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Drug Associated Guillain-Barre Syndrome: Analysis of the FDA Adverse Event Reporting System (FAERS) Database and Review of Literature

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Abstract

Background: Guillain-Barre Syndrome (GBS) is an autoimmune-mediated disorder that can be triggered by infections, autoimmune diseases, and certain medications. Still, a comprehensive list of drugs causing GBS has not been established. This study aims to comprehensively characterize patients who have developed GBS concerning various drugs and evaluate and compare their potential associations using the FDA Adverse Event Reporting System (FAERS).

Methods: A Retrospective Pharmacovigilance study of the FAERS database was conducted to extract adverse reports related to GBS and its variants. Using open Vigil 2.1., all the drugs mentioned in the Adverse event reports were identified, and drugs with a reporting frequency> 20 underwent Disproportionality and Bayesian analyses. Furthermore, a literature search was conducted to identify existing evidence on drugs that showed significant associations.

Results: From 1989 to September 2022, 4883 adverse event reports related to GBS, and its variants were retrieved from 24,953,348 reports in the FAERS database. Excluding missing data, the patient's mean age was 53.80 ±18.54 years, and 50.65% were males. 92.4% of adverse event reports did not specify any GBS variant, while Miller-Fisher syndrome and Acute motor-sensory axonal neuropathy were the most reported variants. Most required hospitalization (64.33%), with 428 (9.3%) reported deaths. The Disproportionate and Bayesian analyses identified 60 drugs with significant signals, mainly Antineoplastic, Antimicrobial & Monoclonal antibodies. Drugs with ROR> 10 include Basiliximab, alemtuzumab, atezolizumab, ipilimumab, bortezomib, fludarabine, and stavudine. Basiliximab has the highest ROR (Reporting Odds Ratio) and PRR (Proportionality Reporting Ratio). The literature search verified that many case reports had previously linked these drugs to GBS.

Conclusion: Using FAERS, this study comprehensively characterizes patients who have developed GBS in relation to drugs and found a significant association between GBS and many Antineoplastic, Antimicrobial & Monoclonal antibodies, highlighting the utmost importance for healthcare providers to exercise caution when administering these medications.

Keywords: Drug Associated GBS; Drug Induced GBS; Faers; Drugs; Guillain Barre Syndrome; GBS

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Abbreviations

GBS: Guillain-Barre Syndrome; FAERS: FDA Adverse Event Reporting System; ROR: Reporting Odds Ratio; PRR: Proportionality Reporting Ratio; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; ICI: Immune Checkpoint Inhibitors; PTs: Preferred Terms; BCPNN: Bayesian Confidence Propagation Neural Network; MGPS: Multi-item Gamma Poisson Shrinker.

Introduction

Guillain-Barre syndrome (GBS) is an acute autoimmune-mediated disorder of the peripheral nervous system with an estimated annual incidence of 100,000 cases worldwide [1]. It is characterized by progressive, primarily ascending, bilateral and relatively symmetrical limb weakness, coupled with generalized hyporeflexia or areflexia. In certain instances, it may be further complicated by respiratory failure or autonomic dysfunction [2]. Although the etiology of GBS is not fully understood, it is widely acknowledged that various infectious agents, such as *Campylobacter jejuni, Mycoplasma pneumoniae, Cytomegalovirus, Epstein-Barr virus, Zika Virus,* Severe Acute Respiratory Syndrome Coronavirus 2(SARS-CoV-2), as well as non-infectious triggers such as surgery, trauma, bone marrow transplantation, Hodgkin's disease and other autoimmune diseases like systemic lupus erythematosus and sarcoidosis, can elicit an immune response that ultimately leads to the development of GBS [2-6].

Recently, there has been increasing recognition of GBS as a potential adverse effect of several medications. Many medications, including Immune checkpoint inhibitors (ICI), tumor necrosis factor-alpha antagonists, tacrolimus, and isotretinoin [7-10], have been reported to cause GBS, but no definite relationships have been established [11]. Also, the mechanisms underlying drug associated GBS are not fully understood, and a comprehensive list of medications that may trigger GBS has yet been established. To fill this gap, we sought to analyze FDA Adverse Event Reporting System (FAERS) database. The FAERS is the largest publicly available database for post-marketing drug safety monitoring containing adverse event and medication error reports submitted by health professionals, consumers, and manufacturers worldwide. It is a valuable pharmacovigilance tool in revealing new safety issues, especially for novel drugs and rare adverse drug reactions [12]. Given the potential severity of GBS and the increasing number of drugs implicated in its pathogenesis, there is a need for further research to better understand the relationship between drug exposure and the development of GBS. Analysis of the FEARS database can provide valuable insights into the characteristics, outcomes, and associations between specific drugs and the development of GBS, including any newly identified drug-GBS links. This information can improve our understanding of drug associated GBS, inform clinical decision-making, and promote drug safety. This study aimed to comprehensively characterize the patients who developed GBS associated with various drugs and further evaluate and compare their potential associations using the FAERS.

