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The epidemiology of adverse drug events and medication errors among psychiatric inpatients in Japan: the JADE study

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Abstract

Background: Knowledge of the epidemiology of adverse drug events (ADEs) and medication errors in psychiatric inpatients is limited outside Western countries. The nature of ADEs and medication errors are important for improving the quality of care worldwide; therefore, we conducted the Japan Adverse Drug Events Study, a series of cohort studies at several settings in Japan.

Methods: This report included 448 inpatients with 22,733 patient-days in a psychiatric hospital and psychiatric units at a tertiary care teaching hospital over 1 year. Four psychiatrists and two other physicians reviewed all medical charts and related documents to identify suspected incidents. The physicians later classified those incidents into ADEs, potential ADEs, medication errors, or exclusions and evaluated the severity and preventability if the incidents were events.

Results: During the study period, we identified 955 ADEs and 398 medication errors (incidence: 42.0 and 17.5 per 1000 patient-days, respectively). Among ADEs, 1.4 %, 28 %, and 71 % were life-threatening, serious, and significant, respectively. Antipsychotics were associated with half of all ADEs. The incidence of medication errors was higher in medical care units than in acute and nursing care units (40.9, 15.6, and 17.4 per 1000 patient-days, respectively). The monitoring and ordering stages were the most common error stages (39 % and 34 % of all medication errors, respectively), and 76 % of medication errors with ADEs were found at the monitoring stage. Non-psychiatric drugs were three times as likely to cause ADEs with errors compared to psychiatric drugs.

Conclusions: Antipsychotic use, inadequate monitoring, and treatment of physical ailments by psychiatrists may contribute to the high incidence of medication errors and ADEs among psychiatric inpatients in Japan. Psychiatrists should be cautious in prescribing antipsychotics or unfamiliar medications for physical problems in their psychiatric patients, and should monitor patients after medication administration.

Keywords: Adverse drug event, Medication error, Epidemiology, Psychiatry, Patient safety

Abbreviations: ADE, Adverse drug event; CI, Confidence interval; IQR, Interquartile range; SD, Standard deviation

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Background

Adverse drug events (ADEs) are drug-related injuries resulting from medical intervention [1–3]. ADEs are generally the most frequent cause of injuries due to medical care in hospitals [4, 5]. Psychiatric inpatients are at high-risk for these injuries because pharmacotherapy plays a central role in psychiatric treatment [6, 7]. In addition, many psychiatric patients present with comorbid medical disorders that require treatment with non-psychiatric drugs, and when these conditions are treated in psychiatric hospitals, this puts patients at further risk for ADEs and medication errors [7, 8].

There is a need for more epidemiological data concerning appropriate medication use in order to provide safer and more effective pharmacological treatment for psychiatric inpatients. Previous studies, however, have noted the complexities of identifying ADEs and medication errors in psychiatric settings because it is difficult to distinguish ADEs caused by drugs from symptoms related to mental disorders; in addition, it can be difficult to define medication errors in these settings, as psychiatric pharmacotherapy often deviates from standard treatment [9, 10]. In fact, there have been notably few comprehensive studies on this topic, especially regarding ADEs [7, 11–13]. Furthermore, the studies that have been conducted all took place in Western countries, meaning that their results cannot be generalized to clinical settings in other countries without first assessing local data [14], because mental health services differ between countries. For example, longer hospital stays and lower staff ratios are two characteristics of Japanese psychiatric care [15], while many African countries suffer from a critical lack of psychiatrists and pharmacists [16]. To this end, we conducted a historical cohort study in psychiatric settings to estimate the incidence and nature of ADEs and medication errors among psychiatric inpatients in Japan.

Methods

Study design and patient population

This historical cohort study was conducted as part of a multicenter cohort study known as the Japan Adverse Drug Events (JADE) Study [17, 18]. As part of the JADE study series, we collected information using the standard JADE protocol. [3, 17, 18] Data were collected from the psychiatric inpatient units at one psychiatric hospital and one tertiary care teaching hospital. There were a total of 438 psychiatric inpatient beds between these two hospitals, including beds in acute care units, nursing care units, and medical care units. The acute care unit comprises the main section of a psychiatric department in which patients with an acute mental disorder receive targeted mental care. Psychiatric patients who have recovered from the acute stage of their condition but who still require nursing care are admitted to nursing care units. Medical care units are specialized sections within a psychiatric department that provide treatment to psychiatric patients with physical medical conditions. Both hospitals included in this study used electronic medical records.

At the tertiary care teaching hospital, patients were treated both by attending psychiatrists and by resident psychiatrists, who have <3 years of training after obtaining their medical license. Resident psychiatrists practiced under the supervision of attending psychiatrists and primarily ordered medications. In contrast, most of the psychiatrists at the psychiatric hospital were attending psychiatrists. Both hospitals admitted patients to the acute care or medical care units within the psychiatry department if psychiatric disorders were the main presenting problem and the patients' physical problems were considered to be mild; internists provided medical consultations as needed. Conversely, if patients' physical complications were considered to be more severe than their psychiatric problems, or if patients required intensive care (for example, as a result of myocardial infarction or femoral fracture, or if they required intubation), they were discharged from the psychiatric department and transferred to non-psychiatric wards for subsequent care.

Data were collected from all psychiatric inpatients who were admitted to and discharged from the acute, nursing and medical care units from April 1, 2010 through March 31, 2011. The main measures that were evaluated were patient-days and the number of admissions. The study was approved by the institutional review boards of the Kyoto Prefectural University of Medicine and by the institutional review boards of the two participating hospitals. The need for informed consent was waived because all data were collected as part of the hospitals' daily practices.

Definitions

The primary outcome measured in this study was the number of ADEs, defined as drug-related injuries resulting from medical intervention [1, 2]. The term ADE has a wide spectrum of definitions, including harm caused by drugs at a usual dosage (adverse drug reactions: ADRs) or at an unusual dosage, and also including harm from dose reduction and discontinuation of drug therapy [19]. For example, an extrapyramidal symptom, such as akathisia, occurring after a patient receives antipsychotics, and with no other apparent cause, is considered to be an ADE. Rebound insomnia that occurs following discontinuation of sedatives is another example of an ADE. An ADE was then categorized by severity as fatal, life-threatening, serious or significant. Fatal ADEs were those that resulted in death. Life-threatening ADEs were those that caused such issues as respiratory depression or suicidal behavior. Serious ADEs included gastrointestinal bleeding, falls, or a

decrease in blood pressure. Significant ADEs included cases with milder symptoms, such as diarrhea, constipation, extrapyramidal symptoms or drowsiness.

A secondary outcome that was measured in this study was medication errors. Medication errors could occur at any step of the medication use process (ordering, transcribing, dispensing, administering or monitoring), and medication errors may or may not cause ADEs. If a medication error was found, the type of error and the stage in the process where it occurred were classified. The medication use process included the following stages: ordering by psychiatrists or other physicians; transcription by nurses; dispensing by pharmacists (or by psychiatrists and nurses, as was the case during the night shift and on weekends in the psychiatric hospital); administration by nurses or by patients; and monitoring by psychiatrists, other health professionals or by patients themselves.

