RESEARCH ARTICLE

Association of Terazosin, Doxazosin, or Alfuzosin Use and Risk of Dementia With Lewy Bodies in Men

Alexander Hart, MD, MPH, Georgina Aldridge, MD, PhD, Qiang Zhang, MD, Nandakumar S. Narayanan, MD, PhD, and Jacob E. Simmering, PhD

Correspondence
Dr. Simmering
jacob-simmering@uiowa.edu

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Abstract

Background and Objectives

Terazosin, doxazosin, and alfuzosin (Tz/Dz/Az) are α-1 adrenergic receptor antagonists that also bind to and activate a key adenosine triphosphate (ATP)–producing enzyme in glycolysis. It is hypothesized that the increase in energy availability in the brain may slow or prevent neurodegeneration, potentially by reducing the accumulation of alpha-synuclein. Recent work has suggested a potentially neuroprotective effect of the use of Tz/Dz/Az in Parkinson disease in both animal and human studies. We investigated the neuroprotective effects of Tz/Dz/Az in a closely related disease, dementia with Lewy bodies (DLB).

Methods

We used a new-user active comparator design in the Merative Marketscan database to identify men with no history of DLB who were newly started on Tz/Dz/Az or 2 comparator medications. Our comparator medications were other drugs commonly used to treat benign prostatic hyperplasia that do not increase ATP: the α-1 adrenergic receptor antagonist tamsulosin or 5α-reductase inhibitor (5ARI). We matched the cohorts on propensity scores and duration of follow-up. We followed up the matched cohorts forward to estimate the hazard of developing DLB using Cox proportional hazards regression.

Results

Men who were newly started on Tz/Dz/Az had a lower hazard of developing DLB than matched men taking tamsulosin (n = 242,716, 728,256 person-years, hazard ratio [HR] 0.60, 95% CI 0.50–0.71) or 5ARI (n = 130,872, 399,316 person-years, HR 0.73, 95% CI 0.57–0.93). while the hazard in men taking tamsulosin was similar to that of men taking 5ARI (n = 159,596, 482,280 person-years, HR 1.17, 95% CI 0.96–1.42). These results were robust to several sensitivity analyses.

Discussion

We find an association in men who are taking Tz/Dz/Az and a lower hazard of DLB compared with similar men taking other medications. When combined with the literature of Tz/Dz/Az on Parkinson disease, our findings suggest that glycolysis-enhancing drugs may be broadly protective in neurodegenerative synucleinopathies. A future randomized trial is required to assess these associations for causality.

Classification of Evidence

This study provides Class III evidence that Tz/Dz/Az use reduces the rate of developing DLB in adult men.

From the Department of Neurology (A.H.), University of Michigan, Ann Arbor; Departments of Neurology (G.A., Q.Z., N.S.N.) and Internal Medicine (J.E.S.), University of Iowa, Iowa City.

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Glossary

5ARI = 5α-reductase inhibitor; **AD** = Alzheimer disease; **ATP** = adenosine triphosphate; **Az** = alfuzosin; **BPH** = benign prostatic hyperplasia; **CPT** = Current Procedural Terminology; **DLB** = dementia with Lewy bodies; **Dz** = doxazosin; **HR** = hazard ratio; ***ICD-9-CM*** = *International Classification of Diseases, Ninth Revision, Clinical Modification*; ***ICD-10-CM*** = *International Classification of Diseases, 10th Revision, Clinical Modification*; **PD** = Parkinson disease; **PGK1** = phosphoglycerate kinase-1; **PSA** = prostate-specific antigen; **Tz** = terazosin.

Introduction

Dementia with Lewy bodies (DLB) is a progressive neurodegenerative disorder characterized by cognitive impairment, parkinsonism, dysautonomia, sleep disorders, hallucinations, and cognitive fluctuations.[1] Incidence of DLB has been estimated to be 0.5–1.6 per 1,000 people-per-year and 3.2%–7.1% of cases with dementia.[2] Because age is a primary risk factor, DLB incidence will increase as the population ages.[2] Current pharmacotherapy for DLB focuses on mitigation of symptoms, largely using acetylcholine esterase inhibitors and levodopa. To date, there are no known preventative or disease-modifying treatments for DLB. Finding modifiable risk factors and preventive treatments has the potential to reduce DLB-related morbidity and mortality.[3]

