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An exploratory study evaluating the 20 medications most commonly associated with suicidal ideation and self-injurious behavior in the FAERS database

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Abstract

Background A number of pharmaceuticals, including antidepressants and antiepileptics, have a strong correlation with suicide risk. However, it is not entirely clear which of these medications are more strongly associated with suicide-related behaviors.

Objective This study aims to elucidate the drugs responsible for drug-associated suicidal ideation or self-injurious, recognizing the severe consequences associated with such outcomes. However, it is not entirely clear which specific medications are associated with higher levels of suicide-related behavior. Real-world data from the FDA adverse event reporting system database were analyzed to identify medications correlated with suicidal ideation or self-injurious.

Methods The reporting intensity of the High-Level Term "suicidal ideation or self-injurious behavior" and its Preferred Terms across distinct categories was assessed using the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR).

Results We identified the top 20 drugs with the highest reporting frequencies, spanning sedative-hypnotics, antidepressants, antipsychotics, antiepileptics, antihypertensives, antipyretic/analgesic drugs, and antihyperglycemic drugs. Ranking these medications according to ROR, the top five medications with ROR values related to suicidal ideation or self-injurious were alprazolam, zolpidem, amphetamine, quetiapine, and fluoxetine. Further analysis showed that suicide-related adverse events were more frequently reported in females. Antiepileptics had the highest frequency of reported adverse events in the 51–55 year age group, compared to 16–20 years for antidepressants and 46–50 years for sedative-hypnotics.

Conclusion Our study provides valuable information for clinical drug selection by presenting a potential list of medication classes commonly associated with drug-associated suicidal ideation or self-injurious behavior. We observed a large number of adverse event reports of suicidal ideation with duloxetine and relatively few reports of

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suicide attempts. Acetaminophen and amlodipine had substantial adverse event reports of completed suicides, but may not be associated with drug-induced suicidal behavior. On the other hand, some drugs mentioned in this study, such as quetiapine, aripiprazole, and lamotrigine, are recommended to be used after assessing the risk level of suicide in patients.

Keywords FAERS, Pharmacovigilance, Suicidal ideation, Self-injurious, Disproportionality analysis

Introduction

Suicide is a significant global health issue, causing approximately 800,000 deaths annually and accounting for 1.3% of all deaths worldwide [1, 2]. Research demonstrates that mental distress, physical illness, and treatment-related impairments in social and physical functioning elevate the risk of suicide. In addition to affective disorders and mental illnesses, certain pharmacological agents can heighten the risk of suicide [3]. Individuals with depression, a group at higher risk of suicide, often undergo treatment with selective serotonin reuptake inhibitors (SSRIs). Notably, 10% of clinical trials assessing SSRIs efficacy include individuals with some degree of suicidality [4–6]. In the published studies, encompassing diverse age groups (adults, adolescents, and children), revealed that SSRIs and other antidepressant categories are associated with an increased incidence of treatment-induced suicidal ideation or suicide-related behaviors compared to placebo [7–10]. A real-world study, incorporating a cohort exceeding 100,000 individuals, underscored the propensity of SSRIs to heighten suicide risk in depressed patients. This risk escalation was particularly pronounced among the demographic subset of children and adolescents aged 6–17 years [11].

Antiepileptics may increase the risk of suicidal ideation, suicide attempts, and completed suicides [12]. However, the veracity of this association has been a subject of ongoing contention. A decade-long clinical investigation found that most antiepileptic drugs do not elevate the risk of suicide. However, clonazepam, valproate, lamotrigine, and phenobarbital may associated with a higher risk of suicide after treatment initiation [13]. Additionally, older patients taking antiepileptic drugs showed a tendency for increased suicide-related behavior when prescribed levetiracetam or lamotrigine [14]. On the other hand, other literature unequivocally asserts the absence of a causal link between antiepileptics and suicide-related events [15–17]. However, these studies are not without limitations, encompassing constrained ranges of antiepileptics under scrutiny and being circumscribed by temporal and geographical constraints. The FDA's Adverse Event Reporting System (FAERS) database, constituting a repository of real-world adverse event reports, emerges as a valuable resource in contributing reliable clinical data to this ongoing discourse. FAERS, functioning as a drug safety surveillance database, encapsulates reported adverse events within the real-world clinical milieu.

Based on the FAERS database, our inquiry centered on discerning: "Which pharmacological agents exhibit the highest frequency of reported occurrences linked to suicidal and self-injurious behavior?" To address this, we methodically sifted through Preferred Terms (PTs) belong to the High-Level Term (HLT) "suicidal and self-injurious behavior" within the FAERS database. Subsequently, we quantified their individual Reporting Odds Ratios (RORs) and Proportional Reporting Ratios (PRRs). We classified and analyzed the top 20 drugs based on their frequency of reporting, aiming to establish a reference for clinical drug usage.

Materials and methods

Data sources

A retrospective observational pharmacovigilance study utilized data sourced from the FAERS, which is updated on a quarterly basis [18]. FAERS consists of several files, including demographic information (DEMO), drug information (DRUG), adverse drug reactions (REAC), drug indications (INDI), outcomes (OUTC), therapy dates (THER), and reporter sources (RPSR). These files are linked through a common primary key, "primaryid (unique number for identifying a FAERS report)" for FAERS. The organized data distribution comes from around the world, but primarily from the United States [35326898]. Drugs are reported in the database in the role of four codes, including PS (Primary Suspect Drug), SS (Secondary Suspect Drug), C (Concomitant), I (Interacting). Within the scope of our investigation, adverse events (AEs) reports pertaining to "Suicidal and self-injurious behavior" submitted from the first quarter of 2014 to the third quarter of 2023 were systematically extracted from the FAERS database, with drug effects limited to PS. All data in this study are openly accessed as an ASCII data package from the FAERS website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). Subsequently, the extracted data were processed and in-depth analyzed by Rstudio (Version 2023.06.2+561).

Data processing

Based on the FDA-recommended deduplication method, reports with the same CASEID (Number for identifying a FAERS case) in the DEMO table are retained with

the highest FDA_DT (date FDA received case) value. For reports with both CASEID and FDA_DT identical, the entry with the maximum primaryid value is preserved. Drug-related adverse reactions are classified according to the HLT and PT in the Medical Dictionary for Regulatory Activities (MedDRA) (Version 26.0). Ten preferred terms covering suicidal and self-injurious behavior, including suicidal ideation, completed suicide, suicidal behavior, suicide attempt, intentional self-injury, self-injurious ideation, suicide threat, suspected suicide attempt, suspected suicide, and assisted suicide are extracted and statistically counted (PT_code showed in Supplementary Table S1). Data are extracted for the top 20 drugs with reported frequencies, and the report frequencies and outcome indicators for each PT under the HLT are collected and analyzed.