ADEs were categorized as either preventable or non-preventable. An ADE was considered to be preventable if it resulted from a medication error or was otherwise ameliorable by available means (e.g., switching to a different drug or cautious monitoring after administration). An ADE that occurred in the absence of a medication error was defined as a non-preventable ADE. For example, a rash that occurred due to lamotrigine use in a patient without a history of lamotrigine-induced rash would not be considered a preventable ADE, but it would be considered as a preventable ADE if the patient had a history of such a rash.

We also classified ADEs according to their potential for causing injury. A potential ADE was an error that had the potential for injury but did not actually result in injury, either because of specific circumstances, chance, or because the error was intercepted. For example, if hypnotics were administered several hours earlier than prescribed, this would constitute a medication error and potential ADE, even if no negative effects were observed because hypnotics may cause immediate somnolence. On the other hand, early administration of anti-dementia drugs would be classified as a medication error but not a potential ADE because the drug rarely causes acute side effects.

Data collection and classification

The definitions and methods used in this study were consistent with those from prior studies on this topic [3, 17, 18]. In this study, four psychiatrists and two physicians, all with experience in the classification of ADEs as a result of previous research on this topic, reviewed all patient charts from each participating hospital, along with laboratory results, incident reports and prescription queries. Research assistants used patient charts to compile demographic characteristics and administrative data for all enrolled patients in the cohort.

Once all data were collected from participating hospitals, the reviewers independently classified relevant incidents as an ADE, potential ADE or medication error, while also recording the details of those incidents. This included information about the name, dose, route and class of the drugs, the details of symptoms resulting from ADEs, and the details related to medication errors such as type, stage and persons who were in charge at the time the error occurred. The reviewers also independently classified all incidents according to their severity and preventability. After all suspected incidents were collected, the reviewers met to confirm the final classification for each incident. When the reviewers disagreed on the classification of an incident, they reached a consensus through discussion.

Statistical analyses

The incidences per 1000 patient-days, crude rates per 100 admissions, and 95 % confidence intervals (CIs) were calculated as a whole and by unit types (acute care unit, nursing care unit, and medical care unit). Continuous variables are presented as means with standard deviations (SDs) or medians with interquartile ranges (IQRs), and categorical variables are shown as numbers and percentages. We used the χ^2 test to assess the relationship between drug classes and preventable ADEs. We calculated inter-rater reliabilities using k statistics. Kappa scores between reviewers regarding the presence of an ADE were 0.96 (ADE v. potential ADE or exclude). The kappa for preventability was 0.95 (preventable v. non-preventable), while the kappa for severity was 0.43 (significant v. serious or life-threatening). These values were similar to those published in previous reports by Rothschild et al. (2007) and Morimoto et al. (2011). We performed all analyses using JMP V.11.2 (SAS Institute, Cary, North Carolina, USA) software.

Results

There were a total of 448 admissions with 22,733 patient-days during the study period. The ages of the included patients ranged from 13 to 97 years old, and the mean age was 56 (SD 22) years. Forty-one (185/448) percent of patients were aged ≥65 years, and 247 (55 %) were female. The median hospital stay was 32 (interquartile range 15–75) days. The acute care, nursing care and medical care units admitted 341 (76 %), 75 (17 %), and 32 (7 %) patients, respectively (Table 1). Of all admissions, approximately 42 % were involuntary admissions. The most common reasons for admission were schizophrenic disorders and dementia, and the median number of medications patients were taking on admission was 6 (range 4–8) (Table 1).

Adverse drug events

We identified 1234 suspected incidents, and through reviews and discussions of these suspected incidents, we identified 955 ADEs among 283 patients (63 %) (Fig. 1). The incidence of ADEs was 42.0 [95 % CI 39.4–44.6] per

Table 1 Demographic data for the study population

Factors	No. of patients
	Total (*n* = *448*)
Age ≥ 65 years, *n* (%)	185 (41)
Female, *n* (%)	247 (55)
Admitting unit, *n* (%)	
Acute	341 (76)
Nursing	75 (17)
Medical	32 (7)
Admission pathway, *n* (%)	
Scheduled admission	247 (55)
Emergency admission	201 (45)
Nonresident physician in charge, *n* (%)	379 (85)
Involuntary admission, *n* (%)	186 (41.5)
Number of prescribed medications on admission, median (quartile)	6 (4–8)
Primary diagnosis,[a] *n* (%)	
Dementia	97 (21.7)
Other organic disorders	19 (4.2)
Mental or behavioral disorder due to substance use	48 (10.7)
Schizophrenia and other psychotic disorders	113 (25.2)
Mood disorders	84 (18.8)
Depression	38 (8.5)
Mania, Bipolar disorder	32 (7.1)
Other mood disorders	14 (3.1)
Neurotic, stress-related and somatoform disorders	40 (8.9)
Anorexia	17 (3.8)
Mental retardation	11 (2.5)
Development disorder	12 (2.7)
Other	7 (1.6)

[a]Diagnoses based on the International Classification of Diseases, Tenth Revision [24]

1000 patient-days, and the crude rate was 213 [95 % CI 184–243] per 100 admissions (Table 2). Significant ADEs accounted for 71 % (677 events in 263 patients) of all events, followed by serious ADEs (28 %, 265 in 124) and life-threatening ADEs (1.4 %, 13 in 12). There were no fatal ADEs that occurred during the study.

The most common class of drugs associated with ADEs was atypical antipsychotics (34 %, 323/955), and almost half of ADEs (46.9 %, 448/955) were associated with typical and atypical antipsychotics. Non-psychiatric drugs accounted for 16 % (124/789) of non-preventable ADEs, but were associated with 42 % (69/166) of all preventable ADEs. In other words, the proportion of preventable ADEs to all ADEs associated with non-psychiatric drugs (69 per 193 ADEs; 36 %) was higher compared to psychiatric drugs (97 per 762 ADEs; 13 %) ($P < 0.001$) (Table 3).

When ADEs were assessed by organ system, central nervous system symptoms (including falls, over-sedation and extrapyramidal symptoms) were the most frequent symptoms, accounting for 44 % (415/995) of all ADEs, followed by gastrointestinal symptoms (including diarrhea and constipation) (34 %, 326/955), allergic or skin symptoms (including drip leakage) (6 %, 58/955) and metabolic or liver dysfunction (5 %, 49/955).