Recently, impaired energetics has been explored as a potential target for the prevention and treatment of neurodegenerative diseases, especially Parkinson disease (PD). Impaired metabolic activity, whether due to genetic causes[4] or exposure to mitochondrial toxins,[5] is associated with PD and PD-like symptoms. Improvement of metabolic activity may decrease the risk of PD. Of interest, the commonly used α-1 blockers terazosin (Tz), doxazosin (Dz), and alfuzosin (Az; collectively Tz/Dz/Az) were found to have an additional target: phosphoglycerate kinase-1 (PGK1), the first adenosine triphosphate (ATP)–producing enzyme in glycolysis. In cell lines, animal models, and people with PD, the use of Tz/Dz/Az increases ATP availability.[6,7] In addition, several case reports of genetic PD have been linked to mutations affecting PGK1.[8-10] In preclinical models of PD, the use of Tz/Dz/Az has decreased alpha-synuclein aggregation and neuronal loss.[11] The working hypothesis is that increased ATP availability in neurons resulting from the activation of PGK1 allows better adaptation to the cellular challenges of aging and synuclein aggregation. These preclinical results are supported by several international pharmacoepidemiologic cohort studies.[12-16]

Preclinical studies have suggested a more generalized protection against neurodegeneration, including in amyotrophic lateral sclerosis[17] and Alzheimer disease (AD).[18] If the mechanism of action is improved clearance of aggregation resulting from increased cellular energy, such a broad range of action seems biologically plausible. Given these results and considering the pathologic similarities with PD, especially synuclein aggregation, we asked whether glycolysis-enhancing drugs offered protection against the development of DLB.

Tz/Dz/Az are widely used in older men to manage symptoms related to benign prostatic hyperplasia (BPH).[19] DLB is a disease of aging and disproportionality affects men,[20] yielding an alignment between the people at highest risk of DLB and the primary users of these medications. Of importance, tamsulosin, another α-1 blocker, has similar clinical indications and effectiveness[21] but neither binds to PGK1 nor increases ATP. These features make tamsulosin an ideal active comparator—the observational approximation of a placebo—because men taking tamsulosin or Tz/Dz/Az are likely similar on many observed and unobserved characteristics, but tamsulosin is not expected to have any effect on PGK1. For additional rigor, we investigated an additional comparator also used to treat BPH: the 5α-reductase inhibitors (5ARI) finasteride and dutasteride. These drugs have a distinct mechanism from α-1 blockers and have no known increase in neuronal ATP.[22]

Using these 2 comparators (tamsulosin and 5ARI), we sought to estimate the association between use of Tz/Dz/Az and later development of DLB using a retrospective observational cohort study of insurance claims. We hypothesized that men taking Tz/Dz/Az will have a lower hazard of developing DLB than men taking either comparator. This study will provide evidence toward an answer to the question whether Tz/Dz/Az reduces the risk of DLB in adult men.

Methods

Data Source

The Merative Marketscan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases served as our data source. These databases include health insurance claims data for more than 200 million people with private insurance or Medicare supplemental insurance in the United States from 2001 to 2017. This database and our general analytical framework have previously been used to study the hazard of developing PD and PD-related impairment.[11,13,23]

Cohort Construction

We defined our cohort using a new-user active comparator design, the standard for pharmacoepidemiologic studies.[24,25] Specifically, we identified individuals newly started on medications of interest (Tz/Dz/Az) or active comparators (tamsulosin and 5ARI). We identified dispensing events by matching the National Drug Code numbers included for those medications in the 2015 Redbook. For each individual, we identified the first observed dispensing event of the BPH medications and excluded any enrollee who took more than 1

medication group. To ensure the *new-user* element of our design, we required at least 365 days of enrollment with prescription drug coverage before the first observed dispensing date. In addition, we required at least 1 day of follow-up after the medication date. To reduce potential selection effects due to discontinuation, we required at least a second dispensing claim in the in the first year after the index date. Our reasoning was that individuals who only have a single dispensing event are unlikely to be actually taking the medication while those who have a refill are likely users.

The medications are primarily used for the management of BPH, although less common uses exist (e.g., Tz/Dz/Az for hypertension, tamsulosin for kidney stones, and 5ARI for hair loss). As would be expected given the primary use, most users are male (~87% of Tz/Dz/Az or tamsulosin users and 98.5% of 5ARI users). Of concern would be many male users are due to BPH, while none of the female users have BPH.

Female users of Tz/Dz/Az are very different from male users of Tz/Dz/Az. Compared with male users, female users are older (median age of 65 vs 61 years), use more health care (median of 15.3 vs 9.1 outpatient visits per year), and have greater cardiac disease (85% with hypertension vs 66%, 32% with hypertension-related complications vs 15%, 16% with heart failure vs 8%, and 18% with kidney disease vs 9%).

