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Diclofenac reduces the risk of Alzheimer's disease: a pilot analysis of NSAIDs in two US veteran populations

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Abstract

Background: Our aim was to determine whether specific nonsteroidal anti-inflammatory (NSAID) agents are associated with a decreased frequency of Alzheimer's disease (AD).

Materials and methods: Days of drug exposure were determined for diclofenac, etodolac, and naproxen using US Department of Veterans Affairs (VA) pharmacy transaction records, combined from two separate VA sites. AD diagnosis was established by the International Classification of Diseases, ninth revision (ICD-9)/ICD-10 diagnostic codes and the use of AD medications. Cox regression survival analysis was used to evaluate the association between AD frequency and NSAID exposure over time. Age at the end of the study and the medication-based disease burden index (a comorbidity index) were used as covariates.

Results: Frequency of AD was significantly lower in the diclofenac group (4/1431, 0.28%) compared with etodolac (328/14,646, 2.24%), and naproxen (202/12,203, 1.66%). For regression analyses, naproxen was chosen as the comparator drug, since it has been shown to have no effect on the development of AD. Compared with naproxen, etodolac had no effect on the development of AD, hazard ratio (HR) 1.00 [95% confidence interval (CI): 0.84–1.20, $p = 0.95$]. In contrast, diclofenac had a significantly lower HR of AD compared with naproxen, HR 0.25 (95% CI: 0.09–0.68, $p < 0.01$). After site effects were controlled for, age at end of the study (HR = 1.08, 95% CI: 1.07–1.09, $p < 0.001$) was also found to influence the development of AD, and the medication-based disease burden index was a strong predictor for AD, HR 5.17 (95% CI: 4.60–5.81) indicating that as comorbidities increase, the risk for AD increases very significantly.

Conclusion: Diclofenac, which has been shown to have active transport into the central nervous system, and which has been shown to lower amyloid beta and interleukin 1 beta, is associated with a significantly lower frequency of AD compared with etodolac and naproxen. These results are compelling, and parallel animal studies of the closely related fenamate NSAID drug class.

Keywords: Alzheimer's disease, diclofenac, naproxen, etodolac

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Introduction

Alzheimer's disease (AD) is a chronic, progressive, and irreversible age-related neurodegenerative disorder characterized by cognitive and memory impairment. It is the most common cause of dementia in older adults. It was estimated in 2015 that 44 million people were living with AD worldwide, and this number is expected to double by 2050.[1] More than 95% of people with AD have sporadic or late-onset AD, a multi-factorial disorder with environmental factors and genetic predisposition contributing to the pathology.[1]

The pathophysiology of AD is characterized by abnormal extracellular accumulation of amyloid-β peptide (Aβ) in amyloid plaques, and abnormal intracellular accumulation of tau protein in neurofibrillary tangles (NFTs).[1] Several theories are published regarding the AD pathogenesis. The amyloid cascade theory proposes that the accumulation of Aβ plaques in the brain is the primary pathogenic event.[2–4] The tau hypothesis proposes that tau hyperphosphorylation is the underlying etiology.[5–9] The cholinergic theory suggests AD is associated with a reduction in the choline acetyltransferase

activity and acetylcholine levels in specific areas of the brain such as the cerebral cortex.[10,11] These proposed disease mechanisms result in a loss of synaptic function, mitochondrial damage, activation of microglia, and neuronal death.[12] Neuroinflammation is mediated primarily by microglia cells, and neuroinflammation contributes to AD pathogenesis.[13–15] Microglia activation has a dual effect on AD progression: it leads to (a) a reduction of Aβ accumulation by increasing phagocytosis, clearance, and degradation, and (b) the release of pro-inflammatory cytokines, and triggers the inflammatory cascade that contributes to neuronal damage and death.[12]

Interleukin-1β (IL-1β) is an important pro-inflammatory cytokine in the brain.[16,17] It is generated by the cytosolic nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasomes, where nucleotide-binding oligomerization-domain-like receptors (NLRs) are engaged, resulting in increased IL-1β release.[18] Evidence is growing that IL-1β plays a central role in AD progression.[19,20] The NLRP3-IL-1β is synthesized and released from activated microglia and astrocytes. One study has documented that IL-1β interferes with glutamate reuptake in astrocytes, potentially leading to glutamate toxicity.[21] Another study showed that soluble oligomeric Aβ increases the formation of mature IL-1β in microglia.[12] Over-expression of IL-1β release from microglia and astrocytes surrounding Aβ plaques occurs in the AD brain.[22,23] Several studies have demonstrated that the over-expression of IL-1β exacerbates tau phosphorylation and NFT development.[24–26] Subsequently, synaptic plasticity leads to disruption of the brain's learning and memory processes.[12] Finally, the blockade or neutralization of IL-1β in an AD mouse model was protective against cognitive defects, decreased tau pathology and the synthesis of Aβ.[12]

