

Machine Learning Applications for Identifying Adverse Events of Antidepressants Using FAERS Data Final Reports

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Abstract

Identifying adverse events (AEs) of antidepressants was challenging for researchers because the medical data format was inconsistent with the mix of text and numerical features, and medical knowledge is required. This study uses the FDA's Adverse Event Reporting System (FAERS) from 2018–2023 to apply machine learning (ML) models, including Logistic Regression (LR) and Support Vector Machines (SVM), both combined with Term Frequency-Inverse Document Frequency (TF-IDF), and Clinical-BERT to classify AEs into "System Organ Class" disorders, according to standardised terminologies of Medical Dictionary for Regulatory Activities (MedDRA). The effect of COVID-19 on antidepressant safety was also analysed using LDA Topic Modelling and Disproportion analysis (PRR and ROR ratios). The research resulted in some critical AE patterns for common antidepressants like SSRIs and atypical antidepressants.

Key results show that all the study ML models are effective for AE classification or future prediction, provided that access to MedDRA is limited. Clinical-BERT delivers the best performance when computing resources allow it. Potential risks requiring further investigation are identified through topic modelling, such as the keywords "haemorrhage" and "paraesthesia". It is also shown in this study how current ML models can improve AE categorisation, while future work is recommended to expand Disproportion analyses to broader datasets for a better understanding of antidepressant risk signals.

1 Introduction

Identification of adverse events for antidepressants is one of the common challenges for medical researchers and practitioners. With various and noble side effects of antidepressants that are untreated, it could lead to more significant problems for patients and the healthcare system. The reason behind these challenges is that data for these side effects are a mix of text-based notes, numerical inputs, and medical resources that require extensive processing time and medical knowledge to understand any trend or joint symptoms.

Given these challenges, applying machine learning to process this data becomes essential. The development of many ML models offers significant advantages and potential applications to understand the tremendous amount of clinical and reporting notes. FDA's Adverse Event Reporting System (FAERS) is one of the database systems developed by the U.S. Food and Drug Administration (FDA) to collect data on side effects or any relevant information about approved drugs. Using this database (FAERS) with machine learning advances could help tackle the challenge of understanding antidepressant-related adverse events for better safety medication.

This study aims to examine the FAERS database from 2018 to 2023 to train machine learning (ML) models, including traditional models (Logistics Regression, Support Vector Classifier) and deep learning (DL) model ("BERT: Pre-training of Deep Bidirectional Transformers") in classifying adverse events for antidepressants. In addition, the study considers the impact of COVID-19 on adverse events in antidepressants. Alternatively, it provides a comprehensive step-by-step approach for further researchers to handle the mess and inconsistency in the reported FAERS data.

2 Improvement and additional work

In the project's part A (previous), the author used the International Classification of Diseases (ICD) 11 as a dictionary to classify adverse events by applying the BERT-base uncased model. However, the terminology extracted from ICD 11 is challenging to understand for the public audience, and the model's performance is inconsistent and unable to be validated. The cleaned data remained inconsistent and required a massive amount of manual checking.

To improve the current approach in the project's part B, the author extended the processing steps for the final dataset by removing duplicated case reports with older versions and unnecessary features. The author also implemented MedDRA as an updated dictionary to match the symptoms in FAERS to the standard system organ class disorders in MedDRA after confirmation the recorded "preferred terms" (pt) in FAERS use the same standard format of terminologies from MedDRA. Enhancing from the BERT-base uncased model, the author expanded their literature review with other ML models to classify the adverse event categories by using traditional models, including Logistic Regression (LR), Support Vector Machines (SVM), deep learning model of Clinical-BERT, and included validation steps for the classifier models.

Regarding additional work, to analyse the impact of COVID-19, the author also implemented topic modelling and disproportionality methods to analyse the difference between three periods: before COVID-19 (2018-2019), during COVID-19 (2020-2022), and 'assumed' after COVID-19 (2022-2023) to examine any significant alert or change of adverse

events of using antidepressants.

3 Background

Mental health disorders have impacted worldwide significantly, with 40% of Australians experiencing mental disorders, particularly 20% of Australians having depression symptoms during the COVID-19 pandemic [1]. Depression is the most popular and neglected mental disorder, with 280 million worldwide patients [2]. The common depression symptoms are persistent sadness and loss of interest in life for more than two weeks. With the severity of depression, it highlights the critical need to understand the safety of antidepressant treatments.

In 2015, FDA approved 79 medications for treating neurological disorders in 2015 for neuropsychiatry (depression, schizophrenia), neurotraumatic, and neurodegenerative disorders [3]. There are different terms for diagnosed depression, including major depression disorder, persistent depressive disorder, perinatal depression during pregnancy or after giving birth, seasonal affective disorder, and depression with symptoms of psychosis of delusions and hallucinations (psychotics) [4] [5].

Antidepressant drugs are also used to treat other medical disorders treatments, and vice versa [6]. There are 7 common antidepressant categories, including SSRIs - Selective Serotonin Reuptake Inhibitors, SNRIs - Serotonin and Norepinephrine Reuptake Inhibitors, Tricyclic and Tetracyclic Antidepressants, Atypical Antidepressants, MAOIs - Monoamine Oxidase Inhibitors, NMDA - N-methyl D-aspartate Antagonists, and Neuroactive Steroid Gamma-Aminobutyric Acid (GABA)-A Receptor Positive Modulators [7]. These medicines are used to control depression symptoms with caution of many side effects. The commonly reported adverse symptoms were dizziness, nausea, constipation, dry mouth and issues like seizures, abnormal bleeding, and liver failure with severe side effects [7].

With many approved medical drugs and devices, the FDA monitors and tracks these symptoms with adverse events (AEs) using the FDA Adverse Event Reporting System (FAERS). The reporting system collected data across countries quarterly from patient records, medical practitioners, and manufacturers [8]. Throughout the research of FDA drugs and FAERS for antidepressants [9], only a few numbers of research confirmed the association between antidepressant drugs and severe effects, including escitalopram [10] and quetiapine [11]. With the potential of more FDA-approved antidepressant drugs released since 2015 and the lack of current research, patients could experience side effects of antidepressants without any notice. Moreover, the increase by 25% of depressed-related symptoms during the COVID-19 pandemic should be aware [12]. The reasons for this could be a quarantine, social isolation, or lockdown since 2020 [13], patients with pre-existing depressed conditions that have no proper treatment due to limited access to the healthcare system [12], or from the new antidepressants with side effects have not been alerted.

To understand the actual risk of antidepressants with consideration of COVID-19 factor, the research objectives are established as below:

1. Understand the symptoms of depression and keywords for diagnosed indications;

2. Verify and expand the medicine list used for treating depression to ensure a comprehensive list of antidepressants and other drugs used for the same purpose;
3. Apply ML models to classify standardised AE categories to ease the challenges for medical practitioners of tremendous text-based medical data;
4. Analyse the association between antidepressants and AE categorises by using topic modelling and disproportionality analysis, considering the impact of COVID-19.

4 Methods

4.1 Data collection and cleaning process

As mentioned, the FAERS collected the data with AEs of all medication from manufacturers quarterly. The data collection includes the information below with the relationship as illustrated in Figure 1 under ASCII or SGML format:

1. An instruction for using FAERS data (README)
2. Patient's demographics (DEMO)
3. Drug information (DRUG)
4. Indications/diagnoses (INDI)
5. Reactions of AEs (REAC)
6. Patient outcome after AEs (OUTC)
7. Source of reported symptoms (RPSR)
8. Drug (therapy) start and end dates (THER)

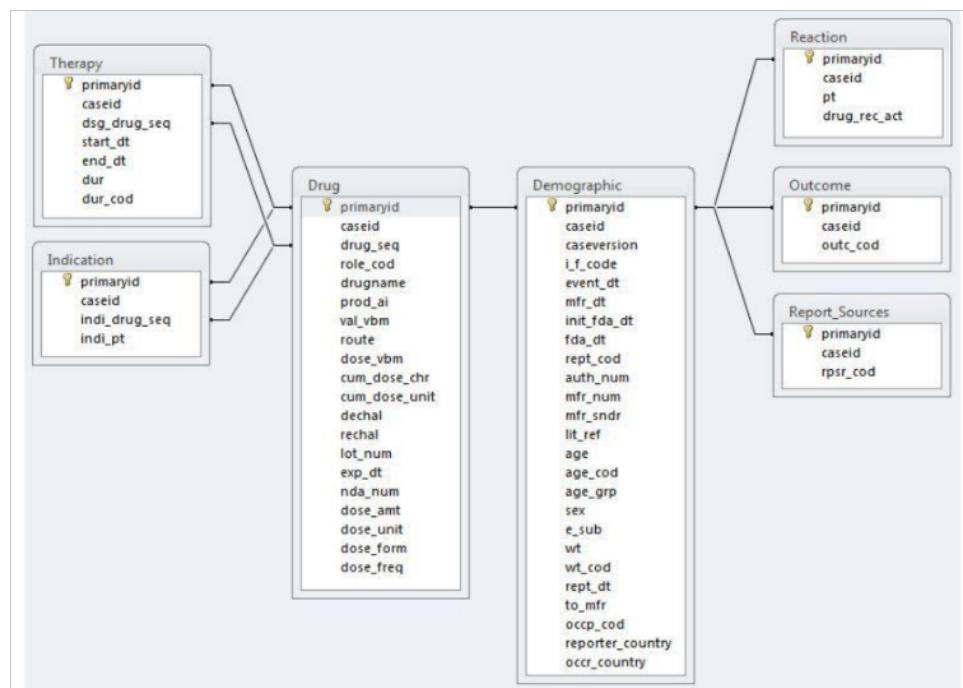


Figure 1: FAERS ASCII Entity Relationship Diagram (ERD) [8]

To handle the large entity of FAERS data, the author employed the collection process as illustrated in Figure 2 with the detailed steps of collection and cleaning process follow, as shown at [author's project code](#).

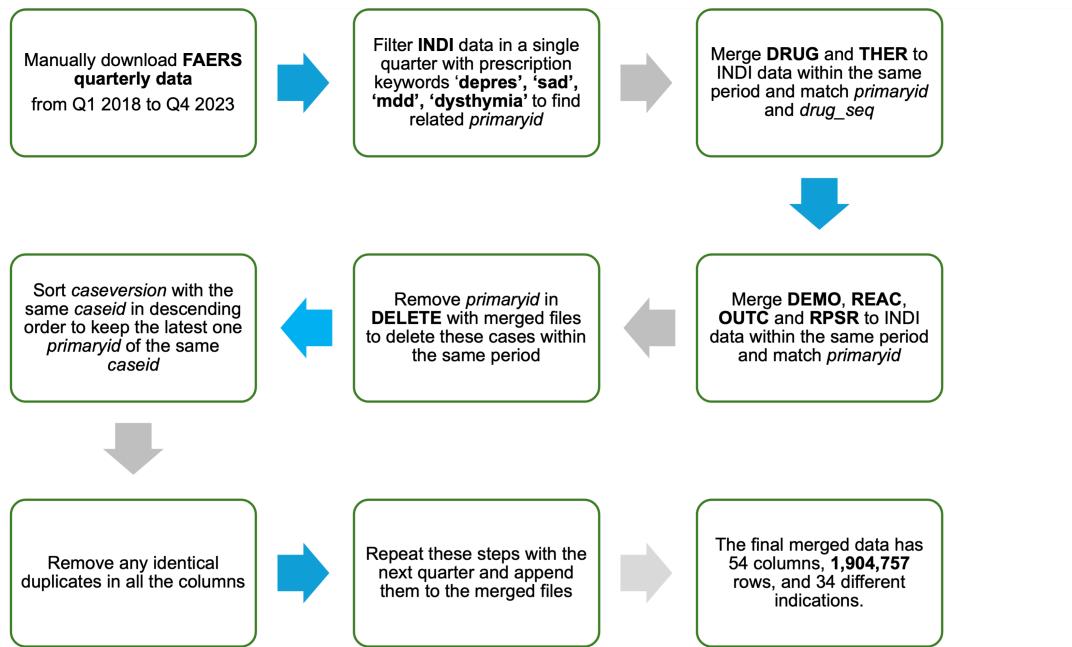


Figure 2: Data collection process of FAERS in terms of treating 'depression'

The quarterly FAERS data [8], from January 2018 (Q1 2018) to December 2023 (Q4 2023), was downloaded manually to analyse the impact of AEs. The year for downloading data was established based on the intention of 3 different periods of COVID-19: pre-COVID (2018-2019), during COVID (2020-2021), and post-COVID (2022-2023). Given the extensive data of FAERS with more than 10 million records and the computing limitations, the author used the prescription keywords of `indi_pt` of "depress", "sad", "mdd", "dysthymia" as indications for major depression disorder in INDI data of each quarter with to find related case reports. Then, we merged the DRUG and THER data in the same period with exact matching `primaryid` and `drug_seq`. Following, we merged the exact matching of `primaryid` to DEMO, REAC, OUTC, and RPSR data in the same period. We compared the DELETE cases to remove confidential reports. Data has repeated those steps each quarter and then appended them to the previous quarter. We also remove the older version of the same `caseid` and any identical duplications. The merged data had 1,904,757 case reports, 54 variables, and 34 indications of "depression".

With the complexity of interaction between drugs used in one prescription, we only focused on examining the antidepressants suspected of causing the AEs; we filtered out the data based on `role_cod` with "primary suspects". Moreover, FAERS data also included some legacy reports from the 1950s. To examine the impact of COVID-19, we only used the reports with event dates (`event_dt`) that happened from 2018 to 2023. Report dates, FDA-received report dates, and manufacturer-received report dates would impute the missing values of event dates. If there were no values to be imputed, those data were filtered out. Moreover, many diagnoses included in the data did not indicate depression, such as torsade de pointes or respiratory depression. To focus on understanding standard depressive disorders for further analysis, the author selected the focused symptoms,

including major depression, antidepressant therapy, depressed mood, mixed anxiety and depressive disorder, depressive symptom, perinatal depression, suicidal depression, adjustment disorder with depressed mood, persistent depressive disorder, schizo-affective disorder depressive type, agitated depression, adjustment disorder with mixed anxiety and depressed mood, depressive delusion, post-stroke depression, childhood depression, menopausal depression, antidepressant drug level, antidepressant discontinuation syndrome, and depression postoperative.

