Department of Pharmacy[1], Teikyo University School of Medicine University Hospital; Laboratory of Basic Chemistry & Molecular Structure[2], Faculty of Pharma Sciences; Department of Lifelong Education for Pharmacists[3], Faculty of Pharma Sciences; Laboratory of Hospital Pharmacy[4], Faculty of Pharma Sciences, Teikyo University, Tokyo, Japan

Adverse drug event profile associated with anti-dementia drugs: analysis of a spontaneous reporting database

E. Kose[1,*], T. Yamamoto[1], N. Tate[2], A. Ando[3], H. Enomoto[3], N. Yasuno[1,3,4]

Received December 12, 2022, accepted January 28, 2023

**Corresponding author: Eiji Kose, Department of Pharmacy, Juntendo University Hospital, Tokyo 113-8431, Japan e.kose.ny@juntendo.ac.jp*

Pharmazie 78: 42-46 (2023) *doi: 10.1691/ph.2023.2584*

Adverse drug events (ADEs) rates associated with anti-dementia acetylcholinesterase inhibitors are estimated to be 5%–20% and show a wide range of symptoms. No report has examined whether there is a difference in the anti-dementia drugs' ADEs profile. This study aimed to establish whether anti-dementia drugs' ADEs profile differed. Data was based on the Japanese Adverse Drug Event Report (JADER) database. The reporting odds ratios (RORs) was used to analyze data for ADEs from April 2004–October 2021. The target drugs were donepezil, rivastigmine, galantamine, and memantine. The top ten most frequently occurring adverse events were selected. The association between the RORs and antidementia drug ADEs was evaluated, and compared the distribution rate of expression age related to ADEs and each ADEs' timing of onset due to anti-dementia drugs. The primary outcome was RORs. Secondary outcome were expression age and time-to-onset of ADE associated with anti-dementia drugs. A total of 705,294 reports were analyzed. The adverse events incidence differed. Bradycardia, loss of consciousness, falls, and syncope incidence were significantly diverse. The Kaplan–Meier curve results for the cumulative ADEs incidence showed that donepezil had the slowest onset, while galantamine, rivastigmine, and memantine had approximately the same timing of onset.

1. Introduction

Donepezil, rivastigmine, and galantamine are acetylcholinesterase (AChE) inhibitors approved by the Food and Drug Administration (FDA) for Alzheimer's dementia, memantine is FDA approved for the treatment of moderate-to-severe Alzheimer's dementia (Atri. 2019). Adverse drug events (ADEs) associated with AChE inhibitors are reported in 5–20% of patients and are usually mild and transient. ADEs' risk and severity are usually associated with a high starting dose and/or rapid dose escalation. Gastrointestinal events related to peripheral cholinomimetic effects are the most common ADEs. Specific ADEs include nausea, vomiting, anorexia, flatulence, loose stools, diarrhea, salivation, and abdominal cramping. Other ADEs include vivid dreams or mild insomnia, skin irritation with transdermal patch administration, reduced heart rate syncope (especially with sick sinus syndrome or atrioventricular block). On the other hand, cholinesterase inhibitors may be associated with increased risk of syncope, but no other fall-related ADEs in older adults with cognitive impairment (Kim et al. 2011). Dizziness, somnolence, headache, and constipation have been reported as relatively frequent adverse memantine effects, an N-methyl-D-aspartic acid receptor antagonist. However, a meta-analysis found no significant difference between memantine and placebo (Matsunaga et al. 2015).

Assessment of ADEs occurrence is important while taking dementia medications. To recognize an adverse event, it is necessary to understand the symptom's mode of appearance that should prompt suspicion of an adverse event. However, as indicated above, there is a wide variety of ADEs associated with dementia drugs. Although not frequent in occurrence, symptoms such as extrapyramidal signs, agitation, and restlessness are difficult to notice unless they are identified as ADEs. If the prescribing physician is not aware, drug dosage could easily be increased or use of other drugs in combination, leading to further deterioration. Therefore, it is extremely important to have a systematic understanding of the ADEs of dementia medications.

