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Safety profile of Alzheimer's disease populations in Alzheimer's Disease Neuroimaging Initiative and other 18-month studies

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Abstract

Background: Demonstration of a disease-modifying effect of a therapeutic agent on Alzheimer's disease (AD) requires a trial lasting for at least 18 months. An understanding of expected rates of adverse events (AEs), overall discontinuations, and discontinuations due to AEs, serious AEs, and deaths would be useful in planning such trials.

Methods: We examined safety information for patients taking placebo from five published 18-month AD trials and for patients from the Alzheimer's Disease Neuroimaging Initiative study.

Results: AEs reported consistently across multiple studies were dyspnea (occurring in 5.3%–5.8% of patients), headache (4.0%–5.5%), constipation (4.3%–4.7%), nausea (2.0%–5.8%), joint swelling (3.6%–3.7%), vomiting (3.6%–3.7%), and anxiety (3.2%–3.6%). Larger multinational studies, as compared with smaller studies with fewer sites and geographies, demonstrated greater overall discontinuations (24.6%–33.0% vs 8.2%–21.0%) and greater discontinuations due to AEs (9.5%–11.6% vs 2.7%–3.2%). Rates of death (1.8%–2.4%) and SAEs (19.9%–21.2%) were consistent across 18 month published studies and in ADNI; fall was the most common SAE (2.6%–4.0%) where SAEs were reported.

Conclusions: In general, comparable types of AEs, frequency of deaths, and serious AEs were seen for patients taking placebo in five randomized, controlled 18-month AD trials and in Alzheimer's Disease Neuroimaging Initiative, whereas rates of discontinuations were more variable. Evaluation across studies was complicated by inconsistent methods of reporting safety information. Evaluation of large databases of placebo patients from therapeutic AD trials is needed to further enhance the understanding of expected safety outcomes in clinical trials of AD patients.

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Keywords: Alzheimer's disease; Safety monitoring; ADNI; Epidemiology; Adverse events; Risk assessment; Clinical outcomes

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative brain disease that insidiously robs patients of their cognition, function, independence, and identity and results in morbidity and eventual mortality. Increasing age is a risk factor for development of AD [1–4], the most common dementing illness, with sporadic AD typically diagnosed in patients aged >65 years. The 2000 U.S. census reported an AD prevalence of 4.5 million people aged >65 years [5]. An estimated 5.4 million people aged >65 have AD in 2011, and the projected prevalence of AD by 2030 is 7.7 million people aged ≥65 years [5]. AD is the fifth leading cause of death in this age group [6]. Currently available AD treatments are "symptomatic," that is, they improve cognition but do not affect the underlying pathology of AD; therefore, they have no action on continued neurodegeneration and disease progression. In recent years, these factors, combined with the increasing age of the population and economic impact of

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://loni.ucla.edu//ADNI//Collaboration//ADNI_Authorship_list.pdf.

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AD, have spurred research into treatments that may slow neurodegeneration and thereby modify the progression of AD. To demonstrate that a compound slows disease progression rather than providing a symptomatic, cognitive-enhancing effect, clinical trials should last for at least 18 months [7,8]; however, studies of this length in an elderly population with AD are difficult for many reasons.

First, although increasing age is a risk factor for AD, advanced age also portends a greater incidence of other acute and chronic medical illnesses. Not surprisingly, most patients with AD or other dementias have at least one comorbid chronic medical condition, including hypertension (60%), coronary artery disease (30%), late effects of cerebrovascular disease (10%), diabetes mellitus (21%), congestive heart failure (28%), and chronic obstructive pulmonary disease (17%) [9]. Thus, designing and monitoring studies to assess potential disease-modifying AD treatments is made challenging by an elderly population with multiple medical comorbidities. Other challenges to such trials include required involvement of a caregiver with his/her own obstacles to long-term participation, the burden of long studies with many visits and procedures, and the lack of perceived treatment benefit that might be evident with a cognitive-enhancing agent. These issues all contribute to high overall discontinuation rates, even in placebo-treated patients (17%–41%) [10], and thus potentially impact study power and interpretability. An accurate estimate of expected discontinuations in an AD population during an 18-month period would help to appropriately design and power future studies.