Materials and Methods

Data Source & Study Design

FAERS database includes the following seven datasets: demographic and administrative information, drug information, adverse events, patient outcomes, report sources, start and end dates for reported drugs and indications for use [12]. A retrospective pharmacovigilance study is conducted using the data extracted from the FAERS database from the 1st quarter of 1983 to the 3rd Quarter of 2022. The adverse event reports of GBS are searched using the preferred terms (PTs) "Guillain-Barre syndrome", "Acute Inflammatory Demyelinating Polyneuropathy", "Miller-Fisher syndrome", "Acute Motor Axonal Neuropathy", and "Acute Motor Sensory Axonal Neuropathy", "Bickerstaff Encephalitis".

Statistical Analysis

Descriptive analysis was conducted using SPSS to summarize the demographic and clinical characteristics of adverse event reports associated with GBS and its variants. To further analyze the adverse event reports, drugs with a reporting frequency of at least 20 were identified and subjected to four data mining algorithms [13], namely the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) of the Disproportionality methods [14,15], as well as the Bayesian Confidence Propagation Neural Network (BCPNN) and Multi-item Gamma Poisson Shrinker (MGPS) of the Bayesian methods [16]. These algorithms were chosen for their effectiveness in generating hypotheses on potential associations between drugs and adverse events. The study aimed to identify signals between drug therapy and adverse events associated with GBS and its variants by combining Disproportionality and Bayesian methods. Table 1 provides the criteria and formulas for the above data mining algorithms. The Open Vigil 2.1 [17], a validated pharmacovigilance data extraction, cleaning, and mining tool of the FAERS database, was used to construct two-by-two tables for each drug and adverse event pair. The four algorithms (ROR, PRR, MGPS, BCPNN) were calculated from these 2x2 tables using the equations shown in the table. A signal for GBS and its variants is considered significant when at least one of the four algorithms meets the criteria, indicating a statistical association between drug therapy and an adverse event.

Reporting Odds Ratio (ROR)	ROR=ad/b/c 95% CI=eIn(ROR)+1.96(1/a+1/b+l/c+1/d)^0.5	The lower limit of 95% CI>I, N≥3
Proportional Reporting Ratio (PRR)	PRR=a(c+d)/c/(a+b) x^2=[(ad-bc)^2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]	PRR≥2, x^2>4, N≥3
Bayesian Confidence Propagation Neural Network (BCPNN)	IC=$\log_2$a(a+b+c+d)/((a+c)(a+b)) 95% CI= E(IC) + 2V(IC)^0.5	IC025>0
Multi-item Gamma Poisson Shrinker (MGPS)	EBGM=a(a+b+c+d)/(a+c)/(a+b) 95%CI=eIn(EBGM)±1.96(1/a+1/b+l/c+l/d)^0.5	EBGM05>2

Table 1: Algorithms which are used for Disproportionality and Bayesian analysis.

In the above equations, the following variables are utilized to examine the relationship between a specific drug and a particular adverse drug reaction (ADR): a) Count of reports containing both the specific drug and the particular ADR, b) Count of reports with the specific drug and different ADRs, c) Count of reports with the particular ADR, but involving other drugs, d) Count of reports including other drugs and different ADRs.

Abbreviations: CI (95%): 95% Confidence Interval, N: Total count of reports, χ^2: Chi-squared test statistic, IC: Information Component, IC025: 95% Confidence Interval's lower limit for the Information Component, E(IC): Information Component's expected value, V(IC): Information Component's variance, EBGM: Empirical Bayesian Geometric Mean, EBGM05: 95% Confidence Interval's lower limit for the Empirical Bayesian Geometric Mean.

Furthermore, a literature search was performed to summarize the existing evidence on the drugs with significant safety signals. Since the FAERS database contains anonymized and de-identified data on adverse drug events and is publicly available, ethics approval was not required for this study. The study followed all ethical principles and guidelines, including confidentiality and data privacy.

