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Cost-Optimized and Efficacy-Driven Analysis of Antidepressants in Major Depressive Disorder: A Machine Learning and Visualization Approach

Rocco de Filippis[1*], Abdullah Al Foysal[2]

[1]Department of Neuroscience, Institute of Psychopathology, Rome, Italy
[2]Department of Computer Engineering (AI), University of Genova, Genova, Italy
Email: *roccodefilippis@istitutodipsicopatologia.it, niloyhasanfoysal440@gmail.com

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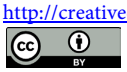

Abstract

The treatment of major depressive disorder (MDD) often involves antidepressants, yet non-response to initial therapies remains a significant clinical and economic burden. This research aims to evaluate the comparative efficacy and cost-efficiency of 13 commonly prescribed antidepressants, spanning four major drug classes: SSRIs, SNRIs, NaSSAs, and TCAs. By employing machine learning and simulated patient data, we model non-response rates over two years, highlighting each drug's cumulative risk trajectories. This study also investigates the direct correlation between non-response rates and estimated healthcare costs, offering insights into the economic implications of antidepressant inefficacy. The analysis reveals distinct patterns of non-response across classes, with SSRIs exhibiting the lowest cumulative risk and cost variability. Conversely, NaSSA and TCA classes demonstrate higher non-response rates, contributing to greater financial strain. Visual representations, including line plots with confidence intervals, bar plots, scatter diagrams, and box plots, provide an intuitive breakdown of risk distribution and economic impact. The primary goal of this research is to guide clinicians and policymakers in selecting cost-effective and efficacious antidepressants, ultimately improving patient outcomes while minimizing unnecessary healthcare expenditure. This study addresses the dual challenges of clinical efficacy and economic sustainability in MDD treatment by integrating statistical modelling with visual analytics. Future work will focus on incorporating real-world demographic and clinical data to enhance the precision and applicability of the findings.

Subject Areas

Mental Health, Pharmacology, Healthcare Economics

Keywords

Antidepressants, Machine Learning, Major Depressive Disorder (MDD), Cost Efficiency, Non-Response Rates

1. Introduction

Despite the availability of numerous pharmacological treatments, nearly 30% - 50% of patients fail to respond to initial antidepressant therapy [1]-[3]. This substantial rate of non-response often necessitates multiple treatment adjustments, leading to prolonged patient suffering, increased hospitalization rates, and escalating healthcare costs. Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), and tricyclic antidepressants (TCAs), remain central to the pharmacological management of Major Depressive Disorder (MDD) [4]-[7]. However, significant variability in patient response across these drug classes underscores the pressing need for tailored and cost-efficient treatment strategies. Among these classes, SSRIs are widely regarded as the first-line treatment due to their favorable side effect profile, improved tolerability, and lower costs compared to other options [8] [9]. They have consistently demonstrated lower rates of adverse events, such as sedation and cardiovascular complications, making them suitable for a broad range of patients. Conversely, TCAs and NaSSAs, while effective in certain cases, are often associated with higher risks of side effects and economic burden, resulting in their use being reserved for treatment-resistant or complex cases where first-line options prove inadequate [10]-[12]. This study aims to address the critical gap in understanding how non-response rates to antidepressants correlate with their economic impact on healthcare systems. By employing machine learning models and simulated patient data, the research offers a novel perspective on visualizing non-response trajectories, cumulative risk, and the financial burden across various antidepressant classes. Through detailed visual representations and cost projections, this study seeks to empower clinicians and policymakers with data-driven insights to make informed prescribing decisions. Ultimately, this research aspires to optimize antidepressant selection, improve patient outcomes, and alleviate the economic strain on healthcare systems.

2. Methods

This study employs a multifaceted approach, integrating machine learning simulations, synthetic data generation, and real-world data to comprehensively model the efficacy and economic impact of 13 antidepressants. The methodology is structured into three primary phases: data acquisition and preparation, non-response rate modelling, and cost estimation.