Second, to identify potential new safety signals as quickly as possible and to ensure patient safety during ongoing blinded studies, routine safety monitoring through blinded reviews of serious and nonserious adverse events (AEs), laboratory, electrocardiogram, and vital sign data should be collected [11–14]. However, the ability to detect a new safety signal is difficult against a complicated background of age- and disease-related medical comorbidities. Screening out the background of AEs, serious AEs (SAEs), deaths, and discontinuations by comparing them with overall background rates in a closely matched untreated AD cohort is one method of adding context to blinded safety review results, aiding proper interpretation of causality and contributing to the emerging safety profile of the drug [15,16]. In fact, the U.S. Food and Drug Administration (FDA) Guidance for Investigational New Drug Safety Reporting now requires an assessment of the most important and common background AEs in the population to be studied. These background rates should be included in the study protocol and compared against rates of AEs in the blinded safety data during the course of the study to determine which SAEs should be reported to the agency [17].

This article describes reference data on rates of AEs, SAEs, deaths, overall discontinuations, and discontinuations due to AEs that occur among reference cohorts of AD patients during an 18-month period. These reference data will be useful for researchers designing AD studies that last for at least 18 months and for monitoring and interpreting blinded safety data during the conduct of these studies.

2. Methods

The Citeline Trial Trove database was used to identify published clinical trials that lasted for at least 18 months in patients with mild-to-moderate AD as of January 12, 2010. Mild-to-moderate severity AD was chosen because this population has been most commonly specified for phase 2/3 treatment studies of potentially disease-modifying therapies. Trials identified are hereafter referred to as "hydroxychloroquine" [18], "atorvastatin" [19,20], "B-vitamin" [21], "tarenflurbil" [22], and "bapineuzumab" [23]. Safety results were summarized for the subjects in the placebo treatment groups (total N = 1512). Safety data included rates of AEs, SAEs, overall discontinuations, discontinuations due to AEs, and deaths, where available.

The Alzheimer's Disease Neuroimaging Initiative (ADNI), a natural history, longitudinal, nontreatment study, was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering, the FDA, private pharmaceutical companies, and nonprofit organizations as a $60 million, 5-year public–private partnership. The primary goal of ADNI has been to test whether biological markers, including serial magnetic resonance imaging (MRI) and positron emission tomography, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment (MCI) and early AD to improve clinical trial design and facilitate the development of new treatments. Eight hundred subjects (200 normal control subjects, 400 patients with MCI, and 200 patients with mild AD), aged 55 to 90 years, were recruited from more than 50 North American sites. Data used in the preparation of this article were obtained from the ADNI database (www.loni.ucla.edu/ADNI). For additional information, see www.adni-info.org.

Although safety data from the five published studies are reported as aggregate data, patient-level data were obtained from ADNI (updated on January 5, 2010) [24]. Safety data were compiled and summarized for patients with mild AD (defined by a Mini-Mental State Examination [MMSE] score of 20–26 at baseline) who participated for up to 18 months (N = 190). Postbaseline AEs were collected as event descriptions, mapped to Medical Dictionary for Regulatory Activities (MedDRA v12.0) lower-level terms and subsequently to preferred terms by the authors, and summarized by frequency. MedDRA terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (MedDRA is a registered trademark of the

Table 1
Baseline characteristics in clinical studies of patients with AD

Baseline characteristic	Placebo groups					ADNI
	Hydroxychloroquine	Atorvastatin	B-vitamin	Tarenflurbil	Bapineuzumab	
Year of study initiation	1996	2002	2003	2005	2005	2004
Sites (N) and geography	4 Amsterdam	87 global	40 US	133 US	30 US	56 US + Canada
Patients (n*)	85	326	169	822	110	190
MMSE inclusion criteria	NS	NS	14–26	20–26	16–26	20–26
Baseline MMSE, mean (SD) [range]	NS	NS	20.9 (3.7)	23.3 (2.0)	20.7 (0.3†)	23.3 (2.0) [18–26]
Age inclusion criteria (years)	NS	50–90	>50	≥55	50–85	55–90
Age (years), mean (SD), [range]	70.7 (8.5)	73.1	77.3 (7.9)	74.7 (8.4) [53–100]	67.9 (0.9†)	75.2 (7.5) [55–91]
% Female	61.0	51.0	53.9	52.5	59.8	47.9

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; MMSE, Mini-Mental State Examination; NS, not specified; SD, standard deviation.