The differences between female users of Tz/Dz/Az and female users of tamsulosin are even greater, with users of Tz/Dz/Az being older (median age of 65 vs 55 years), sicker (85% with hypertension (32% with complications) vs 50% (9% with complications), 16% with heart failure vs 8%, and 18% with chronic kidney disease vs 4%), and using more health care (15.3 vs 12.3 outpatient visits per year).

While propensity score matching may reduce these differences, many important differences may remain unaddressed or unobserved. Our design focuses on male users to mitigate this concern. By using restriction designs, observational studies are better able to mitigate unobserved confounders[26] and yield closer approximations of clinical trial.[27] A male individual newly started on one of the study drugs could have plausibly been started on any of the study drugs; however, such interchangeability does not exist for female users. While restricting to male users necessarily reduces our generalizability, it provides considerable gains in internal validity.

In addition, because BPH and DLB are rare under the age of 40 years, we required enrollees to be at least 40 years of age at the first dispensing date. We excluded anyone with a diagnosis of DLB on or before the medication start date. If a person developed a first diagnosis of DLB after the first medication dispensing event but before the second, they were included in the study.

DLB Case Definition

Patients were defined as having DLB if a claim with 1 or more DLB diagnosis code (*ICD-9-CM*: 331.82 or *ICD-10-CM*: G31.83) in any setting (inpatient or outpatient) was made. A diagnosis of PD with associated dementia/cognitive impairment codes and without a DLB diagnosis was not counted as a case. We defined our outcome date as the first date that the person is diagnosed with DLB.

Propensity Score Matching

To reduce differences between the study cohorts, we used propensity score matching. Our hypothesized relationships are summarized as a directed acyclic graph in eFigure 1. The propensity score included the year of medication start; age at medication start; the number of days with claims for outpatient services divided by the total lookback time; the mean number of unique diagnoses recorded per outpatient visit; the total number of unique outpatient diagnoses during the lookback period divided by the lookback time; the incidence of hospitalization during lookback; a diagnosis of BPH (*ICD-9-CM*: 600.xx or *ICD-10-CM*: N40.x) on or before the index date; whether prostate specific antigen (PSA) levels were measured (Current Procedural Terminology [CPT]: 84152, 84153, 84154) or were diagnosed as abnormal (*ICD-9-CM*: 790.93, *ICD-10-CM*: R97.2, R97.20, R97.21); a diagnosis of slow urinary stream (*ICD-9-CM*: 788.62, *ICD-10-CM*: R39.12); whether a uroflow study was performed (*ICD-9-CM* procedure code: 89.24, *ICD-10-CM* procedure code: 4A1D75Z, CPT: 51736, 51741); whether a cystometrogram was collected (*ICD-9-CM* procedure code: 89.22, *ICD-10-CM* procedure code: 4A0D7BZ, 4A0D8BZ, 4A1D7BZ, 4A1D8BZ, CPT: 51725, 51726); a diagnosis of orthostatic hypotension (*ICD-9-CM*: 458.0 or *ICD-10-CM*: I95.1); a diagnosis of other hypotension (*ICD-9-CM*: 458.1, 458.2x, 458.8, 458.9 or *ICD-10-CM*: I95.0, I95.2, I95.3); and the 30 Elixhauser comorbidities, as revised by Agency for Healthcare Research and Quality.[28]

For the year of medication start, we included a series of dummy variables because we expected changes in medication use patterns, the rate of diagnosis of DLB, and the sample included in the Marketscan database over time. The contribution of data from specific insurance companies to Marketscan changes over time with some companies ending or starting their contribution at the end of the year, potentially causing large changes in the size and composition of Marketscan. Including dummy variables for year reduces these problems. We used splines for the continuous variables (e.g., rate of outpatient encounters during lookback, age) to allow for nonlinear responses. We estimated the propensity score using logistic generalized additive models.

We used a 2-step matching algorithm. First, we required the time from the medication start date to the end of enrollment in the Marketscan database to be similar (±90 days) to ensure balance in time-at-risk between the cases and controls. Second, within the set of possible matches with similar follow-up, we used greedy nearest-neighbor matching based on the estimated log odds.[29] To ensure matches were of high quality, we imposed a caliper equal to 20% of the pooled standard deviation of the log odds. We matched 1:1 without

replacement. In the event of multiple equally good matches, we selected the matching control observation at random. We then had 3 matched cohorts for the 3 comparisons of interest: Tz/Dz/Az vs tamsulosin, Tz/Dz/Az vs 5ARI, and tamsulosin vs 5ARI.