Early studies of AD included the use of non-steroidal anti-inflammatory drugs (NSAIDs).[27] In a Cochrane NSAID and Alzheimer's review, these prior studies in AD patients compared aspirin and NSAID exposures to patients who had not received them and the results from these studies were equivocal.[27] Vlad and colleagues, however, concluded that over time, ibuprofen and NSAIDs as a group have a protective effect but that other individual NSAIDs did not consistently exhibit this effect, perhaps due to 'small numbers of users.'[28] In addition, many studies do not specify which NSAIDs were used, although the effects of indomethacin,[29,30] celecoxib,[31] naproxen[32–35] ibuprofen,[36] and naproxen have been studied. Of these, only indomethacin[29] and ibuprofen[28] were associated with less cognitive decline in AD. A recent meta-analysis of 16 NSAID cohort studies[37] reported a decreased likelihood of AD with the pooled data of 236,022 patients; however, individual NSAIDs had no effect when stratified by NSAID type.

It is important to note that there are eight different chemical classes of NSAIDs[38] and this may have a significant effect on their ability to interrupt the AD process. In 2006, Joo and colleagues[39] found a neuroprotective effect of mefenamic acid administration in *in vitro* and *in vivo* models. In 2016, Daniels and colleagues[40] also detected a protective effect of the fenamate class of NSAIDs against AD and they hypothesized that it was due to inhibition of IL-1β release from the NLRP3 inflammasome in immortalized mouse bone-marrow-derived macrophages. In the initial *in vitro* phase of their study, the fenamates (flufenamic acid, mefenamic acid and meclofenamic acid) were more effective at inhibiting IL-1β release than celecoxib or ibuprofen, which had no effect on IL-1β release.[40] In contrast, diclofenac was associated with a modest but significant reduction in IL-1β release. In the second phase of their study, Daniels and colleagues showed that the fenamate drug class also prevented Aβ-induced memory deficits in rats,[40] and it decreased AD-related neuroinflammation in three AD-transgenic (TG) mice that expressed the presenilin mutation PS1M146V,[41] the mutant amyloid precursor protein APPSwe,[42] and a transgene of the human mutant P301 tau gene (tauP301L transgene).[43] These animals develop a progressive neuropathological phenotype with increasing age that includes Aβ plaques and neurofibrillary tangles.[44] Fenamate treatment was associated with decreased IL-1β expression and microglial activation in AD mice equivalent to levels in wild-type mice.[40]

Very recently, Rivers-Auty and colleagues, evaluating fenamate NSAIDs, reviewed diclofenac use in a database of patients with Alzheimer's disease and found that it reduced cognitive deterioration.[45] At this time, however, this finding has only been presented in abstract form.

The purpose of this retrospective cohort study was to determine whether chronic diclofenac use is associated with a lower frequency of AD in a veteran population compared with chronic use of etodolac or naproxen.

Methods

Study design

This study was a retrospective, observational cohort study conducted at the US Veterans Affairs (VA) North Texas Health Care System (VANTHCS) in Texas. The VANTHCS Institutional Review Board approved the study. Data were extracted from electronic medical records (EMRs) of veterans receiving NSAIDs between 1 October 1998 and 30 September 2016 from the VANTHCS and *via* the Veterans Informatics and Computing Infrastructure (VINCI) for the Central Texas VA Health Care System.

Patient population

Veterans with AD were identified by the International Classification of Diseases, ninth revision (ICD-9)/ICD-10 diagnosis codes in the EMR. Patients were also included in the AD group if they received a prescription for an acetylcholinesterase inhibitor (i.e. donepezil, galantamine, rivastigmine) or memantine. Veterans who received a prescription for an acetylcholinesterase inhibitor (i.e. donepezil, galantamine, rivastigmine) or memantine were reviewed in the EMR for AD ICD-9/ICD-10 codes. AD medications or AD diagnosis were used to classify patients into either cases or control categories; medications and ICD codes were individually reviewed. Patients were excluded from the AD group if other types of dementia (vascular, Lewy body, alcohol induced, hydrocephalus, traumatic brain injury) or Parkinson's disease were documented. The AD patient group included those with dementia but no clear differential diagnosis, and those for whom the EMR diagnosis was mixed dementia.