*Number of patients in the placebo group of each study or in ADNI.

†Standard error.

International Federation of Pharmaceutical Manufacturers and Associations [IFPMA]). Some clinically similar event terms were combined to provide better overall estimates of background rates of AEs. Because patient-level longitudinal data were available for the ADNI subjects, additional summaries of SAEs, AEs, and discontinuation rates at 6 months and 12 months were compiled. These data include all patients who completed or discontinued before 6 months and 12 months, and the AEs were summarized using the methods described previously.

3. Results

The published studies varied in geographic representation (single country to global), number of sites (4–133), and sample size (85–822). The inclusion criterion of an MMSE baseline score of 20 to 26 was the same in the tarenflurbil and ADNI studies, representing a mild AD population. The bapineuzumab study included patients with moderate AD (MMSE score of 16–26) who were the youngest at baseline (mean = 67.9 years). The B-vitamin study also included patients with moderate AD (MMSE baseline score of 14–26) and had the oldest patients at baseline (mean = 77 years). Fewer females participated in ADNI (47.9%) than in the published studies (51%–61%; Table 1).

Exclusion criteria across the studies included brain imaging inconsistent with AD in all but the hydroxychloroquine study. Otherwise, exclusion criteria varied mainly with respect to the concomitant medications allowed and specific medical illnesses excluded. The B-vitamin, tarenflurbil, and bapineuzumab studies excluded anticoagulant therapy. Study complexity was also variable with visit intervals, approximately every 3 months in all but the hydroxychloroquine study (required at baseline, 9, and 18 months and choice of telephone or office visits every 6 weeks) and ADNI (office visits at baseline, 6, and 12 months and telephone visit at 18 months). Neuroimaging was required, and lumbar puncture was optional for subjects participating in ADNI. Among the studies reviewed, the bapineuzumab study had a more intensive protocol for patients and caregivers, with 1-hour intravenous infusions every 13 weeks; MRI scans at baseline, 6 weeks, and after infusions; and optional lumbar puncture.

Requirements for caregiver involvement in the studies were not reported in the bapineuzumab or B-vitamin studies (although patient disposition details in the B-vitamin study included caregiver issues; thus, a caregiver was likely required). The hydroxychloroquine study required caregivers to supervise compliance with medication and to participate in scales assessing activities of daily living, but it did not

Table 2
Rates of overall discontinuation, discontinuation due to AEs, SAEs, and death

Variable	Placebo groups					ADNI
	Hydroxychloroquine	Atorvastatin	B-vitamin	Tarenflurbil	Bapineuzumab	
	N = 85	N = 326	N = 169	N = 822	N = 110	N = 190
DC overall (% pts)	8.2	24.6	17.0	33.0	21.0	18.4*
DC from AE (% pts)	NS	9.5	NS	11.6	2.7	3.2
SAE (% pts†)	NS	21.2	NS	19.9	20.0	21.1‡
Death (% pts)	2.4	1.8	2.4	2.2	0	2.1

Abbreviations: AE, adverse event; DC = discontinuation; % pts = percentage of patients; SAE = serious adverse event.

*Reviewed longitudinally, overall ADNI discontinuation rates were relatively evenly distributed (6-month, 8.4%; 12-month, 12.6%; 18-month, 18.4%).

†Defined as percentage of patients with one or more SAE.

‡Reviewed longitudinally, ADNI SAE rates were relatively evenly distributed (6-month, 10.0%; 12-month, 15.8%; 18-month, 21.1%).

