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Adverse Drug Reactions Reported With Cholinesterase Inhibitors: An Analysis of 16 Years of Individual Case Safety Reports From VigiBase

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Abstract

Background: No worldwide pharmacovigilance study evaluating the spectrum of adverse drug reactions (ADRs) induced by cholinesterase inhibitors (ChEI) in Alzheimer's disease has been conducted since their emergence on the market. **Objective:** To describe ChEI related ADRs in Alzheimer's disease (donepezil, rivastigmine, and galantamine) and characterize their seriousness as reported by national pharmacovigilance systems to VigiBase, a World Health Organization International Drug Monitoring Program database, between 1998 and 2013. **Methods:** All ChEI **related reports**, submitted to VigiBase between 1998 and 2013 from **the five continents** were extracted. Analyses were carried out for general, serious, and nonserious ADRs. **Results:** A total of 18 955 reports (43 753 ADRs) **from 58 countries** were reported: 60.1% in women; mean age 77.4 ± 9.1 years. Most reports originated from Europe (47.6%) and North America (40.4%). Rivastigmine and donepezil were involved in **most** reports (41.4% each). The most frequently reported ADRs were neuropsychiatric (31.4%), gastrointestinal (15.9%), general (11.9%), and cardiovascular (11.7%) disorders. During the 2006-2013 period, serious ADRs remained more often reported than nonserious ones; the most serious were neuropsychiatric (34.0%), general (14.0%), cardiovascular (12.1%), and gastrointestinal (11.6%) disorders. Medication errors were reported in 2.0% of serious cases. Death occurred in 2.3% of the reports. **Conclusions:** This international pharmacovigilance study highlights the ADR pattern induced by ChEIs. Neuropsychiatric events were the most frequently reported ADRs. Serious cardiovascular events were frequently reported, suggesting that their significance has probably been previously underestimated. Given the frailty of the patients and the frequent comedications, caution is advised before introducing a ChEI.

Keywords

adverse drug reactions, cholinesterase inhibitors, pharmacovigilance, VigiBase, Alzheimer's disease

Background

Globally, 35.6 million people were estimated to live with dementia in 2010.[1] A large majority of these patients were 65 years or older, and two-thirds suffered from Alzheimer's disease (AD).[2] Although AD is a cause of great concern in developed countries, two-thirds of AD patients live in low- or middle-income countries.

According to randomized controlled trials, cholinesterase inhibitors (ChEIs) are more effective than placebo for slowing cognitive impairment and deterioration of behavior, thus improving activities of daily living related to AD.[3] Their effectiveness is nevertheless modest in most patients.[4] Three ChEIs have been approved worldwide for the treatment of AD: donepezil (available since 1996), rivastigmine (since 1997), and galantamine (since 2000). All 3 drugs are taken orally, except for rivastigmine, which has been available as a transdermal application since 2007.

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Given the continuous increase in the number of patients with AD worldwide and the emergence of less-costly generic ChEI products, their use will continue to be widespread until disease-modifying therapies become available. These factors make the adverse drug reaction (ADR) profile of ChEIs relevant for clinical and public health considerations. Some reviews on ChEI-induced ADRs have been published on the basis of information found in randomized clinical trials or in observational studies.[3,5-8] The most frequently reported ADR was gastrointestinal (eg, nausea, vomiting, diarrhea), which usually occurs following treatment initiation or during a dose escalation period, in about 10% of patients.[6-8] Because of their mechanism of action, involving an increased amount of acetylcholine available for neuronal and neuromuscular transmission, which in turn may induce overstimulation of muscarinic and nicotinic receptors, ChEIs may increase gastric acid secretion; induce urinary incontinence, tremors, or seizures; or result in vagotropic effects such as bradycardia, heart block, hypotension, or syncope.[5-9] Recently, the cardiovascular risks of ChEIs have been debated in several studies demonstrating either an increased risk of syncope or bradycardia or a decreased risk of myocardial infarction or no association between cardiovascular events and use of ChEIs.[10-15]

