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Analysis of adverse drug events in patients with bipolar disorders using the Japanese Adverse Drug Event Report database

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The aim of the present study was to survey adverse drug events (ADEs) in patients with bipolar disorders and identify risk factors using the Japanese Adverse Drug Event Report (JADER) database, a spontaneous reporting system. Data on patients with bipolar disorders were extracted from the JADER database. The Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT) and standardized MedDRA queries (SMQ) were used to define ADEs. A multiple logistic regression analysis was performed to identify risk factors for ADEs. A total of 8653 reports of 1108 types of ADEs (PT) were registered in data collected on 3521 patients with bipolar disorders. Rash (PT) was the most frequently reported in 549 patients, followed by drug eruption (PT) in 387, fever (PT) in 364, toxicity to various agents (PT) in 291, and Stevens-Johnson syndrome (PT) in 261. Among 24 ADEs (PT) that were reported in more than 50 patients, lamotrigine was associated with increased risks of 13 ADEs (PT), followed by carbamazepine with increased risks of 8 ADEs (PT). The majority of these ADEs belonged to hypersensitivity (SMQ) or hepatic disorder (SMQ). Lithium carbonate was associated with increased risks of rash (PT), drug interaction (PT), and tubulointerstitial diseases (SMQ). All antipsychotics increased the adjusted odds ratio for neuroleptic malignant syndrome (PT). The risk of hyperglycemia/new onset diabetes mellitus (SMQ) was increased by olanzapine, quetiapine fumarate, and risperidone. We are presenting the profiles of ADEs in patients with bipolar disorders using the JADER database, and propose risk factors for 19 ADEs (PT) and 4 ADEs (SMQ).

1. Introduction

Bipolar disorders are a group of chronic mental disorders that include bipolar I disorder and bipolar II disorder. Bipolar I disorder is defined by the presence of a syndromal, manic episode, and bipolar II disorder by a syndromal, hypomanic episode and major depressive episode (McIntyre et al. 2020). The lifetime prevalence of bipolar disorders is estimated to be between 1.3 and 1.6% (Müller-Oerlinghausen et al. 2002). The lifespan of patients with bipolar disorders is reduced by 10 to 20 years, and the risk of suicide death is estimated to be 20- to 30-fold higher than that in the general population (McIntyre et al. 2020).

Medications including lithium carbonate, lamotrigine, carbamazepine, sodium valproate, and antipsychotics are administered for the treatment and prophylaxis of bipolar disorders. Non-adherence has been associated with recurrence in patients with bipolar disorders, and the discontinuation of lithium increases the risk of suicide (Jawad et al. 2018; Baldessarini et al. 1999). A retrospective cohort study estimated that 54% of 873 lithium-treated patients discontinued this therapy, and that its adverse effects were the main reason for discontinuation accounting for 62% of 561 episodes (Öhlund et al. 2018). Adverse effects of medications were identified as one of the factors contributing to poor adherence (Leclerc et al. 2013). The selection of atypical antipsychotics depends on their adverse effects in the latest clinical practice guidelines 2020 for bipolar disorder by the Japanese Society of Mood Disorders (https://www.secretariat.ne.jp/jsmd/). Therefore, an analysis of adverse effects of medications in patients with bipolar disorders from multiple angles is of importance.

A spontaneous reporting system database of adverse drug events (ADEs) has recently been used in pharmacoepidemiological research. It is available for evaluations of ADEs and the screening of novel drugs from the viewpoint of drug repurposing. In Japan, ADEs are spontaneously reported by doctors, pharmacists, patients, and drug industries to the Pharmaceuticals and Medical Devices Agency (PMDA), which then publicly releases them as the Japanese Adverse Drug Event Report (JADER) database. We previously surveyed drug overdose in the JADER database, and found the highest number of reports on lithium carbonate (Uwai and Nabekura 2021). Furthermore, a multivariate analysis using the data of patients with bipolar disorders from the JADER database identified lithium carbonate as a risk factor for drug overdose (Uwai and Nabekura 2021). In the present study, we examined all reports on ADEs in patients with bipolar disorders from the JADER database. In addition, the relationships between ADEs and sex, age, and medications were evaluated using a multiple logistic regression analysis.

2. Investigations and results

2.1. Demographic information of 3521 patients with bipolar disorders

Files containing cases submitted between 2004 and 2020 to the JADER database were downloaded from the PMDA website (www.pmda.go.jp). The downloaded JADER database included data on 678913 patients, and contained 4022 reports of bipolar disorders as primary diseases. After the removal of duplicates and patient datasets with insufficient information, 3521 cases were investigated in the present study. Table 1 shows the patient's demographic information. We regarded 2289 patients as those with bipolar disorder; 1066 and 166 patients had bipolar I disorder and bipolar II disorder, respectively. The numbers of male patients and patients aged <50 years were 1448 and 1605, respectively. There were 1544 users of lithium carbonate, 1497 of lamotrigine, 316 of carbamazepine, 839 of sodium valproate, 470 of aripiprazole, 503 of olanzapine, 503 of quetiapine fumarate, 239 of risperidone, 193 of chlorpromazine, and 256 of levomepromazine.