Veterans were eligible for inclusion if they were 50-years old or older at study end date, and if they had received a $\geqslant$360 days' supply of diclofenac, etodolac, or naproxen, before they started an AD medication. Occurrence of Alzheimer's disease $>$365 days after stopping the study NSAID was not considered related to the NSAID. The days' supply was calculated by subtracting the confounded days patients were on one of the other study NSAIDs from the patients' total days' supply for each specific NSAID (Equation 1). Patients were excluded if they received a $\geqslant$90-day supply for any other study NSAID.

$$\begin{aligned} &\textit{Uniquely Diclofenac TDS} = \textit{Diclofenac TDS} \\ &\quad - \left(\textit{Etodolac TDSc} + \textit{Naproxen TDSc}\right) \end{aligned} \tag{1}$$

Where TDS = total days' supply; c: concomitant with drug being measured for exposure (e.g. diclofenac).

Data collection

Data were electronically extracted from VINCI for the Central Texas VA and *via* the VANTHCS EMR. Data included: date of birth, sex, total days' supply of study NSAID, study NSAID start and end date, and AD medication start and end date. Baseline data were collected on day 1 of study NSAID treatment. The medication-based disease burden index (MBDBI) was calculated for each study participant using a formula that provides an estimate of a patient's disease burden based on an individual's VA prescribed medications (Supplemental Table 1; Equation 2). Each veteran's entire medication history leading up to the baseline date was used to calculate the MBDBI (Supplemental Table 1). If the veteran ever received any of the medications assigned to each condition, the patient was assigned the corresponding score for that condition. Finally, to calculate the MBDBI, a sum score was calculated from the scores associated with all the conditions for each patient's diagnoses.

$$\begin{aligned} \textit{MBDBI} = {} & \textit{Asthma}\,(0.130) + \textit{BPH}\,(0.038) \\ & + \textit{CVD}\,(0.637) + \textit{COPD}\,(0.350) \\ & + \textit{D}\,(0.613) + \textit{DM}\,(0.212) \\ & + \textit{Epilepsy}\,(0.110) + \textit{HIV}\,(0.505) \\ & + \textit{HTN HD}\,(0.352) + \textit{IHD}\,(0.309) \\ & + \textit{Cirrhosis}\,(0.339) \\ & + \textit{Nephritis or Nephrosis}\,(0.230) \\ & + \textit{PD}\,(0.730) + \textit{PUD}\,(0.066) \\ & + \textit{SD}\,(0.056) + \textit{Tb}\,(0.295) \\ & + \textit{vHep}\,(0.430) \end{aligned} \tag{2}[46]$$

Table 1. Baseline characteristics for the combined population*.

Characteristic	Diclofenac (*p* value)§						Etodolac (*p* value)§				Naproxen (*p* value)§						*p* value* (compared with naproxen)	
	Central (*n* = 871)		North Texas (*n* = 560)		Combined (*n* = 1431)		Central (*n* = 5656)		North Texas (*n* = 8990)		Combined (*n* = 14,646)		Central (*n* = 7326)		North Texas (*n* = 4877)		Combined (*n* = 12,203)			
	M	SE (*p*§)	M	SE	M	SE	M	SE (*p*§)	M	SE	M	SE	M	SE (*p*§)	M	SE	M	SE	Dc-Nc	Ec-Nc
Male	89.4% (0.30§)		95%		91.6%		93.5% (0.01§)		94%		93.8%		92% (0.14§)		94%		92.8%		0.14	<0.001
**Time on NSAID, years	2.62	0.07 (0.53§)	2.55	0.08	2.59	0.05	2.73	0.03 (0.93§)	2.74	0.02	2.74	0.02	2.80	0.03 (0.92§)	2.59	0.03	2.72	0.02	0.035	0.55
Dose, mg	137.1	1.1 (0.60§)	138.0	1.24	137.4	0.83	826.3	2.23 (<0.01§)	869.8	1.8	853.0	1.41	945.6	1.96 (0.18§)	950.0	2.62	947.3	1.58	—	
Mean age at start of NSAID, years	60.1	0.31 (0.59§)	60.3	0.36	60.2	0.23	60.9	0.13 (<0.01§)	62.6	0.11	62.0	0.08	58.0	0.12 (<0.01§)	62.2	0.14	59.6	0.09	0.06	<0.001
Mean age at end of NSAID (years)	63.7	0.31 (0.43§)	64.1	0.35	63.9	0.23	65.7	0.13 (<0.01§)	67.3	0.1	66.6	0.08	64.8	0.11 (<0.01§)	66.6	0.13	65.5	0.08	<0.001	<0.001
‡MBDBI	0.71	0.02 (<0.01§)	0.55	0.018	64	0.01	0.86	0.01 (<0.01§)	0.73	0.01	0.78	0.004	0.77	0.01 (<0.01§)	0.70	0.01	0.74	0.01	<0.001	<0.001