Few studies based on spontaneous reports of suspected ChEI-induced ADRs emanating from national pharmacovigilance systems have been published. The seriousness of ChEI-induced ADRs, drug-drug interactions with ChEIs, and the comparative safety profiles of donepezil and memantine (an *N*-methyl-D-aspartate receptor antagonist used in the treatment of moderate to severe AD) have been analyzed in the French pharmacovigilance database.[16-18] Drug-drug interactions accounted for one-third of ChEI-related reported ADRs.[18] The use of antipsychotics, antihypertensives, and drugs for alimentary tract and metabolism increased the risk of serious ADR occurrence.[16-18] To our knowledge, no pharmacovigilance study evaluating the spectrum of all ChEI-induced ADRs reported worldwide has been conducted since the introduction of these drugs. The objectives of this study were (1) to describe ADRs reported for the 3 ChEIs—donepezil, galantamine, and rivastigmine—to the World Health Organization (WHO) Global Individual Case Safety Report (ICSR) database (VigiBase) between 1998 and 2013 and (2) to characterize the serious ADRs related to ChEI use with particular attention to cardiovascular ADRs.

Methods

VigiBase

In 1968, the WHO Program for International Drug Monitoring was created to provide evidence to detect potential risks of medications. National drug monitoring agencies of the participating countries collect suspected ADRs spontaneously reported by health professionals, patients, and manufacturers essentially. Each national drug monitoring agency is responsible for its reports and sends them using a standard electronic transmission format (E2B), at least quarterly to a database named VigiBase, located in the Uppsala Monitoring Center in Sweden. No selection or exclusion of cases is made in VigiBase.[19] As of 2013, VigiBase contained 8 million case reports from more than 100 countries and included information regarding patient demographics, medications, suspected ADRs (date of onset, outcome, seriousness, and causality), and administrative data (type of report and source).[19,20] Drugs were coded according to the WHO Drug Dictionary Enhanced, including the ATC (Anatomical Therapeutic Chemical) classification. ADRs were coded according to the WHO Adverse Reaction Terminology and the Medical Dictionary for Regulatory Authorities (MedDRA). A cross-reference tool allowed establishment of the correspondence between the 2 terminologies. The MedDRA dictionary is organized by System Organ Class (SOC), divided into High Level Group Terms (HLGTs), High-Level Terms (HLTs), Preferred Terms, and Lowest-Level Terms. In addition, for HLGT and HLT, groupings of miscellaneous terms that do not readily fit into other hierarchical classifications within a particular SOC were identified as Not Elsewhere Classified (NEC).

Data and Analysis

All reports related to ChEIs (donepezil, galantamine, and rivastigmine) notified between January 1, 1998, and December 31, 2013, to VigiBase were analyzed. Each report in VigiBase referred to a single individual who may have suffered from one or several ADRs concomitantly. Therefore, the number of reported ADRs was higher than the number of individuals for whom case reports had been collected. ADRs were described according to the MedDRA classification. In addition, a separate category for cardiovascular ADRs was created to more specifically explore this subgroup. This new category corresponds to (1) the Cardiac disorders SOC; (2) the HLTs from the Investigations SOC (ECG investigations, Heart rate and pulse investigations, Skeletal and cardiac muscle analyses, and Vascular tests NEC [including blood pressure]); (3) the HLTs from the Vascular disorders SOC (Accelerated and malignant hypertension, Blood pressure disorders NEC, Circulatory collapse and shock, Vascular hypertensive disorders NEC, and Vascular hypotensive disorders NEC); and (4) the Preferred Term from the Nervous system disorders SOC (*Syncope*). This last Preferred Term was added to the category of cardiovascular ADRs because syncope often results from the vagotonic effects of ChEIs and is thus coded in this way. Finally, ADRs included in the Nervous system disorders SOC (excluding the Preferred Term *Syncope*) and the

