Interpreting the amnesic effect of benzodiazepines using machine learning models

Grace Tan
Monta Vista High School
Cupertino, California
gracexintan@gmail.com

***Abstract*—With the recent increase in the prescription of benzodiazepines, memory impairment becomes a crucial component to be evaluated in weighing the risks and benefits of these anti-anxiety medicines. Memory recall, however, varies greatly depending on a person's unique circumstances, making it difficult to predict the amnesic effect of anti-anxiety medicine on a particular subject using traditional methods of study. Researchers have recently implemented machine learning in their studies of the adverse effects of drugs, which can greatly enhance the accessibility and versatility of healthcare. However, there is a deficit of these machine learning approaches in the research of benzodiazepines, which have been controversial in their alleged side effects due to faulty claims and inconclusive studies. In this paper, the potential of machine learning applications in the research of benzodiazepines is demonstrated through three algorithms: linear regression, decision tree, and gradient boosting. The three models evaluated the age, dosage level, type of drug administered, and memory priming of 198 drugged islanders to estimate the percent difference in memory recall a given subject should expect to experience after the administration of anti-anxiety medicine. The three models were then compared using 10-fold cross validation, and the gradient boosting model was determined to consistently yield the most accurate results out of the three. This work is a proposition for how machine learning can be employed in estimating the adverse effects on memory of benzodiazepines, but also to present the potential of machine learning applications to accelerate and augment prescription processing in general.**

I. Introduction

For over fifty years, benzodiazepines (BDZs) have been commonly prescribed to treat insomnia, anxiety, and seizures, among other clinical uses. BDZs are highly versatile and effective, quickly becoming the world's most prescribed medications just years after they entered the market [3]. Many studies have testified to the efficacy of BDZs over antidepressants for their rapid onset of action, in addition to their application in the treatment of convulsive disorders and muscle spasms. However, BDZs don't come without their own risks, including dependence and cognitive impairment. Like all addictive drugs, BDZs induce heightened dopamine levels in the mesolimbic dopamine system (or rewards system), potentially leading to chronic use and relapse [11]. Furthermore, long-term BDZ use can increase susceptibility to anterograde amnesia, motor incoordination, and ataxia. Anterograde amnesia, in which individuals experience memory loss of events occurring after the administration of the drug, is a heavily debated side effect of BDZs among researchers. In one study, Ballenger et al. [2] concluded that short-term use of BDZs obstructs the formation of new memories, and can debilitate long-term memory. On the other hand, Roth et al. [10] employed a double-blind procedure that presented subjects with four memory tasks to perform after being administered either an active drug or a placebo, proposing that the amnesic effect associated with BDZs is instead due to the retrograde effect of sleep on memory. The influence of BDZs on memory still remains largely inconclusive.

To investigate the side effects of drugs on cognitive functions, machine learning models have been adopted to make predictions about the adverse effects of drugs. For instance, Bresso et al. [5] used relational machine learning to better understand drug side-effect profiles (SEPs) to advance the drug development process. In this study, decision trees and induced logic programming were employed to examine the drug annotations from SIDER [9] and DrugBank [8] databases. By integrating information extracted from the SEPs in conjunction with relational learning methods, they could predict the associations between new drugs and SEPs to suggest, for instance, the amnesic effect of benzodiazepines. Furthermore, in a similar study of the physical and psychological effects of opioids on patients, Dong et al. [6] presented a different machine learning approach to examine the susceptibility of patients prescribed with opioids to opioid use disorder. Opioid use disorder (OUD) is a chronic relapsing disorder that can result from previous or current use of substances, including BDZs, inducing symptoms like withdrawal and dependence, in addition to insomnia, memory loss, and anxiety. In Dong's study, long short-term memory models were applied to predict OUD risk based on electronic health records of patients from Cerner's Health Facts database. The model could accurately predict a patient's susceptibility to OUD based on their electronic health records, presenting a method to reinforce clinical diagnosis and intervention of OUD. Both Bresso et al. and Dong et al.'s applications of machine learning to forecast the adverse effects of drugs on patients can be similarly applied to the investigation of BDZs and memory loss.