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Table 3
Rates of AEs

AE	Placebo Groups					ADNI**	ADNI comments
	Hydroxychloroquine* N = 85 (%)	Atorvastatin† N = 326 (%)	B-vitamin‡ N = 169 (%)	Tarenflurbil§ N = 822 (%)	Bapineuzumab¶ N = 110 (%)	N = 190 (%)	AE term (n)
Fall		5.5		10.1		16.8	
Asthenia						12.6	
Depressed mood						12.1	
Diarrhea		5.5		7.3		11.6	
Cough						10	
Dizziness				5.7		10	
Somnolence						10	
Pollakiuria						9.5	
Arthralgia		5.2	4.1			8.4	
Depression			17.8	8.5		8.4	Depression (15), major depression (1)
Back pain		6.5		5.0	5.5	7.9	
Crying						7.4	
Dry mouth						5.8	
Dyspnea			5.3			5.8	
Headache	4.0		5.3	5.5		5.3	
Musculoskeletal pain						5.3	
Rash						5.3	Rash (9), pruritic rash (1)
Skin cancer						5.3	Squamous cell (3), basal cell (4), malignant melanoma (1), skin cancer NOS (2)
Constipation				4.3		4.7	
Restlessness			8.3			4.7	
Bone fracture		6.8				4.7	1 each of ankle, hip, jaw, spinal, rib, radius, clavicle, upper limb, sacrum
Incontinence						4.2	Incontinence (2), urinary incontinence (2), fecal incontinence (4)
Nausea	2.0	4.9		5.8		4.2	
Syncope					1.8	4.2	Syncope (7), loss of consciousness (1)
UTI		10.2	4.7	13.3		4.2	UTI (7), cystitis (1)
Chest pain						3.7	
Joint swelling			3.6			3.7	
Vomiting					3.6	3.7	
Arrhythmia-related events						3.2	1 each of arrhythmia, atrial fibrillation, bradycardia, palpitations, sinus arrhythmia, ventricular extrasystoles
Abdominal discomfort						3.2	Abdominal pain (1), abdominal discomfort (5)
Agitation		7.4		6.9		3.2	
Anxiety					3.6	3.2	
Hyperhydrosis			4.1			3.2	
Insomnia		7.1				3.2	
Cataract					0.9	2.6	Cataract operation (3), cataract (2)
Seizures					0.9	2.6	Convulsion (5)
Anemia				3.8		2.1	
Blurred vision			1.8			2.1	
Fatigue						2.1	
Gait disturbance					1.8	2.1	

(*Continued*)

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Table 3
Rates of AEs (*Continued*)

AE	Placebo Groups					ADNI**	ADNI comments
	Hydroxychloroquine* N = 85 (%)	Atorvastatin† N = 326 (%)	B-vitamin‡ N = 169 (%)	Tarenflurbil§ N = 822 (%)	Bapineuzumab¶ N = 110 (%)	N = 190 (%)	AE term (n)
Hypersomnia						2.1	
Malignancy						2.1	1 each of adenocarcinoma, bladder cancer, multiple myeloma, prostate cancer
Paranoia					0.9	2.1	Paranoia (1), delusion (2), visual hallucination (1)
Pneumonia				1.7		2.1	Pneumonia (3), pneumonia bacterial (1)
Visual complaints	2.0					2.1	1 each of altered depth perception, phosphene, maculopathy, macular degeneration
Hypertension					3.6	1.6	
Stroke or TIA				2.3		1.6	1 each of CVA, TIA, cerebral hemorrhage
URI		12.3	3.6	5.6		1.6	URI (1), sinusitis (2)
Nasopharyngitis				6.9		1.1	
Skin laceration					2.7	1.1	
Weight loss		4.0			1.8	0.5	Weight decreased
Rhinitis		5.2				0.5	Rhinorrhea

Abbreviations: CVA, cerebral vascular accident; MedDRA, Medical Dictionary for Regulatory Activities; NOS, not otherwise specified; PT, [MedDRA]-preferred terms; TIA, transient ischemic attack; URI, upper respiratory infection; UTI, urinary tract infection. Blanks indicate the rate was not reported, whether the event occurred in that study population or whether it met the publication's specified threshold for reporting is unknown.

*AE frequency of ≥2%; coding not specified.

†AE frequency of ≥5% in atorvastatin or placebo group; MedDRA PT-specified.

‡AE frequency of ≥5% in B-vitamin or placebo group; clinically-similar AE terms were combined but were unspecified, except for "depression," which included the terms depression, depressed mood, and depressive symptoms; other terms coding not specified.

§AE frequency of ≥5% in tarenflurbil or placebo group or with statistically significant difference between groups; MedDRA PT-specified.

¶AE frequency of >5% in bapineuzumab that occurred >2× more often than in placebo or considered important and occurred in a greater proportion of bapineuzumab-treated patients than placebo-treated patients; coding not specified.

