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Androgen-targeting therapeutics mitigate the adverse effect of GnRH agonist on the risk of neurodegenerative disease in men treated for prostate cancer

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Abstract

Background: Prostate cancer and multiple neurodegenerative diseases (NDD) share an age-associated pattern of onset. Therapy of prostate cancer is known to impact cognitive function. The objective of this study was to determine the impact of multiple classes of androgen-targeting therapeutics (ATT) on the risk of NDD.

Methods: A retrospective cohort study of men aged 45 and older with prostate within the US-based Mariner claims data set between January 1 and 27, 2021. A propensity score approach was used to minimize measured and unmeasured selection bias. Disease risk was determined using Kaplan–Meier survival analyses.

Results: Of the 1,798,648 men with prostate cancer, 209,722 met inclusion criteria. Mean (SD) follow-up was 6.4 (1.8) years. In the propensity score-matched population, exposure to ATT was associated with a minimal increase in NDD incidence (relative risk [RR], 1.07; 95% CI, 1.05–1.10; $p < 0.001$). However, GnRH agonists alone were associated with significantly increased NDD risk (RR, 1.47; 95% CI, 1.30–1.66; $p < 0.001$). Abiraterone, commonly administered with GnRH agonists and low-dose prednisone, was associated with a significantly decreased risk (RR, 0.77; 95% CI, 0.68–0.87; $p < 0.001$) of any NDD.

Gregory L Branigan and Georgina Torrandell-Haro are co-first authors.

interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conclusions: Among patients with prostate cancer, GnRH agonist exposure was associated with an increased NDD risk. Abiraterone acetate reduced the risks of Alzheimer's disease and Parkinson's disease conferred by GnRH agonists, whereas the risk for ALS was reduced by androgen receptor inhibitors. Outcomes of these analyses contribute to addressing controversies in the field and indicate that GnRH agonism may be a predictable instigator of risk for NDD with opportunities for risk mitigation in combination with another ATT.

KEYWORDS

abiraterone, Alzheimer's disease, androgen, medical informatics, neurodegenerative disease, prostate cancer

1 | INTRODUCTION

Prostate cancer is the most prevalent non-skin cancer in men and the second leading cause of cancer-related deaths among men worldwide,[1] accounting for 29% of new cancer cases.[2] In 2022, 268,490 new cases of prostate cancer are expected to be diagnosed in the U.S.[2] Androgen deprivation therapy has been effectively used for the treatment of prostate cancer for more than 75 years.[3–8]

Gonadotrophin-releasing hormone (GnRH) agonists (leuprolide, goserelin, triptorelin, and histrelin) and GnRH antagonists (degarelix) constitute the drug class of androgen deprivation therapy (ADT) in the U.S.[3,8,9] Recently, androgen synthesis inhibitors (ketoconazole and abiraterone)[10,11] or androgen receptor (AR) inhibitors (flutamide, bicalutamide, nilutamide, and enzalutamide)[12,13] were added to improve the efficacy of GnRH agonists and antagonists.[14] Although abiraterone's mechanism of action is different from direct AR blockade, the clinical benefits have been indistinguishable from third-generation AR antagonists despite the absence of direct comparisons in clinical trials.[15–18] Both androgen receptor inhibitors and androgen synthesis inhibitors are administered in combination with GnRH agonists, antagonists, or orchiectomy, consistent with the results of randomized clinical trials and FDA approvals for these agents.

There are well-documented neurocognitive side effects due to androgen ablation that have raised concerns regarding a potential association between androgen deprivation and neurodegenerative disease.[19–35] Reduced plasma level of testosterone has been reported in Alzheimer's, Multiple sclerosis, Parkinson's, and ALS (reviewed in Bianchi et al., 2020).[36] In Alzheimer's disease, reduced circulating and brain testosterone was reported and correlated with AD pathology suggesting that low testosterone is a factor that contributes to, rather than results from, the development of AD (reviewed in Rosario et al., 2008).[37,38]

Despite the strong associations with decreased testosterone levels and neurodegenerative disease, the impact of ATT and risk of neurodegenerative diseases,[39] including Alzheimer's disease (AD)[21,30] Multiple sclerosis (MS),[40] Parkinson's disease (PD),[41,42] and Amyotrophic Lateral Sclerosis (ALS),[43,44] remain controversial with few studies reporting the association with androgen receptor and synthesis inhibitors. To address these issues, we conducted analyses of the relationship between androgen-targeting therapeutics with different mechanisms of action and the incidence of age-related neurodegenerative diseases.

2 | METHODS

2.1 | Data source

The Mariner database is an insurance claims data set that serves the United States with patient populations from all US states and territories. The Mariner data set contains patient demographic characteristics, prescription records, and numerous other data points for patients with *Current Procedural Terminology*, *International Classification of Diseases, Ninth Revision (ICD-9)*, and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes. As of October 2020, Mariner encompassed all indications and represents 122 million patients throughout the duration of the set with claims dating from 2010 through the second quarter of 2018.

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This study was approved by the University of Arizona Institutional Review Board. Requirements for informed consent were waived as the data were deidentified.

2.2 | Study design and variables

The subset of 1,798,648 prostate cancer patients was generated from the available Mariner data set for the study group. Participants younger than 45 years old, with a history of neurosurgery, brain cancer, or neurodegenerative disease prior to the diagnosis of prostate cancer, history of exposure to spironolactone or testosterone were excluded from the study. A 3-year active enrollment criterion after the diagnosis of prostate cancer was required before analysis of exposure to ATT or development of NDD for all patients (Figure 1) to account for patients that may be leaving, dying, or changing insurance providers. Additionally, the 3-year follow-up is not based on ATT exposure but instead is based on prostate cancer diagnosis. Patient groups were assigned according to therapeutic intervention used secondary to a prostate cancer diagnosis after meeting enrollment criteria to avoid immortal bias in experimental design. The ATT group was defined as any patient having at least one medication charge for any of the ATT therapeutics occurring after the diagnosis of prostate cancer (Table S1). The outcome variable was defined as the occurrence of the first diagnosis of neurodegenerative disease based on ICD-9 and

ICD-10 codes in the patient's medical claims data starting 1 year after a prostate cancer diagnosis. We defined neurodegenerative disease to include Alzheimer's disease (AD), non-AD dementia, Multiple Sclerosis (MS), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS) (Table S1). An index date 1 year after the diagnosis of prostate cancer was selected to eliminate any acute neurocognitive side effects and to focus on the long-term impact on disease progression given the prodromal nature of NDD. Age in the study is defined by the age at diagnosis of prostate cancer. Following the analytic strategy in Branigan et al. (2020)[45] and Torrandell-Haro et al. (2020),[46] an analysis of comorbidities known to be associated with NDD outcomes was conducted (Table 1, Table S1).

