

Pharmacologic Agents Associated with a Preventive Effect on Alzheimer's Disease: A Review of the Epidemiologic Evidence

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Abbreviations: COX, cyclooxygenase; GABA, γ -aminobutyric acid; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HRT, hormone replacement therapy; H₂, histamine 2; NSAID, nonsteroidal anti-inflammatory drug.

INTRODUCTION

Alzheimer's disease is the most common subtype of dementia. This disease is diagnosed in approximately two thirds of all cases of dementia (1). According to current diagnostic criteria, a diagnosis of Alzheimer's disease is considered probable when alternative causes of dementia have been excluded (2, 3). A clinical diagnosis of dementia is often made according to the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) criteria for dementia, with a subdiagnosis of Alzheimer's disease made according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (2). The pathogenesis of Alzheimer's disease is largely unknown. In short, the most frequently used explanation is that unknown genetic or environmental factors initiate a cascade of neuropathologic events that feature accumulation of β -amyloid and neurofibrillary tangles. This process is clinically characterized by a long latent phase, then a prodromal stage with a gradual and progressive decline in long-term episodic memory and impairment of other cognitive domains of mental functioning (4). Eventually, the person crosses a threshold of cognitive loss, after which the full syndrome is evident (5).

Many patients with Alzheimer's disease have signs of cerebrovascular disease on magnetic resonance imaging, which may contribute to the clinical manifestations of their dementia. Age, depression, low educational level, atherosclerosis, vascular factors (6–8), and smoking (9) are associ-

ated with an increased risk of Alzheimer's disease. In addition, a growing number of genetic factors have been implicated in Alzheimer's disease, including dominant mutations (amyloid precursor protein, presenilins 1 and 2) and susceptibility genes (apolipoprotein E and others under investigation, such as α_2 -macroglobulin) (10, 11).

Currently, the goal in managing patients with Alzheimer's disease is to maximize cognition and overall functioning, which involves a combination of strategies that include education, training, family support, behavioral interventions, and pharmacotherapy. However, the fact that the pathogenesis of Alzheimer's disease is largely unknown makes it difficult to develop effective pharmacotherapy. Until recently, the pharmaceutical industry has focused mainly on cholinergic agents, since a cholinergic neurotransmitter deficit has been held partly responsible for cognitive deterioration. The US Food and Drug Administration approved the drugs tacrine, donepezil hydrochloride, and rivastigmine (12). Recent progress in delineating the disease cascade has made it easier to define potential targets for pharmacologic prevention. This fact is important because, in the long run, the opportunity to prevent or delay onset of clinically apparent Alzheimer's disease is considerably more appealing than symptomatic therapies that may prolong illness with only marginal improvement in quality of life. Therefore, this review focuses on the potential preventive role of pharmacologic agents in the latent and prodromal stages of the disease (13) and not on treatment of Alzheimer's disease.

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METHODS

For this review, we searched PUBMED/MEDLINE (National Institutes of Health, Bethesda, Maryland) until April 2002 by using the terms "drugs" or "pharmacology" on the one hand combined with "dementia" or "Alzheimer's disease" on the other. We also combined the latter two terms with all individual drugs mentioned in this review. Furthermore, we scrutinized the Internet and US congressional material, and we used information from personal communications with the authors regarding the observational and experimental studies mentioned in this review, when possible. We included reviews, data from clinical trials, and observational studies with a reference group as long as the results were published in English, French, German, or Dutch medical journals. Although we included some data from studies without reference groups, case reports and case series were excluded. Throughout our review, we gave priority to well-designed, prospective, double-blind, randomized clinical trials and to prospective cohort studies with incident cases of Alzheimer's disease and complete histories of drug exposure, because they have the highest credibility. Nevertheless, we also covered retrospective case-control studies, historical cohort studies, and cross-sectional studies. Because of the importance of prospective, randomized, double-blind trials, they are discussed under a separate heading. Furthermore, we divided observational studies into those with prevalent cases and those with incident cases because the latter are less vulnerable to bias.

Most drugs currently considered potentially beneficial act as modulators of neurotransmission, atherosclerosis, or inflammation. Consequently, we discuss studies on the association between Alzheimer's disease and 1) nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin; 2) glucocorticoids and other drugs with anti-inflammatory properties; 3) estrogens, in the form of hormone replacement therapy (HRT); 4) histamine 2 (H₂)-receptor antagonists; 5) antihypertensive agents; 6) cholesterol-lowering agents; 7) benzodiazepines; and 8) free-radical scavengers. Subsequently, in the different sections of this review for each drug group, we discuss the putative mechanism by which these drugs might prevent Alzheimer's disease and discuss the most relevant studies. Finally, we systematically summarize and classify the overall evidence and discuss potential future developments.

EPIDEMIOLOGY OF DRUGS IN THE ONSET OF ALZHEIMER'S DISEASE

NSAIDs and aspirin

Biologic rationale. NSAIDs are prescribed for a variety of conditions. Indications for chronic use are (inflammatory) joint diseases such as rheumatoid arthritis and osteoarthritis or other systemic diseases. NSAIDs include salicylates, phenylacetic acid derivatives, propionic acid derivatives, oxicam derivatives, pyrazolone derivatives, and a small group of other compounds. Their best-known common characteristic is (non)specific inhibition of cyclooxygenase (COX): COX-1 and/or COX-2. Strong and compelling evidence now exists that a number of inflammatory mechanisms are intimately involved in the development of

Alzheimer's disease (14, 15). These mechanisms include activation of the complement cascade; up-regulation of a number of acute-phase proteins, cytokines, and chemokines, and their receptors; and reactive astrogliosis and microgliosis. At the very least, this makes it conceivable that neuroinflammation exacerbates Alzheimer's disease pathology. Targeted to the relevant and appropriate neuroinflammatory process, anti-inflammatory drugs may be useful in either delaying onset or slowing the progression of Alzheimer's disease (16). The various biologic activities of NSAIDs make the precise mechanism of a beneficial effect uncertain. However, several theories exist regarding how NSAIDs (and aspirin) could alter this inflammatory course: the first is inhibition of inflammation per se through either a COX- or a non-COX-dependent mechanism by directly activating the peroxisome proliferator-activated receptor-gamma nuclear transcription factor (17–19). This factor acts to suppress expression of certain proinflammatory genes (18, 20). Another theory is that NSAIDs interfere in a process involving postsynaptic signaling events that use the arachidonic pathway (21). NSAIDs suppress the action of COXs, which catalyze synthesis of prostaglandins. The latter have a role in the postsynaptic signal transduction cascade of cells with *N*-methyl D-aspartate-type glutamate receptors. They may also potentiate glutamatergic transmission by inhibiting astrocytic reuptake of glutamate. Both mechanisms can potentiate excitotoxic cell death. Alzheimer's disease may also be a consequence of impaired vascular delivery of nutrients to the brain (22). Another suggested mechanism is the inhibition of local inflammation by blocking induction of interleukin-1, interleukin-1 β , and possibly interleukin-6 (23, 24). Finally, there is recent evidence that a subcategory of NSAIDs suppresses the formation of amyloid- β 42, possibly through a change in γ -secretase activity, while others do not (25).

Studies with prevalent cases. The association of anti-inflammatory therapy with Alzheimer's disease has been studied in a number of ways (table 1). Initial case-control studies examined the association indirectly by using proxies of anti-inflammatory drug therapy, such as rheumatoid arthritis, as the exposure measure (26–34). These studies have been reviewed extensively elsewhere (35, 36). Results of these studies were conflicting but also largely incomparable.

In other studies, the association between a history of anti-inflammatory drug therapy and Alzheimer's disease was examined. Several older case-control studies in which use of analgesics (including acetaminophen) was examined were also inconclusive (37, 38). Two studies on subjects with a shared genetic background (twins and siblings) provided support for a protective role of NSAIDs in Alzheimer's disease (39, 40). In both studies, there was evidence that (long-term) use of NSAIDs significantly reduced the risk of Alzheimer's disease. A number of (population-based) studies on the cross-sectional association between NSAIDs and prevalent Alzheimer's disease show an inverse association (41–44), with an effect size ranging from 0.4 to 0.6.

