Predicting Severity of Adverse Reactions to SSRIs

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Executive Summary

Selective serotonin reuptake inhibitors (SSRIs) are a frequently prescribed class of antidepressants that have received a great deal of attention in the medical literature [1]. Adverse reactions for these medications is a particular area of focus, with possible side effects including but not limited to sexual dysfunction, weight gain, sleep and gastrointestinal disturbances, and increased suicidal ideation [1,2]. The relatively recent provision of open data from the Food and Drug Administration (FDA) on over a decade of reported adverse drug events allows a new opportunity to explore the relationship between adverse effects for individual SSRIs and a variety of patient characteristics such as age, weight, gender, and other drugs taken.

For our exploration, we selected all reported events in the FDA's Adverse Event Reporting System (FAERS) between Quarter 1 2010 and Quarter 4 2015 that featured any of the five most commonly represented SSRIs: sertraline, citalopram, escitalopram, fluoxetine, and paroxetine. Using patient age, sex, weight, the reporter's characterization of the SSRI (suspect for the adverse event, concomitant with the suspect drug, or interacting with the suspect drug), the number of SSRIs the patient was taking, and 50 other non-SSRI drugs most commonly featured in the dataset, we built two predictive models for each SSRI. The first model for each SSRI was a logistic LASSO regression predicting whether the event was classified as serious or not, and the second model was a multinomial LASSO regression predicting the level of severity of the event (death, hospitalization, life threatening, disabling, other, or some combination of these outcomes). We then evaluated our models by testing them on held-out test data, comparing their performance with naïve models that simply predicted the class with the greatest distribution, and examining ROC curves for the binary classifier and precision and recall statistics for the multinomial predictor.

Our multinomial models tended to feature better predictions as compared with the naïve models; although the AUC percentages for the binomial models ranged as high as 0.71, the models were comparable with the naïve models that simply predicted the most prevalent class. In a similar vein, even the stronger multinomial models failed to classify any observations for most of the categories with fewer observations. In summary, while the predictive power of our models is limited, we provide an important proof of concept that OpenFDA FAERS data provides a useful resource for examining drug adverse events. Future research can build upon the work here by examining some of the data we did not explore, such as text in the reaction records capturing descriptions of the adverse events.

Background

Approximately 10% of Americans take antidepressants [3], and some of the most common antidepressants currently in use are selective serotonin reuptake inhibitors (SSRIs). In 2012, at least 9 of the 200 most commonly prescribed medications in the United States fell into this class of drugs [4]. First made available in 1988 with the introduction of fluoxetine, SSRIs represented a significant improvement as compared with tricyclic antidepressants (TCAs), the previous leading class of drugs used to treat

depression [5]. As TCAs inhibit the reuptake of serotonin, norepinephrine, and dopamine for many receptor systems, regardless of whether or not they are related to depression, they are associated with problematic side effects that do not characterize the performance of SSRIs [5]. SSRIs offer comparable efficacy to TCAs and most studies indicate that no other classes of agents demonstrate better outcomes or lower remission rates than SSRIs for major depression [6]. SSRIs currently on the market include fluoxetine (Luvox), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro) [6].

Although side effects for SSRIs tend to be less problematic than those for TCAs, SSRIs are not without their own risks for undesired secondary effects. By decreasing the reuptake of serotonin by presynaptic cells [7], SSRIs can increase the availability of serotonin for interaction with serotonin receptors in the brain [6]. Thus, bodily functions on which serotonin has an effect can be negatively impacted by SSRI usage; these include sexual function, appetite, and sleep, and symptoms such as depression, nausea, and pain [6]. One particular area of concern with SSRIs has been their impact on suicidal ideations; while the use of SSRIs appears to result in an overall reduction in suicide rates, approximately 2 people out of 100 taking an SSRI will experience a suicide-related event, as opposed to 1 person out of 100 treated with a placebo [8].