Drug use in clinical practice is very complex and differs from well-designed clinical trials and epidemiologic studies. ADEs assessment is challenging when it is infrequent or occurs after a long period of time in pre-approval clinical drug trials. In recent years, unknown ADEs detection and safety assessment in clinical practice have been performed using large spontaneous reporting system (SRS) database (Ohta 2021; Kato et al. 2015; Kose et al. 2015; Kose 2018; Noda et al. 2020; Tsuchiya et al. 2020) The Pharmaceuticals and Medical Devices Agency's (PMDA) Japanese Adverse Drug Event Report (JADER) database is the largest and best-known published database that reflects the realities of clinical practice in Japan. Approximately 700,000 adverse event reports have been registered with JADER from April 2004–October 2021. Therefore, this database is often used for pharmacovigilance assessments. Large-scale adverse event spontaneous reporting databases play a major role in epidemiological research, in which ADEs in clinical practice are collected over a long period of time, particularly in drug safety assessment. Time-to-onset data analysis has been proposed as a method to detect ADEs signals in SRS. The time-to-onset analyses for ADEs due to anti-dementia drugs using the JADER database are rare.

Therefore, this study aimed to investigate the association between anti-dementia drugs and ADEs using JADER, as well as the adverse event–time-to-onset analysis to investigate the adverse effect profile of each drug.

2. Investigations and results

2.1. Number of reports during follow-up

The JADER database contains 705,294 reports from April 2004–October 2021. The number of duplicate data was 8056 reports.

Table 1: Number of reports and ROR of adverse drug events associated with anti-dementia drugs

Galantamine

Adverse drug events	a	b	c	d	Reporting Fraction (%)	ROR	95%Cl
Bradycardia	84	1834	235	7718	4.38	1.50	1.321 – 1.713
Loss of appetite	37	1881	220	7733	1.93	0.69	0.578 – 0.827
Loss of consciousnes	74	1844	165	7788	3.86	1.89	1.643 – 2.183
Seizures	20	1898	208	7745	1.04	0.39	0.310 – 0.500
Altered state of consciousness	38	1880	183	7770	1.98	0.86	0.717 – 1.028
Falls	31	1887	176	7777	1.62	0.73	0.600 – 0.884
Delirium	34	1884	172	7781	1.77	0.82	0.688 – 0.987
Vomiting	44	1874	155	7798	2.29	1.18	0.994 – 1.404
Syncope	33	1885	129	7824	1.72	1.06	0.872 – 1.293
Rhabdomyolysis	20	1898	137	7816	1.04	0.60	0.473 – 0.765

Donepezil

Adverse drug events	a	b	c	d	Reporting Fraction (%)	ROR	95%Cl
Bradycardia	160	3787	159	5765	4.05	1.53	1.367 – 1.716
Loss of appetite	146	3801	111	5813	3.70	2.01	1.770 – 2.285
Loss of consciousness	40	3907	199	5725	1.01	0.29	0.247 – 0.351
Seizures	115	3832	113	5811	2.91	1.54	1.345 – 1.765
Altered state of consciousness	88	3859	133	5791	2.23	0.99	0.864 – 1.114
Falls	38	3909	169	5755	0.96	0.33	0.276 – 0.397
Delirium	70	3877	136	5788	1.77	0.77	0.662 – 0.891
Vomiting	68	3879	131	5793	1.72	0.78	0.667 – 0.901
Syncope	76	3871	86	5838	1.93	1.33	1.137 – 1.562
Rhabdomyolysis	96	3851	61	5863	2.43	2.40	2.031 – 2.825