Statistical analysis

Utilizing the disproportionality measurement method, the HLT and PT of each drug were analyzed using the ROR and PRR with its Chi-square ($\chi 2$). The calculation formula is as Supplementary Table S2. ROR ≥ 1 and 95% CI (lower limit)>1 with three or more cases considering a positive signal. A PRR ≥ 2 and $\chi 2 \geq 4$ with a number of reports ≥ 3 indicated a statistical correlation between the drug and the target AE [19–21]. ROR compares the odds of reporting an event of interest for a particular drug to all other events, relative to the reporting odds for other drugs in the FAERS database. PRR is the proportion of spontaneous reports for a particular drug that are related to a particular adverse event, divided by the corresponding proportion for other drugs in the FAERS database. A higher ROR or PRR indicates a stronger correlation between the drug and AE and consequently a stronger risk signal [22, 23].

Results

Top 20 drugs with reporting frequencies of suicidal and self-injurious behavior AEs

We extracted 148,840 adverse event reports categorized as HLT "suicidal and self-injurious behavior" from a total of 13,031,913 reports in the DEMO table. Figure 1 displays the top 20 drugs with the highest reporting frequencies, encompassing medications utilized for sedative-hypnotics (e.g., alprazolam, zolpidem, and sodium hydroxybutyrate), antidepressants (e.g., bupropion, fluoxetine, sertraline, citalopram, venlafaxine, and duloxetine), antipsychotics (e.g., quetiapine and aripiprazole), antiepileptics (e.g., lamotrigine, gabapentin, and pregabalin), antihypertensive drugs (e.g., amlodipine),

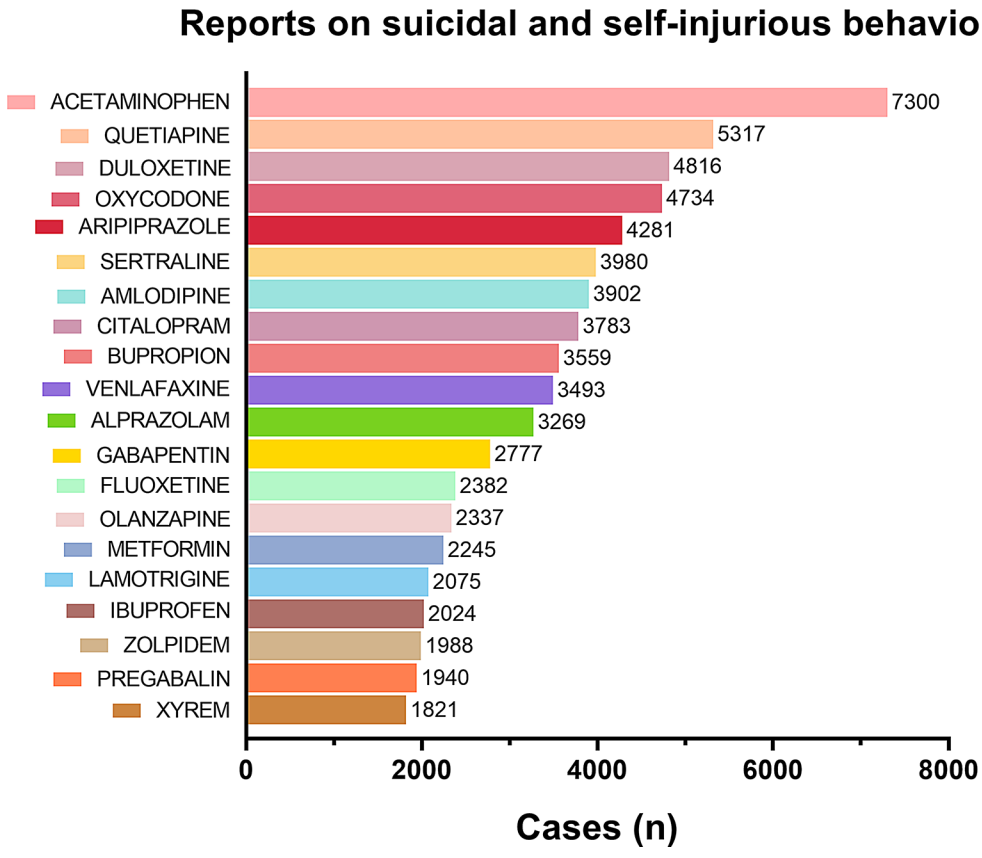

Fig. 1 Top 20 medications associated with suicidal ideation or self-injurious behavior from FAERS arranged by frequency

Table 1 Background information on the top 20 drugs with associated suicidal and self-harming behavior AEs

