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Comparative Analysis of GABAergics vs. Opioids in Chronic Pain Management

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Abstract

Background: Chronic pain management presents significant challenges in clinical practice, particularly in selecting pharmacological treatments that balance efficacy and safety. GABAergic and opioid medications are two commonly prescribed drug classes for pain relief, but their comparative effectiveness and safety profiles remain a topic of ongoing debate. **Objectives:** This study aims to compare the effectiveness and safety of GABAergic and opioid medications in managing chronic pain, using synthetic patient data and advanced machine learning models. **Methods:** Synthetic data simulating a diverse patient population were generated to reflect real-world variations in demographics, treatment regimens, and outcomes. Machine learning models, including Random Forest, Gradient Boosting, and Stacking, were applied to analyze the relationships between patient characteristics, treatment types, and outcomes such as pain reduction and quality of life. SHAP (SHapley Additive exPlanations) analysis was used to interpret the models and identify key predictors influencing treatment responses. **Results:** The Gradient Boosting model demonstrated strong predictive performance, with SHAP analysis highlighting features such as drug type, dosage, and patient age as significant factors influencing treatment outcomes. Opioid treatments were found to be more effective in pain reduction but associated with a higher risk of side effects, whereas GABAergics had a safer profile but were less potent in severe pain cases. **Conclusions:** This study underscores the value of machine learning in chronic pain management by providing insights into the trade-offs between the effectiveness and safety of GABAergic and opioid medications. These findings suggest that personalized treatment plans, informed by patient characteristics and model predictions, could optimize pain management while minimizing adverse effects.

Subject Areas

Drugs & Devices, Neurology

Keywords

Chronic Pain Management, Opioid Treatments, GABAergic Medications, Machine Learning, SHAP Analysis, Quality of Life, Pain Reduction

1. Introduction

Chronic pain is a significant public health issue, affecting millions globally and posing a considerable challenge to healthcare systems. The complexity of chronic pain, which often persists despite standard treatments, necessitates a nuanced approach to pharmacological management [1]. Among the most commonly prescribed treatments for chronic pain are GABAergic and opioid medications, both of which offer distinct mechanisms of action but come with their own benefits and risks. Opioid medications have long been considered a cornerstone of chronic pain management due to their potent analgesic effects [2]. They act on opioid receptors in the central nervous system to block pain signals, making them particularly effective for moderate to severe pain. However, their use is increasingly scrutinized due to a well-documented profile of adverse effects, including a high risk of addiction, tolerance, respiratory depression, and overdose. The global opioid crisis has further intensified the need for safer alternatives, as opioid overuse and dependence have led to widespread public health concerns. On the other hand, GABAergic medications, which modulate the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), offer an alternative mechanism of pain relief, particularly in neuropathic pain conditions. GABAergics are generally perceived as safer compared to opioids, with a lower risk of severe side effects such as dependency and cognitive impairment [3]. However, their efficacy in treating severe chronic pain is often viewed as limited, and they may not provide sufficient pain relief for all patients. Consequently, the comparative effectiveness and safety of GABAergics versus opioids remain areas of active debate, with clinicians needing more evidence to guide treatment decisions that balance efficacy and patient safety [4]. Current literature provides fragmented insights into the relative benefits of these two drug classes. Clinical studies often focus on specific patient populations, making it difficult to generalize findings. Furthermore, most comparative studies are limited by small sample sizes, variability in patient demographics, and inconsistencies in treatment protocols. As a result, there is a critical need for more robust, data-driven comparisons that can provide clinicians with clearer guidance on when and how to use these medications in chronic pain management. To address this gap, this study leverages synthetic patient data and advanced machine learning techniques to conduct a comparative analysis of GABAergic and opioid medications. Synthetic data allows for the simulation of diverse, real-world-like patient populations, overcoming the limitations of traditional clinical datasets by ensuring consistency and eliminating biases [5]. Machine learning models such as Random Forest and Gradient Boosting are used to capture the complex relationships between patient characteristics (e.g., age, dosage, treatment duration) and treatment outcomes. Additionally, SHAP (SHapley Additive exPlanations) analysis provides an interpretable framework, highlighting key features that influence patient responses to each treatment modality [6]. The significance of this research lies in its ability to provide a comprehensive, data-driven comparison of GABAergics and opioids. By using synthetic data and interpretable machine learning models, this study not only contributes to the ongoing debate on the safety and effectiveness of these medications but also offers actionable insights that can guide personalized pain management strategies. In doing so, it responds to the urgent need for more informed clinical decision-making in the context of chronic pain, especially in light of the opioid crisis.

2. Methodology

2.1. Data Simulation and Preprocessing

2.1.1. Data Generation

To accurately assess the comparative effectiveness of GABAergic and opioid treatments in managing chronic pain, we employed synthetic data generation to simulate a dataset reflective of real-world clinical scenarios. This approach allows for controlled experimentation, eliminating the biases and inconsistencies often present in real-world data. The synthetic dataset was meticulously designed to capture a broad range of patient characteristics and treatment variables, including age, medication dosage, treatment duration, the incidence and severity of side effects, and crucial outcomes such as pain reduction and quality of life.

The data generation process was driven by clinical insights and statistical principles to ensure the realism and relevance of the simulated data [7]. By manipulating specific parameters and distributions, we created a dataset that mirrored the diversity and complexity of patient responses to GABAergic and opioid treatments. This approach facilitated a comprehensive analysis of the potential benefits and risks associated with each treatment modality.

2.1.2. Preprocessing

Before applying machine learning models, the synthetic dataset underwent a series of preprocessing steps designed to enhance model performance and ensure the integrity of the analysis:

- Categorical Variables Encoding: Key categorical variables, such as Gender, Medical History, and Drug Type, were converted into binary indicators using one-hot encoding [8]. This transformation allowed the machine learning algorithms to process categorical data effectively, ensuring that the distinctions between different categories, such as male versus female or opioid versus GABAergic, were adequately represented in the models.
- Feature Engineering: To capture the complex relationships inherent in the data, advanced feature engineering techniques were employed. Interaction terms were created to explore how combinations of variables, such as age and

dosage, jointly influence treatment outcomes. Additionally, non-linear transformations were applied to certain variables to better reflect their real-world behavior, such as the potential diminishing returns of increasing dosages on pain reduction [9].

- Scaling: Continuous variables, including age, dosage, and treatment duration, were standardized to a common scale. This process involved adjusting the mean and variance of these variables, which is particularly important for machine learning models that rely on distance metrics or gradient-based optimization [10]. Standardization ensured that no single variable disproportionately influenced the model outcomes due to differences in scale [11].

2.2. Feature Selection

Feature selection was a critical step in the model development process, guided by both clinical relevance and statistical significance [12]. The selection process focused on identifying variables that were most likely to impact the primary outcomes of interest—pain reduction and quality of life. By prioritizing features with established clinical importance, such as patient age, drug type, dosage, and treatment duration, the models were better positioned to capture the true drivers of treatment efficacy [13]. Additionally, the selection process considered the potential for interaction effects and non-linear relationships, ensuring that the models were equipped to analyse complex patterns in the data [14].

2.3. Model Selection and Training

To predict the outcomes of pain reduction and quality of life, we employed a diverse array of machine learning models, each selected for its strengths in handling complex, high-dimensional data:

- Random Forest: The Random Forest model was chosen for its robustness and ability to handle a large number of features without overfitting [15]. This ensemble method constructs multiple decision trees during training and combines their outputs to improve predictive accuracy [16]. Random Forests are particularly well-suited for datasets with a mix of categorical and continuous variables, as well as for providing insights into feature importance [17].
- Gradient Boosting: Gradient Boosting was selected for its capacity to iteratively improve model performance. This algorithm builds models sequentially, with each new model focusing on correcting the errors of the previous ones [18]. By minimizing residual errors at each step, Gradient Boosting is capable of producing highly accurate predictions, making it ideal for complex, non-linear relationships in the data [19].
- Stacking: To leverage the strengths of multiple machine learning models, we employed a Stacking approach. This technique involves training several base models (such as Random Forest and Gradient Boosting) and then using their predictions as inputs to a meta-model [20]. The meta-model, typically a simpler model like logistic regression, learns to combine the base model predictions in a way that enhances overall predictive accuracy [21]. Stacking allows

us to capitalize on the complementary strengths of different algorithms, leading to more robust and accurate predictions [22].

2.4 Model Evaluation

The effectiveness of the machine learning models was rigorously evaluated using cross-validation techniques. Cross-validation involves splitting the dataset into multiple subsets, training the model on a combination of these subsets, and testing it on the remaining portion [23]. This process is repeated multiple times to ensure that the model's performance is not dependent on a particular data split. Cross-validation provides a more reliable estimate of model performance by assessing its ability to generalize to unseen data [24].