Rivastigmine

Adverse drug events	a	b	c	d	Reporting Fraction (%)	ROR	95%Cl
Bradycardia	61	2446	258	7106	2.43	0.69	0.594 – 0.793
Loss of appetite	49	2458	208	7156	1.95	0.69	0.584 – 0.805
Loss of consciousness	43	2464	196	7168	1.72	0.64	0.538 – 0.756
Seizures	38	2469	190	7174	1.52	0.58	0.485 – 0.695
Altered state of consciousness	35	2472	186	7178	1.40	0.55	0.454 – 0.658
Falls	67	2440	140	7224	2.67	1.42	1.219 – 1.647
Delirium	73	2434	133	7231	2.91	1.63	1.407 – 1.900
Vomiting	80	2427	119	7245	3.19	2.01	1.733 – 2.323
Xyncope	10	2497	152	7212	0.40	0.19	0.137 – 0.264
Rhabdomyolysis	5	2502	152	7212	0.20	0.09	0.006 – 0.145

Memantine

Adverse drug events	a	b	c	d	Reporting Fraction (%)	ROR	95%Cl
Bradycardia	14	1485	305	8067	0.93	0.25	0.189 – 0.328
Loss of appetite	25	1474	232	8140	1.67	0.60	0.481 – 0.736
Loss of consciousness	82	1417	157	8215	5.47	3.03	2.634 – 3.480
Seizures	55	1444	173	8199	3.67	1.81	1.542 – 2.113
Altered state of consciousness	60	1439	161	8211	4.00	2.13	1.823 – 2.480
Falls	71	1428	136	8236	4.74	3.01	2.593 – 3.495
Delirium	29	1470	177	8195	1.93	0.91	0.746 – 1.118
Vomiting	7	1492	192	8180	0.47	0.20	0.136 – 0.294
Syncope	43	1456	119	8253	2.87	2.05	1.710 – 2.452
Rhabdomyolysis	36	1463	121	8251	2.40	1.68	1.385 – 2.033

Abbreviations: ROR, Reporting Odds Ratios; 95% CI, 95% Confidence Interval

In this study, 9454 reports in which "donepezil," "galantamine," "rivastigmine," and "memantine" were registered as "suspect drugs" and missing data were excluded in the final data for analysis.

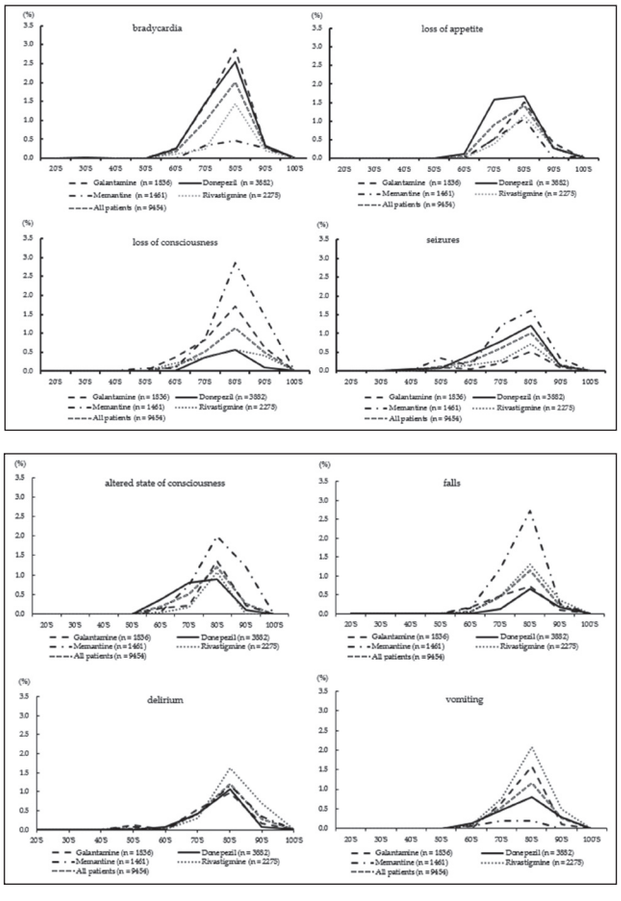
2.2. Comparison of the ROR of Adverse Drug Events with Each Anti-dementia Drugs

Table 1 shows the ROR comparison related to ADEs with anti-dementia drugs. Safety signals for galantamine were detected in bradycardia and loss of consciousness. The RORs for bradycardia and loss of consciousness were nearly equivalent at 1.50 and 1.89, respectively. Safety signals were detected for donepezil for bradycardia, decreased appetite, seizures, syncope, and rhabdomyolysis. The RORs for bradycardia, seizures, and syncope were similar. The RORs for decreased appetite and rhabdomyolysis were slightly higher at 2.01 and 2.40, respectively.