SSRIs can also interact with other drugs to cause problematic outcomes for patients. Some SSRIs have the potential to inhibit cytochrome P450 enzymes, which are used by the body to metabolize certain medications [9,1]. This can lead to increased and potentially toxic drug concentrations in the body, which in turn can cause issues such as extreme fatigue, dizziness, and seizures [9,1]. When combined with nonsteroidal anti-inflammatory drugs (NSAIDs) without use of acid-suppressing agents, SSRIs can also increase the likelihood of upper gastrointestinal bleeds [1]. Finally, and perhaps most problematically, the combination of SSRIs with any drugs that affect serotonin (such as St. John's wort) or monoamine oxidase (such as monoamine oxidase inhibitors or MAOIs, which represent another class of antidepressants) can cause serotonin syndrome [1]. This "potentially life-threatening disorder" [5] is characterized by symptoms such as altered mental status, sweating, shivering, a lack of coordination, and involuntary twitching [5,1].

The relatively recent provision of openly accessible data from the Food and Drug Administration (FDA) allows a new opportunity to examine adverse effects associated with individual SSRIs and explore the relationship between patient characteristics and adverse effects for SSRIs with a large set of observations. OpenFDA is an initiative in the Office of Health Informatics at the FDA that provides access to comprehensive datasets around drugs, medical devices, and foods in the U.S.; data on adverse events associated with different medications are provided by the FDA Adverse Event Reporting System (FAERS). Each report in the FAERS database details an incident of an undesirable experience associated with use of a medical product in patients. Reports contain general information, patient information, list of medical products being used, and a list of patient reactions. Due to the voluntary nature of these reports, it is important to note that this dataset is not a comprehensive representation of all adverse events.

Objectives

Given a specific SSRI and a set of patient factors (age, weight, gender, other medications taken), we will predict:

- whether a patient's adverse reaction is likely to be classified as serious or not serious

- the classification of a patient's serious adverse reaction (e.g., require hospitalization, disabling, life-threatening, death, etc.), for those who are classified as having a serious reaction

Data

We investigated adverse events reported to the FDA for a six-year period from Quarter 1 of 2010 through Quarter 4 of 2015. The data is available for download in zipped JSON files through a web API; the data for our period of interest included 188 download files each ranging in size from several hundred megabytes to approximately 1.5 gigabytes [10]. Since the data is in JSON format, we used the "jsonlite" package in R to read in data and change JSON-formatted data into R data frames. Our data is heavily nested, making each download file very large even though the number of observations (patients) is relatively small (1 megabyte contains about 35 patient records). For example, explanatory variables such as drugs used and patient reaction are saved as JSON-formatted lists in the data frame. One patient can have a number of drugs and adverse reactions recorded in these nested lists.

In order to extract the adverse events involving SSRIs, we first explored a subset of the data (2014 Quarter 3). For each of the 13 most commonly prescribed SSRIs, we looked into each patient's drug records and counted the number of patients reported as having taken it. We identified the 5 most frequently occurring SSRIs in the subset and decided to focus all further analysis on the patients taking them. The 5 SSRIs we selected covered over 50% of the patients who were listed as taking SSRIs. Sertraline was the most prevalent, followed by citalopram, escitalopram, fluoxetine, and paroxetine. It is important to note that the presence of an SSRI does not mean it was the culprit of the adverse reaction. The suspected role of each drug listed was characterized by the event reporter.

In addition to the drug information, the adverse event reports indicated patient onset age, weight, and sex. Patient onset age required additional cleaning, as each age was recorded in one of 6 different units (i.e., decade, year, month, week, day, hour). We standardized age values by their respective age units and converted them to years. For these calculations, we assumed each of the following were equal to one year: 0.1 decades, 52 weeks, 365 days, and 8,760 hours. We considered all ages that were missing an age value, age unit, or both as NA.

Using the standardized age values, we discovered an anomaly in the distribution of patient onset ages (Figure 1). There is a drastic spike in the number of patients around age 0, deviating from the bell-shaped pattern in the rest of the data.