Following, we manually checked and mapped the medication with product active ingredient (PAI) used to treat antidepressants or relevant disorders, resulting in 267 unique PAI in 124 groups of medicines either to treat 'antidepressants' or 'others'. We utilised the WebMD database for the mapping process to understand the PAI groups and their indications [14]. Then, we only focused on examining the AEs in the consented patients above 12 years old. For the adverse events symptoms, there were lots of symptoms such as drug ineffective, drug interaction and off-label use were not classified as adverse events. We manually checked the top 1,000 frequent symptoms (about 90% of AEs) to create a list of non-adverse events to filter out.

Lastly, many variables were not considered in the dataset because of numerous missing values and duplicated information in other variables. These unnecessary variables were removed. The cleaned data was remained 118,577 records with variables of `primaryid`, `role_cod`, `prod_ai`, `indi_pt`, `event_dt`, `age`, `age_grp`, `gender`, `occr_country`, `pt` (AEs), `outc_cod`, `prod_ai_group`, `drug_cate`. The `prod_ai_group` and `drug_cate` ("antidepressants" or "others") variables were added by the author during the manual checking process. Then, the cleaned data was inputted to map the AE categories in the following steps.

4.2 Identification of adverse event categories

With 3,682 unique symptoms of adverse events in the cleaned dataset, classification is essential for further analysis. As instructed in FAERS [8], the reported preferred terms (pt) were based on the MedDRA database [15] [16]. The author used MedDRA version 27.1 to match the preferred terms to the "System Organ Class" (SOC) of disorder in MedDRA to utilise this available resource. We used exact matching keywords using Python programming language, matching 3,621 qualified terms (98%) and 61 unmatched terms (2%). Then, we created a list to manually check these unmatched symptoms to follow the SOC disorder in MedDRA by combining only 1, 2, or 3 words simultaneously. Finally, we transformed 3,682 unique AEs into 27 different SOC categories as in Figure 3.

After the exact matching with MedDRA, there were 27 categories of adverse events. However, some categories with minor reported symptoms (below 1% of the dataset), including "surgical and medical procedures", "social circumstances", "endocrine disorders", "pregnancy puerperium and perinatal conditions", "neoplasms benign malignant and unspecified incl cysts and polyps", "immune system disorders", "congenital familial and genetic disorders", "product issues". Therefore, we combined them as an "others" category, resulting in the final 20 categories, as shown in Figure 4.

```
# recheck ae_cate
cleaned_data['ae_cate'].value_counts()

[20]
... psychiatric disorders 27952
nervous system disorders 21113
general disorders and administration site conditions 13557
gastrointestinal disorders 10097
investigations 6316
skin and subcutaneous tissue disorders 4288
injury poisoning and procedural complications 3842
cardiac disorders 3678
musculoskeletal and connective tissue disorders 3592
metabolism and nutrition disorders 3448
respiratory thoracic and mediastinal disorders 3263
eye disorders 2540
vascular disorders 2363
hepatobiliary disorders 1662
reproductive system and breast disorders 1635
renal and urinary disorders 1585
infections and infestations 1560
blood and lymphatic system disorders 1322
ear and labyrinth disorders 1033
surgical and medical procedures 859
social circumstances 832
endocrine disorders 583
pregnancy puerperium and perinatal conditions 423
neoplasms benign malignant and unspecified incl cysts and polyps 406
immune system disorders 398
congenital familial and genetic disorders 189
product issues 41
Name: ae_cate, dtype: int64
```

Figure 3: Initial SOC categories after exact & manual matching keywords

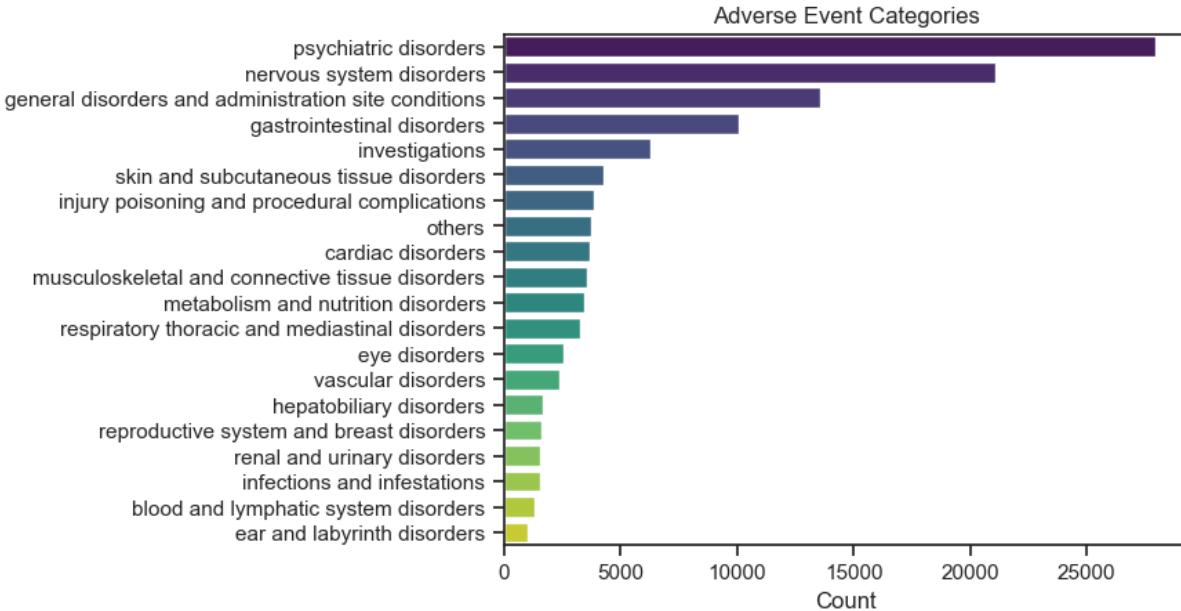


Figure 4: Adverse event categories of antidepressants 2018-2023

4.3 ML models for adverse events classification

Categorising AEs was straightforward and efficient with the MedDRA database [17]. However, access to MedDRA requires a subscription and lots of authentication and registration for the new database version. To be able for future prediction of the AE category of FAERS data without MedDRA, building an effective ML model in classifying the AEs from FAERS would be an excellent benefit for any researcher.

For classification with multi classes, there were two popular models: Logistic Regression

(LR) [18] [19], and Support Vector Machines or Classifier (SVM or SVC) [16] [18] [19]. Both of these models required a combination with TF-IDF (Term Frequency-Inverse Document Frequency), a method of mining text-based data. TF-IDF weighted words based on uniqueness, leading to relevance founded between words or categories. Moreover, TF-IDF could also extract 1, 2, or 3 words together by using the n-gram parameter and max-features of a maximum number of distinct terms [19]. A detailed explanation of applying TF-IDF in training models can be found in William Scott's blog on the Towards Data Science forum [20]. We also split the dataset into training (80%) and testing (20%) datasets. We also performed 5 k-fold cross-validation for the training dataset to ensure our models were not overfitting.

For LR and SVM models, combined with TF-IDF, the chosen parameter applied in these models were instructed as below:

1. **TF-IDF:** For 3,000 unique preferred terms in FAERS with 1-7 words of each term, we set a range of max-features of 5,000 words and n-gram from 1 to 2 words.
2. **LR:** With the medium-sized dataset of 150,000 records, we included an optimisation algorithm of "liblinear" to support L1 (lasso) and L2 (Ridge) regularisation to reduce overfitting and bias with $c=1$ (moderate level of regularisation).
3. **SVM:** With the mix of different types of features and medium-sized dataset, we used the base classifier of SVM - "LinearSVC" [19] with parameters of class weight to handle the imbalance in the data and with same $c=1$ as LR model. Furthermore, "LinearSVC" does not support the probability calculation, so we included CalibratedClassifierCV to calculate the probabilities for predictions [21].

The model performance was evaluated by 3 metrics: Accuracy, F1-score, and AUC score (Area Under the Curve). Accuracy is evaluated based on the number of (True Positives TP + True Negatives TN)/Total predictions [22]. F1-score is the harmonic mean of precision (positive prediction accuracy) and recall (ability to find all positive cases) [23]. AUC measures the probability of true and false positive rates. An AUC score of 1 indicates perfect classification, while 0.5 indicates random guessing [22].

Besides the LR and SVM classification models, we also implemented a deep learning model, Clinical-BERT, with the same approach as the BERT-Based and Uncased model. The Clinical-BERT was pre-trained or fine-tuned clinical text, such as electronic health records (EHRs) [24] [25]. In contrast, the BERT-Based and Uncased model pre-trained on a large corpus of general-domain text with English Wikipedia and BooksCorpus [26]. The model approach was two-way pre-trained unlabeled texts on both left and right context by joint conditioning in all layers. The Transformer encoder architecture was used to process each token (word) in the full context of all tokens before and after [27] as illustrated in Figure 5. Previous work of BERT-Based and Uncased model that is proven to effectively normalisation of biomedical and clinical entity [26]. However, from the author's previous work, the BERT-Based and Uncased model did not classify the AEs in the FAERS current dataset. Therefore, implementing Clinical-BERT is crucial to better enhance the model performance. In addition, to include the COVID-19 impact, we created a COVID text label for the Clinical-BERT training model. Then, we followed the steps from Keras, and Tensorflow [28] [29]. Based on the limitation of computing resources, the final tuned parameters for this model were reasonably selected, which could be found at [author's project code](#).

These ML models (Logistics Regression, SVM, and Clinical-BERT) ran on the author's laptop Macbook Pro (M1, no GPU, 16GB RAM) in the local respiratory.

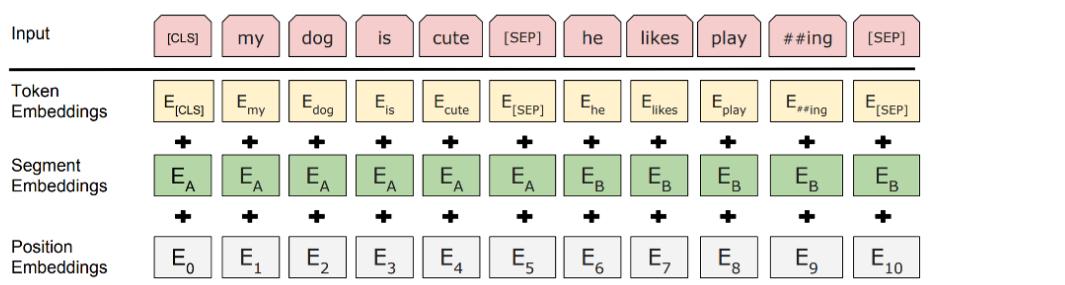


Figure 5: BERT input representation with the sum of the token embeddings and the position of segmentation embeddings [27]

4.4 Topic modelling method

Topic modelling is a Natural Language Processing (NLP) method for analysing common themes [30]. It helps to capture together words in similar contexts [31]. The common approach is Latent Dirichlet Allocation (LDA), which uses the generative model to posterior the probability of data (document). The topic is based on the distributions of word by topic and topic by document [31] [32]. An approach to applying the LDA topic modelling method can be found in Shashank Kapadia's blog on the Towards Data Science forum [33]. Based on this approach, we implemented an LDA model by manually inputting the number of topics (4 to 10). As a result, a 5-topic model provided the most meaningful topics. Then, we combined [Word Cloud generator](#) and pyLDAvis for visualisation [34].

In addition, we also included a Wordcloud visualisation of common words without the LDA model and divided it into 3 COVID periods to see their word distribution changes between these periods.

4.5 Quantitative analysis with disproportionality

Data mining disproportionality is a common approach to identify AE signals in reporting systems [35]. There were four traditional ratios for this analysis, and both calculated the "interesting ratio" association between the ratio of reporting AEs within one (target) drug and that of other drugs. Their calculation formulas are demonstrated below in Figure 6. With this limited scope of the study, we only evaluated 2 key ratios for this analysis, including the "Proportional Reporting Ratio" (PRR) and the "Reporting Odds Ratio" (ROR).

Measure of association	Formula	Probabilistic interpretation
RR (Reporting Ratio)	$\frac{w_{00} \times (w_{00} + w_{01} + w_{10} + w_{11})}{(w_{00} + w_{10}) \times (w_{00} + w_{01})}$	$\frac{pr(ae drug)}{pr(ae)}$
PRR (Proportional Reporting Ratio)	$\frac{w_{00}}{(w_{00} + w_{01})}$	$\frac{pr(ae drug)}{pr(ae drug)}$
ROR (Reporting Odds Ratio)	$\frac{w_{00}/w_{10}}{w_{01}/w_{11}}$	$\frac{pr(ae drug)/pr(-ae drug)}{pr(ae -drug)/pr(-ae drug)}$
IC (Information Component)	$\log_2 \frac{w_{00} \times (w_{00} + w_{01} + w_{10} + w_{11})}{(w_{00} + w_{10}) \times (w_{00} + w_{01})}$	$\log_2 \frac{pr(ae drug)}{pr(ae)}$

Figure 6: Association calculation formula for 4 metrics of disproportionality analysis [35]

5 Results

5.1 Exploratory data analysis

With the final dataset of 118,577 reported AEs among 35,652 different cases or patients, each patient experienced an average of 3-4 AEs when using antidepressants. The patient demographic who reported the AEs was illustrated in Figure 26.

Within 20 categories of AEs, the top 5 that occurred the most AEs from 2018 to 2023 are "psychiatric disorders", "nervous system disorders", "general disorders and administration site conditions", "gastrointestinal disorders", and "investigations" (minor symptoms need further evaluation). We observed fluctuations in all the categories (Figure 7).