Safety signals for rivastigmine were detected for falls, delirium, and vomiting. The RORs for falls and delirium were nearly equivalent at 1.42 and 1.63, respectively. The 2.01 ROR for vomiting was higher than the RORs for falls and delirium. Safety signals for memantine were detected for loss of consciousness, seizures, altered states of consciousness, falls, syncope, and rhabdomyolysis. The RORs for seizures, altered states of consciousness, syncope, and rhabdomyolysis were similar. The RORs for loss of consciousness and falls were higher at 3.03 and 3.01, respectively.

2.3. Distribution rate of expression age related to adverse drug events with anti-dementia drugs

The rate of age at onset of each adverse event caused by galantamine, donepezil, rivastigmine, and memantine is shown in Fig. 1. The age at onset of bradycardia was high in the 80s and was common for each anti-dementia drug. However, the bradycardia incidence with memantine was remarkably lower than that of the other anti-dementia drugs. On the other hand, galantamine and donepezil showed a higher incidence than the other anti-dementia drugs. The age of onset of appetite loss was higher in patients in their 80s, which was common for all anti-dementia drugs. However, only donepezil showed elevated levels in patients in their 70s. The age at onset of loss of consciousness was higher in patients in their 80s, a finding common to all anti-dementia drugs. However, the rate of occurrence with memantine was remarkably higher than that with the other anti-dementia drugs. The age at onset of seizures was higher in patients in their 80s, which was common for all anti-dementia drugs. The age of onset of altered consciousness was higher in patients in their 80s, a finding common to all antidementia drugs. However, memantine was the only anti-dementia drug that also showed a high incidence of seizures in their 70s–90s. The age of onset of falls was high in the 80s, which was common for each anti-dementia drug. However, the age at onset of memantine was remarkably higher than that of the other anti-dementia drugs. The age of onset of delirium was high among patients in their 80s, which was common among all anti-dementia drugs. There was little difference in age of onset by age group among the four anti-dementia drugs. The age of onset of emesis was high in the 80s and was common for each anti-dementia drug. However, the incidence of emesis was remarkably lower with memantine than with the other anti-dementia drugs. The age at onset of syncope was higher in patients in their 80s, which was common among the anti-dementia drugs. However, age at onset of syncope was remarkably higher for memantine than for the other anti-dementia drugs. Age of onset of rhabdomyolysis was seen in the 70s and 80s, but the overall incidence rate was low, with only age of onset with rivastigmine having a remarkably lower incidence rate compared with the other anti-dementia drugs.



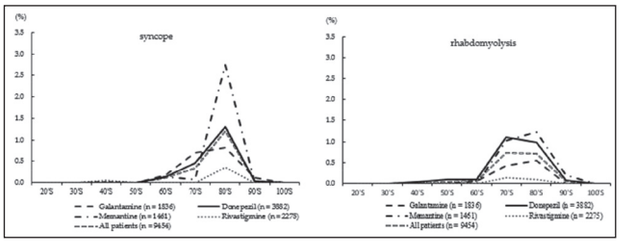


Fig. 1: Distribution rate of expression age related to adverse drug events with anti-dementia drugs.