2.3 | Statistical analysis

Statistical analyses were conducted between January 1 and January 27, 2021. Patient demographic statistics (Table 1) and incidence statistics were analyzed using unpaired two-tailed t tests or $\chi 2$ tests, as appropriate, to test the significance of the differences between continuous
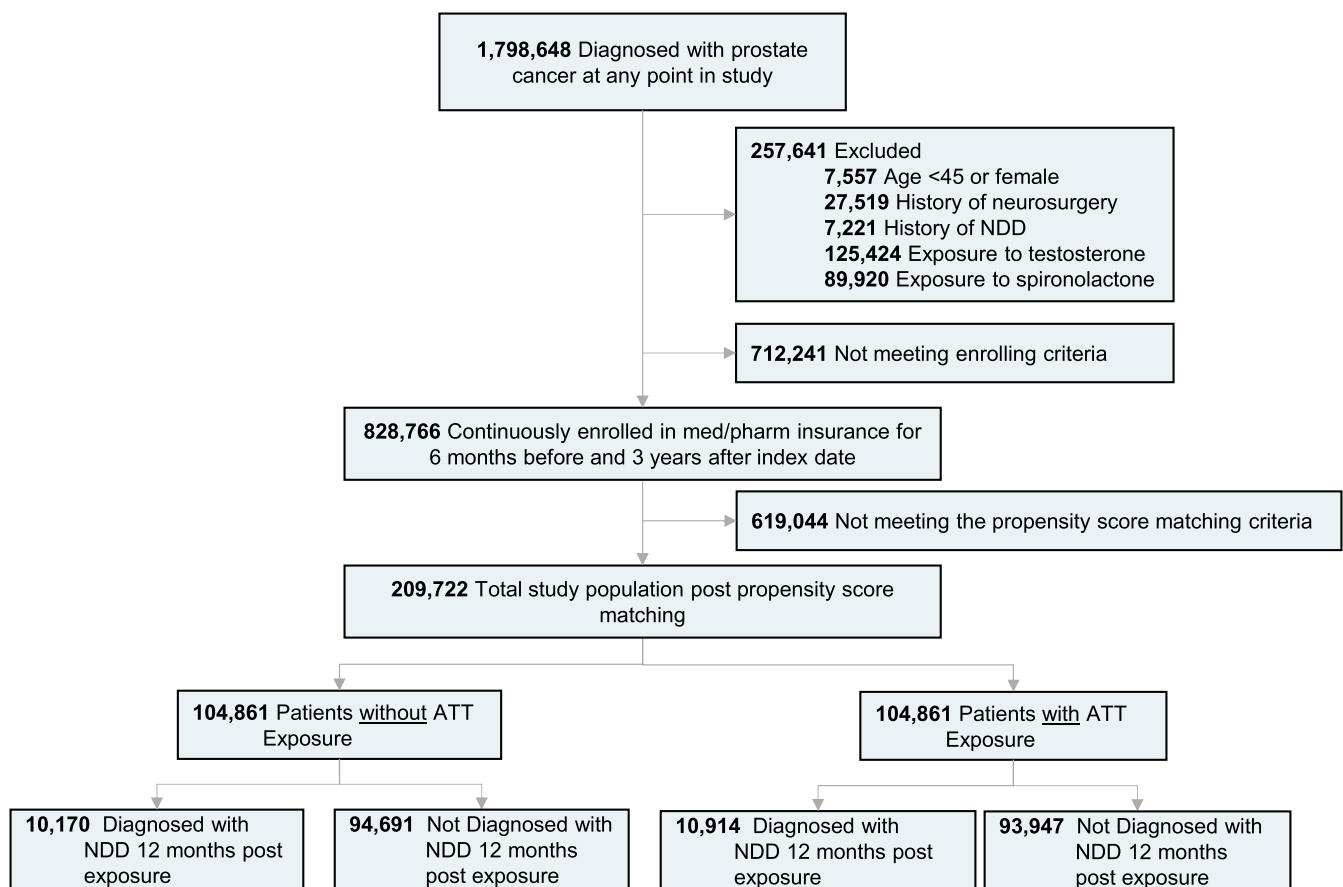

FIGURE 1 Study design and patient breakdown. NDD, Neurodegenerative Diseases; ATT, Androgen-Targeting Therapeutics

TABLE 1 Baseline characteristics for unadjusted and propensity score-matched patients with or without exposure to androgen-targeting therapeutics

	Unadjusted cohort						Propensity score-matched cohort[a]					
	Without exposure to ATT		With exposure to ATT		p value	Std Mean Diff	Without exposure to ATT		With exposure to ATT		p value	Std Mean Diff
	n	%	n	%			n	%	n	%		
Number of Patients	723,905		104,861				104,861		104,861			
Age					<0.001	0.503					<0.001	0.256
45–49	36,098	4.99%	4273	4.07%			4243	4.05%	4273	4.07%		
50–54	85,946	11.87%	9386	8.95%			10,411	9.93%	9386	8.95%		
55–59	106,607	14.73%	12,803	12.21%			14,328	13.66%	12,803	12.21%		
60–64	123,150	17.01%	16,256	15.50%			17,719	16.90%	16,256	15.50%		
65–69	123,498	17.06%	19,073	18.19%			18,483	17.63%	19,073	18.19%		
70–74	187,422	25.89%	32,174	30.68%			30,336	28.93%	32,174	30.68%		
75–79	61,184	8.45%	10,896	10.39%			9341	8.91%	10,896	10.39%		
Region					<0.001	0.186					<0.001	0.038
Midwest	181,296	25.04%	21,558	20.56%			26,123	24.91%	21,558	20.56%		
Northeast	169,690	23.44%	25,938	24.74%			24,849	23.70%	25,938	24.74%		
South	280,049	38.69%	43,787	41.76%			39,241	37.42%	43,787	41.76%		
West	92,104	12.72%	13,463	12.84%			14,548	13.87%	13,463	12.84%		
Unknown	766	0.11%	115	0.11%			100	0.10%	115	0.11%		
Comorbidities												
Asthma	6739	0.93%	2271	2.17%	<0.001	0.038	1169	1.11%	1253	1.19%	0.09	0.012
COPD	13,266	1.83%	2912	2.78%	<0.001	0.032	2091	1.99%	2388	2.28%	<0.001	0.006
Chronic Kidney Disease	30,565	4.22%	8104	7.73%	<0.001	0.066	4862	4.64%	5995	5.72%	<0.001	0.023
Congestive Heart Failure	20,403	2.82%	4609	4.40%	<0.001	0.025	3163	3.02%	3785	3.61%	<0.001	0.018
Coronary Artery Disease	54,876	7.58%	13,316	12.70%	<0.001	0.070	8916	8.50%	10,029	9.56%	<0.001	0.013
Ischemic Heart Disease	51,538	7.12%	11,832	11.28%	<0.001	0.062	8381	7.99%	9461	9.02%	<0.001	0.010
Obesity	36,611	5.06%	9475	9.04%	<0.001	0.059	5863	5.59%	6883	6.56%	<0.001	0.018
Osteoarthritis	61,832	8.54%	14,576	13.90%	<0.001	0.078	10,189	9.72%	11,475	10.94%	<0.001	0.011
Pulmonary Heart Disease	10,785	1.49%	2911	2.78%	<0.001	0.089	1727	1.65%	2071	1.97%	<0.001	0.012
Rheumatoid Arthritis	4149	0.57%	1103	1.05%	<0.001	0.028	686	0.65%	867	0.83%	<0.001	0.010
Stroke	28,366	3.92%	6743	6.43%	<0.001	0.059	4672	4.46%	5260	5.02%	<0.001	0.008

