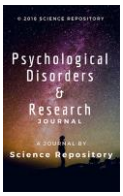

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Research Article

Drug-Associated Delirium Identified in The Food and Drug Administration Adverse Events Reporting System

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ABSTRACT

Introduction: Drug toxicity and polypharmacy are major risk factors for delirium, especially in older adult patients with underlying comorbidities. However, numerous case reports have described drugs with a lower suspicion of being deliriogenic. The objective of this study was to identify deliriogenic drugs in the Food and Drug Administration Adverse Events Reporting System (FAERS) to broaden the public knowledge and understanding.

Study Design: Retrospective pharmacovigilance evaluation.

Methods: FAERS reports from 2004 through 2015 were reviewed for delirium-associated terms, which were utilized to identify drugs most frequently reported to cause delirium. Drugs were categorized as: 1) known to be deliriogenic; 2) potentially deliriogenic; or 3) new potential to be deliriogenic. The 100 most frequently reported drugs were analyzed in reporting odds ratios (ROR).

Results: Of the known deliriogenic drugs (n=32), paroxetine (ROR 4.1, CI 4.0-4.3), olanzapine (ROR 3.3, CI 3.2-3.4), and clozapine (ROR 2.9, CI 2.8-3.0) were most reported. Of the potentially deliriogenic drugs (n=54), duloxetine (ROR 3.2, CI 3.1-3.3), varenicline (ROR 3.1, CI 3.0-3.2), and gabapentin (ROR 2.9, CI 2.7-3.0) were most reported. Three drugs were considered to have new potential to be deliriogenic: heparin (ROR 1.5, CI 1.4-1.6), metformin (ROR 1.3, CI 1.3-1.4), and dalfampridine (ROR 1.1, CI 1.1-1.2).

Conclusion: The majority of drugs were considered potentially deliriogenic. FAERS can provide post-marketing surveillance data to guide future studies on potentially deliriogenic drugs to guide management of causal agents.

Introduction

The reported rate of delirium among hospitalized patients is approximately 10-50% depending on hospitalization status and patient comorbidities [1]. According to Diagnostic and Statistical Manual of Mental Disorders (DSM-5), delirium is defined as "a disturbance in attention, awareness, and cognition that develops over a short period of time; or a condition that is not better explained by another preexisting or established neurocognitive disorder often caused by a medical condition, substance intoxication or withdrawal, or medication side effect" [2]. Patients may present with different signs and symptoms, such as hyperactive, hypoactive, or mixed-type delirium [1, 2]. Signs and symptoms of delirium are usually nonspecific and vary by patient, which may lead to a missed or delayed diagnosis [1, 3]. In addition, delirium or acute confusional st ate is associated with psychomotor behavioral or emotional disturbances [4]. Delirium can be detrimental to patient recovery due to an increased hospital length of stay, increased risk for hospital-acquired complications, and increased hospital costs (up to $152 billion in US dollars in the elderly) [1, 4]. Delirium is a common

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condition caused by a wide variety of risk factors such as physiological abnormalities and drugs [1].

Drug toxicity and polypharmacy are major drug-related risk factors for delirium, especially for older adult patients with underlying comorbidities [5]. Historically, anticholinergic agents, antipsychotics, benzodiazepines, and opioids are known to be highly deliriogenic, but the incidence of their occurrence varies among existing literature [5, 6]. However, numerous case reports demonstrate that drugs with a low suspicion to be deliriogenic may actually be deliriogenic.

The Food and Drug Administration Adverse Event Reporting System (FAERS) includes both manufacturer and consumer-reported adverse events from throughout the world, which supports its utility in screening and analyzing the association between the drugs and delirium [7]. The reports are often voluntary submissions and are reviewed by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for new safety concerns [7]. This database may serve as another mode of evaluating post-market drug safety issues, such as delirium. The objective of this study was to identify known, potential, and new potential deliriogenic drugs through a large database to broaden the public knowledge of drugs related to delirium.