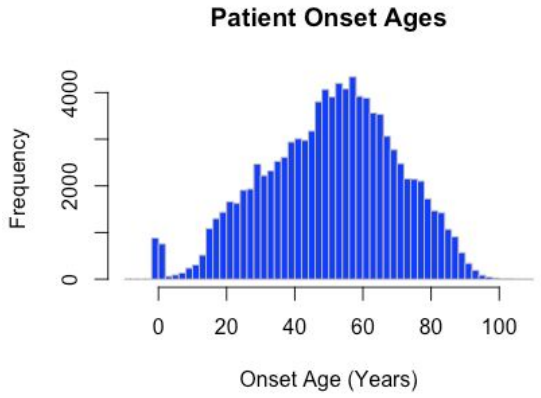

Figure 1: Frequency distribution of patient onset ages

We believe this is indicative of neonatal patients whose mothers were taking SSRIs during pregnancy. Use of SSRIs in the third-trimester has been shown to be linked to adverse reactions in the infant [11]. Since neonatal cases are fundamentally different from those of adults (primary users of SSRIs), we decided to exclude them from our analysis. Additionally, pediatric use of SSRIs is controversial, and some SSRIs are not FDA approved for treatment of patients under the age of 12 [12]. We used the greatest FDA-approved age as our cutoff, removing adverse events involving patients under age 12.

Next, we cleaned patient weight and gender. The 5th percentile in weight for 12 year old females is 30 kg, so we imposed a conservative lower cutoff of 25 kg. We also removed observations with an impossibly large patient weight, as greater than 250 kg. Finally, we removed patients with the gender indicated as 'Unknown'.

An investigation of the missingness of these three patient characteristic values did not reveal any patterns. Patient weight was the most sparse, followed by age and sex (Figure 2). The blue 'Problematic' category displays the values within each variable we deemed to be a threat to our data validity and removed, using the decision points and criteria outlined above (i.e. under age 12, weight above 250 kg and below 25 kg, 'Unknown' sex). All observations were categorized as serious (72%) or not serious (28%).

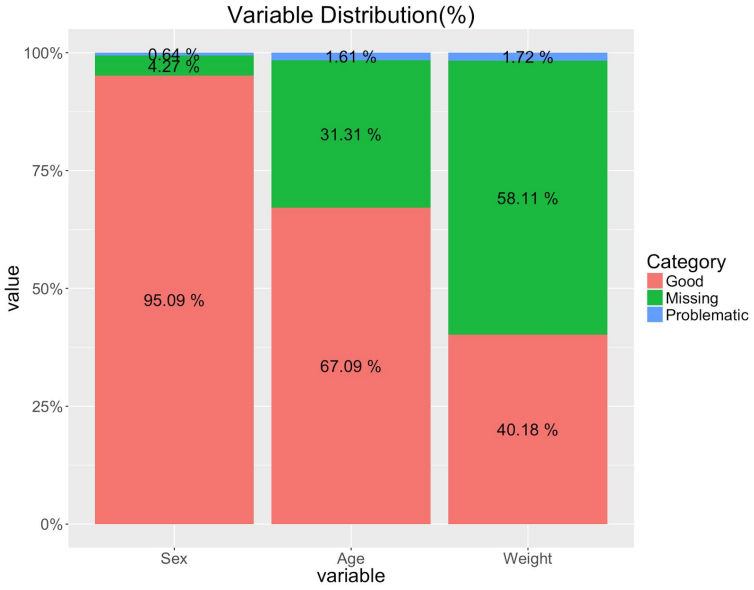

Figure 2: Variable missingness exploration

After removing the observations with problematic values in weight, sex, and age, we used multiple imputation to impute 10 complete datasets and pooled the results into a final complete dataset. We checked the validity of our imputed values by comparing the distribution of the imputed values to the observed values, and found the distributions to be similar (Figure 3). Our final dataset contained 140,720 observations.

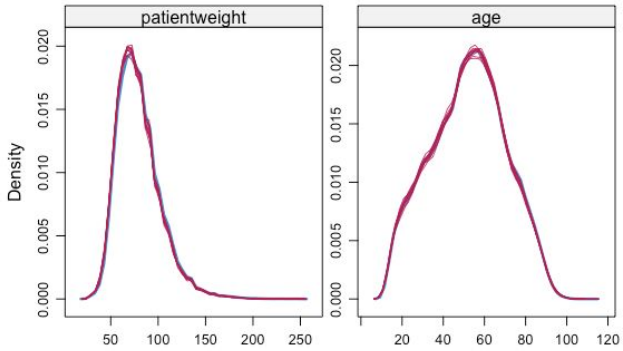

Figure 3: Distribution of imputed weight and age values in comparison with non-missing values