Studies with incident cases. Several incidence studies on the association between NSAIDs and Alzheimer's disease have been published (43, 45–51) (table 1). Some found no association between NSAIDs use and the risk of Alzheimer's

TABLE 1. Studies on anti-inflammatory drugs

Author(s), year (reference no.)	Exposure*	Exposure source	Design	Case source	Control source	RR†/OR† (95% CI†) or probability
<i>Studies of prevalent Alzheimer's disease</i>						
Heyman et al., 1984 (27)	Arthritis	Interview	Matched case-control	Epidemiologic study group (<i>n</i> = 40)	Community	1.19 (NS)
	Ever use of analgesics					1.23 (NS)
French et al., 1985 (30)	Arthritis	Interview with random reconfirmation	Matched case-control	Veterans Administration Medical Center (<i>n</i> = 78)	Hospital and nonhospital controls	0.62 (0.29, 1.29) (hospital controls)
	Hay fever					2.75 (0.81, 10.22)
Amaducci et al., 1986 (37)	Ever use of analgesics	Next of kin	Matched case-control	Consecutive Alzheimer's disease patients of seven neurology centers (<i>n</i> = 116)	Hospital	1.21 (NS)
Jenkinson et al., 1989 (31)	Rheumatoid arthritis	Presence of rheumatoid arthritis according to accepted criteria	Case-control	Consecutive patients of a geriatric unit (<i>n</i> = 96)	Friend	1.0 (NS)
					Consecutive patients of geriatric unit	0.17 (<i>p</i> < 0.005)
Broe et al., 1990 (26)	Arthritis	Interview	Matched case-control	Clinic based (<i>n</i> = 170)	General practitioner practice of corresponding case	0.56 (0.36, 0.87)
	Allergies					0.97 (0.60, 1.58)
Graves et al., 1990 (28)	History of steroid use	Telephone interviews with patients' and controls' surrogates	Matched case-control	Clinic based (<i>n</i> = 130)	Friends and nonblood relatives	0.73 (0.38, 1.38)
	Rheumatoid arthritis					1.18 (0.35, 3.91)
McGeer et al., 1990 (33)	Rheumatoid arthritis	Presence of rheumatoid arthritis	Incidence study	Clinic based (<i>n</i> = 4)	None, but referenced to the Canadian Study of Health and Aging	2.7% vs. 5.1%
Beard et al., 1991 (32)	Rheumatoid arthritis	Presence of rheumatoid arthritis	Incidence study	Clinic based (<i>n</i> = 23)	Reference to other clinical population	4.4% vs. 2.7%
McGeer et al., 1992 (67)	Continuous use of dapsone or closely related agents	Current use	Cohort	Living leprosy patients in Japan (<i>n</i> = 151, all dementia)	Living leprosy patients in Japan	0.63 (0.43, 0.92)
Li et al., 1992 (29)	Arthritis (before onset)	Interview of relatives	Matched case-control	Clinic based (<i>n</i> = 70)	Registration offices in neighborhoods	0.2 (0.06, 0.70)
	Analgesics (≥2 years' use)					1.0 (0.09, 11.03)
Henderson et al., 1992 (38)	Analgesics (ever daily use for >6 months)	Interview of an informant	Matched case-control	General practitioner practice (<i>n</i> = 170) consecutive referrals	General practitioner practice	1.4 (<i>p</i> = 0.05), early onset
						0.5 (NS), late onset
Canadian Health Study, 1994 (41)	Arthritis	Questionnaires completed by proxy respondents	Nested case-control	Communities and institutions (<i>n</i> = 224)	Communities and institutions	0.55 (0.37, 0.82)
	NSAID†					0.75 (0.39, 1.46)
	Steroids					0.54 (0.36, 1.46)

Table continues

disease (43, 45, 46, 48, 51), whereas others showed a nonsignificant trend toward a reduced risk in persons with a history of NSAID use (49, 50). The relative risk of Alzheimer's disease was assessed among reported users of aspirin or

other NSAIDs during a long-term follow-up in the Baltimore Longitudinal Study of Aging. The risk of Alzheimer's disease decreased with increasing duration of NSAID use. Among those subjects with 2 or more years of reported

TABLE 1. Continued

Author(s), year (reference no.)	Exposure*	Exposure source	Design	Case source	Control source	RR†/OR† (95% CI)† or probability
Breitner et al., 1994 (39)	Anti-inflammatory drugs (use for >1 year; began >2 years before onset)	Self-reporting or, if not possible, from surrogates	Co-twin control	Male and female twins from the United States	Male and female twins from the United States	1.0 (0.21, 4.73) (male)
						0.0 (0.01, 0.43) (female)
Breitner et al., 1995 (40)	NSAID (duration)	Interview of unaffected persons and/or collateral information	Sibship study	Siblings (n = 107)	Siblings	0.19 (0.06, 0.64)
	Steroids Aspirin					0.63 (0.12, 2.63) 0.34 (0.14, 0.84)
Rich et al., 1995 (34)	NSAID daily for 12 months	Interview	Cohort	Cohort of Alzheimer's disease patients	NA†	Better performance on MMSE,† Boston Naming Test, and others
Andersen et al., 1995 (42)	NSAID (use in past week, dose)	Interview of subjects and/or proxy informants	Population-based cohort study	Cohort (n = 339)	Population-based cohort (total)	0.38 (0.15, 0.95)
					Topical medication users (subgroup)	0.54 (0.16, 1.78)
Endoh et al., 1999 (68)	Dapsone, rifampicin, clofazimine, minomycin, or ofloxacin	Medical files	Cohort	Leprosy patients of the national leprosarium in Tokyo, Japan (n = 35)	Leprosy patients of the national leprosarium in Tokyo, Japan	0.79 (0.53, 1.84)
						3.37 (1.87, 5.97), <80 years
Anthony et al., 2000 (44)	NSAID	Interview/medicine chest inventory	Case-control	Cache County, Utah, cohort (n = 201)	Cache County, Utah, cohort	0.47 (0.24, 0.90)
<i>Studies of incident Alzheimer's disease</i>						
Kukull et al., 1994 (45)	NSAID (5 years prior)	Computerized pharmacy data	Case-control	Alzheimer's disease patient registry health maintenance organization (n = 268)	Health maintenance organization	
	Ever >180 daily doses					0.8 (0.6, 1.2) 1.1 (0.7, 1.8)
Fourrier et al., 1996 (46)	NSAID use (both at baseline and 1 year later)	Repetitive interviews	Prospective population-based cohort study	Random sample of the population of France (n = 47)	Random sample of the population of France	0.98 (0.23, 4.16)
Stewart et al., 1997 (47)	NSAID (<2 years)	Repetitive interviews	Nested case-control in the Baltimore Longitudinal Study of Aging	Volunteers (n = 81)	Volunteers	0.65 (0.33, 1.29)
	NSAID (≥2 years)					0.40 (0.19, 0.84)
	Aspirin (<2 years)					0.58 (0.28, 1.18)
	Aspirin (≥2 years)					0.82 (0.50, 1.36)

Table continues

NSAID use, the relative risk was lower than for those who used NSAIDs for less than 2 years. Overall use of aspirin and acetaminophen was not associated with Alzheimer's disease (47). In a larger and more recent investigation from the Rotterdam Study, a similar observation was made with

respect to the use of NSAIDs, but not for aspirin (52). Use of NSAIDs for more than 2 years was associated with an 80 percent risk reduction. This study had the advantage of the availability of unbiased drug dispensing data and a larger set of incident cases. As a consequence, misclassification of