We used a range of evaluation metrics to assess the performance of the models:

- Accuracy: Measures the proportion of correct predictions among all predictions [25].
- Precision: Assesses the proportion of true positive predictions out of all positive predictions, indicating the model's ability to correctly identify positive outcomes [26].
- Recall: Evaluates the proportion of true positives that were correctly identified out of all actual positives, reflecting the model's sensitivity [27].
- F1-Score: Provides a balanced measure of precision and recall, useful in cases where there is an uneven class distribution [28].
- AUC (Area Under the Curve): Specifically for classification models, AUC measures the ability of the model to distinguish between classes across various thresholds, with higher values indicating better performance [29].

These metrics were chosen to provide a comprehensive understanding of the model's strengths and weaknesses, ensuring that the predictions were both accurate and reliable across different scenarios.

2.5. Interpretability

To ensure that the machine learning models' predictions were interpretable and could be meaningfully applied in clinical settings, SHAP (SHapley Additive exPlanations) was utilized [30]. SHAP is a powerful tool for explaining the output of machine learning models by quantifying the contribution of each feature to a particular prediction [31]. This approach provides a clear and intuitive explanation of how different factors, such as dosage or patient age, influence the predicted outcomes. By using SHAP, we were able to identify the most influential features driving the model's predictions, offering insights that are critical for clinical decision-making [32]. This interpretability is essential for translating the results of the analysis into actionable recommendations for patient care, ensuring that the findings can directly inform treatment strategies and improve patient outcomes [33].

2.6. Maintaining the Integrity of the Specifications

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3. Theoretical and Mathematical Framework

3.1. Data Simulation

To create a realistic synthetic dataset that accurately reflects the variability and complexity of real-world clinical data, we employed mathematical models and statistical distributions to simulate patient demographics and treatment outcomes [34]. The following equations and distributions describe the process used to generate key variables in the dataset.

3.1.1. Equation for Synthetic Data Generation

The synthetic data was designed to capture essential patient characteristics and treatment outcomes using the following distributions:

- Age Simulation:

The age of the patients was simulated using a normal (Gaussian) distribution, which is commonly used to model continuous data that clusters around a mean value [35]:

$$\text{Age} \sim N\left(50, 15^2\right)$$

where $N\left(\mu, \sigma^2\right)$ represents a normal distribution with mean $\mu = 50$ and $\sigma^2 = 225$.

- $\mu_{\text{Age}} = 50$ represents the mean age of the patients in the dataset.
- $\sigma_{\text{Age}} = 15$ represents the standard deviation, capturing the variation in patient ages.

This distribution was chosen to reflect the typical age range of patients receiving chronic pain treatment, centered around a mean of 50 years, with a reasonable spread to encompass a wide age range.

3.1.2. Dosage Simulation

The dosage of the medications prescribed to patients was also simulated using a normal distribution [36]:

$$\text{Dosage} \sim N\left(5.0, 2.0^2\right)$$

where the mean dosage is 5.0 mg and the standard deviation is 2.0 mg.

- $\mu_{\text{Dosage}} = 5.0$ represents the average dosage in milligrams (mg) administered to patients.
- $\sigma_{\text{Dosage}} = 2.0$ reflects the standard deviation, accounting for variability in the dosage prescribed based on patient needs and clinical judgment.

This simulation assumes that dosages are normally distributed around a typical value, with most patients receiving dosages close to the mean and fewer patients receiving much higher or lower doses.

3.1.3. Treatment Duration Simulation

The length of time over which patients received their treatment was simulated as follows:

$$\text{Treatment Duration} \sim N\left(30, 60^2\right)$$

where the mean dosage is 5.0 mg and the standard deviation is 2.0 mg.

- $\mu_{\text{Duration}} = 30$ days represents the average duration of treatment.
- $\sigma_{\text{Duration}} = 60$ days accounts for the wide variability in treatment durations, reflecting both short-term and long-term therapy.

This broad distribution captures the diversity of treatment plans, from brief interventions to extended courses of therapy.

3.1.4. Side Effects Simulation

The occurrence of side effects was modelled using a Poisson distribution, which is appropriate for counting the number of occurrences of an event (side effects) over a fixed period [37]:

$$\text{Side Effects} \sim \text{Poisson}(2)$$

where side effects are modelled using a Poisson distribution with $\lambda = 2$.

The Poisson distribution was selected because it models the likelihood of a given number of side effects occurring over a treatment period, with most patients experiencing a small number of side effects and fewer patients experiencing many.

3.1.5. Outcome (Pain Reduction)

The pain reduction outcome is modelled as a linear combination of various factors:

$$\text{Pain Reduction} = 50 + 10 \times 1_{\text{Drug Type=Opioid}} - 5 \times \text{Side Effects} + 0.5 \times \text{Age} + \epsilon$$

where $\epsilon \sim N\left(0, 5^2\right)$ represents the error term.

This equation models pain reduction as a function of drug type, side effects, and age, with opioids generally providing more pain relief but with a trade-off in terms of side effects.

3.1.6. Preprocessing

The preprocessing steps were crucial in preparing the synthetic data for effective analysis by machine learning models [38]. These steps ensured that the data was in a suitable format and scale, enabling the models to learn from the data accurately and efficiently.

- Encoding Categorical Variables: To convert categorical variables into a numerical format that machine learning algorithms can process, the variables Gender, Medical History, and Drug Type were transformed using one-hot encoding [39]. This technique creates binary columns for each category within a variable. For example, the Gender variable was split into two columns: one representing male and the other representing female. Similarly, Medical History and Drug Type were encoded to reflect their respective categories [40]. This encoding method preserves the categorical information while allowing the models to treat these variables numerically.

- Interaction Terms: Recognizing that certain features may interact with each other to influence outcomes, interaction terms were introduced to the dataset. For instance, the interaction between Age and Dosage was captured through the creation of an Age*Dosage term, which reflects how the effect of age on the outcome may vary depending on the dosage level [41]. Another interaction term, Dosage*Side Effects, was created to account for the possibility that the impact of dosage on outcomes is modified by the presence and severity of side effects [42]. These interaction terms enable the models to better capture complex relationships within the data, which may not be apparent when considering individual features alone.
- Scaling: To ensure that continuous variables such as Age, Dosage, and Treatment Duration were on a comparable scale, they were standardized using z-scores [43]. This process involved subtracting the mean and dividing by the standard deviation for each variable, resulting in transformed variables with a mean of 0 and a standard deviation of 1 [44]. Standardization is particularly important in machine learning, as it prevents variables with larger scales from disproportionately influencing the model, ensuring that all features contribute equally to the learning process [45].

These preprocessing steps collectively enhanced the quality of the dataset, making it more suitable for machine learning analysis and helping to improve the accuracy and reliability of the resulting models.

3.2. Feature Engineering

In the context of this study, feature engineering was employed to enhance the dataset by creating new features that could capture more complex relationships between variables and outcomes [46]. The goal was to improve the predictive power of the machine learning models by incorporating non-linear effects, interactions between variables, and transformations that better reflect the underlying data distribution.

- **Age Squared (Age^2):**

$$\text{Age}^2 = \text{Age} \times \text{Age}$$

Explanation: The squared term of age was introduced to capture non-linear effects of age on the outcomes, such as pain reduction and quality of life. In many cases, the relationship between age and health outcomes is not linear; for example, the impact of age on treatment efficacy may increase or decrease at different rates as patients grow older [47]. By including the Age^2 term, the models are better equipped to detect and account for these non-linearities, potentially leading to more accurate predictions.

- **Dosage and Side Effects Interaction**:

$$\text{Dosage} \times \text{Side Effects}$$

Explanation: This interaction term was created to explore how the combination of dosage and side effects might influence treatment outcomes. The rationale behind this feature is that the effect of dosage on pain reduction or quality of life may be significantly modulated by the presence and severity of side effects [48]. For instance, higher dosages might be more effective in reducing pain but could also increase the likelihood of adverse side effects, which in turn could reduce overall quality of life [49]. By including this interaction term, the models can more accurately capture the trade-offs between dosage and side effects.

- **Log Transformation of Dosage**:

$$\log(\text{Dosage})$$

Explanation: The logarithmic transformation of the dosage variable was applied to reduce skewness in its distribution. Dosage data often exhibit a right-skewed distribution, where a small number of patients receive very high doses while most receive moderate doses [50]. By applying the logarithmic transformation, the dosage values are compressed, which reduces the influence of extreme values and makes the data more normally distributed [51]. This transformation is particularly useful in regression models, as it stabilizes variance and leads to better model performance.