Assessing Propensity Score Match Balance

Groups were compared before and after matching on all variables included in the propensity score model. We used Cohen *d* to assess balance. Cohen *d* is a common standardized measure of effect size between groups. We predefined the absolute value of Cohen *d* of <0.1 as indicating minimal difference between the various covariates.[30,31]

Analysis

Our primary outcome variable was time from medication start to the diagnosis of DLB. Our estimand is the average treatment effect in the treated. For men who are not diagnosed with DLB before leaving the Marketscan database or December 31, 2017, we censored follow-up on the last observed date. The division of time into lookback, follow-up, and the event or censoring dates are described in eFigure 2. We estimated the survival function using the Kaplan-Meier estimator and tested for equality of the survival curves using the log-rank test. We quantified the difference in survival using Cox proportional hazards regression using robust errors clustered by the pairing generated through the propensity score matching. The proportional hazards assumption was assessed using the Schoenfeld residuals.

Sensitivity Analyses

First, we estimated Cox models with time-interacted covariates to mitigate any violations of the proportional hazards assumption. A major concern would be if the first year had very different hazard ratios (HRs) than the later years, suggesting treatment selection was endogenous to the future outcome. This may happen if people were sorted between treatments by (unobserved) risk of orthostatic hypotension, a symptom of DLB.[32] People with undiagnosed DLB causing orthostatic hypotension may be preferentially prescribed non–Tz/Dz/Az therapies for BPH. If this were the case, we may see a strong association during DLB and treatment choice initially (first 1–2 years) but no association with longer time differences.

Second, we restricted our sample to men with a diagnosis of BPH, elevated PSA, a history of PSA measurement, or other diagnosis or procedure suggestive of urinary dysfunction. Relative to the overall cohort, this smaller subsample should have less heterogeneity in treatment indication. Our estimates should be consistent between the overall sample and this narrow subsample if the groups are truly balanced.

Third, we included the requirement that men have 2 or more claims for dispensing of the medication to count as users of the medication. Men with a single claim are likely not users because these medications are generally used for long time durations as opposed to acute or one-off treatments (e.g., antibiotics). However, this poses a threat: men who immediately discontinue are excluded under this rule. If discontinuation varies by medication and is correlated with our outcome of DLB, as might be the case with orthostatic hypotension, then a bias in favor of Tz/Dz/Az is introduced. To evaluate this threat, we performed an intent-to-treat analysis including anyone who has ever had a dispensing event for the medication.

Fourth, we varied the start of follow-up from immediately upon starting the mediation to 1, 2, or 3 years later. If the HR is substantially different—if it starts low and goes to 1—this is suggestive that treatment selection is endogenous to future DLB risk and the observed results are due to selection effects.

Fifth, we repeated our main analysis using inverse propensity score weighting as opposed to matching, given recent concerns about the validity of propensity score matching.[33] We re-estimate both our main and intent-to-treat models using inverse propensity score weights.

Finally, to ensure our matching on enrollment duration in Marketscan does not introduce a bias related to follow-up time, we repeated our main analysis on a cohort matched only on the propensity score and not on the propensity score and follow-up duration.

All analyses were performed in R 4.2.2,[34] the icd package was used to calculate the Elixhauser comorbidities, the propensity score generalized additive models were estimated using the mgcv package,[35,36] and survival analyses were performed using the survival[37] package. All codes used in this analysis are accessible online.[38]

Standard Protocol Approvals, Registrations, and Patient Consents

All analyses were completed on deidentified precollected data; therefore, it was exempt from institutional review board review. There were no interventions completed in this study on either human or nonhuman subjects. Because the Marketscan database is a secondary use of deidentified data, it is not possible to gather informed consent.

Data Availability

The Merative Marketscan data are used under license from Merative, which prohibits redistribution of the data by the research team. Data may be acquired through licensing with Merative.

Results

We identified 1,128,652 people taking Tz/Dz/Az, 2,552,687 taking tamsulosin, and 918,230 taking 5ARI in the Marketscan database. After applying our exclusion rules (excluding anyone aged 39 years or younger, female,

Table 1 Number of People, Duration of Follow-Up, Number of Cases, and Cumulative Incidence by Cohort, Medication Before and After Propensity Score Matching

	Before matching				After matching			
Medication	**No. of people**	**Person-years**	**No. of cases**	**Cases per 10k per year**	**No. of people**	**Person-years**	**No. of cases**	**Cases per 10k per year**
Tz/Dz/Az vs tamsulosin								
Tz/Dz/Az	126,313	373,989	195	5.21	121,358	363,311	193	5.28
Tamsulosin	437,045	1,195,288	1,286	10.76	121,358	364,945	323	8.85
Tz/Dz/Az vs 5ARI								
Tz/Dz/Az	126,313	373,989	195	5.21	65,436	199,561	111	5.56
5ARI	80,158	248,090	193	7.78	65,436	199,755	152	7.61
Tamsulosin vs 5ARI								
Tamsulosin	437,045	1,195,288	1,286	10.76	79,798	246,086	224	9.10
5ARI	80,158	248,090	193	7.78	79,798	246,194	192	7.80