Methods

Adverse event reports in FAERS for 7.2 million reports from Q1 2004 through Q3 2015 were reviewed to identify the most specific and relevant search terms for delirium. Three investigators examined the list of terms independently (SC, AW, SKG), and the (Table 1) shows the final list of 82 delirium-associated words that were agreed upon by all three investigators. The FAERS database was utilized to compile adverse event reports according to the delirium search terms. The dataset was sorted and organized to identify drugs that were reported to be the primary drug associated with delirium.

Table 1: Delirium-associated terms (n=82)

Acute psychosis	Delusional disorder persecutory	Hypnopompic hallucination
Agitated depression	Delusional disorder, somatic type	Hypomania
AGITATED DEPRESSION	Delusional disorder, unspecified	Hysterical psychosis
Agitation[a]	Delusional perception	Illogical thinking
Agnosia	Delusions, mixed	Illusion
Altered state of consciousness	Depersonalisation	Impaired reasoning
Anterograde amnesia	Depressed level of consciousness[a]	Incoherent
Anticholinergic syndrome	Depressive delusion	Jealous delusion
Behavioral and psychiatric syndrome	Derealisation	Judgement impaired
Borderline mental impairment	Disorganized speech	Mental impairment[a]
Brief psychotic disorder	Disorientation[a]	Mental status changes[a]
Change in sustained attention	Dissociation	Neurological decompensation
Cognitive deterioration	Dissociative amnesia	Neuropsychiatric syndrome
Cognitive disorder[a]	Dissociative disorder	Paramnesia
Confabulation	Dissociative fugue	Paranoia
Confusional arousal	Dissociative identity disorder	Persecutory delusion
Confusional state[a]	Disturbance in attention[a]	Pseudodementia
Consciousness fluctuating	Dreamy state	Psychiatric evaluation abnormal
Delirium[a]	Hallucination[a]	Psychiatric symptom
Delusion	Hallucination, auditory	Psychomotor agitation
Delusion of grandeur	Hallucination, gustatory	Psychomotor hyperactivity
Delusion of reference	Hallucination, olfactory	Psychomotor retardation
Delusion of replacement	Hallucination, synaesthetic	Psychomotor skills impaired
Delusional disorder, erotomania	Hallucination, tactile	Psychotic behaviour
Delusional disorder, grandiose	Hallucination, visual	Reactive psychosis
Delusional disorder, jealous type	Hallucinations, mixed	Rebound psychosis
Delusional disorder, mixed type	Hypnagogic hallucination	Time perception altered
		Transient psychosis

a. Top 10 terms that were most frequently associated with delirium

Drugs that were most frequently associated with selected delirium terms were extracted. These drugs were further evaluated for other possible names for the drugs including different brand names, dosage forms, multiple doses, and misspelled names. The top 100 drugs were analyzed. Two drug information databases (Lexi-Comp, Micromedex), one reference book, and one review article were referenced to categorize the top 100 drugs that were associated with the most frequently reported delirium cases [8-11]. This approach to categorize drugs has been used previously [12, 13]. Those drugs were then classified into one of three categories:

1) drugs known to be deliriogenic if the drug is associated with delirium in at least 3 of 4 references,
2) drugs with potential to be deliriogenic if listed in 1 to 2 references, or
3) drugs with new potential to be deliriogenic if the drug was not listed in any of the drug references.

Statistical Analysis

The top 100 drugs that had the highest numbers of reports associated with delirium terms were analyzed by reporting odds ratio (ROR), which is the ratio of the odds of reporting of one specific event compared to all other events of a given drug for all other drugs present in the database [14].

$$\text{ROR} = \frac{(\text{n11 x n00})}{(\text{n10 x n01})}$$ [15].

n11 = reports of delirium for the drug of interest
n01 = reports of delirium not including the drug of interest
n10 = reports not including delirium for the drug of interest
n00 = reports including neither delirium nor the drug of interest

The ROR has its utility in estimating risk, with a higher value for the ratio representing stronger disproportionality [14]. In other words, the higher the ROR is, the drug is more likely to be reported for delirium compared to other drugs. Individual drugs that were coded into specific formula for SPSS Statistics Software version 25 (IBM Corp., Armonk, NY). The 95% confidence intervals were also calculated.