TABLE 1. Continued

Author(s), year (reference no.)	Exposure*	Exposure source	Design	Case source	Control source	RR†/OR† (95% CI)† or probability
Henderson et al., 1997 (48)	NSAID, aspirin	Interview	Prospective cohort study	Community	Community	NS
Beard et al., 1998 (49)	NSAID, aspirin for ≥ 7 days in the 2 years before onset	Medical records	Matched case-control	Clinic based ($n = 302$)	Clinic	0.47 (0.20, 1.10), NSAID 0.90 (0.51, 1.59), NSAID + aspirin
Brooks et al., 1998 (43)	NSAID (current use), aspirin	Interview	Prospective cohort study	Community (8.4% = 53)	Community	NS
Cornelius et al., 1998 (51)	NSAID taken regularly	Interview	Prospective population-based cohort study	Cohort ($n = 110$)	Cohort	0.8 (0.4, 1.9)
in 't Veld et al., 1998 (50)	NSAID (in the 10 years before diagnosis)	General practitioners' medical records	Nested matched case-control study within the Rotterdam Study	Cohort ($n = 101$)	Cohort (population based)	
	<2 months					0.76 (0.37, 1.57)
	2–6 months					0.97 (0.44, 2.17)
	>6 months					0.27 (0.05, 1.51)
in 't Veld et al., 2001 (52)	NSAID (8-year follow-up)	Pharmacy filling records	Prospective population-based cohort study	Cohort ($n = 293$)	Cohort (population based)	
	<1 month					0.95 (0.70, 1.29)
	1–24 months					0.83 (0.62, 1.11)
	>24 months					0.21 (0.05, 0.83)
<i>Trials</i>						
Rogers et al., 1993 (54)	Randomization to placebo or indomethacin	NA	Placebo-controlled secondary prevention trial	Volunteer Alzheimer's disease cases ($n = 44$)	NA	Significantly better performance on cognitive tests ($p < 0.003$)
Scharf et al., 1999 (55)	Randomization to placebo or diclofenac/misoprostol	NA	Placebo-controlled secondary prevention trial	Volunteer Alzheimer's disease cases ($n = 41$)	NA	Test-battery: no significant differences in intention-to-treat analyses
Aisen et al., 2000 (70)	Randomization to placebo or prednisone (10 mg) for 1 year	NA	Placebo-controlled secondary prevention trial	Volunteer Alzheimer's disease cases ($n = 138$)	NA	No difference on ADAS-cog† ($p = 0.16$) Behavioral decline in treatment group

* Exposure or exposure proxied by disease.

† RR, relative risk; OR, odds ratio, CI, confidence interval; NS, nonsignificant; NSAID, nonsteroidal anti-inflammatory drug; NA, not applicable; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale.

exposure was less of a problem. A phenomenon observed in the Baltimore, Maryland, study; the Rotterdam Study; and a yet-unpublished study from Cache County, Utah, was that NSAIDs may offer protection until only a few years before the actual diagnosis (13).

Studies on NSAIDs are particularly vulnerable to misclassification of exposure. Because NSAIDs are often used periodically and to a different extent by different age groups, it is difficult to obtain reliable information on exposure. Reliable and valid data might be particularly difficult to obtain from proxy interviews (48). Over-the-counter sales may reduce

the validity of medical and pharmacy records as sources of drug exposure. In general, measurement of exposure has been a problem to some extent in all follow-up studies on NSAIDs. In some studies, duration was not taken into account at all (43, 45, 46, 48, 49, 51). In others, and if assessed, the methodology used to measure duration of exposure may have introduced misclassification bias. Repeated cross-sectional measurements could have led to an overestimation of drug use (47). In earlier analyses in the Rotterdam Study, the missing duration of individual prescriptions was imputed, which might have led to system-

atic or random misclassification (50). A problem in almost all studies was that it was unclear which particular NSAID was responsible for the risk reductions observed. Furthermore, only a few studies (47, 50, 52) took into account the timing of intake in relation to time of onset; this difference may be important given the unknown duration of the latent and prodromal stages of Alzheimer's disease.

Finally, confounding by indication and contraindication may be important. First, pain perception and expression may be different in those becoming cognitively impaired or in demented subjects (53). If either pain perception or expression is impaired in (those developing) Alzheimer's disease, this impairment may lead to a lesser use of NSAIDs and an ostensible protective effect of NSAIDs. In addition, because of the higher chance of adverse events in cognitively impaired subjects, physicians may be less likely to prescribe NSAIDs in the preclinical and clinical phases of Alzheimer's disease. On the other hand, prescription behavior may be influenced by early publications on potential beneficial effects of NSAIDs.

Clinical trials. To our knowledge, no primary prevention trials have been published on anti-inflammatory drugs and Alzheimer's disease. A 6-month secondary prevention trial on indomethacin in Alzheimer's disease showed that patients performed significantly better on a battery of cognitive tests after 6 months of therapy compared with placebo (54). However, a large number of participants reported adverse effects; consequently, the dropout rate was high. Currently, an attempt is being made to reproduce these results in a larger multicenter study in the Netherlands (unpublished data). The efficacy and safety of diclofenac in combination with misoprostol were evaluated in 41 patients with mild-to-moderate Alzheimer's disease in a prospective, 25-week, randomized, double-blind, placebo-controlled trial (55). This small pilot study did not demonstrate a significant effect of NSAID treatment in Alzheimer's disease but observed trends that justify further investigations with a larger number of participants. Before more definite conclusions can be drawn, final results of studies on COX-2 inhibitors are awaited (56, 57) but do not appear to be promising (58). However, it is questionable whether it is valid to extrapolate findings of these trials to primary prevention. Therefore, we must await the results from the recently initiated Alzheimer's Disease Anti-Inflammatory Prevention Trial (59). This trial, estimated to last for 6 years, is designed to test naproxen and celecoxib for their ability to prevent Alzheimer's disease. The uncertainty regarding the target mechanism and the absence of a well-accepted model for Alzheimer's disease-type neuroinflammation may have contributed to the decision to treat subjects with either a selective or a nonselective NSAID.

Studies on aspirin have focused mainly on stroke, showing a protective effect in secondary prevention (60). Whether and to what extent this protective effect can be extrapolated to nonvascular dementia and, in particular, to Alzheimer's disease remains to be elucidated.

Glucocorticoids and other anti-inflammatory drugs

Biologic rationale. Glucocorticoids are used mainly to treat noninfectious inflammatory systemic diseases and for chronic obstructive pulmonary disease. These potent anti-inflammatory/immunosuppressive drugs are also used to suppress inflammatory processes in the brain. They suppress acute-phase response neutrophil adherence and monocyte accumulation as well as inhibit prostaglandin production (61). However, doses commonly used to suppress secondary brain inflammation in other diseases are toxic with long-term treatment and lead to a high incidence of severe adverse effects such as osteoporosis, behavioral disturbances, and other problems (62, 63). It has been suggested that glucocorticoids may be toxic to the hippocampus (64, 65), a vital memory structure. Moreover, postmortem studies in non-Alzheimer's subjects suggest that corticosteroids, in contrast to NSAIDs, do not seem to reduce microglial activation (66).

Studies with prevalent cases. Thus far, only a few epidemiologic studies exist on the association between glucocorticoid use and Alzheimer's disease (table 1). In a twin study, onset of Alzheimer's disease was inversely associated with prior concomitant use of corticosteroids or adrenocorticotropic (ACTH) (39). In a larger study of siblings who had a high risk of Alzheimer's disease, no significant difference in risk was found after exposure to glucocorticoids (40). Two other studies that were considerably larger (28, 41), one of which was population based (41), did not find a significant association (table 1). In a review on the role of anti-inflammatory drugs in Alzheimer's disease, pooling of data from the above studies yielded a significant inverse association (36).

In a Japanese study on leprosy, the anti-inflammatory/bacteriostatic agent dapsone (diaphenylsulfone) seemed to have a protective effect on dementia (67). In a more recent study from Japan of prevalent Alzheimer's disease cases, in which a variety of antileprosy drugs were investigated, this protective effect was not confirmed (68). In subjects less than 80 years of age, there was an increased risk of Alzheimer's disease in users.

Clinical trials. Results from the secondary prevention Multicenter Trial of Prednisone in Alzheimer's Disease (69) have recently become available (70) (table 1). A total of 138 subjects were randomly assigned to receive either placebo or an initial dose of 20 mg of prednisone, tapered after 4 weeks to 10 mg and continued for a year. There were no differences in performance on the cognitive subscale of the Alzheimer's Disease Assessment Scale. However, prednisone-treated subjects showed a behavioral decline compared with the placebo group.

A trial on the effect of hydroxychloroquine on progression of Alzheimer's disease revealed no beneficial effect after 18 months of treatment (71). Finally, colchicine, normally prescribed for gout, has been proposed as a potential beneficial agent in Alzheimer's disease (72), and secondary prevention trials in Alzheimer's disease have been started.