TABLE 1 (Continued)

CCI	Unadjusted cohort					Propensity score-matched cohort[a]				
	Without exposure to ATT		With exposure to ATT		p	Without exposure to ATT		With exposure to ATT		p
	n	%	n	%		n	%	n	%	
					0.724					0.223
0	328,635	45.40%	41,828	39.89%	0.39	42,322	40.36%	41,828	39.89%	>0.99
1	154,810	21.39%	21,206	20.22%		22,085	21.06%	21,206	20.22%	
2	109,748	15.16%	19,152	18.26%		17,872	17.04%	19,152	18.26%	
3	58,257	8.05%	9858	9.40%		9794	9.34%	9858	9.40%	
4	27,794	3.84%	4736	4.52%		4699	4.48%	4736	4.52%	
5–10	41,573	5.74%	7559	7.21%		7452	7.11%	7559	7.21%	
11+	3088	0.43%	522	0.50%		637	0.61%	522	0.50%	

Abbreviations: ATT, Androgen-Targeting Therapeutics; COPD, Chronic Obstructive Pulmonary Disease; CCI, Charlson Comorbidity Index.

aAdjusted for age, region, comorbidities, and CCI.

and categorical variables. In all analyses, a two-sided $p < 0.01$ was considered statistically significant.

A propensity score-matched population was generated by using logistic regression to identify confounding factors for ATT usage as outcome between the treatment and control groups as previously reported.[45] In brief, the resulting factors included age, region, Charlson Comorbidity Index (CCI) rank as well as variable comorbidities listed in Table S1 which special attention is given to factors associated with NDD risk. CCI was calculated at the time of prostate cancer diagnosis. These factors were then integrated to match patients using a 1:1 ratio in the treatment (ATT) group to patients in the control (no-ATT exposure) group to minimize confounding variables in the patient populations. The matching was assessed by standardized mean difference with percentage balance improvement (Table S2). Kaplan–Meier survival curves for NDD-Free Survival were created using the propensity score-matched population in the Bellwether–PearlDiver interface. We then conducted a sensitivity analysis to address the impact of surgery (orchiectomy or prostatectomy) and prednisone in the study population (Table S3; Table S4; Figure S4).

Biological pathway analysis was conducted using the Drug–Target Interaction (DTI) network approach (Figure S3). For each ATT identified, the related gene targets were extracted using the DrugBank database.[47]

3 | RESULTS

Of the 1,798,648 prostate cancer patients within the Mariner data set, 828,766 met the inclusion/exclusion criteria and claims enrollment period requirements for analysis (Figure 1). After 1:1 propensity score matching, 209,722 patients remained in the study (Figure 1). In the postmatching group, 104,861 patients (mean [SD] age, 62.83 [3.56] years) were assigned to the control group and 104,861 patients (mean [SD] age, 63.42 [3.77] years) were assigned to the ATT treatment group. ATT was started on average (SD) 1114.36 (822.62) days after the diagnosis of prostate cancer, consistent with the expectation that most men initiated ATT for either biochemical progression or the discovery of the metastatic disease. The mean (interquartile range) filled prescription days was 2326 (IQR, 1772–2915). Drugs defined as ATT, patient counts, and median adherence rate for each drug are reported in Table 2. Generic drug codes used within the PearlDiver database are included in Table S2. Patient groups were then followed for the duration of their claims data entries and surveyed for any diagnosis of NDD. The mean (SD) follow-up was 6.4 (1.8) years.

In the unadjusted cohort, age, region, comorbidity rates indicated statistically significant differences between

TABLE 2 List of androgen-targeting therapeutics and number of patients per group

Group	Drug	n (%)	Median % adherence
GnRH agonists	Goserelin	67 (0.06)	81.62
	Histrelin	15 (0.01)	80.89
	Leuprolide	1216 (1.08)	—
	Triptorelin	352 (0.31)	85.91
GnRH antagonists	Degarelix	117 (0.10)	90.81
Androgen receptor inhibitors	Bicalutamide	17,949 (15.96)	85.23
	Enzalutamide	2549 (2.27)	—
	Flutamide	426 (0.38)	80.54
	Nilutamide	166 (0.15)	94.49
Androgen synthesis inhibitors	Abiraterone	2993 (2.66)	92.98
	Ketoconazole	86,638 (77.02)	16.44

the control and ATT exposure group (Table 1). Most patients were from the southern region of the United States (280,049 of 723,905 [38.69%] and 43,787 of 104,861 [41.76%]). The age range of the study population was 45–79 for both the control and ATT-exposed groups, where the majority of patients were aged 70–74 (187,422 controls of 723,905 [25.89%] and 32,174 ATT treated of 104,861 [30.68%]). Incidence of 11 representative comorbidities associated with NDD that were different between the control and treatment groups are reported in Table 1. CCI was not statistically different between the unadjusted control and the ATT treatment group. To address the impact of the above demographic differences between groups, propensity score matching was conducted to generate representative groups that controlled for differences in demographic and comorbid characteristics. Demographics of populations generated by propensity matching appear in Table 1.