**AEs occurring in ≥2% of patients; actual terms manually mapped to MedDRA by authors.

specify a minimum time per week with the patient. The tarenflurbil study required at least 4 hours per week of caregiver time with patient, and ADNI mandated at least 10 hours. The atorvastatin study contained the most robust caregiver requirement of at least 5 days and 10 hours per week of caregiver time with the patient.

Overall discontinuation rates varied from a low of 8.2% to a high of 33.0% and showed a pattern suggestive for higher rates of discontinuation in studies with more sites. This pattern was also observed for discontinuation due to AEs. Reviewed longitudinally, overall ADNI discontinuation rates were relatively evenly distributed (6-month, 8.4%; 12-month, 12.6%; 18-month, 18.4%). Rates of SAEs (20%–21%) and deaths (0%–2.4%) were consistent across the published literature and the ADNI data (Table 2). Longitudinal ADNI SAE rates were also relatively evenly distributed, increasing approximately 5% for every subsequent 6 months of observation (6-month, 10.0%; 12-month, 15.8%; 18-month, 21.1%).

Table 3 shows the rates of AEs occurring in ≥2% of patients in the ADNI study or reported in the published AD studies (various reporting thresholds in published studies are described in the table footnotes). As noted in Table 3, not all studies reported many of the AEs, although it is unknown whether this is because the AE did not occur in the study or failed to meet the study-specified threshold for reporting.

Rates of individual SAEs were reported in the atorvastatin study and were summarized for ADNI (Table 4). Fall was the most common SAE in both studies. Pneumonia, syncope, and cerebrovascular accident-related SAEs occurred at rates of 1% to 2% in both patient populations.

Cause of death was reported in the atorvastatin and hydroxychloroquine studies and was summarized for ADNI (Table 5). Cause of death was coded to death not otherwise specified for two patients in the ADNI study and one in the atorvastatin study. This is interpreted as death of unknown etiology.

Table 4
Rates of SAEs in studies reporting cause

SAE*	Placebo group Atorvastatin N = 326 (%)	ADNI N = 190 (%)	ADNI comments AE term (n)
Fall	4.0	2.6	
Chest pain	NS	2.1	
Pneumonia	0.9	2.1	Pneumonia, bacterial pneumonia
CVA	0.9	1.6	Cerebral hemorrhage, CVA, TIA
Syncope	1.8	1.6	
Cellulitis	NS	1.1	
Dehydration	NS	1.1	
Aggression	0.9	0.5	
Hip fracture	1.2	0.5	
Prostate cancer	0.6	0.5	
Delusion	NS	0.5	
Delirium	0.6	0	
Agitation	0.6	0	
Appendicitis perforated	0.6	0	
Confusional state	0.6	0	
Diarrhea	0.3	0	
Inguinal hernia	0.6	0	
Metastasis	0.6	0	
Myocardial infarction	1.5	0	
Rectal cancer	0.6	0	
Rib fracture	0.6	0	
Sick sinus syndrome	0.6	0	
Vertigo	0.6	0	
Wrist fracture	0.9	0	

Abbreviations: NS = not specified (whether the event occurred in that study population or whether it met the publication's specified threshold for SAE reporting is unknown).

*SAEs reported by at least two placebo-treated patients in atorvastatin or at least two patients in the ADNI study.

Table 6 repeats the listing of AEs in the ADNI database at 18 months, but also includes the 6- and 12-month data for comparison.

