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Real-world effects of anti-dementia treatment on mortality in patients with Alzheimer´s dementia

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Abstract

To examine the real-world effects of the cholinesterase inhibitors (AChEI) on all-cause mortality. A nationwide, retrospective cohort study. Participants were diagnosed with incident AD in Denmark from January 1, 2000 to December 31, 2011 with follow-up until December 31, 2012. A total of 36,513 participants were included in the current study with 22,063 deaths during 132,426 person-years of follow-up. At baseline, patients not treated with AChEI (n = 28,755 [9961 males (35%)]) had a mean age ± standard deviation (SD) of 80.33 ± 7.98 years (78.97 ± 8.26 for males and 81.04 ± 7.98 for females), as compared to 79.95 ± 7.67 (78.87 ± 7.61 for males and 80.61 ± 7.63 for females) in the group exposed at baseline. Patients treated with AChEI had a beneficial hazard ratio (HR) of 0.69, 95% confidence interval (CI) (0.67–0.71) for all-cause mortality as compared to patients not treated, with donepezil (HR 0.80, 95% CI [0.77–0.82]) and galantamine (HR 0.93,95% CI [0.89–0.97]) having beneficial effects on mortality rate as compared to non-treatment, whereas rivastigmine (HR 0.99, 95% CI [0.95–1.03]) was associated with a mortality rate comparable to non-treatment with AChEI. Patients were primarily exposed to donepezil (65.8%) with rivastigmine (19.8%) and galantamine (14.4%) being used less often. These findings underscore the effect of AChEI on not only reducing speed of cognitive decline but also directly prolonging life, which could result in changes in treatment recommendation for when to stop treatment.

Abbreviations: AChEI = cholinesterase inhibitors, AD = Alzheimer´s dementia, ATC = anatomical therapeutic chemical, CI = confidence interval, DDD = daily defined dosages, HR = hazard ratio, ICD = international classification of diseases, MD = medical doctor, MSM = marginal structural modeling, SD = standard deviation.

Keywords: antidementia drugs, dementia, mortality, nationwide, pharmacoepidemiology

1. Introduction

Alzheimer's disease is the most common cause of dementia and incidence increases with increasing age.[1] Worldwide demographic transition with increases in age have raised concerns regarding higher rates of dementia, but secular trends observed in epidemiological studies support a decrease in age-adjusted dementia incidence.[2] Alzheimer´s dementia (AD) is associated with an increased mortality rate in general and an increasing secular trend in mortality rates over the last decades in most studies, albeit a new Danish study has supported an unchanged mortality rate as compared to the general population.[3,4] Average survival time from diagnosis is 4 to 8 years, but with a high variance between subjects.[3] Patients with AD spend a considerable portion of the time from diagnosis till end of life in a state of severe dementia resulting in either nursing home care or dependence on caregivers at home.[3,5]

Symptomatic pharmacological treatment of dementia in connection with Alzheimer´s disease consists of acetylcholinesterase inhibitors (AChEI) or memantine which give short-term cognitive benefits, albeit data have questioned if there is a disease modifying effect beyond the initial 6-18 months of treatment when compared to placebo.[6] AChEI are most effective in mild to moderate dementia, and consensus criteria classify AChEI as inappropriate for severe dementia due to modest evidence supporting the effectiveness and a high risk of adverse events.[7,8] Despite thereof, discontinuation of AChEI is low in patients with severe dementia,[8] perhaps due to a perceived increased risk of behavioral and psychological symptoms of dementia in relation to stopping treatment. Data do,

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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however, not support an increase in behavioral and psychological symptoms of dementia, just as there is no increase in antipsychotic treatment, which is often used to minimize aggressive behavior in patients discontinuing AChEI.[9]

AChEI are generally well-tolerated; however, gastrointestinal symptoms are being reported together with other commonly reported side-effects like agitation, fatigue, dizziness, headache and sleep disturbances.[10] Side-effects are dose-dependent, and a low initial dosage and a slow taper have been proposed to diminish side-effects.[10] Data on effects of AChEI on death have been scarce, but has supported an increased mortality rate in patients treated with rivastigmine, but not donepezil or galantamine using voluntarily reported pharmacovigilance data.[11] The effects of AChEI on mortality in patients with AD has only once been investigated in a RCT supporting a lower mortality rate in patients treated long-term with galantamine as compared to placebo.[12]

1.1. Aims of the study

The aim of this study was to examine the real-world effects of AChEI on the rate of all-cause mortality in a nationwide population of patients diagnosed with AD utilizing marginal structural modeling (MSM) to adjust for confounders.