In the unadjusted population, exposure to ATT was associated with an increased risk of all combined neurodegenerative diseases (NDD) (65,278 of 723,905 [9.02%] vs. 11,127 of 104,861 [10.61%]; relative risk [RR], 1.18; 95% CI, 1.16–1.20; $p < 0.001$) as well as AD, non-AD Dementia, MS, and PD. There was no statistical difference in ATT exposure to ALS risk in the overall ATT unadjusted population (Table 3). In the propensity score-adjusted population, statistical differences were sustained for NDD (10,170 of 104,861 [9.70%] vs. 10,914 of 104,861 [10.41%]; relative risk [RR], 1.07; 95% CI, 1.05–1.10; $p < 0.001$), and PD (2586 of 104,861 [2.47%] vs. 3534 of 104,861 [3.37%]; relative risk [RR], 1.37; 95% CI, 1.30–1.44; $p < 0.001$). In contrast, the impact of the ATT group was no longer statistically significant for AD (2939 of 104,861 [2.80%] vs. 3025 of 104,861 [2.88%]; relative risk [RR], 1.03; 95% CI, 0.98–1.08; $p = 0.26$), non-AD dementia (5069 of 104,861 [4.83%] vs. 5159 of 104,861 [4.92%]; relative risk [RR], 1.02; 95% CI, 0.98–1.06; $p = 0.37$), and MS (420 of 104,861 [0.40%] vs. 416 of 104,861 [0.40%]; relative risk [RR], 0.99; 95%

CI, 0.87–1.13; $p = 0.92$) postmatching in the ATT exposure group. Propensity score–matched data are presented in Figure S1. Kaplan–Meier survival curves for NDD-free survival for each NDD subtype were generated using propensity score–matched population data to evaluate incidence rate and percent of population for each disease (Figure S2). Observed changes in the rate of disease incidence between control patient and those patients receiving ATT confirmed the results shown in Table 3.

To assess the strength of the association between ATT and diagnosis of NDD, multiple types of sensitivity analyses were conducted. Subgroups of treatment combinations were analyzed including surgical interventions of prostatectomy and orchiectomy (Table S3). In patients without surgical intervention, ATT use had a higher hazard of diagnosis for all neurodegenerative disease (RR, 1.48; 95% CI, 1.44–1.53, p value < 0.001). In patients with surgery, only the orchiectomy population was associated with an increased risk of neurodegenerative diseases (RR, 2.25; 95% CI, 1.65–3.03, p value < 0.001) further strengthening the validity of the association as prostatectomy could be considered a negative surgical control (Table S3). Further, because abiraterone is almost always prescribed with low doses of prednisone, consistent with the FDA approval, a subanalysis was conducted to (1) address clinical prescribing guidelines and (2) determine if prednisone exposure was associated with impact on NDD in this drug type (Table S4). Consistent with medical practice, the majority of patients (90.6%) received prednisone with abiraterone. Outcomes of subanalysis indicated no association between prednisone and NDD providing support that the reduced NDD risk reduction profile was driven by abiraterone exposure (Table S4).

Further, an analysis of the incidence of each NDD with exposure to a subclass of ATT was conducted to address the selectivity of ATT drug action. Patients receiving ATT were divided into four groups based on therapeutic mechanism:

TABLE 3 Relative risk of unadjusted and propensity score-matched patients with or without exposure to ATT to develop NDDs

	All NDD combined	AD	Non-AD dementia	MS	PD	ALS
Unadjusted cohort						
Patients not receiving Androgen-Targeting Therapy	65,278	18,975	32,428	2431	17,060	618
%	9.02%	2.62%	4.48%	0.34%	2.36%	0.09%
Patients receiving Androgen-Targeting Therapy	11,127	3096	5288	432	3600	85
%	10.61%	2.95%	5.04%	0.41%	3.43%	0.08%
Relative risk	1.18	1.13	1.13	1.23	1.46	0.95
95% CI	1.16–1.20	1.09–1.17	1.09–1.16	1.11–1.36	1.41–1.51	0.76–1.19
NNT	62.75	301.9	177.5	1313	92.9	23,198
p value	<0.001	<0.001	<0.001	<0.001	<0.001	0.69
Propensity score-matched cohort						
Patients not receiving Androgen-Targeting Therapy	10,170	2939	5069	420	2586	86
%	9.70%	2.80%	4.83%	0.40%	2.47%	0.08%
Patients receiving Androgen-Targeting Therapy	10,914	3025	5159	416	3534	83
%	10.41%	2.88%	4.92%	0.40%	3.37%	0.08%
Relative risk	1.07	1.03	1.02	0.99	1.37	0.97
95% CI	1.05–1.10	0.98–1.08	0.98–1.06	0.87–1.13	1.30–1.44	0.71–1.30
NNT	140.9	1219	1165	26,215	110.6	34,954
p value	<0.001	0.26	0.37	0.92	<0.001	0.88

Abbreviations: ATT, Androgen-Targeting Therapeutics; NDD, Neurodegenerative Diseases; AD, Alzheimer's Disease; MS, Multiple Sclerosis; PD, Parkinson's Disease; ALS, Amyotrophic Lateral Sclerosis; CI, Confidence Interval; NNT, Number Needed to Treat.

GnRH agonists, androgen receptor inhibitors, androgen synthesis inhibitors, and ketoconazole, a drug used prior to the introduction of abiraterone due to its low-affinity inhibition of androgen synthesis (Figure 2). Of note, androgen receptor inhibitors and androgen synthesis inhibitors are prescribed in combination with GnRH agonists or antagonists, thus, the two groups in this analysis represent a combined therapeutic exposure. GnRH antagonists were not included in this analysis as there were too few patients in the cohort receiving these therapies. Mechanistic pathway targets of these drugs are presented in Figure S4.