4. Discussion

In this study, patient-level safety data from the ADNI study were compared with published safety data from five therapeutic AD trials lasting at least 18 months; despite limitations, particularly in published reports, comparable types of AEs and frequency of deaths and SAEs were seen, whereas rates of overall discontinuations and discontinuations due to AE were more variable. These data provide a reference point for AD clinical trial design and for monitoring and evaluating blinded safety data in ongoing AD clinical trials. Although extensive literature has been published on cognitive and functional outcomes and biomarker results from ADNI, the safety data have only been reported previously in abstract form [25]. Several patterns of note regarding discontinuations are apparent in this review. The bapineuzumab, B-vitamin, and ADNI studies had similar geographic representation, number of sites and patients, and discontinuation rates (17%–21%). Interestingly, despite a more intensive protocol, the bapineuzumab study did not have the highest overall discontinuation rate (21%) and had a lower discontinuation due to AE rate in placebo patients (2.7%) than the ADNI study (3.2%). In comparison, the larger more globally represented tarenflurbil and atorvastatin studies had the highest overall placebo discontinuation (33% and 24.6%, respectively) and discontinuation due to AE rates (11.6% and 9.5%, respectively), whereas the rates of SAEs and deaths were similar to that of the other studies. The lowest overall placebo discontinuation rate (8.2%) was in the hydroxychloroquine study, which had only four sites (in Amsterdam) and followed a flexible protocol allowing some visits to occur by telephone and requiring office visits at only three time points in 18 months. Although caregiver burden is another consideration when evaluating discontinuation rates in AD studies, these data do not provide enough information to draw definitive conclusions. Only the B-vitamin article specifically listed "caregiver unwillingness to continue" as a factor in early discontinuations. In addition, no consistent pattern was apparent between caregiver requirements and the discontinuation data; although having the highest placebo discontinuation rate, the tarenflurbil study only required $\geq$4 hours per week of caregiver time with the AD patient.

Longitudinally, the ADNI data showed relative consistency of SAEs and discontinuation rate across 6-, 12-, and

Table 5
Events causing death in studies reporting cause of death

Reported cause of death	Placebo groups Hydroxychloroquine N = 85 (%)	Atorvastatin N = 326 (%)	ADNI N = 190 (%)
Pneumonia	0	1 (0.3)	1 (0.5)
Death NOS	0	1 (0.3)	2 (1.1)
Rectal cancer	0	1 (0.3)	0
Rectal cancer/metastasis	0	1 (0.3)	0
Myocardial infarction	0	2 (0.6)	0
Bladder cancer	1 (1.2)	0	0
Suicide	1 (1.2)	0	0
CVA	0	0	1 (0.5)
Total	2 (2.4)	6 (1.8)	4 (2.1)

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Table 6
Rates of AEs in ADNI by time point

AE	6 Mo %Pts	12 Mo %Pts	18 Mo %Pts	ADNI* comments AE term (n)
Fall	6.8	13.2	16.8	
Asthenia	3.2	7.9	12.6	
Depressed mood	7.4	8.9	12.1	
Diarrhea	4.7	8.4	11.6	
Cough	5.3	6.8	10.0	
Dizziness	3.7	6.3	10.0	
Somnolence	4.7	7.9	10.0	
Pollakiuria	4.7	7.4	9.5	
Arthralgia	4.2	6.8	8.4	
Depression	5.3	7.4	8.4	Depression (15), major depression (1)
Back pain	4.7	6.3	7.9	
Crying	4.2	6.3	7.4	
Dry mouth	1.1	3.7	5.8	
Dyspnea	2.6	4.2	5.8	
Headache	1.6	4.7	5.3	
Musculoskeletal pain	2.6	3.7	5.3	
Rash	3.2	4.7	5.3	Rash (9), pruritic rash (1)
Skin cancer	2.1	5.3	5.3	Squamous cell (3), basal cell (4), malignant melanoma(1), skin cancer NOS (2)
Constipation	1.6	4.2	4.7	
Restlessness	1.6	2.6	4.7	
Bone fracture	0.5	3.2	4.7	1 each of ankle, hip, jaw, spinal, rib, radius, clavicle, upper limb, sacrum
Incontinence	1.1	1.6	4.2	Incontinence (2), urinary incontinence (2), fecal incontinence (4)
Nausea	0.5	1.6	4.2	
Syncope	2.1	2.6	4.2	Syncope (7), loss of consciousness (1)
UTI	3.2	3.7	4.2	UTI (7), cystitis (1)
Chest pain	1.6	2.1	3.7	
Joint swelling	1.6	2.1	3.7	
Vomiting	0.5	2.1	3.7	
Arrhythmia-related events	1.1	2.6	3.2	1 each of arrhythmia, atrial fibrillation, bradycardia, palpitations, sinus arrhythmia, ventricular extrasystoles
Abdominal discomfort	1.1	2.1	3.2	Abdominal pain (1), abdominal discomfort (5)
Agitation	0.0	1.6	3.2	
Anxiety	1.6	2.1	3.2	
Hyperhydrosis	1.1	1.6	3.2	
Insomnia	0.5	1.1	3.2	
Cataract	1.6	2.6	2.6	Cataract operation (3), cataract (2)
Seizures	0.5	1.1	2.6	Convulsion (5)
Anemia	0.0	0.5	2.1	
Blurred vision	1.1	1.6	2.1	
Fatigue	1.6	1.6	2.1	
Gait disturbance	1.1	1.6	2.1	
Hypersomnia	1.1	2.1	2.1	
Malignancy	1.6	1.6	2.1	1 each of adenocarcinoma, bladder cancer, multiple myeloma, prostate cancer
Paranoia	0.5	1.1	2.1	Paranoia (1), delusion (2), visual hallucination (1)
Pneumonia	0.0	1.1	2.1	Pneumonia (3), pneumonia bacterial (1)
Visual complaints	0.5	1.6	2.1	1 each of altered depth perception, phosphene, maculopathy, macular degeneration
Hypertension	1.1	1.6	1.6	
Stroke or TIA	0.5	1.6	1.6	1 each of CVA, TIA, cerebral hemorrhage
URI	0.5	1.1	1.6	URI (1), sinusitis (2)
Nasopharyngitis	0.5	0.5	1.1	