Methods

As we were interested in examining the adverse events for individual SSRIs, we subset the data by our 5 SSRIs of interest (escitalopram, citalopram, fluoxetine, paroxetine, sertraline). If a patient who experienced an adverse event was on multiple SSRIs, the observation for that patient was included in each pertinent SSRI data subset. We trained two logistic models for each SSRI, one to predict whether or not the adverse event was classified as serious, and another to predict the level of severity (or 'seriousness') for serious events. For the multiclass predictor, we examined 9 different levels for our response variable, including combinations of the various levels of severity (hospitalization, disabling, life threatening, death, other). Our choice of these combinations (e.g., hospitalization and life threatening) as separate levels was influenced by the fact that many patients were listed with multiple serious outcomes as well as the practical difficulty of introducing ordering comparisons between hospitalization, disabling, and life threatening classifications. One exception to this protocol was that we grouped together all patients who had death as an adverse event regardless of whether they had other serious outcomes as well, with the rationale that death can be considered a more serious event than the rest of the serious outcomes.

The predictor and response variables we used for our 10 models (one binary and one multinomial predictor for each of the 5 SSRIs) are featured in the table below. One set of predictors for each of our models were non-SSRI drugs patients were reported as taking. The total number of unique non-SSRI drgus was 3,035, so to minimize our predictor space, we selected only the 50 most common non-SSRI drugs in our dataset. The most commonly listed non-SSRI drugs ranged from a frequency of 14,805 records for quetiapine fumarate, an antipsychotic, to 3,772 records for potassium chloride, a potassium supplement [13,14]. Also of note, there are several clear problems with the OpenFDA drug list. For one, drug names are often misspelled (both "ibuprofen" and "ibupfrofen" [sic] are included in the 50 most common drugs). In addition, groups of similar drugs (e.g., aspirin, aspirin 81 mg, aspirin 325 mg, regular strength aspirin) frequently are listed in the place of the specific drug the patient was taking. Because of these issues, the list of the most commonly appearing drug names should be treated with caution.

Predictor	Type	Description
Patient Age	Numeric	Age of the patient when the event occurred

Patient Weight	Numeric	Patient weight in kilograms
Patient Sex	Categorical	1 = Male, 2 = Female
Drug Characterization	Categorical	1 = Suspect (reporter believes the SSRI caused the adverse event) 2 = Concomitant (the SSRI was taken in addition to the suspect drug, but the reporter does not believe the SSRI to be the cause of the adverse event or to have interacted with the suspect drug) 3 = Interacting (reporter believes the SSRI interacted with the suspect drug)
Number of SSRIs	Numeric	Count of other SSRIs the patient was taking (including escitalopram, citalopram, fluoxetine, paroxetine, sertraline)
Other Drugs (50)*	Categorical	0 = Not reported as taking the drug 1 = Reported as having taken the drug *A full list of the 50 drugs included as individual predictors is offered in the Appendix
Response	**Type**	**Description**
Serious	Binary	0 = The adverse event did not result in serious outcomes for the patient 1 = The adverse event resulted in serious outcomes for the patient
Seriousness	Categorical	death = Death d = Disabling dl = Disabling and Life Threatening h = Hospitalization hd = Hospitalization and Disabling hdl = Hospitalization, Disabling, and Life Threatening hl = Hospitalization and Life Threatening l = Life Threatening other = Other serious result

Figure 4: Predictor and response variables

To further minimize our predictor space and to highlight the most important regressors, we used LASSO for both our logistic and multinomial regression models. Based on the LASSO trace plots, we selected several log lambdas for training our models, then selected a 'final' log lambda for each model based on performance on held-out test data (approximately one-fifth of our data in each SSRI data set). To evaluate performance, we used ROC curves for our binary classifier model and precision and recall statistics for our multiclass model. In addition, we compared the raw prediction accuracy of each of our 10 models to the performance of naïve models that simply predicted the class of greatest frequency for every observation.