Results

Among 7.2 million FAERS reports, 277,123 (3.8%) were due to delirium associated adverse events. Varenicline was the drug with the most number of reports for delirium (2.8%). Drugs that had the highest ROR were zanamivir (ROR 8.32, CI 7.69-9.00), memantine (ROR 8.15, CI 7.70-8.63), valacyclovir (ROR 7.87, CI 7.49-8.27), lithium (ROR 7.08, CI 6.50-7.69), zolpidem (ROR 6.74, CI 6.41-7.11), lorazepam (ROR 6.39, CI 5.90-6.92), donepezil (ROR 5.98, CI 5.55-6.44), acyclovir (ROR 5.88, CI 5.43-6.37), valproic acid (ROR 5.47, CI 5.23-5.72), and oseltamivir (ROR 5.15, CI 4.88-5.43). (Table 2) Twenty-six drugs of the top 100 drugs had an ROR less than 1.

Table 2: Numbers of delirium-associated reports, reporting odds ratio, and confidence for top 100 drugs

Drug	Numbers of delirium associated reports	Reporting odds ratio	Confidence interval
Varenicline	7703	3.08	3.01-3.16
Natalizumab	7056	1.23	1.20-1.26
Pregabalin	5634	2.20	2.14-2.26
Interferon beta-1a	5453	1.33	1.30-1.37
Paroxetine	5166	4.15	4.02-4.27
Quetiapine	4956	2.51	2.44-2.59
Duloxetine	4554	3.23	3.13-3.33
Clozapine	4098	2.92	2.83-3.02
Risperidone	3291	2.88	2.77-2.98
Olanzapine	3161	3.27	3.15-3.40
Sertraline	2829	3.28	3.15-3.41
Oxycodone	2769	2.91	2.79-3.02
Gabapentin	2691	2.86	2.75-2.98
Venlafaxine	2665	4.00	3.84-4.17
Lamotrigine	2619	2.28	2.19-2.37
Aripiprazole	2603	2.52	2.42-2.63
Valproic acid	2315	5.47	5.23-5.72
Bupropion	2280	3.09	2.96-3.23
Adalimumab	2211	0.21	0.20-0.22
Atomoxetine	2171	3.51	3.36-3.67
Valacyclovir	2030	7.87	7.49-8.27
Citalopram	2005	4.33	4.13-4.54
Zoledronic acid	2004	1.11	1.07-1.17
Rofecoxib	1938	0.77	0.74-0.81
Fentanyl	1893	2.00	1.91-2.10
Etanercept	1843	0.15	0.14-0.16
Baclofen	1800	2.98	2.83-3.12
Zolpidem	1797	6.74	6.41-7.11
Rivastigmine	1715	4.89	4.64-5.15
Lenalidomide	1672	0.46	0.44-0.48
Teriparatide	1620	0.62	0.59-0.65
Oseltamivir	1594	5.15	4.88-5.43
Morphine	1568	3.12	2.96-3.29
Alendronate	1556	0.89	0.85-0.94
Memantine	1548	8.15	7.70-8.63
Carbamazepine	1497	3.07	2.91-3.24