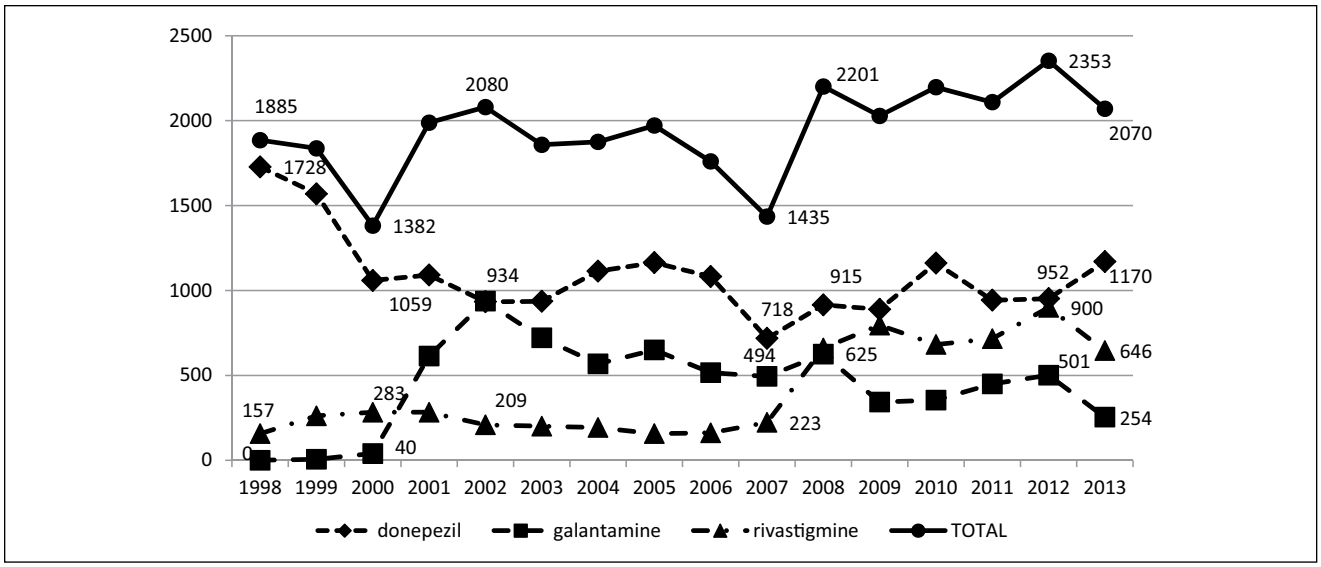

Figure 1. Number of adverse drug reactions by cholinesterase inhibitors from 1998 to 2013 in VigiBase.[a]
[a]Donepezil and rivastigmine arrived on the market before 1998, and galantamine arrived in 2000.

Psychiatric disorders SOC were grouped in the neuropsychiatric symptoms category.

Reporting regions were grouped into 5 categories: North America, Latin America (including Mexico, the Caribbean, and South America), Africa, Europe, and Asia-Pacific. An ADR was considered serious if it (1) resulted in death, (2) required hospitalization or prolongation of existing hospitalization, (3) resulted in a persistent or significant disability, (4) was life-threatening, (5) induced congenital malformations, or (6) induced other medically important events. ADR seriousness was only available in the E2B format; the E2B reports prevalence in VigiBase has steadily increased since 2000. This is why we restricted our study to years with less than 20% missing information—namely, years 2006 to 2013, to study this outcome. Descriptive statistics were computed using SAS software version 9.3.

Results

Characteristics of Reports

Between January 1, 1998, and December 31, 2013, 18 955 reports based on ADRs related to the 3 ChEIs (donepezil, rivastigmine, or galantamine) were extracted from VigiBase. These 18 955 reports involved 43 753 ADRs (median number of ADRs per report = 2; interquartile range = 1-3). The mean age was 77.4 ± 9.1 years (based on 14 407 participants); 39.9% cases occurred in men and 60.1% in women (based on 18 096 reports with nonmissing information). Reports were issued by physicians (42.8%), other health professionals (17.3%), and by other reporter categories such as manufacturers and patients (23.0%; based on 15 674 reports with nonmissing information). Rivastigmine and donepezil together generated 82.8% of the reports (41.4 % each), and 17.2% of reports involved galantamine.

Reporting Geographical Regions

Reports were issued by 58 countries, with most originating from Europe (47.6%). The 3 European countries that contributed the majority of reports were the United Kingdom (9.8%), Germany (7.8%), and France (4.4%). There were 40.4% of reports originating from North America (United States, 28.1%; Canada, 11.7%). Asia-Pacific generated 9.1% of reports, Latin America/Caribbean 2.7%, and Africa 0.2%.