Drug	N	Gender (n, %)			Age (n, %)				
		Female	Male	Missing	<18	>85	18~64.9	65~85	Missing
Acetaminophen	7142	4520 (63.3%)	2274 (31.8%)	348 (4.9%)	615 (8.6%)	136 (1.9%)	4276 (59.9%)	1084 (15.2%)	1031 (14.4%)
Quetiapine	5027	3179 (63.2%)	1651 (32.8%)	197 (3.9%)	335 (6.7%)	28 (0.6%)	3598 (71.6%)	335 (6.7%)	731 (14.5%)
Oxycodone	4538	2194 (48.3%)	2203 (48.5%)	141 (3.1%)	132 (2.9%)	52 (1.1%)	1947 (42.9%)	533 (11.7%)	1874 (41.3%)
Duloxetine	4309	2606 (60.5%)	1100 (25.5%)	603 (14.0%)	52 (1.2%)	5 (0.1%)	1450 (33.7%)	163 (3.8%)	2639 (61.2%)
Amlodipine	3859	1816 (47.1%)	1704 (44.2%)	339 (8.8%)	132 (3.4%)	139 (3.6%)	2415 (62.6%)	790 (20.5%)	383 (9.9%)
Sertraline	3502	2096 (59.9%)	1041 (29.7%)	365 (10.4%)	561 (16.0%)	26 (0.7%)	2050 (58.5%)	160 (4.6%)	705 (20.1%)
Bupropion	3494	2011 (57.6%)	1081 (30.9%)	402 (11.5%)	230 (6.6%)	9 (0.3%)	2452 (70.2%)	186 (5.3%)	617 (17.7%)
Citalopram	3427	1894 (55.3%)	1089 (31.8%)	444 (13.0%)	173 (5.0%)	27 (0.8%)	1966 (57.4%)	242 (7.1%)	1019 (29.7%)
Aripiprazole	3389	1605 (47.4%)	1220 (36.0%)	564 (16.6%)	231 (6.8%)	1 (0.0%)	1485 (43.8%)	51 (1.5%)	1621 (47.8%)
Venlafaxine	3249	2155 (66.3%)	830 (25.5%)	264 (8.1%)	89 (2.7%)	19 (0.6%)	2250 (69.3%)	279 (8.6%)	612 (18.8%)
Alprazolam	3178	2012 (63.3%)	1072 (33.7%)	94 (3.0%)	163 (5.1%)	49 (1.5%)	2332 (73.4%)	385 (12.1%)	249 (7.8%)
Gabapentin	2662	1469 (55.2%)	912 (34.3%)	281 (10.6%)	31 (1.2%)	17 (0.6%)	1858 (69.8%)	318 (11.9%)	438 (16.5%)
Metformin	2225	994 (44.7%)	1086 (48.8%)	145 (6.5%)	182 (8.2%)	16 (0.7%)	1441 (64.8%)	403 (18.1%)	183 (8.2%)
Olanzapine	2142	1091 (50.9%)	860 (40.1%)	191 (8.9%)	107 (5.0%)	16 (0.7%)	1410 (65.8%)	90 (4.2%)	519 (24.2%)
Fluoxetine	2130	1429 (67.1%)	575 (27.0%)	126 (5.9%)	405 (19.0%)	10 (0.5%)	1130 (53.1%)	118 (5.5%)	467 (21.9%)
Lamotrigine	1989	1178 (59.2%)	503 (25.3%)	308 (15.5%)	110 (5.5%)	4 (0.2%)	1276 (64.2%)	89 (4.5%)	510 (25.6%)
Ibuprofen	1980	1124 (56.8%)	669 (33.8%)	187 (9.4%)	475 (24.0%)	12 (0.6%)	1047 (52.9%)	139 (7.0%)	307 (15.5%)
Zolpidem	1919	1089 (56.7%)	692 (36.1%)	138 (7.2%)	41 (2.1%)	21 (1.1%)	1169 (60.9%)	350 (18.2%)	338 (17.6%)
Pregabalin	1809	1019 (56.3%)	670 (37.0%)	120 (6.6%)	18 (1.0%)	7 (0.4%)	1088 (60.1%)	232 (12.8%)	464 (25.6%)
Sodium oxybate	1574	1075 (68.3%)	465 (29.5%)	34 (2.2%)	56 (3.6%)	0 (0%)	648 (41.2%)	11 (0.7%)	859 (54.6%)

Table 2 Top 20 medications associated with suicidal ideation or self-injurious behavior from FAERS ranked by ROR

Ranking	Drug name	ROR (95%CI)	PRR (X^2)
1	Alprazolam	13.48 (13.01-13.96)	12.86 (35102.65)
2	Zolpidem	13.29 (12.7-13.91)	12.69 (21199.5)
3	Bupropion	11.58 (11.19-11.98)	11.13 (32140.9)
4	Quetiapine	10.66 (10.36-10.96)	10.28 (43123)
5	Fluoxetine	10.63 (10.2-11.08)	10.25 (19644.09)
6	Sertraline	9.43 (9.14-9.74)	9.14 (28183.39)
7	Citalopram	9.35 (9.05-9.67)	9.06 (26552.45)
8	Venlafaxine	8.06 (7.79-8.34)	7.85 (20462.09)
9	Amlodipine	7.66 (7.42-7.91)	7.47 (21384.95)
10	Acetaminophen	7.29 (7.11-7.46)	7.12 (35417.11)
11	Aripiprazole	7.18 (6.96-7.4)	7.01 (21506.44)
12	Duloxetine	7.15 (6.94-7.36)	6.98 (23989.85)
13	Olanzapine	6.09 (5.85-6.35)	5.97 (9565.52)
14	Lamotrigine	5.35 (5.12-5.59)	5.26 (7090.12)
15	Gabapentin	4.89 (4.71-5.08)	4.82 (8270.69)
16	Ibuprofen	3.53 (3.38-3.69)	3.49 (3568.71)
17	Metformin	3.43 (3.29-3.57)	3.4 (3752.76)
18	Sodium oxybate	2.56 (2.45-2.68)	2.55 (1697.59)
19	Oxycodone	2.48 (2.41-2.55)	2.47 (4009.57)
20	Pregabalin	2.03 (1.94-2.12)	2.02 (990.25)

antipyretic/analgesic drugs (e.g., acetaminophen, ibuprofen), and antihyperglycemic drugs (e.g., metformin). The reporting frequency spans from 1821 to 7300, with the top five drugs identified as acetaminophen (frequency: 7300), quetiapine (frequency: 5317), duloxetine (frequency: 4816), oxycodone (frequency: 4734), and aripiprazole (frequency: 4281). Background information for these drugs is listed in Table 1. In Table 2, We rearranged the above 20 drugs according to the value of ROR. The ROR ranges from 2.03 to 13.48, and the PRR ranges from 2.02 to 12.86 for the top 20 drugs. Notably, the top five drugs with the highest ROR and PRR are alprazolam (ROR: 13.48, PRR: 12.86), zolpidem (ROR: 13.29, PRR: 12.69), bupropion (ROR: 11.58, PRR: 11.13), quetiapine (ROR: 10.66, PRR: 10.28), and fluoxetine (ROR: 10.63, PRR: 10.25).

ROR and PRR values of PTs under the HLT of suicidal and self-injurious behavior

Within the HLT framework of suicidal and self-injurious behavior, ten PTs are identified: suicidal ideation, completed suicide, suicidal behavior, suicide attempt, intentional self-injury, self-injurious ideation, suicide threat, suspected suicide attempt, suspected suicide, and assisted suicide. Of these, reports pertaining to suicidal behavior, self-injurious ideation, assisted suicide, suicide threat, suspected suicide attempt, and suspected suicide are relatively infrequent and are excluded from analysis (detail in Supplementary Table S3–S8). As shown in Tables 3, 4, 5 and 6, the ROR range for suicidal ideation spans from 0.33 to 15.98, with the top five drugs identified as duloxetine (ROR: 15.98, PRR: 15.70), aripiprazole (ROR: 9.43, PRR: 9.34), fluoxetine (ROR: 9.43, PRR: 9.33), sertraline (ROR: 9.19, PRR: 9.10), and venlafaxine (ROR: 8.15, PRR: 8.08). For the Suicide attempt, the ROR range is from 1.91 to 16.92, with alprazolam (ROR: 16.92, PRR: 16.70), zolpidem (ROR: 15.47, PRR: 15.28), quetiapine