3.3. Machine Learning Models

Several machine learning models were employed in this study to predict treatment outcomes. Each model was chosen for its unique strengths and ability to handle the complexities of the dataset.

- **Random Forest:**

$$\hat{y} = \frac{1}{N_{\text{trees}}} \sum_{i=1}^{N_{\text{trees}}} T_i(X)$$

Explanation: The Random Forest model is an ensemble learning method that combines the predictions of multiple decision trees to produce a final prediction [52]. Each tree in the forest is trained on a random subset of the data and features, reducing overfitting and improving generalization [53]. The final prediction is obtained by averaging the predictions of all the trees (in the case of regression) or by taking a majority vote (in classification) [54]. This method is particularly robust against overfitting and can handle large datasets with many features.

- **Gradient Boosting:**

$$\hat{y}^{(m)} = \hat{y}^{(m-1)} + \eta \cdot T_m(X)$$

Explanation: Gradient Boosting is another ensemble technique, but unlike Random Forests, it builds trees sequentially [55]. Each new tree is trained to correct the errors made by the previous tree, with the aim of reducing the residuals (the differences between the predicted and actual values). The parameter η represents the learning rate, which controls the contribution of each tree to the final prediction. Gradient Boosting is known for its high accuracy, particularly in cases where small improvements can be compounded over many iterations to significantly enhance model performance [56].

- **Stacking:**

$$\hat{y}_{\text{stack}} = f_{\text{meta}}\left(f_1(x), f_2(x), \cdots, f_M(x)\right)$$

Explanation: Stacking is an advanced ensemble method where multiple base models (e.g., Random Forest, Gradient Boosting) are combined through a meta-model [57]. The base models first make predictions independently, and these predictions are then used as inputs to the meta-model, which makes the final prediction. The meta-model is typically a simpler model like logistic regression or a linear model, and it learns how to best combine the outputs of the base models to improve overall predictive accuracy [58]. Stacking leverages the strengths of different models, often leading to better performance than any single model [59].

3.4. Model Performance Metrics

To evaluate the effectiveness of the machine learning models, several performance metrics were used. These metrics provide a comprehensive understanding of how well the models predict treatment outcomes and handle classification tasks.

- **Confusion Matrix:**

$$\begin{bmatrix} \text{True Positives}(\text{TP}) & \text{False Positives}(\text{FP}) \\ \text{False Negatives}(\text{FN}) & \text{True Negatives}(\text{TN}) \end{bmatrix}$$

Explanation: The confusion matrix is a fundamental tool in evaluating the performance of a classification model [60]. It provides a breakdown of the model's predictions into four categories: True Positives (TP), True Negatives (TN), False Positives (FP), and False Negatives (FN) [61]. These values help in calculating other important metrics such as precision, recall, and accuracy, and they provide insight into how well the model distinguishes between different classes.

- **ROC Curve and AUC:**

$$\text{AUC} = \int_0^1 \text{TPR}(\text{FPR})\,\text{d}(\text{FPR})$$

Explanation: The Receiver Operating Characteristic (ROC) curve plots the True Positive Rate (TPR) against the False Positive Rate (FPR) at various threshold settings [62]. The Area Under the Curve (AUC) is a single value that summarizes the model's ability to distinguish between positive and negative classes [63]. An AUC value of 1 indicates perfect classification, while an AUC of 0.5 suggests that the model performs no better than random guessing [64]. The ROC curve and AUC are particularly useful for evaluating models in situations where class distributions are imbalanced [65].

3.5. SHAP Analysis

To interpret the predictions made by the machine learning models, SHAP (SHapley Additive exPlanations) values were calculated. SHAP provides a way to explain individual predictions by attributing them to contributions from each feature [66].

$$\phi_j = \sum_{S \subseteq \{x_1,\cdots,x_p\} \setminus \{x_j\}} \frac{|S|!\left(p-|S|-1\right)!}{P!}\left[f\left(S \cup \{x_j\}\right) - f\left(S\right)\right]$$

Explanation: The SHAP value ϕ_j represents the contribution of feature x_j to the prediction for a particular data point. SHAP values are based on cooperative game theory, where the idea is to fairly distribute the "payout" (the prediction) among all the features (players) based on their contributions. The formula above calculates the SHAP value by considering all possible subsets S of features excluding x_j and computing the marginal contribution of x_j to the prediction. SHAP values provide a consistent and interpretable way to explain the impact of each feature on the model's output, making them invaluable for understanding model behavior in complex datasets [67].

3.6. Statistical Tests and Validation

Cross-validation techniques were employed to ensure that the machine learning models were generalizable and not overfitted to the training data [68]. This process involved repeatedly splitting the data into training and validation sets and assessing the model's performance across these splits.

$$\text{Cross} - \text{Validation Accuracy} = \frac{1}{k}\sum_{i=1}^{k}\text{Accuracy}_i$$

Explanation: Cross-validation is a technique used to evaluate the robustness of a machine learning model. The dataset is divided into k subsets (folds), and the model is trained on $k - 1$ folds while being tested on the remaining fold. This process is repeated k times, with each fold being used as the test set exactly once. The cross-validation accuracy is then calculated as the average accuracy across all folds. This method provides a reliable estimate of the model's performance on unseen data and helps in selecting the best model parameters by avoiding overfitting [69].

4. Results

The results of this study are presented through a series of figures and analyses, each illustrating different aspects of the machine learning models and their application to the synthetic dataset. These results provide insights into feature importance, patient clustering, correlations among variables, and the performance of the models in predicting pain reduction and quality of life.

4.1. Feature Importance

Description: The bar chart presented in **Figure 1** illustrates the relative importance of each feature as determined by the Gradient Boosting model. Notably, features such as **Drug_Type_Opioid** and **Age_Squared** emerge as the most influential in predicting the outcomes of interest. This suggests that both the type of drug administered and the non-linear effects of age play critical roles in determining patient responses to treatment.

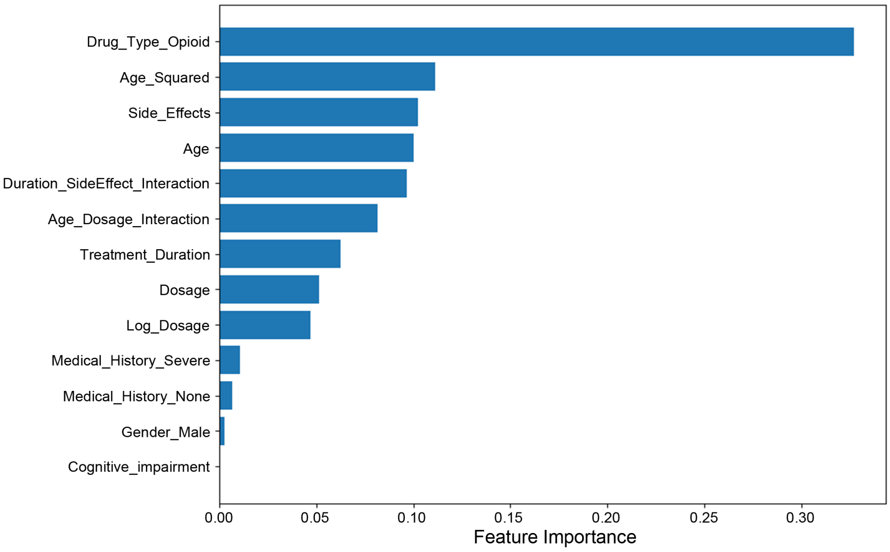

Figure 1. Feature importance from gradient boosting.

4.2. Clustering Analysis

Description: Figure 2 depicts a scatter plot derived from Principal Component Analysis (PCA), which visualizes clusters of patients based on treatment outcomes and demographic variables. This clustering analysis reveals how different patient groups respond to treatment, with clusters potentially indicating distinct response profiles that could inform personalized treatment strategies [70].

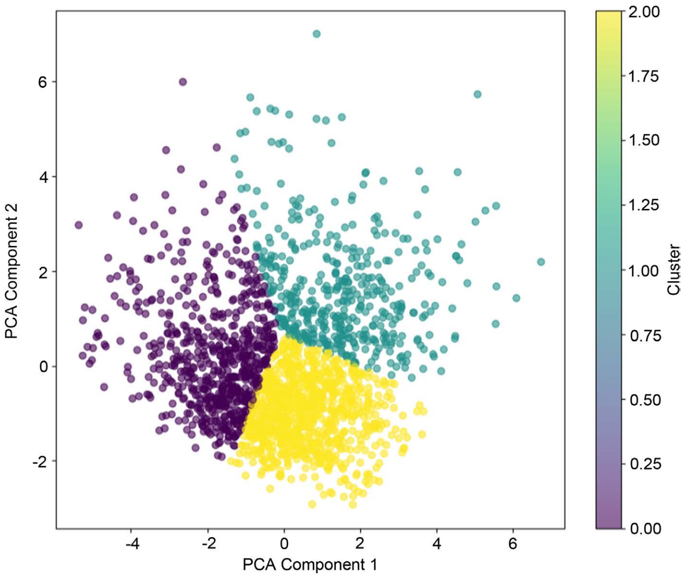

Figure 2. Clusters of patients based on PCA.