Reports of ChEI-Induced ADRs (1998-2013)

The overall number of ChEI-induced ADRs increased during the 16-year period from 1924 ADRs in 1998 to 2961 in 2013, with 2 peaks occurring in 2001 (3618 ADRs) and 2012 (3720 ADRs; Figure 1). Globally, the ADR number for each ChEI increased in the years following its introduction and slightly decreased thereafter. For rivastigmine, we observed a new increase in ADR reports from 2008.

Between 1998 and 2013, among the 43 753 ADRs recorded, the most common were neuropsychiatric symptoms (31.4%), encompassing ADRs of the Nervous system disorders SOC (after excluding 812 cases of syncope; 17.1%) and the Psychiatric disorders SOC (14.3%). Other reported ADRs pertained to Gastro-intestinal SOC (15.9%) and General disorders and administration site conditions SOC (11.9%). The Cardiovascular ADRs category accounted for 11.7% of ADRs (6.9% ADRs in the Cardiac disorders SOC, 0.9% in the Investigations SOC, 1.9% syncope in the Nervous system disorders SOC, and 2.0% in the Vascular disorders SOC).

Comparison of Serious and Nonserious ChEI-Induced ADRs (2006-2013)

During the period 2006-2013, 23 874 ChEI-induced ADRs were reported, among which 71.2% (16 995) were serious. Globally, the serious to nonserious ADR ratio was 2.5; it was higher for rivastigmine (3.0) than for donepezil (2.2) or galantamine (1.7; Table 1). Globally, the serious to nonserious ADR ratio ranged from 1.5 in 2006 to 3.6 in 2013 (Figure 2). The distribution of all ADRs was somewhat similar for the 3 ChEIs, except for rivastigmine, which was more frequently involved in serious skin and subcutaneous tissue disorders (74.8%) than the 2 other ChEIs (Table 1). The most frequent ADRs were related to neuropsychiatric (31.1%), gastrointestinal (15.2%), general and administration site (14.0%), and cardiovascular (10.5%) conditions. However, the distribution of ADR subgroups differed between serious and nonserious ADRs. A third of serious ADRs (34.0%; 5780) involved neuropsychiatric symptoms, with 18.8% (3206) pertaining to Nervous system disorders SOC (including 289 cases of syncope) and 15.2% (2574) to Psychiatric disorders SOC. General disorders and administration site conditions were the second-most-frequent serious ADRs (14.0%; 2373), followed by cardiovascular ADRs (12.1%; 2048). The category of Cardiovascular ADRs included 7.0% (1198) ADRs in the Cardiac disorders SOC, 1.3% (217) in the Investigations SOC, 1.7% (289) syncope in the Nervous system disorders SOC, and 2.0% (344) in the Vascular disorders SOC. Finally, 11.6% (1972) of all serious ADR reports concerned Gastrointestinal disorders SOC (Table 1).

Among serious ADRs, expected cholinergic adverse effects were those that were frequently reported (2085/16 995, 12.3%) and involved the following symptoms (Table 2): nausea and vomiting (787), confusion (517), diarrhea (258), bronchospasm and dyspnea (166), tremor (131), urinary disorders (145), muscle contractions (49), and myoclonus (32). ChEIs were reported (Table 2) to have induced excitatory reactions of the central nervous system because 943 of 16 995 (5.5%) serious reports concerned seizures (247), anxiety (368), aggressive behavior (215), and insomnias (113). Medication error and maladministration were reported in 347 cases (2.0%) of all serious reports.

Discussion

This study provides a global description of spontaneously reported ADRs related to the 3 ChEIs used worldwide since 1998 and considers both the characteristics and the seriousness of the ADRs over time. ADRs were principally reported from North America and Europe (88.0% of reports), which is somewhat consistent with data on worldwide ChEI consumption in AD treatment. About 70% of worldwide costs for AD medications stem from their consumption in North America and Western Europe, with AD diagnoses being more frequent in high-income countries where patients have access to these medications.[21,22] Moreover, high-income countries contributed the highest ADR reporting rates to VigiBase, whereas low-income countries contributed the lowest reporting rates, with important variations between countries.[23] The ChEIs most frequently involved in reports were rivastigmine and donepezil (41.4% each). The relatively high proportion of reports related to donepezil and rivastigmine is comparable with the global market for AD medications, where these 2 products are leaders.[24] Regarding prescriptions in Europe and the United States, nearly 60% of patients with AD were prescribed donepezil up to 2007, whereas for that time period in Europe, galantamine and rivastigmine were used, each by about 20% of AD patients.[25,26]