Overall, all the AEs decreased between 2018 and 2023, with a profound decrease in Q4 2020. There was no evidence of fewer depressed patients. Still, the lockdown of COVID-19 at the end of 2020 could have prevented the patients accessed the antidepressants, leading to fewer adverse events [36]. Similar trends were observed for the top 6 to 20 categories (Figures 23, 24, 25).

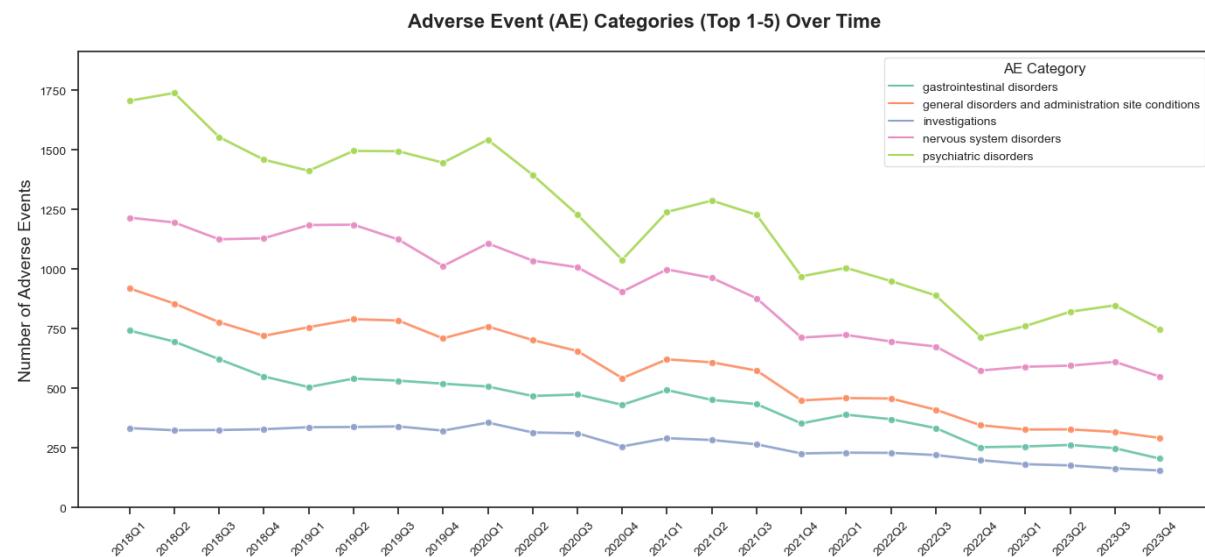


Figure 7: Top 5 adverse event categories of antidepressants 2018-2023

With the reported AEs (Figures 8 and 9), these medicine types caused the most reported adverse events:

1. "Selective Serotonin Reuptake Inhibitors (SSRI)" with product active ingredient (PAI) of sertraline (top 1) in Figure 9, fluoxetine (top 4), escitalopram (top 5), citalopram, vortioxetine, paroxetine;
2. "Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)" with PAI venlafaxine (top 2), duloxetine, desvenlafaxine;
3. "Atypical Antidepressants" with PAI of bupropion, quetiapine, aripiprazole (also used for antipsychotics), brexpiprazole;
4. "N-methyl D-aspartate (NMDA) Antagonist" with PAI of esketamine (top 3);
5. "Tricyclic and Tetracyclic Antidepressants" with PAI of mirtazapine, amitriptyline.

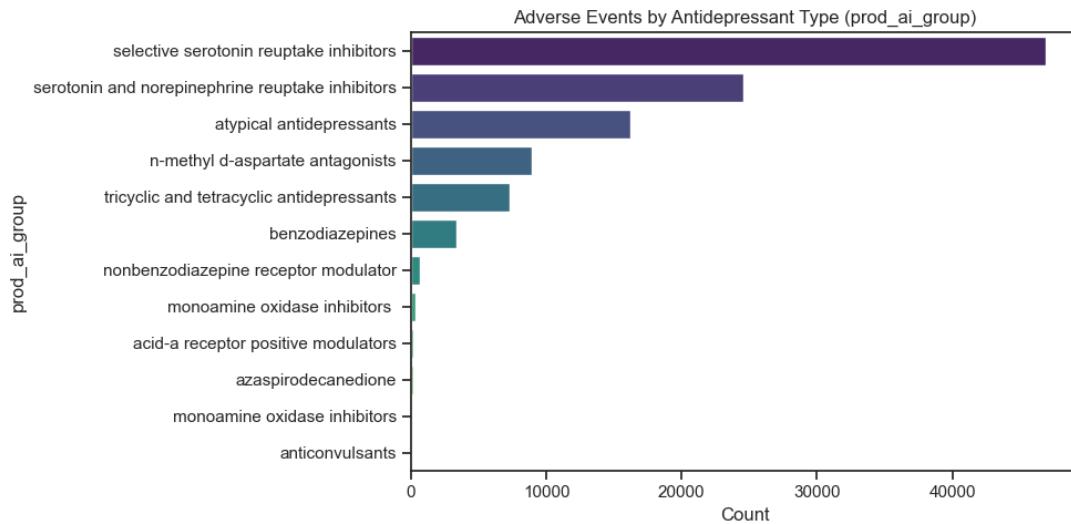


Figure 8: Number of adverse events related to antidepressants 2018-2023

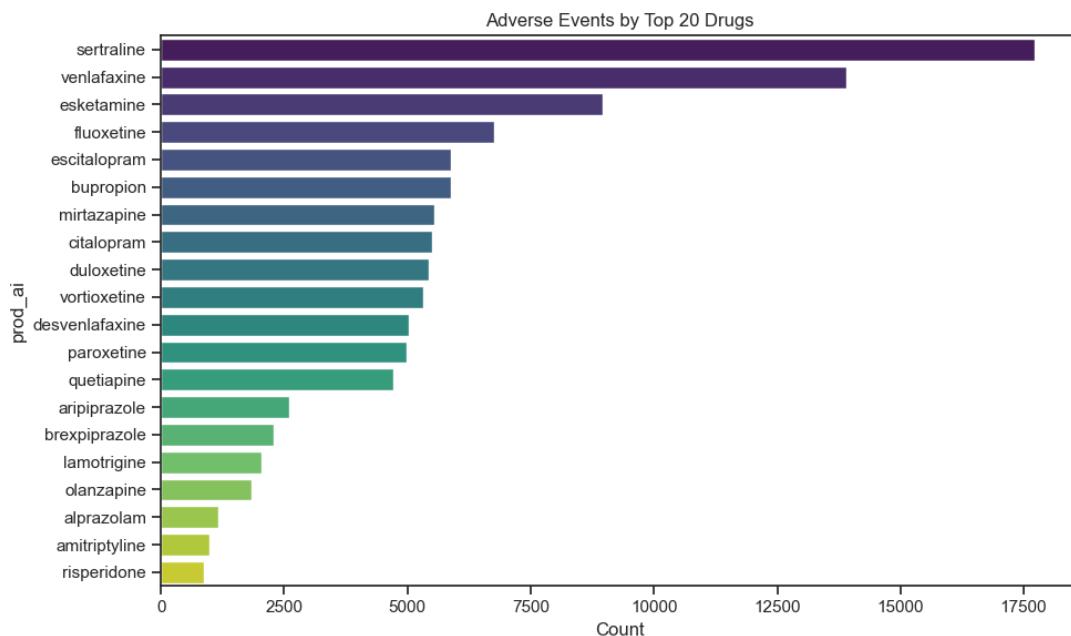


Figure 9: Number of adverse events by Product Active Ingredient

With the high proportion of reported symptoms from these antidepressants, the manufacturers should investigate more about these antidepressants. However, these reports could be from the reasons that these antidepressants were the most popular antidepressants prescribed by medical practitioners [37]. The most common reported symptoms (Figure 10) were nausea, suicidal ideation, anxiety, dizziness, depression, headache, insomnia, fatigue, vomiting, and tremor; aligned with FDA reports [7], noted that suicidal ideation, anxiety, and depression were also depressive symptoms.

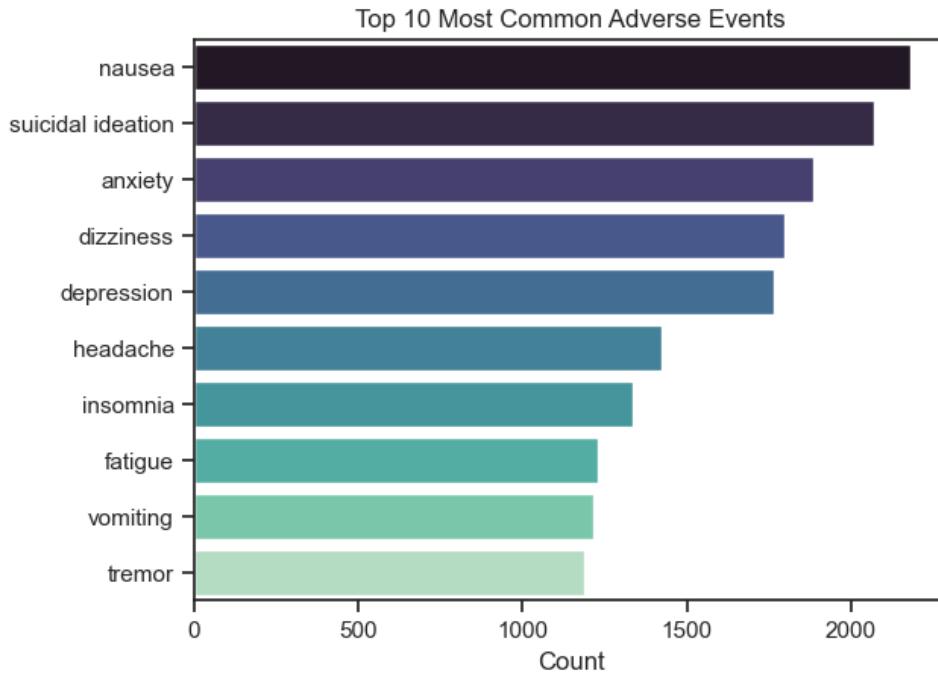


Figure 10: Number of adverse events by Symptoms

For the deeper layer in Figure 11, we observed that "psychiatric disorders" and "nervous system disorders" occurred in all the patients with any antidepressants. The reasons behind these categories might also include the symptoms of depression itself. "Gastrointestinal disorders" AEs should be noticed due to their occurrence among different types of antidepressants.

We also observed distributions of adverse events based on age and gender (Figures 12 and 13). Some AEs, such as "metabolism and nutrition disorders" and "renal and urinary disorders", occurred more in patients above 60 years old. These symptoms could belong to other disorders related to the elderly instead of antidepressants. Besides, females are more dominant to reported AEs in antidepressants with severity in "psychiatric disorders" and "nervous system disorders", which should be investigated in further research.