2. Methods

2.1. Design

A nationwide, population-based, retrospective cohort study.

2.2. Sample

The sample consisted of patients with incident AD defined as either receiving an ICD-10 F00x. diagnosis (Dementia in Alzheimer's disease) or a G30x. (Alzheimer´s disease) diagnosis, from January 1, 2000 to December 31, 2011 from the total Danish population. Persons previously diagnosed with an ICD-8 dementia diagnosis in the period from January 1, 1980 throughout 1993, or an ICD-10 diagnosis of dementia (F00x., F01x., F02x., F03x., G30x., G31x.) in the period from January 1, 1994 throughout 1999 were excluded from the analysis. Patients were followed from diagnosis until December 31, 2012 or death, whichever came first.

2.3. Outcomes

All-cause mortality within the study period.

2.4. Exposure

Participants were classified as having received AChEI (ATC N06DA) at baseline or not. We coded exposure variables as time-dependent with cumulative dosages for each single participant and individual AChEI (tacrine (ATC N06DA01), donepezil (ATC N06DA02), rivastigmine (ATC N06DA03), galantamine (ATC N06DA04), and ipidacrine (ATC N06DA05)). The cumulative AChEI dosages from dementia diagnosis until end of study for each participant were calculated and divided into groups (more than 0 DDDs but less than 400, more than or equal to 400 DDDs but less than 800, more than or equal to 800 DDDs but less than 1600, or more than or equal to 1600 DDDs, and compared to no treatment at all). Participants moved to a new group according to cumulative drug dosage received during the study period.

2.5. Confounding factors

2.5.1. Antipsychotics. Antipsychotics were defined as ATC N05A, excluding lithium (ATC N05AN), and included as time-varying continuous variable, measuring cumulative dosages in number of daily defined dosages (DDDs).

2.6. Severity of AD

The current Danish registers do not include data on severity of AD, and cognitive function. To compensate for these deficits, we used number of psychiatric bed days as proxy markers of disease severity. Severity of AD was included as time-varying variable.

2.7. Psychiatric co-morbid disorder

We defined a psychiatric co-morbidity score ranging from 0 to 5 and determined by the aggregated diagnosis status in the following categories: psychosis, affective disorders, substance misuse, other psychiatric diagnosis, and intentional self-harm. The score was cumulative for all patients since the initiation of the Danish Psychiatric Central Research Registry in 1969. The score has previously been utilized in similar studies.[13–15]

2.8. Somatic co-morbid disease

We divided somatic diseases into the following groups: cardiovascular disease, cancer, infection, diabetes, epilepsy, lower respiratory disease, and other somatic diseases. For the somatic comorbid score, 1 point was added for a diagnosis in each of the groups unless the diagnosis occurred before the age of 51 years for males and 56 years for females, where 2 points were added due to an increased risk associated with early onset of disease. The score was cumulative for all patients since the initiation of the Danish Nation Patient Registry in 1977. The score has previously been utilized in similar studies.[13–15]

2.9. Cardiovascular risk factors

The current Danish registers do not include data on blood pressure or blood test results such as lipid and glucose levels. General practitioners examining and treating the majority of patients diagnosed with hypertension, increased lipids, or type II diabetes do not record diagnoses in the Danish healthcare registers, and we therefore utilized prescription data proxy measures of arterial hypertension (antihypertensive drugs [ATC C02]), increased cholesterol (drugs used to lower lipids [ATC C10]), and drugs for treatment of diabetes (blood glucose lowering drugs [excl. insulins]: ATC A10B, A10XA; insulins: ATC A10A) in addition to the actual diagnoses (see above under somatic co-morbid disease).

2.10. Statistical analysis

Initially, we conducted a descriptive analysis on above defined confounders at baseline comparing subjects on whether they received AChEI or not. Continuous variables were presented as means and standard deviations (SD) and compared using the student's *t* test, while factor variables were presented as frequencies and percentages and compared using the chi-squared test.