Table 3 Top 20 medications associated with suicidal ideation ranked by ROR

Ranking	Drug name	Frequency	ROR (95%CI)	PRR (X2)
1	Duloxetine	3408	15.98 (15.43-16.55)	15.7 (43685.15)
2	Aripiprazole	1850	9.43 (9-9.89)	9.34 (13266.42)
3	Fluoxetine	711	9.43 (8.75-10.16)	9.33 (5216.6)
4	Sertraline	1298	9.19 (8.7-9.72)	9.1 (9118.85)
5	Venlafaxine	1177	8.15 (7.69-8.64)	8.08 (7134.58)
6	Citalopram	1040	7.64 (7.18-8.13)	7.58 (5817.26)
7	Bupropion	664	6.31 (5.85-6.82)	6.27 (2906.06)
8	Sodium oxybate	1225	5.33 (5.04-5.64)	5.3 (4173.77)
9	Quetiapine	797	4.63 (4.32-4.97)	4.61 (2221.03)
10	Olanzapine	532	4.15 (3.81-4.52)	4.13 (1251.16)
11	Gabapentin	730	3.86 (3.59-4.16)	3.85 (1519.37)
12	Pregabalin	1116	3.6 (3.39-3.82)	3.58 (2034.24)
13	Lamotrigine	454	3.51 (3.2-3.85)	3.5 (803.63)
14	Zolpidem	181	3.5 (3.03-4.06)	3.49 (321.23)
15	Alprazolam	286	3.39 (3.02-3.81)	3.38 (476.91)
16	Oxycodone	1089	1.72 (1.62-1.82)	1.72 (317.92)
17	Acetaminophen	387	1.1 (1-1.22)	1.1 (3.79)
18	Amlodipine	186	1.06 (0.92-1.23)	1.06 (0.69)
19	Ibuprofen	111	0.58 (0.48-0.7)	0.58 (34.06)
20	Metformin	72	0.33 (0.26-0.41)	0.33 (99.09)

(ROR: 15.11, PRR: 14.94), aripiprazole (ROR: 13.18, PRR: 13.05), and sertraline (ROR: 9.47, PRR: 9.4) ranking as the top five drugs. The ROR range for completed suicide is from 0.16 to 21.94, with bupropion (ROR: 21.94, PRR: 21.42), alprazolam (ROR: 21.04, PRR: 20.56), zolpidem (ROR: 20.69, PRR: 20.22), amlodipine (ROR: 17.75, PRR: 17.43), acetaminophen (ROR: 14.95, PRR: 14.73). For intentional self-injury, it is from 0.61 to 22.13, the top five drugs associated with this term is sertraline (ROR: 22.13, PRR: 21.96), zolpidem (ROR: 18.77, PRR: 18.64), alprazolam (ROR: 17.81, PRR: 17.69), quetiapine (ROR: 16.94, PRR: 16.84), and fluoxetine (ROR: 15.34, PRR: 15.26).

Table 4 Top 20 medications associated with suicide attempt ranked by ROR

Ranking	Drug name	Frequency	ROR (95%CI)	PRR (X2)
1	Alprazolam	906	16.92 (15.83-18.08)	16.7 (13002.88)
2	Zolpidem	513	15.47 (14.17-16.88)	15.28 (6742.91)
3	Quetiapine	1634	15.11 (14.38-15.89)	14.94 (20193.14)
4	Aripiprazole	1671	13.18 (12.54-13.85)	13.05 (17639.44)
5	Sertraline	879	9.47 (8.85-10.13)	9.4 (6423.75)
6	Acetaminophen	1918	8.86 (8.46-9.28)	8.81 (12487.49)
7	Fluoxetine	428	8.61 (7.82-9.47)	8.55 (2818.15)
8	Olanzapine	700	8.43 (7.82-9.09)	8.38 (4456.07)
9	Citalopram	745	8.34 (7.75-8.97)	8.29 (4669.17)
10	Amlodipine	897	8.06 (7.54-8.61)	8.01 (5354.2)
11	Venlafaxine	744	7.82 (7.27-8.42)	7.78 (4297.14)
12	Ibuprofen	932	7.65 (7.17-8.17)	7.61 (5199.64)
13	Bupropion	475	6.88 (6.28-7.54)	6.85 (2339.33)
14	Lamotrigine	452	5.36 (4.88-5.88)	5.34 (1571.6)
15	Metformin	749	5.34 (4.96-5.74)	5.32 (2567.74)
16	Duloxetine	669	4.48 (4.15-4.83)	4.46 (1762.02)
17	Sodium oxybate	454	2.97 (2.7-3.26)	2.96 (582.35)
18	Gabapentin	272	2.18 (1.93-2.45)	2.17 (170.93)
19	Oxycodone	872	2.11 (1.97-2.25)	2.1 (492.12)
20	Pregabalin	394	1.91 (1.73-2.11)	1.91 (168.44)

General characteristics of antiepileptics, antidepressants and sedative-hypnotics related suicidal and self-injurious behavior AEs

Next, we display the general characteristics of antidepressants (bupropion, fluoxetine, sertraline, citalopram, venlafaxine, and duloxetine), antiepileptics (lamotrigine, gabapentin, and pregabalin), and sedative-hypnotics (alprazolam, zolpidem, and sodium hydroxybutyrate), which are shown to have a high relevance to suicidal and self-injurious behavior adverse events. Figure 2a illustrates that drug-associated suicidal behaviors are more frequent in female, antiepileptics accounted for 63.73% (frequency: 3695), antidepressant drugs accounted for 68.03% (frequency: 12314), and sedative-hypnotics