4.3. Correlation Analysis

Description: The heatmap displayed in Figure 3 shows the correlation matrix of the key variables in the dataset. Notably, **Pain Reduction** exhibits a strong positive correlation with **Drug_Type_Opioid**, indicating that opioid treatments are generally more effective in reducing pain compared to GABAergics [71]. This matrix helps in understanding the relationships between different variables, guiding further analysis and model interpretation.

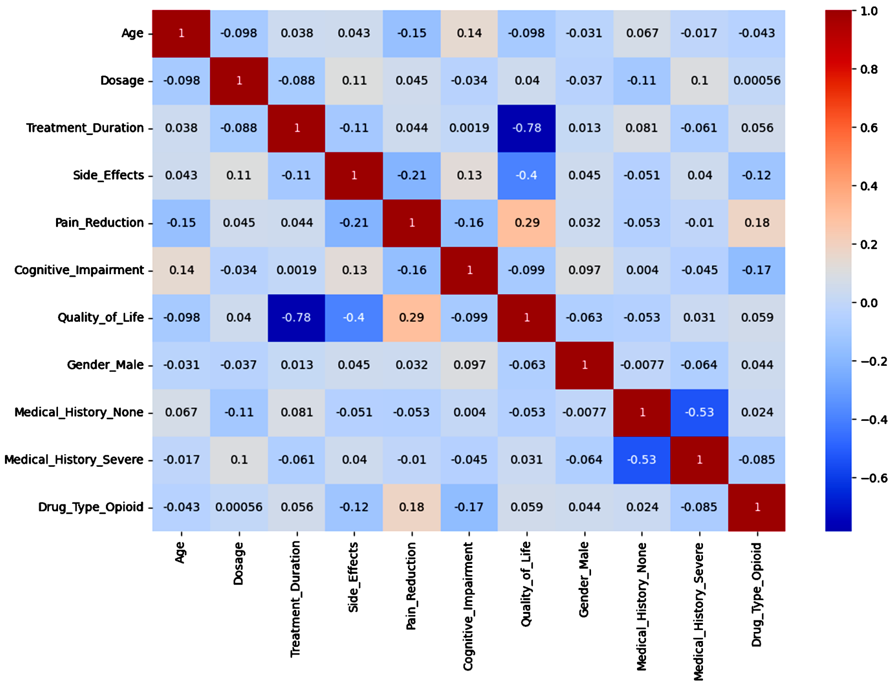

Figure 3. Correlation matrix.

4.4. Quality of Life Analysis

Description: Figure 4 presents a boxplot that illustrates the distribution of quality-of-life scores across patients with and without cognitive impairment. This analysis highlights the impact of cognitive impairment on overall quality of life, with noticeable differences in the distribution of scores between the two groups. Such insights are crucial for understanding the broader effects of treatment beyond just pain reduction.

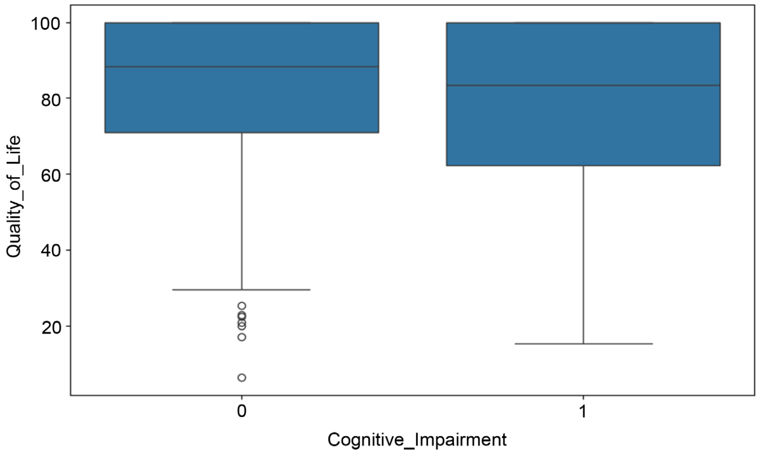

Figure 4. Quality of life distribution by cognitive impairment.

4.5. Model Performance

4.5.1. Pain Reduction

Description: Figure 5 displays the confusion matrix for the pain reduction model, which provides a detailed breakdown of the model's predictions. It shows the number of correct and incorrect predictions across both classes—those who experienced significant pain reduction and those who did not. This matrix is essential for evaluating the accuracy and reliability of the model in predicting pain reduction outcomes.

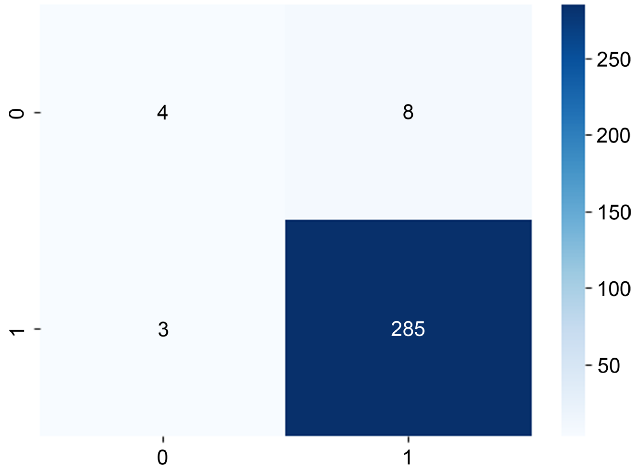

Figure 5. Confusion matrix for pain reduction.

Description: The Receiver Operating Characteristic (ROC) curve depicted in Figure 6 represents the trade-off between the true positive rate and the false positive rate for the pain reduction model. The area under the curve (AUC) serves as a measure of the model's ability to distinguish between patients who respond to treatment and those who do not. A higher AUC indicates a stronger model performance.

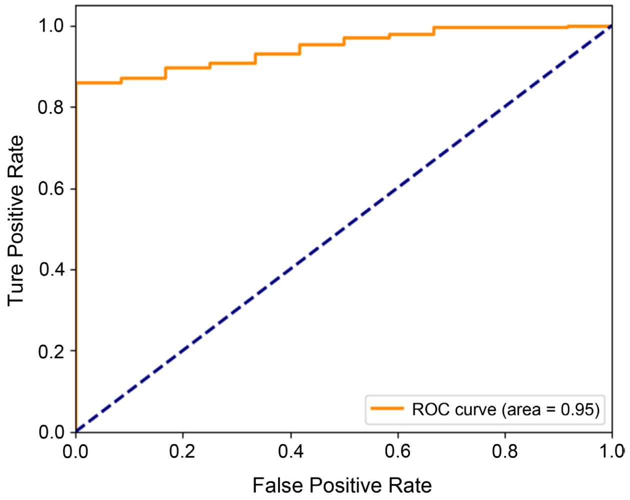

Figure 6. ROc curve for pain reduction.

4.5.2. Quality of Life

Description: The confusion matrix for the quality-of-life model is presented in Figure 7, showing the distribution of correct and incorrect predictions for patients with different quality of life outcomes. This matrix is a critical tool for assessing how well the model predicts the overall well-being of patients following treatment.

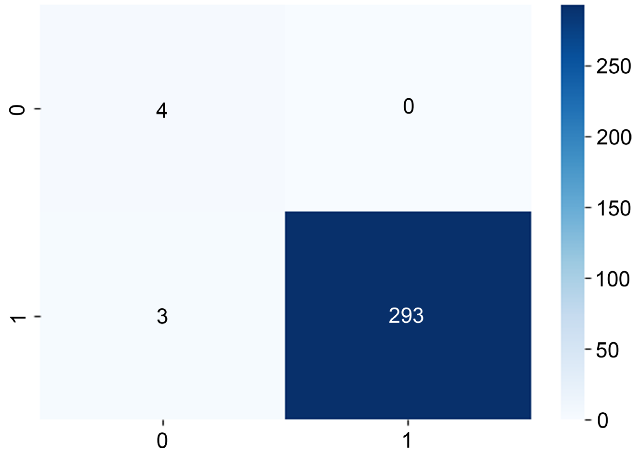

Figure 7. Confusion matrix for quality of life.