Medication errors and potential adverse drug events

We identified 398 medication errors among 174 patients (39 %). The incidence was 17.5 [95 % CI 15.8–19.2] per 1000 patient-days, and the crude rate was 88.8 [95 % CI 72.9–105] per 100 admissions. Among the 398 medication errors, 166 actually resulted in ADEs and were therefore classified as preventable ADEs, whereas 186 had the potential to cause injury but did not result in observed harm (Fig. 1). The incidence and crude rates were approximately two times higher in the medical care units compared to the other units. Furthermore, the

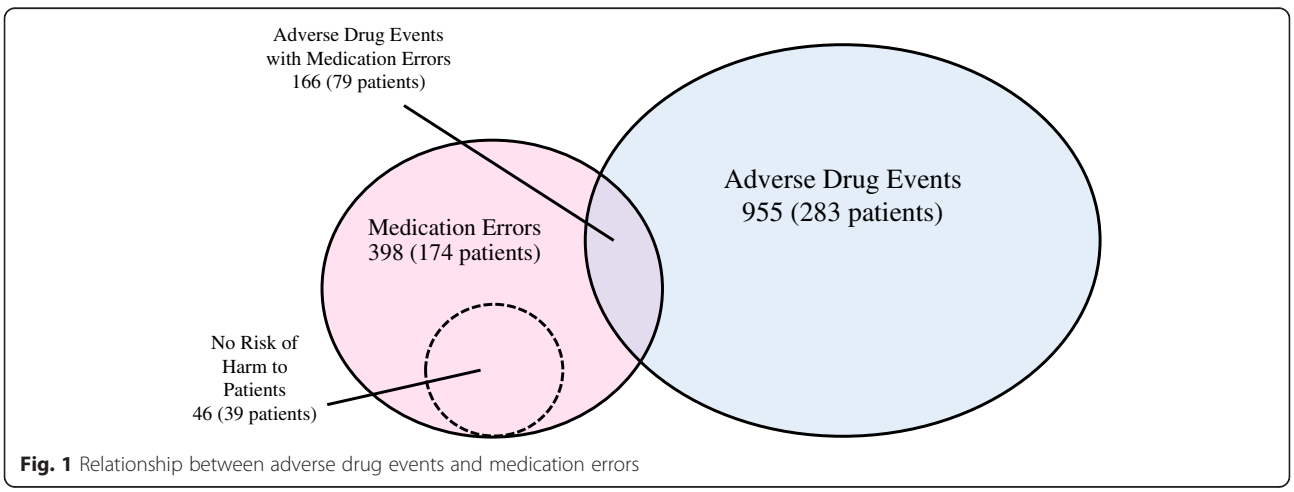

Fig. 1 Relationship between adverse drug events and medication errors

Table 2 Incidences of adverse drug events, medication errors and preventable adverse drug events

Unit	*n*	Patient-days	ADEs	Incidence[a]	95 % CI	Crude rate[b]	95 % CI
Acute	341	16834	725	43.1	40.0–46.1	213	179–246
Nursing	75	4480	157	35.0	29.7–40.4	209	144–275
Medical	32	1419	73	51.4	40.0–62.9	228	88.6–368
Total	448	22733	955	42.0	39.4–44.6	213	184–243
Unit	*n*	Patient-days	Medication Errors	Incidence[a]	95 % CI	Crude rate[b]	95 % CI
Acute	341	16834	262	15.6	13.7–17.4	76.8	62.0–91.7
Nursing	75	4480	78	17.4	13.6–21.2	104	56.3–152
Medical	32	1419	58	40.9	30.6–51.2	181	73.4–289
Total	448	22733	398	17.5	15.8–19.2	88.8	72.9–105
Unit	*n*	Patient-days	Preventable ADEs	Incidence[a]	95 % CI	Crude rate[b]	95 % CI
Acute	341	16834	86	5.1	4.0–6.2	25.2	16.4–34.1
Nursing	75	4480	38	8.5	5.8–11.2	50.7	17.5–83.8
Medical	32	1419	42	29.6	20.8–38.4	131	35.9–227
Total	448	22733	166	7.3	6.2–8.4	37.1	25.8–48.3

ADEs adverse drug events, *CI* confidence interval
[a]Per 1000 patient-days
[b]Per 100 admissions

incidence of preventable ADEs in the medical care units (29.6) was much higher compared to the acute care units (5.1) and nursing care units (8.5) (Table 2).

The incidence of preventable ADEs and non-preventable ADEs was 7.3 [95 % CI 6.2–8.4] and 34.7 [95 % CI 32.3–37.1] per 1000 patient-days, respectively. Thus, 17.4 % (166/955) of ADEs were considered preventable. The incidence of potential ADEs was 8.2 [95 % CI 7.0–9.4] per 1000 patient-days. Forty-six medication errors were determined to carry no risk of injury to patients, so these errors were not considered to be potential ADEs. Twelve percent of potential ADEs (23 cases) were intercepted before a drug was administered and were thus classified as intercepted potential ADEs. Medication errors were most frequently associated with the monitoring stage (39 %, 155/398) and ordering stage (34 %, 134/398) of treatment. In addition, 76 % (126/166) of preventable ADEs occurred during the monitoring stage. Potential ADEs occurred most frequently during the ordering stage, accounting for 46 % (86/186) of all potential ADEs, followed by the administering stage (36 %, 67/186).

Discussion

We determined that ADEs and medication errors were common in Japanese psychiatric inpatient settings. ADEs were observed in 63 % of psychiatric inpatients with an incidence of 42 per 1000 patient-days, and medication errors were observed in 39 % of inpatients with an incidence of 17.5 per 1000 patient-days. Most of these ADEs were not preventable (83 % of ADEs), and 29 % of ADEs were classified as serious or life-threatening. In addition, we identified frequent medication errors at the monitoring stage (39 % of all medication errors), and this was more evident for preventable ADEs (76 % of all preventable ADEs occurred at this stage).

Comparison with findings from previous studies in psychiatric settings

Although there have been several previous studies on ADEs (or ADRs) and medication errors in psychiatric settings, comparisons between the previous studies were difficult because they used different designs and denominators [20]. In addition, among studies utilizing the same denominator but with different study designs, there were significant differences in the reported rates of medication errors (e.g., 0.79 potential ADEs per 1000 patient-days based on a reporting system [21] vs. 1516 medication errors per 1000 patient-days on a retrospective chart review [8]). Therefore, in order to compare our findings with those of previous studies in different settings, we adopted the same definition and methodology used in the study performed by Rothschild et al., which took place in psychiatric settings in the USA [7], as well as those of other studies in general settings in the USA [2] and Japan [17]. In comparison with the present study, Rothschild et al. reported one-quarter incidence of ADEs (10 per 1000 patient-days) and one-third medication errors (6.3 per 1000 patient-days). The difference become even more evident regarding the crude rate of ADEs per 100 admissions (213 v. 10.2) and medication errors (88.8 v. 6.4); this is likely a result of the fact that the mean length of stay is much longer in Japan compared to the USA (50.7 v. 10.3 days).