Table 5 Top 20 medications associated with completed suicide ranked by ROR

Ranking	Drug name	Frequency	ROR (95%CI)	PRR (X2)
1	Bupropion	2039	21.94 (20.97-22.95)	21.42 (37960.36)
2	Alprazolam	1569	21.04 (19.99-22.14)	20.56 (28221.59)
3	Zolpidem	956	20.69 (19.39-22.07)	20.22 (17118.98)
4	Amlodipine	2674	17.75 (17.07-18.47)	17.43 (39005.86)
5	Acetaminophen	4365	14.95 (14.49-15.43)	14.73 (50534.46)
6	Quetiapine	1712	11.04 (10.51-11.58)	10.91 (14844.6)
7	Citalopram	1319	10.55 (9.98-11.14)	10.43 (10933.16)
8	Fluoxetine	681	9.73 (9.01-10.5)	9.63 (5192.25)
9	Gabapentin	1464	8.54 (8.1-9)	8.47 (9338.78)
10	Venlafaxine	1059	7.89 (7.42-8.38)	7.82 (6162.56)
11	Lamotrigine	747	6.28 (5.84-6.76)	6.25 (3240.33)
12	Metformin	1167	5.9 (5.57-6.26)	5.87 (4598.07)
13	Sertraline	619	4.63 (4.28-5.01)	4.61 (1728.96)
14	Oxycodone	2468	4.35 (4.17-4.53)	4.33 (5980.7)
15	Olanzapine	450	3.77 (3.44-4.14)	3.76 (904.21)
16	Ibuprofen	651	3.71 (3.43-4.01)	3.7 (1265.06)
17	Duloxetine	434	2.02 (1.84-2.23)	2.02 (222.38)
18	Aripiprazole	329	1.73 (1.56-1.93)	1.73 (101.41)
19	Pregabalin	174	0.59 (0.51-0.68)	0.59 (49.33)
20	Sodium oxybate	35	0.16 (0.11-0.22)	0.16 (155.52)

Table 6 Top 20 medications associated with intentional self-injury ranked by ROR

Ranking	Drug name	Frequency	ROR (95%CI)	PRR (X2)
1	Sertraline	959	22.13 (20.73-23.63)	21.96 (18002.68)
2	Zolpidem	302	18.77 (16.75-21.05)	18.64 (4945.59)
3	Alprazolam	464	17.81 (16.23-19.53)	17.69 (7089.39)
4	Quetiapine	886	16.94 (15.83-18.14)	16.84 (12452.33)
5	Fluoxetine	366	15.34 (13.83-17.03)	15.26 (4763)
6	Olanzapine	575	14.52 (13.36-15.79)	14.44 (6931.07)
7	Citalopram	509	11.86 (10.86-12.96)	11.81 (4873.82)
8	Venlafaxine	362	7.84 (7.06-8.7)	7.82 (2102.61)
9	Lamotrigine	248	6.07 (5.35-6.88)	6.06 (1030.82)
10	Aripiprazole	306	4.78 (4.27-5.35)	4.77 (894.62)
11	Ibuprofen	217	3.61 (3.15-4.12)	3.6 (402.44)
12	Gabapentin	196	3.25 (2.82-3.74)	3.25 (301.04)
13	Acetaminophen	311	2.83 (2.53-3.17)	2.83 (360.39)
14	Bupropion	86	2.54 (2.05-3.14)	2.54 (79.63)
15	Duloxetine	170	2.32 (1.99-2.7)	2.32 (126.14)
16	Pregabalin	150	1.5 (1.27-1.76)	1.5 (24.46)
17	Amlodipine	61	1.1 (0.85-1.41)	1.1 (0.53)
18	Metformin	73	1.05 (0.83-1.32)	1.05 (0.18)
19	Oxycodone	147	0.72 (0.61-0.85)	0.72 (15.94)
20	Sodium oxybate	46	0.61 (0.46-0.82)	0.61 (11.22)

accounted for 65.42% (frequency: 4285). In Fig. 2b, a higher frequency of suicidal and self-injurious behavior was reported among individuals aged 16–60. Among these age groups, antiepileptic drugs had the highest frequency in the range of 51–55 (frequency: 591), antidepressant drugs had the highest frequency in the range of 16–20 (frequency: 1745), and sedative-hypnotic drugs had the highest frequency in the range of 46–50 (frequency: 634). Figure 3a–c depicts the reporting timelines. Antiepileptic drugs had the highest frequency of reports in the first quarter of 2019, antidepressant drugs in the first quarter of 2017, and sedative-hypnotic drugs in the first quarter of 2014. The outcomes are summarized in Fig. 4, where antiepileptic drugs accounted for 26.2% (frequency: 2544) of reported deaths, antidepressant drugs accounted for 22.2% (frequency: 6647), and sedative-hypnotic drugs accounted for 25.8% (frequency: 2573).

As shown in Fig. 5a, the onset time of suicidal and self-injurious behaviors reported for most of the antiepileptics, antidepressants, and sedative-hypnotics was obtained following the flow. In Fig. 5b–d, the most of onset time were concentrated within 0–30 days, with the highest percentage of sedative-hypnotic drug-related suicidal and self-injurious behavior occurring in more than 360 days, at 20.73%. The cumulative curves of antiepileptic, antidepressant, and sedative-hypnotic onset time are shown in Fig. 5e–g.

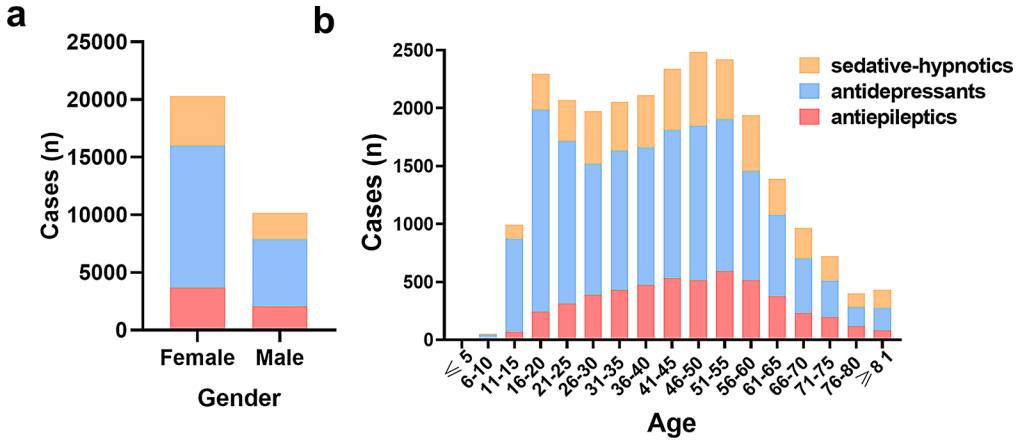

Fig. 2 Gender and age distribution of suicidal and self-injurious behavior AEs associated with antiepileptics, antidepressants, and sedative-hypnotics. **a** Histogram of gender distribution. **b** Histogram of age distribution