Results

From 1989 to September 2022, 4883 adverse event reports related to GBS, and its variants were retrieved from 24,953,348 reports in the FAERS database. Table 2 shows that the mean age (SD) of patients, excluding the missing data, was 53.80(18.54) years; 1860(39.72%) were female, 2372(50.65%) were male, and the remainder did not specify their gender. Of the suspected drugs identified, the most reported indications for use were rheumatoid arthritis, plasma cell myeloma, and malignant myeloma. Overall, the indications for use were diverse; the top 12 indications accounted for almost 23% of all the reported indications. Adverse events were reported by both healthcare professionals and consumers, seen most frequently in those patients who were aged 18-64 years (48.17%), followed by those aged 65-85 years (25.30%), with adverse events being least common in those aged 0-1 month (0.04%). The United States, France, and Great Britain notified most cases of drug associated GBS. Most cases reported developing an unspecified variant of GBS (92.40%), while Miller-Fisher syndrome (3.46%) and acute motor-sensory axonal neuropathy (3.13%) were the most frequently reported variants. 3013(64.33%) patients were hospitalized, with 468(9.99%) life-threatening cases. 428(9.13%) reported deaths, and 13.83% of the patients had a disability.

	Reports N (%)
Age Group	
0 - 1 Month	2 (0.04%)
2 Months - 2 Years	17 (0.36%)
3 - 11 Years	80 (1.71%)
12 - 17 Years	100 (2.14%)
18 - 64 Years	2256 (48.17%)
65 - 85 Years	1185 (25.30%)
More than 85 Years	24 (0.51%)
Not Specified	1019 (21.76%)
Mean Age (excluding missing data)	53.80 ± 18.54
Median Age (excluding missing data)	58.0 (24.0)
Sex	

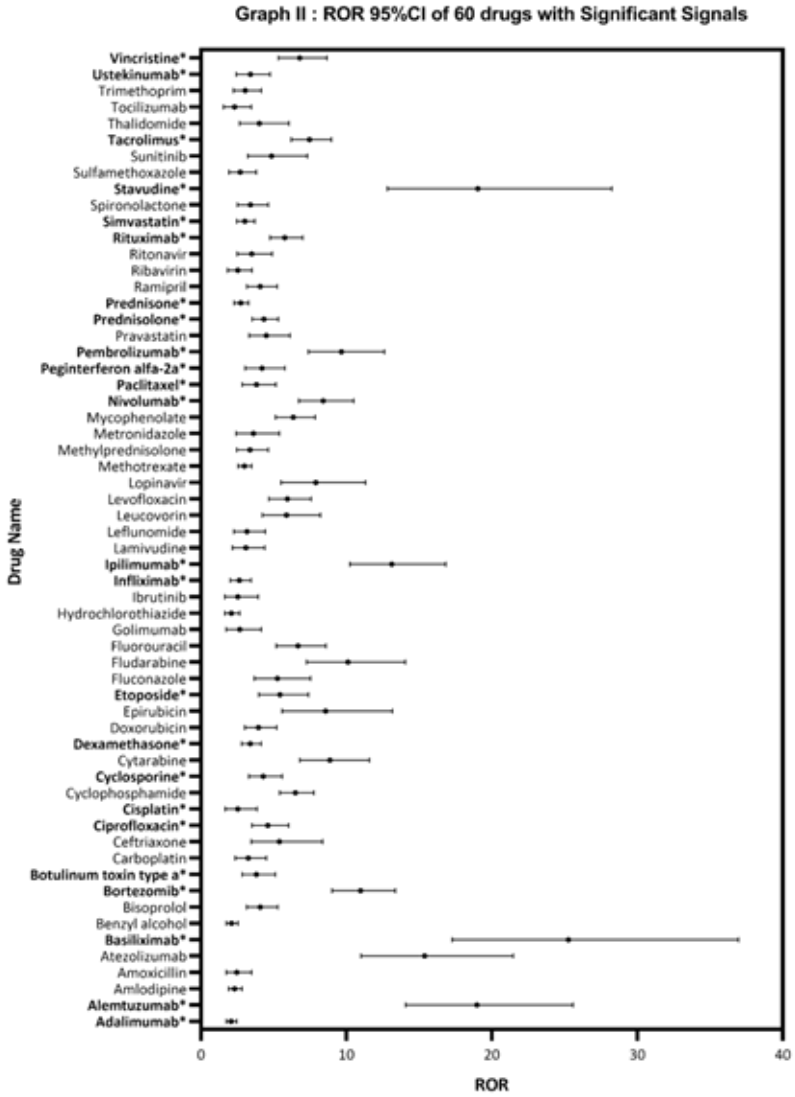
Female	1860 (39.72%)
Male	2372 (50.65%)
Not Specified	451 (9.63%)
Variants	
Variant not specified (labeled as Guillain-Barre Syndrome)	4327 (92.39%)
Miller-Fischer Syndrome	162 (3.45%)
Acute motor-sensory axonal neuropathy	147 (3.13%)
Acute motor axonal neuropathy	73 (1.55%)
Bickerstaff encephalitis	13 (0.27%)
Top 12 Reasons for Use	
Rheumatoid Arthritis	227 (4.84%)
Plasma Cell Myeloma	129 (2.75%)
Malignant Melanoma	121 (2.58%)
Psoriasis	120 (2.56%)
Multiple Sclerosis	100 (2.13%)
HIV Infection	87 (1.85%)
Psoriatic Arthropathy	76 (1.62%)
Hepatitis C	69 (1.47%)
Crohn's Disease	60 (1.28%)
Urinary Tract Infection	60 (1.28%)
Non-Small Cell Lung Cancer	58 (1.23%)
Chronic Lymphocytic Leukemia	54 (1.15%)
Reporter type	
Healthcare professional	1034 (22.08%)
Consumer	3384 (72.26%)
Not Specified	265 (5.66%)
Outcomes	
Hospitalized	3013 (64.33%)
Disabled	648 (13.83%)
Life-threatening	468 (9.99%)
Died	428 (9.13%)
Other outcomes	2559 (54.64%)
Top 10 Countries reporting cases	
United States	1173 (25.05%)
France	326 (6.96%)
Great Britain	247 (5.27%)
Japan	237 (5.06%)
Germany	196 (4.19%)
Italy	174 (3.72%)
Canada	137 (2.93%)
Spain	126 (2.69%)
The Netherlands	74 (1.58%)
Australia	57 (1.22%)