*Both diclofenac and etodolac were independently compared with naproxen using Dunnett's *C*, except for sex, which was Chi-square or Fisher's exact test, where appropriate.
**Equation 1: all *p* values one-way ANOVA with Tukey HSD.
‡Equation 2: all *p* values one-way ANOVA with Tukey HSD.
§*p* value of Central compared with North Texas within this column.
ANOVA, analysis of variance; Dc, diclofenac combined; Ec, etodolac combined; HSD, honestly significant difference; M, mean; Nc, naproxen combined; MBDBI, medication-based disease burden index; NSAID, non-steroidal anti-inflammatory drug; SE, standard error.

BPH, benign prostatic hyperplasia; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; D, dementia; DM, diabetes mellitus; HIV, human immunodeficiency virus; HTN HD, hypertensive heart disease; IHD, ischemic heart disease; MBDBI, medication-based disease burden index; PD, Parkinson's disease; PUD, peptic ulcer disease; SD, skin disease; Tb, tuberculosis; vHep, viral hepatitis.
(Supplemental Table 1).

Statistical analysis

Baseline characteristics of AD and non-AD patients in the study population were compared using one-way analysis of variance (ANOVA); Tukey's test was performed to determine the differences between the groups. The primary outcome by NSAID exposure was analyzed by using the Fisher's exact or Chi-square test, where appropriate. The Bonferroni correction was used to adjust the *p* value for multiple comparisons. Cox regression survival analysis was used to analyze AD over time with drug exposure as the independent variable. Age at the end of the study, time on NSAID and the MBDBI comorbidity index were covariates. Diclofenac–naproxen matched propensity-score analysis was done using logistic regression and reporting an odds ratio (OR) tested with McNemar for paired samples. SPSS v.25 (IBM SPSS, Chicago, IL USA) was used to conduct the statistical analyses.

Results

Study patients

Data were available for veterans receiving diclofenac ($n = 1431$), etodolac ($n = 14{,}646$), and naproxen ($n = 12{,}203$; Table 1). At the end of the study, patients in the diclofenac group were significantly younger (63.9 years) ($p < 0.01$) than naproxen (65.5 years) and etodolac patients (66.6 years) and had a lower MBDBI disease burden index, both p values <0.01. There were slightly but not significantly more males in the naproxen (92.8%) and etodolac (93.8%) groups compared with diclofenac (91.6%; Table 1).

AD development

AD patients' characteristics did not significantly differ between groups (Table 2). AD occurred in 328/14,646 patients [2.24%; 95% confidence

interval (CI): 2.01–2.49] in the etodolac group, 202/12,203 patients (1.66%; 95% CI: 1.44–1.90) in the naproxen group and in 4/1431 patients (0.28%; 95% CI: 0.076–0.714) in the diclofenac group. The frequency of AD in the diclofenac group was significantly lower than other groups (Table 3). The unadjusted AD prevalence was higher in both the naproxen and etodolac groups compared with diclofenac [Figure 1(a–c)]. Incidence of AD based on patient years of NSAID exposure [Figure 2(a–c)] between groups parallel those of the AD prevalence. In the combined cohort, etodolac had a slightly higher unadjusted incidence rate of AD than naproxen but both are significantly higher than diclofenac. Cox regression survival analysis of AD for the study NSAIDs indicated a significant protective effect of diclofenac [Figure 3(a–c)] compared with naproxen (reference group). Naproxen is a commonly used NSAID that has previously been shown to have no effect on the development of AD.[32,33] Thus, naproxen is an appropriate baseline group in the present study. The hazard ratios (HRs) for AD were significantly lower for diclofenac (0.25, $p=0.007$), but not different for etodolac (1.00, $p=0.95$) compared with naproxen after controlling for site, age, and the MBDBI (comorbidity index; Table 4). In addition, the present analysis also revealed that age is an independent predictor of developing AD with an HR of 1.08 ($p<0.001$), the MBDBI (comorbidity index) was shown to be a very significant predictor of AD with an HR of 5.17 ($p<0.001$), and the site was an independent predictor with an HR of 2.71 ($p<0.001$; Table 5).