Table 1: Demographic information on 3521 patients with bipolar disorders

	n
Type of bipolar disorder	
Bipolar disorder	2289
Bipolar I disorder	1066
Bipolar II disorder	166
Sex	
Male	1448
Female	2073
Age	
<10 years	2
10–19 years	70
20–29 years	313
30–39 years	559
40–49 years	661
50–59 years	726
60–69 years	650
70–79 years	414
80–89 years	121
90–99 years	5
Administration	
Lithium carbonate	1544
Lamotrigine	1497
Carbamazepine	316
Sodium valproate	839
Aripiprazole	470
Olanzapine	503
Quetiapine fumarate	503
Risperidone	239
Chlorpromazine	193
Levomepromazine	256

Table 2: ADEs (PT) in 3521 patients with bipolar disorders and case numbers

ADE (PT)	n
Total	8653
Rash	549
Drug eruption	387
Fever	364
Toxicity to various agents	291
Stevens-Johnson syndrome	261
Drug reaction with eosinophilia and systemic symptoms	235
Erythema	199
Neuroleptic malignant syndrome	188
Erythema multiforme	155
Mania	109
Hepatic function abnormal	103
Nephrogenic diabetes insipidus	99
Altered state of consciousness	81
Drug interaction	74
Suicide attempt	71
Pruritus	68
Rhabdomyolysis	65
Toxic epidermal necrolysis	62
Aspartate aminotransferase increased	62
Oral mucosa erosion	60
Alanine aminotransferase increased	59
Lymphadenopathy	56
Liver disorder	55
Lip erosion	52
Others	4948

ADE: adverse drug event; PT: preferred term.

2.2. ADEs (PT) in 3521 patients with bipolar disorders

A total of 8653 reports of 1108 types of ADEs (PT) were registered in data on 3521 patients. Table 2 shows the ADEs (PT) reported in more than 50 patients. Rash (PT) was the most frequently reported in 549 patients, followed by drug eruption (PT) in 387, fever (PT) in 364, toxicity to various agents (PT) in 291, Stevens-Johnson syndrome (PT) in 261, and drug reaction with eosinophilia and systemic symptoms (PT) in 235. The ADEs (PT) reported in 103–199 patients were erythema (PT), neuroleptic malignant syndrome (PT), erythema multiforme (PT), mania (PT), and hepatic function abnormal (PT). Nephrogenic diabetes insipidus (PT) was reported in 99 patients. Drug interaction (PT) was registered in 74 patients. Seventy-one patients attempted suicide. Toxic epidermal necrolysis (PT) was reported in 62 patients.

2.3. Association of ADEs (PT) with sex, age, and medicines

We performed multiple logistic regression analyses of the ADEs (PT) in Table 2, and the results of 19 ADEs (PT) are shown in Table 3. Sex and age were associated with the risks of 6 and 8 ADEs (PT), respectively. Lithium carbonate increased the aORs of rash (PT), toxicity to various agents (PT), and drug interaction (PT). Lamotrigine was identified as a risk factor for 13 ADEs (PT), including rash (PT), drug eruption (PT), fever (PT), Stevens-Johnson syndrome (PT), and toxic epidermal necrolysis (PT). Carbamazepine was associated with an increased risk of 8 ADEs (PT). All antipsychotics examined increased the risk of neuroleptic malignant syndrome (PT). Chlorpromazine was associated with increased risks of Stevens-Johnson syndrome (PT), erythema (PT), hepatic function abnormal (PT), and lymphadenopathy (PT). Levomepromazine was identified as a risk factor for toxic epidermal necrolysis (PT).

Since all patients who exhibited nephrogenic diabetes insipidus (PT) were lithium carbonate users, no results were obtained. Similarly, analyses showed no results for pruritus (PT), oral mucosa erosion (PT), or lip erosion (PT). None of the factors tested were associated with an altered state of consciousness (PT).

2.4. Association of ADEs (SMQ) with sex, age, and medicines

To identify risk factors for low-reported ADEs (PT), they were grouped using the SMQ index. Table 4 shows the case numbers of ADEs (SMQ) and of PT that belong to them. Five types of ADEs (PT) related to acute renal failure (SMQ) were reported 90 times. Renal impairment (PT) was reported in 43 patients, which was the most frequent event, followed by acute kidney injury (PT) in 40. Eighty-nine patients were considered to have acute renal failure (SMQ). There were 113 reports of 15 types of ADEs (PT) pertaining to hyperglycemia/new onset diabetes mellitus (SMQ), and 98 patients were judged to have developed hyperglycemia/new onset diabetes mellitus (SMQ). Parkinson-like events (SMQ) was considered to have occurred in 52 patients. There were 110 reports of three types of ADEs (PT) related to tubulointerstitial diseases (SMQ), and 99 reports were regarding nephrogenic diabetes insipidus (PT). One hundred and seven patients had tubulointerstitial diseases (SMQ).

Table 5 shows the results of multiple logistic regression analyses. Male sex was identified as a risk factor for hyperglycemia/new onset diabetes mellitus (SMQ). Age ≥50 years was associated with Parkinson-like events (SMQ) and tubulointerstitial diseases (SMQ). Lithium carbonate was identified as a risk factor for tubulointerstitial diseases (SMQ). Sodium valproate increased the risks of acute renal failure (SMQ), Parkinson-like events (SMQ), and tubulointerstitial diseases (SMQ). Aripiprazole, quetiapine fumarate, and chlorpromazine were associated with increased risks of Parkinson-like events (SMQ). Olanzapine, quetiapine fumarate, and risperidone increased the aOR of hyperglycemia/new onset diabetes mellitus (SMQ).