2.1. Data Acquisition and Preparation

Data acquisition forms the foundation of this study, combining population-based treatment records with synthetic data to ensure broader applicability and real-world relevance. Treatment records from clinical studies and trials provided baseline non-response rates, ranging from 48% to 82% over a two-year period [13] [14]. To address data gaps and enhance the robustness of the analysis, synthetic patient data was generated, reflecting variability in age, sex, comorbidities, and prior treatment responses. The dataset encompasses 13 antidepressants classified into four primary drug classes, as shown in Table 1 below.

Table 1. Classification of antidepressants by drug class.

Drug Class	Antidepressants
SSRIs	Sertraline, Citalopram, Fluoxetine, Paroxetine, Escitalopram
SNRIs	Venlafaxine, Duloxetine
NaSSA	Mirtazapine, Mianserin
TCAs	Amitriptyline, Nortriptyline, Clomipramine, Dosulepin

2.2. Machine Learning Simulation

A custom machine-learning pipeline was developed to model non-response rates over 104 weeks. The goal was to predict patient outcomes based on historical data and relevant clinical factors. The pipeline follows a structured process:

- **Model Selection:** Three machine learning algorithms—Random Forest, XGBoost, and Logistic Regression—were employed to analyse patterns in non-response trajectories. Each model's performance was evaluated to ensure accurate predictions.
- **Training and Validation:** The dataset was split into training (70%) and validation (30%) subsets, ensuring the models could generalize to new data. Cross-validation was applied to reduce overfitting and improve robustness.
- **Confidence Intervals (CI):** Bootstrapping techniques were applied to derive 95% confidence intervals for the predicted non-response rates, capturing potential variability and uncertainty in patient outcomes.
- **Feature Engineering:** Critical predictors such as baseline depression severity, medication adherence, socio-economic status, and prior treatment history were included in the models. Feature importance rankings were generated to identify key factors influencing non-response.

2.3. Model Selection and Justification

This study utilized three machine learning algorithms—Random Forest, XGBoost, and Logistic Regression—to model non-response rates among patients treated with antidepressants. These models were selected based on their complementary strengths:

- **Random Forest:** Effective in handling high-dimensional data and capturing

non-linear interactions between clinical variables.

- **XGBoost:** Known for its gradient-boosting framework, offering superior accuracy in complex datasets while mitigating overfitting through regularization.
- **Logistic Regression:** A baseline model ideal for binary classification tasks, allowing for straightforward interpretation of predictor contributions.

The diversity of these algorithms ensures robust predictions while addressing the varied complexities of clinical data.

2.4. Hyperparameter Tuning and Validation

To optimize model performance, hyperparameters were fine-tuned using grid search with cross-validation. For Random Forest, parameters such as the number of trees and maximum tree depth were calibrated. XGBoost's learning rate, tree depth, and number of boosting rounds were adjusted to maximize predictive accuracy. Logistic Regression utilized regularization techniques (L1 and L2 penalties) to prevent overfitting. Models were trained on 70% of the dataset and validated on the remaining 30%, ensuring generalizability.

Feature Engineering

Key clinical predictors were engineered to improve model inputs:

- **Baseline depression severity:** Quantified through established scales such as the Hamilton Depression Rating Scale (HDRS).
- **Medication adherence:** Represented as a binary variable, indicating whether patients followed prescribed regimens.
- **Socio-economic status:** Derived from simulated demographic data, reflecting income and employment stability.
- **Prior treatment history:** Categorized based on the number of failed treatment attempts and class of previous antidepressants.

The importance of these features was ranked using feature importance metrics in Random Forest and Shapley additive explanations (SHAP) for XGBoost, offering transparency in model predictions.

2.5. Cost Estimation

The financial burden of non-response was quantified by correlating non-response rates with economic factors, encompassing both direct and indirect healthcare costs [15]-[18]. The cost model was divided into three components:

- **Direct Costs:** This category includes expenditures on medication, psychiatric consultations, emergency visits, and hospitalizations [19]-[21].
- **Indirect Costs:** Productivity loss, absenteeism, and caregiver burdens were factored into the model to estimate broader economic impacts [22]-[24].
- **Monte Carlo Simulation:** To account for cost variability across different patient demographics, Monte Carlo simulations were performed. This approach modelled a range of potential outcomes, providing probabilistic estimates for different scenarios [25]-[27].