Discussion

In the present investigation, diclofenac use is associated with a very low 0.28% prevalence of AD, whereas the prevalence for AD with naproxen (1.66%) and etodolac (2.24%) were much higher. After controlling for age, comorbidities and site effects, diclofenac was found to have a significantly lower HR for AD compared with naproxen or etodolac. Subjects in the diclofenac group were healthier at the beginning of the study period than patients in the other groups, perhaps because they were slightly younger at baseline. This may confound the development of an age-related disease such as AD. Therefore, in the final analysis age, comorbidities and site effects were controlled in the Cox regression survival analysis, in which the protective effect of diclofenac

Table 2. Characteristics of the AD population in combined cohort.*

Characteristic	Diclofenac ($n=4$)						Etodolac ($n=328$)						Naproxen ($n=202$)						*p* value* (compared with naproxen)	
	Central ($n=2$)		North Texas ($n=2$)		Combined ($n=4$)		Central ($n=81$)		North Texas ($n=247$)		Combined ($n=328$)		Central ($n=79$)		North Texas ($n=123$)		Combined ($n=202$)		Dc–Nc	Ec–Nc
	M	SE (p§)	M	SE	M	SE	M	SE (p§)	M	SE	M	SE	M	SE (p§)	M	SE	M	SE		
Male (%)	50% (0.9)		100%		75%		93.8% (0.9)		98.4%		97.3%		92.4% (0.9)		97.6%		95.5%		0.18	0.29
**Time on NSAID, years	3.52	0.39 (0.9)	3.87	2.55	3.69	1.06	2.52	0.19 (0.4)	2.34	0.11	2.38	0.10	3.03	0.21 (0.01)	2.41	0.14	2.65	0.12	0.23	0.08
Daily dose, mg	150	0.00 (0.42)	112.5	37.5	131.3	18.7	813	18.0 (0.02)	864	11.1	851.0	9.5	929	17.4 (0.92)	926	16.7	927	12.2	–	
Mean age at start of NSAID, years	78.8	9.36 (0.48)	70.3	3.06	74.6	4.7	70.3	1.21 (0.16)	72.0	0.6	71.6	0.53	66.4	1.4 (0.001)	71.2	0.72	69.3	0.72	0.31	0.01
Age at AD diagnosis, years	83.0	6.97 (0.43)	74.2	5.61	78.6	4.45	74.6	1.2 (0.38)	75.6	0.5	75.3	0.5	73.1	1.2 (0.25)	74.6	0.7	74.0	0.64	0.32	0.12
‡MBDBI	1.16	0.2 (0.44§)	0.92	0.14	1.05	0.12	1.37	0.07 (<0.01§)	1.42	0.03	1.41	0.03	1.39	0.07(<0.01§)	1.37	0.04	1.38	0.04	0.34	0.82

*Both diclofenac and etodolac were independently compared to naproxen using Dunnett's C test, except for gender which was Chi-square or Fisher's exact test where appropriate.
**Equation 1: all *p* values one-way ANOVA with Tukey HSD.
‡Equation 2: all *p* values one-way ANOVA with Tukey HSD.
§*t*-test: equal variance (*p* value) of Central compared with North Texas within this column.
AD, Alzheimer's disease; ANOVA, analysis of variance; Dc, diclofenac combined; Ec, etodolac combined; HSD, honestly significant difference; M, mean; MBDBI, medication-based disease burden index; NSAID, non-steroidal anti-inflammatory drug; Nc, naproxen combined; SE, standard error.

Table 3. Frequency of AD in combined cohort.

	CTX AD frequency	*p* values*	NTX AD frequency	*p* values*	AD frequency	*p* values*
Diclofenac	0.23%	–	0.36%	–	0.28%	–
Etodolac	1.43%	0.002	2.75%	<0.001	2.24%	<0.001
Naproxen	1.08	0.02	2.52%	<0.001	1.66%	<0.001

*Diclofenac compared with etodolac and naproxen *via* Fisher's exact test, *p* values are Bonferroni corrected.
AD, Alzheimer's disease; CTX, Central Texas; NTX, North Texas.