We employed MSM in the primary and secondary analyses to adjust for time-varying cumulative use of antipsychotics, thereby lowering the risk of introducing selection bias. Moreover, we incorporated stabilized weights for the inverse propensity scores as well as inverse probability of censoring weights. We used all defined confounders including age and sex as independent factors for the denominator and all but the time-varying variables for the numerator. Subjects were followed from incident diagnosis of dementia until death or end of study whichever came first. In the analysis of individual AChEI, we utilized truncated stability weights to adjust for

later treatment with other AChEI to minimize the effects of channeling bias. In the analysis, patients exposed to an individual AChEI were compared to the remaining group of other AChEI and non-treated, and the analysis was then adjusted for remaining AChEI.

All analyses were performed in Stata 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

A *P* value below .05 was considered statistically significant.

2.11. Registers used in the study

Data on psychiatric contacts and psychiatric disorders were retrieved from the Danish Psychiatric Central Research Register[16] and Danish National Patient Register[17] from which data on hospital contacts and somatic diseases also were retrieved.

Data on deaths were retrieved from the Danish Register of Causes of Death.[18]

Data on prescription of medication were retrieved from the Danish National Prescription Registry,[19] albeit data on inpatients´ medication use linked to the individual patients are not available. To minimize the effects thereof, we assumed that patients had been treated with a specific drug during hospitalization if a prescription was redeemed within ten days after discharge, just as we assumed that medications were continued during hospitalization.

All register data were linked to each individual patient via the unique personal identification number assigned to all residents at birth or upon immigration.

3. Ethics

The Danish Data Protection Agency, the Danish Health Authority and Statistics Denmark approved data access for the study (data are not subject to public access). No ethical research committee approval was needed, as data were obtained from registers for statistical purposes only.

4. Results

A total of 36,513 (12,896 males [36%]) participants were included in the current study with 22,063 deaths (8234 males [37%]) for 132,426 person-years (42,714 person-years in males [32%]) of follow-up. At baseline, patients not treated with AChEI (n = 28,755 [9961 males (35%)]) had a mean age ± SD of 80.33 ± 7.98 years (78.97 ± 8.26 for males and 81.04 ± 7.98 for females), as compared to 79.95 ± 7.67 (78.87 ± 7.61 for males and 80.61 ± 7.63 for females) in the group exposed at baseline. No statistically significant differences between groups were observed on cardiac risk factors, mean somatic score, mean cumulative psychiatric antipsychotic drug dosage as well as mean cumulative psychiatric bed days. Patients exposed to AChEI at baseline were more frequently males, had a shorter follow-up in the study and a higher mean psychiatric score as shown in Table 1.

Through MSM, adjusted for antipsychotic drug use, AD severity, psychiatric and somatic co-morbidities as well as cardiovascular risk factors, we showed that patients treated with AChEI had a beneficial hazard ratio (HR) 0.69, 95%CI (0.67–0.71), $P < .001$ for all-cause mortality as compared to patients not treated. When comparing individual AChEI to no treatment, donepezil (HR 0.80, 95%CI [0.77–0.82]) and galantamine (HR 0.93, 95%CI [0.89–0.97]) had beneficial effects on mortality rate as compared to non-treatment, whereas rivastigmine (HR 0.99, 95%CI [0.95–1.03]) was associated with a mortality rate comparable to non-treatment with AChEI. Similar effects on all-cause mortality were seen independently of increasing cumulative cholinesterase inhibitor drug dosages, as shown in Table 2.

At the end of study, males and females were distributed similarly when comparing the different groups defined by cumulative AChEI dosages, but with an increasing mean duration at end of study for patients exposed to increasingly higher dosages, as shown in Table 3.

In the current study, patients were primarily exposed to donepezil (65.8%) with rivastigmine (19.8%) and galantamine (14.4%) being used less often, as shown in Table 4. Tacrine and ididacrine were not marketed in Denmark during the study period.

Table 1

Demographics at baseline.

Antidementia drug	Not prescribed	Prescribed	*P*
n	28,755	7758	
Mean age in yrs (SD)	80.33 (7.98)	79.95 (7.67)	**<.001**
Male sex (%)	9961 (34.6)	2935 (37.8)	**<.001**
Cardiovascular risk factors present (%)	8129 (28.3)	2208 (28.5)	.751
Mean somatic score (SD)	2.47 (1.34)	2.46 (1.32)	.822
Mean psychiatric score (SD)	0.36 (0.67)	0.40 (0.68)	**<.001**
Mean cumulative antipsychotic drug dosage (SD)	32.42 (266.16)	38.82 (276.21)	.062
Mean cumulative psychiatric bed days used (SD)	8.05 (70.79)	8.98 (51.96)	.277

SD = standard deviation.