R: range, SD: standard deviation.

Table 2: Clinical and demographic characteristics of 4883 adverse event reports.

Signal Detection

Eight hundred forty-nine drugs mentioned in the adverse event reports of GBS & its variants are identified. Among them, 95 drugs with reporting frequency (N) >20 were selected for Signal detection. Sixty drugs were identified as having significant signals as they have met the criteria for at least one of the four algorithms (PRR, ROR, BCPNN, and MPGS). ROR & PRR detected significant signals for 60 drugs, MPGS detected significant signals for 29 drugs, and BCPNN(IC) detected significant signals for only one drug, as shown in Table 3 & Figure 1. Basiliximab was the only drug that generated positive signals using all four algorithms, and it had the highest ROR (95% CI) of 25.261(17.272 - 36.945) and the highest PRR (95% CI) of 25.127 (17.216 - 36.672. All 60 drugs are classified into various drug classes, as shown in Figure 2. A significant proportion of drugs (70%) belong to three drug categories, namely Antineoplastic agents (26.7%), Antimicrobial agents (23.3%), and Monoclonal Antibodies (20%) group.



*Drugs with significant signals detected by three algorithms (ROR, PRR, MPGS). **Drugs with significant signals detected all four algorithms (ROR, PRR, MPGS, BCPNN).

Abbreviations: PRR: Proportional Reporting Ratio, ROR: Reporting Odds Ratio, χ2: Chi-squared, IC: Information Component, IC025>0: the lower limit of the confidence interval of IC more than zero, MGPS: multi-item gamma Poisson shrinker, EBGM05>2: Empirical Bayesian geometric mean lower limit confidence interval more than 2.

Table 3: Drugs with significant signals.

Discussion

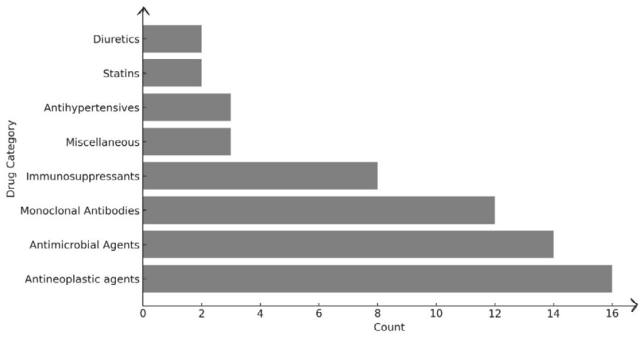
Drug-induced Guillain-Barre Syndrome (GBS) is a rare adverse event that has received limited attention in the literature. To improve understanding of such rare adverse drug events, spontaneous reporting systems (SRSs) can be a valuable tool for collecting adverse drug events from a large pool of real-world patients [13]. This study comprehensively characterized the patients who developed GBS associated with drugs and identified 60 drugs with significant signals belonging to three major drug classes Antibiotics, Monoclonal Antibodies, and Antineoplastics.