The outcomes of these analyses indicated that in contrast to the analysis of all ATT as an overall group, subgroups of ATT therapies were associated with distinct and statistically significant risk profiles for each NDD subtype. GnRH agonists and androgen receptor inhibitors were both associated with an increased risk of AD (RR, 1.79; 95% CI, 1.14–2.23; and RR, 1.23; 95% CI, 1.13–1.33; p <0.001), non-AD dementia (RR, 1.57; 95% CI, 1.31–1.86; and RR, 1.25; 95% CI, 1.18–1.33; p <0.001). These subgroups represent GnRH agonists and a given second-line ATT. In contrast to the increased risk profile of GnRH agonists alone, the addition of abiraterone was associated with a significantly reduced risk of AD (RR, 0.61; 95% CI, 0.46–0.80; p < 0.001) and a non-significant effect on non-AD dementia (RR, 0.89; 95% CI, 0.75–1.06; p = 0.29). Of note, ketoconazole did not show a statistically significant impact on AD or dementia risk. For MS, the administration of androgen receptor inhibitors was associated with a decreased risk (RR, 0.65; 95% CI, 0.49–0.87, p < 0.01), whereas the other therapies did not significantly impact the risk of MS. For PD, abiraterone was associated with a decreased risk (RR, 0.58; 95% CI, 0.43–0.78; p < 0.001), whereas ketoconazole was associated with an increased risk (RR, 1.48; 95% CI, 1.40–1.55; p < 0.001). For ALS, abiraterone (RR, 4.46; 95% CI, 2.40–8.27; p < 0.001) and androgen receptor inhibitors (RR, 8.40; 95% CI, 4.50–15.60; p < 0.001) were associated with a significantly increased risk of ALS (Figure 2).

To further evaluate the impact of individual ATT drug classes on NDD risk, survival analysis was conducted for AD in populations stratified by the ATT group (Figure 3). Kaplan–Meier probability analyses confirmed the associations of chi-square analyses and illustrated that GnRH agonists alone exerted the greatest acceleration of AD incidence, followed by androgen receptor inhibitors, and ketoconazole.
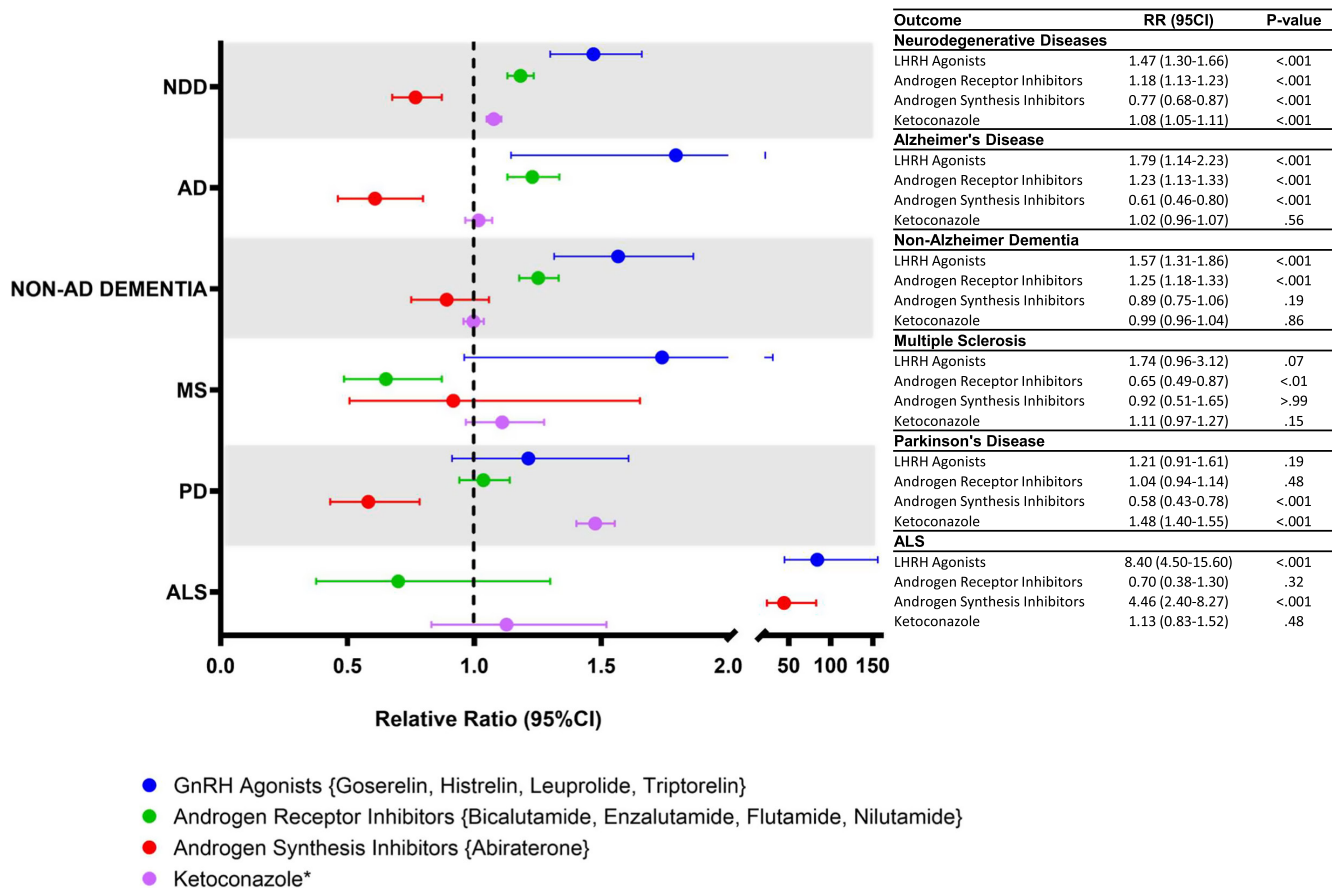
Outcome	RR (95CI)	P-value
Neurodegenerative Diseases		
LHRH Agonists	1.47 (1.30-1.66)	<.001
Androgen Receptor Inhibitors	1.18 (1.13-1.23)	<.001
Androgen Synthesis Inhibitors	0.77 (0.68-0.87)	<.001
Ketoconazole	1.08 (1.05-1.11)	<.001
Alzheimer's Disease		
LHRH Agonists	1.79 (1.14-2.23)	<.001
Androgen Receptor Inhibitors	1.23 (1.13-1.33)	<.001
Androgen Synthesis Inhibitors	0.61 (0.46-0.80)	<.001
Ketoconazole	1.02 (0.96-1.07)	.56
Non-Alzheimer Dementia		
LHRH Agonists	1.57 (1.31-1.86)	<.001
Androgen Receptor Inhibitors	1.25 (1.18-1.33)	<.001
Androgen Synthesis Inhibitors	0.89 (0.75-1.06)	.19
Ketoconazole	0.99 (0.96-1.04)	.86
Multiple Sclerosis		
LHRH Agonists	1.74 (0.96-3.12)	.07
Androgen Receptor Inhibitors	0.65 (0.49-0.87)	<.01
Androgen Synthesis Inhibitors	0.92 (0.51-1.65)	>.99
Ketoconazole	1.11 (0.97-1.27)	.15
Parkinson's Disease		
LHRH Agonists	1.21 (0.91-1.61)	.19
Androgen Receptor Inhibitors	1.04 (0.94-1.14)	.48
Androgen Synthesis Inhibitors	0.58 (0.43-0.78)	<.001
Ketoconazole	1.48 (1.40-1.55)	<.001
ALS		
LHRH Agonists	8.40 (4.50-15.60)	<.001
Androgen Receptor Inhibitors	0.70 (0.38-1.30)	.32
Androgen Synthesis Inhibitors	4.46 (2.40-8.27)	<.001
Ketoconazole	1.13 (0.83-1.52)	.48