2.4. Comparison of the timing of onset of each adverse drug events

In the cumulative ADEs incidence rate in each drug using the Kaplan–Meier method, donepezil was the slowest to develop, whereas galantamine, rivastigmine, and memantine each developed at approximately the same time (Fig. 2). The Weibull distribution parameters for each anti-dementia drugs are summarized in Table 2. The lower 95% CI of β for all anti-dementia drugs were <1 (Table 2). Therefore, all anti-dementia drugs were rated as early failure type.

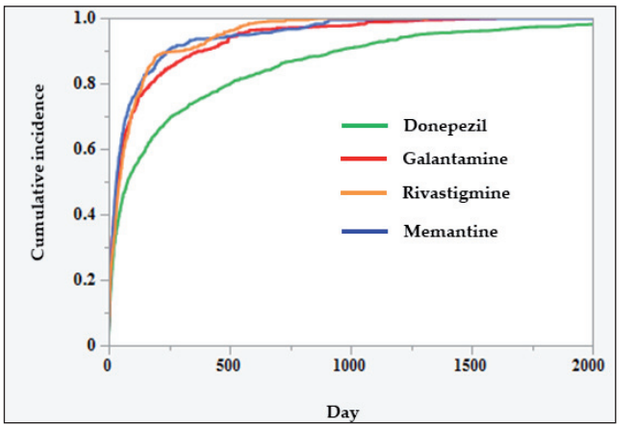


Fig. 2: Comparison of the cumulative incidence of adverse events.

Table 2: Time–to–onset analysis of anti-dementia drugs using Weibull distributions

Drug	α	95% CI	β	95% CI	Pattern
Total of antidementia drugs	114.05	(95.13–136.35)	0.57	(0.53–0.62)	Early failure
Galantamine	93.06	(83.21–103.96)	0.64	(0.61–0.68)	Early failure
Donepezil	203.57	(188.57–219.64)	0.59	(0.57–0.61)	Early failure
Rivastigmine	86.28	(79.05–94.08)	0.74	(0.71–0.78)	Early failure
Memantine	78.11	(70.42–86.55)	0.66	(0.63–0.70)	Early failure

$0 < \beta < 1$, early failure; $\beta = 1$, random failure; $\beta > 1$, wear out failure
Abbreviations: 95% CI, 95% Confidence Interval

3. Discussion

The most important clinical findings of this study is that it suggests that the age of onset or timing of ADEs due to anti-dementia drugs differs among drugs. This study's findings are completely new as there have been no previous comprehensive analysis reports of the incidence profile of anti-dementia drugs adverse events using SRS. The age of onset or rate of each ADEs caused by anti-dementia drugs differed among the four drugs. The adverse events' age of onset peaked in the 80s for bradycardia, loss of consciousness, seizures, altered consciousness, falls, delirium, vomiting, and syncope. This did not differ among the anti-dementia drugs galantamine, donepezil, rivastigmine, and memantine. However, loss of appetite and rhabdomyolysis occurred more frequently in patients in their 70s and 80s (Kröger et al. 2015). Therefore, it was considered necessary to pay attention to the occurrence of adverse events when administering anti-dementia drugs, especially to elderly patients in their 80s. On the other hand, the incidence of adverse events differed among the drugs. The incidence of bradycardia, loss of consciousness, falls, and syncope varied significantly. Bradycardia was significantly less common with memantine, while loss of consciousness, falls, and syncope were most common with memantine. The drug's package insert often states that the frequency is unknown although they list the incidence of adverse events. In fact, the package insert for memantine states that the loss of consciousness and syncope frequency is unknown. However, caution should be exercised when administering the drugs since the ROR of SRS shows safety signals for loss of consciousness and syncope, which are higher than the safety signals for other ADEs. The frequency of bradycardia is not specified in the package insert for donepezil. However, it is suggested that the frequency of occurrence is comparable and caution should be exercised when administering this drug.

The adverse event–time analysis using the Weibull distribution in this study was also performed since the Weibull distribution has recently been reported to be useful in examining the adverse event timing profile of drugs (Yamada et al. 2014; Matsui et al. 2015). The results showed that the shape parameter β of all anti-dementia drugs was <1, suggesting that they were early failure type drugs. Therefore, these drugs may develop adverse events relatively early and early adverse event monitoring in clinical practice was considered important.