The pathogenesis of drug-induced Guillain-Barre Syndrome (GBS) remains unclear. Molecular mimicry suggests that while treating a bacterial infection with antibiotics, such as amoxicillin and ciprofloxacin, the destroyed bacteria may release components that share structural similarities with the peripheral nervous system. This, in turn, can lead to the production of cross-reactive antibodies, which can potentially induce GBS alongside the infectious triggers themselves [18]. A study on NOD wild-type (WT) mice and their congenic interleukin (IL)-10 or B7-2 knockouts demonstrated that following C. jejuni infection, antibiotic treatment in NOD IL-10-/- mice exacerbated neurological signs, lesions, and the production of antiganglioside autoantibodies [19].

Immune dysregulation is another possible explanation, particularly with monoclonal antibodies such as adalimumab, alemtuzumab, atezolizumab, basiliximab, infliximab, ipilimumab, nivolumab, pembrolizumab, and rituximab. These drugs may alter the immune system's balance, leading to an increased risk of GBS [10,20-28]. Lastly, direct toxicity to peripheral nerves could be a contributing factor, especially with antineoplastic agents such as cisplatin, doxorubicin, etoposide, fluorouracil, paclitaxel, and vincristine. These chemotherapeutic agents have been associated with the development of neuropathy, including GBS, due to their direct neurotoxic effects [29-32]. The most common indications for the use of drugs that can trigger GBS are Rheumatoid Arthritis, Plasma Cell Myeloma, Malignant Melanoma, Psoriasis, and Multiple Sclerosis. These conditions are characterized by aberrant immune responses and chronic inflammation, which may indicate that the host's fundamental immune dysregulation and inflammatory milieu could also contribute to the development of drug-induced GBS [21,33-35].

The mean age of patients in our study was 53.80 ± 18.54 years, which suggests that elderly patients may be more vulnerable to drug associated GBS. These results align with a previous prospective, population-based survey on GBS, which reported a mean age of 51.2 years (SD 21.5) among patients with GBS [36]. While the underlying mechanisms contributing to the higher susceptibility of elderly patients to drug associated GBS are not fully understood, age-related changes in the immune system and decreased regenerative capacity may play a role [37]. These findings highlight the importance of monitoring adverse drug events in older patients and tailoring drug therapy accordingly. A slight male predominance (male-to-female ratio of 1.27:1) found in our study also correlates with previous epidemiological studies on GBS [38-40]. Our study suggests that Drug-Induced GBS is associated with poor outcomes, as evidenced by a mortality rate of 9.13% - higher than the reported mortality rate for GBS in the literature. This finding is in line with Berg B, et al. [41] prospective cohort study of 527 patients, which found a mortality rate of 2.8% in the first six months, as well as a large cohort study conducted in the United States with 4,954 patients, which reported an in-hospital mortality rate of 2.58% [42]. These findings suggest that patients with drug associated GBS may have similar characteristics (such as age and sex) to those with the typical form of GBS, except for a higher mortality rate.

Using this comprehensive search strategy, we uncovered evidence in the literature for many drugs (Table 4), including Adalimumab, Alemtuzumab, Etoposide, Cisplatin, Bortezomib, Botulinum toxin type A, Ciprofloxacin, Cyclosporine, Infliximab, Ipilimumab, Nivolumab, Nab-Paclitaxel, Pegylated interferon α 2a, Pembrolizumab, Prednisone, Dexamethasone, Rituximab, Simvastatin, Stavudine, Tacrolimus, Basiliximab, Ustekinumab, Vincristine and Prednisolone [21-35,43-86] which are highlighted in Figure 2. All patients in these case reports were hospitalized, recovery was the most common outcome, and death was reported in 23.8% of cases. The Naranjo ADR [44] score for these case reports ranged from 2 to 6, with most cases scored as "possible" or "probable" ADRs. The score suggests a strong likelihood of the drugs being the cause of GBS in these patients. It should be noted that this score was calculated based on the limited information provided in the case report and may change if additional information becomes available and should be interpreted accordingly.



Note: To prevent overlap between drug classes, some drugs which belong to both antineoplastics & monoclonal antibodies are included in the monoclonal antibody group.
Figure 2: Drug Classification.