Table 3 Frequency of adverse drug events according to drug class

Drug Class	ADEs, *n* (%) (*n = 955*)	Preventable ADEs, *n* (%) (*n = 166*)	Non-preventable ADEs, *n* (%) (*n = 789*)	Potential ADEs, *n* (%) (*n = 186*)	Intercepted potential ADEs, *n* (%) (*n = 23*)	Non-intercepted potential ADEs, *n* (%) (*n = 163*)
Antibiotics	10 (1.0)	0 (0)	10 (1.3)	2 (1.1)	0 (0)	2 (1.2)
Antihypertensives	14 (1.5)	3 (1.8)	11 (1.4)	7 (3.8)	1 (4.3)	6 (3.7)
Cardiovascular drugs	8 (0.8)	1 (0.6)	7 (0.9)	12 (6.5)	2 (8.7)	10 (6.1)
Anticoagulants	9 (0.9)	2 (1.2)	7 (0.9)	1 (0.5)	0 (0)	1 (0.6)
Antihyperlipidemics	1 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)
Antidiabetics	10 (1.0)	2 (1.2)	8 (1.0)	9 (4.8)	1 (4.3)	8 (4.9)
Peptic ulcer drugs	1 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)
Laxatives	40 (4.2)	10 (6.0)	30 (3.8)	7 (3.8)	0 (0)	7 (4.3)
NSAIDs	6 (0.6)	0 (0)	6 (0.8)	7 (3.8)	0 (0)	7 (4.3)
Antiallergic agents	2 (0.2)	0 (0)	2 (0.3)	0 (0)	0 (0)	0 (0)
Electrolytes or fluids	58 (6.1)	50 (30.1)	8 (1.0)	21 (11.3)	1 (4.3)	20 (12.3)
Chinese herbal medicines	2 (0.2)	0 (0)	2 (0.3)	0 (0)	0 (0)	0 (0)
Sedatives (benzodiazepine)	66 (6.9)	28 (16.9)	38 (4.8)	53 (28.5)	0 (0)	53 (32.5)
Sedatives (other)	15 (1.6)	4 (2.4)	11 (1.4)	5 (2.7)	1 (4.3)	4 (2.5)
Anxiolytics	31 (3.2)	6 (3.6)	25 (3.2)	5 (2.7)	2 (8.7)	3 (1.8)
Antidepressants (SSRI, SNRI, NaSSA)	58 (6.1)	2 (1.2)	56 (7.1)	4 (2.2)	3 (13.0)	1 (0.6)
Antidepressants (other)	62 (6.5)	6 (3.6)	56 (7.1)	1 (0.5)	1 (4.7)	0 (0)
Mood stabilizers	45 (4.7)	14 (8.4)	31 (3.9)	4 (2.2)	2 (8.7)	2 (1.2)
Antipsychotics (atypical)	323 (33.8)	32 (19.3)	291 (36.9)	34 (18.3)	6 (26.1)	28 (17.2)
Antipsychotics (typical)	125 (13.1)	4 (2.6)	121 (15.3)	1 (0.5)	0 (0)	1 (0.6)
Anticonvulsants	8 (0.8)	1 (0.6)	7 (0.9)	3 (1.6)	0 (0)	3 (1.8)
Anti-parkinsonian drugs	24 (2.5)	0 (0)	24 (3.0)	1 (0.5)	0 (0)	1 (0.6)
Anti-dementia medicines	5 (0.5)	0 (0)	5 (0.6)	1 (0.5)	1 (4.3)	0 (0)
Other drugs	32 (3.4)	1 (0.6)	31 (3.9)	8 (4.3)	2 (8.7)	6 (3.7)
Psychiatric drugs[a]	762 (79.8)	97 (58.4)	665 (84.3)	112 (60.2)	16 (69.6)	96 (58.9)
Non-psychiatric drugs[b]	193 (20.2)	69 (41.6)	124 (15.7)	74 (39.8)	7 (30.4)	67 (41.1)
All drugs	955 (100)	166 (100)	789 (100)	186 (100)	23 (100)	163 (100)

ADEs adverse drug events, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SSRI* selective serotonin reuptake inhibitor; *SNRI* serotonin-noradrenaline reuptake inhibitor, *NaSSA* noradrenergic and specific serotonin antidepressants

[a]Psychiatric drugs include: sedatives (benzodiazepine), sedatives (other), anxiolytics, antidepressants (SSRI, SNRI, NaSSA), antidepressants (other), mood stabilizers, antipsychotics (atypical), antipsychotics (typical), anticonvulsants, anti-parkinsonian drugs and anti-dementia medicines

[b]Non-psychiatric drugs include: antibiotics, antihypertensives, cardiovascular drugs, anticoagulants, antihyperlipidemics, antidiabetics, peptic ulcer drugs, laxatives, NSAIDs, antiallergic agents, electrolytes or fluids, Chinese herbal medicines and other drugs

The reasons for the higher incidence of ADEs in the present study may result from differences inpatient characteristics between this study and the USA study. The most common diagnosis in the USA study was mood disorders (66.4 %), while schizophrenic disorder (25 %) followed by dementia (22 %) were the most common disorders in the present study. In accordance with this finding, Schmidt et al. (1984) reported a similar rate of ADRs (346 per 100 admissions) in a previous study performed in Germany in which schizophrenic disorder was the most common diagnosis (37 %) [11], and Hermesh et al. (1985) reported that elderly patients with organic brain disorders were at high risk of ADRs [12].

Differences of the medical system in the treatment of physical complications in psychiatric inpatients may be another possible reason for the discrepancy between our findings and prior reports on this topic. Patients in psychiatric settings in Japan tend to receive more extensive treatments for physical complications compared to patients in the USA, where patients with severe physical complications are commonly transferred to a general-care setting, especially in cases that require electrocardiographic monitoring or a continuous intravenous drip [7]. As a result, patients in Japanese inpatient psychiatric units may be at higher risk of ADEs and medication errors, as prescribing unfamiliar drugs is associated with

medication errors due to lack of experience and knowledge for practitioners in both psychiatric and general settings [7, 22]. In the present study, the proportion of preventable ADEs associated with non-psychiatric drugs was three times higher compared to psychiatric drugs (36 % v. 13 %, respectively), and the incidence of preventable ADEs was higher in the medical care units compared to acute and nursing care units (27.5 v. 5.1 v. 9.2 per 1000 patient-days, respectively).

Comparison to general-care settings in Japan

Compared with a previous study on ADEs in general-care settings in Japan [17], we also found a higher incidence of ADEs (42.0 v. 17.0 per 1000 patient-days) and medication errors (17.5 v. 8.7 per 1000 patient-days). The higher incidence of ADEs and medication errors in psychiatry units may result from the specific complexities of the medications used to treat psychiatric patients. Our results demonstrated that almost half of ADEs were associated with antipsychotics, which is in accordance with previous studies that also found that antipsychotics were the drug class most frequently associated with ADEs [7, 11, 13]. Antipsychotics are prescribed for many patients—not only for the treatment of schizophrenia but also for sedation in agitated patients—and they may cause a wide range of ADEs, including neurological, gastrointestinal, cardiovascular, metabolic and endocrine symptoms. The frequency and intensity of ADEs resulting from the use of antipsychotics (especially when used at high dosages for patients with severe mental disorders) may contribute to the high incidence of ADEs in psychiatric units. In addition, psychiatric patients with severe mental disorders may lack self-awareness, and as a result, they may not be able to fully report their symptoms due to ADEs to medical staff. Furthermore, if they unexpectedly refuse to take their medications, this may cause more frequent medication errors. Finally, monitoring errors may occur due to a combination of lack of experience and knowledge regarding the management of physical complications on the part of psychiatrists as well as inadequate staffing in psychiatric units [15].