Abbreviations: 5ARI = 5α-reductase inhibitor; Az = alfuzosin; Dz = doxazosin; Tz = terazosin.

lookback less than 1 year, less than 1 day of follow-up, prior diagnosis of DLB, <2 dispensing claims in the first year of follow-up, or switched between Tz/Dz/Az, tamsulosin, or 5ARI classes), we had 126,313 men taking Tz/Dz/AZ, 437,045 men taking tamsulosin, and 80,158 men taking 5ARI. After matching, we analyzed 121,358 pairs of men (728,256 person-years, mean follow-up = 3.0 years, median follow-up = 2.1 years) in the Tz/Dz/Az vs tamsulosin analysis, 65,436 pairs of men (399,316 person-years, mean follow-up = 3.1 years, median follow-up = 2.2 years) in the Tz/Dz/Az vs 5ARI analysis, and 79,798 pairs of men (482,280 person-years, mean follow-up = 3.1 years, median follow-up = 2.2 years) in the tamsulosin vs 5ARI analysis. A flowchart describing the sample size by inclusion and exclusion steps for each of the 3 cohorts is in eFigure 3. All matched groups were well balanced (the absolute value of Cohen *d* or w less than 0.10) on all included covariates with a good overlap in the estimated scores (eTables 1–3). Summaries of the duration of follow-up and cumulative incidence are reported for each of the 3 cohorts in Table 1.

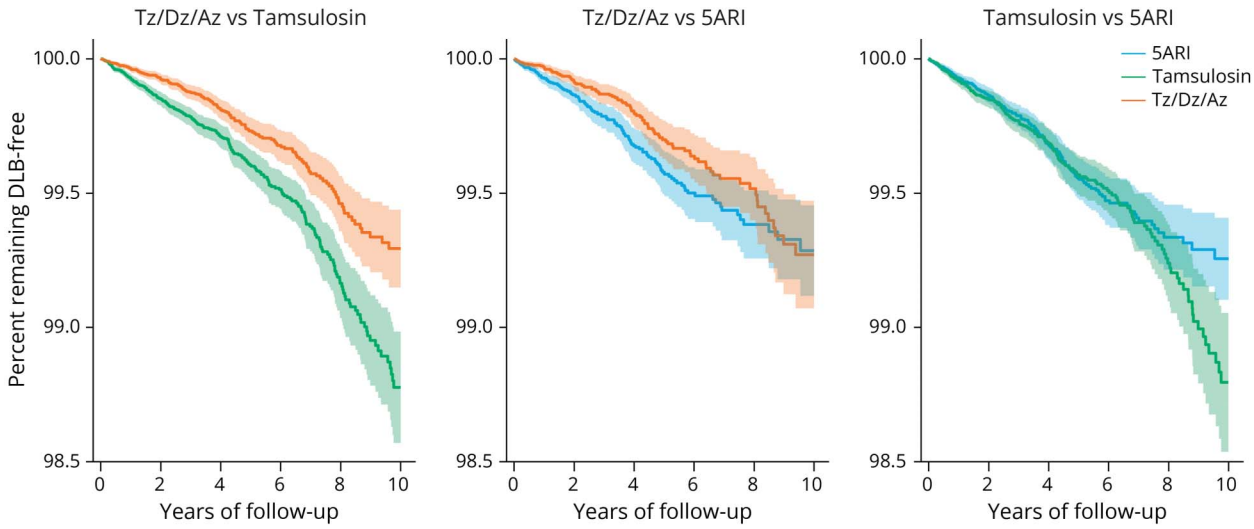
Kaplan-Meier survival curves for the matched cohorts are shown in Figure 1. In the Cox regressions, after matching, men taking Tz/Dz/Az had lower hazards of DLB than men taking tamsulosin (HR 0.60, 95% CI 0.50–0.71) or 5ARI (HR 0.73, 95% CI 0.57–0.93), while men taking tamsulosin had similar hazards to men taking 5ARI (HR 1.17, 95% CI 0.96–1.42). Full details are summarized in Table 2. Accounting for multiple comparisons using a Bonferroni correction, the hazards of DLB among users of Tz/Dz/Az remain statistically significantly lower against those among users of both tamsulosin and 5ARI.