By integrating machine learning predictions with cost estimations, this study

provides a comprehensive evaluation of the long-term implications of antidepressant non-response, informing both clinical decisions and healthcare policy [28] [29].

3. Results and Visual Analysis

Understanding the progression of non-response risk and its economic burden is critical for optimizing antidepressant prescriptions [30] [31]. This section presents visual analyses of the longitudinal trends and class-specific variations in non-response rates, followed by an economic assessment of cost burdens.

This plot in **Figure 1** tracks the evolving risk of non-response for 13 antidepressants over 104 weeks. Confidence intervals (shaded areas) widen with time, reflecting increasing uncertainty and treatment variability. SSRIs like Sertraline exhibit lower cumulative risk compared to TCAs like Dosulepin and NaSSA-class drugs such as Mianserin [32].

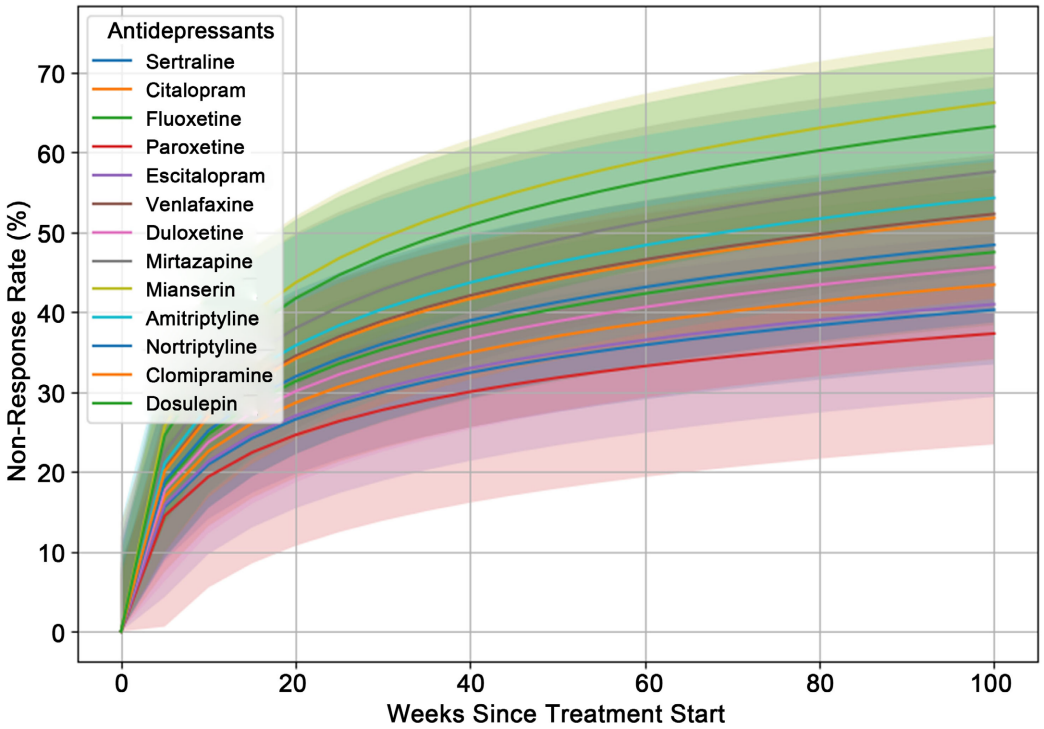

Figure 1. Risk of non-response over time (with 95% CI).

Bar plots here in **Figure 2** show the non-response rates for each antidepressant, grouped by class. Mianserin (NaSSA) exhibits the highest non-response rate (82%), while SSRIs demonstrate comparatively lower rates. This visualization underscores class differences and highlights potential targets for intervention.

Box plots in **Figure 3** depict non-response rate variability within each antidepressant class. SSRIs show lower dispersion, indicating more consistent performance, while NaSSA and TCA classes display greater variability, suggesting higher risk and unpredictability.