Clinical implications

Psychiatrists usually regard ADEs like constipation from antipsychotics and drowsiness from sedatives as common and unavoidable consequences of medication, and believe that such ADEs seldom cause serious outcomes. However, serious ADEs are not rare, even though only a small percentage of ADEs are serious because ADEs occur frequently in medical care. According to the results of this research, life-threatening and serious ADEs accounted for 1.4 % (13 events in 12 patients) and 28 % (265 events in 124 patients) of events, respectively. Psychiatrists sometimes have to decide whether or not to continue administering medications associated with ADEs to treat patients with serious mental conditions; therefore, it is important to identify ADEs at an earlier stage to prevent serious events or to ameliorate their severity.

Moreover, as demonstrated by the results of the present study, psychiatrists were likely to make medication errors with ADEs during physical treatments, especially during the monitoring stage. This may be because psychiatrists focus on psychiatric problems and are less likely to treat physical problems, especially in psychiatric settings. Physicians usually tend to keep psychiatric inpatients at a distance, and psychiatrists in Japan may thus have to treat physical complications, with the exception of very severe physical conditions. Fragmentation of the physical and mental health systems is one of the barriers that hinders patients from receiving adequate care; [23] therefore, fixing the fragmented systems and increasing communication between physicians and psychiatrists could improve patients' physical health and minimize injury from medications among psychiatric inpatients in Japan and other countries.

Study limitation and strengths

Our study had several limitations. First, we conducted this study at one psychiatric hospital and one tertiary care teaching hospital. Therefore, our results may not represent other hospitals, although we attempted to mitigate this limitation by including both a psychiatric hospital and a tertiary care teaching hospital to represent a wide range of psychiatric settings. Second, we could not estimate the incidence and nature of ADEs and medication errors caused by doctors with other specialties in psychiatric settings because almost all medications were prescribed by psychiatrists in this study. Third, some ADEs and medication errors may have been missed, which would mean that our results underestimate the true incidence. However, we were able to precisely evaluate and collect data on confirmed incidents, especially physical symptoms due to ADEs; this was because internists with experience in the classification of ADEs as a result of previous research on this topic [17, 18] played a leading role in this study. In addition, more robust alternatives for measuring ADEs and medication errors have not yet been developed, and the approach we used is the approach that is currently used most widely, suggesting that the figures obtained in this study are the best that are currently available.

Conclusions

We found high incidences of ADEs and medication errors in general psychiatric settings and identified some risk factors for ADEs, including prescription of antipsychotics and treatment during the monitoring stage after drugs are administered. Therefore, clinicians should be

cautious in prescribing antipsychotics and while monitoring patients after administration, especially when patients are unable to report their symptoms due to a severe mental condition. Furthermore, because of the higher risk of ADEs and medication errors during the treatment of physical complications, consultation with physicians in other departments is essential when psychiatrists are considering prescribing unfamiliar medications for physical problems in their psychiatric patients.

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Availability of data and materials
We do not wish to share the datasets because only a portion of the datasets was used in the reported study, and we are going to conduct a secondary analysis using the datasets. We will share the datasets if the datasets have been entirely processed.

Authors' contributions
All authors were involved in the design of the study. NA, MS, TM, TK, KW, and JN collected the data. NA analyzed the data under the technical supervision of MS and TM. NA and JN interpreted study results, and NA wrote the first draft of the manuscript. All authors reviewed the manuscript, provided substantive intellectual contributions, and approved the final version of the manuscript for publication.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study was approved by the institutional review boards of the Kyoto Prefectural University of Medicine. The need for informed consent was waived because all data were collected as part of the hospitals' daily practices.

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Epidemiology of Adverse Events and Medical Errors in the Care of Cardiology Patients

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Objectives: There have been epidemiological studies of adverse events (AEs) among general patients but those of patients cared by cardiologist are not well scrutinized. We investigated the occurrence of AEs and medical errors (MEs) among adult patients with cardiology in Japan.

Methods: We conducted a cross-sectional study of adult outpatients at a Japanese teaching hospital from February through November 2006. We measured AE and ME incidents from patient report, which were verified by medical records, laboratory data, incident reports, and prescription queries. Two independent physicians reviewed the incidents to determine whether they were AEs or MEs and to assess severity and symptoms.

Results: We identified 144 AEs and 30 MEs (16.3 and 3.9 per 100 patients, respectively). Of the 144 AEs, 99 were solely adverse drug events (ADEs), 20 were solely non-ADEs, and the remaining 25 were both causes. The most frequent symptoms of ADEs were skin and allergic reactions due to medication. The most frequent symptoms of non-ADEs were bleeding due to therapeutic interventions. Among AEs, 12% was life threatening. Life-threatening AEs were 25% of non-ADEs and 5% of ADEs ($P = 0.0003$). Among the 30 MEs, 21MEs (70%) were associated with drugs.

Conclusions: Adverse events were common among cardiology patients. Adverse drug events were the most frequent AEs, and non-ADEs were more critical than ADEs. Such data should be recognized among practicing physicians to improve the patients' outcomes.

Key Words: adverse drug event, adverse event, epidemiology, medical error, patient safety, cardiology

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Injuries due to medical care, referred to as adverse events (AEs), are an important medical issue because they place an additional burden on the health care system and are associated with symptoms ranging from slight illness to death. Vincent et al[1] have observed that AEs occur frequently, at the rate of 11% of hospitalized patients. In the U.S., adverse drug events (ADEs) have been reported to occur in 3.9 events of hospitalized cardiac patients per 100 patients.[2] Gandhi et al[3] found a higher incidence in a prospective cohort study of adult outpatients where 25 of 100 outpatients experienced ADEs in the U.S., which represent the most frequent cause of injury due to medical care in developed countries,[4,5] and implied that ADEs occur more frequently among outpatients than hospitalized patients.

Adverse events can be either preventable or unpreventable, and preventable AEs are associated with medical errors (MEs). In 2000, the Institute of Medicine (IOM) estimates that MEs kill between 44,000 and 98,000 people every year in U.S. hospitals.[6] James[7] reported updated estimate that a lower limit of 210,000 deaths per year was associated with preventable AEs in U.S. hospital. Phillips et al[8] reported that from 1983 to 1993, the number of outpatient visits in the U.S. increased by 75% and ME deaths rose 8.48-fold (from 172 to 1459).

However, studies of AEs among outpatients and studies using patient reporting of AEs are limited. Therefore, we conducted a cross-sectional survey using patient reporting of AEs among adult Japanese cardiovascular outpatients and investigated AEs and MEs during their hospitalization and ambulatory care.

METHODS

Study Design and Patients

We conducted a cross-sectional study at a Japanese teaching hospital equipped with electronic medical records and computerized physician ordering entry. The computerized physician ordering entry did not offer default doses and did not perform automatic checks for allergies or drug interactions.

We included all consecutive patients aged 18 years or older who visited the cardiovascular outpatient clinic of Kyoto University Hospital from February through November 2006. The cardiovascular outpatients include all outpatient visits, including initial consultation, examinations, and postoperative follow-up. Research assistants who were trained by the investigators in an identical manner conducted the survey using the questionnaire (Supplemental Digital Content 1, http://links.lww.com/JPS/A45) for each patient at the outpatient clinic. The patients reported AE and ADE for their entire medical history including the past hospital admission, which were both cardiac and noncardiac care. The research assistants reviewed the patients' medical records to confirm the potential incidents if reported. They also made telephone calls to the patients if any query needed to be clarified.