Inspection of the Schoenfeld residuals indicated no meaningful correlation with time for Tz/Dz/Az vs tamsulosin (r = −0.25; 95% CI −0.10 to 0.08; p = 0.803), but potential violations of the proportional hazards assumption for Tz/Dz/Az vs 5ARI (r = 0.14; 95% CI 0.02–0.26; p = 0.022) and tamsulosin vs 5ARI (r = 0.13; 95% CI 0.03–0.22; p = 0.009). We repeated our analysis using time-interactions. The overall estimate and the time-interaction estimate are very similar for at least 5 years of follow-up, eTable 4. Compared with the overall estimates, men taking Tz/Az/Az have a greater reduction in the hazard of DLB during the first few years of follow-up (0–4 years) and closer to a null effect for years 5 and later. The tamsulosin vs 5ARI comparison is consistently near a HR of 1 for years 0–7.5. However, these later periods seem to have poorly estimated HRs, likely due to relatively sparse data at extremely long follow-up periods.

Restriction to men with a BPH diagnosis, PSA measurement, or lower urinary tract symptom–related procedural code had directionally consistent results, eTable 5. Our primary comparison—Tz/Dz/Az vs tamsulosin—remained statistically significant (HR 0.73, 9% CI 0.55–0.97). Men taking Tz/Dz/Az had nonsignificantly lower hazard of DLB than men taking 5ARI (HR 0.87, 95% CI 0.63–1.20), while men on tamsulosin had similar hazard as men taking 5ARI (HR 1.23, 95% CI 0.95–1.59). In each of these analyses, there is a 25% decrease in sample size compared with the overall sample.

Intent-to-treat analysis including all men who ever had a dispensing event for one of the study drugs had estimated results almost identical to the main analysis. Men taking Tz/Dz/Az had lower hazards of DLB than men taking tamsulosin (HR 0.69; 95% CI 0.59–0.81; p < 0.001) or 5ARI (HR 0.75; 95% CI 0.61–0.93; p = 0.010), while the hazard was similar

Figure 1 Kaplan-Meier Survival Curves for Tz/Dz/Az vs Tamsulosin, Tz/Dz/Az vs 5ARI, and Tamsulosin vs 5ARI



Number at risk:

	Tz/Dz/Az	Tamsulosin
Year 0	121,358	121,358
Year 2	61,459	61,826
Year 4	33,055	33,133
Year 6	17,281	17,304
Year 8	8,503	8,491
Year 10	3,638	3,584

Number at risk:

	Tz/Dz/Az	5ARI
Year 0	65,436	65,436
Year 2	34,101	34,212
Year 4	18,201	18,265
Year 6	9,543	9,506
Year 8	4,595	4,596
Year 10	1,926	1,913

Number at risk:

	Tamsulosin	5ARI
Year 0	79,798	79,798
Year 2	42,699	42,426
Year 4	22,607	22,571
Year 6	11,713	11,709
Year 8	5,630	5,591
Year 10	2,287	2,290

All comparisons are after propensity score matching. Shaded regions denote 95% CIs. 5ARI = 5α-reductase inhibitor; Az = alfuzosin; Dz = doxazosin; Tz = terazosin.

between men taking tamsulosin and men taking 5ARI (HR 1.13; 95% CI 0.94–1.35; $p = 0.189$).

In addition, varying the start of follow-up resulted in directionally consistent HRs for all 3 comparisons. Increasing delays of follow-up reduce the sample size leading to broader 95% CIs and reduced power with sample sizes dropping by 50% or more in 3 years. The sample size, number of cases, and estimated HRs are reported in Table 3.

Finally, our analysis using inverse propensity score weights (eTable 6) or when matching only on the propensity score (eTable 7) yielded estimates similar to those arrived at using our 2-step protocol.

Classification of Evidence

This study provides Class III evidence that Tz/Dz/Az use reduces the rate of developing DLB in adult men.

Discussion

We extend prior research studying showing a protective association of Tz/Dz/Az use in PD to the closely related disease of DLB. The protective association with Tz/Dz/Az use is seen in both comparisons against another alpha-blocker tamsulosin and in the clinically but not pharmacologically related 5ARI. There was no significant difference in the hazard of DLB between men who took tamsulosin or those taking 5ARI after matching. While

Table 2 Estimated HR and 95% CIs by Cohort Before and After Propensity Score Matching

		Before matching			After matching		
Treatment	**Reference**	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**
Tz/Dz/Az	Tamsulosin	0.48	0.41–0.56	<0.001	0.60	0.50–0.71	<0.001
Tz/Dz/Az	5ARI	0.67	0.55–0.82	<0.001	0.73	0.57–0.93	0.012
Tamsulosin	5ARI	1.40	1.20–1.62	<0.001	1.17	0.96–1.42	0.116

Abbreviations: 5ARI = 5α-reductase inhibitor; Az = alfuzosin; Dz = doxazosin; HR = hazard ratio; Tz = terazosin.