There were 39 patients with agranulocytosis (SMQ code: 20000023), 79 patients with convulsions (SMQ code: 20000079), 61 patients with noninfectious encephalopathy/delirium (SMQ

Table 4. ADEs (PT) related with acute renal failure (SMQ), hyperglycemia/new onset diabetes mellitus (SMQ), Parkinson-like events (SMQ), and tubulointerstitial diseases (SMQ), and the case number in 3521 patients.

Code ADE (SMQ)	n	ADE (PT)	n
20000003 Acute renal failure	89	Acute kidney injury	40
		Anuria	2
		Oliguria	2
		Renal failure	3
		Renal impairment	43
20000041 Hyperglycemia/new onset diabetes mellitus	98	Blood glucose increased	10
		Diabetes mellitus	19
		Diabetes mellitus inadequate control	3
		Diabetic hyperosmolar coma	1
		Diabetic ketoacidosis	25
		Diabetic ketoacidotic hyperglycemic coma	1
		Diabetic ketosis	6
		Fulminant type 1 diabetes mellitus	4
		Gestational diabetes	3
		Glycosylated hemoglobin increased	2
		Hyperglycemia	26
		Hyperglycemic hyperosmolar nonketotic syndrome	1
		Ketosis	3
		Type 1 diabetes mellitus	7
		Type 2 diabetes mellitus	2
20000099 Parkinson-like events	52	Bradykinesia	2
		Cogwheel rigidity	1
		Hypertonia	1
		Muscle rigidity	5
		Parkinson's disease	1
		Parkinsonian gait	3
		Parkinsonism	43
		Propulsive gait	1
20000221 Tubulointerstitial diseases	107	Nephrogenic diabetes insipidus	99
		Renal tubulär acidosis	1
		Tubulointerstitial nephritis	10

ADE: adverse drug event; PT: preferred term; SMQ: standardized MedDRA Query.

code: 20000133), 63 patients with gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ code: 20000140), and 50 patients with depression (excluding suicide and self-injury) (SMQ code: 20000167). Multivariate analyses did not identify their risk factors.

3. Discussion

The number of reports on analyses using a spontaneous reporting system database for ADEs, such as the JADER database, has recently been increasing, with the majority starting from an ADE or medication. We utilized data on primary diseases in the JADER database, patients with bipolar disorders were selected, and their ADEs were analyzed. An analysis using the JADER database is considered to be meaningful when difficulties are associated with performing a clinical trial. For example, an ADE rarely occurs or takes a long time to develop. Another advantage of this method is that it allows for a comprehensive examination of risk factors.

Rash (PT) was the most frequently reported ADE (PT), followed by drug eruption (PT) and fever (PT) (Table 2). Among 24 ADEs (PT) that were reported in more than 50 patients, multivariate analyses gave risk factors for 19 ADEs (PT) (Table 3). Lamotrigine was associated with increased risks of 13 ADEs (PT), including the three ADEs (PT) described above, followed by carbamazepine with 8 ADEs (PT). All ADEs (PT) associated with carbamazepine were related to lamotrigine, and the majority of the ADEs (PT) associated with lamotrigine and carbamazepine belonged to hypersensitivity (SMQ code: 20000214) or hepatic disorder (SMQ code: 20000005). In our data, 49 patients were co-administered lamotrigine and carbamazepine. It may be difficult to identify the cause of these ADEs, when lamotrigine and carbamazepine are simultaneously administered. The number of lamotrigine users was much higher than that of carbamazepine users (Table 1). And, the values of almost aORs for the ADEs (PT) related with lamotrigine was higher than carbamazepine (Table 3). These findings indicate that the majority of reports of ADEs (PT) were associated with lamotrigine in the data of patients with bipolar disorders from the JADER database.

Lithium carbonate was administered to 1544 out of 3521 patients, and, thus, was the most frequently used medication (Table 1). This may be related to lithium carbonate exerting antimanic, antidepressant, and anti-suicide effects and being accepted as the gold standard mood stabilizer (McIntyre et al. 2020), and that the onset of its adverse effects is common (Öhlund et al. 2018). Nephrogenic diabetes insipidus is the representative adverse effect of lithium carbonate, and it occurs in up to 40% of patients (Grünfeld and Rossier 2009). The present results revealed a relationship between lithium carbonate and increased risk of tubulointerstitial diseases (SMQ) (Table 5). The majority of the patients with tubulointerstitial diseases (SMQ) exhibited nephrogenic diabetes insipidus (Table 4), suggesting the association of lithium carbonate with nephrogenic diabetes insipidus. Sodium valproate was associated with the risks of acute renal failure (SMQ), Parkinson-like events (SMQ), and tubulointerstitial diseases (SMQ) (Table 5). All antipsychotics examined increased the risk of neuroleptic malignant syndrome (PT) (Table 3). The present study showed a relationship between medicines for bipolar disorders and their representative adverse effects. Cases registered in the JADER database include data on post-marketing surveillance, and are mainly spontaneous reports. Therefore, ADEs in the JADER database only account for a portion of those in clinical practice. In addition, reports are known to contain biases. For example, the number of reported ADEs decreases over time after an immediate transient increase, and the number of reported ADEs on a topic increase overall (Hartnell and Wilson 2004; Pariente et al. 2007). The time to the onset of each ADE is considered to influence results. Nevertheless, the present method of searching for factors associated with ADEs by the JADER database and a multivariate analysis may be valid.