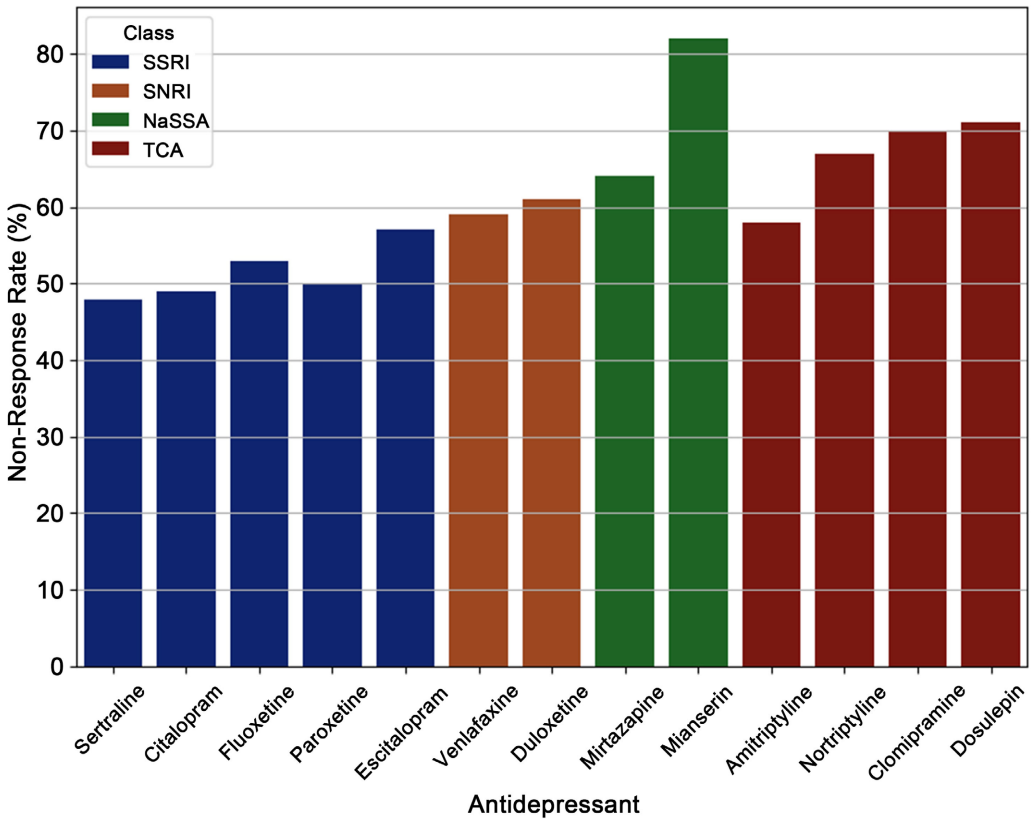

Figure 2. Non-response rates by antidepressant and class.