The Kaplan–Meier curve results for the cumulative ADEs incidence showed that the timing of adverse event onset differed among the anti-dementia drugs with donepezil having the slowest onset. On the other hand, galantamine, rivastigmine, and memantine each had approximately the same timing of onset. Differences in pharmacological mechanisms and pharmacokinetic parameters of the drugs may be related to the different timing of ADEs among the anti-dementia drugs. Donepezil is highly selective for central acetylcholinesterase, but has fewer side effects due to its low cholinesterase inhibitory activity in peripheral tissues. It is also characterized by a long blood half-life of approximately 70–80 h and a slow rise in blood levels. In contrast, the blood half-life of rivastigmine and galantamine are 3.3 h and 5–7 h, respectively. Thus, their blood levels rise more rapidly than donepezil. In addition, rivastigmine decreases cholinesterase in the blood in a dose-dependent manner, with an approximately 40% decrease at 18 mg, as stated in the review report pertaining to drug approval. Additionally, rivastigmine also inhibits butyrylcholinesterase in the blood, which may increase the risk of developing acetylcholine excess symptoms. Furthermore, rivastigmine and memantine are drugs excreted renally, while donepezil is a hepatic metabolite. Anti-dementia drugs are mostly used in older people. Renal function is impaired in older people leading to increased blood concentrations that are more likely to result in the development of ADEs. Therefore, it is possible that differences in each anti-dementia drug's pharmacological characteristics and pharmacokinetics affect the cumulative incidence of ADEs.

It is necessary to carefully understand the limitations of data in order to interpret the results obtained from the SRS. SRS is not recommended to calculate true risk because it lacks direct information (i.e., the number of people using drugs) to be the denominator. Furthermore, reporting bias (i.e., underreport, safety information, and market trends), incorrect drug name or adverse events coding, and lack of basic information (i.e., age or sex) are known to occur in SRS (Ohta 2021). However, it has been known that some adverse events cannot be found in a clinical trial (Werner et al. 2014). Prospective observational studies are required in order to verify the hypothesis that there is an association between drugs and adverse events if the ROR signal suggesting the potential for adverse event is detected from the JADER database. Therefore, SRS was suggested to be an informational source for post-marketing surveillance.

In conclusion, the current study revealed that the age of onset or timing of ADEs associated with anti-dementia drugs differs among drugs. This finding could be invaluable to the management of dementia in these patients. However, further studies are required to ascertain whether our findings can be applied to early detection and response efforts in clinical settings.

4. Experimental

4.1. Design and data source

We used PMDA's JADER database as a large SRS database (Ohta 2021; Kato et al. 2015; Kose et al. 2015; Kose 2018, Noda et al. 2020; Tsuchiya et al. 2020) to establish the ADEs profile of anti-dementia drugs. The JADER database is freely obtainable from the PMDA website, and was accessed from April 2004–October 2021. The database consists of four data tables: patient demographic information ("Demo"), drug information ("Drug"), ADEs ("Reac"), and primary disease ("Hist"). The Demo file included demographic information stored in 10-year age intervals (e.g., 60–69 years). The data from other age classification codes were excluded because the actual ages were unclear, such as first trimester, second trimester, third trimester, newborn, infant, pediatric, youth, adult, elderly, and unknown. Duplicate reports were also excluded, and only the latest list of ADE reports were extracted. ADEs in the Reac file were coded according to the medical dictionary terminology for regulatory activities (Szarfman et al. 2002). A drug information table was created in the Drug file with the following codes: suspected (higiyaku, in Japanese), interacting (sougosayou), and concomitant (heiyouyaku). However, "concomitant" referred to an unknown specific ADEs causal relationship, and was considered unlikely that "interacting" was only reported for anti-dementia drugs. Therefore, these categories were excluded and only "suspected" data were analyzed.