Drug interaction (PT) was registered in 74 cases (Table 2). Age ≥50 years was associated with its increased risk (Table 3). This should be related with the report showing that older patients received more medicines in the JADER database (Abe et al. 2017). Among the medicines examined, only lithium carbonate increased the risk of drug interaction (PT) (Table 3). Lithium carbonate was administered to 64 patients among the 74 patients, and its involvement in drug interaction was reported in 61. Drug interactions of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with lithium carbonate were registered in 22. Drug interactions between lithium carbonate and nonsteroidal anti-inflammatory drugs, including celecoxib, were reported in 21 patients. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs have been shown to delay the elimination of lithium from the circulation (Finley 2016). The present study indicated that caution is needed when concomitantly administering medicines to patients receiving lithium carbonate. Frequent therapeutic drug monitoring for lithium contributes to early detection of drug interaction with lithium carbonate. However, the annual prevalence of therapeutic drug monitoring for lithium was low, 14.9% between 2005 and 2014 in Japan (Ooba et al. 2018). It is required to determine serum level of lithium actively as well as to elucidate a patient more politely about drug interaction with lithium in Japan. Patients with bipolar disorders may not tell a cardiologist their medicines. Blood pressure determination of patients taking lithium carbonate by a psychiatrist may reduce the occurrence of drug interaction between lithium carbonate and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Table 3: Multiple logistic regression analysis of ADEs (PT) in 3521 patients with bipolar disorders

ADE (PT)		Female	Age ≥50 y	Lithium	Lamotrigine	CBZ
Rash	aOR	1.23	0.913	1.14	7.69	1.18
	95% CI	1.10–1.38	0.820–1.02	1.02–1.28	6.06–9.75	0.905–1.54
	P value	0.0003	0.0943	0.0179	<0.0001	0.2204
Drug eruption	aOR	1.02	1.05	1.11	4.79	1.38
	95% CI	0.904–1.15	0.932–1.18	0.980–1.25	3.94–5.82	1.08–1.76
	P value	0.7484	0.4414	0.1033	<0.0001	0.0100
Fever	aOR	1.18	0.818	1.04	4.63	1.35
	95% CI	1.04–1.35	0.724–0.923	0.922–1.18	3.77–5.68	1.05–1.75
	P value	0.0093	0.0011	0.4968	<0.0001	0.0205
Toxicity to	aOR	1.03	1.58	4.93	0.322	0.930
various agents	95% CI	0.902–1.19	1.34–1.86	3.71–6.54	0.248–0.418	0.750–1.15
	P value	0.6245	<0.0001	<0.0001	<0.0001	0.5084
Stevens-Johnson	aOR	1.19	1.06	0.936	4.23	1.88
syndrome	95% CI	1.03–1.37	0.926–1.21	0.810–1.08	3.39–5.29	1.47–2.40
	P value	0.0216	0.4004	0.3679	<0.0001	<0.0001
Drug reaction with	aOR	0.979	0.697	0.954	2.45	2.78
eosinophilia and	95% CI	0.847–1.13	0.601–0.807	0.823–1.11	2.05–2.92	2.28–3.39
systemic symptoms	P value	0.7754	<0.0001	0.5296	<0.0001	<0.0001
Erythema	aOR	1.10	1.17	1.02	7.17	1.30
	95% CI	0.933–1.29	1.01–1.36	0.865–1.19	4.87–10.6	0.922–1.83
	P value	0.2647	0.0421	0.8476	<0.0001	0.1346
Neuroleptic	aOR	0.968	1.23	1.15	0.415	0.886
malignant	95% CI	0.830–1.13	1.04–1.45	0.984–1.35	0.325–0.530	0.689–1.14
syndrome	P value	0.6794	0.0137	0.0775	<0.0001	0.3449
Erythema	aOR	1.17	1.10	1.19	4.66	1.24
multiforme	95% CI	0.979–1.41	0.932–1.31	0.998–1.41	3.39–6.42	0.843–1.82
	P value	0.0834	0.2525	0.0531	<0.0001	0.2761
Mania	aOR	0.708	0.973	0.833	1.07	0.635
	95% CI	0.582–0.860	0.799–1.19	0.679–1.02	0.872–1.30	0.382–1.05
	P value	0.0005	0.7876	0.0795	0.5358	0.0795
Hepatic function	aOR	0.836	0.934	0.920	1.87	1.47
abnormal	95% CI	0.683–1.02	0.762–1.15	0.744–1.14	1.49–2.35	1.07–2.01
	P value	0.0830	0.5130	0.4386	<0.0001	0.0170
Drug interaction	aOR	0.842	1.33	2.48	0.442	0.707
	95% CI	0.664–1.07	1.01–1.76	1.76–3.48	0.297–0.659	0.443–1.13
	P value	0.1527	0.0445	<0.0001	<0.0001	0.1463
Suicide attempt	aOR	0.967	0.558	0.693	0.815	0.659
	95% CI	0.757–1.24	0.426–0.733	0.525–0.914	0.633–1.05	0.365–1.19
	P value	0.7872	<0.0001	0.0093	0.1124	0.1653
Rhabdomyolysis	aOR	0.730	1.10	0.957	0.653	0.788
	95% CI	0.565–0.944	0.848–1.43	0.740–1.24	0.480–0.889	0.492–1.26
	P value	0.0162	0.4693	0.7391	0.0068	0.3207
Toxic epidermal	aOR	1.10	0.771	0.502	2.94	1.68
necrolysis	95% CI	0.830–1.47	0.584–1.02	0.342–0.736	1.97–4.39	1.06–2.67
	P value	0.4975	0.0662	0.0004	<0.0001	0.0259
Aspartate	aOR	1.07	1.00	1.02	5.45	1.13
aminotransaminase	95% CI	0.815–1.41	0.773–1.30	0.773–1.33	3.01–9.84	0.617–2.06
increased	P value	0.6144	0.9800	0.9106	<0.0001	0.6963
Alanine	aOR	1.04	0.928	1.10	5.22	1.13
aminotransaminase	95% CI	0.784–1.37	0.710–1.21	0.840–1.45	2.89–9.42	0.616–2.07
increased	P value	0.7980	0.5853	0.4755	<0.0001	0.6958
Lymphadenopathy	aOR	1.24	0.550	0.975	3.66	2.32
	95% CI	0.914–1.70	0.391–0.772	0.723–1.31	2.29–5.84	1.51–3.56
	P value	0.1650	0.0005	0.8669	<0.0001	0.0001
Liver disorder	aOR	1.39	1.00	0.926	1.48	2.30
	95% CI	1.02–1.89	0.762–1.32	0.694–1.23	1.10–1.99	1.66–3.19
	P value	0.0375	0.9793	0.5981	0.0106	<0.0001