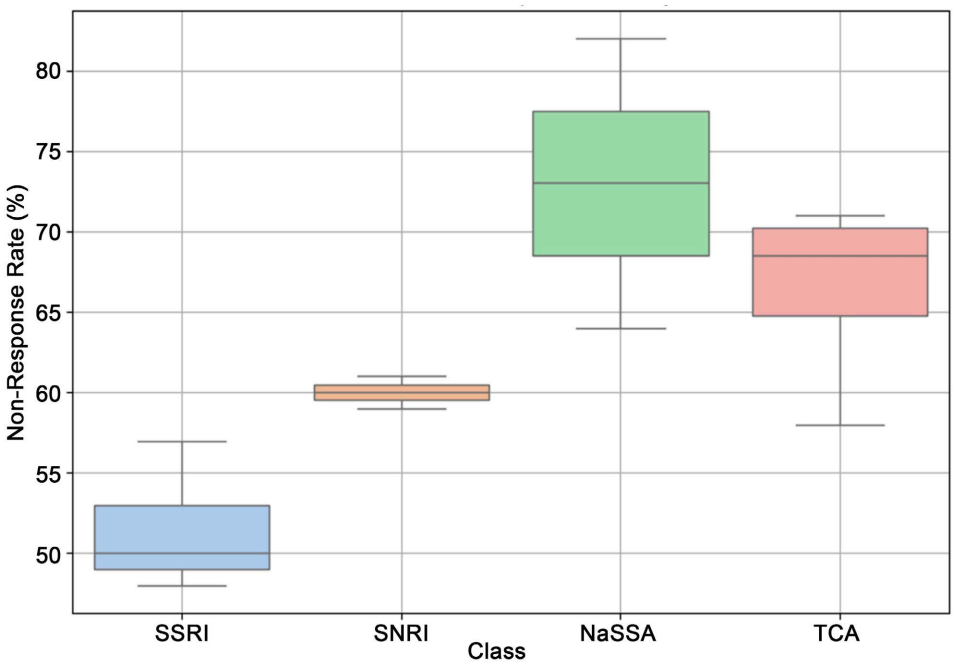

Figure 3. Distribution of non-response rates by class.

This cumulative risk graph here in **Figure 4** highlights the increasing burden of non-response as treatment progresses. By week 104, the cumulative risk approaches

100% for some antidepressants, particularly in the NaSSA and TCA classes. SSRIs remain below 60% cumulative risk.

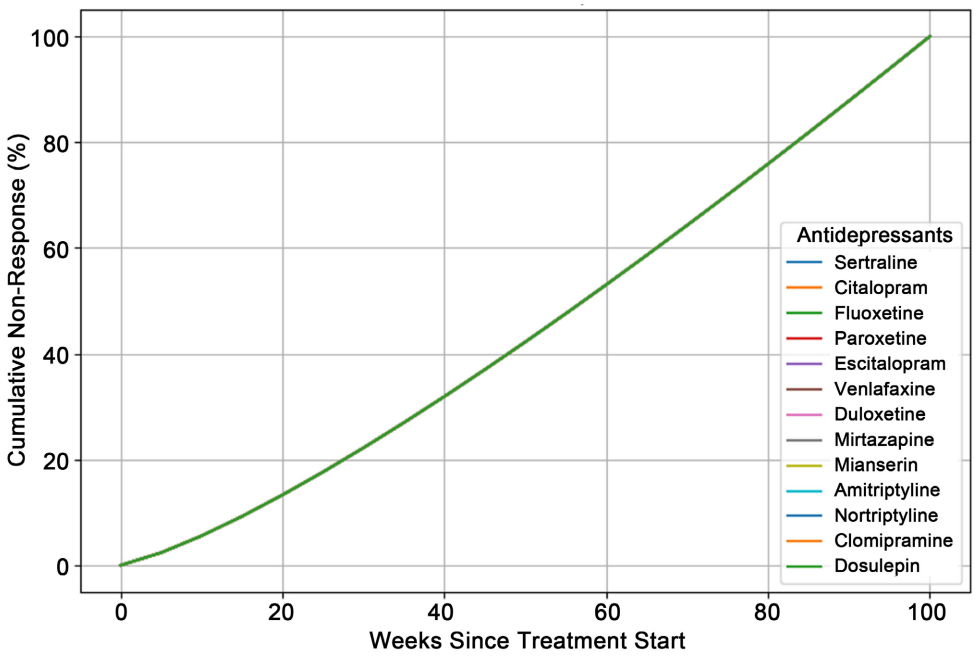

Figure 4. Cumulative risk of non-response over time.