Results

None of our logistic regression models had a statistically significantly higher prediction accuracy than the corresponding naïve models (Figure 6). Since most of the reactions were serious, the naïve models that predicted all reactions to be serious performed well on the testing set. By observing raw accuracy and ROC curves alone, our best performing logistic model was on patients who took citalopram and our worst performing logistic model was on patients who took sertraline (Figure 7). All of our

multinomial regression models resulted in higher accuracies than the corresponding naïve models (Figure 8). Since there were nine serious subclasses -- with 'hospitalization' accounting for about 40% of all subclasses -- the naïve model performed poorly on the testing set. By observing the increase in accuracy performance of the multinomial regressions from the naïve models, the best performing model was on patients who took fluoxetine, and the worst performing model was on patients who took paroxetine. Interestingly, the model for fluoxetine had perfect precision on the disabling subclass but had very low recall for this subclass (Figure 9). Thus, one can confidently predict a patient on fluoxetine would be disabled if the model predicted it. The model predicted four cases of disabling (which were truly disabling), but missed the 95 other cases of disabling. The highest recall corresponded to the subclass death at a level of 0.528, which showed that over 50% of the relevant death subclass was identified by the model. For the model for patients taking paroxetine, precision was low for death and hospitalization/ disabling at 0.267 and 0.250 respectively. This meant that of the predicted outcome that a patient would die or be hospitalized and disabled, the accuracy of this prediction was only about 25% correct. Similarly the recall for death and hospitalization/disabling were very low, at 0.023 and 0.029 respectively, which showed that only about 2% of the relevant death and hospitalization/disabling subclasses were identified by the model.

In all of our multinomial models, and four out of five of our logistic models, weight had a significant negative coefficient, which matched our intuition that a heavier patient would be less likely to have a serious reaction to an SSRI. The logistic regression for sertraline found weight to be insignificant. In all 10 of our models, patient sex had a statistically significant negative coefficient. Though the results showed that females had a higher chance of having a serious adverse reaction, 68% of our dataset were females, which may explain the negative coefficient. Though age had a positive coefficient in most of our models, the coefficients were close to 0, which may indicate age not being a factor in predicting a serious adverse reaction. Characterization had a statistically significant negative coefficient which matches our intuition that if the reporter suspected that the drug caused an adverse event, the event would be serious. Interestingly the number of SSRIs had a positive coefficient for our logistical models, but a negative coefficient in most of our multinomial models, which suggests that as the number of SSRIs a patient takes increases, the probability of having a serious adverse effect increases, but given that the patient had a serious adverse reaction, the number of SSRIs a patient takes is negatively correlated with the outcome of the patient dying. Furthermore acetaminophen, furosemide, and diphenhydramine HCl had positive coefficients for all 10 of our models. Acetaminophen is a common pain reliever (such as Tylenol) and diphenhydramine HCl is an antihistamine used for allergic reactions. Furosemide is a diuretic that treats swelling and fluid build-up caused by heart failure, liver disease, or kidney disease. Further investigation is needed to conclude whether these drugs along with the SSRIs causes serious adverse reaction and death, or that taking these drugs is correlated to a confounding variable (such as patients who are already in very serious conditions need to take these drugs to improve their condition).

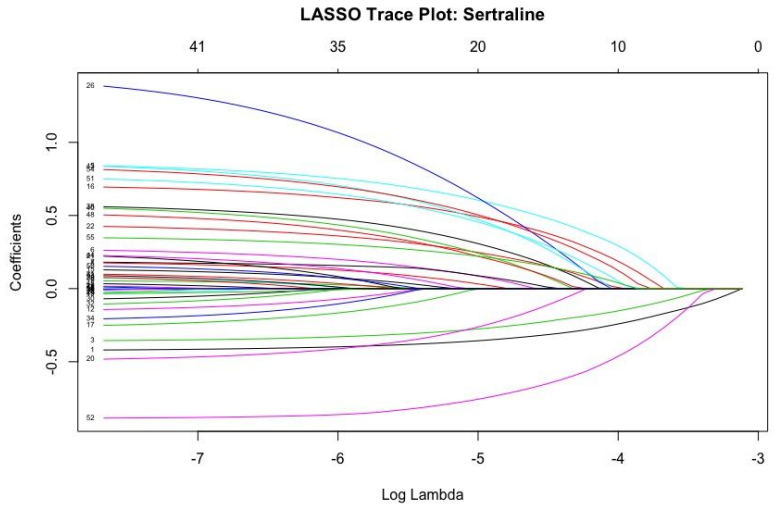

Figure 5: LASSO trace plot for sertraline binary logistic regression (response = serious/not serious)