ADE: adverse drug event; PT: preferred term; CBZ: carbamazepine; CPZ: chlorpromazine; LVPZ: levomepromazine; aOR: adjusted odds ratio; CI: confidence interval.

Valproate	Aripiprazole	Olanzapine	Quetiapine	Risperidone	CPZ	LVPZ
0.896	0.820	0.844	1.04	0.850	0.978	0.890
0.790–1.02	0.695–0.968	0.720–0.989	0.901–1.21	0.659–1.09	0.726–1.32	0.680–1.17
0.0855	0.0189	0.0361	0.5690	0.2079	0.8828	0.3958
1.03	0.691	0.857	0.958	0.982	1.04	1.08
0.905–1.18	0.564–0.846	0.720–1.02	0.813–1.13	0.759–1.27	0.776–1.41	0.838–1.40
0.6224	0.0003	0.0825	0.6055	0.8893	0.7741	0.5375
1.00	0.929	0.899	1.04	0.964	1.30	1.11
0.873–1.15	0.776–1.11	0.752–1.08	0.886–1.23	0.741–1.25	0.988–1.72	0.851–1.44
0.9816	0.4189	0.2450	0.6072	0.7833	0.0608	0.4473
0.809	0.756	0.634	0.772	0.551	0.770	1.10
0.670–0.978	0.589–0.970	0.486–0.828	0.608–0.980	0.379–0.803	0.568–1.04	0.878–1.37
0.0287	0.0276	0.0008	0.0338	0.0019	0.0928	0.4171
1.00	0.935	0.924	0.907	0.924	1.35	0.951
0.858–1.17	0.761–1.15	0.758–1.13	0.745–1.10	0.681–1.25	1.00–1.82	0.692–1.31
0.9744	0.5255	0.4360	0.3297	0.6135	0.0469	0.7581
1.10	0.978	0.806	0.998	1.05	1.20	1.20
0.940–1.28	0.792–1.21	0.642–1.01	0.815–1.22	0.806–1.37	0.911–1.58	0.922–1.55
0.2374	0.8351	0.0638	0.9880	0.7064	0.1941	0.1765
1.11	1.12	0.923	0.951	0.917	1.53	1.19
0.940–1.32	0.907–1.38	0.736–1.16	0.767–1.18	0.649–1.30	1.10–2.12	0.874–1.63
0.2152	0.2954	0.4899	0.6499	0.6242	0.0106	0.2657
0.897	1.31	1.39	1.37	1.66	1.42	1.64
0.747–1.08	1.08–1.60	1.16–1.68	1.13–1.66	1.34–2.06	1.10–1.82	1.34–2.01
0.2426	0.0072	0.0005	0.0016	<0.0001	0.0060	<0.0001
0.942	0.995	0.746	0.846	0.763	1.12	0.593
0.769–1.15	0.776–1.28	0.560–0.994	0.653–1.09	0.480–1.21	0.726–1.73	0.329–1.07
0.5663	0.9688	0.0454	0.2034	0.2534	0.6053	0.0825
0.960	0.922	0.910	1.18	0.962	0.591	0.856
0.762–1.21	0.686–1.24	0.683–1.21	0.925–1.51	0.630–1.47	0.291–1.20	0.539–1.36
0.7305	0.5938	0.5168	0.1818	0.8583	0.1457	0.5109
1.18	0.791	0.834	1.10	0.743	1.53	0.868
0.949–1.47	0.558–1.12	0.606–1.15	0.844–1.44	0.446–1.24	1.08–2.17	0.545–1.38
0.1356	0.1892	0.2642	0.4728	0.2556	0.0170	0.5505
0.941	0.870	0.533	0.915	0.871	1.01	0.719
0.687–1.29	0.581–1.30	0.297–0.957	0.625–1.34	0.517–1.47	0.630–1.63	0.429–1.21
0.7046	0.4984	0.0351	0.6494	0.6044	0.9528	0.2118
1.14	0.996	1.10	1.11	0.941	1.35	0.942
0.874–1.48	0.706–1.40	0.800–1.52	0.810–1.53	0.587–1.51	0.893–2.03	0.584–1.52
0.3416	0.9819	0.5552	0.5081	0.7996	0.1557	0.8054
1.02	1.63	1.30	0.636	1.29	1.34	1.27
0.771–1.36	1.23–2.14	0.955–1.77	0.381–1.06	0.869–1.91	0.905–2.00	0.887–1.83
0.8693	0.0006	0.0955	0.0842	0.2069	0.1432	0.1892
1.02	0.659	0.876	0.812	0.499	1.05	1.78
0.756–1.37	0.393–1.11	0.584–1.31	0.528–1.25	0.184–1.36	0.568–1.93	1.12–2.83
0.9108	0.1141	0.5233	0.3449	0.1731	0.8836	0.0141
0.981	0.920	1.08	1.11	0.944	1.19	1.37
0.726–1.33	0.614–1.38	0.761–1.54	0.796–1.56	0.519–1.72	0.647–2.17	0.838–2.23
0.9001	0.6839	0.6624	0.5286	0.8504	0.5819	0.2105
1.08	0.790	1.18	1.21	0.791	1.00	1.25
0.803–1.46	0.495–1.26	0.837–1.65	0.871–1.68	0.385–1.63	0.482–2.06	0.729–2.14
0.6064	0.3233	0.3519	0.2557	0.5230	0.9943	0.4190
1.00	0.728	0.598	0.824	0.770	1.65	0.609
0.728–1.38	0.433–1.22	0.330–1.08	0.530–1.28	0.373–1.59	1.01–2.69	0.222–1.67
0.9913	0.2296	0.0890	0.3899	0.4808	0.0475	0.3350
1.24	0.516	1.07	0.998	1.41	1.17	0.480
0.923–1.66	0.254–1.05	0.739–1.54	0.681–1.46	0.933–2.14	0.683–1.99	0.177–1.30
0.1539	0.0685	0.7339	0.9927	0.1025	0.5748	0.1497