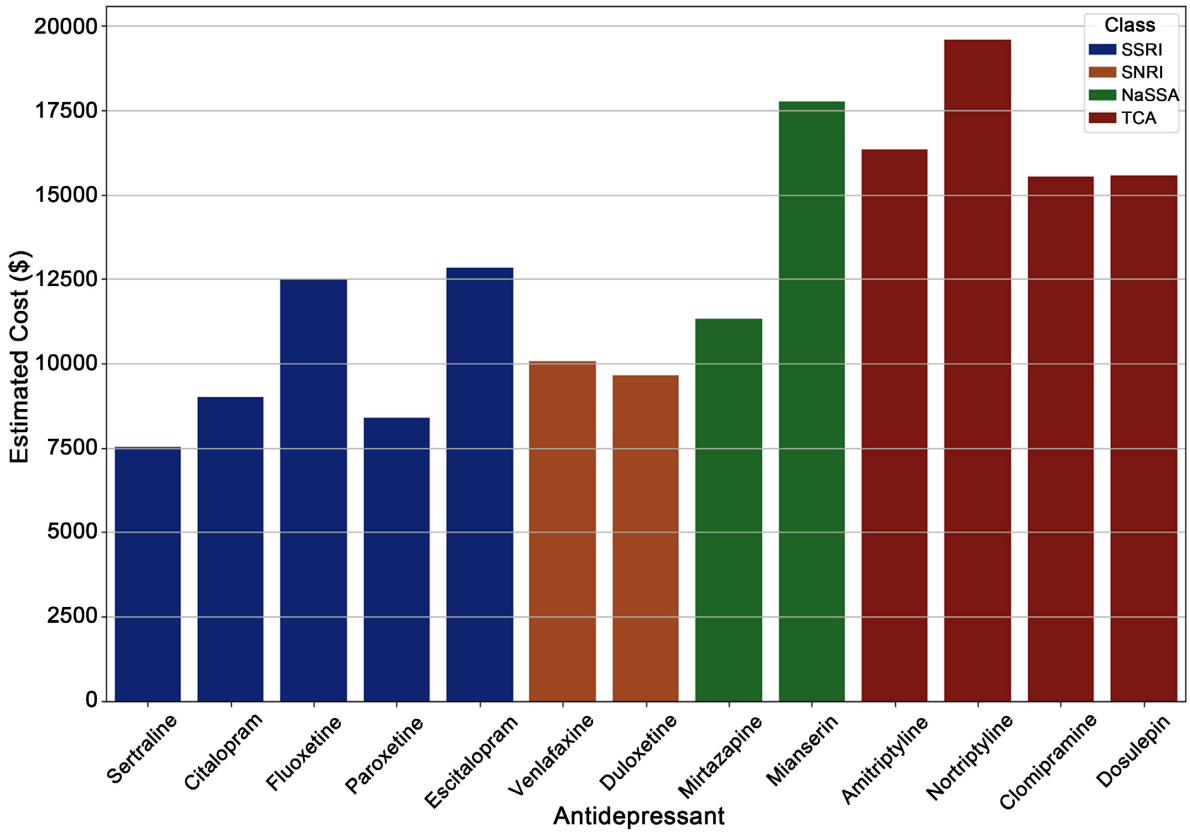

Figure 5. The estimated cost of non-response by antidepressant and class.