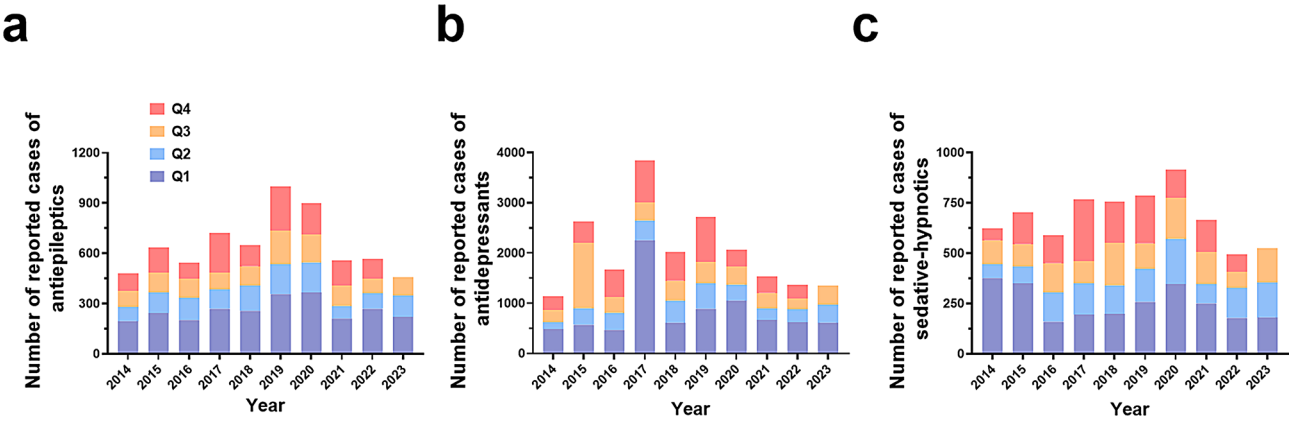

Fig. 3 Reporting time distribution of suicidal and self-injurious behavior AEs associated with antiepileptics, antidepressants, and sedative-hypnotics. **a**–**c** Histogram of reporting time distribution for antiepileptics, antidepressants, and sedative-hypnotics

Discussion

This study elucidates the top 20 drugs with the highest frequency of reported adverse reactions related to suicidal and self-injurious behavior gleaned from the FAERS database over the past decade. It is essential to clarify that the observed correlation in the frequency or intensity of these AEs does not necessarily infer a direct causal link between the administration of these drugs and the subsequent emergence of suicidal tendencies. It is also important to distinguish between self-injurious behavior and suicidal behavior, acknowledging that the former is typically not accompanied by suicidal ideation. The study encompasses a range of pharmaceutical categories, including antidepressants, antipsychotics, sedatives, and antiepileptic medications, thereby offering valuable insights into the potential risks that may be inherent in the clinical use of these medications.

Currently, commonly used antidepressant medications are concerned that they might increase suicide risk in depressed patients, especially in the early stages of treatment and in younger populations [24, 25]. In our analysis of antidepressants, a notable high correlation of suicide ideation, suicide attempt, completed suicide, and Intentional self-injury was observed. Notably, although the number of reports and ROR value for suicidal ideation were significantly higher for duloxetine, the number of reports and ROR value for suicide attempt and completed suicide were significantly lower for duloxetine. On the other hand, the higher number of antidepressant-associated AEs to suicidal or self-injurious behaviors in the 16–20 years of age deserves our attention, and patients in this age group should be more cautious about exposure to antidepressants.

It is noteworthy that despite the known association of many antidepressants with suicidal thoughts or behavior, population cohort studies highlight the reduction in suicide risk associated with long-term treatment using SSRIs [26–28]. Moreover, suicidal ideation or behavior related to antidepressants may correlate with the patient's psychiatric hyperactivity, undiagnosed bipolar disorder, or inadequate response to antidepressants [4, 29, 30]. Questions remain over whether drugs induce suicidal

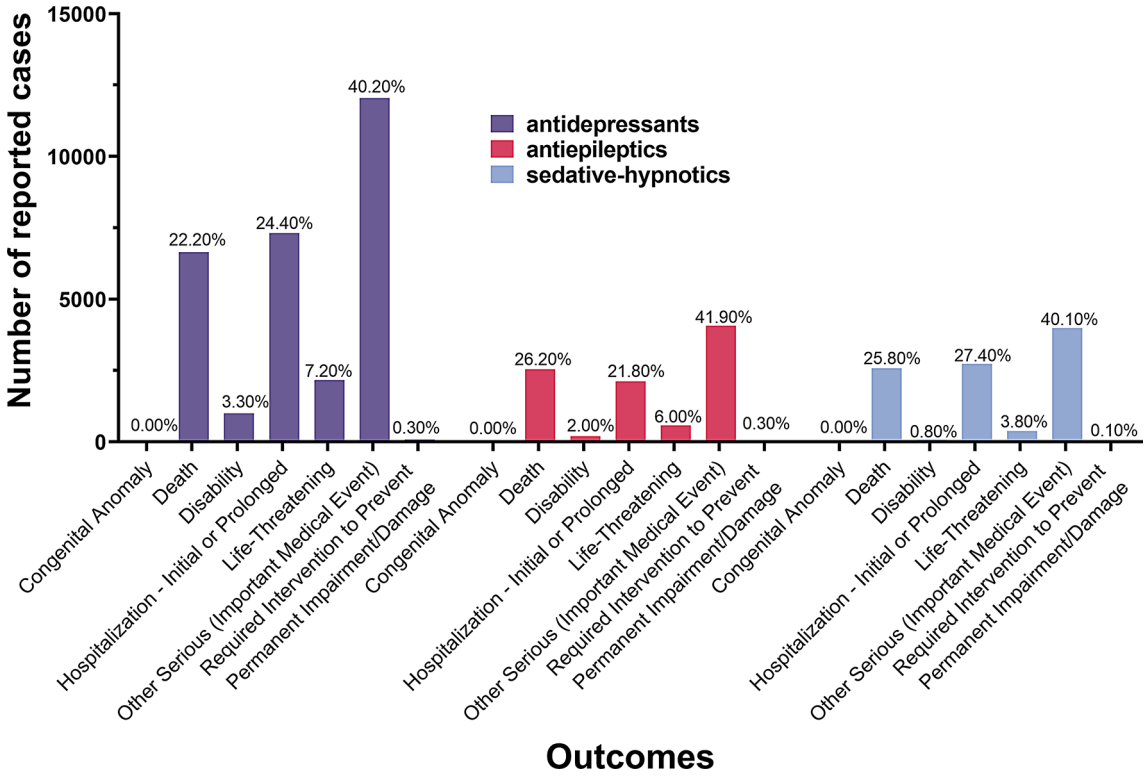

Fig. 4 The outcomes of antidepressants, antiepileptics, and sedative-hypnotics

behaviour, while several studies also indicate that the benefits of antidepressants outweigh the risks, as suicides among depressed patients are more prevalent in those not receiving antidepressant treatment [31]. Hence, antidepressants are encouraged in depressed patients, and the data presented in this study serve as a valuable resource for medication selection and pharmacological monitoring assessments.