Table 3 Effect of Delayed Start of Follow-Up on Estimated HR

Comparison	Delay (y)	No. of cases	No. of people	No. of pairs	HR	95% CI
Tz/Dz/Az vs tamsulosin	0	Tz/Dz/Az = 192 Tamsulosin = 322	242,716	121,358	0.60	0.50–0.71
	1	Tz/Dz/Az = 155 Tamsulosin = 231	175,968	87,984	0.67	0.55–0.82
	2	Tz/Dz/Az = 127 Tamsulosin = 158	121,908	60,954	0.80	0.64–1.01
	3	Tz/Dz/Az = 101 Tamsulosin = 141	88,908	44,454	0.72	0.55–0.92
Tz/Dz/Az vs 5ARI	0	Tz/Dz/Az = 107 5ARI = 153	130,872	65,436	0.73	0.57–0.93
	1	Tz/Dz/Az = 91 5ARI = 109	95,754	47,877	0.84	0.63–1.10
	2	Tz/Dz/Az = 76 5ARI = 86	68,158	34,079	0.89	0.65–1.22
	3	Tz/Dz/Az = 54 5ARI = 59	49,414	24,707	0.92	0.63–1.32
Tamsulosin vs 5ARI	0	Tamsulosin = 221 5ARI = 191	159,596	79,798	1.17	0.96–1.42
	1	Tamsulosin = 187 5ARI = 141	118,624	59,312	1.33	1.07–1.65
	2	Tamsulosin = 131 5ARI = 109	84,724	42,362	1.20	0.93–1.55
	3	Tamsulosin = 72 5ARI = 80	61,732	30,866	0.90	0.66–1.23

Abbreviations: 5ARI = 5α-reductase inhibitor; Az = alfuzosin; Dz = doxazosin; HR = hazard ratio; Tz = terazosin.

this does not eliminate the possibility that tamsulosin or 5ARI is associated with dementia, it would require the association between the 2 medication groups, from different classes with different structures, to have a similar association with dementia. Taken together, these data provide evidence for a neuroprotective role of Tz/Dz/Az in the development of DLB.

These results are in broad agreement with the emerging literature for a neuroprotective effect of Tz/Dz/Az. Our research group has previously reported neuroprotective effects in animal models of PD[11] and PD-dementia[23] and finding negative associations between Tz/Dz/Az use and PD symptoms,[11] development of PD dementia,[23] and lower hazard of developing PD in both the United States and Denmark.[12] A pilot clinical trial confirmed increased ATP levels in the brain among people with PD who were given Tz.[39] Our findings of an observational protective association of Tz/Dz/Az were replicated by independent groups using health insurance claims in the United States[15] and Canada.[14] Preclinical animal models of AD in mice[18] and amyotrophic lateral sclerosis in zebrafish, mouse, and neuron models[17] have added support to a neuroprotective role. This emerging evidence of a protective association across a spectrum of diseases suggests a broad neuroprotective effect for Tz/Dz/Az, consistent with our hypothesized mechanism that activation of PGK1 increases brain ATP and mitigates neurodegeneration.

There are functionally no effective, affordable, and safe disease-modifying therapies for these fatal neurodegenerative diseases. Emerging monoclonal antibodies for AD are likely not cost-effective at current prices,[40] but there will be considerable pressure for Medicare to cover these medications. Repurposing an existing Food and Drug Administration–approved medication, such as Tz/Dz/Az, or targeting PGK1 activity may offer greater effectiveness at lower cost.

Any observational study must address many threats of confounding. Unobserved factors may relate both to the outcome of interest and the choice of medication. Our design, a new-user, active comparator design paired with propensity score matching, reduces many threats of confounding and is the gold standard design in pharmacoepidemiology.[24,25,41,42] By using an active comparator, we have a situation where cases or controls could have been started on either the study medication or the control medication. This reduces the risk of unobserved confounders and helps ensure the groups are as homogenous as possible, even before using propensity score matching.