Author & year	Age/ Sex	Main drug suspected to cause GBS	Variant of GBS	Underlying disease	The onset of GBS after the first dose of the drug was given	Outcome (Recovery/ Death)	Naranjo ADR Score[44] (Interpretation)
Lee JH, et al. [43]	33yr/F	Adalimumab	NA	Chron's Disease	Two months	Recovery	5(Probable ADR)
Cançado GGL, et al. [45]	64yr/M	Adalimumab	AIDP	Chron's Disease	Two weeks	Recovery	3(Possible ADR)
Cesarini M, et al. [46]	71yr/M	Adalimumab	NA	Chron's Disease	One month	Recovery	5(Probable ADR)
Manganelli S, et al. [20]	57yr/M	Adalimumab	NA	Chron's Disease	Seven years	Recovery	4(possible ADR)
Mendez PL, et al. [47]	31yr/M	Adalimumab	NA	Chron's Disease	Two weeks	Recovery	4(possible ADR)
Abbi KKS, et al. [48]	73/M	Alemtuzumab	NA	T-cell Prolymphocytic Leukemia	62 days	Recovery	3(Possible ADR)
Chan C, et al. [49]	mid 30's/F	Alemtuzumab	NA	Multiple Sclerosis	Eight months	Recovery	3(Possible ADR)
Zwan M, et al. [22]	54yr/M	Alemtuzumab	NA	Polycystic kidney disease with Renal Transplantation	Four months	Recovery	2(Possible ADR)
Zwan M, et al. [22]	57 yr/F	Alemtuzumab	NA	Reflux nephropathy with Renal Transplantation	Eight months	Recovery, Death (due to malignancy six months later)	3(Possible ADR)
Hradilek P, et al. [21]	35yr/F	Alemtuzumab	AMAN	Multiple Sclerosis	One month	Recovery	6(Probable ADR)
Verdonk RC, et al. [30]	41yr/M	BEP (Bleomycin, Etoposide, Cisplatin)	-	Stage IV non-seminoma of the left testis	Two months	Recovery	NC
Herraez-Albendea MM, et al. [50]	77yr/F	Bortezomib	NA	Multiple Myeloma	29 days	Recovery	5(Probable ADR)
Xu YL, et al. [34]	45yr/M	Bortezomib	NA	Multiple Myeloma	56 days	Recovery	3(Possible ADR)
Haug BA, et al. [51]	63yr/M	Botulinum toxin type A	NA	Bilateral blepharospasm	Two years	NA	6(probable ADR)
Popescu C [52]	62yr/M	Ciprofloxacin	AMSAN	Urinary Tract Infection	Four days	Recovery	2(Possible ADR)
Cicero G, et al. [31]	55yr/F	Cisplatin-Gemcitabine	AIDP	Metastatic Lung Cancer	Six days	Recovery, Death (due to metastatic Lung cancer)	NC
Falk J, et al. [53]	58yr/M	Cyclosporine	AMSAN	Lung Transplant recipient	13 days	Recovery	3(Possible ADR)
Cisternas M, et al. [35]	34yr/M	Infliximab	AIDP	Psoriatic Arthritis	Two months	Recovery	3(Possible ADR)
Faivre A, et al. [54]	64yr/F	Infliximab	AMSAN	Chron's Disease	Four weeks	Recovery	4(possible ADR)

Bouchra A, et al. [23]	47yr/F	Infliximab	AIDP	Ulcerative colitis	Eight weeks	Recovery	4(possible ADR)
Silburn S, et al. [33]	46yr/F	Infliximab	AIDP	Rheumatoid Arthritis	NA (5 weeks after the last infusion)	Recovery	4(possible ADR)
Indini A, et al. [55]	71yr/M	Infliximab	pharyngeal-cervical-brachial syndrome	Uveal Melanoma	Ten weeks	Death (from melanoma progression)	5(possible ADR)
Gravbrot N, et al. [56]	71yr/M	Ipilimumab	NA	stage IIC left postauricular melanoma.	Seven weeks	Recovery	4(Possible ADR)
Patel RJ, et al. [57]	71yr/M	Ipilimumab	NA	Melanoma	Seven weeks	Recovery	6(Probable ADR)
Garcia CA, et al. [58]	55yr/M	Ipilimumab	AIDP	Stage IIIB superficial spreading melanoma	Three weeks	Recovery	6(Probable ADR)
Gaudy-Marqueste C, et al. [24]	65yr/M	Ipilimumab	NA	Superficial spreading melanoma	Three weeks	Death (due to multi-organ Failure)	3(Possible ADR)
Bot I, et al. [59]	63yr/M	Ipilimumab	AMSAN	Metastatic Melanoma	12 weeks	Death (due to respiratory failure)	7(probable ADR)
Gu Y, et al. [60]	49yr/F	Ipilimumab& Nivolumab	NA	metastatic melanoma	Five days following induction	Recovery	NC
Supakornnumporn S, et al. [61]	77yr/M	Ipilimumab& Nivolumab	AIDP	Metastatic Melanoma	Seven weeks	Recovery	NC
Pina Y, et al. [62]	28yr/F	Ipilimumab& Nivolumab	AMAN	Metastatic Melanoma	30 days	Recovery, Death (due to Melanoma Progression 7 months later)	NC
Pomerantz M, et al. [25]	58yr/M	Ipilimumab& Nivolumab	AIDP	stage IV small cell Lung cancer (SCLC)	59 days	Recovery	NC
Litsardopoulos P, et al. [32]	75yr/F	Nab-Paclitaxel	AMAN	Metastatic Breast Cancer	Two weeks	No improvement, Death (due to AMAN-induced respiratory failure)	4(Possible ADR)
Mazzaschi G, et al. [63]	80yr/F	Nivolumab	NA	Lung Adenocarcinoma	12 days	Recovery	4(possible ADR)
Schneiderbauer R, et al. [64]	51yr/M	Nivolumab	AIDP	metastatic melanoma	Five months	Recovery	3(possible ADR)