In 2008, the FDA issued a warning based on a meta-analysis involving over 40,000 individuals, highlighting the potential of antiepileptic drugs to increase the suicide rate [12]. This warning encompassed drugs such as carbamazepine, gabapentin, lamotrigine, pregabalin, oxcarbazepine, and others. Our findings are not contradictory to the results of this study, suggesting that the use of these medications has a higher incidence of reported adverse events of suicide attempt or intentional self-injury. Hence, prior to initiating treatment with these drugs, patients should undergo a comprehensive assessment for suicide risk and be provided with pertinent precautions. A subsequent meta-analysis by Klein et al. evaluated the prospective suicide risk associated with newer antiepileptic medications post-2008. The analysis revealed that eslicarbazepine acetate, perampanel, brivaracetam, cannabidiol, and saquinavir did not elevate the risk of suicidal ideation or behavior [31]. Further investigation is imperative to delineate the complex relationship between the use of antiepileptic medications and the associated risks of suicidality.

Suicidal ideation and behavior are markedly prevalent among individuals diagnosed with schizophrenia. Epidemiological studies have indicated that approximately 25–50% of individuals with schizophrenia manifest suicidal intent, with 4–13% ultimately succumbing to suicide [32, 33]. Notably, antipsychotic medications have been correlated with a diminished risk of suicide [34, 35]. A cohort study involving over 90,000 individuals with schizophrenia in Sweden and Finland found that clozapine, the only antipsychotic medication that significantly reduces suicide risk, is associated with a lower risk of suicide compared to non-medicated patients, while benzodiazepines increase the risk of suicide among individuals with schizophrenia [36]. Within the scope of this investigation, quetiapine, olanzapine, and aripiprazole were found to have a large number of reported AEs related to suicide attempt or intentional self-injury with high ROR value. Given the substantially elevated risk of suicide or self-injury among individuals with schizophrenia and the absence of evidence supporting an increased suicide risk with antipsychotics, it is postulated that these medications may exhibit a comparatively attenuated effect in mitigating suicide-related risks for this demographic. Consequently, the utilization of clozapine may present as a more advantageous approach when managing

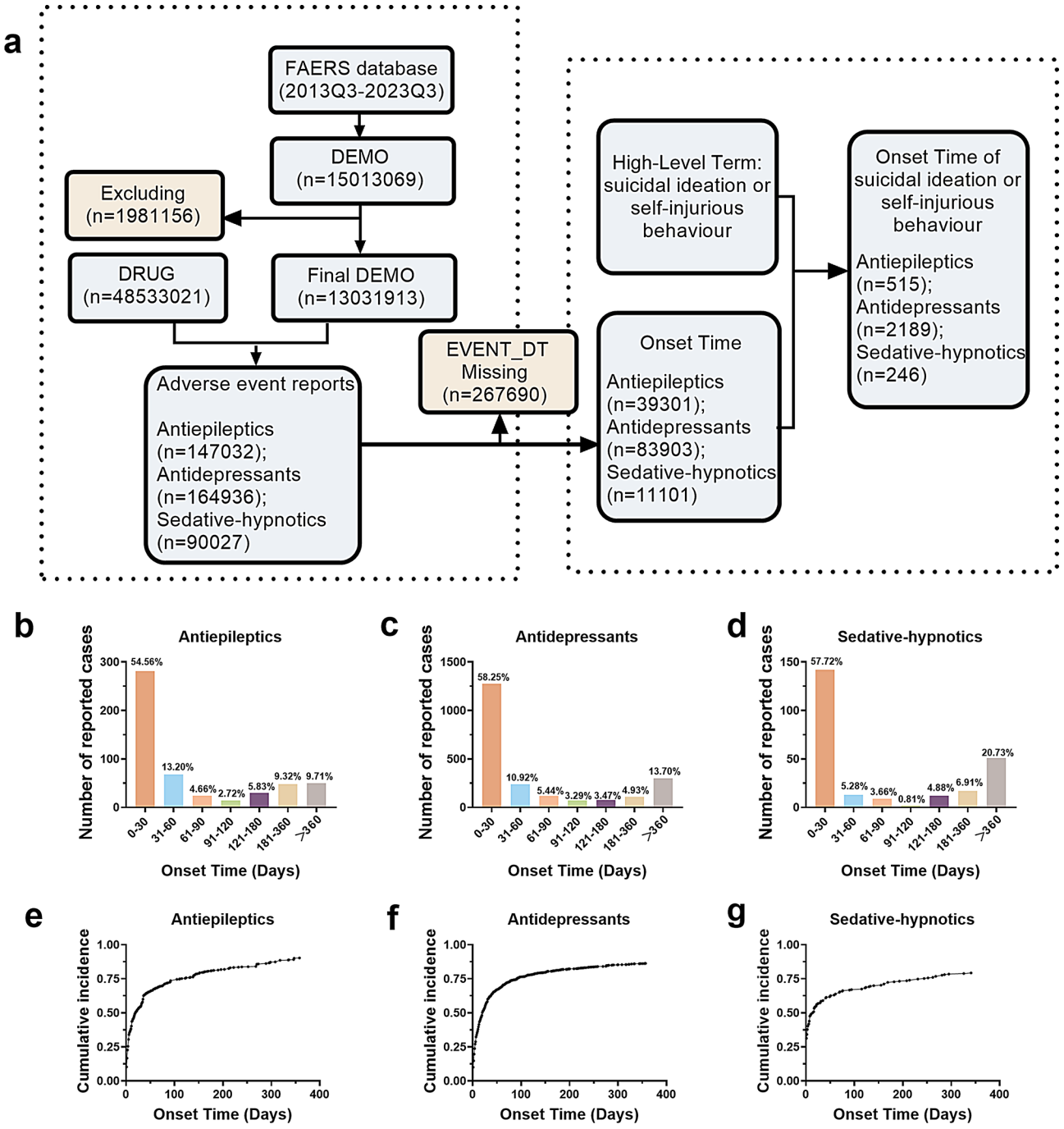

Fig. 5 Onset time for antiepileptics, antidepressants and sedative-hypnotics. **a** Analysis flow of Onset time. **b**–**d** Histogram of Onset time distribution of antiepileptics, antidepressants, and sedative-hypnotics. **e**–**g** Cumulative curves of onset time for antiepileptics, antidepressants, and sedative-hypnotics

individuals with schizophrenia predisposed to suicidal tendencies.