In previous studies of the consequences of long-term BDZ use on memory, results have differed greatly from study to study, some affirming the amnesic effect of BDZs and others suggesting the influence of other factors. What these

studies fail to account for is the influence of the physical and psychological differences of the test subjects on their response to the drug and their memory capacity. The application of machine learning models, however, is able to factor in the distinct characteristics of each subject and predict the amnesic effect that the individual will experience. Furthermore, the application of machine learning is very limited in studying BDZs, and existing research does not address their amnesic effect, which is a highly overlooked yet greatly detrimental consequence. In this paper, we employ three machine learning models to deliberate how BDZs affect the memory of novel islanders.

II. Methods

A. Source Data

The source data used in this work is from Kaggle, under the title "Memory Test on Drugged Islanders Data" [1]. The experiment was conducted in 2019 by Steve Ahn under the supervision of Mr. Almohalwas at UCLA. It is inspired by Breggin's paper on the adverse effects of BDZs on cognition [4].

The study's participants consist of 198 novel islanders of all genders and of ages ranging from 25 to 82 years old to guarantee a fully developed pre-frontal cortex, which is responsible for higher-level cognition and memory recall. Each islander was administered one of three test articles at one of three dosage levels. In order to mimic addition, they were tested every day for a week on their performance on a memory test (measured in seconds taken to complete the test) before drug administration and after addiction was achieved.

The three test articles in the study were Alprazolam, Triazolam, and a sugar tablet, which functioned as the placebo. Alprazolam is a long-acting drug, with an elimination half-life of around 11 hours, while Triazolam has a rapid onset, with an elimination half-life of around 1.5 to 5.5 hours [7]. In this experiment in particular, Xanax (alprazolam) was administered to 67 participants, Halcion (triazolam) to 65, and a sugar tablet to 66 participants. Within each group, subjects were divided into three dosage levels: Dosage 1, 2, or 3. Dosages were labeled 1-3 to indicate low dosage, medium dosage, and high dosage (over the recommended daily intake), respectively. The Xanax was administered in 1 mg, 3 mg, or 5 mg dosages, and the Halcion in 0.25 mg, 0.5 mg, or 0.75 mg dosages. Subjects in the sugar tablet group took either one, two, or three tablets. To ensure validity, the number of subjects in each dosage group followed a 1:1 ratio. Additionally, half of the subjects in each group were primed with happy memories and the other half with sad memories ten minutes prior to the memory test to assess how memory recall may be influenced by recent memories.

B. Preprocessing

Before splitting into training and test sets, the data needed to be cleaned up and standardized in order to set all the features to a common scale. First, irrelevant features, including the first name and last name of the islanders, were removed from the dataset. The percent difference in memory score before and after the administration of the drug was assigned to be our label, and the age, dosage, memory score before taking the drug, and the priming of either a happy or sad memory were the selected features. To convert categorical into numerical variables, the data were encoded using the one-hot encoding method. We also decided to eliminate the placebo data from the dataset because the correlation between variables was relatively weak within the placebo group, especially for our label, which showed little relationship with any of the features (as shown in Fig. 1). On the other hand, Fig. 2 depicts a positive correlation between dosage and memory score difference within the active drug group.

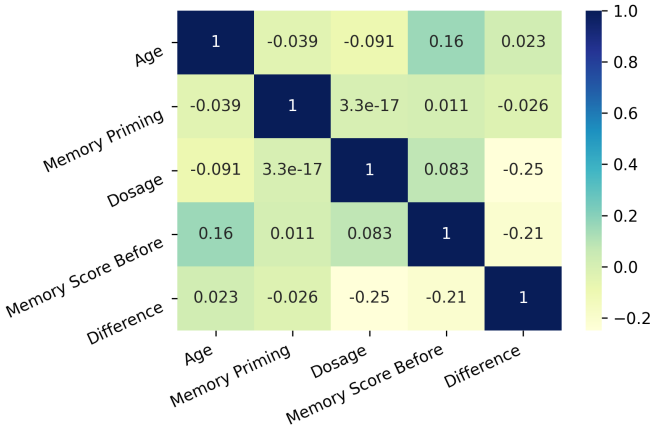

Fig. 1. Correlation heatmap for the placebo group. There is no significant correlation between the difference in memory recall and any of the other variables for the placebo group.