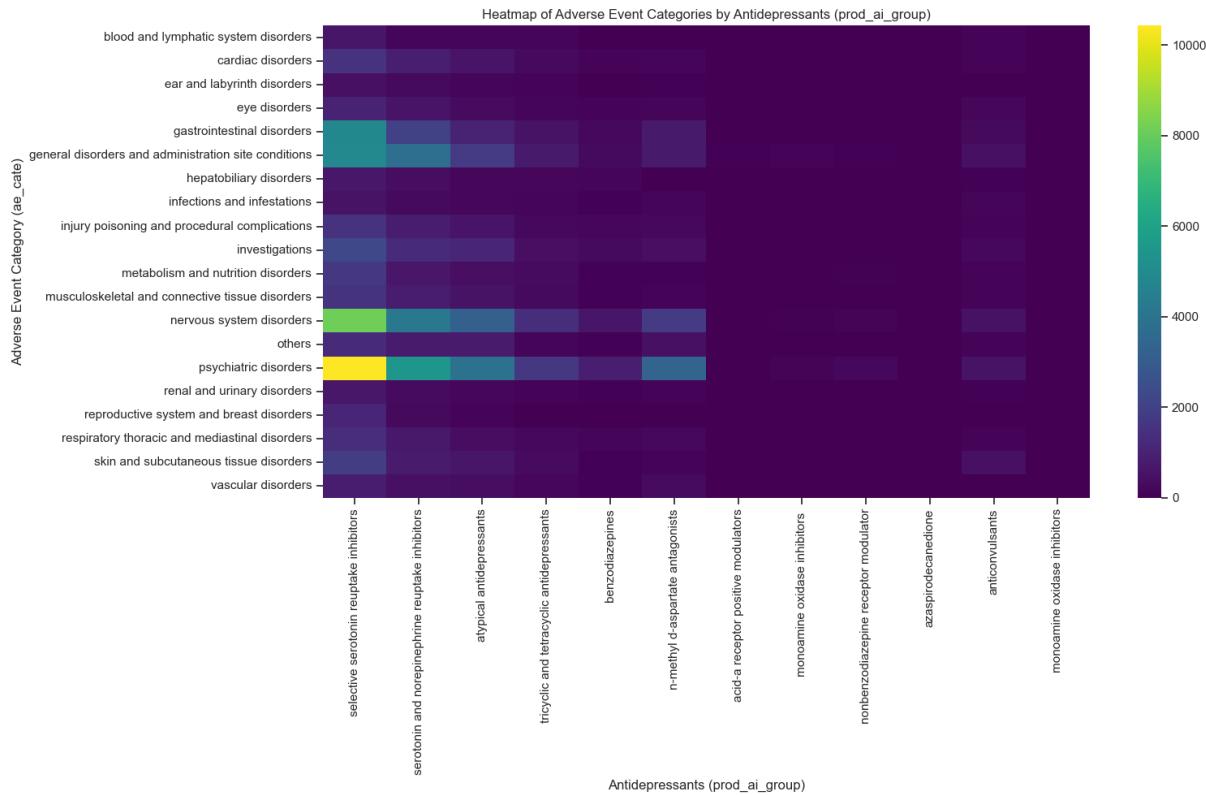


Figure 11: Heatmap of adverse events by antidepressants 2018-2023

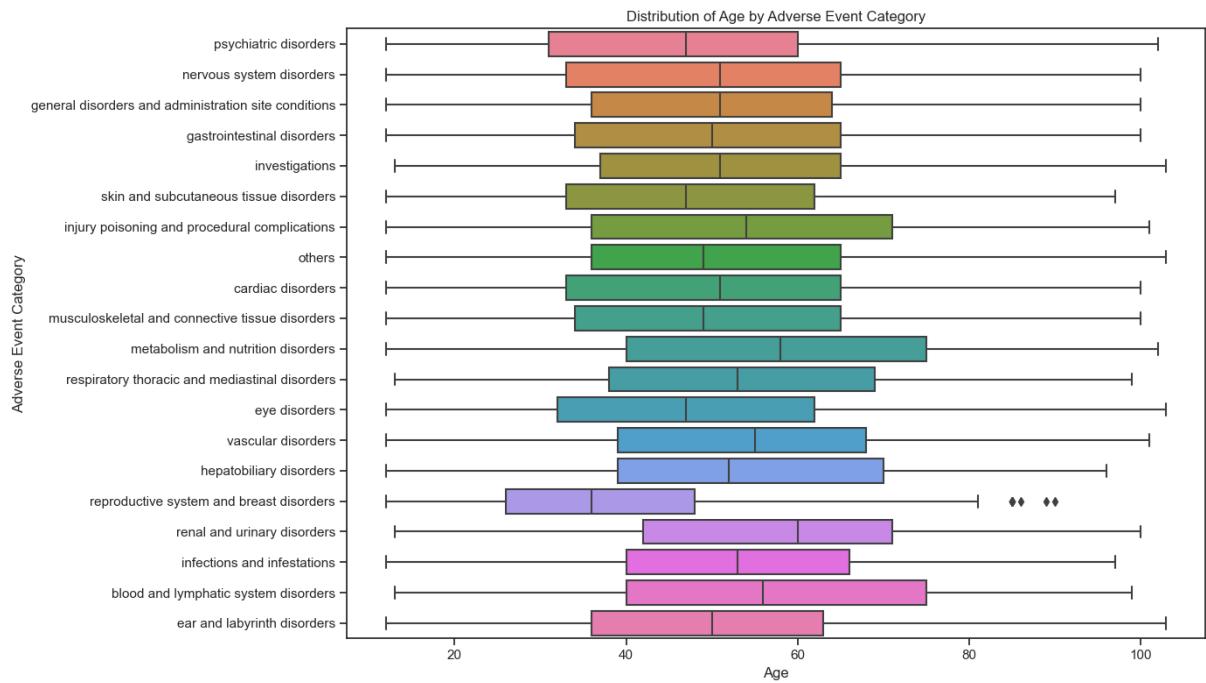


Figure 12: Distribution of adverse events by age 2018-2023

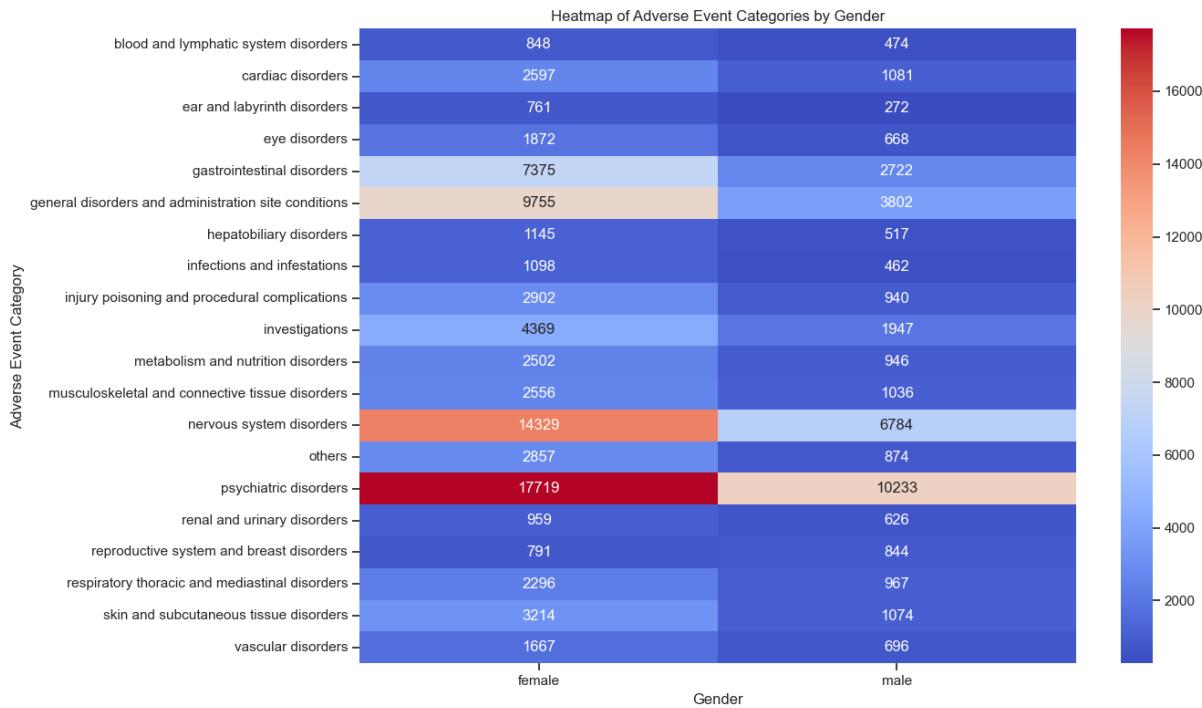


Figure 13: Heatmap of adverse events by gender 2018-2023

5.2 Classification machine learning models

After training and validating the model, the model performances on the test dataset were illustrated below in Figure 14.

Model	Accuracy	F1 Score	ROC_AUC
Logistic Regression	0.9756	0.9694	0.9989
SVC	0.9948	0.9930	0.9986
Clinical BERT	0.9858	0.9743	0.9995

Figure 14: Model performance of 3 different machine learning tools

Both were well performed in accuracy, F1-score, and AUC. The SVC had the highest accuracy, while the Clinical-BERT model had the best AUC performance with almost 100%. The Clinical-BERT used data trained from clinical and biomedical sources, which was the reason for its best performance [24] [25]. Detailed confusion matrix and ROC curve were illustrated in Figures 15 and 16.

However, the Clinical-BERT is a deep learning model requiring lots of time and computing resources. To be able to run the model on a local server, it took 5 hours of processing. This could be a constraint of any deep learning model. Therefore, with limited resources, the Logistics Regression and Support Vector Classifier are still an excellent alternative to classifying adverse events (Figures 33, 34, 35, and 35).

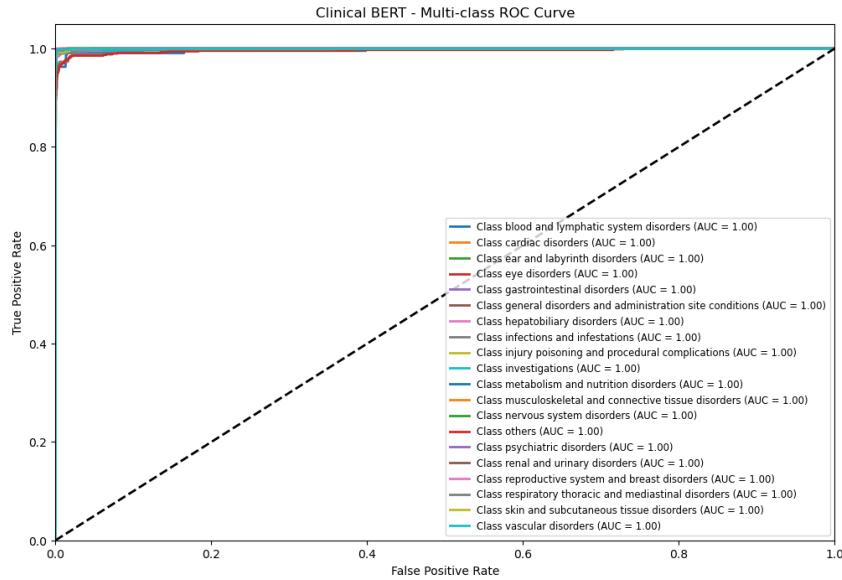


Figure 15: Performance of Clinical-BERT in ROC curve

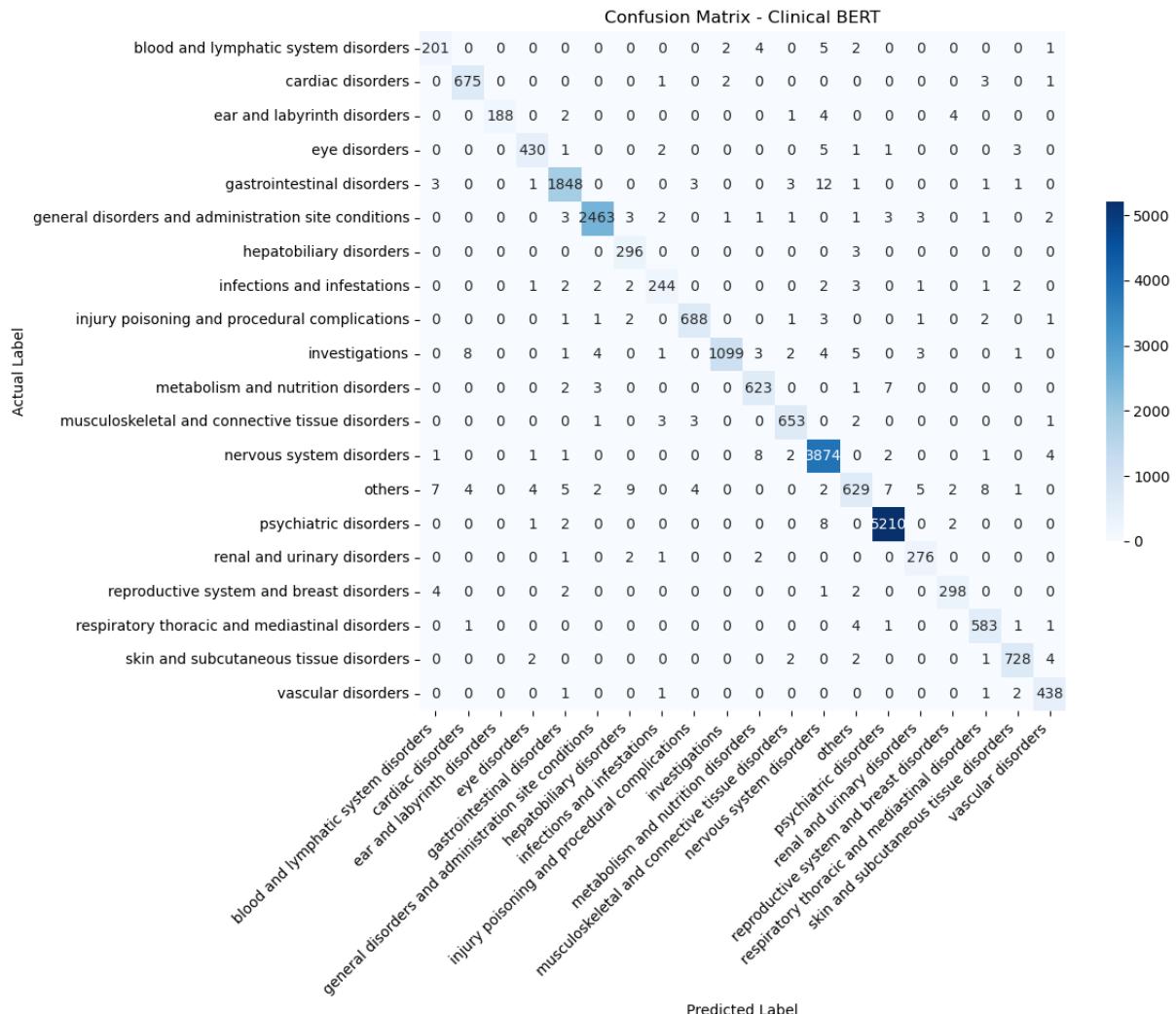


Figure 16: Performance of Clinical-BERT in confusion matrix

5.3 Topic modelling result

Before using the LDA model, we also performed a basic Wordcloud with the data divided into three different periods, pre-COVID (2018-2019), during COVID (2020-2021), and post-COVID (2022-2023) to observe any differences in the frequency of each word. Figure 17 illustrated the different topics between COVID periods with the density in Figure 37. The words "nausea", "dizziness", and "tremor" appeared more frequently during and post-COVID.

