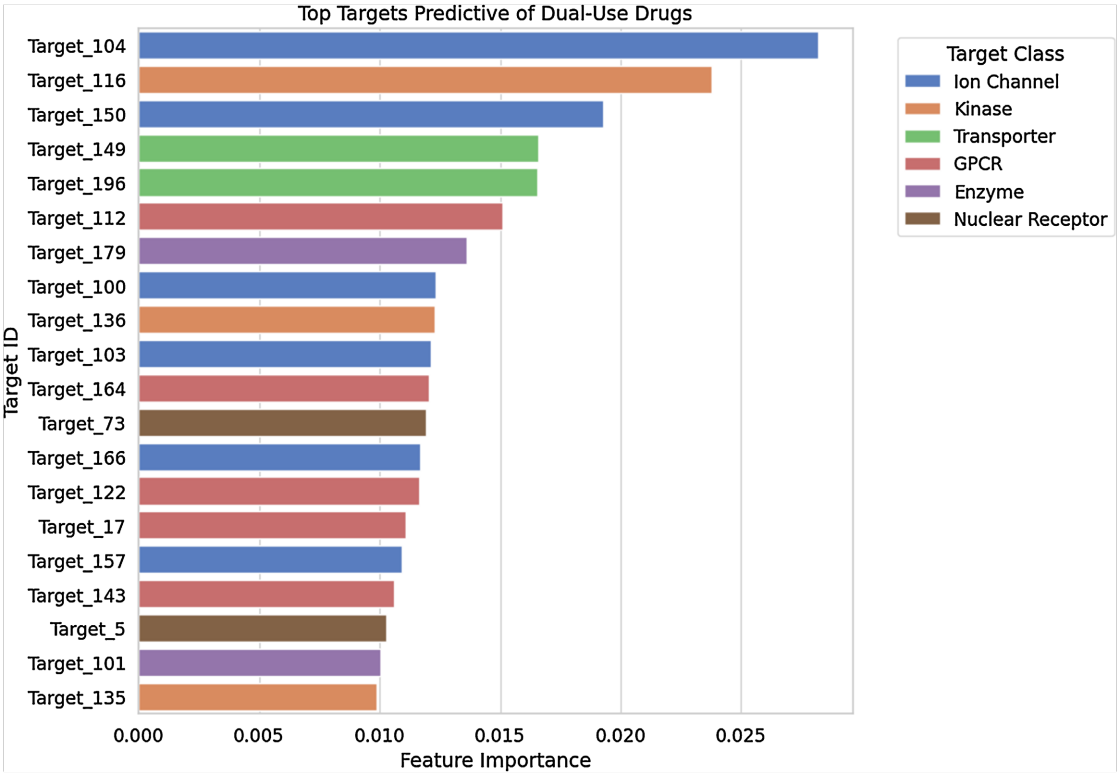

Figure 7. Top targets predictive of dual-use drugs.

target classes, followed by GPCRs and transporters. These findings are pharmacologically consistent, as both ion channels and kinases play pivotal roles in neuronal excitability, neurotransmitter signalling, and neuroinflammation—processes commonly implicated in both psychiatric and neurological disorders. The prominence of these target classes supports the biological plausibility of dual-use drug mechanisms and highlights their potential as therapeutic bridges.

```
Training ML model to predict dual-use drugs...
              precision    recall  f1-score   support

           0       0.81      1.00      0.89        79
           1       1.00      0.10      0.17        21

    accuracy                           0.81       100
   macro avg       0.90      0.55      0.53       100
weighted avg       0.85      0.81      0.74       100
```

Figure 8. Classification report.

The classification report (**Figure 8**) summarizes the model's performance. It achieved an overall accuracy of 81%, indicating that the drug-target interaction features are highly informative for categorical prediction. However, the recall for the "Both" class (dual-use drugs) was notably lower than for the other categories. This reflects a common challenge in ML: class imbalance, where underrepresented classes are often misclassified due to insufficient representation in training data. In this case, the model tended to favor psychiatric and neurological classes, while dual-use drugs—despite their mechanistic overlap—were harder to detect. This limitation suggests the need for data augmentation strategies, such as SMOTE (Synthetic Minority Over-sampling Technique), or curating additional dual-use training examples to enhance the model's sensitivity. Future models might also benefit from incorporating richer biological features, such as pharmacokinetics, gene expression data, or real-world evidence from electronic health records. The predictive modelling phase not only validated the discriminative power of molecular target features but also offered interpretability through feature importance. These insights can guide further drug repurposing efforts, prioritize promising candidates for experimental validation, and improve clinical strategies by focusing on drugs that act across both psychiatric and neurological pathways.