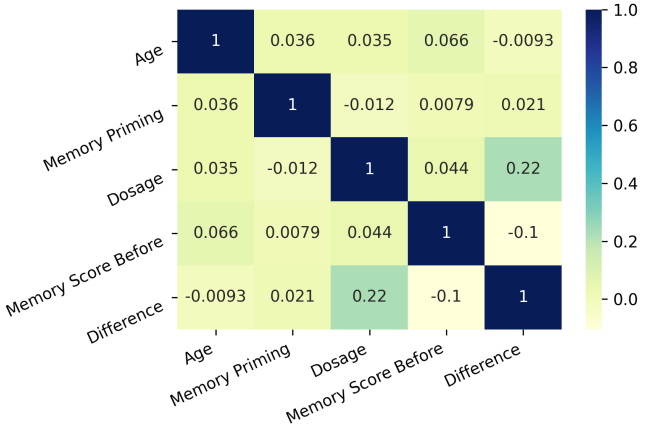

Fig. 2. Correlation heatmap for the anti-anxiety drug group. The correlation between most variables is negligible, besides the positive relationship between dosage and memory score difference.

In addition to feature selection and encoding, the features were standardized using StandardScaler, in which features are scaled individually for each feature, to ensure a mean value of 0 in each feature and center the values around 0. Once the

data was preprocessed, we split the data into training and test sets, with eighty percent of it assigned to training and twenty for testing.

C. Algorithms

1) Linear Regression: Linear regression is a supervised machine learning model that predicts the dependent variable (the label), based on the given independent variables (features) by identifying the best fit linear relationship between the input and output. In this study, multiple linear regression was used since our data contained multiple features to be considered. The linear regression model in this work was implemented using the Scikit-learn library using the default parameters.

2) Decision Tree: Decision tree learning is a supervised machine learning technique that predicts values based on a sequence of decision rules. The decision tree algorithm applied here was also done using the Scikit-learn library. To achieve an optimal model with minimal error, we employed GridSearch to tune the parameters. The parameters that were changed were *max_depth* = 4, *min_samples_leaf* = 4, and *splitter* = *"random"*, and the rest were set to their default values.

3) Gradient Boosting: Gradient boosting is a machine learning method that builds an additive model that combines decision trees (weaker prediction models) to create a stronger prediction model in a step-wise manner similar to other boosting techniques in order to predict the dependent variable. However, as opposed to other boosting methods, gradient boosting employs the optimization of a differentiable loss function in its algorithm. The gradient boosting model used here was written with the Scikit-learn library. Hyperparameter tuning was also applied to this model in order to reduce the algorithm's error, with the altered parameters being *learning_rate* = 0.007, *max_depth* = 3, *n_estimators* = 400, and *subsample* = 0.2, with all other parameters their remaining default values.

D. Model Evaluation

All three models were evaluated using 10-fold cross validation. To identify the optimal algorithm for predicting the effect of BDZs on memory recall, we compared the root mean square error (RMSE) of each of the models, which is a measure of how well a regression line fits the data.

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(Predicted - Actual)^2}{n}} \quad (1)$$

III. Results and Discussion

Upon comparing the performance of the three models, we found that gradient boosting consistently yielded a lower RMSE of approximately 15.331 from the 10-fold cross validation test, relative to the decision tree and linear regression models. The decision tree model outperformed the linear regression model, yielding errors of 16.097 and 17.699, respectively. Evaluating the RMSE of the three models reveals that the gradient boosting algorithm predicted values with the least amount of error and was, therefore, the most accurate of the three.