Where do we stand now with respect to the overall evidence regarding anti-inflammatory drugs in Alzheimer's disease? Given the current research, it seems unlikely that corticosteroids will be of great benefit in preventing Alz-

TABLE 2. Studies on hormone replacement therapy

Author(s), year (reference no.)	Exposure	Exposure source	Design	Case source	Control source	RR*/OR* (95% CI*) or probability
<i>Studies in prevalent Alzheimer's disease</i>						
Heyman et al., 1984 (27)	Ever HRT* in the last 3 months	Interview	Matched case-control	Epidemiologic study group (n = 28)	Community	2.32 (NS*)
Amaducci et al., 1986 (37)	Ever HRT	Interview next of kin	Matched case-control	Seven centers (n = 116)	Hospital/population	Hospital: 0.71 (NS) Population: 1.67 (NS)
Graves et al., 1990 (28)	Ever HRT	Telephone interviews with patients' and controls' surrogates	Matched case-control	Clinic based (n = 60)	Friends and nonblood relatives	1.15 (0.50, 2.64)
Broe et al., 1990 (26)	Ever HRT	Interview	Matched case-control	Clinic based (n = 106)	General practice of corresponding case	0.78 (0.39, 1.56)
Henderson et al., 1994 (90)	Ever HRT	Interview nondemented subjects and primary Alzheimer's disease caregivers	Case-control	Volunteer sample of consecutively enrolled women (n = 143)	Volunteer sample of consecutively enrolled women	0.33 (0.15, 0.74)
Birge, 1994 (88)	Current use and duration of HRT	Interview	Matched case-control	Clinic (n = 158)	Clinic	0.07 (p < 0.01)
Mortel and Meyer, 1995 (89)	Ever HRT	Medical record/proxy informant	Case-control	306 subjects referred to clinic (n = 93)	Friend/relative	0.53 (0.27, 0.94)
Lerner et al., 1997 (91)	Ever HRT	Interview nondemented subjects and primary Alzheimer's disease caregivers	Case-control	Unknown (n = 88)	Unknown	0.58 (0.25, 0.91)
Balderischi et al., 1998 (87)	Ever HRT	Interview	Population-based cohort	8 municipal population registers (n = 92)	8 municipal population registers	0.28 (0.08, 0.98)
Slooter et al., 1999 (93)	Ever HRT	Interview next of kin	Matched case-control	All patients with early-onset Alzheimer's disease in two regions of the Netherlands (n = 109)	Municipal population register	0.44 (0.21, 0.96)
<i>Studies in incident Alzheimer's disease</i>						
Brenner et al., 1994 (92)	All HRT before onset	Computerized pharmacy data for a maximum of 15 years	Case-control	Alzheimer's disease registry from health plan population (n = 107)	Stratified random sample of health plan population	1.1 (0.6, 1.8)
	Oral HRT before onset					0.7 (0.4, 1.5)

Table continues

heimer's disease (70). Although some clinicians already recommend NSAIDs as a primary or secondary preventive agent for Alzheimer's disease and available evidence is strong and increasing, we do not think that the evidence warrants their preventive prescription yet. To draw more definite

conclusions, results from the earlier-mentioned Alzheimer's Disease Anti-Inflammatory Prevention Trial and others must be awaited. In addition, the focus has to be on NSAID groups with a potential effect on peroxisome proliferator-activated receptor and amyloid formation.

TABLE 2. Continued

Author(s), year (reference no.)	Exposure	Exposure source	Design	Case source	Control source	RR*/OR* (95% CI*) or probability
Paganini-Hill and Henderson, 1996 (111)	HRT for ≤ 3 years	Interview (repetitive)	Nested matched case-control	Retirement community ($n = 248$)	Retirement community	0.83 (0.56, 1.22)
	HRT for 4–14 years					0.50 (0.31, 0.81)
	HRT for ≥ 15 years					0.44 (0.26, 0.75)
Tang et al., 1996 (96)	HRT for ≤ 1 year	Interview	Prospective cohort	Medicare recipients, senior centers, and elderly housing sites ($n = 167$)	Medicare recipients, senior centers, and elderly housing sites	0.47 (0.2, 1.10)
	HRT for > 1 year					0.13 (0.02, 0.92)
Kawas et al., 1997 (97)	HRT for > 0 –5 years	Repetitive interviews	Cohort	Community volunteers ($n = 34$)	Community volunteers	0.44 (0.12, 1.51)
	HRT for 5–10 years					0.34 (0.05, 2.52)
	HRT for > 10 years					0.50 (NS)
Waring et al., 1999 (98)	HRT for < 6 months	Review of medical records	Matched case-control	Mayo clinic residents of Rochester, Minnesota ($n = 222$)	Sample from the Rochester population	0.85 (0.44, 1.62)
	HRT for ≥ 6 months					0.42 (0.18, 0.96)
in 't Veld et al., 2000 (99)	HRT for < 12 months	Interview	Prospective cohort	All new female patients from population-based cohort ($n = 79$)	Cohort	0.9 (0.37, 2.21)
	HRT for ≥ 12 months					1.03 (0.32, 3.30)
<i>Trials</i>						
Schneider et al., 1996 (106)	HRT/tacrine	NA*	Randomized placebo-controlled secondary prevention trial	Multicenter ($n = 318$)	NA	Enhancement of tacrine effect by estrogens
Mulnard et al., 2000 (106)	Randomization to placebo or estrogen replacement therapy (0.625/1.25 mg) for 1 year	NA	Randomized placebo-controlled secondary prevention trial in women with hysterectomies	Multicenter ($n = 120$)	NA	Clinical Global Impression Scale ($p = 0.43$)
Henderson et al., 2000 (101)	Randomization to placebo or estrogen replacement therapy (1.25 mg) for 16 weeks	NA	Randomized placebo-controlled secondary prevention trial	Multicenter ($n = 42$)	NA	Alzheimer's Disease Assessment Scale (NS)

* RR, relative risk; OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy; NS, nonsignificant; NA, not applicable.

HRT

Biologic rationale. HRT in the form of estrogen (in combination with progestins) is generally prescribed for estrogen-dependent perimenopausal complaints and for preventing and treating osteoporosis. It has been hypothesized that decreasing levels of circulating estrogen after

menopause might increase the risk of Alzheimer's disease and that substitution may postpone or even prevent onset of the disease.

Proposed biologic mechanisms by which estrogen might attenuate neuronal injury are through direct stimulation of cholinergic neurons, development of gliocytes, antioxidative

properties, down-regulation of amyloid- β -42 production, and a decrease in excitotoxicity (73–79). In addition, estrogen may alter brain activation patterns in postmenopausal women during the performance of verbal memory functions (80). Finally, estrogen may be involved in the pathogenesis of Alzheimer's disease through its role in vascular disease (81, 82).

Studies with prevalent cases. Evidence exists that reduced production of estrogen may be linked to onset of Alzheimer's disease. Several studies suggest that proxy measures of higher levels of exposure to estrogen—a higher body mass index (83, 84), late age at menopause (85), and early age at menarche—are inversely associated with the risk of Alzheimer's disease. On the other hand, data suggest that there may be no relation or even an inverse relation between duration of the reproductive period, a measure of total natural estrogen exposure, and risk of dementia (86).

Studies relating HRT to the risk of Alzheimer's disease have yielded inconsistent results (table 2). Initial case-control studies showed that estrogen use was inversely associated with Alzheimer's disease (26–28, 37). However, these studies included limited measures of exposure (ever/recent), investigated the association in prevalent cases, and were designed to examine multiple risk factors. Furthermore, these earlier studies did not adequately control for potential confounders such as education and age at menopause. In later case-control studies (87–92), exposure was measured with relatively unbiased methods, for example, by abstracting medical records (89). Only two studies (87, 93) were population based. These latter studies all suggested a risk reduction of approximately 50 percent.

Studies with incident cases. In the Leisure World Cohort, an upper-middle-class elderly population in Leisure World Laguna Hills, a retirement community in southern California, information on hormone use by nondemented women was collected during a baseline interview (94). Alzheimer's disease, dementia, or senility was diagnosed on the basis of death certificates. Estrogen users had a significantly lower risk of Alzheimer's disease and associated disorders. The risk was lowest for those women who used the highest dose of HRT for the longest period of time (94). An important limitation of this study is that Alzheimer's disease cases were identified on the basis of death certificates, which underestimate dementia (95).