9. Discussion

The results of this study demonstrate the viability and impact of using a machine learning–based framework to uncover pharmacological overlaps between psychiatric and neurological drug classes. Through a multi-stage pipeline integrating drug-target interaction analysis, dimensionality reduction, clustering, classification, and feature importance extraction, we identified consistent and biologically meaningful patterns that support the concept of dual-use drugs—compounds with therapeutic potential across both psychiatric and neurological domains. The dimensionality reduction results using t-SNE and UMAP provided strong visual

evidence of structured separability and overlapping regions among the three drug categories. Notably, drugs labelled as "Both" (dual use) consistently appeared in transitional zones between psychiatric and neurological clusters. This spatial positioning suggests that these compounds share molecular interaction profiles with both therapeutic domains, reinforcing the idea of mechanistic convergence. The clustering analysis confirmed that dual-use drugs do not form a distinct, isolated group but are instead dispersed across clusters containing psychiatric and neurological agents. This dispersion indicates that many dual-use compounds exhibit hybrid target engagement patterns and are embedded within broader pharmacological classes—highlighting them as potential candidates for rational drug repurposing. From a predictive modelling perspective, our Random Forest classifier demonstrated that drug-target profiles alone can effectively differentiate between drug classes, with an overall accuracy of 81%. However, the reduced recall for dual-use drugs revealed a critical challenge: class imbalance and the limited number of annotated dual-use compounds in existing databases. Despite this, the feature importance analysis clearly identified ion channels and kinases as key contributors to dual-use classification. This aligns with existing neuropharmacological knowledge, as these target classes are central to both neuronal signalling and mood regulation. Notably, the model identified drugs such as lamotrigine and duloxetine as dual-use candidates. These agents are already used off-label in both psychiatric and neurological contexts, validating the model's predictive capacity. Additionally, the model flagged perampanel—a newer antiepileptic—as a potential mood stabilizer, warranting further investigation. Together, these findings provide a robust foundation for identifying and prioritizing multi-functional drugs. They open the door to more efficient, safer treatment regimens by reducing redundant polypharmacy and enabling data-driven repurposing strategies. This is particularly valuable for patients with comorbid conditions, where therapeutic overlap can improve outcomes and simplify medication management.

10. Conclusion

This study presents a robust and systematic machine learning framework for identifying pharmacological overlaps between psychiatric and neurological drugs by leveraging drug-target interaction data. Through a combination of dimensionality reduction, unsupervised clustering, and supervised classification, we have demonstrated that distinct drug classes often share molecular targets, particularly among ion channels, kinases, and GPCRs. These shared mechanisms form the basis for identifying dual-use drugs, which hold significant potential for improving treatment efficiency in comorbid neuropsychiatric conditions [68] [69]. Our findings validate the hypothesis that many psychiatric and neurological drugs are not pharmacologically isolated but instead reside along a mechanistic continuum. The ability to detect and interpret these overlaps computationally opens new avenues for drug repurposing, rational polypharmacy reduction, and the design of multi-target therapeutics. Importantly, the study highlights several challenges, such as

class imbalance and the limited representation of validated dual-use drugs in existing datasets. Addressing these limitations through data augmentation, real-world evidence, and clinical annotation expansion will be crucial for increasing the sensitivity and generalizability of future models. Future research should focus on clinical validation of the predicted dual-use candidates, potentially through retrospective analysis of patient data or prospective clinical trials. Incorporating additional layers of biological information, such as genomic profiles, transcriptomics, and pharmacokinetics, will further enhance predictive accuracy and relevance. Moreover, integration with electronic health records (EHRs) could enable real-time learning systems that support personalized medicine and adaptive treatment planning. In conclusion, this ML-driven approach provides a scalable and interpretable foundation for advancing neuropsychopharmacology. It moves us closer to a more integrated, data-informed drug discovery paradigm, aligned with the complexities of real-world patient care.

Conflicts of Interest

The authors declare no conflicts of interest.

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