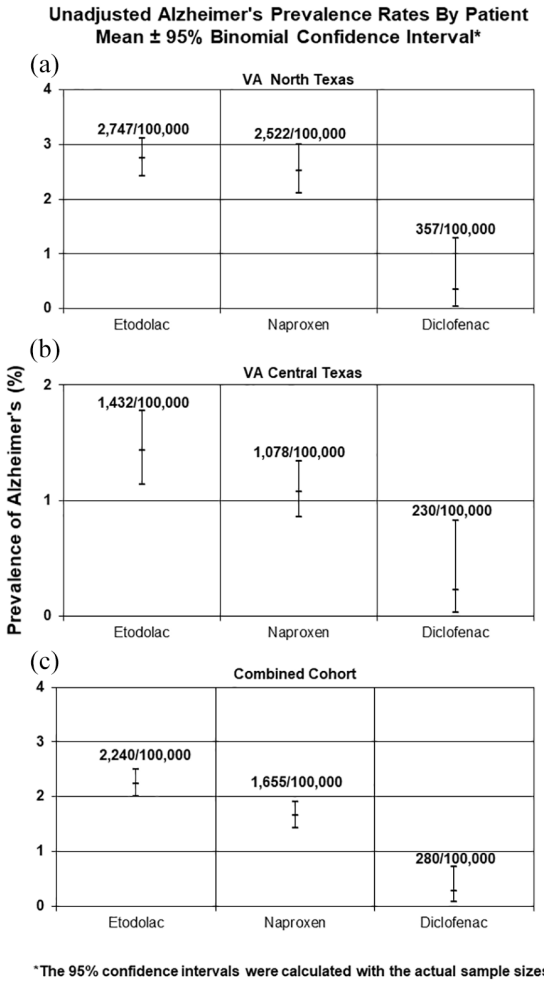

Figure 1. The 95% binomial confidence interval of the prevalence of AD under pharmacotherapy with etodolac, naproxen, and diclofenac based on patient numbers.
The 95% binomial confidence interval of the prevalence of AD under pharmacotherapy with etodolac, naproxen, and diclofenac based on the number of patients in (a) patients at the VA North Texas, (b) the VA Central Texas, and (c) the combined cohort.
AD, Alzheimer's disease; VA, Veteran Affairs.

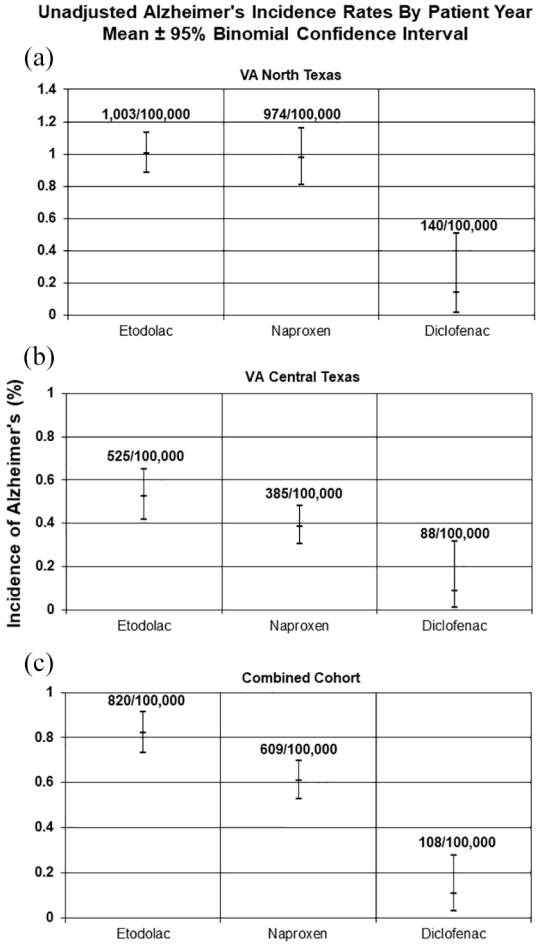

Figure 2. The 95% binomial confidence interval of the incidence of AD under pharmacotherapy with etodolac, naproxen, and diclofenac based on patient years.
The 95% binomial confidence interval of the incidence of AD under pharmacotherapy with etodolac, naproxen, and diclofenac based on patient years in (a) patients at the VA North Texas, (b) the VA Central Texas, and (c) the combined cohort.
AD, Alzheimer's disease; VA, Veteran Affairs.