Toxic epidermal necrolysis is a severe cutaneous adverse drug reaction that is caused by some antiepileptic drugs (Mullan et al. 2019). The present study showed the association of toxic epidermal necrolysis (PT) with lamotrigine, carbamazepine, and levomepromazine (Table 3). The average mortality rate is 25-50%, and ocular sequelae developed in a patient with toxic epidermal necrolysis (Kinoshita and Saeki 2017; Sotozono et al. 2021). Therefore, an effective treatment for toxic epidermal necrolysis is desired. The present study showed that lithium carbonate decreased the aOR of toxic epidermal necrolysis (PT) (Table 3). Furthermore,

Table 5: Multiple logistic regression analysis of ADEs (SMQ) in 3521 patients with bipolar disorders

ADE (SMQ)		Female	Age ≥50 y	Lithium	Lamotrigine	CBZ
Acute renal	aOR	0.817	1.24	1.25	0.689	1.03
failure	95% CI	0.660–1.01	0.982–1.56	0.997–1.55	0.530–0.895	0.740–1.43
	P value	0.0652	0.0709	0.0527	0.0052	0.8645
Hyperglycemia/	aOR	0.602	0.865	0.677	0.396	0.796
new onset diabetes	95% CI	0.483–0.752	0.699–1.07	0.540–0.848	0.286–0.547	0.532–1.19
mellitus	P value	<0.0001	0.1829	0.0007	<0.0001	0.2648
Parkinson-like	aOR	1.20	2.68	0.924	0.762	0.764
events	95% CI	0.897–1.61	1.72–4.15	0.693–1.23	0.549–1.06	0.417–1.40
	P value	0.2167	<0.0001	0.5894	0.1036	0.3829
Tubulointerstitial	aOR	1.15	1.50	4.40	0.195	0.849
diseases	95% CI	0.936–1.42	1.16–1.94	2.79–6.93	0.096–0.395	0.608–1.19
	P value	0.1813	0.0023	<0.0001	<0.0001	0.3385

ADE: adverse drug event; SMQ: standardized MedDRA Query; CBZ: carbamazepine; CPZ: chlorpromazine; LVPZ: levomepromazine; aOR: adjusted odds ratio; CI: confidence interval.

the aOR of hyperglycemia/new onset diabetes mellitus (SMQ) was decreased by lithium carbonate, while lamotrigine decreased those of neuroleptic malignant syndrome (PT) and rhabdomyolysis (PT) (Tables 3 and 5). An inverse signal may become a trigger for drug development through drug repurposing in the present study. Lamotrigine reduced the aOR of drug interaction (PT) in the present study (Table 3); however, this is impossible. An inverse signal must be carefully interpreted when analyzing the spontaneous reporting system database of ADEs (Noguchi et al. 2021).