- ● GnRH Agonists {Goserelin, Histrelin, Leuprolide, Triptorelin}
- ● Androgen Receptor Inhibitors {Bicalutamide, Enzalutamide, Flutamide, Nilutamide}
- ● Androgen Synthesis Inhibitors {Abiraterone}
- ● Ketoconazole*

FIGURE 2 Relative risk of propensity score-matched prostate cancer patients with exposure to different ATT classes to develop NDD. *Ketoconazole is considered an Androgen Synthesis Inhibitor. ATT, Androgen-Targeting Therapeutics; NDD, Neurodegenerative Diseases; AD, Alzheimer's Disease; MS, Multiple Sclerosis; PD, Parkinson's Disease; ALS, Amyotrophic Lateral Sclerosis; RR, Relative Risk; CI, Confidence Interval; GnRH. Luteinizing Hormone-Releasing Hormone
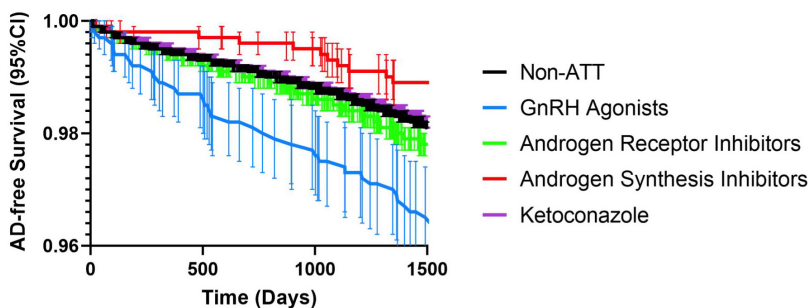

FIGURE 3 Kaplan–Meier AD survival curves for propensity score-matched prostate cancer patients with exposure to different ATT classes. ATT, Androgen-Targeting Therapeutics; AD, Alzheimer's Disease; CI, Confidence Interval; GnRH. Luteinizing Hormone-Releasing Hormone

No. at Risk	Day 0	Day 500	Day 1000	Day 1500
Non-ATT	104,861	104,159	104,159	90,735
GnRH Agonists	1,572	1,551	1,536	1,120
Androgen Receptor Inhibitors	19,153	19,010	18,894	15,896
Androgen Synthesis Inhibitors	2,993	2,986	2,978	1,899
Ketoconazole	86,638	86,077	85,638	76,649

4 | DISCUSSION

The analyses described herein are the largest report to date examining the impact of a broad range of androgen-targeting therapies that included androgen receptor inhibitors and androgen synthesis inhibitors on neurodegenerative disease incidence in a cohort of men with prostate cancer. Previous studies focused

on the androgen deprivation therapy (ADT) drug class in reporting associations with AD and dementia risk.[21,24,27,31] These studies reported variable results with controversies around controls and confounding factors.[25,48–50] A recent meta-analysis evaluating the association between androgen deprivation therapy and dementia or Alzheimer's disease (AD) found a positive association.[21] However, the study was limited to the effect of GnRH agonists and antagonists. Consistent with clinical practice, our study determined the impact of ATT drug combination risk profiles for adjuvant ATT to GnRH agonists. Further, we extended analyses that determined the impact of ATT on a broad range of NDD disorders including non-AD dementia, Parkinson's, MS, and ALS. Outcomes of these analyses reported herein will be useful as a comparison to analyses of a single class of ATT which may provide insights into variances across reports which may be, in part, due to the therapies selected and, in part, due to the control group used for comparison (healthy control vs prostate cancer patients without ATT exposure).[25,28,29,31,51–53]

When taken together as a group, the impact of ATT on all NDD is associated with a slight increase in NDD incidence which was driven by the incidence of Parkinson's disease, whereas the remaining disease incidences were not statistically significantly different from the control (Figure S1). When stratified into subgroup drug classes (e.g., synthesis or receptor inhibitors), the results indicated three risk profiles associated with exposure to a given class of ATT. For AD and non-AD dementia, GnRH agonists and androgen receptor inhibitors were associated with an increased risk. Conversely, exposure to the second-generation androgen synthesis inhibitor, abiraterone, was associated with decreased incidence of AD and non-AD dementia (Figure 2). Of note, exposure to ketoconazole, which had been used as an androgen synthesis inhibitor, had no impact on the risk of AD or non-AD dementia. Based on the drug-target network generated from the biological pathway analysis, ketoconazole targets both the androgen receptor and CYP21A2 (21-Hydroxylase) among others (Figure S3) but is known to be less potent than abiraterone in affecting androgenesis and less specific.[15,16,51–53] Moreover, the biological pathway analysis indicated that flutamide targets NR1I2 and AHR in addition to the androgen receptor and that goserelin targets LHCGR in addition to GNRHR. Further research is needed to evaluate if these differential targets exert an impact on the risk of NDD associated with these drug groups.

Similar risk profiles for individual ATT exposure occurred for MS, PD, and ALS with variances in which therapeutics were driving the protective or increased risk profiles. As noted for MS, exposure to the androgen receptor inhibitors was associated with a decreased risk, whereas for PD exposure to ketoconazole was associated with an increased risk. Most notably, both GnRH agonists and abiraterone were associated with a significantly increased risk of ALS (Figure 2).

The mechanisms underlying the relationship between androgen loss and NDD are likely complex and involve multiple systems of biology. Mechanistically, the different risk profiles associated for each of the NDD may be due, in part, to general or specific inhibition and subsequent feedback within the androgen pathway. ATT represents a heterogeneous group of medications with distinct mechanisms and physiologic effects. For example, GnRH agonists cause an initial surge in testosterone via luteinizing hormone (LH), whereas therapeutics that block androgen receptors, no surge is experienced.[49,54,55] Additionally, each therapeutic class has different effects on follicle-stimulating hormone and LH, which in turn, impact the inflammatory, vascular, and metabolic systems.[56,57] Thus, it follows that there can be differential risk profiles and neurological adverse events between forms of ATT. The data reported herein indicate that mechanisms of action of ATT can differentially impact outcomes on the risk of age-associated neurodegenerative diseases and illustrates the complexity of interaction between androgen pathways and the nervous system.

