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Assessment of Reported Adverse Events on Anti-Depressants

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ABSTRACT

A mental disorder is characterized by a clinically significant disturbance in an individual's cognition, emotional regulation, or behavior. One in every eight people around the world was living with a mental disorder in 2019, with depression and anxiety the most common. Currently, popular prescribed types of antidepressants include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). For such medications, limited adverse effects and reasonable tolerability are critically important in addition to the efficacy in treating depression and their affordability. In this study, I quantitatively assessed the adverse events reported in the comprehensive FAERS (FDA Adverse Event Reporting System) database in terms of case count by received year, by age group, by sex, by reaction type, and by outcome, with respect to those commonly used antidepressants. Although the total count of adverse events increases every year before 2019, my analysis shows an alarming decrease in total count over the COVID pandemic period (2020 & 2021) while the number of people with depression rose significantly because of the pandemic. "Completed suicide" turns out to be one of the main side reactions reported across all anti-depression medications. Statistical analysis demonstrated that the reported number of "completed suicide" correlates with the report number of "suicide attempt" (or "suicidal ideation"). Surprisingly, the reported case count by females is significantly larger than that by males regardless of the grouping approach. It was evident that such insights could provide meaningful guidance on strengthening mental health systems for COVID-19 & future public health emergencies and further support relevant scientific studies on adverse effects & tolerability of effective antidepressant medications.

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Introduction

A mental disorder, also known as a mental illness or psychiatric disorder is a clinically significant behavioural or psychological pattern that causes distress or impairment in personal, social, or occupational functioning [1-5]. In 2019, close to a billion people worldwide were living with a mental disorder, with depression and anxiety ranking as the most prevalent conditions [6]. Despite this considerable global burden, health systems have not sufficiently addressed the needs of individuals with mental disorders, facing significant resource deficits. Research highlights a stark reality where only one-third of individuals experiencing depression receive formal mental health care [7].

Anti-depressants constitute a class of psychoactive drugs primarily utilized for treating depression and various mental health conditions, such as anxiety [8]. Their mechanism involves modifying the balance of neurotransmitters, key chemicals in the brain regulating mood and emotions [9-11]. In 2013, anti-depressants ranked as the most frequently prescribed medication in the United States [12]. Currently, widely prescribed types include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) [13-14]. SSRIs are the most commonly prescribed anti-depressants globally while SNRIs may offer advantages over other anti-depressants due to their balanced dual inhibition of monoamine reuptake [15,16].

My previous study reveals that the average cost per prescription fill for brand-name drugs is alarmingly 14 to 71 times higher compared to their generic counterparts [17]. Nowadays, while cost represents an important factor influencing health care decision making, safety and side effects are of paramount importance for individuals seeking treatment for depression. Anti-depressants generally take time to work, usually 4 to 8 weeks and often accompany with various adverse side effects throughout the treatment period [18]. Best anti-depressants should generate the fewest adverse side effects while provide the most effective treatment.

With these considerations in mind, the primary research question emerges: Are we currently providing treatment for common mental health conditions in a way that is not only effective & affordable but also safe with minimized adverse effects? This issue has gained added significance in light of the COVID-19 pandemic.

In an effort to explore this question, this study conducts a quantitative assessment of the reported adverse events related to the two primary categories of antidepressant medications. It aims to examine the influence of age groups and sex on the reported adverse events and to identify the critical adverse reaction types that need to be considered for safety risk evaluation associated with anti-depressant drugs. Such discoveries could provide valuable guidance on supporting scientific studies on adverse effects & tolerability of anti-depressant medications.

Methods

Throughout this study, I utilized the United States Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) and directly extracted the raw data from its public dashboard. This comprehensive database provides information on the number of adverse event reports received by FDA for drugs and therapeutic biologic products. The sourced data include direct reports voluntarily submitted through the MedWatch program by consumers and healthcare professionals, mandatory reports submitted by manufacturers, and the BSR reports [19].

Using the raw data available as of June 30, 2022, I conducted an analysis on the reported adverse event counts under various categories, including received year, age group, sex, reaction type and outcome. This analysis encompassed most commonly prescribed anti-depressants as outlined in Table 1 [20].