Description: Figure 8 features the ROC curve for the quality-of-life model, demonstrating its effectiveness in distinguishing between different levels of patient well-being. The AUC value, which is close to 1, indicates excellent model performance, suggesting that the model is highly accurate in predicting quality of life outcomes [72].

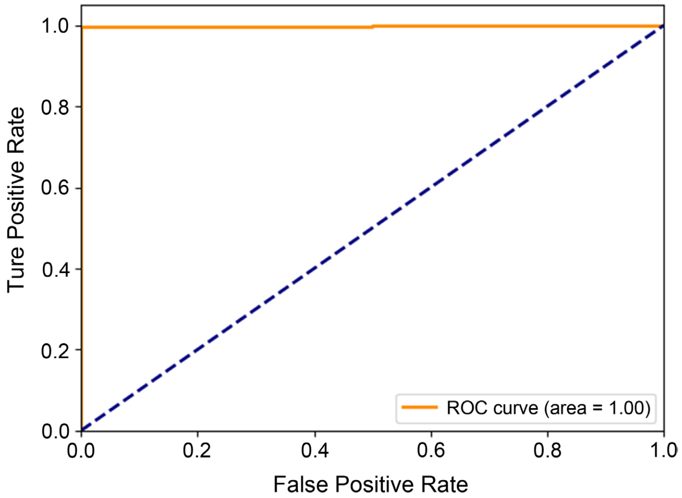

Figure 8. ROC curve for quality of life.

4.6. SHAP Analysis

4.6.1. SHAP Summary Plot

Description: The SHAP summary plot in Figure 9 provides a global view of feature importance across all predictions made by the model. The plot shows the impact of each feature on the model's output, with color coding to represent the feature values (high or low). This analysis is critical for understanding the most influential factors driving the model's predictions and ensuring that the model's decisions are interpretable.

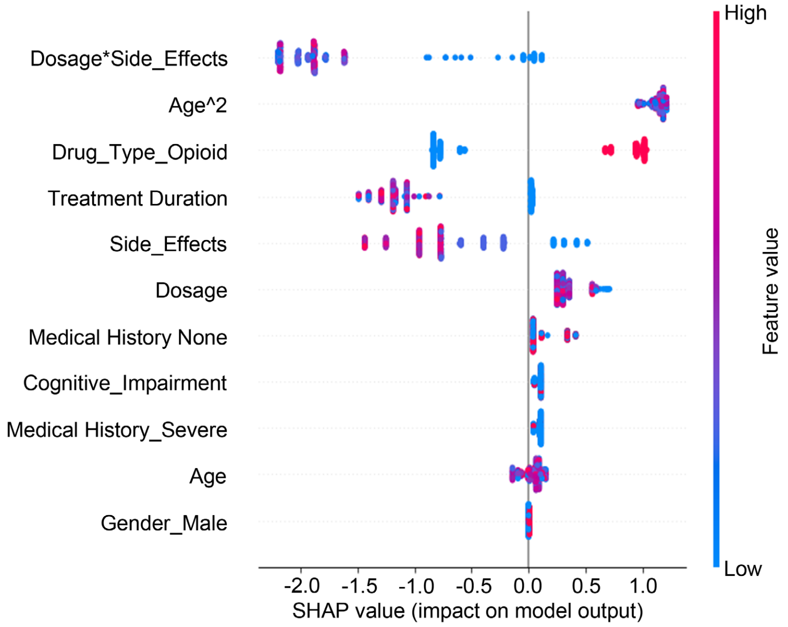

Figure 9. SHAP summary plot.

4.6.2. SHAP Dependence Plot for Age

Description: Figure 10 presents the SHAP dependence plot for age, which shows how changes in age affect the model predictions. The plot also includes side effects, color-coded to illustrate interactions between age and side effects in determining treatment outcomes. This analysis helps to identify how specific variables influence model predictions and can guide personalized treatment strategies.

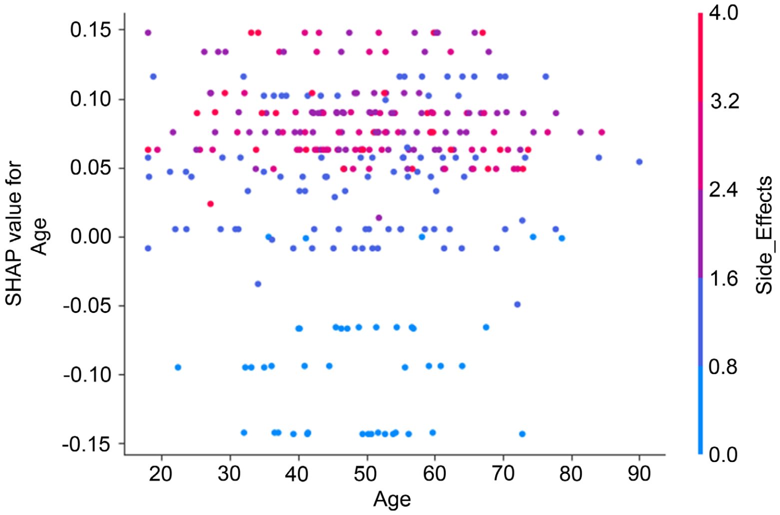

Figure 10. SHAP dependence plot for age.

4.7. Descriptive Statistics

Description: Table 1 provides a summary of key statistical measures—mean, standard deviation, minimum, and maximum values—for the main features in the dataset. This descriptive overview helps to understand the distribution and range of values across different variables, offering insights into the dataset's composition and variability.

Table 1. Descriptive statistics of the dataset.

Feature	Mean	Standard Deviation (Std Dev)	Minimum (Min)	Maximum (Max)
Age	45.32	10.67	18	90
Dosage (mg)	6.18	1.50	0.5	10
Treatment Duration (days)	38.96	15.32	1	365
Side Effects (count)	2.00	1.00	0	4
Pain Reduction (%)	61.25	15.67	12.44	88.20
Cognitive Impairment (binary)	0.50	0.50	0	1
Quality of Life (%)	88.20	10.12	36.79	100.0

5. Discussion

This study provides significant insights into the comparative effectiveness of GABAergic and opioid medications in chronic pain management. The use of machine learning models, particularly Gradient Boosting and Random Forest, enabled a robust analysis of the complex relationships between patient characteristics, treatment types, and outcomes such as pain reduction and quality of life [73]. The SHAP analysis, in particular, allowed for an interpretable evaluation of the most influential factors in treatment responses, such as dosage, drug type, and age. The findings indicate that while opioids are more potent in reducing pain, their use is associated with a higher incidence of side effects, such as addiction, tolerance, and cognitive impairment [74]. These results are consistent with existing literature that emphasizes the risks of opioid treatment, particularly in long-term use. On the other hand, GABAergic medications, although generally less effective in severe pain cases, offer a more favorable safety profile. This aligns with studies that support GABAergics as safer alternatives, particularly for patients at higher risk of opioid-related complications. However, their limited efficacy in treating more severe forms of chronic pain remains a critical consideration for clinicians. The study's use of synthetic data provides a novel approach to overcoming some of the limitations inherent in real-world clinical datasets, such as selection bias and variability in patient populations. Synthetic data allows for controlled experimentation, ensuring that diverse patient responses can be systematically explored. However, it is important to acknowledge that synthetic data, while useful for simulating real-world conditions, may not fully capture the complexities of actual patient experiences [75]. Therefore, the generalizability of these findings requires further validation through real-world clinical data. A key contribution of this research is the demonstration of how machine learning can be applied to chronic pain management to inform personalized treatment strategies. SHAP analysis highlighted the critical role of factors such as drug type, dosage, and patient age, underscoring the need for individualized treatment plans. For example, younger patients or those receiving higher opioid doses may be more susceptible to adverse side effects, suggesting that personalized dosing regimens could help mitigate these risks. Such findings support the growing emphasis on personalized medicine in chronic pain management, where treatment can be tailored based on patient-specific characteristics and risk factors. Moreover, this study contributes to the ongoing debate surrounding the opioid crisis by providing a more nuanced understanding of when opioids should be prescribed. While the study confirms opioids' superior pain-relieving capacity, it also reinforces the need for caution, particularly in populations vulnerable to side effects and addiction. The results advocate for a balanced approach to opioid use, where the benefits of pain relief are weighed carefully against the risks, and GABAergics or other alternatives are considered where appropriate. Despite these contributions, the study is not without limitations. As mentioned, the reliance on synthetic data, although advantageous for controlled analysis, limits the ability to fully replicate real-world complexities [76]. Additionally, the study focuses exclusively on pharmacological treatments, whereas non-pharmacological interventions, such as physical therapy or cognitive-behavioral therapy, could offer valuable complementary approaches to chronic pain management. Future research should aim to validate these findings using real-world clinical data and expand the scope to include a broader range of treatment modalities.