Carlsten et al. established a correlation between sedative administration and elevated suicide risk, persisting after adjusting for any Diagnostic and Statistical Manual of Mental Disorders, thereby designating sedatives as an autonomous suicide risk factor. Additionally, hypnotic drugs exhibit a fourfold surge in suicidal ideation, accompanied by a rise in suspected suicides and suicide attempts linked to antipsychotic or sedative-hypnotic drugs [37]. This is especially notable among individuals aged 13–19, with consequential clinical implications [38]. Nevertheless, the potential for intentional self-injury through the excessive use of sedative hypnotics is also a notable concern [39]. Our study reveals that both suicide attempt and completed suicide, along with intentional

self-injury, exhibit top-tier RORs for both aprazolam and zolpidem. And, the ROR for zolpidem-associated suicidal ideation was 3.5 (3.03–4.06), and for alprazolam, it was 3.39 (3.02–3.81). Overall, the occurrence of suicidal behaviors related to zolpidem and aprazolam surpasses that of suicidal ideation. This is likely attributed to their involvement in deliberate self-poisoning. Therefore, the elevated ROR for these medications in relation to suicide attempts, completed suicides, and intentional self-injury underscore the necessity for a deeper understanding of the mechanisms underlying these associations. It is crucial to accumulate more robust clinical data to validate these findings and to elucidate the precise nature of the relationship between sedative use and suicidal behaviors.

Surprisingly, acetaminophen, ibuprofen, amlodipine, and metformin emerge within the top 20 drugs with notable reporting frequencies of adverse events related to suicidal and self-injurious behavior. In the analysis of PT report intensity, the ROR for suicidal ideation spans from 0.33 to 1.10, while for completed suicide, it ranges from 3.71 to 17.75. Amlodipine exhibits the highest ROR for completed suicide, and acetaminophen stands out with the highest reported cases. A study based on the FAERS highlights acetaminophen, promethazine, amlodipine, quetiapine, and metformin as the most commonly used drugs in deliberate self-poisoning incidents [40]. Incidents of suicide attempts involving excessive doses of amlodipine and acetaminophen have been reported in various studies [41–43]. Given the widespread use and accessibility of medications such as acetaminophen, ibuprofen, amlodipine, and metformin, their frequent association with suicide attempts is not entirely surprising. The most recent data from the ClinCalc DrugStats Database shows metformin and amlodipine ranked #2 and #5, respectively, in terms of number of prescriptions in the U.S. in 2022, and have remained in the top 10 list of prescriptions between 2013 and 2022 [44]. The analysis of the FAERS data underscores the need for a nuanced interpretation of these findings. While these drugs may not be directly linked to drug-induced suicidal behavior, the high incidence of deliberate self-poisoning incidents involving these substances, as reported in various studies, warrants a reevaluation of their regulatory status. Therefore, a more stringent regulatory framework may be necessary to ensure that these drugs are used safely and responsibly, without compromising their availability for legitimate medical purposes.

While this article leverages a substantial sample size from the FAERS database, inherent limitations warrant consideration. FAERS operates as a self-reporting system, introducing potential biases, duplications, and information incompleteness due to the diverse backgrounds of reporting personnel. Additionally, factors such as the progression of underlying diseases or concomitant medication usage may contribute to deviations in the results. The use of ROR and PRR in this study provides insights into the correlation between drugs and adverse effects. However, it is crucial to acknowledge their limitation in accurately calculating the incidence of adverse reactions or establishing a direct causal relationship. Notably, the reported data in FAERS predominantly originate from European and American countries, with relatively sparse data from other countries. Further research is essential to verify whether population differences may impact the generalizability of the study results. Furthermore, the majority of medications discussed in this study are intended for neurological purposes. The observed correlation between these medications and suicidal behavior can partly be attributed to the inherent risk of suicide among the patient population. It's important to note that we lacked information regarding the patients' mental state or disease progression prior to medication initiation, which may have influenced our results. Although our data are objective, there may still be some bias, and thus our data can only support a correlation, not causation, between drug use and suicidal behavior.

Conclusion

We conducted a pharmacovigilance analysis utilizing real-world data from the FAERS database employing the disproportionality method to analyze the 20 drugs exhibiting the highest reported rates of suicidal ideation or self-injurious behavior. Our findings indicate that antidepressants constitute the most reported medication type for AEs associated with suicidal ideation or self-injurious behavior. However, we observed a large number of adverse event reports of suicidal ideation with duloxetine and relatively few reports of suicide attempts. Antiepileptic drugs, such as lamotrigine, gabapentin, and pregabalin, have a high number of suicide-related adverse event reports, and more careful discretion is needed when applying these drugs. Similarly, antipsychotics such as quetiapine and aripiprazole may require a comprehensive assessment of the benefit of the medication over the risk to the patient in patients at higher risk for suicide. Commonly utilized medications like acetaminophen, ibuprofen, amlodipine, and metformin are frequently implicated in deliberate self-harm incidents due to their widespread availability. Consequently, enhanced management protocols for these drugs are imperative to mitigate associated risks effectively. In general, females report a higher number of AEs of suicidal ideation or self-injurious behavior, particularly among individuals aged 16–60 years. Within this age range, individuals who are 16–20 years old and taking antidepressants necessitate the utmost caution.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-025-00858-7.

Supplementary Material 1

Author contributions

Methodology, Wen-long Xie and Dao-chun Xiang. Software, Wen-long Xie and Dao-chun Xiang. Data curation, Wen-long Xie, Dao-chun Xiang, and Meng-lan Ge. Formal analysis, Wen-long Xie, Meng-lan Ge and Yuan-yuan Li. Funding acquisition, Yuan-yuan Li and Ai-ping Deng. Supervision, Yuan-yuan Li and Ai-ping Deng. Writing original draft, Wen-long Xie, Dao-chun Xiang and Ai-ping Deng. All authors contributed to the article and approved the submitted version.

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Data availability

The original contributions presented in the study are included in the article/Supplementary Material. The raw data for this study are all available from the FAERS website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). Other requests about the data in the manuscript can be submitted in writing to the corresponding author.

Declarations

Ethics approval and consent to participate

Ethical approval was not required for the study involvinghumans in accordance with the local legislation and institutionalrequirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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