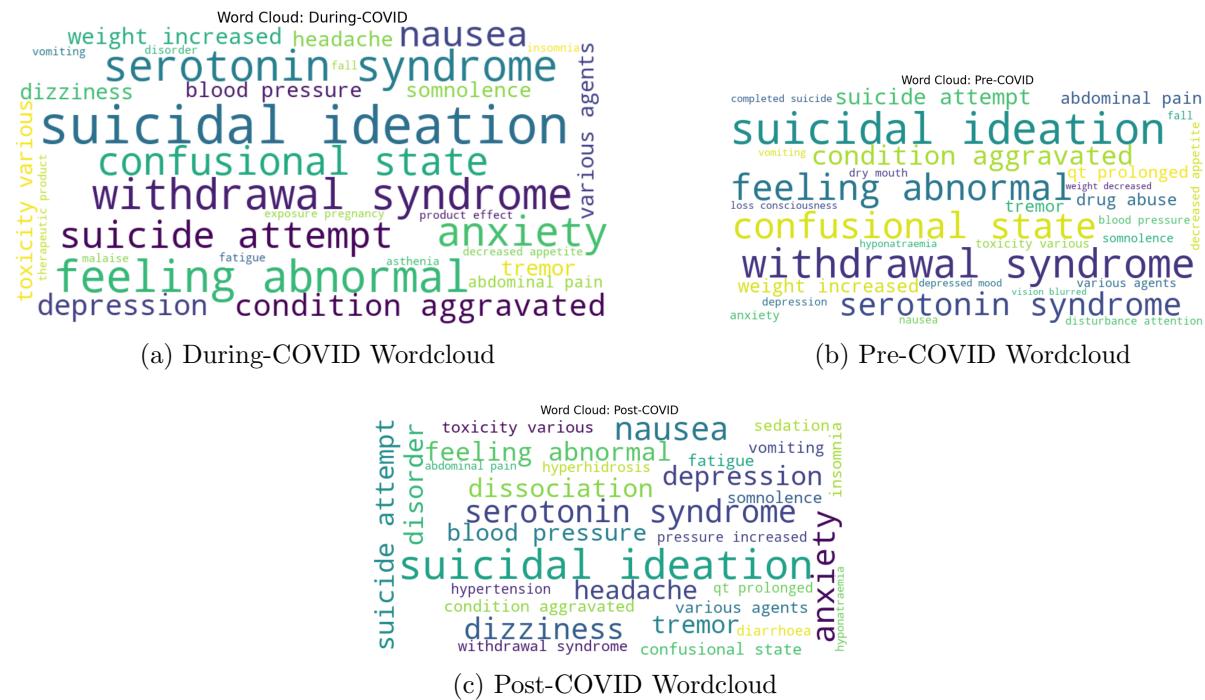


Figure 17: Wordcloud by Period

After observing the LDA model result in word density (Figure 18), we can see that Topic 1 contained 40% word density over time, while the other 4 topics only around 3-20%. Moreover, Topic 1 decreased since 2019, while Topic 2 and 4 slightly increased. In topic 4, the keyword "suicidal ideation" has become more triggered since 2021.

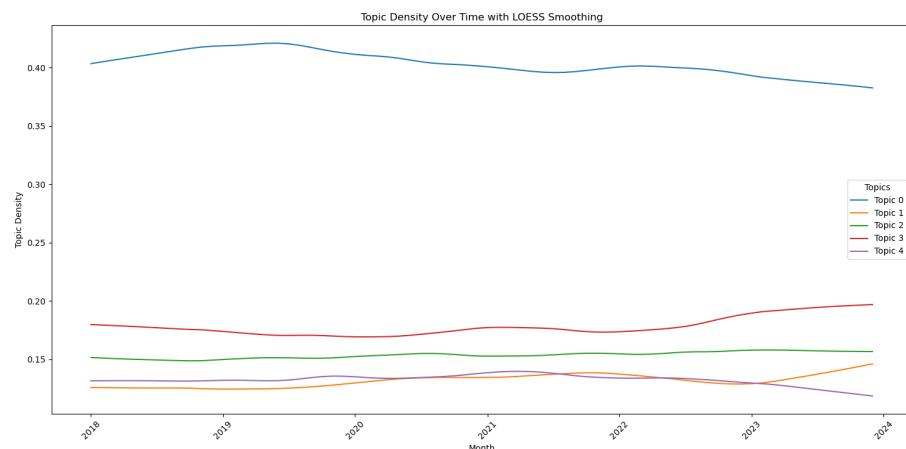
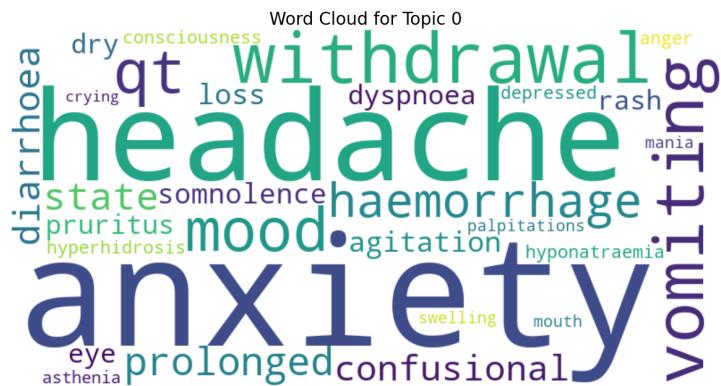
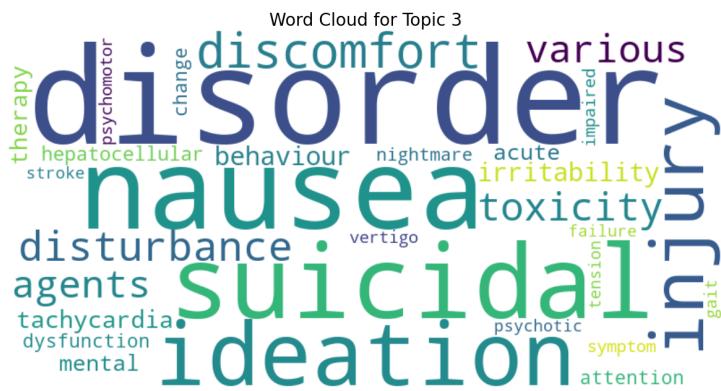


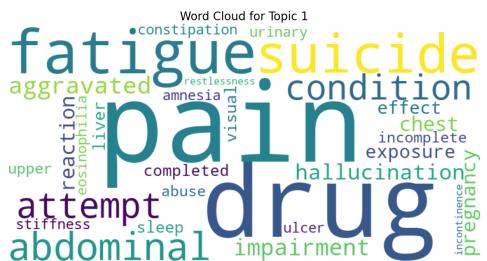
Figure 18: Word density of LDA topic model 2018-2023



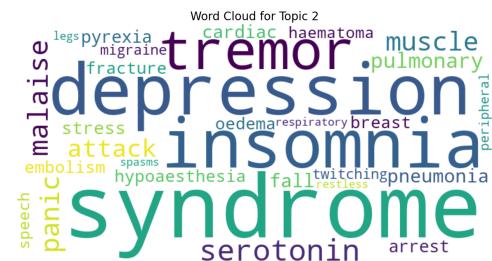
(a) Wordcloud Topic 1



(b) Wordcloud Topic 4



(c) Wordcloud Topic 2



(d) Wordcloud Topic 3



(e) Wordcloud Topic 5

Figure 19: Wordcloud of each topic by LDA model 2018-2023

The overall detailed proportion of each word by topic was illustrated below (Figure 20). Topic 1, representing 30.3% of data, included the themes of "anxiety mood" (6% of word density), "prolonged qt state" (5%), "headache" (3%), "withdrawal" symptoms (2%), "vomiting" (2%), "diarrhoea" (2%), and "haemorrhage" (2%). This result suggested that, despite using antidepressants, patients continued to report depressive symptoms. Moreover, significant adverse effects associated with antidepressant use may have contributed to a complex clinical picture, potentially hindering overall treatment efficacy and patient well-being.

Some AE symptoms identified in the data, such as various toxicity agents (7%), prolonged qt state (5%), "serotonin syndrome" (4% - linked to antidepressants), paraesthesia (4%), haemorrhage (2%), hallucination (2%), and pulmonary issues (2%) do not fall into typical depressive side effects on the FDA's caution list [7]. These findings highlight the need for medical practitioners to remain vigilant about these symptoms, as they could indicate unexpected or severe reactions to antidepressant use.

Topic 1 (30.3%)	$0.052^{**}\text{"anxiety"} + 0.034^{**}\text{"headache"} + 0.024^{**}\text{"withdrawal"} + 0.023^{**}\text{"vomiting"} + 0.019^{**}\text{"qt"} + 0.018^{**}\text{"mood"} + 0.018^{**}\text{"haemorrhage"} + 0.018^{**}\text{"prolonged"} + 0.017^{**}\text{"state"} + 0.016^{**}\text{"diarrhoea"}$
Topic 2 (19%)	$0.090^{**}\text{"pain"} + 0.080^{**}\text{"drug"} + 0.050^{**}\text{"fatigue"} + 0.045^{**}\text{"suicide"} + 0.036^{**}\text{"abdominal"} + 0.031^{**}\text{"attempt"} + 0.030^{**}\text{"condition"} + 0.028^{**}\text{"aggravated"} + 0.026^{**}\text{"impairment"} + 0.024^{**}\text{"hallucination"}$
Topic 3 (17.9%)	$0.132^{**}\text{"syndrome"} + 0.082^{**}\text{"depression"} + 0.076^{**}\text{"insomnia"} + 0.047^{**}\text{"tremor"} + 0.040^{**}\text{"serotonin"} + 0.034^{**}\text{"malaise"} + 0.030^{**}\text{"panic"} + 0.030^{**}\text{"muscle"} + 0.026^{**}\text{"attack"} + 0.019^{**}\text{"pulmonary"}$
Topic 4 (17%)	$0.104^{**}\text{"disorder"} + 0.071^{**}\text{"nausea"} + 0.058^{**}\text{"suicidal"} + 0.056^{**}\text{"ideation"} + 0.037^{**}\text{"injury"} + 0.028^{**}\text{"discomfort"} + 0.026^{**}\text{"disturbance"} + 0.025^{**}\text{"toxicity"} + 0.024^{**}\text{"agents"} + 0.024^{**}\text{"various"}$
Topic 5 (15.8%)	$0.091^{**}\text{"increased"} + 0.090^{**}\text{"abnormal"} + 0.071^{**}\text{"decreased"} + 0.066^{**}\text{"dizziness"} + 0.062^{**}\text{"feeling"} + 0.040^{**}\text{"weight"} + 0.035^{**}\text{"paraesthesia"} + 0.029^{**}\text{"appetite"} + 0.029^{**}\text{"blood"} + 0.021^{**}\text{"seizure"}$

Figure 20: Proportion % of each topic of LDA model 2018-2023

Furthermore, an interactive visualisation (Figure 21) was created for any researcher interested in having an overview of the results of topic modelling, which could be found at [Interactive visualisation of antidepressants topic modelling](#) (in HTML format).

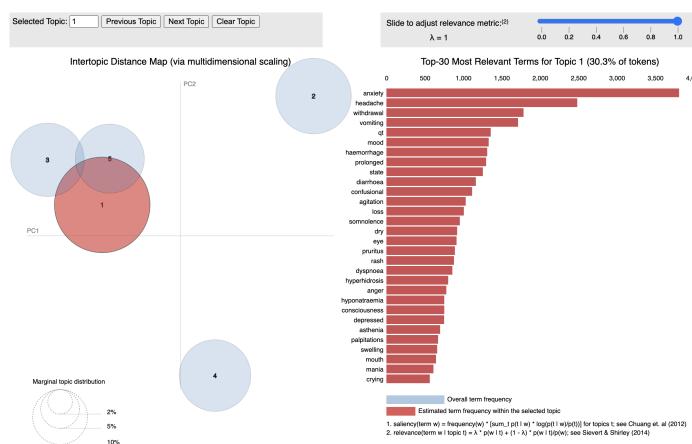


Figure 21: Snapshot of Topic 1 interactive visualisation of topic modelling

5.4 Disproportionality analysis result

The PRR and ROR ratio results are illustrated in Figure 22 and Figure 38. We observed that, except for "selective serotonin reuptake inhibitors" (SSRIs), all antidepressants showed non-significant signals for risk events across different COVID periods. SSRIs exhibited a significantly higher proportion of AEs during the COVID-19 period (2020–2021) compared to other antidepressants, with a PRRR increase of 1.0675 (6.75%) and a statistically significant p-value of $0.04 \leq 0.05$. However, the overall non-significant results may be attributed to the filtered dataset based on indications for treating depressive symptoms, which might have limited the representativeness of the observed odds.

Antidepressant_Type	Pre-COVID		During-COVID		After-COVID	
	PRR	p-value	PRR	p-value	PRR	p-value
selective serotonin reuptake inhibitors	1.0150	0.18	1.0675	0.04	1.0455	0.10
serotonin and norepinephrine reuptake inhibitors	0.9480	0.22	0.9220	0.26	1.1187	0.20
atypical antidepressants	0.9630	0.21	0.9601	0.25	0.9340	0.23
n-methyl d-aspartate antagonists	0.7994	0.21	0.7220	0.07	0.7810	0.10
tricyclic and tetracyclic antidepressants	1.0679	0.09	1.1907	0.22	1.1117	0.22
benzodiazepines	1.0693	0.18	1.0126	0.11	1.1036	0.30
nonbenzodiazepine receptor modulator	0.8091	0.22	0.8112	0.39	1.1567	0.54
monoamine oxidase inhibitors	0.7982	0.59	NaN	NaN	NaN	NaN
acid-a receptor positive modulators	0.5994	0.75	0.6329	0.57	0.9731	0.61
azaspirodecanedione	0.9395	0.68	1.4424	0.31	1.1247	0.74
anticonvulsants	NaN	NaN	0.0000	1.00	NaN	NaN

Figure 22: PRR result in overtime 2018-2023

6 Discussion

The large volume of reported AEs for antidepressants included many overlapping with depressive symptoms, such as "psychiatric disorders", "nervous system disorders", and "general disorders and administration site conditions" [38]. These findings highlight the difficulty in distinguishing between symptoms of depression and adverse effects caused by the medications.

Selective Serotonin Reuptake Inhibitors (SSRIs), particularly sertraline [39], fluoxetine [40], and escitalopram [10], accounted for the highest number of reported AEs in the FAERS database. This was supported by significant PRR value (during COVID) and the appearance of related terms in Topic 3 of the LDA model, which comprised 4% of the word density [41]. Similarly, atypical antidepressants, such as quetiapine, demonstrated a notable association with increased AEs, consistent with findings from previous research [11]. However, it is essential to note that these AEs might occur primarily during the early phases of treatment and may decrease over time as therapy progresses [40] [41]. Therefore, these findings could underestimate the long-term efficacy of these antidepressants [42].