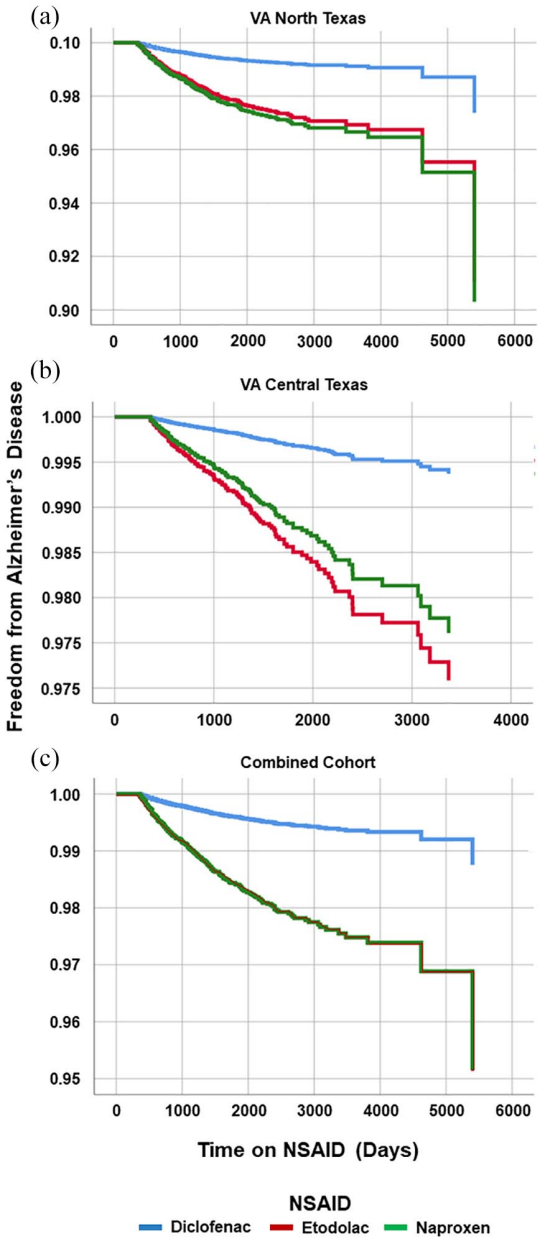

Figure 3. Cox regression survival analysis for freedom from AD controlling for time on etodolac, naproxen, and diclofenac.
Cox regression survival analysis for freedom from AD controlling for time on etodolac, naproxen, and diclofenac in (a) patients at the VA North Texas, (b) the VA Central Texas, and (c) the combined cohort.
AD, Alzheimer's disease; NSAID, non-steroidal anti-inflammatory drug; VA, Veteran Affairs.

remained significant (HR = 0.25, $p=0.007$). A matched propensity analysis yielded a consistent result (OR = 0.23, $p<0.001$).

Table 4. Hazard ratios of the primary outcome controlling for age, site and MBDBI[$*].

Combined				Dallas			Central Texas		
Predictors	**Hazard ratio**	**95% confidence interval**	***p* value**	**Hazard ratio**	**95% confidence interval**	***p* value**	**Hazard ratio**	**95% confidence interval**	***p* value**
Diclofenac	0.25	0.09–0.68	0.007	0.26	0.06–1.06	0.06	0.26	0.06–1.06	0.06
Etodolac	1.004	0.84–1.20	0.949	0.92	0.74–1.14	0.44	1.22	0.90–1.67	0.21
Naproxen reference	1.0	–	–	1.0	–	–	1.0	–	–
Age at end of study, years	1.08	1.07–1.09	<0.001	1.08	1.07–1.10	<0.001	1.08	1.06–1.09	<0.001
MBDBI[$], comorbidity	5.17	4.60–5.81	<0.001	6.05	5.28–6.93	<0.001	3.63	2.94–4.49	<0.001
Site	2.71	2.24–3.29	<0.001	–	–	–	–	–	–

[$]MBDBI, medication-based disease burden index.
*Compared with naproxen.

Table 5. Matched propensity-score analysis.

	Alzheimer's disease	
	No	**Yes**
Naproxen	1414	17
Diclofenac	1427	4

OR = 0.23, 95% CI: 0.08–0.70, $p < 0.001$.
McNemar's test $p < 0.001$.
CI, confidence interval; OR, odds ratio.

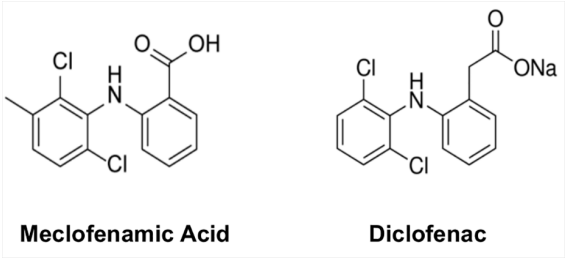

Figure 4. Chemical structures of meclofenamic acid and diclofenac.