Other prospective studies are based on clinically assessed Alzheimer's disease. In the Manhattan, New York, cohort, the relative risk of developing Alzheimer's disease for users of oral and transdermal estrogen was significantly lower after adjustment for education, ethnic group, and sample source but not for other behavioral and medical risk factors. For women who had used estrogen for longer than a year, the risk reduction was larger than that for women who had used HRT for a shorter period of time (96). In this study, participants were sampled from Medicare recipients, senior centers, and elderly housing sites. This sampling may have led to biased estimates if a group with a different risk of Alzheimer's disease also had a different chance of receiving HRT. In a sample of 472 peri- and postmenopausal women in the Baltimore Longitudinal Study of Aging followed for up to 16 years, HRT use (45 percent) was prospectively

documented during each visit. Although the number of cases was small ($n = 34$), the risk of Alzheimer's disease in HRT users was significantly reduced; no effect of duration of therapy was found (97). A study based on the Mayo Clinic cohort (Rochester, Minnesota) found a significantly inverse association between long-term (>6 months) estrogen therapy and Alzheimer's disease after adjustment for education and age at menopause. There was a significant trend of decreasing risk with increasing duration of use (98). Finally, an 8-year follow-up study of 3,066 postmenopausal women from the population-based Rotterdam cohort did not confirm a protective effect observed earlier in other longitudinal studies (99). Although the latter study accounted for a number of potential confounders, it lacked power as a consequence of the low postmenopausal HRT exposure in the Netherlands.

Clinical trials. No known published primary prevention data are available on HRT and Alzheimer's disease. However, primary prevention trials are ongoing. The Women's Health Initiative Memory Study (100) is a component of the National Institutes of Health (Bethesda, Maryland)-funded Women's Health Initiative. This multicenter trial is designed to test the hypothesis that HRT reduces all-cause dementia in women aged 65 years or older. This trial is designed to show a 40 percent risk reduction, and it was anticipated that more than 7,500 women would be randomly assigned. Other ongoing investigations are 1) the Women's International Study of Long Duration Estrogen for Menopause and 2) the Preventing Postmenopausal Memory Loss and Alzheimer's with Replacement Estrogens study (101).

In several small secondary prevention trials, some evidence exists that estrogen may be beneficial in improving specific cognitive domains (102–104) and that it modifies the effect of cholinesterase inhibitors (105). These beneficial results were not confirmed in a larger, more recent trial, in which a 16-week treatment did not improve symptoms. Moreover, in an even longer and larger trial, estrogen replacement therapy for 1 year did not slow disease progression or improve global, cognitive, or functional outcomes in women with mild-to-moderate Alzheimer's disease (106).

Although there is relatively consistent evidence of a protective effect of HRT, selection bias is possible in observational studies in which HRT is used as an exposure factor. Women taking HRT may be healthier in general (107–109) and consequently have a reduced risk of Alzheimer's disease. Furthermore, a higher educational level and a higher socioeconomic status are associated with HRT use, both of which are associated with a reduced risk of Alzheimer's disease (110). Selection bias pertaining to HRT users might arise from increased estrogen-related mortality due to breast cancer or thrombotic complications. On the other hand, if HRT has a positive prognostic effect on survival after onset of Alzheimer's disease, as suggested by some (94, 111), a prevalent series of Alzheimer's disease cases may overrepresent women who use HRT. This possibility would make it more difficult to find an association if one existed. The need for caution in interpreting results is highlighted in a large-scale secondary prevention trial on HRT use and coronary heart disease (112). This study did not confirm a protective effect found earlier in a large number of observational

TABLE 3. Observational studies on histamine 2-receptor blocking agents

Authors, year (reference no.)	Exposure	Exposure source	Design	Case source (n°)	Control source	RR*/OR* (95% CI*) or probability
<i>Studies of prevalent Alzheimer's disease</i>						
Breitner et al., 1995 (40)	H ₂ -receptor antagonists (duration)	Interview of unaffected persons and/or collateral information	Sibship study	Siblings (n = 107)	Siblings	0.2 (0.1, 0.7), 1–12 months 0.06 (0.0, 0.3), >12 months
Launer et al., 1997 (115)	H ₂ -receptor antagonists (use in the past week, dose)	Interview	Population-based cohort study	Cohort (n = 208)	Cohort	1.24 (0.52, 2.98)
Anthony et al., 2000 (44)	H ₂ -receptor antagonists	Interview/medicine chest inventory	Case-control	Cache County, Utah, cohort (n = 201)	Cache County, Utah, cohort	0.47 (0.24, 0.90)

* RR, relative risk; OR, odds ratio; CI, confidence interval; H₂, histamine 2.

studies, suggesting the possibility that undetected selection and observation biases could be responsible for the lowered risk found previously. On the other hand, the pathologic substrate and therefore intervention strategies may be different once clinical disease exists. Other problems not frequently addressed are the changing prescription habits and contents of HRT products over time. Today's HRT preparations contain more progestins (if any) than those prescribed in the last 20 years and are based on different types of estrogen. These changes may affect the efficacy of the drug. In spite of the preventive evidence and biologic plausibility, there is room for some skepticism; a number of good observational studies and secondary prevention studies are negative. For a more definite answer, results from ongoing primary prevention studies will have to be awaited.

H₂-receptor blocking agents

Biologic rationale. H₂-receptor antagonists are frequently prescribed for duodenal ulcers, reflux esophagitis, or ulcerative lesions caused by the use of NSAIDs. Histamine is a neurotransmitter in the brain, which has not been clearly implicated in major diseases. All histaminergic neurons reside in the posterior hypothalamus and innervate most brain areas, which is compatible with the idea that histamine is involved in general central regulatory mechanisms. A postmortem study in humans suggested that a decrease in brain histamine levels may contribute to the cognitive decline occurring in Alzheimer's disease directly or through the cholinergic system (113). Furthermore, evidence exists that H₂-receptor antagonists can aggravate the neuronal damage in the hippocampus caused by ischemia (114). These latter data seem to be in contrast to the hypothesis that H₂-receptor antagonists may inhibit the cascade leading to excitotoxic cell death (40).

Studies with prevalent cases. Until now, we know of only three studies that have been published; two showed a risk reduction for H₂-receptor antagonists independent of NSAID exposure (40, 44), and the other found no associa-

tion (115) (table 3). It may be difficult to study the independent effect of H₂-receptor antagonists because previous (undetected) NSAID use may induce the prescribing of H₂-receptor antagonists if adverse gastrointestinal effects occur. Given the current evidence, we think that the most likely future role of H₂-receptor antagonists in the (trials on the) prevention of Alzheimer's disease is protection against NSAID-induced gastrointestinal side effects, although further studies are needed.

Antihypertensives

Biologic rationale. Antihypertensives are prescribed mainly for hypertension but also after myocardial infarction to prevent the heart from remodeling (particularly angiotensin-converting-enzyme inhibitors) and for postmenopausal complaints and chronic pain conditions (clonidine hydrochloride). Evidence is increasing that hypertension may contribute to development of cognitive impairment and dementia (116–119). This possibility logically leads to the hypothesis that antihypertensive drugs might protect against development of cognitive dysfunction and dementia. It is currently unclear whether a protective effect on the brain is the consequence of the lowering of high blood pressure or whether other mechanisms are also involved (120). Another suggested explanation is that some antihypertensives (i.e., calcium antagonists) may beneficially influence calcium homeostasis of neurons, thereby preventing or delaying onset of Alzheimer's disease (121).