5 | LIMITATIONS

As a retrospective analysis of a claims database, there are important limitations to consider. Patients included may have obtained services outside those included in this database and there could be factors, known and unknown, that even with propensity matching may not be adequately addressed. Claim records do not include the results of cognitive exams or lab results thus a diagnosis of the disease is based on the presence of ICD codes associated with a given disease which may represent a source of inaccuracy. In addition, data on specific prostate pathologic conditions on contraindications for therapy cannot be assessed in this data set. With respect to patient profiles, small differences in comorbidity may reflect the different disease state of exposed and unexposed patients, which we are unable to fully account for with the propensity score matching. In this respect, this data set does not include lab or genetic values nor pathological staging and was not available for inclusion in the analyses. These limitations are reported here for reference compared with clinical trial data. Despite these limitations, the outcomes of analyses reported herein represent clinically relevant observational findings regarding the association of ATT exposure and NDD risk.

6 | CONCLUSIONS

Outcomes of these analyses contribute to addressing controversies in the field and indicate that GnRH agonism to induce cessation of gonadal steroid production is associated with the greatest risk for NDD. However, combination ATT therapy indicated potential risk mitigation with targeted androgen synthesis inhibition exhibiting the greatest risk reduction. Further investigation of the direct and combinatorial/adjuvant effects of androgen-targeting therapeutics on diseases of the nervous system is warranted and could improve patient compliance given the growing concern of neurological impairment in aging populations.[58]

CONFLICT OF INTEREST

AUTHOR CONTRIBUTIONS

Mr. Branigan, Miss Torrandell-Haro, Dr. Kathleen Rodgers, and Dr. Roberta Brinton had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Mr. Branigan and Miss Torrandell-Haro are co-first authors. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Torrandell, Branigan. Obtained funding: Brinton. Administrative, technical, or material support: Brinton, Rodgers. Supervision: Brinton.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from PearlDiver Inc. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of PearlDiver Inc.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. _CA Cancer J Clin._ 2019;69(1):7-34.
2. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. _CA Cancer J Clin._ 2000;50(1):7-33.
3. Barsouk A, Padala SA, Vakiti A, et al. Epidemiology, staging and management of prostate cancer. _Med Sci._ 2020;8(3):28.
4. Gelmann EP. Molecular biology of the androgen receptor. _J Clin Oncol._ 2002;20(13):3001-3015.
5. Niu Y, Chang T, Yeh S, Ma W, Wang Y, Chang C. Differential androgen receptor signals in different cells explain why androgen-deprivation therapy of prostate cancer fails. _Oncogene._ 2010;29(25):3593-3604.
6. Rawla P. Epidemiology of prostate cancer. _World J Oncol._ 2019;10(2):63-89.
7. Shand RL, Gelmann EP. Molecular biology of prostate-cancer pathogenesis. _Curr Opin Urol._ 2006;16(3):123-131.
8. NCCN NCCN clinical practice guidelines in oncology.
9. Schatten H. Brief overview of prostate cancer statistics, grading, diagnosis and treatment strategies. _Adv Exp Med Biol._ 2018;1095:1-14.
10. Sathianathen NJ, Oestreich MC, Brown SJ, et al. Abiraterone acetate in combination with androgen deprivation therapy compared to androgen deprivation therapy only for metastatic hormone-sensitive prostate cancer. _Cochrane Database of Systematic Reviews._ 2020;1–38. http://dx.doi.org/10.1002/14651858.cd013245.pub2
11. De Bono J, Logothetis C, Molina A, et al. Abiraterone and increased survival in metastaticprostate cancer. _N Engl J Med._ 2011;364(21):1995-2005.
12. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. _New England Journal of Medicine._ 2012;367(13):1187-1197.
13. Etheridge T, Damodaran S, Schultz A, et al. Combination therapy with androgen deprivation for hormone sensitive prostate cancer: a new frontier. _Asian Journal of Urology._ 2019;6(1):57-64.
14. Schröder F, Crawford ED, Axcrona K, Payne H, Keane TE. Androgen deprivation therapy: past, present and future. _BJU Int._ 2012;109(s6):1-12.
15. McKay RR, Werner L, Jacobus SJ, et al. A phase 2 trial of abiraterone acetate without glucocorticoids for men with metastatic castration-resistant prostate cancer. _Cancer._ 2019;125(4):524-532.
16. Taplin ME, Montgomery B, Logothetis CJ, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. _J Clin Oncol._ 2014;32(33):3705-3715.
17. Attard G, Borre M, Gurney H, et al. Abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. _J Clin Oncol._ 2018;36(25):2639-2646.
18. Attard G, Reid AH, A'Hern R, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. _J Clin Oncol._ 2009;27(23):3742-3748.
19. Pike CJ, Rosario ER, Nguyen T-VV. Androgens, aging, and Alzheimer's disease. _Endocrine._ 2006;29(2):233-241.

20. Kluger J, Roy A, Chao HH. Androgen deprivation therapy and cognitive function in prostate cancer. *Curr Oncol Rep.* 2020;22(3):1-10.

21. Jayadevappa R, Chhatre S, Malkowicz SB, Parikh RB, Guzzo T, Wein AJ. Association between androgen deprivation therapy use and diagnosis of dementia in men with prostate cancer. *JAMA Netw Open.* 2019;2(7):e196562.

22. Rosario ER, Carroll JC, Oddo S, LaFerla FM, Pike CJ. Androgens regulate the development of neuropathology in a triple transgenic mouse model of Alzheimer's disease. *J Neurosci.* 2006;26(51):13384-13389.

23. Ross RK, Pike MC, Coetzee GA, et al. Androgen metabolism and prostate cancer: establishing a model of genetic susceptibility. *Cancer Res.* 1998;58(20):4497-4504.

24. Robinson D, Garmo H, Van Hemelrijck M, et al. Androgen deprivation therapy for prostate cancer and risk of dementia. *BJU Int.* 2019;124(1):87-92.

25. Nead K, Sinha S, Nguyen P. Androgen deprivation therapy for prostate cancer and dementia risk: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis.* 2017;20(3):259-264.

26. Khosrow-Khavar F, Rej S, Yin H, Aprikian A, Azoulay L. Androgen deprivation therapy and the risk of dementia in patients with prostate cancer. *J Clin Oncol.* 2017;35(2):201-207.