Fig. 3, which visualizes the comparison between the measured values and the values predicted by the models, also depicts the differences in the regression lines for each model. Gradient boosting has the closest to a perfect correlation between the measured and its predicted values out of the three, followed by the decision tree and then linear regression, suggesting that the percent difference predicted by the gradient boosting model produced results closest to the actual measured values. Furthermore, the regression lines for all three models show a positive correlation between the actual and predicted values, indicating that the predicted values are reasonably close to the actual values in all models. Additionally, from the confidence interval (indicated by the shaded areas around each regression line), the predicted values tend to deviate from the measured values as the percent difference diverges from a measured value of approximately 10 percent, which is where the confidence interval seems to be the smallest. Among the three models, the confidence intervals seemed similar, though the decision tree seemed to produce the largest interval of the three, suggesting that there is more variance in its predicted values as compared to the gradient boosting and linear regression models. Thus, the gradient boosting algorithm proved to be the most effective because it produces the least amount of error and predicts the percent difference in memory recall most accurately out of the three models.

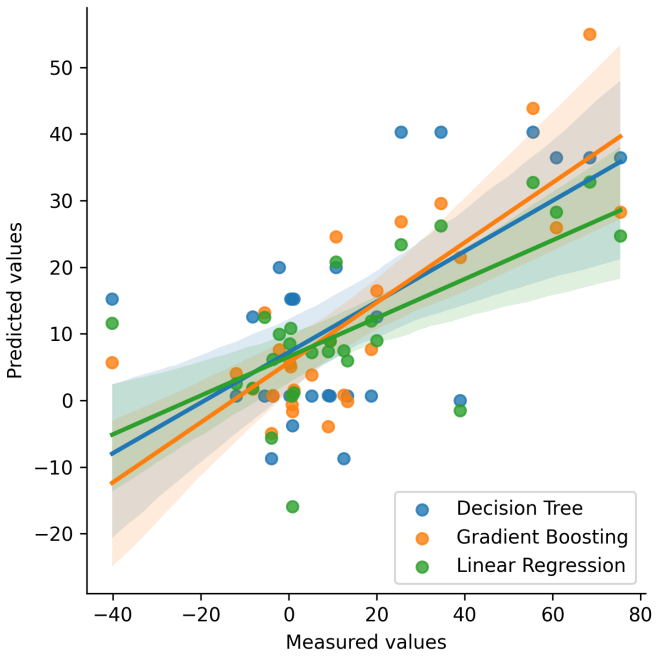

Fig. 3. This plot compares the measured percent difference in memory score from the test set with the percent difference forecasted by each of the three models. The regression lines, as well as a 95% confidence interval (depicted by the shaded regions) for each model, are also depicted in the plot.

The results of our study suggest a promising method of anticipating the amnesic effect that a patient will experience from taking BDZs while taking into account other factors that may influence their memory recall. One main reason why stud-

ies about BDZs produce contradicting results is that memory recall can be affected by innumerable factors, which is difficult to account for with traditional experimental practices. The models presented in this study, on the other hand, demonstrate their ability to predict amnesic effect with considerable accuracy and efficiency. As shown in the correlation plot for the active drug group (Fig. 2), a multitude of factors contributed to the islander's difference in memory recall, with some features having a greater influence than others. Going forward, more accurate predictions can be made with the consideration of additional factors (e.g. sleeping habits and physical fitness) using similar methods as the ones presented in this study.

Using a machine learning approach to predict the decrease in one's memory can be an efficient tool in prescription processing, a procedure that evaluates the risks and side effects of a prescription that requires a precise filing process. Depending on the drug, this process can be lengthy and tedious when done manually and requires specialized knowledge to properly inform the patient about their prescription. And while machine learning can not replace this traditional method entirely, it can certainly reinforce it by accelerating the process and acting as verification to mitigate the possibility of inaccuracies that come with processing prescriptions manually.

IV. Conclusion

Our study proposes three machine learning approaches for predicting the amnesic effect of BDZs on an individual. External factors including age and drug dosage are also evaluated in the prediction for their potential influence on a subject's change in memory. For a dataset consisting of 198 novel islanders, feature selection and one-hot encoding were applied in order to focus on our assessment of memory impairment due to benzodiazepines. From there, the data was standardized and split into testing and training sets. Three machine learning models, namely decision trees, gradient boosting trees, and linear regression, were constructed to make predictions on the percent difference in the memory score of subjects before and after the administration of the BDZs. Using 10-fold cross validation, it was concluded that the gradient boosting algorithm had the narrowest confidence interval and least error out of the three models.