In addition, using a second independent control group of men who are newly started on 5ARI allows us to assess the validity of our tamsulosin control. While not as clinically interchangeable with Tz/Dz/Az or tamsulosin, 5ARI are primarily used to

manage BPH symptoms. By considering men using 5ARI, we are making a comparison with men with BPH who have opted into pharmacologic treatment of their condition. These men likely have more in common with men starting Tz/Dz/Az or tamsulosin than men who either do not have BPH or who do have BPH but elect to opt out of treatment for their symptoms. We found no statistically significant increase in risk in men taking tamsulosin compared with 5ARI, suggesting that either tamsulosin is a viable, null effect control medication or that both tamsulosin and 5ARI, despite being very different classes of medication, have a similar effect on DLB by chance. The former interpretation seems more plausible than the latter. This makes the results noted in prior studies finding an increased risk of developing dementia and other synucleinopathies among patients who take tamsulosin less likely.[15,43]

The similarity of the results using time-interacted covariates during the first 5 years or when using a delayed start to follow-up suggest that selection on unobserved factors (e.g., known but not documented orthostatic hypotension) is not driving our result. The estimated effects are present even with a 3-year delay. In addition, our results are nearly identical when using an intent-to-treat analysis, and the 2+ dispensing analysis suggesting discontinuations during the first course are not causing selection bias that determines our result. Reducing our sample to only men with a diagnosis of BPH, history of PSA measurement, or lower urinary tract symptom–related procedures yields directionally consistent results, although the sample size reduction of nearly one-third reduces our power in this analysis.

Our study includes 5 major limitations. First, the diagnosis of DLB may be challenging. Because the diagnosis of DLB is typically made by a specialist, it is likely our case definition has high specificity but potentially low sensitivity. Chart validations for other causes of dementia, such as PD and AD, have been done[44,45]; however, there are no studies reporting the performance of diagnostic codes in DLB.[45] It is likely that some people with DLB may never be diagnosed with the disease and be improperly classified as healthy controls. However, this is likely to be a small number of the controls because DLB is a relatively uncommon condition, and this misclassification will likely bias our analysis to the null.

Second, DLB is a complex systemic disease and may cause autonomic dysfunction, including urinary retention and orthostatic hypotension. In men who have undiagnosed DLB, this may influence treatment selection. Compared with tamsulosin, Tz/Dz/Az is more likely to cause hypotension and may be selected against in these patients. This could result in a spurious protective association for Tz/Dz/Az. While we attempt to mitigate this problem in several ways (propensity score matching in a model that includes orthostatic hypotension and sensitivity analysis with delayed start of follow-up), residual biases may remain.

Third, we face the limits of administrative data. All claims analyses are limited by the sensitivity and specificity of codes included on billing data. A diagnosis may be made by a provider and recorded on the medical record but, for whatever reason, not appear on a claim submitted to the insurance company. Some codes, such as those for orthostatic hypotension and BPH, may have low sensitivity—many people who have the condition lack claim with a diagnosis related to that condition. For instance, our study drugs are primarily used to treat BPH; however, most of the men in our sample do not have a diagnosis of BPH. We are further limited by what data are captured by the administrative record. We are unable to use neuropathology results, which would not be provided to the insurance company, to validate our case definition. Merative Marketscan does not include important socioeconomic factors such as income, education, and race.

Fourth, our new-user active comparator design, while the gold standard for pharmacoepidemiology, creates issues with generalizability. We are selecting men who are electing to undergo pharmacologic treatment of lower urinary tract symptoms, most likely due to BPH. Men who opted out of treatment may systematically differ from treated men. In addition, while both active comparators are used to treat BPH, they may not be clinically interchangeable. Tz/Dz/Az and tamsulosin are of similar clinical effectiveness and indication, typically offering immediate relief from symptoms. The 5ARI, on the contrary, may take 90 days until symptom relief. We did not explore whether the association differed by dose—it is possible that the dose needed to manage BPH and that to slow neurodegeneration, assuming a causal relationship, are not the same. A dose-finding study may provide a better ratio of therapeutic effects vs side effects for this application.

Finally, to increase our internal validity, we excluded female individuals from our sample. This is a major limitation, and the generalizability of this result to female individuals needs to be assessed.

As with any observational study, we are limited in our ability to assess cause and effect. While we have attempted to address many challenges through our study design and analysis, we are unable to conclusively demonstrate causal relationships. Future preclinical, prospective, observational, and, ultimately, randomized trials are needed to evaluate causality.

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Appendix Authors

Name	Location	Contribution
Alexander Hart, MD, MPH	Department of Neurology, University of Michigan, Ann Arbor	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Georgina Aldridge, MD, PhD	Department of Neurology, University of Iowa, Iowa City	Drafting/revision of the article for content, including medical writing for content; study concept or design
Qiang Zhang, MD	Department of Neurology, University of Iowa, Iowa City	Drafting/revision of the article for content, including medical writing for content
Nandakumar S. Narayanan, MD, PhD	Department of Neurology, University of Iowa, Iowa City	Drafting/revision of the article for content, including medical writing for content; study concept or design
Jacob E. Simmering, PhD	Department of Internal Medicine, University of Iowa, Iowa City	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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