Descriptive analyses of spontaneous reporting of ChEI-induced ADRs over a 16-year period revealed that there was an increase in reports during the first years after marketing, followed by a slight decrease. The increase in reports immediately following marketing is likely attributable to the Weber effect traditionally described in the pharmacovigilance literature, where the reporting rate adjusts to the increase in volume of prescriptions during the first years postmarketing and then decreases over time.[27] However, in our study, the Weber effect was hardly noticeable for serious ADRs because we observed a relatively steady number of serious ADRs related to ChEI use (from 2154 in 2008 to 2321 in 2013), and the serious to nonserious ADR ratio for ChEIs was high (ratio = 2.5). Similarly, in the French pharmacovigilance database, the serious to nonserious ADR ratio for galantamine was >1 over time, showing that the notification of serious ADRs related to ChEI use remained high.[28] Physicians are generally aware of the main, mostly serious ADRs—for example, those indicated in product summaries—and are, therefore, more prone to report these serious ADRs. The high number of these serious ADRs may also be exacerbated by the poor health status of the treated population, including mainly frail and older patients who are particularly sensitive to drug-drug interactions and are more susceptible to ADRs.[29] For rivastigmine, a second increase was observed in the years that followed the introduction of the rivastigmine patch. It is worth noting that in 2010, several national pharmacovigilance systems issued a warning about serious adverse events related to rivastigmine patches.[30-32]

The relative distribution of ChEI-related ADRs in VigiBase differs from that indicated in the different summaries of the product characteristics, which are based on premarket clinical trials. According to these summaries, gastrointestinal effects are the most frequent ADRs.[33] In the present study, however, neuropsychiatric ADRs were most prevalent. Prior research hypothesized that neuropsychiatric events, such as aggressiveness, anxiety, and abnormal

Table 1. Nonserious and Serious ADRs Related to Cholinesterase Inhibitors by MedDRA SOCs, VigiBase, 2006-2013.[a]

	Donepezil		Galantamine		Rivastigmine		Total		
MedDRA SOC	Nonserious ADR (n)	Serious ADR (n)	Nonserious ADR (n)	Serious ADR (n)	Nonserious ADR (n)	Serious ADR (n)	Nonserious ADR, n/(%)	Serious ADR, n/(%)	Total ADRs, n/(%)
Blood and lymphatic system disorders	13	70	11	29	7	49	31/0.4	148/0.9	179/0.7
Cardiac disorders	92	448	72	210	93	540	257/3.7	1198/7.0	1455/6.1
Ear and labyrinth disorders	13	19	10	11	11	17	34/0.5	47/0.3	81/0.3
Eye disorders	29	57	3	12	14	66	46/0.7	135/0.8	181/0.8
Gastrointestinal disorders	693	658	407	249	549	1065	1649/24.0	1972/11.6	3621/15.2
General disorders and administration site conditions	227	555	115	228	617	1590	959/13.9	2373/14.0	3332/14.0
Hepatobiliary disorders	7	47	7	21	11	53	25/0.4	121/0.7	146/0.6
Infections and infestations	29	144	16	51	45	264	90/1.3	459/2.7	549/2.3
Injury, poisoning, and procedural complications	37	216	52	244	50	591	139/2.0	1051/6.2	1190/5.0
Investigations[b]	61	276	51	115	81	397	193/2.8	789/4.6	982/4.1
Metabolism and nutrition disorders	82	171	54	71	80	268	216/3.1	510/3.0	726/3.0
Musculoskeletal and connective tissue disorders	65	122	16	34	30	155	111/1.6	311/1.8	422/1.8
Neoplasms benign, malignant, and unspecified	2	29	2	7	9	75	13/0.2	111/0.6	124/0.5
Nervous system disorders[c]	481	1210	251	417	428	1579	1160/16.9	3206/18.9	4366/18.3
Psychiatric disorders	384	789	135	306	322	1479	841/12.2	2574/15.2	3415/14.3
Renal and urinary disorders	33	111	19	39	28	150	80/1.2	300/1.8	380/1.6
Respiratory, thoracic, and mediastinal disorders	46	139	16	64	40	224	102/1.5	427/2.5	529/2.2
Skin and subcutaneous tissue disorders	126	132	46	43	570	458	742/10.8	633/3.7	1375/5.8
Vascular disorders[d]	38	125	12	69	83	290	133/1.9	484/2.8	617/2.6
Others[e]	14	40	10	11	34	95	58/0.8	146/0.9	204/0.8
All SOCs	2472	5358	1305	2232	3102	9405	6879/100	16 995/100	23 874/100
Proportion of serious ADR (%)	31.5		13.1		55.3		100		
Ratio of serious to nonserious ADRs	2.2		1.7		3.0		2.5		