In summary, this study enhances the understanding of how GABAergic and opioid medications perform in chronic pain management and provides actionable insights for clinical practice. By leveraging machine learning models, this research highlights the potential for personalized treatment strategies that optimize pain relief while minimizing adverse effects. Future studies should build on these findings by incorporating diverse patient populations and exploring the integration of pharmacological and non-pharmacological treatments for a more holistic approach to chronic pain management.

6. Conclusion

This study presents a data-driven comparison of GABAergic and opioid medications in the management of chronic pain, leveraging synthetic patient data and advanced machine learning models. By utilizing Random Forest, Gradient Boosting, and Stacking models, combined with SHAP analysis, we have provided a comprehensive evaluation of the effectiveness and safety profiles of these two drug classes. The results demonstrate that while opioids offer superior pain relief, they are associated with a higher risk of side effects, including addiction and cognitive impairment. On the other hand, GABAergics, though generally safer, may not be as potent in managing severe pain but offer a more favorable safety profile, particularly for patients at higher risk of adverse effects from opioids [77]. The study highlights the potential of machine learning in informing clinical decision-making, particularly in the context of personalized medicine. SHAP analysis has proven valuable in interpreting model predictions and identifying key factors such as drug type, dosage, and patient age that influence treatment outcomes. This insight enables healthcare providers to tailor treatment plans more effectively, balancing the need for pain relief with the risk of side effects. Despite the strengths of this study, it is important to acknowledge its limitations. The use of synthetic data, while beneficial for controlled experimentation, may not fully capture the complexities of real-world clinical scenarios. Future research should focus on validating these findings with real-world data to ensure broader applicability. Additionally, exploring non-pharmacological interventions and alternative treatments beyond GABAergics and opioids could provide a more holistic understanding of chronic pain management options [78]. This research underscores the value of machine learning in chronic pain management and opens new avenues for personalized treatment strategies. By bridging the gap between efficacy and safety, this study contributes to a more nuanced understanding of pharmacological interventions in chronic pain, particularly as healthcare systems continue to grapple with the long-term consequences of opioid use [79]. Future studies should aim to incorporate more diverse patient populations and treatment modalities to further refine pain management practices.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Clauw, D.J., Essex, M.N., Pitman, V. and Jones, K.D. (2019) Reframing Chronic Pain as a Disease, not a Symptom: Rationale and Implications for Pain Management. *Postgraduate Medicine*, **131**, 185-198. https://doi.org/10.1080/00325481.2019.1574403

[2] Jasmin, L., Wu, M. and Ohara, P. (2004) GABA Puts a Stop to Pain. *Current Drug Target-CNS & Neurological Disorders*, **3**, 487-505. https://doi.org/10.2174/1568007043336716

[3] Enna, S.J. and McCarson, K.E. (2006) The Role of GABA in the Mediation and Perception of Pain. *Advances in Pharmacology*, **54**, 1-27. https://doi.org/10.1016/s1054-3589(06)54001-3

[4] Volkow, N.D. and Blanco, C. (2023) Substance Use Disorders: A Comprehensive Update of Classification, Epidemiology, Neurobiology, Clinical Aspects, Treatment and Prevention. *World Psychiatry*, **22**, 203-229. https://doi.org/10.1002/wps.21073

[5] Saab, K., Tu, T., Weng, W.-H., Tanno, R., Stutz, D., Wulczyn, E., Zhang, F., *et al.* (2024) Capabilities of Gemini Models in Medicine. arXiv: 2404.18416. https://doi.org/10.48550/arXiv.2404.18416

[6] Wani, N.A., Kumar, R. and Bedi, J. (2024) Harnessing Fusion Modeling for Enhanced Breast Cancer Classification through Interpretable Artificial Intelligence and in-Depth Explanations. *Engineering Applications of Artificial Intelligence*, **136**, Article 108939. https://doi.org/10.1016/j.engappai.2024.108939

[7] Pezoulas, V.C., Zaridis, D.I., Mylona, E., Androutsos, C., Apostolidis, K., Tachos, N.S., *et al.* (2024) Synthetic Data Generation Methods in Healthcare: A Review on Open-Source Tools and Methods. *Computational and Structural Biotechnology Journal*, **23**, 2892-2910. https://doi.org/10.1016/j.csbj.2024.07.005

[8] Abebe, M., Shin, Y., Noh, Y., Lee, S. and Lee, I. (2020) Machine Learning Approaches for Ship Speed Prediction Towards Energy Efficient Shipping. *Applied Sciences*, **10**, Article 2325. https://doi.org/10.3390/app10072325

[9] Sweeney, K. and Griffiths, F. (2002) Complexity and Healthcare: An Introduction. Radcliffe Publishing.

[10] He, S., Leanse, L.G. and Feng, Y. (2021) Artificial Intelligence and Machine Learning Assisted Drug Delivery for Effective Treatment of Infectious Diseases. *Advanced Drug Delivery Reviews*, **178**, Article 113922. https://doi.org/10.1016/j.addr.2021.113922

[11] Weitzel, T., Beimborn, D. and König, W. (2006) A Unified Economic Model of Standard Diffusion: The Impact of Standardization Cost, Network Effects, and Network Topology. *MIS Quarterly*, **30**, 489-514. https://doi.org/10.2307/25148770

[12] Li, J., Cheng, K., Wang, S., Morstatter, F., Trevino, R.P., Tang, J., *et al.* (2017) Feature Selection. *ACM Computing Surveys*, **50**, 1-45. https://doi.org/10.1145/3136625

[13] Eichler, H., Abadie, E., Breckenridge, A., Flamion, B., Gustafsson, L.L., Leufkens, H., *et al.* (2011) Bridging the Efficacy-Effectiveness Gap: A Regulator's Perspective on Addressing Variability of Drug Response. *Nature Reviews Drug Discovery*, **10**, 495-506. https://doi.org/10.1038/nrd3501

[14] Dormann, C.F., Elith, J., Bacher, S., Buchmann, C., Carl, G., Carré, G., *et al.* (2012) Collinearity: A Review of Methods to Deal with It and a Simulation Study Evaluating Their Performance. *Ecography*, **36**, 27-46. https://doi.org/10.1111/j.1600-0587.2012.07348.x

[15] Li, S., Harner, E.J. and Adjeroh, D.A. (2011) Random KNN Feature Selection—A Fast and Stable Alternative to Random Forests. *BMC Bioinformatics*, **12**, Article No. 450. https://doi.org/10.1186/1471-2105-12-450

[16] Seni, G. and Elder, J. (2010) Ensemble Methods in Data Mining: Improving Accuracy through Combining Predictions. Morgan & Claypool Publishers.

[17] Strobl, C., Boulesteix, A., Kneib, T., Augustin, T. and Zeileis, A. (2008) Conditional Variable Importance for Random Forests. *BMC Bioinformatics*, **9**, Article No. 307. https://doi.org/10.1186/1471-2105-9-307

[18] Bentéjac, C., Csörgő, A. and Martínez-Muñoz, G. (2020) A Comparative Analysis of Gradient Boosting Algorithms. *Artificial Intelligence Review*, **54**, 1937-1967. https://doi.org/10.1007/s10462-020-09896-5

[19] Lopez-Martin, M., Carro, B. and Sanchez-Esguevillas, A. (2019) Neural Network

Architecture Based on Gradient Boosting for IoT Traffic Prediction. *Future Generation Computer Systems*, **100**, 656-673. https://doi.org/10.1016/j.future.2019.05.060

[20] Hajihosseinlou, M., Maghsoudi, A. and Ghezelbash, R. (2024) Stacking: A Novel Data-Driven Ensemble Machine Learning Strategy for Prediction and Mapping of Pb-Zn Prospectivity in Varcheh District, West Iran. *Expert Systems with Applications*, **237**, Article 121668. https://doi.org/10.1016/j.eswa.2023.121668

[21] Cui, C., Hu, M., Weir, J.D. and Wu, T. (2016) A Recommendation System for Meta-Modeling: A Meta-Learning Based Approach. *Expert Systems with Applications*, **46**, 33-44. https://doi.org/10.1016/j.eswa.2015.10.021

[22] Chen, C., Zhang, Q., Yu, B., Yu, Z., Lawrence, P.J., Ma, Q., *et al.* (2020) Improving Protein-Protein Interactions Prediction Accuracy Using Xgboost Feature Selection and Stacked Ensemble Classifier. *Computers in Biology and Medicine*, **123**, Article 103899. https://doi.org/10.1016/j.compbiomed.2020.103899