The present study represents the association of ADEs with atypical antipsychotics (Tables 3 and 5). There were no ADEs (PT) and ADEs (SMQ) common to association with the 4 medicines, other than neuroleptic malignant syndrome (PT). Olanzapine and clozapine are associated with type 2 diabetes mellitus (Hirsch et al. 2017). The present study showed an increased risk of hyperglycemia/new onset diabetes mellitus (SMQ) by olanzapine, quetiapine fumarate, and risperidone (Table 5). Since clozapine was only administered to 8 patients in our data, an analysis of clozapine was avoided in the present study. In November 2002, emergency intelligence regarding diabetic ketoacidosis and diabetic coma due to elevated blood glucose levels by quetiapine fumarate was announced in Japan, suggesting a relationship with the present results. Among females, Asians are at a higher risk of developing type 2 diabetes than Caucasians (Shai et al. 2006). Furthermore, the dosages of atypical antipsychotics differ between Japan and the United States of America. The detailed profiles of ADEs by atypical antipsychotics are expected to vary among countries.

The present study had other limitations besides the reporting biases described above. There were no control patients. Furthermore, confounding factors may have affected the results of the multivariate analysis. Therefore, the present results need to be interpreted in consideration of these limitations.

To the best of our knowledge, this is the first study to show profiles of ADEs in patients with bipolar disorders using the JADER database, a spontaneous reporting system. Based on multiple logistic regression analyses, we identified the risk factors for 19 ADEs (PT) and 4 ADEs (SMQ). It was suggested that the number of reports on ADEs associated with lamotrigine was the highest. We consider the present results to provide useful information for predicting the onset of ADEs in patients with bipolar disorders and their relationship with medications in Japan.

4. Experimental

4.1. Data on patients with bipolar disorder

The JADER data structure consists of 4 datasets: patient demographic information (DEMO), drug information (DRUG), adverse reactions (REAC), and primary disease (HIST). Data on 3521 patients with bipolar disorders in our previous study were used in the present study as well (Uwai and Nabekura 2021). Briefly, patients with bipolar disorder, bipolar I disorder, and bipolar II disorder were extracted from HIST data. Their demographic information was linked using ID numbers, and the occurrence of ADEs was investigated using REAC data. The administration of lithium carbonate, lamotrigine, carbamazepine, sodium valproate, aripiprazole, olanzapine, quetiapine fumarate, risperidone, chlorpromazine, or levomepromazine was examined using DRUG data. After the exclusion of patients with missing data on sex or age and duplicates, data of 3521 patients were examined.

4.2. Definition of ADEs

ADEs in the JADER database are coded according to the terminology preferred by the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J, https://www.jmo.pmrj.jp). The standardized MedDRA Queries (SMQ) index, a comprehensive search formula, is widely accepted and used in analyses of the JADER database (Abe et al. 2017; Okada et al. 2019; Mizuno et al. 2021). This consists of groupings of MedDRA preferred terms (PT), which are related to a defined medical condition or area of interest. The grouping of SMQ exists in both the "narrow" and "broad" scope, and the "narrow" scope was employed in the present study. We used SMQ version 24.1 to extract case reports related to acute renal failure (SMQ code: 20000003, containing 19 related PT), hyperglycemia/new onset diabetes mellitus (SMQ code: 20000041, containing 54 related PT), Parkinson-like events (SMQ code: 20000099, containing 18 related PT), and tubulointerstitial diseases (SMQ code: 20000221, containing 25 related PT).

4.3. Identification of risk factors for ADEs by a multivariate analysis

A multiple logistic regression analysis with covariates including sex, age, and the use of medicines was performed to identify risk factors for ADEs. Regarding age, reports were stratified by age as <50 and ≥50 years. The following multiple logistic regression model was used in the analysis:

$$\text{Log (odds)} = \beta_0 + \beta_1 \times X_1 + \beta_2 \times X_2 + \beta_3 \times X_3 + \beta_4 \times X_4 + \beta_5 \times X_5 + \beta_6 \times X_6 + \beta_7 \times X_7 + \beta_8 \times X_8 + \beta_9 \times X_9 + \beta_{10} \times X_{10} + \beta_{11} \times X_{11} + \beta_{12} \times X_{12}$$

where X_1 is sex and X_2 is the stratified age group. X_3 to X_{12} are the uses of lithium carbonate, lamotrigine, carbamazepine, sodium valproate, aripiprazole, olanzapine, quetiapine fumarate, risperidone, chlorpromazine, and levomepromazine, respectively. The adjusted odds ratio (aOR) was calculated using the estimated value of beta, and the 95% confidence interval (CI) was obtained using the estimated value of beta and its standard error, according to the following equations:

$$\text{aOR} = \exp(\beta)$$

$$95\%\ \text{CI} = \exp(\beta \pm 1.96 \times \text{standard error})$$

aORs were calculated using male sex, the <50-year-old group, and the non-user group of each medicine as a reference group.

4.4. Ethical approval

All reports were obtained freely available online via the PMDA website, and they were fully anonymized by the relevant regulatory authority before they were accessed. Accordingly, ethical approval was not required for the present study.

4.5. Statistical analysis

A multiple logistic regression analysis was performed using JMP Pro 15.0 (SAS Institute, Cary, NC, USA). A P value of <0.05 was considered to be significant.

Conflicts of interest: The authors declare no conflicts of interests.