Studies with incident cases. There is some evidence of a beneficial effect of antihypertensive drugs on the risk of Alzheimer's disease (table 4). In the population-based Kungsholmen study of subjects aged 75 years or older, persons using antihypertensive medication or diuretic monotherapy at baseline, compared with nonusers, had a reduced risk of developing dementia (122). An investigation from the Rotterdam Study yielded comparable risk estimates for users of antihypertensive drugs. However, results were significant for vascular dementia only, not for Alzheimer's disease

TABLE 4. Studies on antihypertensives

Authors, year (reference no.)	Exposure	Exposure source	Design	Case source (n°)	Control source	RR*/OR* (95% CI*) or probability
<i>Studies of incident Alzheimer's disease</i>						
Guo et al., 1999 (122)	Use of antihypertensive in the 2 weeks before interview	Interview	Prospective population-based cohort study	Community cohort (n = 204, all dementia)	Community cohort	0.7 (0.6, 1.0), all antihypertensives 0.6 (0.4, 0.9), diuretics 0.6 (0.3, 1.2), beta-blockers or calcium antagonists
<i>Primary prevention trial</i>						
Forette et al., 1998 (121)	Randomization to placebo or nitrendipine (+ enalapril and/or hydrochlorothiazide, if necessary)	Dispensed in trial	Randomized placebo-controlled trial	People with systolic hypertension (n = 23)	NA*	p = 0.05, 50% lower risk

* RR, relative risk; OR, odds ratio; CI, confidence interval; NA, not applicable.

(123). Both studies were hampered by a relatively short follow-up and cross-sectional assessment of drug exposure.

Clinical trials. Currently, the only known primary prevention trial on the association between antihypertensives use and the risk of Alzheimer's disease is the Systolic Hypertension in Europe Trial (table 4). In this trial of isolated systolic hypertension (160–219 mmHg), subjects were treated with nitrendipine, and, if blood pressure was not lowered sufficiently, enalapril and/or hydrochlorothiazide were added. Results showed that the incidence of dementia was 50 percent lower in the treatment group (121). However, it is unclear whether this protective effect, if real, was a consequence of the lower blood pressure or of a specific neuroprotective effect of calcium channel blockade (120). This was a small study with a short-term follow-up, which needs to be replicated.

In a trial on stroke prevention by using thiazide diuretics in older persons with isolated systolic hypertension, treatment significantly reduced the risk of stroke but not of cognitive impairment (124). In a secondary prevention trial, sabeluzole, a new benzothiazole derivative (calcium channel blocker), appeared to exert beneficial effects on memory in Alzheimer's disease patients (125). Another secondary prevention study showed that treatment of hypertension with captopril did not appear to be hazardous or beneficial to cognitive function in older people with preexisting cognitive impairment (126).

It is now clear that both diastolic and systolic hypertension are associated with increased risk of cardio- and cerebrovascular morbidity and mortality. Because of ethical problems, it is unlikely that future placebo-controlled primary prevention trials will be initiated. Future trials can only compare different antihypertensive agents, not the overall effect of antihypertensive treatment within the current treatment boundaries. Large and, in particular, long-term prospective, population-based studies will be needed to study the overall effect of antihypertensive drugs on Alzheimer's disease.

However, observational studies on antihypertensives and Alzheimer's disease are seriously limited by confounding by indication and comorbidity. Specific drugs are prescribed according to degree of severity and comorbidity. Furthermore, this comorbidity is sometimes in itself associated with the occurrence of Alzheimer's disease (e.g., cardiac problems, diabetes mellitus, and stroke) or death as a competing risk. Another potential problem is that hypertension may lead to cognitive impairment, which appears to be associated with less-compliant behavior and exposure misclassification (127). Despite the possibility of multivariate adjustment, it may therefore be difficult to determine the actual effect of antihypertensive drugs. However, in weighing the current evidence, it is likely that adequate antihypertensive treatment will contribute to the prevention of Alzheimer's disease.

Lipid-lowering drugs

Biologic rationale. Lipid-lowering drugs are prescribed to treat high (high density lipoprotein) cholesterol levels. The pathophysiology of Alzheimer's disease appears to be related to cholesterol metabolism. Apolipoprotein E type 4 is a cholesterol transport protein (128, 129) and an important risk factor for Alzheimer's disease. Patients carrying an apolipoprotein E type 4 allele have more cardiovascular disease and, at least partly because of this disease, a higher risk of Alzheimer's disease (130). Cholesterol is also involved in the biology of β -amyloid, a protein that accumulates in the affected brains of Alzheimer's disease patients. Cholesterol increases production of this β -amyloid in some cells (131).

Studies with prevalent cases. Studies with prevalent cases currently provide some evidence of a potential effect of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also called statins (132, 133) (table 5). However, because of their design, these two database studies

TABLE 5. Studies on lipid-lowering agents

Authors, year (reference no.)	Exposure	Exposure source	Design	Case source	Control source	RR*/OR* (95% CI*) or probability
<i>Studies of prevalent Alzheimer's disease</i>						
Wolozin et al., 2000 (132)	Current use of HMG-CoA-Ri*	Hospital database	Cross-sectional	Three hospital databases	Total patient population using at least eight drugs	Prevalence lower for lovastatin and/or pravastatin, but not simvastatin, users compared with controls
Jick et al., 2000 (133)	Current use of HMG-CoA-Ri	General Practice Research Database	Nested case-control	Sample from the General Practice Research Database (n = 284)	General Practice Research Database	0.29 (0.13, 0.63)
	Nonstatin lipid-lowering agents					0.96 (0.47, 1.97)

* RR, relative risk; OR, odds ratio; CI, confidence interval; HMG-CoA-Ri, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

suffer from the usual methodological problems in prevalence studies. In particular, the relatively short availability of this drug class investigated in subjects with prevalent Alzheimer's disease (which may have lasted for over 10 years) makes the suggested risk reduction, at the least, less valid. Another problem in both studies is the lack of uniformity of the diagnosis of Alzheimer's disease and the potential of underascertainment of Alzheimer's disease. Furthermore, there is the possibility of differential prescription behavior with respect to the relatively new class of HMG-CoA reductase inhibitors over age classes and socioeconomic status for which these studies cannot adjust.

Clinical trials. To our knowledge, the Prospective Study of Pravastatin in the Elderly at Risk is currently the only trial that looks into the effect of HMG-CoA reductase inhibitors and the occurrence of cognitive deterioration (134). The study, which will end in 2002, has included 5,804 subjects followed for a mean of 3.5 years regarding a number of endpoints. Until results are available, the evidence is insufficient to warrant any preventive prescription for Alzheimer's disease (135). However, because hypercholesterolemia causes vascular disease and this vascular disease appears to contribute to development of Alzheimer's disease, it is likely that these lipid-lowering drugs will be implemented as a preventive agent once the Prospective Study of Pravastatin in the Elderly at Risk trial suggests a protective effect on cognitive deterioration.

Benzodiazepines

Biologic rationale. Benzodiazepines are among the most frequently prescribed drugs in the elderly. Their clinical applications include administration as sedatives-hypnotics, anti-convulsants, and anxiolytics. In animal models of cerebral ischemia, the inhibitory neurotransmitter γ -aminobutyric acid (GABA) and GABA-mimetic drugs (benzodiazepines) have been reported to protect against neuronal damage (136–140). Benzodiazepines may protect neurons by reducing cerebral oxygen demand via a reduction in synaptic transmission (141). A multicenter study on risk factors for incident cognitive dysfunction after operations performed under general anesthesia was indeed suggestive for a preventive effect of benzodiazepines started prior to the operation (142). On the other hand, a large number of experimental studies are available on the potential (short-term) reversible adverse effects of benzodiazepines on memory performance (143–148). However, very little is known about the cognitive effects of chronic benzodiazepine exposure.

Studies with prevalent cases. To our knowledge, studies with prevalent cases on the association of benzodiazepines and Alzheimer's disease are not available (table 6). This lack may reflect the fact that benzodiazepines are often prescribed for behavioral and sleeping problems related to Alzheimer's disease, making it impossible to study associations.

Studies with incident cases. The relation between chronic use of benzodiazepines and incident dementia was examined in the Kungsholmen Study (149) (table 6). Users of benzodi-

TABLE 6. Studies on benzodiazepines

Authors, year (reference no.)	Exposure	Exposure source	Design	Case source	Control source	Probability
<i>Studies of incident Alzheimer's disease</i>						
Fastbom et al., 1998 (149)	Benzodiazepines (regular)	Interview	Prospective population-based cohort study	Cohort (n = 33)	Cohort	$p = 0.012$ (all benzodiazepines) $p = 0.013$ (hypnotics)

azepines at both baseline and follow-up had a lower incidence of Alzheimer's disease compared with nonusers, after adjustment for age, sex, education, and use of NSAIDs and estrogen. Because this is probably the first study on the association, other studies are needed before any conclusion can be drawn. A potential threat to the validity of studies relating benzodiazepines to Alzheimer's disease is that preclinical symptoms in Alzheimer's disease, such as sleeping problems, may be treated with benzodiazepines, although such a bias would tend to overestimate the risk.