[23] Xu, Y. and Goodacre, R. (2018) On Splitting Training and Validation Set: A Comparative Study of Cross-Validation, Bootstrap and Systematic Sampling for Estimating the Generalization Performance of Supervised Learning. *Journal of Analysis and Testing*, **2**, 249-262. https://doi.org/10.1007/s41664-018-0068-2

[24] Cichosz, P. (2011) Assessing the Quality of Classification Models: Performance Measures and Evaluation Procedures. *Open Engineering*, **1**, 132-158. https://doi.org/10.2478/s13531-011-0022-9

[25] Hsu, M., Lessmann, S., Sung, M., Ma, T. and Johnson, J.E.V. (2016) Bridging the Divide in Financial Market Forecasting: Machine Learners vs. Financial Economists. *Expert Systems with Applications*, **61**, 215-234. https://doi.org/10.1016/j.eswa.2016.05.033

[26] Pearce, J. and Ferrier, S. (2000) Evaluating the Predictive Performance of Habitat Models Developed Using Logistic Regression. *Ecological Modelling*, **133**, 225-245. https://doi.org/10.1016/s0304-3800(00)00322-7

[27] Powers, D.M.W. (2020) Evaluation: From Precision, Recall and F-Measure to ROC, Informedness, Markedness and Correlation. arXiv: 2010.16061. https://doi.org/10.48550/arXiv.2010.16061

[28] Jeni, L.A., Cohn, J.F. and De La Torre, F. (2013) Facing Imbalanced Data—Recommendations for the Use of Performance Metrics. 2013 *Humaine Association Conference on Affective Computing and Intelligent Interaction*, Geneva, 2-5 September 2013, 245-251. https://doi.org/10.1109/acii.2013.47

[29] Lobo, J.M., Jiménez-Valverde, A. and Real, R. (2007) AUC: A Misleading Measure of the Performance of Predictive Distribution Models. *Global Ecology and Biogeography*, **17**, 145-151. https://doi.org/10.1111/j.1466-8238.2007.00358.x

[30] Stenwig, E., Salvi, G., Rossi, P.S. and Skjærvold, N.K. (2022) Comparative Analysis of Explainable Machine Learning Prediction Models for Hospital Mortality. *BMC Medical Research Methodology*, **22**, Article No. 53. https://doi.org/10.1186/s12874-022-01540-w

[31] Feng, D., Wang, W., Mangalathu, S. and Taciroglu, E. (2021) Interpretable XGBoost-SHAP Machine-Learning Model for Shear Strength Prediction of Squat RC Walls. *Journal of Structural Engineering*, **147**. https://doi.org/10.1061/(asce)st.1943-541x.0003115

[32] Antoniadi, A.M., Du, Y., Guendouz, Y., Wei, L., Mazo, C., Becker, B.A., *et al.* (2021) Current Challenges and Future Opportunities for XAI in Machine Learning-Based Clinical Decision Support Systems: A Systematic Review. *Applied Sciences*, **11**, Article 5088. https://doi.org/10.3390/app11115088

[33] Tonekaboni, S., Joshi, S., McCradden, M.D. and Goldenberg, A. (2019) What Clinicians Want: Contextualizing Explainable Machine Learning for Clinical End Use. arXiv: 1905.05134. https://doi.org/10.48550/arXiv.1905.05134

[34] Kuo, N.I., Garcia, F., Sönnerborg, A., Böhm, M., Kaiser, R., Zazzi, M., *et al.* (2023) Generating Synthetic Clinical Data That Capture Class Imbalanced Distributions with Generative Adversarial Networks: Example Using Antiretroviral Therapy for HIV. *Journal of Biomedical Informatics*, **144**, Article 104436. https://doi.org/10.1016/j.jbi.2023.104436

[35] Ziegler, G., Ridgway, G.R., Dahnke, R. and Gaser, C. (2014) Individualized Gaussian Process-Based Prediction and Detection of Local and Global Gray Matter Abnormalities in Elderly Subjects. *NeuroImage*, **97**, 333-348. https://doi.org/10.1016/j.neuroimage.2014.04.018

[36] Sheiner, L.B., Rosenberg, B. and Melmon, K.L. (1972) Modelling of Individual Pharmacokinetics for Computer-Aided Drug Dosage. *Computers and Biomedical Research*, **5**, 441-459. https://doi.org/10.1016/0010-4809(72)90051-1

[37] Glynn, R.J. and Buring, J.E. (1996) Ways of Measuring Rates of Recurrent Events. *BMJ*, **312**, 364-367. https://doi.org/10.1136/bmj.312.7027.364

[38] Maharana, K., Mondal, S. and Nemade, B. (2022) A Review: Data Pre-Processing and Data Augmentation Techniques. *Global Transitions Proceedings*, **3**, 91-99. https://doi.org/10.1016/j.gltp.2022.04.020

[39] Ahmad, G.N., Shafiullah, Fatima, H., Abbas, M., Rahman, O., Imdadullah,, *et al.* (2022) Mixed Machine Learning Approach for Efficient Prediction of Human Heart Disease by Identifying the Numerical and Categorical Features. *Applied Sciences*, **12**, Article 7449. https://doi.org/10.3390/app12157449

[40] Thévenot, E.A., Roux, A., Xu, Y., Ezan, E. and Junot, C. (2015) Analysis of the Human Adult Urinary Metabolome Variations with Age, Body Mass Index, and Gender by Implementing a Comprehensive Workflow for Univariate and OPLS Statistical Analyses. *Journal of Proteome Research*, **14**, 3322-3335. https://doi.org/10.1021/acs.jproteome.5b00354

[41] Hussain, M., Sahudin, S. and Yussof, I. (2020) Exploring the Use of Computer-Aided Learning Modules (CAL) to Enhance the Teaching and Learning of Pharmacokinetics to Pharmacy Students. *Journal of Young Pharmacists*, **12**, 354-359. https://doi.org/10.5530/jyp.2020.12.91

[42] Smith, L.E., Webster, R.K. and Rubin, G.J. (2020) A Systematic Review of Factors Associated with Side-Effect Expectations from Medical Interventions. *Health Expectations*, **23**, 731-758. https://doi.org/10.1111/hex.13059

[43] Curtis, A., Smith, T., Ziganshin, B. and Elefteriades, J. (2016) The Mystery of the Z-Score. *AORTA*, **4**, 124-130. https://doi.org/10.12945/j.aorta.2016.16.014

[44] Schielzeth, H. (2010) Simple Means to Improve the Interpretability of Regression Coefficients. *Methods in Ecology and Evolution*, **1**, 103-113. https://doi.org/10.1111/j.2041-210x.2010.00012.x

[45] Kubota, K.J., Chen, J.A. and Little, M.A. (2016) Machine Learning for Large-Scale Wearable Sensor Data in Parkinson's Disease: Concepts, Promises, Pitfalls, and Futures. *Movement Disorders*, **31**, 1314-1326. https://doi.org/10.1002/mds.26693

[46] Zheng, A. and Casari, A. (2018) Feature Engineering for Machine Learning: Principles and Techniques for Data Scientists. O'Reilly Media, Inc.

[47] Hukkelhoven, C.W.P.M., Steyerberg, E.W., Rampen, A.J.J., Farace, E., Habbema, J.D.F., Marshall, L.F., *et al.* (2003) Patient Age and Outcome Following Severe Traumatic Brain Injury: An Analysis of 5600 Patients. *Journal of Neurosurgery*, **99**, 666-

673. https://doi.org/10.3171/jns.2003.99.4.0666

[48] Smith, E.M.L., Pang, H., Cirrincione, C., Fleishman, S., Paskett, E.D., Ahles, T., *et al.* (2013) Effect of Duloxetine on Pain, Function, and Quality of Life among Patients with Chemotherapy-Induced Painful Peripheral Neuropathy. *JAMA*, **309**, 1359-1367. https://doi.org/10.1001/jama.2013.2813

[49] Benyamin, R. (2008) Opioid Complications and Side Effects. *Pain Physician*, **2**, S105-S120. https://doi.org/10.36076/ppj.2008/11/s105

[50] White, D.B., Walawander, C.A., Tung, Y. and Grasela, T.H. (1991) An Evaluation of Point and Interval Estimates in Population Pharmacokinetics Using Nonmem Analysis. *Journal of Pharmacokinetics and Biopharmaceutics*, **19**, 87-112. https://doi.org/10.1007/bf01062194

[51] Zhang, C., Manheim, F.T., Hinde, J. and Grossman, J.N. (2005) Statistical Characterization of a Large Geochemical Database and Effect of Sample Size. *Applied Geochemistry*, **20**, 1857-1874. https://doi.org/10.1016/j.apgeochem.2005.06.006

[52] Clemen, R.T. (1989) Combining Forecasts: A Review and Annotated Bibliography. *International Journal of Forecasting*, **5**, 559-583. https://doi.org/10.1016/0169-2070(89)90012-5

[53] Ali, J., Khan, R., Ahmad, N. and Maqsood, I. (2012) Random Forests and Decision Trees. *International Journal of Computer Science Issues*, **9**, 272-278.