27. Tae BS, Jeon BJ, Shin SH, Choi H, Bae JH, Park JY. Correlation of androgen deprivation therapy with cognitive dysfunction in patients with prostate cancer: a nationwide population-based study using the national health insurance service database. *Cancer Res Treat.* 2019;51(2):593-602.

28. Khosrow-Khavar F. Androgen deprivation therapy associated with dementia? *Reactions.* 2016;1630:4-3.

29. Deka R, Simpson DR, Bryant AK, et al. Association of androgen deprivation therapy with dementia in men with prostate cancer who receive definitive radiation therapy. *JAMA Oncol.* 2018;4(11):1616-1617.

30. Baik SH, Kury FSP, McDonald CJ. Risk of Alzheimer's disease among senior medicare beneficiaries treated with androgen deprivation therapy for prostate cancer. *J Clin Oncol.* 2017;35(30):3401-3409.

31. Nead KT, Gaskin G, Chester C, Swisher-McClure S, Leeper NJ, Shah NH. Association between androgen deprivation therapy and risk of dementia. *JAMA Oncol.* 2017;3(1):49-55.

32. Nead KT, Gaskin G, Chester C, et al. Androgen deprivation therapy and future Alzheimer's disease risk. *J Clin Oncol.* 2016;34(6):566-571.

33. Huang W-K, Liu C-H, Pang S-T, et al. Type of androgen deprivation therapy and risk of dementia among patients with prostate cancer in Taiwan. *JAMA Netw Open.* 2020;3(8):e2015189.

34. Falchook AD, Basak R, Mohiuddin JJ, Chen RC. Use of androgen deprivation therapy with radiotherapy for intermediate- and high-risk prostate cancer across the United States. *JAMA Oncol.* 2016;2(9):1236-1238.

35. Tully KH, Nguyen DD, Herzog P, et al. Risk of dementia and depression in Young and middle-aged men presenting with non-metastatic prostate cancer treated with androgen deprivation therapy. *Eur Urol Oncol.* 2021;4(1):66-72.

36. Bianchi VE, Rizzi L, Bresciani E, Omeljaniuk RJ, Torsello A. Androgen therapy in neurodegenerative diseases. *J Endocr Soc.* 2020;4(11):bvaa120.

37. Rosario ER, Chang L, Stanczyk FZ, Pike CJ. Age-related testosterone depletion and the development of Alzheimer disease. *Jama.* 2004;292(12):1431-1432.

38. Rosario ER, Pike CJ. Androgen regulation of beta-amyloid protein and the risk of Alzheimer's disease. *Brain Res Rev.* 2008;57(2):444-453.

39. Plata-Bello J, Plata-Bello A, Pérez-Martín Y, Fajardo V, Concepción-Massip T. Androgen deprivation therapy increases brain ageing. *Aging (Albany NY).* 2019;11(15):5613-5627.

40. Ysrraelit MC, Correale J. Impact of sex hormones on immune function and multiple sclerosis development. *Immunol.* 2019;156(1):9-22.

41. Young JWS, Sutradhar R, Rangrej J, Marras C, Fleshner N, Alibhai SMH. Androgen deprivation therapy and the risk of parkinsonism in men with prostate cancer. *World J Urol.* 2017;35(9):1417-1423.

42. Elshaikh MA, Underwood W, Soto DE. Androgen deprivation therapy for patients with prostate carcinoma and Parkinson's disease: case report and review of literature. *Can J Urol.* 2009;16(1):4495-4497.

43. Aggarwal T, Polanco MJ, Scaramuzzino C, et al. Androgens affect muscle, motor neuron, and survival in a mouse model of SOD1-related amyotrophic lateral sclerosis. *Neurobiol Aging.* 2014;35(8):1929-1938.

44. McLeod VM, Lau CL, Chiam MDF, et al. Androgen receptor antagonism accelerates disease onset in the SOD1G93A mouse model of amyotrophic lateral sclerosis. *Br J Pharmacol.* 2019;176(13):2111-2130.

45. Branigan GL, Soto M, Neumayer L, Rodgers K, Brinton RD. Association between hormone-modulating breast cancer therapies and incidence of neurodegenerative outcomes for women with breast cancer. *JAMA Netw Open.* 2020;3(3):e201541.

46. Torrandell-Haro G, Branigan GL, Vitali F, Geifman N, Zissimopoulos JM, Brinton RD. Statin therapy and risk of Alzheimer's and age-related neurodegenerative diseases. *Alzheimers Dement (N Y).* 2020;6(1):e12108.

47. Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res.* 2018;46(D1):D1074-D1082.

48. Bowen RL, Butler T, Atwood CS. Not all androgen deprivation therapies are created equal: leuprolide and the decreased risk of developing Alzheimer's disease. *J Clin Oncol.* 2016;34(23):2800.

49. Leow JJ, Cole AP, Sun M, Trinh Q-D. Association of androgen deprivation therapy with Alzheimer's disease: unmeasured confounders. *J Clin Oncol.* 2016;34(23):2801-2803.

50. Nead KT, Gaskin G, Chester C, et al. Influence of age on androgen deprivation therapy-associated Alzheimer's disease. *Sci Rep.* 2016;6(1):1-4.

51. Nakabayashi M, Oh WK, Jacobus S, et al. Activity of ketoconazole after taxane-based chemotherapy in castration-resistant prostate cancer. *BJU Int.* 2010;105(10):1392-1396.

52. Sartor O, Nakabayashi M, Taplin ME, et al. Activity of dutasteride plus ketoconazole in castration-refractory prostate cancer after progression on ketoconazole alone. *Clin Genitourin Cancer.* 2009;7(3):E90-E92.

53. Taplin ME, Regan MM, Ko YJ, et al. Phase II study of androgen synthesis inhibition with ketoconazole, hydrocortisone, and dutasteride in asymptomatic castration-resistant prostate cancer. *Clin Cancer Res.* 2009;15(22):7099-7105.

54. Loblaw DA, Mendelson DS, Talcott JA, et al. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. *J Clin Oncol.* 2004;22(14):2927-2941.

55. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol.* 2007;25(12):1596-1605.

56. Casarini L, Crépieux P. Molecular mechanisms of action of FSH. *Front Endocrinol.* 2019;10:305.

57. Davis JS. Mechanisms of hormone action: luteinizing hormone receptors and second-messenger pathways. *Curr Opin Obstet Gynecol.* 1994;6(3):254-261.

58. Hou Y, Dan X, Babbar M, et al. Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol.* 2019;15(10):565-581.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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