Several studies analyzed chronic NSAID use and the AD progression, but with contradictory results. In one study of 246,199 veterans ⩾50 years of age (1 October 1998 to 30 September 2005) who were AD free at baseline, 49,349 had a new diagnosis for AD during the study period. Ibuprofen and naproxen were the most frequently used NSAIDs.[28] In their retrospective study, the OR of AD seemed to decrease with longer durations of NSAID use.[28] The OR for AD among patients with NSAID use ⩽1 year was 0.98 (95% CI: 0.95–1.00) compared with 0.76 (95% CI: 0.68–0.85) for those who used NSAIDs for >5 years.[28] The study showed the protective effects of NSAIDs against AD occurrence, but the investigators reported ORs, and not HRs, as would be appropriate with time-to-event data. Therefore, progression of AD over time cannot be interpreted from their results.

Neither fenamate NSAIDs nor adequate sample-sized diclofenac studies were included in previous large-scale retrospective studies of AD. The studies by Joo and colleagues[39] and Daniels and colleagues[40] reviewed a fenamate NSAID, mefenamic acid and AD. The effect of mefenamic acid on mouse models of AD was marked. There are several reasons why a protective effect has not been discovered by clinical observation. First, fenamate NSAIDs may have no beneficial AD effect in humans, as animal models have limited predictive value in humans. Secondly, fenamate NSAIDs were released to the market in the early 1960s and were generically available in the early 1980s. They have not been marketed to physicians or patients, leading to low utilization. Finally, when fenamate NSAIDs were used, they were primarily marketed for menstrual symptoms, primarily limiting their use to women <50 years of age, who are very unlikely to have AD.

For agents utilized in central nervous system (CNS)-related diseases such as AD, CNS bioavailability is a requirement. A study in 2005 by Fukada and colleagues[47] studied the brain penetration of diclofenac and mefenamic acid compared with acetaminophen in unstressed mice and in mice with actively induced inflammation. Diclofenac and mefenamic acid had good brain penetration, with or without active inflammation, probably due to the drugs' carboxyl groups and an anion transport system into the CNS. Fukuda and colleagues stated, 'These data suggest that diclofenac might potentially penetrate into brain more so than other COX inhibitors used in this study.'[47] In addition, Zecca and colleagues demonstrated that diclofenac achieves significant cerebrospinal fluid (CSF) levels in adults.[48] Similarly, a study of 31 children found that diclofenac penetrates well into the CSF with levels significant enough to block cyclooxygenase for nociceptive effects and peroxisome proliferator-activated receptor-gamma involved in the inhibition of microglia-associated inflammatory pathways.[49]

Diclofenac's chemical structure is similar to meclofenamic acid, a fenamate NSAID that inhibits IL-1β release (Figure 4). Diclofenac is also associated with a significant reduction in IL-1β, suggesting the drug may be associated with protection against AD as data suggest for fenamate NSAIDs. Evidence of a protective effect of fenamate NSAIDs against AD is in a small, randomized, double-blind trial of diclofenac/misoprostol *versus* placebo in AD by Scharf and colleagues.[50] In this small prospective study of 25 weeks in patients with Alzheimer's disease, there was no detectable statistical difference in cognition, but the authors did state that their small sample size (diclofenac = 12 and placebo = 17) was the likely reason. Nevertheless, a beneficial trend in mini mental-state examination was noted.

After our study was initiated, other investigators published an abstract from an AD patient registry and noted a beneficial effect from diclofenac.[45] This is consistent with the aforementioned study,[50] which trended toward a protective effect of diclofenac.

The results of the present study are compelling, despite several limitations. The primary limitations of this study are (a) small sample size and (b) retrospective design that can only demonstrate associations, but not causation. In addition, patients' compliance with prescribed regimen can only be assessed by prescription refill history in the US Department of VA EMR, a method inferior to prospective pill counts. Small sample sizes did not allow for matching on baseline characteristics of patients in the NSAID groups. If an AD protective effect exists, it is unknown how long any protective effect of an NSAID might last post exposure.

Conclusion

Diclofenac is chemically related to fenamate NSAIDs, which have been shown to improve cognition in two separate studies using known AD mouse models. Here, we show in two independent cohorts that diclofenac is associated with a much lower incidence of AD when compared with drugs known to not affect AD, namely etodolac and naproxen. Diclofenac is also actively transported into the CNS and has been shown to lower Aβ. The results for diclofenac are promising, and suggest that diclofenac may also be associated with a decreased hazard of developing AD. A randomized prospective study is needed to determine if diclofenac is an effective treatment against the development of AD.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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