Valproate	Aripiprazole	Olanzapine	Quetiapine	Risperidone	CPZ	LVPZ
1.29	0.964	0.861	0.761	0.822	1.08	1.13
1.02–1.62	0.703–1.32	0.616–1.21	0.525–1.10	0.517–1.31	0.724–1.62	0.799–1.59
0.0354	0.8174	0.3842	0.1484	0.4080	0.6796	0.4959
0.871	1.16	1.70	2.00	1.41	0.705	0.886
0.680–1.12	0.871–1.54	1.36–2.13	1.60–2.50	1.01–1.97	0.390–1.28	0.584–1.34
0.2733	0.3116	<0.0001	<0.0001	0.0418	0.2490	0.5683
1.78	1.88	1.19	1.40	1.48	1.67	0.570
1.34–2.37	1.39–2.55	0.833–1.71	1.01–1.96	0.964–2.27	1.04–2.68	0.273–1.19
<0.0001	<0.0001	0.3346	0.0458	0.0728	0.0327	0.1338
1.44	0.433	0.639	0.734	0.808	1.00	0.752
1.14–1.82	0.240–0.780	0.417–0.981	0.508–1.06	0.521–1.25	0.664–1.52	0.503–1.12
0.0026	0.0053	0.0407	0.0996	0.3402	0.9819	0.1644

References

Abe J, Umetsu R, Uranishi H, Suzuki H, Nishibata Y, Kato Y, Ueda N, Sasaoka S, Hatahira H, Motooka Y, Masuta M, Nakamura M (2017) Analysis of polypharmacy effects in older patients using Japanese Adverse Drug Event Report database. PLoS One 12: e0190102.

Baldessarini RJ, Tondo L, Viguera AC (1999) Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. Bipolar Disord 1: 17–24.

Finley PR (2016) Drug interactions with lithium: an update. Clin Pharmacokinet 55: 925–941.

Grünfeld JP, Rossier BC (2009) Lithium nephrotoxicity revisited. Nat Rev Nephrol 5: 270–276.

Hartnell NR, Wilson JP (2004) Replication of the Weber effect using postmarketing adverse event reports voluntarily submitted to the United States Food and Drug Administration. Pharmacotherapy 24: 743–749.

Hirsch L, Yang J, Bresee L, Jette N, Patten S, Pringsheim T (2017) Second-generation antipsychotics and metabolic side effects: a systematic review of population-based studies. Drug Saf 40: 771–781.

Jawad I, Watson S, Haddad PM, Talbot PS, McAllister-Williams RH (2018) Medication nonadherence in bipolar disorder: a narrative review. Ther Adv Psychopharmacol 8: 349–363.

Kinoshita Y, Saeki H (2017) A review of toxic epidermal necrolysis management in Japan. Allergol Int 66: 36–41.

Leclerc E, Mansur RB, Brietzke E (2013) Determinants of adherence to treatment in bipolar disorder: a comprehensive review. J Affect Disord 149: 247–252.

McIntyre RS, Berk M, Brietzke E, Goldstein BI, López-Jaramillo C, Kessing LV, Malhi GS, Nierenberg AA, Rosenblat JD, Majeed A, Vieta E, Vinberg M, Young AH, Mansur RB (2020) Bipolar disorders. Lancet 396: 1841–1856.

Mizuno T, Sakai T, Tanabe K, Umemura T, Goto N, Ohtsu F (2021) Visualization of kinase inhibition-related adverse events using the Japanese Adverse Drug Event Report database. Drugs Real World Outcomes 8: 197–206.

Mullan KA, Anderson A, Illing PT, Kwan P, Purcell AW, Mifsud NA (2019) HLA-associated antiepileptic drug-induced cutaneous adverse reactions. HLA 93: 417–435.

Müller-Oerlinghausen B, Berghöfer A, Bauer M (2002) Bipolar disorder. Lancet 359: 241–247.

Noguchi Y, Tachi T, Teramachi H (2021) Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source. Brief Bioinform 22: bbab347.

Öhlund L, Ott M, Oja S, Bergqvist M, Lundqvist R, Sandlund M, Salander Renberg E, Werneke U (2018) Reasons for lithium discontinuation in men and women with bipolar disorder: a retrospective cohort study. BMC Psychiatry 18: 37.

Okada N, Niimura T, Zamami Y, Hamano H, Ishida S, Goda M, Takechi K, Chuma M, Imanishi M, Ishizawa K (2019) Pharmacovigilance evaluation of the relationship between impaired glucose metabolism and BCR-ABL inhibitor use by using an adverse drug event reporting database. Cancer Med 8: 174–181.

Ooba N, Tsutsumi D, Kobayashi N, Hidaka S, Hayashi H, Obara T, Satoh M, Kubota K, Fukuoka N (2018) Prevalence of therapeutic drug monitoring for lithium and the impact of regulatory warnings: analysis using Japanese claims database. Ther Drug Monit 40: 252–256.

Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N (2007) Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf 30: 891–898.

Shai I, Jiang R, Manson JE, Stampfer MJ, Willett WC, Colditz GA, Hu FB (2006) Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care 29: 1585–1590.

Sotozono C, Ueta M, Kinoshita S (2021) Japan: diagnosis and management of Stevens-Johnson syndrome/toxic epidermal necrolysis with severe ocular complications. Front Med (Lausanne) 8: 657327.

Uwai Y, Nabekura T (2021) Surveillance of drug overdose and identification of its risk factors by a multivariate analysis using the Japanese Adverse Drug Event Report database. Asian J Psychiatr 65: 102826.