Abbreviations: ADR, adverse drug reaction; ECG, electrocardiogram.

[a]The MedDRA (Medical Dictionary for Regulatory Authorities) is organized by SOC (System Organ Class), divided into High Level Terms (HLTs), Preferred Terms (PT), and NEC (Not Elsewhere Classified).

[b]Including 253 cases (and 217 serious cases) of HLT codes following ECG investigations, Heart rate and pulse investigations, Skeletal and cardiac muscle analyses, and Vascular tests NEC (including blood pressure).

[c]Including 364 cases (and 289 serious cases) of PT codes following Syncope.

[d]Including 432 cases (and 344 serious cases) of HLT codes following Accelerated and malignant hypertension, Blood pressure disorders NEC, Circulatory collapse and shock, Vascular hypertensive disorders NEC, and Vascular hypotensive disorders NEC.

[e]SOC <50 cases (Congenital, familial, and genetic disorders; Endocrine disorders; Immune system disorders; Pregnancy puerperium and perinatal conditions; Reproductive system and breast disorders; Social circumstances; Surgical and medical procedures).

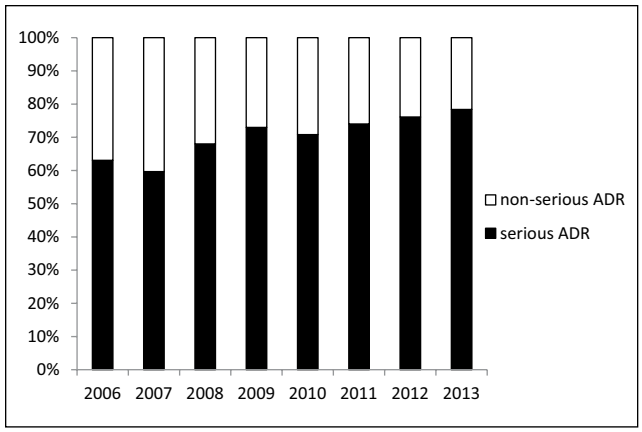

Figure 2. Ratio of serious and nonserious adverse drug reactions (ADRs) related to cholinesterase inhibitors from 2006 to 2013, VigiBase.

dreams, could be a signal of ChEI-related ADRs, but this was based on a small-scale study limiting the impact of this conclusion.[34] A recent French study showed that among dementia patients, ChEIs were the main source of ADRs and that neuropsychiatric ADRs were frequent.[35] However, neuropsychiatric ADRs tend to be more frequent in pharmacovigilance databases in general, which limits our ability to be able to more strongly conclude this result from the present study.[36] Moreover, neuropsychiatric symptoms are frequent among AD patients, further limiting conclusions on the associations between ChEIs and neuropsychiatric ADRs. Finally, common comedications among AD patients, mainly psychotropic drugs, may also be responsible for neuropsychiatric ADRs. Nevertheless, there exists a pharmacological rationale for the occurrence of this type of ADRs because ChEIs increase acetylcholine levels in the brain, which in turn may lead to an increase in neuronal excitation.[37]

Cardiovascular ADRs were the fourth most frequently reported ADRs and the third most frequently serious ADR category. To date, there is not sufficient evidence to either support or reject the hypothesis of cardiovascular risks associated with ChEI use. Two studies from Canadian health administrative databases showed an increased risk of bradycardia, syncope, and consequent falls in AD patients using ChEIs compared with nonusers.[12,13] Another database study, which compared the risk of syncope among patients with AD in the periods before and since ChEI use, found no increased risk with ChEI administration.[14] A small-scale clinical study found no evidence of change from baseline in cardiac parameters among AD patients starting ChEI therapy.[11] A cohort study found a reduced risk of myocardial infarction or cardiac death among ChEI users.[15] Each of these studies had inherent methodological limitations, including heterogeneity of the AD state, comorbidity, and use of comedications among patients using ChEIs and those not using them. Their results should, thus, be interpreted with caution. Further high-quality research on this question seems warranted, given the costs of these medications and their widespread use in a frail population with frequent cardiac problems and other comorbidities.[38]