Free-radical scavengers

Biologic rationale. Oxidative stress may play an important etiologic role in Alzheimer's disease (150, 151). Free-radical scavengers are agents that sequester free radicals so they do not initiate oxidative reactions that can lead to cellular damage. These free-radical scavengers can be naturally occurring substances (beta-carotene, vitamins C and E, estrogen (152, 153), and Ginkgo biloba) or synthetically prepared substances (selegiline, a monoamine oxidase-B inhibitor established in the therapy of Parkinson's disease; lazabemide, another more selective monoamine oxidase-B inhibitor (154, 155); and tenilsetam, thought to be an advanced glycation end-products inhibitor (156)).

Studies with incident cases. Observational data on free-radical scavengers and the risk of Alzheimer's disease are limited (table 7). We are not aware of studies with prevalent cases, but there are some with incident cases. In an analysis of data from the Rotterdam Study that included 58 subjects with incident dementia, dietary intake of antioxidants was not associated with a reduced incidence of dementia (152) (table 7). Observational data on the use of vitamin E and vitamin C supplements and incident Alzheimer's disease have been reported in one study (153). In this prospective study of 633 persons aged 65 years or older, a stratified random sample was selected from a disease-free population. At baseline, all vitamin supplements taken in the previous 2 weeks were identified by direct inspection. After an average follow-up of 4.3 years, 91 of the sample participants for whom vitamin information was available met accepted criteria for the clinical diagnosis of Alzheimer's disease. These study data suggest an inverse association between high vitamin E and vitamin C intakes and Alzheimer's disease. However, further exploration is needed; this is probably the first longitudinal study, and results were significant for vitamin C only.

One of the reasons for the scarcity of observational studies may be the complicated assessment of exposure: some antioxidants are in the form of over-the-counter supplements, herbs, or food. High over-the-counter sales mean that medical or pharmacy records do not provide a valid measure of intake. In addition, similar to the use of HRT, the healthy-user effect may hamper valid assessments.

Clinical trials. Ginkgo biloba (157–160), selegiline, or α -tocopherol (vitamin E) and thiamine (vitamin B₁) (161) have been studied as secondary protective agents against Alzheimer's disease (162). The largest known Ginkgo biloba trial published thus far, in which primary outcome measures included the Alzheimer's Disease Assessment Scale-cogni-

tive subscale, the Geriatric Evaluation by Relative's Rating Instrument, and the Clinical Global Impression of Change, showed the superiority of Ginkgo biloba extract over placebo. In comparison to the baseline values, the placebo group worsened statistically significantly regarding all domains of assessment, whereas the group receiving Ginkgo biloba extract was considered slightly improved with regard to cognitive assessment and to daily living and social behavior. Regarding the safety of Ginkgo biloba, no differences were observed (159). However, not all studies confirm these positive findings (163). The recently started Ginkgo Evaluation of Memory Study may resolve the question as to whether these findings can be extrapolated to primary prevention.

The selegiline/ α -tocopherol trial showed that, in patients with moderately severe impairment from Alzheimer's disease, treatment with selegiline or α -tocopherol slowed progression of the disease. A potential limitation of this trial is that progression was defined as a nonspecific outcome that included time until institutional placement, loss of ability to perform basic activities of daily living, or severe dementia or death. There were no significant differences in any of the cognitive test scores. Furthermore, selegiline may act as an antidepressant, which could lead to improved cognition. Results of trials with lazabemide (a monoamine oxidase-B inhibitor) (155) and *N*-acetylcysteine (164) must be awaited. Fewer than 50 people were included in the studies of thiamine, and the reported results are inadequate (161).

That vitamins and food supplements are popular substances for intervention studies is suggested by the fact that a vitamin E primary prevention trial, despite the absence of convincing evidence (165), received a grant from the National Institutes of Health. On the other hand, given methodological difficulties, studying this type of substance is the only way to obtain a reliable answer.

Recent research has increasingly suggested a central role for free-radical-induced tissue damage in the pathogenesis of Alzheimer's disease. In this review, we assess evidence for the interaction between free radicals and other major factors/metabolic areas that have also been implicated in Alzheimer's disease, including beta-amyloidosis, inflammatory cytokines, mitochondrial dysfunction, and metal ions/homocysteine. Free radicals and antioxidants should not be considered in isolation in the etiology and treatment of Alzheimer's disease. It is the reciprocal induction and self-amplifying interplay between the above factors that is important in the pathogenesis of this disorder and to which multipharmacologic therapeutic strategies could be directed. Although some tend to think otherwise, we feel that, although some evidence exists in favor of the use of antioxidative substances in preventing Alzheimer's disease, their use is not yet advised.

DISCUSSION

Literature is abundant on the association between drugs and prevention of Alzheimer's disease. In view of the scarcity of well-designed clinical trials, most of the current epidemiologic knowledge comes from observational studies. Such studies have potential limitations that may jeopardize the validity of the results. Before we present the

TABLE 7. Studies on radical scavengers and antioxidants

Authors, year (reference no.)	Exposure	Exposure information	Design	Case source	Control source	RR*/OR* (95% CI*) or probability
<i>Studies of prevalent Alzheimer's disease</i>						
Broe et al., 1990 (26)	Vitamin E by proxy informants	Interview	Case-control study	General practice (n = 170)	General practice	1.3 (0.6, 1.65), vitamin E 1.17 (0.5, 2.5), iron
<i>Studies of incident Alzheimer's disease</i>						
Morris et al., 1998 (153)	Vitamins C and E taken in the previous 2 weeks	Interview with direct inspection	Prospective cohort study	Stratified sample of cohort of disease-free subjects (n = 91)	Stratified sample of cohort of disease-free subjects	p = 0.10, vitamin C p = 0.04, vitamin E No reduction
Launer and Kalmijn, 1998 (152)	Antioxidants	Food questionnaire interview	Prospective population-based cohort study	Cohort (n = 58)	Cohort	
<i>Trials</i>						
Haase et al., 1996 (160)	EGb 761* intravenous 4 days per week for 4 weeks	NA*	Randomized double-blind secondary prevention trial	(Alzheimer, vascular dementia, or mixed type)	NA	p = 0.05, NAB* p = 0.05, CGI* IADL*
Maurer et al., 1997 (158)	EGb 761 oral 240 mg per day	NA	Randomized double-blind parallel group design	20 outpatients with Alzheimer's disease	NA	p < 0.013, SKT-test* ADAS-cog* (NS*)
Sano et al., 1997 (162)	Selegiline (10 mg) and/or α -tocopherol (2,000 IU)	NA	Randomized double-blind secondary prevention trial	23 centers (n = 341)	NA	Significant delay until institutionalization for treatment group
Le Bars et al., 2000 (159)	EGb 761 40 mg three times a day	NA	Randomized double-blind secondary prevention trial	Multicenter (n = 309) (Alzheimer, vascular dementia)	NA	p = 0.04, ADAS-cog p = 0.007, GERRI* CGI

* RR, relative risk; OR, odds ratio; CI, confidence interval; EGb 761, Ginkgo biloba special extract 761; NA, not applicable; NAB, Nurnberger-Altters-Beobachtungsskala; CGI, Clinical Global Impression of Change; IADL, Instrumental Activities of Daily Living; SKT-test, psychometric test for attention and memory; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; GERRI, Geriatric Evaluation by Relative's Rating Instrument.

overall results of this review, we must discuss these potential limitations.