The institutional review board of Kyoto University Graduate School of Medicine approved the study, and informed consent was obtained from each patient.

Definitions

The primary outcome was AEs, defined as injuries due to medical care. The causes of all AEs were determined, and multiple

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causes were permitted. For example, hepatitis C virus infection after emergent blood transfusion against hemorrhage during an operation was considered to be associated with both a drug and an operation. Adverse events were classified by type, ADEs, and non-ADEs. Adverse drug events included AEs caused by medication use, and non-ADEs included decision-making AEs such as misdiagnosis, operation-related AEs, procedure-related AEs such as cardiac catheterization, and other AEs. For example, cough after receiving angiotensin-converting enzyme (ACE) inhibitors with no other apparent cause was considered an ADE due to medication use, whereas peripheral neuropathy after an operation with no other apparent cause was considered an operation-related AE. Although MEs can occur at any step of the medical process and may or may not cause AEs, for the purposes of this study, we considered AEs without MEs as unpreventable and those resulting from MEs as preventable because we assumed that AEs associated with MEs could have been prevented if the errors had been avoided or intercepted. For example, allergy due to an ACE inhibitor in a patient without a history of ACE inhibitor-induced allergic symptoms was not considered to be the result of a medication error but was considered a medication error if the patient had a history of such allergic symptoms. Minor errors in medication use that had little or no potential for harm, for example, when a dose of noncritical medication such as docusate was administered several hours late, were not considered potential ADEs, but rather medication errors. An error that had the potential for harm, for example, a dose of critical medication such as an intravenous antibiotic not being administered, was considered both a medication error and a potential ADE. A potential ADE was defined as a medication error with the potential to cause injury but did not actually do so either because of specific circumstances, chance, or because the error was intercepted and corrected, such as a prescription with an overdose of medication being written by the physician but then intercepted by the pharmacist.

Data Classification

The methods of data collection and classification were modified from a previous report.[9] We developed a questionnaire asking patients about their characteristics and any suspicions of AEs or MEs. They also inquired about the details of cardiovascular comorbidities as well as comorbidities listed in the Charlson comorbidity index.[10]

Two independent physician reviewers who were internists without the affiliation with study clinic had enough experience to review AEs and evaluated all incidents and classified them

TABLE 1. Patients' Characteristics

Variables	All (n = 759) n (%)	AEs (n = 124) n (%)	Non-AEs (n = 635) n (%)	*P*-value
Age, mean ± SD, years	65 ± 12	64 ± 13	65 ± 12	0.2
Sex				
Male	423 (56)	70 (56)	353 (56)	0.9
Medical history				
Hypertension	369 (49)	68 (55)	301 (47)	0.1
Myocardial infarction	93 (12)	18 (15)	75 (12)	0.4
Angina	176 (23)	32 (26)	144 (23)	0.5
Congestive heart failure	109 (14)	16 (13)	93 (15)	0.6
Arteriosclerosis	57 (8)	12 (10)	45 (7)	0.3
Cerebral infarction	41 (5)	5 (4)	36 (6)	0.5
Dyslipidemia	157 (21)	36 (29)	121 (19)	0.01
Diabetes	142 (19)	15 (12)	127 (20)	0.04
Osteoporosis	43 (6)	8 (6)	35 (6)	0.7
Lung disease	14 (2)	3 (2)	11 (1)	0.6
Gastric ulcer	82 (11)	19 (15)	63 (10)	0.08
Duodenal ulcer	41 (5)	6 (5)	35 (6)	0.8
Chronic hepatitis	23 (3)	7 (6)	16 (3)	0.06
Malignant tumor	122 (16)	30 (24)	92 (14)	0.01
Others	337 (44)	60 (48)	277 (44)	0.3
Outpatient visits to a doctor				0.5
>2 times/month	86 (11)	17 (14)	69 (11)	
2 times/month	80 (11)	18 (15)	62 (10)	
1 time/month	208 (27)	31 (25)	177 (28)	
1 time/2 months	115 (15)	16 (13)	99 (16)	
1 time/3-6 months	82 (11)	11 (9)	71 (11)	
<1 time/6 months	188 (25)	31 (25)	157 (25)	
Pre hospital admission	665 (88)	116 (94)	549 (86)	0.03
1–3 times	415 (62)	61 (53)	354 (64)	0.07
4–10 times	216 (32)	46 (40)	170 (31)	
≥10 times	8 (1)	3 (3)	5 (1)	
Unknown	26 (4)	6 (5)	20 (4)	

SD, standard deviation

according to whether they were AEs or MEs and judged whether they occurred in the outpatient or hospital setting. They considered the timing of symptoms and whether the patients attributed their symptoms to the medical care they received. The reviewers also classified AEs according to type, severity, and symptoms. Categories of severity were fatal, life threatening, serious, and significant.[9] Briefly, fatal AEs resulted in death; life-threatening AEs required successful cardiopulmonary resuscitation or transfer to intensive care and were anaphylactic shock or critical surgical events such as requiring cardiac reoperation. Serious AEs included gastrointestinal bleeding, altered mental status, excessive sedation, renal dysfunction, a decrease in blood pressure, and peripheral arterial embolism. Significant AEs included, for example, cases with peripheral neuropathy, rash, diarrhea, or nausea. Categories of symptoms were bleeding, central nervous system symptoms,allergic or skin reactions, metabolic or liver disorders, cardiovascular symptoms, gastrointestinal symptoms, kidney injury, respiratory system symptoms, bone marrow depression, and other. When the reviewers disagreed over the classification of an event, consensus was reached through discussion. Inter-rater reliability for reviewer judgments is calculated using percentage of agreement and the kappa statistic.[11] The percentage of agreement is calculated by dividing the number of agreed cases by the total cases. Kappa is calculated from ($Po - Pc$) / ($1 - Pc$), where Po = proportion of observed agreement and Pc = proportion of agreement expected by chance and ranges from −1 (complete disagreement) to +1 (perfect agreement). The significance of kappa are values less than 0 as indicating no agreement and 0 to 0.2 as slight, 0.21–0.4 as fair, 0.41–0.6 as moderate, 0.61–0.8 as substantial, and 0.81-1 as almost perfect agreement.

Statistical Analysis

For AE and ME, crude rates per 100 patients and their 95% confidence intervals (CIs) were calculated. Continuous variables are presented as mean with standard deviation (SD) values or median with interquartile ranges, and categorical variables are shown as numbers and percentages. Relationships between patients' demographics and AEs were assessed using the Student t test or the Wilcoxon rank sum test when the data were continuous or the χ^2 test when the data were categorical. To assess associations between ADEs and severity or durability, and setting and severity for AEs, ADEs, or non-ADEs, we used χ^2 test. We carried out all statistical analysis using JMP version 8 (SAS Institute Inc., Cary, NC). P values of less than 0.05 were considered statistically significant.