Topic modelling revealed keywords such as "various toxic agents" in Topic 4 [43], "prolonged qt state" [44] and "haemorrhage" [45] in Topic 1, "serotonin" syndrome [41] and "pulmonary" [46] in Topic 3, "hallucination" [47] in Topic 2, and "paraesthesia" [48] in Topic 5, suggesting potential risks that warrant further investigation. These findings expand on previous work by identifying less recognised AE symptoms that may require additional clinical scrutiny.

The ML models (Logistic Regression, SVM, and Clinical-BERT) demonstrated strong performance in classifying AE categories, aligning with findings from related studies [19] [24] [25]. Clinical-BERT, trained on clinical and biomedical data, exhibited near-perfect performance but required significant computational resources. As an alternative, Logistic Regression and SVM are practical for researchers lacking access to advanced tools like MedDRA or requiring more straightforward implementation.

While this study successfully categorised AEs and identified trends, certain limitations must be acknowledged. Firstly, the inability to confirm definitive associations between antidepressants and AEs of different COVID periods due to dataset constraints and reliance on PRR and ROR metrics. Secondly, the focus on depressive symptoms limited the generalisability of findings across other medication indications. Lastly, computational resource constraints restricted the use of more advanced DL models.

7 Conclusion

This study achieved its research objectives by analysing AEs reported in the FAERS database and demonstrating the utility of ML models for AE classification. SSRIs exhibited the highest proportion of AEs, with significant PRR values during COVID. Topic modelling identified potential risks, such as "prolonged qt state" and "pulmonary" issues, that require further investigation. ML models, particularly Logistic Regression and SVM, provided effective alternatives for AE categorisation when access to MedDRA or advanced computing resources is limited.

Healthcare practitioners should remain vigilant for non-typical AE symptoms, such as SSRI "toxicity", and prioritise individualised monitoring for these patients who experience depression. Policymakers should consider expanding access to mental health treatments during crises like COVID-19 to ensure consistent reporting and management of AEs.

To overcome current limitations, future research should expand the analysis to include an extended FAERS database with diverse indications beyond depressive symptoms, explore resource-efficient implementations of Clinical-BERT for broader use in AE classification, and conduct longitudinal studies to confirm associations between antidepressants and emerging AE categories. By addressing these gaps, researchers can contribute to improved antidepressant safety, refined treatment approaches, and better outcomes for patients managing depression.

Acknowledgements

Firstly, I want to express my heartfelt gratitude to Dr Indu Bala, Associate Lecturer of the School of Computer and Mathematical Sciences (Faculty of Sciences, Engineering and Technology) of the University of Adelaide, for her invaluable guidance, constructive feedback and continuous encouragement throughout this research project for six months. Her expertise and insights have been instrumental in shaping the direction and outcomes of this study.

I also thank our FAERS research project group of fellow students for their collaboration, thought-provoking discussions, and support throughout our weekly meetings.

Lastly, I would like to thank my family and friends, especially my husband - Huynh Nhat Minh, for their unwavering encouragement, patience, and understanding, which have been a great source of strength and motivation during challenging times.

Besides the support I received from people around me, I also want to acknowledge the use of [OpenAI - ChatGPT](#) to generate ideas and materials for computing parts of this research. Extensive prompts will be available based on direct request.

Appendices

Some resources and data were relevant to the report, but due to their limitations, the author would like to include them in the appendices for further reference.

1. This research used data from quarter 1 in 2018 to quarter 4 in 2023 that is downloaded from the [FAERS Quarterly Data Extract Files](#).
2. For analysis, the author wrote Jupyter Notebooks from step 1 to step 7 using Python programming languages and uploaded the code to the [GitHub repository](#) for further reference and auditing.
3. For mapping adverse events from the FAERS to a standardised medical terminology, the author exported the data from [MedDRA Version 27.1 September 2024](#).

Some other analysis results were mentioned in the report but not included in the main part to avoid distraction. They are illustrated in the following figures:

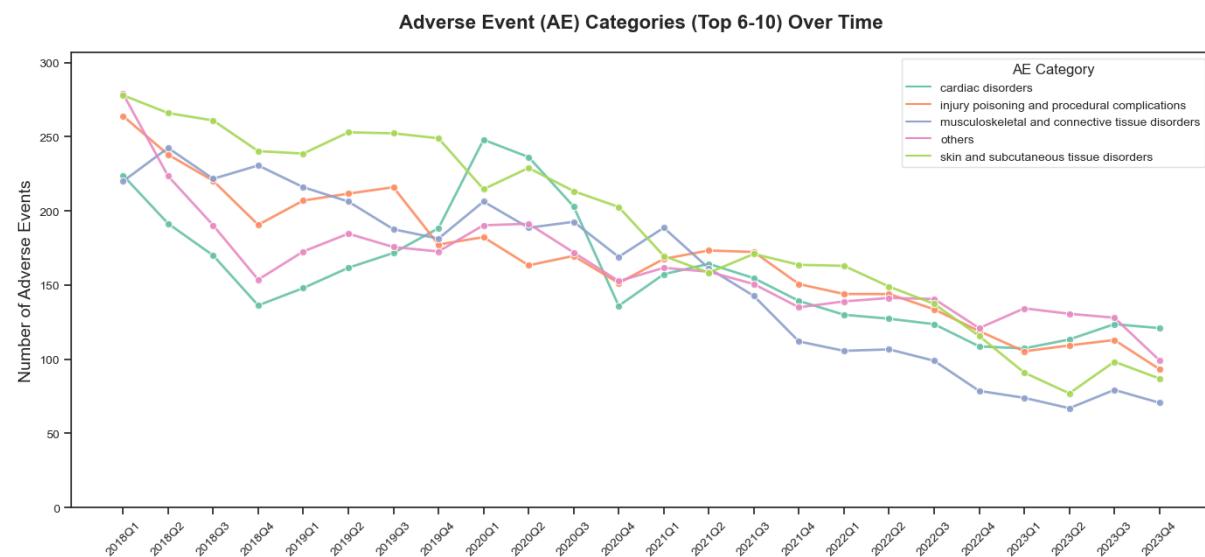


Figure 23: Top 6-10 adverse event categories of antidepressants 2018-2023

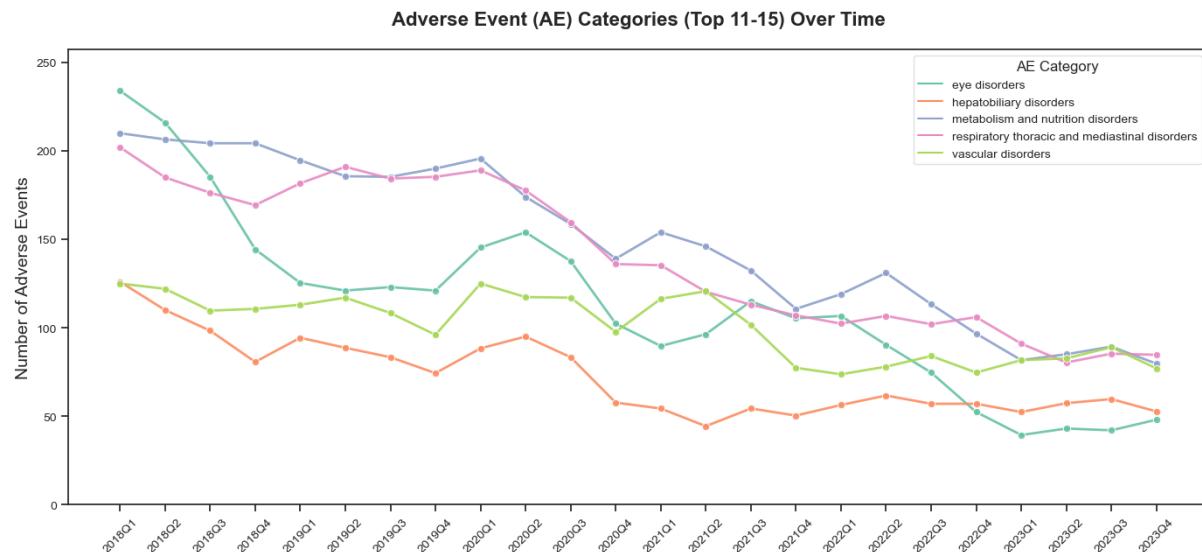


Figure 24: Top 11-15 adverse event categories of antidepressants 2018-2023

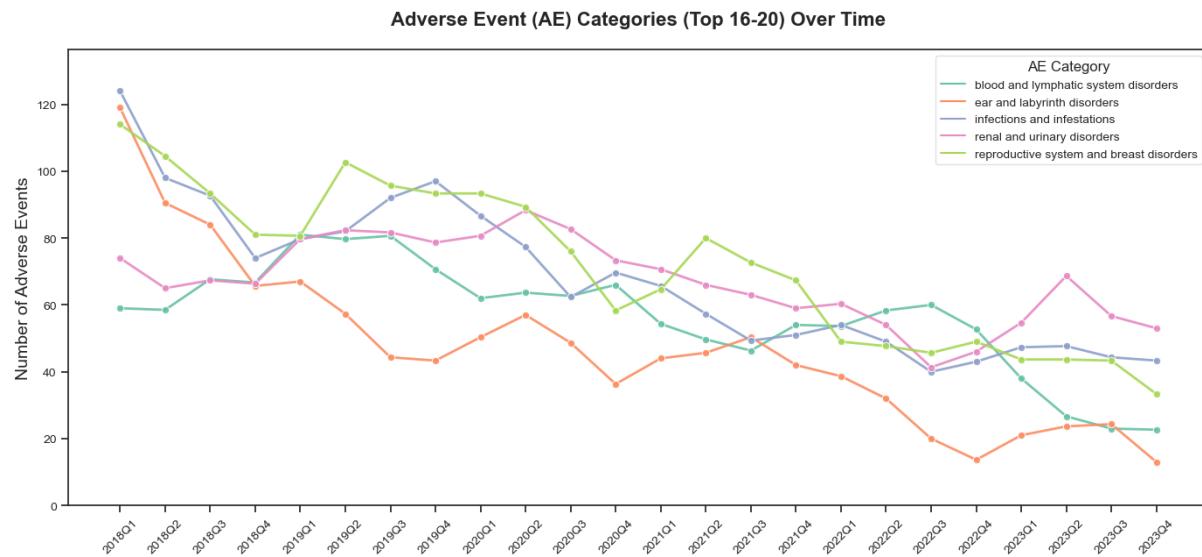


Figure 25: Top 16-20 adverse event categories of antidepressants 2018-2023

Demographic		Count	Percentage (%)
Gender	female	24,070	67.51
	male	11,582	32.49
Age Group	adult (21-64yo)	23,525	65.99
	elderly	9,725	27.28
	adolescent	2,402	6.74
Country	US	12,449	34.92
	france	5,545	15.55
	UK	4,796	13.45
	italy	1,886	5.29
	canada	1,701	4.77
	germany	1,591	4.46
	spain	1,174	3.29
	japan	1,165	3.27
	poland	532	1.49
	portugal	490	1.37
	sweden	465	1.30
	china	451	1.27
	netherlands	344	0.96
	turkey	273	0.77
	brazil	263	0.74
	australia	221	0.62
	belgium	167	0.47
	switzerland	150	0.42
	greece	145	0.41
	czechia	111	0.31
	others	1,733	4.86
Outcome	others	21,251	59.61
	hospitalisation	10,186	28.57
	life threatening	1,430	4.01
	disability	1,376	3.86
	death	1,329	3.73
	required intervention	47	0.13
	congenital anomaly	33	0.09