With the models presented in this paper, the magnitude of memory impairment that an individual can expect to experience after having taken BDZs can be predicted with considerable accuracy. Further experimentation and advancement could potentially allow for the application of machine learning techniques in measuring the side effects of prescription drugs, not only limited to anti-anxiety medicine. Not only would machine learning accelerate the prescription process, but it also has the potential to make healthcare more accessible and cost-efficient in the long term. In countries where healthcare is inaccessible due to lower income or a shortage of healthcare workers, machine learning can be a versatile and sustainable method for making medical diagnoses and prescriptions, as well as evaluating the risks and benefits of prescription drugs based on the patient's medical history. Furthermore, because machine learning is far less reliant on specialized knowledge, the adoption of artificial intelligence (AI) in prescription processing would reduce the demand for medical specialists, which can be a big step toward universal healthcare.

The methods presented in this paper are a proposition for how machine learning algorithms can be applied to the study of BDZs and memory impairment, but there certainly is more work to be done before they can become fully functional. For one, the dataset investigated in this study was somewhat limited in that it comprised the data of less than 200 subjects, and only 132 when the placebo group was taken out of consideration. Because of how limited our dataset was, our models are especially susceptible to overfitting. Going forward, we may consider combining multiple datasets to validate our results and produce a more accurate model. Additionally, there are plenty more variables that the dataset did not include that likely played a part in the difference in memory recall. Working with a more comprehensive dataset with more data points, as well as variables to be considered, will greatly enhance the accuracy of the models.

References

[1] Steve Ahn. *Memory test on drugged islanders data*. Aug. 2019. URL: https://www.kaggle.com/datasets/steveahn/memory-test-on-drugged-islanders-data.

[2] James C Ballenger. "Anxiety and depression: optimizing treatments". In: *Primary care companion to the Journal of clinical psychiatry* 2.3 (2000), p. 71.

[3] Richard Balon et al. *The rise and fall and rise of benzodiazepines: a return of the stigmatized and repressed*. 2020.

[4] Peter R. Breggin. "Analysis of Adverse Behavioral Effects of Benzodiazepines With a Discussion on Drawing Scientific Conclusions from the FDA's Spontaneous Reporting System". In: *The Journal of Mind and Behavior* 19.1 (1998), pp. 21–49. ISSN: 02710137. URL: http://www.jstor.org/stable/43854146 (visited on 08/11/2022).

[5] Emmanuel Bresso et al. "Integrative relational machine-learning for understanding drug side-effect profiles". In: *BMC bioinformatics* 14.1 (2013), pp. 1–11.

[6] Xinyu Dong et al. "Identifying risk of opioid use disorder for patients taking opioid medications with deep learning". In: *Journal of the American Medical Informatics Association* 28.8 (2021), pp. 1683–1693.

[7] Doyun Kim et al. "Use of triazolam and alprazolam as premedication for general anesthesia". In: *Korean Journal of Anesthesiology* 68.4 (2015), pp. 346–351.

[8] Craig Knox et al. "DrugBank 3.0: a comprehensive resource for 'omics' research on drugs". In: *Nucleic acids research* 39.suppl_1 (2010), pp. D1035–D1041.

[9] Michael Kuhn et al. "The SIDER database of drugs and side effects". In: *Nucleic acids research* 44.D1 (2016), pp. D1075–D1079.

[10] T Roth et al. "Benzodiazepines and memory." In: *British journal of clinical pharmacology* 18.S1 (1984), 45S–49S.

[11] Kelly R Tan, Uwe Rudolph, and Christian Lüscher. “Hooked on benzodiazepines: GABAA receptor subtypes and addiction”. In: *Trends in neurosciences* 34.4 (2011), pp. 188–197.