RESULTS

Among 1144 eligible patients, 846 (74%) agreed to participate, and valid questionnaire responses were collected from 759 (90%). Among these 759 patients, 423 (56%) were men and the mean age was 65 ± 12 years. Half of the patients had hypertension, and ischemic heart disease and dyslipidemia affected 35% and 21%, respectively. Twenty-seven percent of the patients visited outpatient clinics once a month. Six hundred sixty-five patients (88%) had a history of hospitalization, and 415 patients had been hospitalized less than 4 times (Table 1).

Adverse Events

The patients reported 225 potential incidents in the questionnaires. The kappa score regarding the presence of an AE between reviewers was 0.69. The reviewers identified 144 AEs in 124 patients, and the crude rate per 100 outpatients was 16.3% (95% confidence interval [CI], 13.9%–19.1%). Of the 144 AEs, 99 were solely ADEs, 20 were solely non-ADEs, and the remaining 25 were multiple causes (Table 2). Adverse events by type, including those classified as more than one type, were as follows: 120 ADEs (83%), 22 decision-making AEs (15%), 17 operation-related AEs (12%), 5 procedure-related AEs (3%), and 7 others (5%). Patients experienced 66 AEs (46%) during outpatient visits and 78 AEs (54%) during hospitalization. Among the 66 AEs that occurred during outpatient visits, 60 (91%) were ADEs. Among the 78 AEs that occurred during hospitalization, 60 (78%) were ADEs.

None of the AEs were fatal. Fifteen life-threatening AEs occurred in 13 inpatients and 2 in 1 outpatient (Table 3). There were solely 6 ADEs and solely 8 non-ADEs, and 3 multiple causes. Serious and significant AEs accounted for 41 and 86 AEs, respectively. Among the 41 serious AEs, 35 involved ADEs. Among the 86 significant AEs, 78 involved ADEs. Two life-threatening AEs (3%), 18 serious AEs (27%), and 46 significant AEs (70%) occurred during outpatient visits. Fifteen life-threatening AEs (19%), 23 serious AEs (29%), and 40 significant AEs (51%) occurred during hospitalization (Fig. 1). Non-ADEs were more severe than ADEs and longer failure than ADEs (Table 4). Among 144 AEs, 113 AEs (78%) resulted in transient injury and 31 AEs (22%) resulted in permanent injury or injury that compromised the patient's life.

Allergic or skin reactions were the most frequent symptoms followed by cardiovascular symptoms of all AEs and ADEs. Bleeding was the most frequent symptom followed by allergic

TABLE 2. Causes of AEs

	AEs (n = 144) n (%)	First Cause	Second Cause	Third Cause
Single cause	99 (69)	Drug		
	14 (10)	Operation		
	2 (1)	Procedure		
	4 (3)	Decision-making		
Two causes	1 (1)	Drug	Procedure	
	12 (8)	Drug	Decision making	
	6 (4)	Drug	Other	
	2 (1)	Operation	Decision making	
	2 (1)	Procedure	Decision making	
Three causes	1 (1)	Drug	Operation	Decision making
	1 (1)	Drug	Decision making	Other

TABLE 3. Details of Life-Threatening AEs (n = 17)

	Outpatient		Inpatient	
	Details	**No. of AEs**	**Details**	**No. of AEs**
ADEs	Anaphylactic shock	2	Anaphylactic shock	1
			Steven Johnson syndrome	2
			Loss of consciousness or syncope	2
Non-ADEs	Poor communication about drug with known allergy (multiple causes)	1	Syncope due to delayed diagnosis	1
			Bleeding requiring unexpected transfusion during operation (multiple causes)	6
			Surgical events such as suture failure and infection requiring reoperation	3
			Bleeding postcatheterization requiring operation (multiple causes)	2

or skin reactions and cardiovascular symptoms of non-ADEs (Table 5).

Medical Errors

We identified 30 MEs among 30 patients; the incidence rate was 3.9 (95% CI, 2.8%–5.6%) per 100 patients. Among the 30 MEs, 29 resulted in AEs, meaning that 20% of the 144 AEs were considered preventable. Among the 29 MEs with AEs, 4 MEs (14%) resulted in life-threatening AEs, 12 (41%) in serious AEs, and 13 (45%) in significant AEs. The other ME did not result in AE. This event was a medication error, which had the potential to harm the patient; however, this medication error was intercepted before the drug was administered. Among 30 MEs, 18 MEs (60%) were associated with drugs (Table 6). Fifteen MEs occurred during outpatient visits (50%) and 15 occurred during hospitalization (50%). Among the 15 MEs during outpatient visits, 8 were associated with drugs. Among the 15 MEs during hospitalization, 10 were associated with drugs.

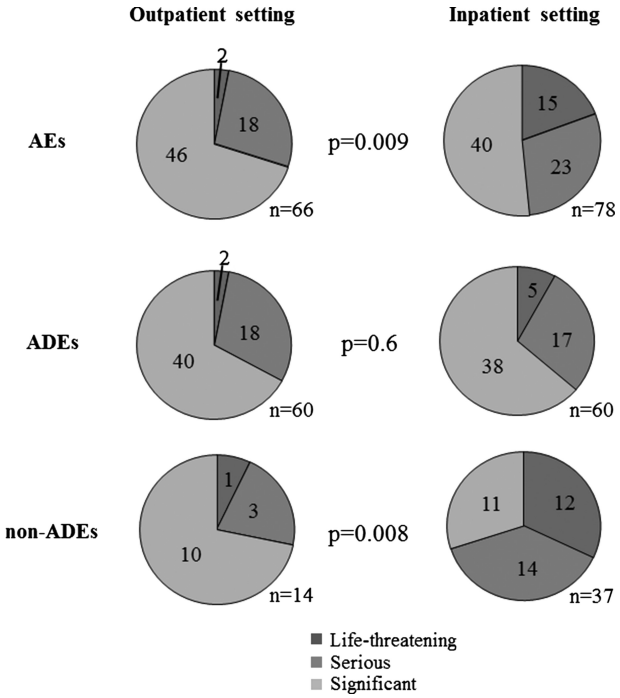

FIGURE 1. Severity of AEs, ADEs, and non-ADEs by setting. Some AEs were attributable to both ADEs and non-ADEs.

DISCUSSION

Studies concerning patient reporting of AEs were limited. Recently, efforts to use patient-reported information would be more important. Yelp[12] jointed with ProPublica are utilized and give consumers satisfaction with medical care. In the United States, a new system for patients to report medical mistakes was constructed. The Obama administration wants consumers to report medical mistakes and unsafe practices by doctors, hospitals, pharmacists, and others who provide treatment.[13] Thus, we considered this survey using the questionnaire for each patient at the outpatient clinic was patient-oriented outcome, and this survey was important.

We assessed the frequency of AEs and MEs in daily practice in Japan and found that they occur often and cause substantial harm. The crude rate of AEs was 16 per 100 outpatients, and 20% of AEs were associated with MEs. Among the 144 AEs, 120 (83%) were ADEs and 51 (35%) were non-ADEs including 17 surgical AEs (12%). Seven ADEs (6%) and 8 surgical AEs (47%) were life-threatening. Adverse drug events were more frequent in outpatients, and surgical AEs were the most dangerous. Although the symptoms among non-ADEs were different, the symptoms among ADEs were similar; allergic or skin reactions were the most frequent symptoms among all ADEs, followed by cardiovascular and gastrointestinal symptoms.