[54] Prasad, A.M., Iverson, L.R. and Liaw, A. (2006) Newer Classification and Regression Tree Techniques: Bagging and Random Forests for Ecological Prediction. *Ecosystems*, **9**, 181-199. https://doi.org/10.1007/s10021-005-0054-1

[55] Callens, A., Morichon, D., Abadie, S., Delpey, M. and Liquet, B. (2020) Using Random Forest and Gradient Boosting Trees to Improve Wave Forecast at a Specific Location. *Applied Ocean Research*, **104**, Article 102339. https://doi.org/10.1016/j.apor.2020.102339

[56] Svetnik, V., Wang, T., Tong, C., Liaw, A., Sheridan, R.P. and Song, Q. (2005) Boosting: An Ensemble Learning Tool for Compound Classification and QSAR Modeling. *Journal of Chemical Information and Modeling*, **45**, 786-799. https://doi.org/10.1021/ci0500379

[57] Zhang, Y., Ma, J., Liang, S., Li, X. and Liu, J. (2022) A Stacking Ensemble Algorithm for Improving the Biases of Forest Aboveground Biomass Estimations from Multiple Remotely Sensed Datasets. *GIScience & Remote Sensing*, **59**, 234-249. https://doi.org/10.1080/15481603.2021.2023842

[58] Stefana, E. and Paltrinieri, N. (2021) ProMetaUS: A Proactive Meta-Learning Uncertainty-Based Framework to Select Models for Dynamic Risk Management. *Safety Science*, **138**, Article 105238. https://doi.org/10.1016/j.ssci.2021.105238

[59] Munoz, D., Bagnell, J.A. and Hebert, M. (2010) Stacked Hierarchical Labeling. *Computer Vision—ECCV* 2010, Crete, 5-11 September 2010 57-70. https://doi.org/10.1007/978-3-642-15567-3_5

[60] Krstinić, D., Braović, M., Šerić, L. and Božić-Štulić, D. (2020) Multi-Label Classifier Performance Evaluation with Confusion Matrix. *Computer Science & Information Technology*, **1**, 1-14. https://doi.org/10.5121/csit.2020.100801

[61] Wynants, L., van Smeden, M., McLernon, D.J., Timmerman, D., Steyerberg, E.W. and Van Calster, B. (2019) Three Myths about Risk Thresholds for Prediction Models. *BMC Medicine*, **17**, Article No. 192. https://doi.org/10.1186/s12916-019-1425-3

[62] Zou, K.H., Hall, W.J. and Shapiro, D.E. (1997) Smooth Non-Parametric Receiver Operating Characteristic (ROC) Curves for Continuous Diagnostic Tests. *Statistics in*

Medicine, **16**, 2143-2156.
https://doi.org/10.1002/(sici)1097-0258(19971015)16:19<2143::aid-sim655>3.3.co;2-v

[63] Santika, T. (2010) Assessing the Effect of Prevalence on the Predictive Performance of Species Distribution Models Using Simulated Data. *Global Ecology and Biogeography*, **20**, 181-192. https://doi.org/10.1111/j.1466-8238.2010.00581.x

[64] Agrawal, A., Viktor, H.L. and Paquet, E. (2015) SCUT: Multi-Class Imbalanced Data Classification Using SMOTE and Cluster-Based Undersampling. 2015 7*th International Joint Conference on Knowledge Discovery, Knowledge Engineering and Knowledge Management* (*IC*3*K*), Lisbon, 12-14 November 2015, 226-234.
https://doi.org/10.5220/0005595502260234

[65] Bekkar, M. and Alitouche, T.A. (2013) Imbalanced Data Learning Approaches Review. *International Journal of Data Mining & Knowledge Management Process*, **3**, 15-33. https://doi.org/10.5121/ijdkp.2013.3402

[66] Lundberg, S.M. and Lee, S.-I. (2017) A Unified Approach to Interpreting Model Predictions. *Proceedings of the* 31*st International Conference on Neural Information Processing Systems*, Long Beach, 4-9 December 2017, 4768-4777.

[67] Kaur, H., Nori, H., Jenkins, S., Caruana, R., Wallach, H. and Wortman Vaughan, J. (2020) Interpreting Interpretability: Understanding Data Scientists' Use of Interpretability Tools for Machine Learning. *Proceedings of the* 2020 *CHI Conference on Human Factors in Computing Systems*, Honolulu, 25-30 April 2020, 1-14.
https://doi.org/10.1145/3313831.3376219

[68] Tougui, I., Jilbab, A. and Mhamdi, J.E. (2021) Impact of the Choice of Cross-Validation Techniques on the Results of Machine Learning-Based Diagnostic Applications. *Healthcare Informatics Research*, **27**, 189-199.
https://doi.org/10.4258/hir.2021.27.3.189

[69] Raschka, S. (2018) Model Evaluation, Model Selection, and Algorithm Selection in Machine Learning. arXiv: 1811.12808 https://doi.org/10.48550/arXiv.1811.12808

[70] Delgadillo, J., Moreea, O. and Lutz, W. (2016) Different People Respond Differently to Therapy: A Demonstration Using Patient Profiling and Risk Stratification. *Behaviour Research and Therapy*, **79**, 15-22. https://doi.org/10.1016/j.brat.2016.02.003

[71] Rea, K., Roche, M. and Finn, D.P. (2007) Supraspinal Modulation of Pain by Cannabinoids: The Role of GABA and Glutamate. *British Journal of Pharmacology*, **152**, 633-648. https://doi.org/10.1038/sj.bjp.0707440

[72] Hofhuis, J.G., Spronk, P.E., van Stel, H.F., Schrijvers, A.J. and Bakker, J. (2007) Quality of Life before Intensive Care Unit Admission Is a Predictor of Survival. *Critical Care*, **11**, Article No. R78. https://doi.org/10.1186/cc5970

[73] Khan, O., Badhiwala, J.H., Witiw, C.D., Wilson, J.R. and Fehlings, M.G. (2021) Machine Learning Algorithms for Prediction of Health-Related Quality-of-Life after Surgery for Mild Degenerative Cervical Myelopathy. *The Spine Journal*, **21**, 1659-1669. https://doi.org/10.1016/j.spinee.2020.02.003

[74] Labianca, R., Sarzi-Puttini, P., Zuccaro, S.M., Cherubino, P., Vellucci, R. and Fornasari, D. (2012) Adverse Effects Associated with Non-Opioid and Opioid Treatment in Patients with Chronic Pain. *Clinical Drug Investigation*, **32**, 53-63.
https://doi.org/10.2165/11630080-000000000-00000

[75] Tucker, A., Wang, Z., Rotalinti, Y. and Myles, P. (2020) Generating High-Fidelity Synthetic Patient Data for Assessing Machine Learning Healthcare Software. *npj Digital Medicine*, **3**, Article No. 147. https://doi.org/10.1038/s41746-020-00353-9

[76] El Emam, K., Mosquera, L. and Hoptroff, R. (2020) Practical Synthetic Data Generation: Balancing Privacy and the Broad Availability of Data. O'Reilly Media.

[77] Paul, A.K., Smith, C.M., Rahmatullah, M., Nissapatorn, V., Wilairatana, P., Spetea, M., *et al.* (2021) Opioid Analgesia and Opioid-Induced Adverse Effects: A Review. *Pharmaceuticals*, **14**, Article 1091. https://doi.org/10.3390/ph14111091

[78] Shi, Y. and Wu, W. (2023) Multimodal Non-Invasive Non-Pharmacological Therapies for Chronic Pain: Mechanisms and Progress. *BMC Medicine*, **21**, Article No. 372. https://doi.org/10.1186/s12916-023-03076-2

[79] Sud, A., Buchman, D.Z., Furlan, A.D., Selby, P., Spithoff, S.M. and Upshur, R.E.G. (2022) Chronic Pain and Opioid Prescribing: Three Ways for Navigating Complexity at the Clinical-Population Health Interface. *American Journal of Public Health*, **112**, S56-S65. https://doi.org/10.2105/ajph.2021.306500

Abbreviations

GABA	Gamma-Aminobutyric Acid
SHAP	SHapley Additive exPlanations
RF	Random Forest
GB	Gradient Boosting
AUC	Area Under the Curve
AI	Artificial Intelligence
ML	Machine Learning
ROC	Receiver Operating Characteristic
PCA	Principal Component Analysis
MSE	Mean Squared Error
TPR	True Positive Rate
FPR	False Positive Rate