4.2. Target drugs and adverse events

The target drugs were donepezil, rivastigmine, galantamine, and memantine. The top ten most frequently occurring adverse events were selected for these four drugs, which were bradycardia, loss of appetite, loss of consciousness, seizures, altered state of consciousness, falls, delirium, vomiting, syncope, and rhabdomyolysis.

4.3. Outcomes and analysis

In Japan, the reporting odds ratio (ROR) is an index used to assess the risk of ADEs in pharmacovigilance analyses, especially by the PMDA. The empirical Bayes geometric mean (Evans et al. 2001) is a similar index, which is often used by the FDA and the proportional reporting ratio (Nomura et al. 2015), which is often used by the Medicines and Healthcare Products Regulatory Agency. Previous studies have reported the RORs for some drugs and ADEs based on information from the JADER (Ohta 2021; Kato et al. 2015; Kose et al. 2015; Kos. 2018, Noda et al. 2020; Tsuchiya et al. 2020). RORs with 95% confidence intervals (CI) were therefore calculated, as indicated in Table 3, in a 2 × 2 table, as follows: a) number of cases that occurred interested ADEs after using anti-dementia drugs, b) number of cases that occurred all other ADEs after using anti-dementia drugs, c) number of cases that occurred interested ADEs after using all other drugs, and d) number of cases that occurred all other ADEs after using all other drugs.

Table 3: Two-by-two table used for the calculation of reporting odds ratios

	Adverse event of interest	Other adverse event of interest	Total
Drug of interest	a	b	a + b
Other drugs of interest	c	d	c + d
Total	a + c	b + d	a + b + c + d

$$ROR = \frac{a/c}{b/d} = \frac{ad}{bc} \qquad 95\%CI = \exp\left[\ln(ROR) \pm 1.96 \times \sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}\right]$$

Abbreviations: ROR, Reporting Odds Ratios; 95% CI, 95% Confidence Interval

Qualitative judgments were used for signal detection, which was dependent on signal indices exceeding the predefined thresholds. ROR values <1 indicated no association between exposure and event, whereas estimates >1 indicated potentially relevant ADE safety signals for the exposure. Safety signals were considered significant when the ROR estimates and the lower limits of the corresponding 95% CI were >1 (Rothman et al. 2004; van Puijenbroeks et al. 2002). The age at which ADEs occurred was also extracted based on the information in the Demo file. The distribution ratios of the number of reports in each age divided from 10's–100's were calculated. JADER has the drug administration start date data and the date of ADEs occurrence. The period from the beginning of the time of a subject's first prescription to the occurrence of the ADEs was calculated for each drug. Moreover, the time-to-onset analysis was performed using the Weibull distribution and the ADEs expression profile was examined for each drug (Sauzet et al. 2013). The data with the oldest start date was used as the administration start date if there was more than one start date of administration data for a patient. In addition, data lacking either year, month, or day were excluded. The Weibull shape parameter test is used for statistical time-to-onset data analysis and can describe the non-constant ADEs incidence rate (i.e., the increase or decrease risk over time). The shape parameter β of the Weibull distribution indicated that the hazard was without a reference population; whenβ is equal to 1 (random failure), the hazard is estimated to be constant over time. If β was >1 (wear out failure) and the 95% CI of β excluded the value 1, the hazard was considered to increase over time. If β was <1 (early failure), the hazard was considered to increase at an early stage, but then decreases (Yamada et al. 2014). Plots of the ADEs' cumulative incidence in each drug were constructed by the Kaplan–Meier method and were compared.

4.3. Statistical analysis

All data analyses were performed by JMP Pro® 16.0 (SAS Institute Inc., Cary, NC, USA).

4.4. Ethics

The Japanese Adverse Drug Event Report database used in this study is a public database published by the Japanese Ministry of Health, Labour and Welfare and can be downloaded free of charge from the Internet. Therefore, the Ethics Committee of our hospital decided that approval was not required.