Some reports were related to medication errors. A previous study using pharmacovigilance databases has shown that older persons more often fall victim to medication errors, but ChEIs did not seem to be significantly involved.[39] The present study shows the seriousness of medication errors regarding ChEIs occurring in a frail population affected by several risk factors, such as higher age and cognitive deficits.

The main strength of the present study is its use of a large and long-term international pharmacovigilance database. VigiBase is the largest database of its kind that is publicly available and based on spontaneous reporting in countries with a large variety of populations and health systems. Although the reports in VigiBase are heterogeneous, because data originate from multiple sources and present varying degrees of exhaustiveness, this international pharmacovigilance database is considered to be a reliable and important tool for ADR surveillance.[19,20,23]

There are, however, some limitations to our work. First, statistical measures of disproportionality (reporting odds ratio, proportional reporting ratio, or others) were not applied to our study because our aim was not to quickly generate signals after the beginning of ChEI marketing, or to compare the potential association between a particular ADR and ChEIs or with other drugs, or to confirm a pharmacological hypothesis between ChEIs and a particular ADR.[40] Our aim was to describe the pattern of ChEI-induced ADRs since their arrival on the world market. Therefore, not all ADRs are reported, and reporting varies with marketing intensity and public reports on adverse events. Underreporting is the main problem with this kind of data. In a systematic review, Hazell and Shakir[41] calculated that the median underreporting rate across 37 studies they examined was 85% to 94%, depending on the surveillance method. This underreporting has an important impact on the knowledge gathered on drug safety and on the ensuing health decisions. The rate of underreporting may vary depending on the type of ChEI and the type of ADR induced. In the present study, parameters such as outcome, dose, time for onset of ADR, time of first use, and challenge and rechallenge were often ill-reported, limiting a complete interpretation of ChEI-related ADRs. Moreover, drug indications, medical history, and comedications were not included in the extraction of data. Similarly, because figures on ChEI sales are kept confidential by the industry, we could only describe the distribution of ChEI-related ADR reports. The causal inferred link between an ADR and a specific ChEI may have been overestimated in some reports

Table 2. Description of Serious ADRs Related to Cholinesterase Inhibitors According to MedDRA Classification, VigiBase, 2006-2013.[a]

	Number
Cardiac disorders[b]	**1198**
Cardiac conduction disorders	134
Atrioventricular block (111), bundle branch block (23)	
Rate and rhythm disorders NEC	397
Bradycardia (291), arrhythmia (69), other rhythm disorders (37)	
Supraventricular arrhythmias	75
Ventricular arrhythmias and cardiac arrest	151
Cardiac arrest (100), ventricular arrhythmia (51)	
Others	441
Gastrointestinal disorders	**1972**
Diarrhoea (excludes infective)	258
Nausea and vomiting symptoms	787
Gastrointestinal and abdominal pains (excludes oral and throat)	117
Gastrointestinal signs and symptoms NEC	153
Dysphagia (68), abdominal discomfort (44), faecal incontinence (31), others (10)	
Non–site-specific gastrointestinal haemorrhages	127
Hematemesis (31), melaena (13), gastrointestinal haemorrhage (7), others (76)	
Others	530
General disorders and administration site conditions	**2373**
Application and instillation site reactions	410
Asthenic conditions	439
Asthenia (162), malaise (157), fatigue (118), others (2)	
Body temperature altered	20
Hypothermia (19), hyperthermia (1)	
Febrile disorders *Pyrexia*	63
Death and sudden death	432
Interactions	115
Therapeutic and nontherapeutic responses	146
Drug effect decreased or ineffective	
Gait disturbances	157
General signs and symptoms	185
Condition aggravated (185)	
Others	406
Pain (101), oedema (60), irritability (26), others (219)	
Hepatobiliary disorders	**121**
Hepatocellular damage and hepatitis NEC	28
Hepatitis or hepatotoxicity	
Hepatic and hepatobiliary disorders NEC	13
Liver injury	
Hepatic enzymes and function abnormalities	19
Cholestasis and jaundice	22
Hepatitis cholestatic	
Others	39
Injury, poisoning, and procedural complications	**1051**
Maladministrations	198
Incorrect drug administration(80), dose (47), route (64) or duration (7)	
Overdose	85
Medication errors NEC	149
Non-site specific injuries NEC	360
Falls (342), others (18)	
Others	259
Investigations	**789**
ECG investigations[b]	72
Heart rate and pulse investigations[b]	48
Vascular tests NEC (includes blood pressure)[b]	83
Skeletal and cardiac muscle analyses[b]	10
Cardiac function diagnostic procedure[b]	4
Liver function analyses	96
Others	476