Methodological considerations

Prevalent or incident cases. For methodological reasons, we distinguished between observational studies with prevalent cases and those with incident cases. An obvious problem with prevalent cases is that it is usually unclear how long cognitive impairment exists, whether drug use preceded the onset of Alzheimer's disease, and, if so, for how long. Most potential sources of bias may play a role in studies with prev-

alent cases but can be dealt with satisfactorily in prospective population-based cohort studies by regularly assessing cognitive function and incident case enrollment. Additionally, restricted analyses of the effects of drug exposure in such studies, after subtracting the assumed latent period between onset of cognitive impairment and date of diagnosis of Alzheimer's disease ("lagging"), may add further information and increase validity (166–168). Therefore, for every drug (group), this review distinguished between studies including patients with prevalent Alzheimer's disease and studies focusing on incident cases of Alzheimer's disease, discussing potential weaknesses. However, even some very

well designed prospective cohort studies with incident case collection use drug exposure data from a baseline interview. Such cross-sectional drug assessment as an approximation of chronic use may lead to nondifferential misclassification of exposure and a bias toward the zero hypothesis, sometimes even to differential misclassification of chronic use (169). Therefore, the best observational prospective cohort studies are those with continuous registration of drug use, for instance, by reimbursement or automated pharmacy data and, if possible, a compliance parameter.

Selection bias, information bias, and confounding. Several sources of bias are important in interpreting epidemiologic studies on the association between drugs and Alzheimer's disease (35). Bias is generally divided into selection bias, information bias, and confounding. Some of these types of bias may be particularly important in studies on drugs in Alzheimer's disease.

Selection bias may occur when selection of subjects for the drug exposure group and the reference group of a cohort study differs between Alzheimer's patients and nondiseased persons. Similarly, selection of cases and controls in a case-control study may be different and may depend on exposure status. Elderly with painful osteoarthritis and with adequate cognitive function might be more successful than severely demented persons in communicating their complaints to their caretakers or in contacting their prescribing physicians. In this instance, use of NSAIDs could be spuriously associated with a protective effect. Selection bias may also occur if cases and controls are drawn from different source populations (170, 171). For example, studies based on cases referred to health services may be subject to selection bias if cases and controls differentially use one type of health service over another (172). Another example of potential selection bias is when elderly women with normal cognitive function use HRT more readily than do women with Alzheimer's disease because news media make the former aware of the potentially protective effects of estrogens. This possibility would tend to bias the relative risk toward a protective effect or exaggerate a true protective effect. The large majority of these problems can be overcome by using a prospective population-based study design.

Information bias may occur if classification of disease status depends on exposure status, or vice versa. Of major concern in observational studies of Alzheimer's disease is the potential for misclassification of exposure to drugs because patients experiencing cognitive decline have impaired recall. Another potential source of misclassification is information from proxy informants. Proxy informants such as spouses, relatives, or other caregivers of demented persons may supply exposure information that differs from the exposure information obtained from proxies of persons whose cognitive function is normal. Some evidence exists that information with respect to dramatic exposures is reported reliably by proxy informants. However, this finding does not appear to be true for drug use (173), particularly not when it comes to more detailed aspects such as drug types, duration of use, and dosage. Furthermore, for over-the-counter drugs, this method has been reported to be highly unreliable for exposure classification (174). In addition, use of this type of information has been reported to lead to bias

due to differential nonresponse or even differential misclassification (169). Another difficulty is the degree of compliance of each person, because it has been shown that even in nondemented subjects, cognitive function is a determinant of compliance (175).

Confounding by independent risk factors for Alzheimer's disease, such as socioeconomic status or education, which may also be associated with drug use, can usually be dealt with in the analyses of observational studies. A conceptually more difficult type of confounding is confounding by indication (176, 177). This type occurs when a particular indication for a certain drug is also a direct risk factor for Alzheimer's disease. However, because not many indications for drug use are known to be direct risk factors for Alzheimer's disease, confounding by indication will usually be less of a problem. This situation is different with vascular dementia, in which antihypertensives and other cardiovascular drugs may erroneously be associated with a risk increase as a result of confounding by indication (52).

Conclusions

In recent years, progress has been made in unraveling presumed protective effects of drugs used in Alzheimer's disease. Despite this progress, hardly any effective therapy is available. Even those clinical trials demonstrating a beneficial effect of the cholinesterase inhibitor rivastigmine suggest only a modest effect on the three hallmarks of Alzheimer's disease: impaired cognition, changed behavior, and inability to perform daily activities (178). The data from our review do not suggest that there is a highly effective treatment among the currently used pharmacologic agents, but at least some of them deserve further study.

In view of the scarcity of primary prevention trials, observational population-based studies can contribute to current knowledge on the pharmacologic prevention of Alzheimer's disease. Our review addressed several general methodological problems encountered in such epidemiologic research on drug effects and Alzheimer's disease. When studying drug effects, an adequate definition of exposure is needed, one that provides details about when the drug was used relative to onset of the disease, at what dose, and for how long. Currently, however, both the definition and the assessment of drug use are imprecise and lack uniformity. Standardization of criteria to define Alzheimer's disease would also increase the ability to compare studies in a useful way. Although National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria are frequently used, use of different diagnostic criteria in the remainder may lead to very different case populations (179) and potentially to risk estimates that are difficult to compare. The time of first clinical symptoms should be well documented; for obvious reasons, exposure can be preventive only if it occurs before the disease does. Even if a drug is not preventive but slows the development of Alzheimer's disease, precise temporal relations are needed to judge the association. Unfortunately, such details are often difficult to obtain.

What can we conclude from the medical literature included in this review, taking into account all methodolog-

ical issues? Mainly, evidence for a protective effect on Alzheimer's disease is strongest for NSAIDs and HRT. In addition to reviews, based mainly on studies on prevalent Alzheimer's disease (36), several high-quality prospective studies now support a primary preventive role for (certain) NSAIDs in Alzheimer's disease. However, given the high percentage of potential adverse effects of NSAIDs (54, 180), their role in primary or secondary prevention of Alzheimer's disease is far from clear-cut. It is possible that positive results from the Alzheimer's Disease Anti-Inflammatory Prevention Trial or other pharmaceutical trials, as well as development of more selective COX-2 inhibitors or of nitric oxide-releasing (181, 182) or amyloid-specific NSAIDs, may change this situation. A protective effect was also consistently demonstrated for long-term use of HRT, although only two thirds of the studies have been positive. A meta-analysis comprising the large majority of these studies also confirmed a protective effect. Because of (suggested) beneficial effects on postmenopausal complaints, osteoporosis (183, 184), and atherosclerosis (82, 185), HRT use is currently increasing in western countries. If a beneficial effect of HRT in Alzheimer's disease is demonstrated in (ongoing) clinical trials, the benefits may be considered so large that, in spite of the increased risk of venous thromboembolism (112) and breast cancer (186), its use may increase further, a development that will be strengthened if selective estrogen receptor modulators, a new class of synthetic estrogens, really prove to retain beneficial estrogenic effects in the brain without exhibiting the adverse effects of HRT (187, 188).

Evidence with regard to a protective effect on Alzheimer's disease of corticosteroids, aspirin, H₂-receptor antagonists, and free-radical scavengers is highly inconsistent. This evidence is slightly better for antihypertensives and benzodiazepines, although it is unlikely that the latter will ever be introduced as primary preventive agents because of the high risk of addiction, short-term memory problems, and a higher risk of fractures and accidents. Studies on a protective effect of antihypertensive therapy on Alzheimer's disease are promising, but scanty, and methodologically insufficient. The evidence of a causal involvement of high blood pressure is firm, however. Research on the role of antihypertensives in Alzheimer's disease should probably focus on the potential mechanism and thus on the question of whether a protective effect, if present, is explained solely by lowering of blood pressure. Because of beneficial effects in cardiovascular and cerebrovascular disease in general, when proven effective in Alzheimer's disease, it is likely that treatment with antihypertensive drugs will be further intensified.

In conclusion, data from observational studies are helpful as long as we know little about potentially protective drug effects in Alzheimer's disease. For the future, placebo-controlled trials for primary prevention are essential. In light of the currently developing large-scale efforts regarding HRT, NSAIDs, HMG-CoA reductase-inhibiting statins, vitamin E, and Ginkgo biloba, it may prove possible to study most of the suggested hypotheses mentioned in this review. In the meantime, available observational data should be explored further. In particular, prospective, population-

based cohort studies with incident case enrollment, genotyping, and adequate and continuous gathering of data on drug use may be important tools to gain more insight into potential agents to treat a disease from which so many people suffer and for which so little therapy is available.

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