Table 2

Mortality and cumulative cholinesterase inhibitor dosage in patients exposed as compared to non-exposed.

Cumulative cholinesterase inhibitor dosage	Hazard Ratio	Std. Err.	z	95% CI		*P*
0 > DDDs < 400	0.71	0.014	-17.05	0.68	0.74	<.001
400 ≥ DDDs < 800	0.69	0.016	-15.90	0.66	0.72	<.001
800 ≥ DDDs < 1600	0.69	0.015	-16.85	.066	.072	<.001
DDDs ≥ 1600	0.68	0.017	-15.39	.065	0.71	<.001

CI = confidence interval, DDD = daily defined dosages, Std. Err. = standard error.

Table 3

Description of patients stratified according to cumulative exposure to cholinesterase inhibitors.

Cumulative cholinesterase inhibitor dosages	DDDs = 0	0 > DDDs < 400	400 ≥ DDDs < 800	800 ≥ DDDs < 1600	DDDs ≥ 1600
n	9137	6713	5363	7921	7379
Mean age in yrs at baseline (SD)	84.60 (8.09)	83.75 (7.38)	83.01 (7.52)	83.33 (7.35)	84.30 (7.59)
Male sex (%)	3281 (35.9)	2462 (36.7)	1968 (36.7)	2790 (35.2)	2395 (32.5)
Mean duration in study (months) at endpoint (SD)	31.87 (24.30)	33.92 (26.98)	34.10 (22.52)	45.58 (22.31)	71.32 (27.12)
Mean cumulative drug dosage at endpoint (SD)	0.00 (0.00)	166.94 (117.99)	582.30 (117.16)	1155.07 (230.22)	2490.50 (796.42)

DDD = daily defined dosages, SD = standard deviation.

Table 4

Distribution of patients treated with investigated drugs.

ATC code	Drug name	Cumulative dosages in DDDs (SD)	# patients exposed	Male sex (%)
N06DA02	Donepezil	1204.8 (1045.5)	19,952	34.1
N06DA03	Rivastigmine	562.0 (545.8)	6003	38.1
N06DA04	Galantamine	1060.1 (954.0)	4379	36.4

ATC = anatomical therapeutic code, DDD = daily defined dosages.
#number of SD: Standard Deviation.

5. Discussion

In total, 36,513 persons (with 30,334 exposed to AChEI) were followed for 132,426 person years over a study period of 13 years in which 22,063 deaths occurred. Through MSM we were able to show a beneficial HR of 0.69, 95%CI (0.67–0.71) for those exposed to AChEI in a model adjusted for age, gender, severity of AD, psychiatric and somatic co-morbidity as well as antipsychotic drug treatment. Furthermore, we were able to show that donepezil and rivastigmine were associated with a lower mortality rate than galantamine or non-treatment with AChEI.

Previous pharmacovigilance data have supported a decreased mortality rate associated with donepezil treatment, and an increased mortality rate associated with rivastigmine treatment, albeit in a selected and small study population and utilizing unadjusted models with data being reported voluntarily risking underreporting or systematic biases.[11]

Utilizing data from Medicaid databases, real-world effects of AChEI on all-cause mortality stratified according to drug administered have been investigated in a study by Bhattacharjee et al (2019), who showed a general lowered mortality rate in patients exposed in a model utilizing inverse probability weighting to adjust for confounders, similar to the present study, albeit almost exclusively investigating the effects of donepezil, being more than 80% of the sample of AChEI exposed participants.[20] Their results and model used are similar to the present study, but contrary to Bhattacharjee et al (2019), we were able to investigate the effects on AChEI on a dataset only consisting of 2/3 donepezil exposed patients, and with the remaining patients being exposed to other AChEI.

Utilizing the healthcare registers in Taiwan, the effect of anti-dementia treatment was investigated in a nationwide sample consisting of more than 12,000 patients with a mean follow-up of more than 3 years, showing no significant difference in mortality rate ratio when comparing patients with degenerative dementia exposed to anti-dementia medication to matched controls utilizing survival analysis, in a model adjusted for sex, age, socioeconomic status, urbanity and comorbidity.[21] The authors did show, that not being treated with medication was associated with an increased hazard rate ratio of death during the study. The main finding here is not in contrast to our results when mainly focusing on degenerative dementia, but is based on a wider selection of treatments including both AChEI and memantine.[21]

The findings by Wu et al (2015) were similar to the findings of a Swedish nationwide study investigating the effects of AChEI on mortality and myocardial infarction.[22] Nordström et al (2013) investigated a population of 7073 persons followed for a mean period of 503 days showing a reduced risk of death similar to our study,[22] albeit in a significantly smaller sample and with a shorter follow-up utilizing Cox regressions modeling.