Figure 26: Patients' demographic reported adverse events 2018-2023

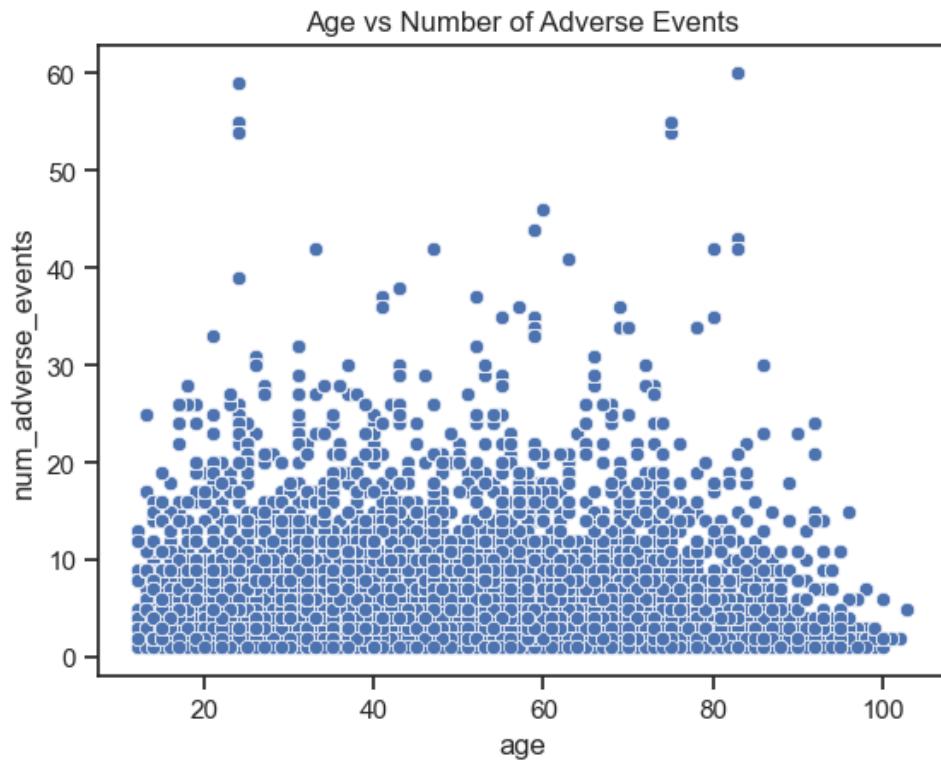


Figure 27: Distribution of adverse events by Age

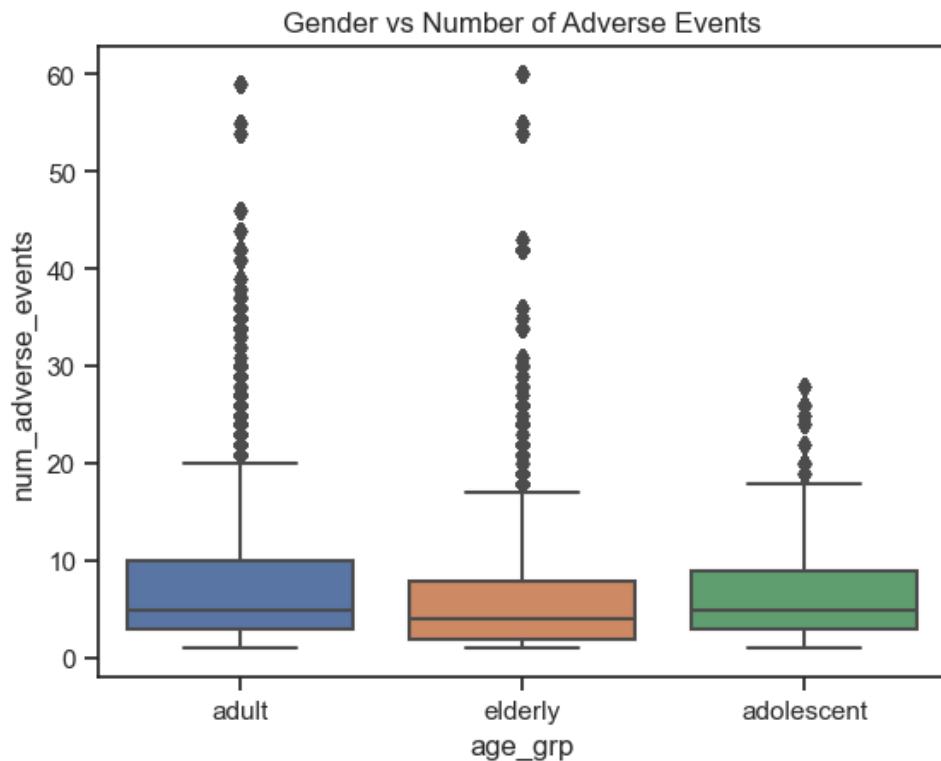


Figure 28: Distribution of adverse events by Age group

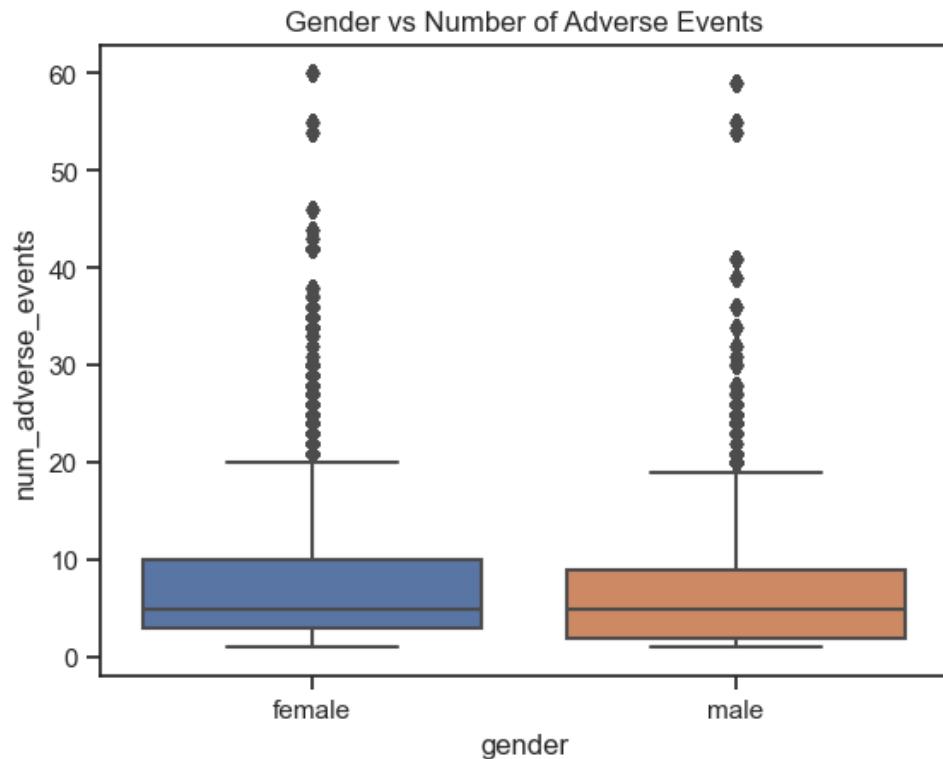


Figure 29: Distribution of adverse events by Gender

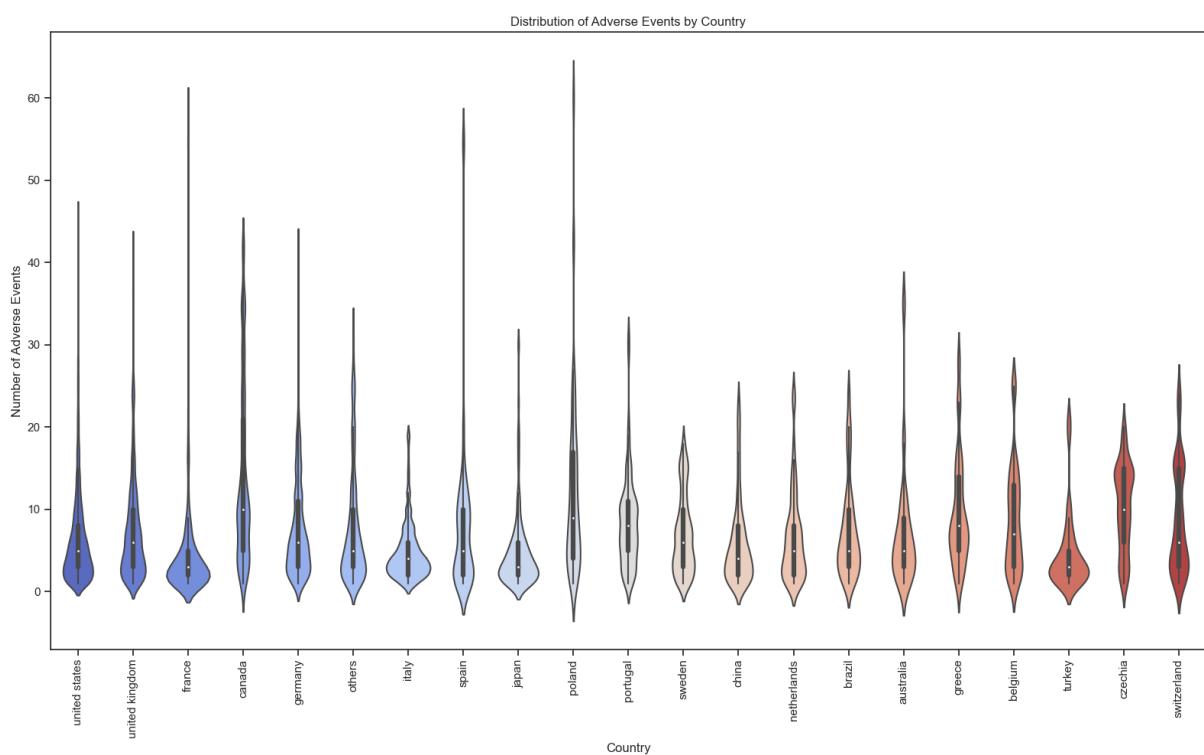


Figure 30: Distribution of adverse events by Country

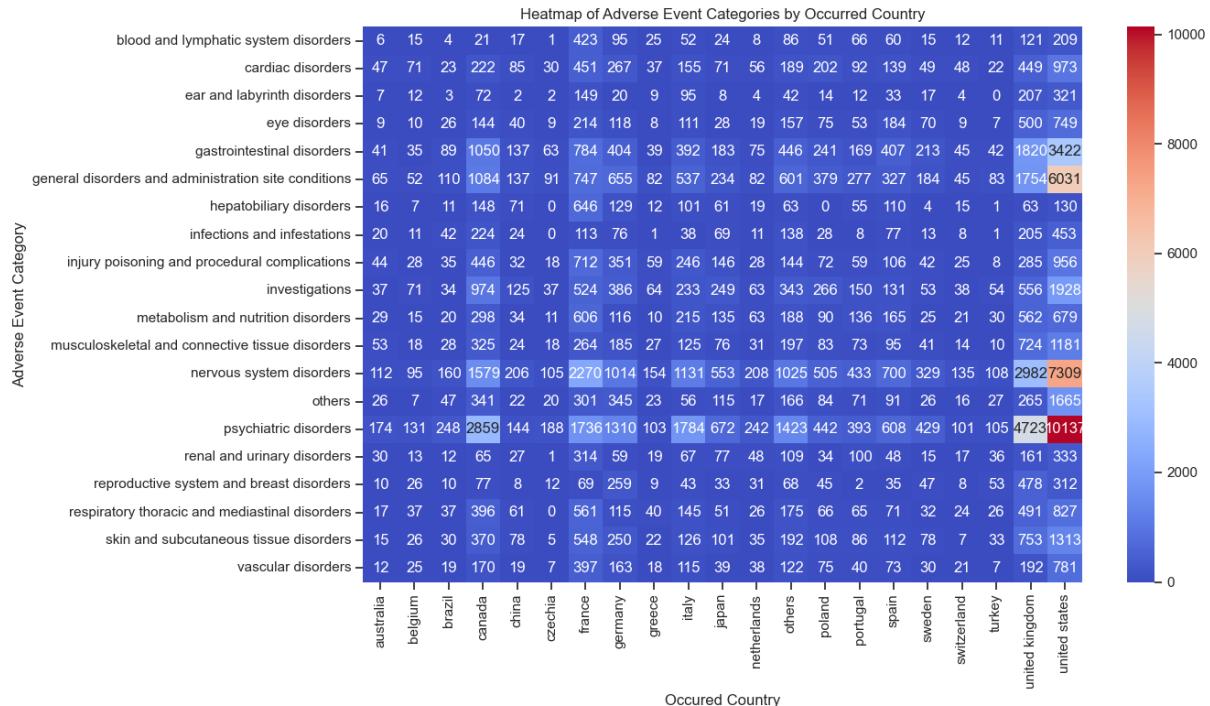


Figure 31: Heatmap of adverse events by Country

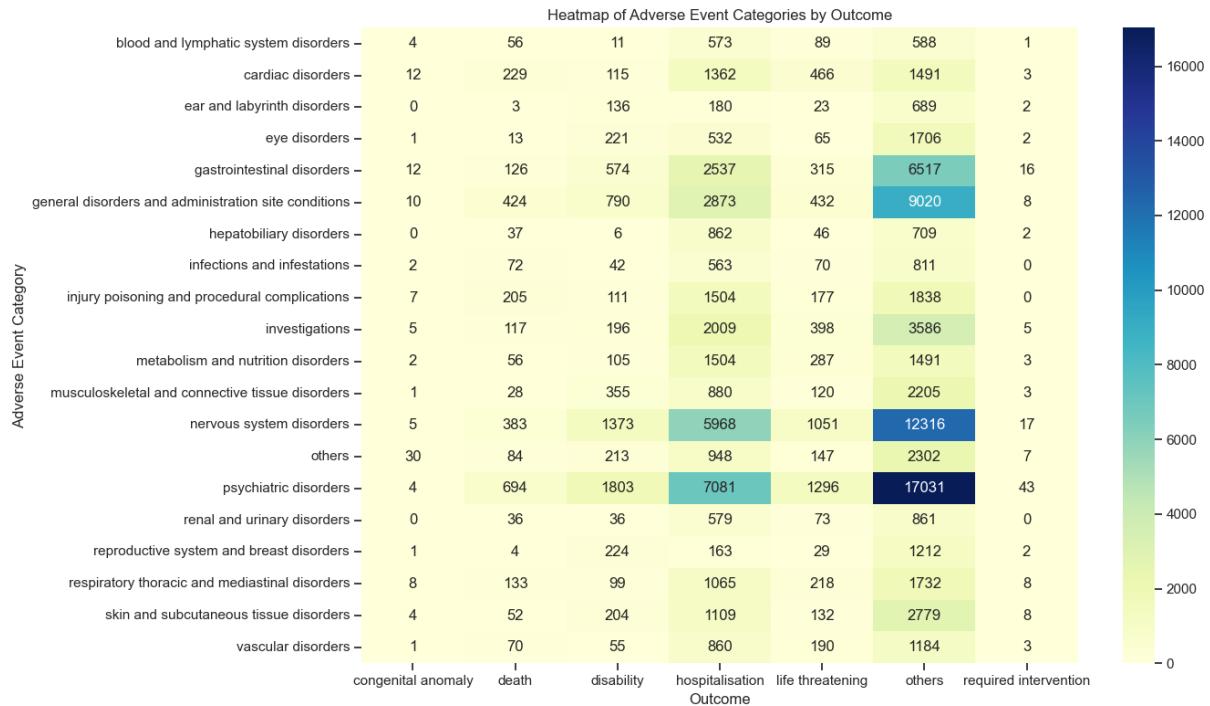


Figure 32: Heatmap of adverse events by Outcome

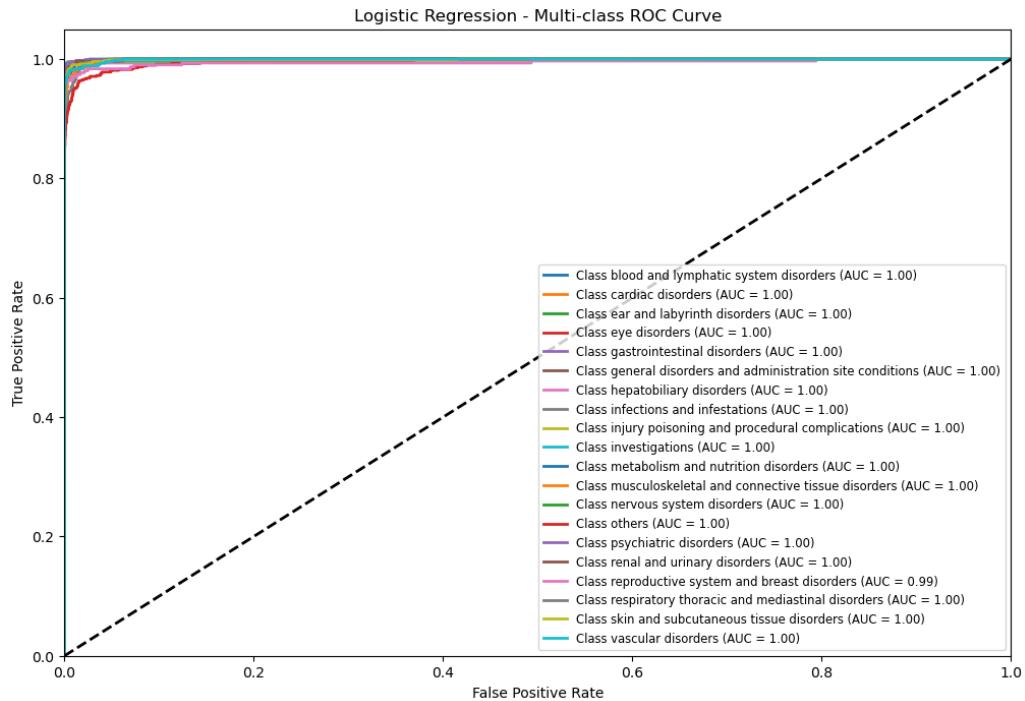


Figure 33: Performance of Logistic Regression in ROC curve

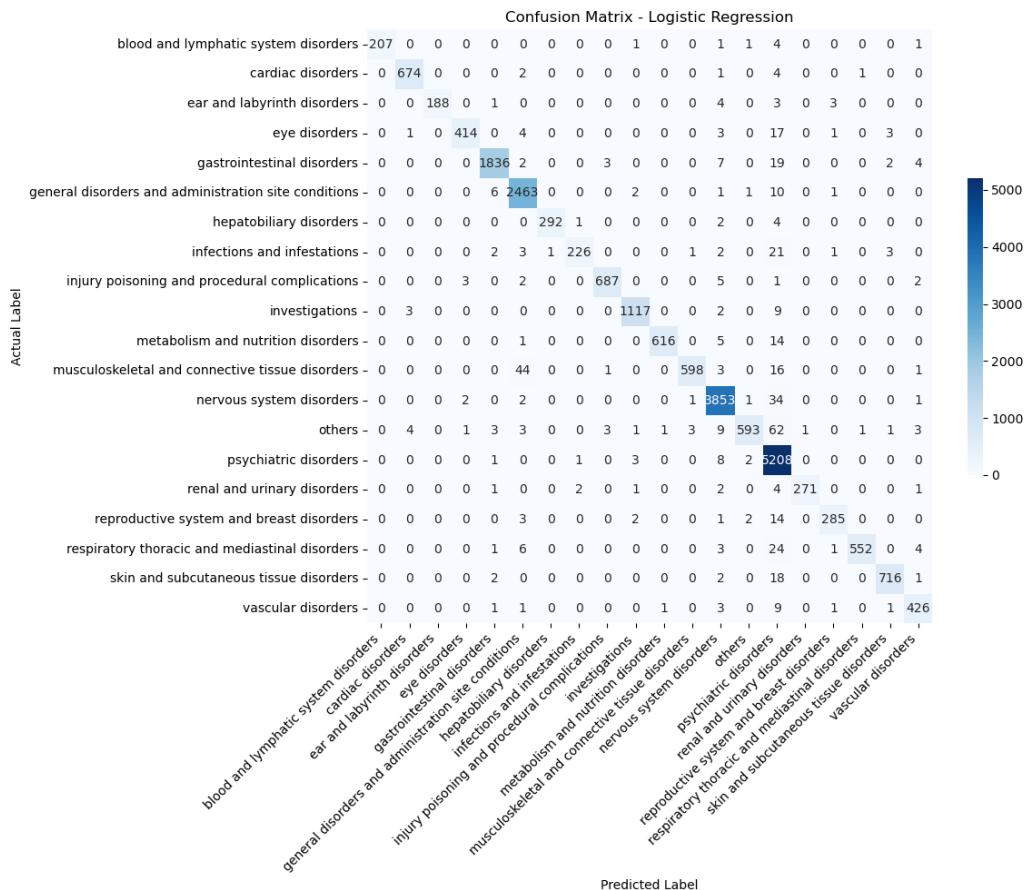


Figure 34: Performance of Logistic Regression in confusion matrix

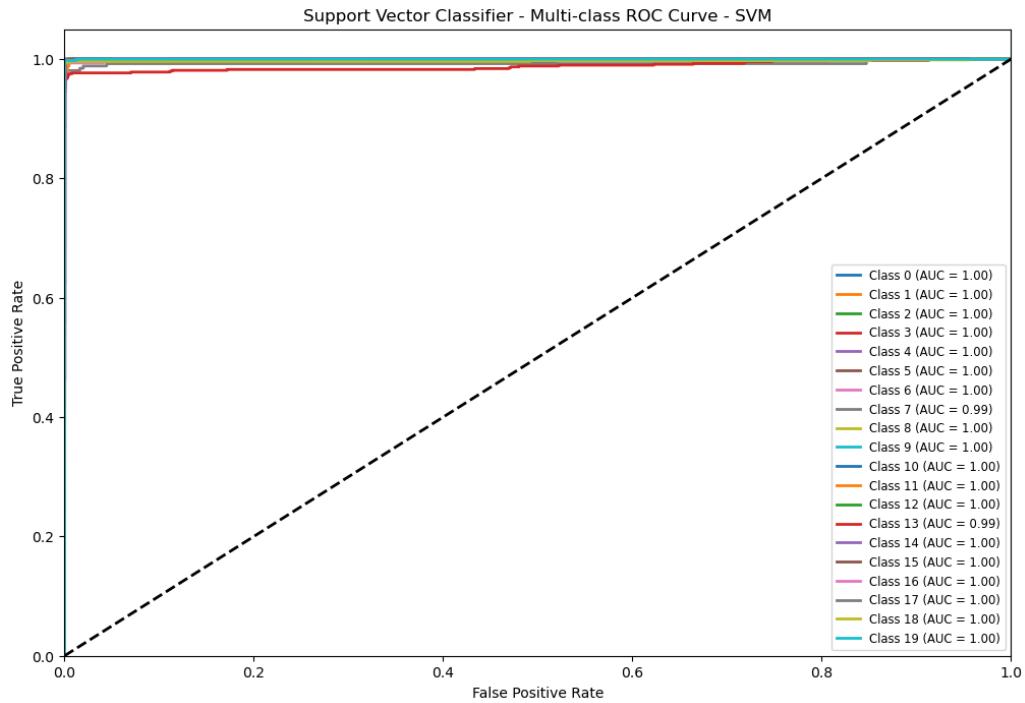


Figure 35: Performance of SVC in ROC curve

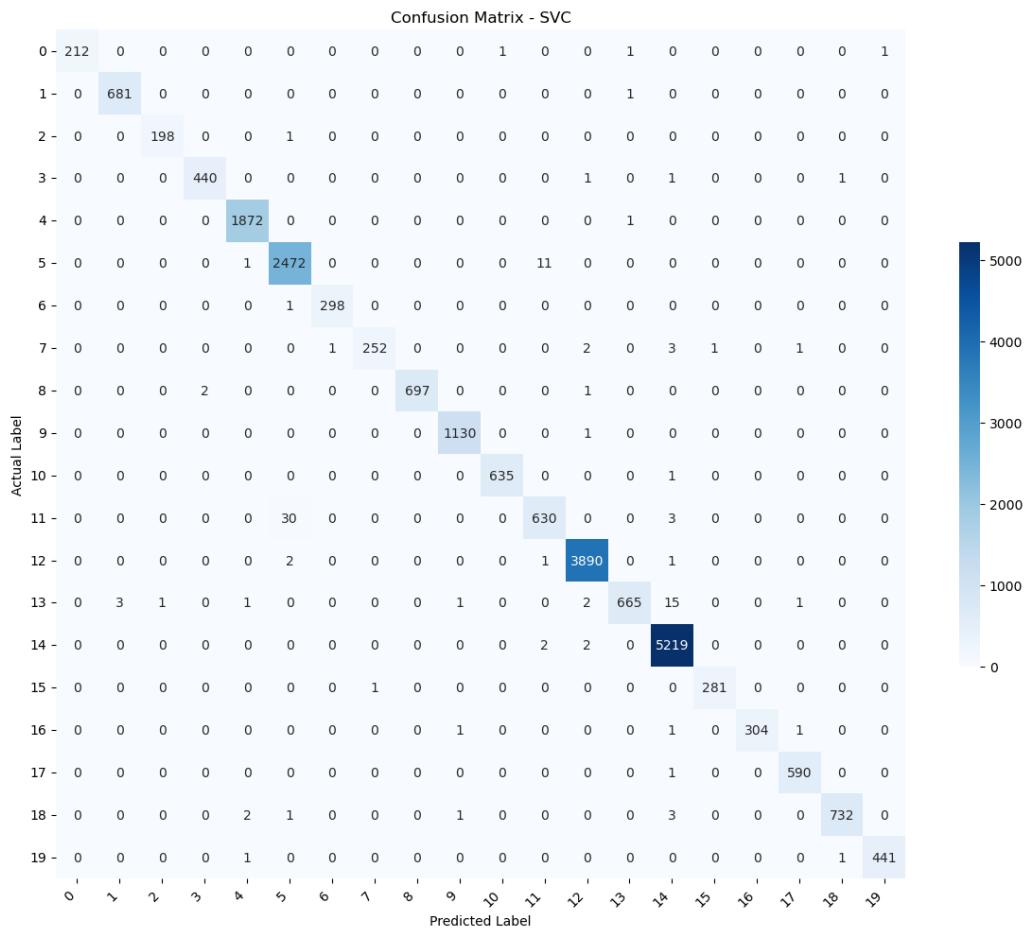


Figure 36: Performance of SVC in confusion matrix