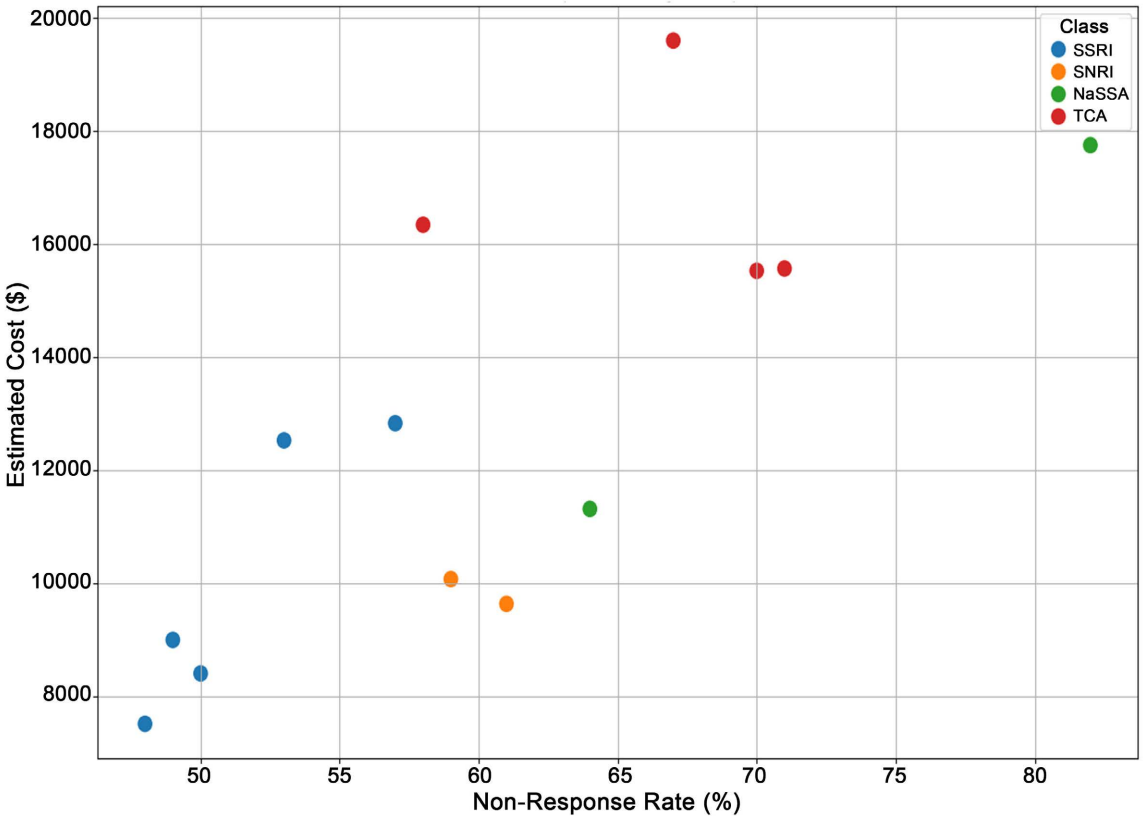

Figure 6. Cost vs non-response rate by antidepressant.

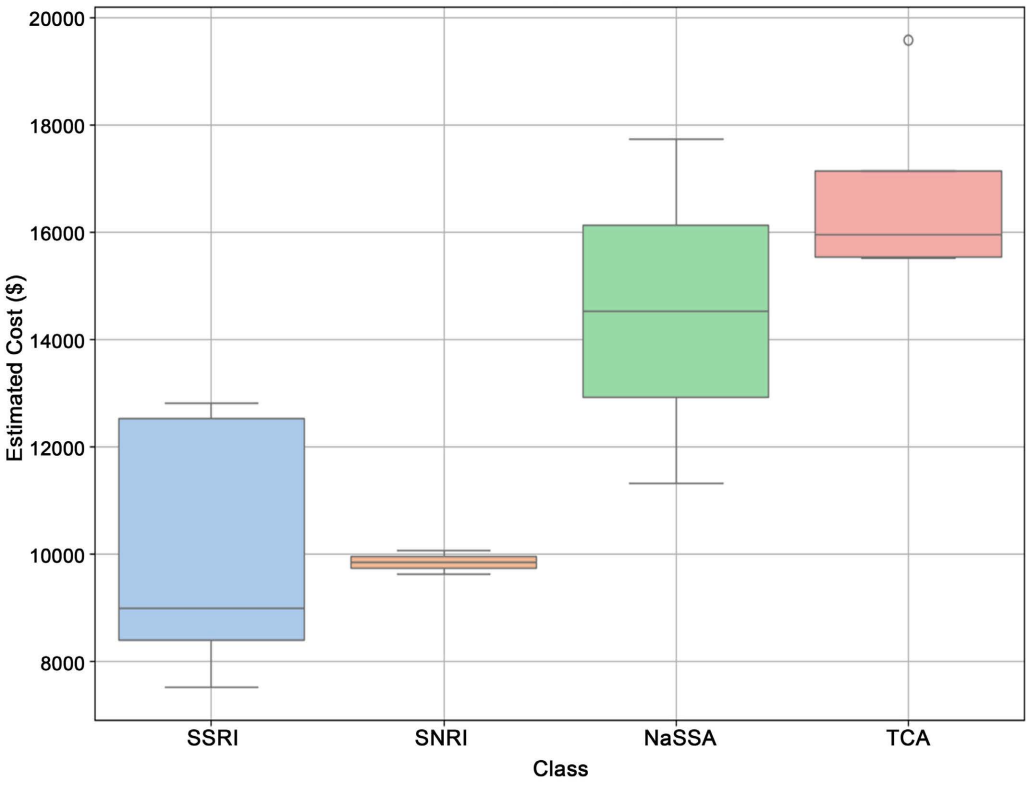

Figure 7. Distribution of cost by antidepressant class.