Table 1: Most Common Anti-Depression Medications

	Generic Drug
Serotonin Reuptake Inhibitor (SSRI)	Sertraline
	Citalopram
	Fluoxetine
	Escitalopram
	Paroxetine
	Fluvoxamine
	Vilazodone
Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)	Venlafaxine
	Duloxetine
	Desvenlafaxine
	Levomilnacipran

Results & Discussions

Figure 1 illustrates the total number of reported adverse events from the FAERS database. The blue line represents the total count for all pharmaceutical drugs, while the red line denotes the total counts for all anti-depressants listed in Table 1. It is evident that the total reported adverse events for all pharmaceutical drugs show a consistent yearly increase. However, an alarming trend emerges with a reduction in total anti-depressant adverse event count during the COVID-19 pandemic period. The combined adverse events associated with anti-depressants listed in Table 1 decrease by over 18% from 2019 to 2021. However, based on the scientific brief published by the World Health Organization in 2022 the number of people living with depression rose significantly (over 25% increase in one year) over the COVID pandemic period [21]. The results from my previous study also reveal a consistent year-over-year increase in the total number of 30-day anti-depressant prescription fills since 2013 with COVID-19 period included [17]. Over the course of nice years, from 2013 to 2021, there was a 57% increase in annual antidepressant prescription fills, implying a continuous rise in the number of individuals contending with depression on an annual basis. Then what is the reason behind the drop of reported adverse events over the pandemic period? This may suggest potential under-reporting or under-treatment of mental disorders. It is likely that under-prescription during pandemic period existed, or some patients were reluctant to take medicine after prescription, or some patients reduce follow-up visits with physicians due to the fear of COVID, possible medical facility shutdowns, or staffing & resource shortage. This observation poses significant implications for the nation's healthcare system around mental disorders. It is essential to further analyze the 2022 and 2023 adverse event reporting data, once available, to ascertain whether this trend persists as pandemic restrictions gradually ease.

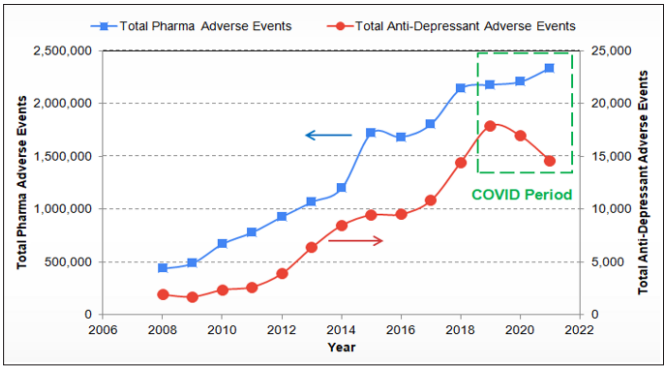

Figure 1: Total Number of Reported Adverse Events from 2008 to 2021

Figure 2 depicts the total number of reported adverse events categorized by different age groups. The "18-64 Years" age group stands out as predominant; however, it is noteworthy that the total anti-depressant adverse events for teenagers (age group 12-17 years) and the elderly (age group 65-85 years) remain highly concerning.

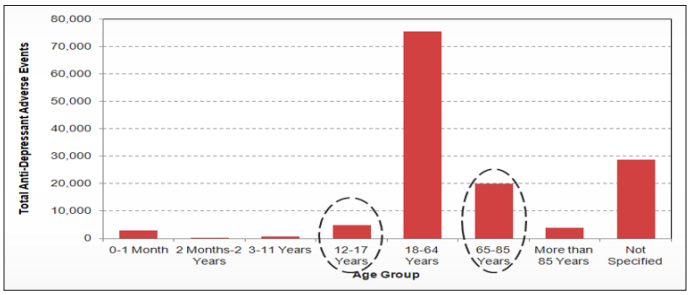

Figure 2: Total Number of Reported Adverse Events Under Different Age Groups

Figure 3 shows the total number of reported adverse events categorized by sex groups. The data clearly indicate that females reported adverse events almost twice as often as males. This discrepancy may be partially due to the fact that in general women are more prone than men to experience common mental health problems.

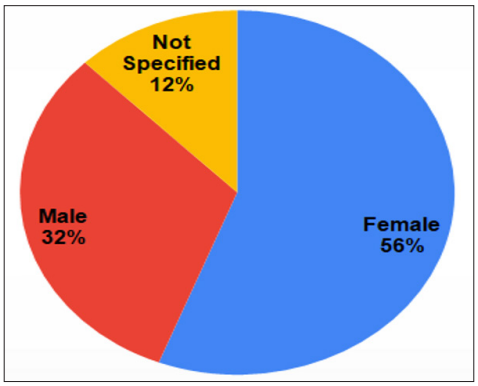

Figure 3: Total Number of Reported Adverse Events Under Different Sex Groups

To investigate further, I specifically checked the adverse event counts for the two concerning age groups (teenagers and the elderly) with the most severe outcome (death). Table 2 presents the number counts with respect to females and males. Under such

grouping, there are nearly twice as many females reported as males. The p-value derived from the Chi-Squared statistical analysis is 0.97, further conforming that the reported case count by females is significantly larger than that by males, regardless of the grouping approach.