Escitalopram	1488	4.09	3.87-4.32
Levetiracetam	1431	2.65	2.51-2.80
Fluoxetine	1417	2.95	2.80-3.12
Atorvastatin	1390	0.65	0.61-0.68
Topiramate	1366	3.29	3.11-3.49
Dianeal	1366	0.35	0.33-0.36
Bevacizumab	1322	0.78	0.74-0.83
Montelukast	1309	3.24	3.05-3.43
Mirtazapine	1294	4.49	4.23-4.76
Paliperidone	1254	2.61	2.47-2.77
Ziprasidone	1253	3.91	3.69-4.15
Fingolimod	1243	1.24	1.17-1.31
Ciprofloxacin	1206	2.28	2.15-2.42
Methylphenidate	1158	4.25	4.00-4.52
Sunitinib	1158	0.96	0.70-1.02
Simvastatin	1110	1.40	1.31-1.48
Digoxin	1096	3.00	2.82-3.20
Alprazolam	1065	2.20	2.07-2.34
Levofloxacin	1056	1.66	1.56-1.77
Pamidronate	1055	3.28	2.98-3.39
Desvenlafaxine	1051	2.13	2.00-2.27
Infliximab	1040	0.26	0.24-0.27
Metformin	1035	1.34	1.25-1.42
Haloperidol	1009	4.50	4.21-4.82
Moxifloxacin	1000	1.88	1.77-2.01
Sorafenib	952	1.26	1.18-1.35
Exenatide	950	0.42	0.39-0.44
Pramipexole	949	3.85	3.59-4.12
Drospirenone/ethinyl estradiol	950	0.34	0.32-0.36
Ropinirole	911	3.70	3.45-3.96
Phenytoin	908	2.17	2.03-2.32
Cyclosporine	905	1.53	1.43-1.64
Lisdexamfetamine	897	4.68	4.36-5.03
Clarithromycin	883	3.40	3.17-3.65
Donepezil	863	5.98	5.55-6.44
Zanamivir	822	8.32	7.69-9.00
Tramadol	805	3.78	3.51-4.07
Dabigatran	781	0.44	0.41-0.48
Esomeprazole	769	0.45	0.42-0.49
Lorazepam	768	6.39	5.90-6.92
Rituximab	748	0.59	0.55-0.63
Heparin	747	1.51	1.40-1.63
Acyclovir	735	5.88	5.43-6.37
Bortezomib	725	0.96	0.89-1.03
Nicotine	719	0.71	0.66-0.77
Lithium	697	7.08	6.50-7.69
Telaprevir	686	0.66	0.61-0.71
Acetaminophen	664	1.25	1.16-1.35
Ibuprofen	660	0.71	0.66-0.77
Dalfampridine	660	1.15	1.06-1.24
Insulin lispro	642	0.54	0.50-0.59
Tacrolimus	639	0.82	0.76-0.89
Buprenorphine	613	0.68	0.62-0.73
Erlotinib	596	0.54	0.50-0.58
Levothyroxine	595	1.08	0.99-1.17

Diazepam	585	2.68	2.46-2.92
Temozolamide	574	1.97	1.81-2.15
Rosuvastatin	568	0.44	0.41-0.48
Ramipril	562	1.97	1.81-2.14
Oxcarbazepine	559	2.84	2.60-3.09
Clonazepam	557	3.69	3.38-4.04
Omeprazole	549	1.16	1.06-1.26
Octreotide	543	1.02	0.93-1.11
Celecoxib	541	0.41	0.37-0.44