Jacob A, et al. [65]	68yr/F	Nivolumab	NA	stage III squamous cell carcinoma of the lung	Three months	No improvement, Death	3(possible ADR)
Yildirim N, et al. [66]	70yr/M	Nivolumab	AMAN	Metastatic Renal cell Carcinoma	11 weeks	Death (due to AMAN induced Respiratory failure)	3(possible ADR)
Pierrard J, et al. [67]	70yr/M	Nivolumab	AIDP	advanced urothelial cancer of the left kidney.	16 weeks	Recovery	4(possible ADR)
McNeill CJ, et al. [68]	68yr/M	Nivolumab	MFS	Metastatic RCC	Seven weeks	Recovery	4(Possible ADR)
Kyriazoglou A, et al. [69]	74yr/M	Nivolumab	AIDP	Metastatic Bladder cancer	Six weeks	Recovery, Death (due to sepsis four months later)	4(Possible ADR)
Thapa B, et al. [26]	60yr/M	Nivolumab	NA	Non-small cell Lung cancer	12 weeks	Minimal recovery	4(Possible ADR)
Fukumoto Y, et al. [70]	66yr/M	Nivolumab	AIDP	Non-small cell Lung cancer	NA (Five days after two courses of nivolumab treatment	Recovery	4(Possible ADR)
Khiani V, et al. [71]	65yr/F	pegylated interferon α 2a	AIDP	Chronic Hepatitis C	16 weeks	Recovery	3(possible ADR)
Satish R, et al. [72]	58yr/F	pegylated interferon α 2a	AIDP	Chronic Hepatitis C	Two weeks	Recovery, death due to worsening Infection (Pneumonia)	3(possible ADR)
Moon H, et al. [73]	69yr/F	pembrolizumab	MFS	Refractory metastatic epithelial ovarian cancer	15 weeks	Recovery	5(Probable ADR)
Brzezinska BN, et al. [74]	72yr/F	pembrolizumab	AIDP	stage IVB uterine adenocarcinoma	Four weeks	Recovery, Death (later due to large bowel perforation and cancer progression)	4(Possible ADR)
Aoki S, et al. [75]	85yr/F	pembrolizumab	NA	Stage IV ureter cancer	15 weeks	Recovery	4(Possible ADR)
Manam R, et al. [27]	73 yr/M	Pembrolizumab	AIDP	stage IV poorly differentiated adenocarcinoma of the lung	Three weeks	Recovery	4(Possible ADR)