Table 2: The Reported Adverse Event Count by Outcome, Age and Sex

	"Died in ages 12-17" Count	"Died in ages 65-85" Count
Females	425	2,394
Males	223	1,252

In certain instances, patients may encounter an elevation in suicidal thoughts or behaviour when undergoing anti-depressant treatment, particularly in the first few weeks after initiating the medication [22]. Table 3 outlines the six most prevalent reaction types reported, including three suicide types: completed suicide, suicide attempt and suicidal ideation. The adverse event counts under "completed suicide" are notably concerning. For example, Citalopram, a widely-used generic SSRI medication and the 31st most frequently prescribed medication in the United States in 2020 reported 3,200 cases of completed suicide [23].

Table 3: The Reported Adverse Event Count by Reaction Type

Major Reaction Type	Selective Serotonin Reuptake Inhibitors (SSRIs)							Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)			
	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Vilazodone	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Drug Interaction	2232	1083	2059	333	1060	2114	9	81	859		1294
Toxicity to Various Agents	3543	816	2286	192	982	1902	44	147	1230	6	2309
Drug Ineffective	1016	945	1114	144	690	1490	19	115	958	10	1186
Completed Suicide	3200	1057	2447	131	852	1625	83	151	1467	13	2168
Suicide Attempt	863	474	715	79	442	848	5	23	192	9	688
Suicidal Ideation	758	460	793	70	616	1096	2	41	382	1	603

Among the three suicide reactions, I conducted further investigation to assess their correlation, as illustrated in Figures 4-5. The calculated R squared values (0.7931 & 0.6441) indicate a decent level of correlation. However, they fall short of a strong linear relationship. Therefore, when the FDA evaluates the safety risk associated with anti-depressant drugs, consideration should be given to all three reactions (completed suicide, suicide attempt, and suicidal ideation).

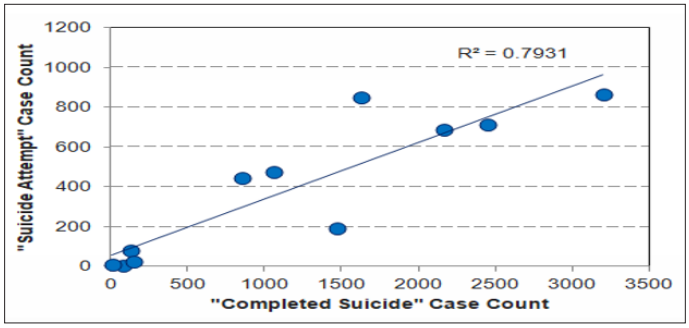

Figure 4: The Correlation of "Suicide Attempt" Adverse Event Count and "Completed Suicide" Adverse Event Count

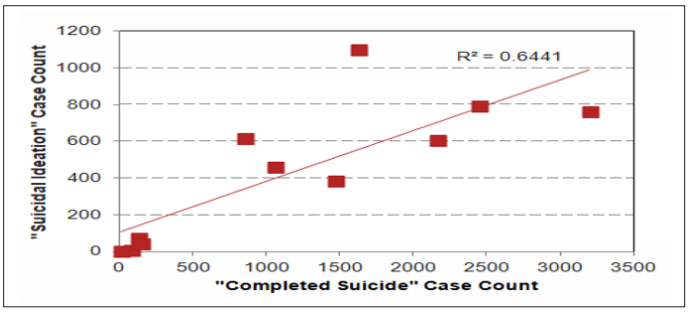

Figure 5: The Correlation of "Suicidal Ideation" Adverse Event Count and "Completed Suicide" Adverse Event Count

This study relies on public data released by the Food and Drug Administration, which may not encompass all known adverse events for a specific drug product. Although it might signify incomplete, inaccurate or unverified data, the analysis in this study and the identified trends remain pertinent and meaningful. Future studies exploring additional grouping categories to offer further insights into anti-depressant safety could be beneficial.

Conclusion

In summary, this study revealed an alarming decrease in total anti-depressant adverse events during the COVID pandemic period, along with concerning numbers of reported adverse events for teens (12-17 years old) and the elderly (65-85 years old). Additionally, the reported adverse case count by females significantly outweighs that by males regardless of the grouping approach. While "Completed Suicide" turns out to be one of the main side reactions reported across all anti-depression medications, other two suicide reactions (Suicide Attempt, Suicidal Ideation) should also be taken into account when the safety risk associated with anti-depressant drugs is assessed.

These findings underscore the critical need for enhanced monitoring of the safety and tolerability associated with anti-depression medications available on the market. Administrators, policymakers, and manufacturers could leverage this information to guide their efforts in providing not only affordable, but also high-quality medication with minimized adverse effects, ultimately enhancing the overall well-being of those affected by mental health conditions.

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