Drugs with ROR greater than 1 are bolded

Table 3: Categorization of top 100 drugs

Drugs known to be deliriogenic[a] (n=32)	**Drugs with potential to be deliriogenic[a] (n=54)**	**Drugs with new potential to be deliriogenic[a] (n=14)**
[3] Pregabalin	[1] Varenicline	[24] Rofecoxib[b]
[5] Paroxetine	[2] Natalizumab	[26] Etanercept[b]
[6] Quetiapine	[4] Interferon beta-1a	[42] Dianeal[b]
[8] Clozapine	[7] Duloxetine	[58] Infliximab[b]
[9] Risperidone	[13] Gabapentin	[59] Metformin
[10] Olanzapine	[16] Aripiprazole	[63] Exenatide[b]
[11] Sertraline	[19] Adalimumab[b]	[74] Dabigatran[b]
[12] Oxycodone	[20] Atomoxetine	[77] Rituximab[b]
[14] Venlafaxine	[21] Valacyclovir	[78] Heparin
[15] Lamotrigine	[22] Citalopram	[83] Telaprevir[b]
[17] Valproic acid	[23] Zoledronic acid	[86] Dalfampridine
[18] Bupropion	[27] Baclofen	[87] Insulin lispro[b]
[25] Fentanyl	[28] Zolpidem	[90] Erlotinib[b]
[33] Morphine	[29] Rivastigmine	[91] Levothyroxine
[39] Fluoxetine	[30] Lenalidomide[b]	
[45] Mirtazapine	[31] Teriparatide[b]	
[47] Ziprasidone	[32] Oseltamivir	
[49] Ciprofloxacin	[34] Alendronate[b]	
[53] Digoxin	[35] Memantine	
[54] Alprazolam	[36] Carbamazepine	
[55] Levofloxacin	[37] Escitalopram	
[60] Haloperidol	[38] Levetiracetam	
[67] Phenytoin	[40] Atorvastatin[b]	
[70] Clarithromycin	[41] Topiramate	
[73] Tramadol	[43] Bevacizumab	
[76] Lorazepam	[44] Montelukast	
[82] Lithium carbonate	[46] Paliperidone	
[85] Ibuprofen[b]	[48] Fingolimod	
[89] Buprenorphine[b]	[50] Methylphenidate	
[92] Diazepam	[51] Sunitinib[b]	
[97] Clonazepam	[52] Simvastatin	
[100] Celecoxib[b]	[56] Pamidronate	
	[57] Desvenlafaxine	
	[61] Moxifloxacin	
	[62] Sorafenib	
	[64] Pramipexole	
	[65] Drospirenone/ethinyl estradiol[b]	
	[66] Ropinirole	
	[68] Cyclosporine	
	[69] Lisdexafetamine	
	[71] Donepezil	
	[72] Zanamivir	
	[75] Esomeprazole[b]	

	[79] Acyclovir [80] Bortezomib[b] [81] Nicotine[b] [84] Acetaminophen [88] Tacrolimus[b] [93] Temozolamide [94] Rosuvastatin[b] [95] Ramipril [96] Oxcarbazepine [98] Omeprazole [99] Octreotide	

a. ranked by the number of the delirium-associated reports (e.g., [1] had the most reports)
b. indicates the drug with ROR less than 1

Of 100 drugs that had the highest frequencies of delirium-associated adverse events reports, 32 drugs were identified as known to be deliriogenic, 54 drugs were found to have potential to be deliriogenic, and 14 drugs were identified as drugs with new potential to be deliriogenic. (Table 3) Of the known deliriogenic drugs, paroxetine (ROR 4.15, CI 4.02-4.27), olanzapine (ROR 3.27, CI 3.15-3.40), clozapine (ROR 2.92, CI 2.83-3.02), quetiapine (ROR 2.51, CI 2.44-2.59), and pregabalin (ROR 2.20, CI 2.14-2.26) were most frequently reported. Ibuprofen, buprenorphine, and celecoxib were recognized as drugs known to be deliriogenic since they were referenced in 3-4 sources; however, their RORs were less than 1. Of the potentially deliriogenic drugs (n=54), duloxetine (ROR 3.23, CI 3.13-3.33), varenicline (ROR 3.08, CI 3.01-3.16), gabapentin (ROR 2.86, CI 2.75-2.98), interferon beta-1a (ROR 1.33, CI 1.30-1.37), and natalizumab (ROR 1.23, CI 1.20-1.26) were most reported. Among these 54 drugs, 11 had ROR less than 1.

A total of 14 drugs were identified as drugs with new potential to be deliriogenic. Only three of the 14 drugs had RORs that were greater than 1: heparin (ROR 1.51, CI 1.40-1.63), metformin (ROR 1.34, CI 1.25-1.42), and dalfampridine (ROR 1.15, CI 1.06-1.24). The calculated ROR for varenicline was 3.08, which means that varenicline was three times more likely to be reported for delirium compared to other adverse events. Zanamivir, which was categorized as a drug with potential to be deliriogenic, was associated with the highest ROR of 8.32 (CI 7.69-9.00). However, the number of adverse events reports for zanamivir was only 822 compared to 7703 for varenicline.

Discussion

This was a retrospective pharmacovigilance analysis of one of the most frequently reported adverse drug events, delirium, using almost 12 years of FAERS data. There are multiple challenges in identifying drug-associated causes of delirium in clinical practice with the major one being our understanding of definitive causal relationships. We have identified the top 100 drugs that had the most reports associated with delirium. Of those drugs, 29 were known to be deliriogenic, 43 had potential to be deliriogenic, and 3 were with the new potential to be deliriogenic.