SSRI	Log of Lambda	Raw Prediction Accuracy	Naive Model Performance	AUC
Citalopram	-6.5	0.769	0.773	0.72
Escitalopram	-5.5	0.698	0.695	0.68
Fluoxetine	-5	0.815	0.819	0.71
Paroxetine	-6.0	0.688	0.685	0.65
Sertraline	-5.5	0.6886	0.6863	0.62

Figure 6: Performance for binary logistic models for each SSRI (response = serious/not serious)

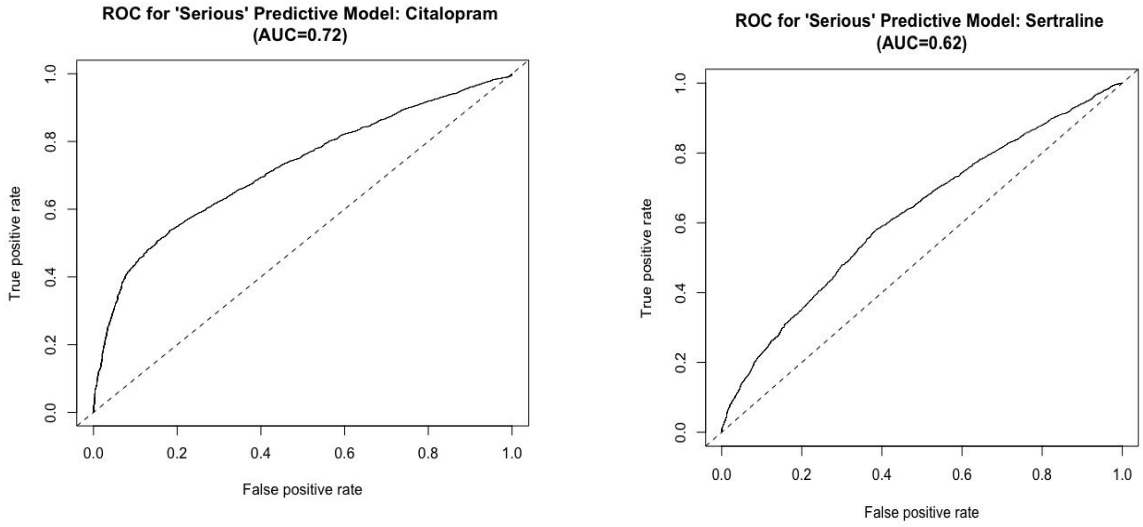

Figure 7: ROC Curves for 'best' and 'worst' binary predictor models
(response = serious/not serious)

SSRI	Log of Lambda	Raw Prediction Accuracy	Naive Model Performance
Citalopram	-7.3	0.434	0.357
Escitalopram	-5.5	0.456	0.406
Fluoxetine	-8	0.437	0.349
Paroxetine	-6.2	0.447	0.408
Sertraline	-6.5	0.4676	0.4131

Figure 8: Performance for multinomial logistic models for each SSRI
(response = levels of severity)

SSRI	Metric	DEATH	D	DL	H	HD	HL	L	OTHER
Citalopram	Precision	0.026	NaN	NaN	0.446	NaN	NaN	NaN	0.393
	Recall	NaN	0.161	NaN	0.621	NaN	NaN	NaN	0.362
Escitalopram	Precision	NaN	NaN	NaN	0.460	NaN	NaN	NaN	0.456
	Recall	NaN	NaN	NaN	0.659	NaN	NaN	NaN	0.505
Fluoxetine	Precision	0.471	1.000	NaN	0.428	0.0	0.0	NaN	0.421
	Recall	0.528	0.040	0.0	0.414	0.0	0.0	0.0	0.520
Paroxetine	Precision	0.267	NaN	NaN	0.424	0.250	NaN	NaN	0.468
	Recall	0.023	0.0	0.0	0.459	0.029	0.0	0.0	0.644
Sertraline	Precision	0.472	NaN	NaN	0.453	NaN	NaN	NaN	0.478
	Recall	0.069	0.0	0.0	0.525	0.0	0.0	0.0	0.670

Figure 9: Precision and recall statistics for multinomial logistic models for each SSRI (response = levels of severity)

Conclusions

We used linear statistical models to predict whether a patient's adverse reaction is likely be serious or not given a specific SSRI. We then took one step further and classified the seriousness of the adverse reaction. The logistic regression models have almost the same prediction accuracy as the naïve models while multinomial models performed slightly better than the naïve models. Due to high percentage of missingness in key variables (such as patient weight and age) and mistyped data entries (such as an adult patient weighing 20 kg), our final models might not accurately predict seriousness of a patient especially if the patient is younger than 12 years old or if the patient's weight is too high or too low. Moreover, high percentage of missingness in our data might cause the problem that the data we obtained fails to represent the true distribution of the population, which makes our models biased. Voluntary response bias also occurs in our data since the data was collected from self-reported adverse reaction responses. Once again, the sample we obtained is not representative of the population.