This bar plot in Figure 5 visualizes the estimated cost of non-response per antidepressant. SSRIs generally show lower costs, while TCAs and NaSSA antidepressants incur higher costs due to increased non-response rates. The financial burden of Mianserin (NaSSA) and Amitriptyline (TCA) is notably high.

A scatter plot in Figure 6 shows the relationship between non-response rates and the estimated cost of treatment. TCAs and NaSSA drugs cluster at higher non-response rates and costs, suggesting an economic impact aligned with lower treatment efficacy.

Box plots here in Figure 7 depict the distribution of estimated costs across different antidepressant classes. SSRIs show narrower cost variability, while NaSSA and TCA classes demonstrate broader distributions, indicating higher financial risks and variability in treatment outcomes.

4. Discussion

The findings of this study reinforce the superiority of SSRIs as the primary pharmacological intervention for managing MDD, given their consistently lower non-response rates and reduced cumulative risk over time [33] [34]. SSRIs stand out not only for their clinical efficacy but also for their economic advantages, minimizing the financial strain on healthcare systems by reducing the need for frequent treatment adjustments, hospitalizations, and additional psychiatric interventions [35] [36]. This makes them a cost-effective solution for patients initiating antidepressant therapy. However, the study highlights significant outliers, particularly within the NaSSA and TCA classes. Mianserin and TCAs such as Clomipramine and Dosulepin exhibit higher non-response rates [37], leading to greater healthcare expenditures over the treatment period. While these drugs remain valuable options for treatment-resistant depression, their use should be carefully weighed against their economic burden. This finding suggests that healthcare providers should adopt a stepped approach to prescribing antidepressants, prioritizing SSRIs for initial treatment, and reserving NaSSAs and TCAs for patients who demonstrate poor responses to first-line therapies. Despite the promising results, certain limitations must be acknowledged. The simulated data used in this study lacks granularity in demographic variations, which could influence real-world outcomes. Additionally, while confidence intervals account for variability, they may not fully capture extreme outliers or rare patient responses. Finally, cost estimates are generalized and may differ across healthcare systems, underscoring the need for localized studies to validate these findings further. Future research should integrate diverse patient populations and real-world clinical data to enhance the model's applicability across different demographic and economic contexts.

5. Conclusion

This study leverages machine learning and visual analytics to optimize antidepressant selection by analyzing non-response rates and associated healthcare costs.

The findings underscore the superiority of selective serotonin reuptake inhibitors (SSRIs) as the most effective and economically viable option for treating major depressive disorder (MDD) [38]. SSRIs consistently demonstrated lower non-response rates and slower cumulative risk progression over a two-year period, reinforcing their status as the preferred first-line treatment [39]-[41]. Their use minimizes treatment adjustments, reduces hospitalizations, and alleviates indirect costs such as productivity loss, contributing to broader economic benefits for healthcare systems. In contrast, antidepressants within the noradrenergic and specific serotonergic antidepressants (NaSSAs) and tricyclic antidepressants (TCAs) classes exhibited higher non-response rates and greater economic burdens [42]-[46]. Drugs like Mianserin (NaSSA) and Clomipramine (TCA) emerged as costly outliers, suggesting that their use should be reserved for patients who do not respond to SSRIs or other lower-risk options [47] [48]. The study highlights the importance of a tiered prescribing approach, prioritizing SSRIs while reserving higher-risk medications for more severe, treatment-resistant cases [49]-[51]. By adopting such strategies, clinicians can improve patient outcomes while curbing unnecessary healthcare expenditure. Future research should focus on integrating real-world clinical data to refine the predictive accuracy of cost and risk models, ensuring applicability across diverse patient populations and healthcare environments [52]. This approach will further enhance personalized treatment strategies and economic sustainability in MDD management.

Conflicts of Interest

The authors declare no conflicts of interest.

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