Drug-associated delirium occurs in 30% of patients, with benzodiazepines a leading cause of delirium [16]. However, our findings through FAERS data demonstrated that there were other drug classes that have reports associated with delirium. While a list of known deliriogenic drugs can be constructed, the list of potential deliriogenic drugs is more substantial. This analysis demonstrated that in a post-marketing surveillance database almost twice the number of reports (out of the top 100) were attributed to potentially deliriogenic drugs compared to drugs that were known to be deliriogenic. Understanding the frequency at which these potentially deliriogenic drugs are attributed as a primary cause of delirium assists with clinician's knowledge and possible prevention of delirium in practice with these new causal agents.

Among the drugs that were known to be deliriogenic (n=32), three drugs (ibuprofen, buprenorphine, and celecoxib) had RORs less than 1, indicating that these drugs were more likely to be associated with non-delirium adverse events when compared to other drugs. Even though the majority of the common drug information resources identified them as deliriogenic, FAERS database did not show the significance in reporting of deliriogenicity for those drugs, demonstrating that there is a gap in between available drug resources and post-market drug adverse event reports. Thus, we need to be more vigilant in investigating adverse effects of already marketed drugs with various strategies.

Notably, only three drugs were identified as new potential to be deliriogenic. This being a relatively small number is supported by a previous study, which conducted a similar analysis using FAERS to identify known, potential, and new potential drugs associated with acute kidney injury [12]. In the analysis, 64.8% of drugs were identified to be new potential nephrotoxins. Also, search terms for acute kidney injury were narrowed to 22 terms, which is a significantly smaller number of terms compared to 82 terms that we used for delirium [12]. This may be attributed to the subjectivity and ambiguity in defining and diagnosing the delirium. In our identification of three newly potential deliriogenic drugs, it is unclear if heparin and metformin have a direct association or if the "delirium" is attributed to significant bleeding or symptoms of hypoglycemia associated with other antidiabetic drugs, respectively. The deliriogenicity of dalfampridine should be investigated further. It is possible that progression of multiple sclerosis while on dalfampridine may affect the central nervous system, leading to symptoms misdiagnosed as delirium. Still, the FAERS database identified dalfampridine as a primary reported cause of delirium, indicating the person reporting believed the event to be worth the time and effort to report.

Post-marketing surveillance is lacking and the FAERS database provides

a unique opportunity to generate hypothesis-driven data. The list of potential and new potential deliriogenic drugs requires mechanistic plausibility research to determine a definitive association. Updating a list of drugs associated with delirium provides insight for clinicians, which may allow for the prevention of delirium or more timely diagnosis of delirium, preventing further adverse effects. To our knowledge, this is the first analysis of the FAERS database to identify deliriogenic drugs.

Limitations

There are limitations associated with this analysis. Even though an attempt was made to standardize drug names, there may still be old or new brand names or other dosage forms that may have not been included in the analysis. We used RORs for a comparison of other reports in the database; while this is a common approach for previous FAERS research, it is important to note that RORs are influenced by the number of reports. For example, memantine had a ROR of 8.15, which is significantly higher than varenicline, which had an ROR of 3.08. However, memantine's reported delirium-associated events were 1548, compared to 7703 reports for varenicline. The number of reports analyzed would be affected by the selection of delirium terms. There were 82 terms that were selected for the data analysis for this study, but if we were to use just the term "delirium", then the results may have been different. Our term selection process was intentionally inclusive in an effort to capture the full magnitude of deliriogenic drugs. However, this was a subjective process that may be overestimating the actual rate of these events. The data in the FAERS are limited by a formal causal analysis and confounders are not available to be considered either.

Conclusion

The majority of drugs identified were considered potentially deliriogenic. Large databases such as FAERS can provide post-marketing surveillance data to guide future studies on potentially deliriogenic drugs to guide future management of causal agents.

Acknowledgments

None.

Conflicts of Interest

The authors declare no conflict of interest.

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