Data that represents the outcome of the reaction of a patient at the time of last observation was excluded in our analysis due to the problem of missingness and difficulty of extracting useful information from long texts. An extension of our analysis or a possible improvement would be including this data in future analysis. It would be useful to use text mining methodology and extract meaningful numeric indices from the texts. Reaction can be either used as predictors or it can help us evaluate our models.

In summary, although our analysis captured some patterns on how patient's physical characteristics and other non-SSRI drugs might be correlated with serious adverse reaction, further studies need to be done in order to determine whether a causal relationship exists between certain SSRIs and serious adverse reactions. Our analysis provided an insight on predicting adverse reactions and hopefully this paves a path for further research and the production of reliable results that will benefit patients who suffer from adverse reactions, possibly saving their lives.

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Appendix

50 Most Frequent 'Other' Drugs		
Acetaminophen	Lorazepam	Hydrochlorothiazide
Quetiapine Fumarate	Ethinyl Estradiol	Oxycodone Hydrochloride
Aspirin	Zolpidem Tartrate	Metformin
Alprazolam	Drospirenone	Diphenhydramine Citrate
Aspirin 81 mg	Diphenhydramine HCL	Risperidone
Aspirin 325 mg	Esomeprazole Magnesium	Lamotrigine
Regular Strength Aspirin	Pregabalin	Atenolol
Gabapentin	Esomeprazole Sodium	Ibuprofen 200 mg
Ibuprofen	Prednisone	Ibuprofen 200mg
Simvastatin	Albuterol Sulfate	Clopidogrel Bisulfate
Omeprazole	Metoprolol Tartrate	Methotrexate Sodium
Furosemide	Folic Acid	Amlodipine
Lisinopril	Bupropion Hydrochloride	Ibupfrofen
Clonazepam	Fluticasone Propionate	Methotrexate
Levothyroxine Sodium	Atorvastatin Calcium	Omeprazole Magnesium
Ergocalciferol	Metoprolol	Ondansetron Hydrochloride
Hydrocodone Bitartrate	Diazepam	

Logistic Regressions Coefficients for Serious vs. Non-Serious Adverse Reactions					
	Escitalopram	**Citalopram**	**Paroxetine**	**Sertraline**	**Fluoxetine**
Weight	**-0.0016**	**-0.003**	**-0.0011**	**.**	**-0.0028**
Sex	**-0.353**	**-0.449**	**-0.2603**	**-0.1902**	**-0.2791**
Age	**0.001**	**0.003**	**.**	**.**	**-0.001**
Characterization	**-1.105**	**-1.55**	**-0.9924**	**-0.2844**	**-1.0288**
# of SSRIs	**0.357**	**0.20428**	**0.0592**	**0.1013**	**0.2536**
ACETAMINOPHEN	**x**	**x**	**x**	**x**	**x**
FUROSEMIDE	**x**	**x**	**x**	**x**	**x**
DIPHENHYDRAMINE HCL	**x**	**x**	**x**	**x**	**x**

Multinomial Regressions Coefficients for Death Subclass Adverse Reaction					
	Escitalopram	Citalopram	Paroxetine	Sertraline	Fluoxetine
Weight	-0.003	-0.00352	-0.0028	-0.0016	-0.0039
Sex	-0.5	-0.44	-0.4803	-0.5778	-0.4563
Age	0.008	0.00002	0.0199	0.0175	0.0103
Characterization	-0.17808	-1.015	0.2062	-0.3685	-1.2508
# of SSRIs	0.06079	-0.15368		-0.0815	-0.0665
ACETAMINOPHEN	x	x	x	x	x
FUROSEMIDE	x	x	x	x	x
DIPHENHYDRAMINE HCL	x	x	x	x	x