Furthermore, Carney et al (2019) by utilizing data on patients from British Columbia, established a cohort of 29,047 patients to investigate the effects on mortality rates in patients exposed to AChEI utilizing a propensity score-adjusted cohort model, showing mainly no effects of AChEI on mortality rates in exposed patients.[23]

Lastly, data from a randomized controlled trial with more than 1000 exposed participants showed a decreased mortality rate over a 2 year period in patients exposed to galantamine as compared to placebo.[12] RCTs are the golden standard from a methodological view-point limiting sources of confounding and selection bias, but with an inherent risk of not representing the clinical sample of patients due to the in- and exclusion criteria selected.[24] In the study by Hager et al (2014), patients with known cerebrovascular disease or psychiatric disorder were excluded, as were patients with epilepsy, hepatic, renal or pulmonary disturbances or patients with urinary flow obstructions minimizing generalizability to the broader clinical population.[12] In the present study, including all treated, adjusting for confounders, we find a similar effect of rivastigmine on mortality rates, albeit with larger effects in patients exposed to donepezil.

Previous studies have used various methodologies to investigate a possible association between exposure and mortality rates, some of which are like the methodology employed. In the current study, we used MSM in which a propensity score for exposure was initially estimated. Secondly, an inverse probability weight for being exposed was calculated to create a weighted sample unconfounded by known covariates. The model minimizes residual confounding and helps establishing unbiased groups for comparison resulting in causal effects being estimated.[25,26] Utilizing this approach, we can determine the effects of AChEI on mortality rates in patients with AD over a long follow-up period in more patients than previously investigated covering a nationwide sample in which treatment is freely available increasing the generalizability of findings to all diagnosed with AD. Furthermore, we included all patients with AD treated with AChEI, despite of previous psychiatric disorders or somatic

disease which might influence mortality, but have adjusted for the effects thereof in the analyses.[27]

5.1. Strength and limitations

The main strength of the study is the use of the extensive Danish healthcare registers enabling a 13-year study period with no loss to follow-up. In the current study, we have investigated the, to our knowledge, largest sample to date with treatment stratified between 3 different AChEI in a population with AD, contrasting other studies mainly investigating a single drug. The validity of the AD diagnosis in the Danish registers is high as is the validity of our primary outcome.[18,28] Healthcare in Denmark is free and accessible to all, removing a potential confounder as compared to other studies in which free and easy access to healthcare for all is less available.

There are also several limitations to the current study. First, treatment exposure was based on whether patients redeemed prescriptions. We cannot be certain that the patients were actually taking the prescribed medication, yet we assume that when patients redeem prescriptions, they intent to take their medications and patients with AD most often have caregivers ensuring compliance. Second, there is no information specifically regarding severity of AD, albeit we adjusted utilizing proxy measures thereof. Third, the study employs a long study period, which entails a risk of treatment patterns and guideline recommendations for treatment of dementia having changed. However, we indirectly accounted for these changes by comparing exposed to non-exposed patients as well as adjusting for calendar year in the statistical model. Fourth, the data represents associations between AChEI exposure and mortality rates in patients with AD, in which new or different treatment options and paradigms may have impacted mortality rates. In the analyses investigating effects of individual AChEI we adjusted for treatment with other AChEI, resulting in numerically smaller reductions in HR as compared to the overall analyses in which all AChEI were compared to patients not treated. Despite adjusting for multiple confounders in the MSM analysis, it is possible that some residual confounding may have occurred.

6. Conclusions

In the largest study to date, to our knowledge, investigating the effects of AChEI on mortality in patients with AD, we showed a 29% to 33% reduced mortality rate in those exposed as compared to the non-exposed. The effects were driven by a decreased mortality rate in patients exposed to donepezil and galantamine, whereas no effects on mortality rate was observed in patients treated with rivastigmine. These findings underscore the effect of AChEI on not only reducing speed of cognitive decline but also directly prolonging life, which could result in changed recommendations for when to stop treatment.

Author contributions

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