(continued)

Table 2. (continued)

	Number
Nervous system disorders	**3206**
Disturbances in consciousness NEC	715
Syncope[b] *(289), loss of consciousness (186), somnolence (172), lethargy (37), sedation (17), others (14)*	
Neurological signs and symptoms NEC	348
Dizziness (281), myoclonus (32), others (35)	
Seizures and seizure disorders NEC	247
Convulsion (142), epilepsy (105)	
Neuromuscular disorders NEC	49
Muscle contractions involuntary	
Dyskinesias and movement disorders NEC	155
Tremor (excludes congenital)	131
Speech and language abnormalities	87
Speech disorder (49), dysarthria (27), others (11)	
Headaches NEC	117
Central nervous system haemorrhages and cerebrovascular accidents	55
Others	1302
Psychiatric disorders	**2574**
Confusion and disorientation	517
Behaviour and socialisation disturbances	215
Aggression (158), paranoia (39), others (18)	
Anxiety symptoms	368
Agitation (248), anxiety (120)	
Disturbances in initiating and maintaining sleep	113
Insomnia	
Depressive disorders	114
Perception disturbances	393
Hallucination	
Others	854
Renal and urinary disorders	**300**
Bladder and urethral symptoms	145
Urinary incontinence (47), urinary retention (35), others (63)	
Renal failure and impairment	97
Others	58
Respiratory, thoracic, and mediastinal disorders	**427**
Breathing abnormalities	123
Dyspnea (80), respiratory distress (29), others (14)	
Bronchospasm and obstruction	43
Chronic obstructive pulmonary disease (24), asthma (12), others (7)	
Others	261
Respiratory failure (24), cough (23), others (214)	
Skin and subcutaneous tissue disorders	**633**
Apocrine and eccrine gland disorders	70
Hyperhidrosis	
Rashes, eruptions, and exanthemas NEC	147
Pruritus NEC	89
Others	327
Vascular disorders	**484**
Vascular hypotensive disorders[b]	175
Vascular hypertensive disorders NEC[b]	118
Circulatory collapse and shock[b]	38
Blood pressure disorders NEC[b]	13
Others	140
Other SOC	**1867**
All SOC	**16 995**

Abbreviations: ADR, adverse drug reaction; HLT, High-Level Terms; MedDRA, The Medical Dictionary for Regulatory Authorities; NEC, Not Elsewhere Classified; PT, Preferred Terms; SOC, System Organ Class.

[a]In the first column, bold font refers to SOC MedDRA level, normal font to HLT level, and italics to PT level.

[b]ADR included in the category of cardiovascular ADRs.

because neuropsychiatric ADRs, for example, might have been caused by psychotropic comedications or the disease itself.

Conclusion

This large international pharmacovigilance study covering a 16-year period highlights the ADR patterns associated with the use of the 3 main ChEIs since their introduction on the market. After an overall increase in reports during the first years of marketing of each ChEI, serious ADRs remained more often reported than nonserious ones. Reported neuropsychiatric events were particularly frequent compared with gastrointestinal ones. In clinical practice, if a patient with dementia is being treated with a ChEI and experiences neuropsychiatric symptoms, then the possibility of a ChEI ADR should be considered before treating with corrective drugs. Serious cardiovascular events were also frequently reported, suggesting that their significance has probably been underestimated previously. Finally, before introducing a ChEI, we recommend considering the overall cardiovascular situation of the patient in addition to any comedications that may elevate a preexisting risk of cardiovascular events.

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