(*Continued*)

Table 6
Rates of AEs in ADNI by time point (*Continued*)

AE	6 Mo %Pts	12 Mo %Pts	18 Mo %Pts	ADNI* comments AE term (n)
Skin laceration	0.5	0.5	1.1	
Weight loss	0.0	0.5	0.5	Weight decreased
Rhinitis	0.5	0.5	0.5	Rhinorrhea

% Pts = percentage of enrolled baseline patients (N = 190). ADNI actual terms manually mapped to MedDRA v12.0 by authors.
*Adverse events occurring in ≥2% of patients, all timepoints combined; actual terms manually mapped to MedDRA by authors.

18-month time points; however, below-mentioned differences in the ADNI population compared with patients enrolling in potentially therapeutic drug trials need to be considered.

One consideration when anticipating discontinuation rates in 18-month studies of potentially disease-modifying therapies for AD is the sometimes inaccurate expectations of the caregiver and patient. On hearing the phrase "potentially disease-modifying," there may be a false expectation for improvement of AD rather than slowing of progression. Because an individual patient's future rate of progression is unknown, caregivers and patients may withdraw from studies that are burdensome with no apparent "improvement." This reason for discontinuation is commonly combined in the study database with "patient/caregiver decision" and is usually not listed separately in publications. Therefore, attempts to minimize discontinuation in 18-month studies of potentially disease-modifying therapies for AD should include education by investigators that longer periods of treatment will increase any potential benefit from these therapies but "improvement" or drug efficacy will not be immediately apparent.

Taken as a whole, these data suggest that when designing a large international study of a potentially disease-modifying treatment lasting at least 18 months in patients with AD, researchers should anticipate higher rates of discontinuation for power and sample size calculations. Schneider and Sano [10] had similar findings in their review of completed 18-month AD studies; in general, studies with higher numbers of sites had higher placebo discontinuation rates, although broader geographic representation of sites did not portend higher rates of discontinuation.

Rates of SAEs and deaths were consistent for placebo patients across the five AD treatment trials and patients in the ADNI database, suggesting that these rates are reliable for providing context to blinded safety reviews during ongoing AD trials over 18 months.

The comparisons of AEs across the published treatment studies proved problematic based on distinct reporting thresholds and disparate or undesignated coding methods, precluding a complete evaluation and comparison of the data. In contrast, patient-level ADNI safety data were publicly available in toto, and the authors were able to analyze the complete data set, including any uncommon events. In addition, the authors were able to combine clinically similar AEs to get a more accurate estimate of the AE rates (e.g., rash = rash + pruritic rash; or depression = major depression + depression).

When using these data for comparison with blinded safety data from ongoing trials, AE frequencies that occur in at least two studies at a similar rate are the most likely to be reliable. If the rate of an AE or SAE of interest differs among the studies in this review, the range of frequencies should be used as context. For example, where ADNI AEs were ≥3%, rates of dyspnea, headache, constipation, nausea, joint swelling, vomiting, and anxiety were similar among trials, suggesting that these background rates are the most reliable for patients with AD followed up for 18 months. For AE rates that differed substantially among trials, the highest rates across trials are the most conservative estimates for planning, and the range should be used to put findings from blinded safety reviews in context.