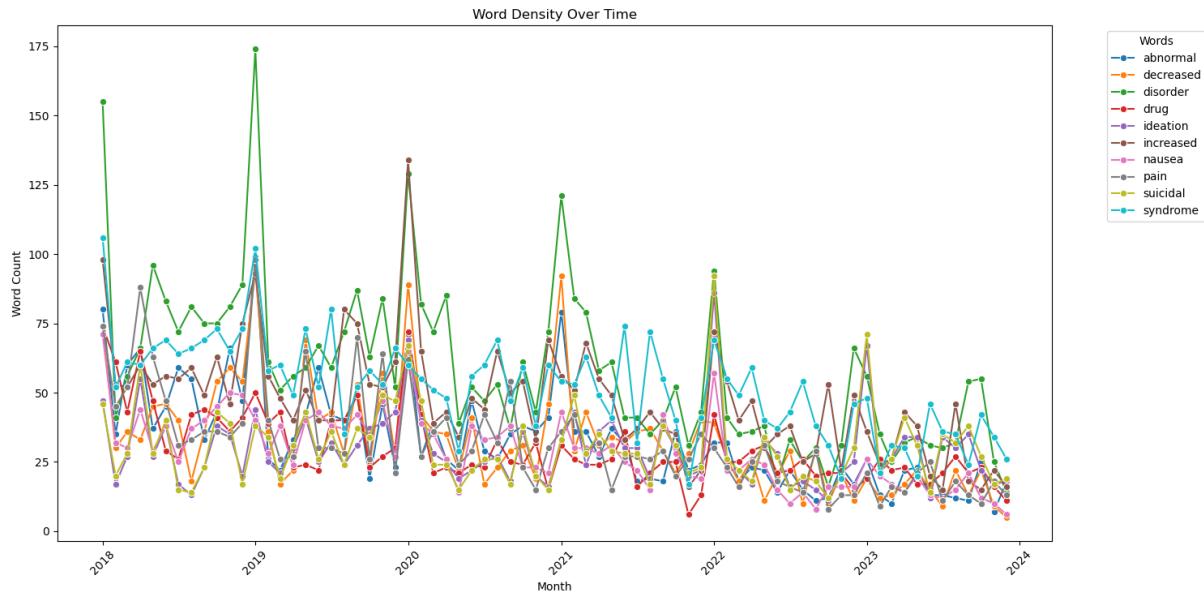


Figure 37: Topic density without LDA model 2018-2023

Antidepressant_Type	Pre-COVID		During-COVID		After-COVID	
	ROR	p-value	ROR	p-value	ROR	p-value
selective serotonin reuptake inhibitors	1.0798	0.38	1.1874	0.20	1.1408	0.29
serotonin and norepinephrine reuptake inhibitors	0.9445	0.45	0.9190	0.49	1.1648	0.44
atypical antidepressants	0.9698	0.45	0.9651	0.50	0.9339	0.46
n-methyl d-aspartate antagonists	0.8018	0.43	0.7279	0.20	0.8016	0.22
tricyclic and tetracyclic antidepressants	1.0832	0.27	1.2279	0.45	1.1408	0.45
benzodiazepines	1.0790	0.38	1.0317	0.31	1.1325	0.56
nonbenzodiazepine receptor modulator	0.8108	0.52	0.8122	0.68	1.1667	0.78
monoamine oxidase inhibitors	0.7991	0.72	NaN	NaN	NaN	NaN
acid-a receptor positive modulators	0.6000	0.51	0.6334	0.96	0.9758	0.62
azaspirodecanedione	0.9418	0.79	1.4501	0.48	1.1296	0.60
anticonvulsants	NaN	NaN	0.0000	NaN	NaN	NaN

Figure 38: ROR result in overtime 2018-2023

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