TABLE 4. Relationship Between AEs and Severity or Outcome

	ADEs (%)	**Non-ADEs (%)**	***P***
Severity			
Life threatening	7 (6)	13 (25)	0.0003
Serious	35 (29)	17 (33)	0.6
Significant	78 (65)	21 (41)	0.004
Outcome			
Transient injury	107 (88)	28 (55)	0.6
Permanent injury or injury that compromised the patient's life	13 (11)	23 (45)	0.004

TABLE 5. Symptoms of AEs

Symptoms	AEs (%)	Non-ADEs (%)	ADEs (%)	ADEs in Outpatient (%)	ADEs in Inpatient (%)
Bleeding	12 (8)	13 (25)	4 (3)	3 (5)	1 (2)
Central nervous system	11 (7)	4 (8)	11 (9)	2 (3)	9 (15)
Allergic or skin symptom	45 (31)	9 (18)	43 (36)	21 (35)	22 (36)
Liver disorder or metabolic disorder	10 (7)	2 (4)	9 (7)	2 (3)	7 (11)
Cardiovascular	26 (18)	9 (18)	22 (18)	13 (22)	9 (15)
Gastrointestinal	13 (9)	2 (4)	13 (11)	9 (15)	4 (7)
Kidney injury	1 (1)	0 (0)	1 (1)	1 (2)	0 (0)
Respiratory	5 (3)	0 (0)	5 (4)	4 (7)	1 (2)
Bone marrow depression	3 (2)	1 (2)	3 (2)	0 (0)	3 (5)
Others	18 (12)	11 (22)	9 (7)	5 (8)	4 (7)

Regarding the occurrence of AEs, a systematic review on hospitalized patients found a median rate of 9.2% for AEs and 43.5% for preventable AEs.[14] The occurrence of AEs approximately 20 years ago was fewer than it is now. The Harvard Medical Practice Study I showed 3.7% had AEs.[15] A 1992 study surveying 15,000 patients in Colorado and Utah reported that 3% of patients had AEs.[16] Updated estimate showed 13.5% of hospitalized patients had at least one AE. Overall, at least 44% of these events were judged as being preventable and 51% unpreventable.[17] Landrigan et al[18] reported that among 2341 admissions, internal reviewers identified 588 harms (25.1 harms per 100 admissions) and harms remain common. Merino et al[19] reported that 29% of hospitalized patients had AEs, with 62% not causing any harm. Among the no-harm events, 90% were classified as preventable AEs.

Although methodological differences between these studies and the current study made comparisons difficult, we believe the AE rate in the current study was generally similar to these other reports; however, our ME rate was lower. Because the first step of our methodology was a patient questionnaire, underestimating the incidence of MEs was inevitable. If patients were not aware of MEs that were intercepted or did not cause harm or symptoms, they could not report these in the questionnaire. Another reason why our rate of MEs was lower than that of other recent studies could be due to the increase in awareness of AEs among health care providers. Merino et al reported that the overall rate of AEs was 98% and although surgery-related incidents were few (3%), they were considered to be severe. Our results were consistent with those of Merino et al. Recently, several studies assessing strategies to avoid surgery-related AEs have been performed in the surgical setting and have reported that following interventions are effective in reducing surgical AEs.[20–24] Howell et al[25] reviewed interventions to reduce AEs such as increasing nursing staff, subspecialized services, checklists, team training, safety devices, and care pathways; our finding showing the common epidemiological characteristics of AEs may suggest that such interventions to reduce surgical AEs could be effective.

We showed the occurrence of AEs in the outpatient and hospital settings. The most frequent type of AEs was ADEs in both settings. The incidence of ADEs was the same in both settings, but life-threatening ADEs occurred more frequently in hospitals (8%) than in outpatient settings (3%). The Centers for Medicare and Medicaid services, Partnership for Patients program found that ADEs as the most common AE accounted for 43.8%.[26] The most frequent type of incident in the intensive care unit was also ADEs.[14] A systematic review of the incidence and nature of AEs in hospitalized patients reported that approximately 50% of AEs were surgery-related AEs (39.6%) or ADEs (15.1%).[14]

A systematic review studying ADEs in ambulatory care reported a prevalence of 12.8 per 100 outpatients.[27] Gandhi et al[14] reported that the incidence of ADEs was 27 per 100 outpatients. Cardiovascular agents such as beta-blockers, ACE inhibitors, and calcium-channel blockers were most frequently implicated in these ADEs. Studies from a U.S. ambulatory department reported that cardiovascular medications were the most commonly implicated ADEs.[28] Our results showed that the incidence of cardiovascular symptoms in the outpatient setting was higher than that in the hospital setting, and those cardiovascular symptoms were the second most frequent symptoms of ADEs. Elsewhere, Gandhi et al[29] reported that the most frequent symptoms of ADEs were gastrointestinal followed by sleep disturbances, fatigue, and mood change. Weingart et al[30] reported that the most frequent symptoms of ADEs were gastrointestinal followed by fatigue, dizziness, and rash or itching. We found that the most frequent symptoms of ADE were allergic or skin reactions followed by cardiovascular symptoms including dizziness, and gastrointestinal symptoms. If the patients were prescribed new antihypertensive agents and the physician detected hypotension or the patients recovered after self-cessation of them, we diagnosed the conditions of dizziness or fatigue as hypotension due to antihypertensive agents. Although our results were consistent with past reports, these symptoms were peculiar to cardiovascular outpatients.

Our study had several limitations. First, because the potential incidents were obtained from patient questionnaires and then verified by physicians, our results may not reflect incidents that occurred of which patients were unaware. In addition, we could

TABLE 6. Details of MEs

Causes	Type of Error	Medical Errors (n = 30) n (%)
Drug	Wrong action against the symptoms	11 (37)
	Different drug	2 (7)
	Ignoring interaction	1 (3)
	Wrong dose	1 (3)
	Omission	2 (7)
	Wrong route	1 (3)
	Drug with known allergy	1 (3)
Operation	Inappropriate operation	3 (10)
Procedure	Inappropriate procedure	5 (17)
Decision making	Misdiagnosis	4 (13)

not obtain potential incidents associated with fatalities; thus, we might have missed critical and severe AEs and MEs. Indeed, there were no fatal AEs in our study. Second, the patients were from a single cardiovascular clinic of a teaching hospital. Although the sample was sufficiently large to allow reasonably accurate estimates of AE and ME incidence, the results might not be generalizable to other settings. However, our results may be applicable to Japanese outpatients.

CONCLUSION

We showed that AEs were common among cardiology patients. Adverse drug events were the most frequent AEs, and non-ADEs were more critical than ADEs. Adverse events and non-ADEs were more severe in hospitalized patients than in outpatients. The proportion of MEs was significant, and most were related to medication use. Such data should be recognized among practicing physicians to improve the patients' outcomes.

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