Table 6 summarizes ADNI AE data for mild AD patients observed for 6 months and 12 months and makes comparisons with the 18-month data previously reported in Table 3. This may be helpful for researchers monitoring blinded safety data in AD studies of shorter duration. However, the below-mentioned differences in the ADNI population compared with patients enrolling in potentially therapeutic drug trials need to be considered. Overall, the AE rates increase with longer observation periods, with fall, asthenia, depressed mood, diarrhea, cough, dizziness, and somnolence being most commonly reported in slightly variable order across the 6-, 12-, and 18-month time points.

Although the data contained in this review may be useful, several limitations in interpretation exist. First, as previously mentioned, the published data are limited by differing reporting thresholds between articles, leaving obvious gaps in the reported safety data. Second, this article reviews safety data for mild-to-moderate AD patients. Although beyond the scope of this article, an interesting follow-up review could summarize the safety data for the approximately 400 MCI subjects in ADNI. The mild AD ADNI patients summarized herein are a relatively small sample (N = 190). In addition, patients who chose to participate in the ADNI study are likely to differ from those who chose to participate in an active AD treatment trial. The ADNI patients did not expect to receive treatment, and many agreed to multiple invasive biomarkers, such as MRI, positron emission tomography scans, and lumbar puncture. Thus, these patients were motivated differently than those enrolling in an active treatment trial.

Therefore, the reported AEs in ADNI may not accurately predict what will be seen in an 18-month active treatment trial for AD. In addition, the ADNI sites were limited to North America and included mainly academic sites, whereas several of the published studies occurred in various geographies and included nonacademic clinical trial sites. Because of these limitations, a larger data set of placebo patients from potentially disease-modifying AD treatment studies is needed to summarize and fully characterize the expected safety profile of an AD population over 18 months. Fortunately, several such safety databases should become available in the future. The Alzheimer's Disease Cooperative Study (ADCS) was formed in 1991 as a cooperative agreement between the NIA and the University of California, San Diego. The ADCS includes research centers in the United States and Canada and is a major initiative for AD clinical studies in the U.S. federal government, addressing treatments for both cognitive and behavioral symptoms. The ADCS was developed in response to a perceived need to advance research in the development of drugs that might be useful for treating patients with AD, particularly drugs that might not be developed by industry [26]. The ADCS will compile, and make available, full placebo data sets (approximate N = 1100) from several studies lasting at least 18 months (J. Siuciak, personal communication, March 2011).

In addition, a similar database of placebo-treated AD patients has been compiled by the Critical Path Institute (C-Path), a private, nonprofit organization created by the University of Arizona and the U.S. FDA in 2005 that is dedicated to supporting the FDA's Critical Path Initiative [27]. The Critical Path Initiative is the "FDA's national strategy to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured" [28]. The C-Path Online Data Repository is currently available and contains deidentified data from >4000 placebo-treated patients from 11 AD clinical trials [29]. Although AE data will ultimately be included in this database, they are not yet available.

The ADCS and C-Path pooled placebo AD databases will avoid many of the limitations of the currently available data. The databases will be larger than currently available data from ADNI or published 18-month studies, including patients who chose to enroll in active treatment studies, and complete patient-level safety data will be available for analysis, thereby avoiding the problems with disparate reporting thresholds contained in the published AD studies summarized in this article. The authors have submitted a proposal to the ADCS to evaluate and summarize the safety data from their database using methodology similar to that used with the ADNI database described herein.

5. Conclusions

Designing and monitoring studies to assess potentially disease-modifying AD treatments is made challenging by an elderly patient population with multiple medical comorbidities that can adversely impact discontinuation rates and complicate determination of new safety signals. Cumulative background rates of deaths, SAEs, and discontinuation can be considerable in an AD patient population during the 18 months necessary to evaluate potentially disease-modifying drugs. Understanding expected rates of SAEs, deaths, and discontinuations can help in the calculation of power and sample size for trials of patients with AD and aid researchers monitoring safety in ongoing blinded trials. Although the data provided in this article are a useful starting point, future summaries of the safety data from pooled placebo AD databases, such as those from ADCS and C-Path, will extend the understanding of background safety events in AD populations substantially.

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