Manam R, et al. [27]	81yr/M	Pembrolizumab	AIDP	Melanoma	Four weeks	No improvement, Death	3(possible ADR)
Steiner I, et al. [76]	65yr/F	Prednisone	AIDP	Ulcerative colitis	Two weeks	Recovery	3(Possible ADR)
Steiner I, et al. [76]	68yr/F	Prednisone	NA	Multiple Sclerosis	Five weeks	Recovery	3(Possible ADR)
Steiner I, et al. [76]	61yr/M	Dexamethasone	AIDP	Aqueductal Stenosis	Four weeks	Recovery	3(Possible ADR)
Jaso R, et al. [28]	86yr/M	Rituximab	NA	ITP	15 weeks	Recovery	4(Possible ADR)
Carmona A, et al. [77]	57yr/M	Rituximab	AMSAN	Diffuse large B-cell lymphoma (DLBCL)	Seven months	Recovery	4(Possible ADR)
Terenghi F, et al. [78]	51yr/M	Rituximab	NA	non-Hodgkin lymphoma	Nine weeks	Recovery	2(Possible ADR)
Rajabally YA, et al. [79]	58 yr/M	Simvastatin	NA	hypertension and hyper-cholesterolemia	One week	Recovery	4(Possible ADR)
Shah SS, et al. [80]	42yr/F	Stavudine	MFS	HIV infection	31 months	Death (due to Aspiration Pneumonia)	2(Possible ADR)
Kaushik P, et al. [81]	46yr/M	Tacrolimus	MFS	End-stage liver disease with liver transplantation.	Six months post-transplant	Recovery	3(Possible ADR)
Jakes AD, et al. [82]	44yr/M	Tacrolimus, Basiliximab	NA	Polycystic kidney disease with Renal Transplantation	Two days post-transplant	Recovery	NC
Fukushima T, et al. [83]	23yr/M	Ustekinumab	NA	Chron's Disease	One year	Recovery	3(Possible ADR)
Moudgil SS, et al. [84]	48yr/M	Vincristine	NA	Acute lymphoblastic leukemia	Four weeks	Death (due to neutropenic bacterial sepsis and disseminated aspergillosis)	2(Possible ADR)
Bahl A, et al. [85]	8yr/M	Vincristine	NA	Non-Hodgkins Lymphoma (NHL)	11 days	Recovery	4(Possible ADR)
Norman M, et al. [86]	3.5 yr/M	Vincristine	NA	Acute lymphoblastic leukemia	Four weeks	Recovery	2(Possible ADR)
Re D, et al. [29]	21yr/F	vincristine, daunorubicin, L-asparaginase and prednisolone	NA	Non-Hodgkins Lymphoma (NHL)	Three weeks	Recovery	NC

Abbreviations: GBS: Guillain-Barre syndrome, AIDP: Acute Inflammatory Demyelinating Polyneuropathy, MFS: Miller-Fisher syndrome, AMAN: Acute Motor Axonal Neuropathy, AMSAN: Acute Motor Sensory Axonal Neuropathy, ADR: Adverse Drug Report, NC: Not calculated (The Naranjo ADR probability score has been calculated from the information provided in the case reports when a single main suspect drug is present. It has not been calculated if multiple drugs are primary suspects.)

Table 4: Summary of Published case reports related to drugs suspected to cause GBS.

Interestingly, despite Basiliximab exhibiting the highest Relative Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) among all the drugs analyzed, we could not find much literature evidence for this drug, apart from one case report where both tacrolimus and Basiliximab were identified as suspects [82]. This finding highlights the importance of exploring potential drug associated GBS associations, even in drugs that may not have significant supporting evidence in the literature. While a limited number of systematic reviews exist on drug-induced Guillain-Barre syndrome (GBS), they either focus exclusively on a single drug group, such as immune checkpoint inhibitors [9] or are outdated [87]. Moreover, due to the lack of knowledge on all the drugs that can cause GBS, a comprehensive search strategy for conducting a systematic review is difficult to develop. To address this gap, our study provides a valuable contribution as we have identified numerous drugs that may induce GBS and found supporting evidence in the literature. Consequently, this list of drugs/drug classes found in our study can serve as a foundation for the development of a robust search strategy in future systematic reviews on this topic.

Although FAERS is valuable in identifying and evaluating rare safety concerns like GBS, it is important to consider its limitations. Firstly, the self-reported nature of the database and the varying backgrounds of the individuals reporting adverse events can result in inaccuracies and incomplete data. Additionally, the FAERS data analysis is based on reported events rather than actual occurrences, making it impossible to accurately calculate the incidence rate of Drug-Induced GBS. Furthermore, the absence of a requirement for causality assessment in FAERS reporting makes it challenging to establish a causal link between drug exposure and adverse events. The lack of crucial patient information, such as previous autoimmune disorders, concurrent use of neurotoxic drugs, and ethnicity information, may also affect the assessment of GBS risk. Additionally, drugs that are closely monitored during administration may appear to have a lower rate of GBS due to prompt recognition, further adding to the limitations of FAERS. These limitations are compounded by the need for denominator data and the selection and reporting biases in the database, making it unsuitable for determining the actual incidence of GBS related to drugs. Despite these limitations, our analysis of FAERS data confirms the findings of previous studies on Drug- Induced GBS. It is crucial to recognize the limitations of the database and interpret the results with caution. Future studies should consider employing additional data sources and methodologies to complement FAERS data analysis.

Conclusion

This study provides valuable insights into the characteristics, outcomes, and associations between specific drugs and the development of GBS using a large real-world patient population based on the FAERS database. The study also identified many drugs, such as Antineoplastic agents, Antibiotics, and Monoclonal antibodies that may contribute to the syndrome, thus making it imperative for healthcare providers to be mindful when administering these drugs. Further investigation is required to fully comprehend these drugs' role in causing GBS.

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