Acknowledgement: We would like to acknowledge and thank the PMDA for granting permission to use data provided in this study.

Funding: None.

Conflicting of interests: No conflicts of interests to declare.

References

Atri A. (2019) The Alzheimer's disease clinical spectrum: diagnosis and management. Med Clin North Am 103: 263–293.

Evans SJ, Waller PC, Davis S (2001) Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 10: 483–486.

Kato Y, Umetsu R, Abe J, Ueda N, Nakayama Y, Kinosada Y, Nakamura M. (2015) Hyperglycemic adverse events following antipsychotic drug administration in spontaneous adverse event reports, J Pharm Health Care Sci 1: 15.

Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD (2011) Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. J Am Geriatr Soc 59: 1019–1031.

Kose E (2018) Adverse drug event profile associated with pregabalin among patients with and without cancer: analysis of a spontaneous reporting database. J Clin Pharm Ther 43: 543–549.

Kose E, Uno K, Hayashi H. (2017) Evaluation of the expression profile of extrapyramidal symptoms due to antipsychotics by data mining of Japanese Adverse Drug Event Report (JADER) Database. Yakugaku Zasshi 137: 111–120.

Kröger E, Mouls M, Wilchesky M, Berkers M, Carmichael PH, v. Marum R, Souverein P, Egberts T, Laroche ML (2015). Adverse drug reactions reported with cholinesterase inhibitors: an analysis of 16 years of individual case safety reports from VigiBase. Ann Pharmacother 49: 1197–1206.

Matsui T, Umetsu R, Kato Y, Ueda N, Abe J, Nakayama Y, Hane Y, Kinosada Y, Nakamura M (2015) Adverse event signals of interstitial lung disease in the FDA adverse event reporting system (FAERS) database and the Japanese Adverse Drug Event Report (JADER) Database. Jpn. J. Drug Inform 17: 145–154.

Matsunaga S, Kishi T, Iwata N (2015) Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis. PLoS One 10: e0123289.

Noda A, Sakai T, Obara T, Miyazaki M, Tsuchiya M, Oyanagi G, Murai Y, Mano N (2020) Characteristics of pediatric adverse drug reaction reports in the Japanese Adverse Drug Event Report Database. BMC Pharmacol Toxicol 21: 36.

Nomura K, Takahashi K, Hinomura Y, Kawaguchi G, Matsushita Y, Marui H, Anzai T, Hashiguchi M, Mochizuki M (2015) Effect of database profile variation on drug safety assessment: an analysis of spontaneous adverse event reports of Japanese cases. Drug Des Devel Ther 9: 3031–3041.

Ohta M (2021) Causality assessment between reported fatal cerebral haemorrhage and suspected drugs: developing a new algorithm based on the analysis of the Japanese Adverse Event Report (JADER) database and literature review. Eur J Clin Pharmacol 77: 1443–1452.

Rothman KJ, Lanes S, Sacks ST (2004) The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf 13: 519–523.

Sauzet O, Carvajal A, Escudero A, Molokhia M, Cornelius VR (2013) Illustration of the weibull shape parameter signal detection tool using electronic healthcare record data. Drug Saf 36: 995–1006.

Szarfman A, Machado SG, O'Neill RT (2002) Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf 25: 381–392.

Tsuchiya M, Obara T, Sakai T, Nomura K, Takamura C, Mano N (2020) Quality evaluation of the Japanese Adverse Drug Event Report database (JADER). Pharmacoepidemiol Drug Saf 29: 173–181.

van Puijenbroek EP, Bate A, Leufkens HG, Orre R, Egberts ACG (2002) A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf 11: 3–10.

Werner FM, Coveñas R. (2014) Safety of antipsychotic drugs: focus on therapeutic and adverse effects. Expert Opin Drug Saf 3: 1031–1042.

Yamada M, Handa J (2014) Comparison of the onset time profile among the interferon formulations in adverse drug reaction of suicide-or diabetes-related. Jpn J Pharmacoepidemiol 19: 23–30.