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ARTICLE

Risk of cognitive impairment in men with advanced prostate cancer treated with NHAs: A systematic review and network meta-analysis

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Abstract

Novel hormonal agents (NHAs) have significantly improved outcomes in men with advanced prostate cancer. However, it remains unclear whether NHAs are associated with subsequent cognitive impairment. Thus, we sought to perform a network meta-analysis to compare the risk of cognitive impairment across NHA types. Databases (PubMed, Embase, Scopus, and Web of Science), trial registries (Clinicaltrial.gov), the European Medicines Agency, and the US Food and Drug Administration drug safety reports were searched from inception through July 30, 2021. Eligible studies were clinical trials evaluating the risk of cognitive impairment between NHAs and placebo/standard care. Two independent investigators extracted the data and performed quality assessments using the Cochrane Risk of Bias Tool and ROBINS-I. We estimated the risk ratios by the frequentist approach and calculated the ranking probabilities of all treatments with the surface under the cumulative ranking probabilities. The primary outcome and secondary outcome were odds ratio (OR) and incidence rate ratio of cognitive impairment, respectively. We identified 15 trials with 14,723 participants comparing HNAs with placebo/standard care. Treatments associated with cognitive impairment, from the most to the least, were enzalutamide (OR, 3.66; 95% confidence interval [CI], 2.84–4.73), apalutamide (OR, 1.76; 95% CI, 1.08–2.87), abiraterone acetate (OR, 1.64; 95% CI, 1.01–2.45), and darolutamide (OR, 1.11 95% CI, 0.51–2.39). After adjustment of treatment time duration, enzalutamide still had the highest risk of cognitive impairment with an incidence rate ratio of 2.17 (95% CI, 1.65–2.78). These findings suggest that NHAs, especially enzalutamide, may increase the risk of cognitive impairment compared with placebo/standard care.

Registration: CRD42021251520 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=251520).

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Novel hormonal agents (NHAs) for advanced prostate cancer significantly increase patient survival. However, their effect on cognitive function and the risk between different agents is unclear.

WHAT QUESTION DID THIS STUDY ADDRESS?

Do NHAs for the treatment of advanced prostate cancer increase the risk of cognitive impairment?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

In a network meta-analysis of 15 trials that included 14,732 participants, NHAs, especially enzalutamide, increased the risk of cognitive impairment, followed by apalutamide and abiraterone. Darolutamide (DARO) had the lowest risk of cognitive impairments. However, there was only a single study of DARO included in this analysis, so more evidence is needed in the future.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The risk of cognitive impairment from NHAs has been overlooked and underestimated. The potential negative impact of NHAs should be emphasized in treating advanced prostate cancer among clinicians and pharmacists.

INTRODUCTION

Prostate cancer is the second most common cancer and the fifth leading cause of cancer mortality among men in the world.[1] With a median age of 67 years at diagnosis and a 5-year survival rate of 97.5% in combined cancer stages, prostate cancer represents the most common cancer in elderly men.[2] Besides, the risk of neurocognitive impairment increased after 60 years old in healthy populations.[3] As a consequence, the neurocognitive decline in older men contributes to loss of independence, an increased incidence of falls, and associated risk of fracture, affecting patients' quality of life (QOL) and increasing cancer-related mortality.[4–6] Hence, any medication which might deteriorate cognitive function should be used cautiously in the older population.

Cognitive function alteration is frequently observed in patients with prostate cancer due to the nature of old age in patients, disease progression, and treatment-related side effects.[7] Patients receiving androgen deprivation therapy (ADT) may experience significant cognitive impairment especially in performing visuomotor and verbal memory tasks after 6–12 months of treatment.[8,9] The declined cognitive function might be improved after discontinuation of ADT which implies that low testosterone may be a risk factor for cognitive decline.[10]

In recent years, novel hormonal agents (NHAs; abiraterone acetate [ABI], enzalutamide [ENZA], apalutamide [APA], and darolutamide [DARO]) were developed and subsequently approved by the US Food and Drug Administration (FDA) in treatment for patients with advanced prostate cancer. Large randomized controlled trials (RCTs) had demonstrated that, in addition to ADT, it significantly prolonged the overall survival and progression-free survival in patients with advanced prostate cancer.[11–14]

ABI is an androgen biosynthesis inhibitor, and ENZA, APA, and DARO are androgen receptor (AR) antagonists that act by disrupting the process of AR translocation to nuclei, inhibiting AR binding to DNA, and preventing recruitment of necessary coactivators to the ligand-AR binding complex.[15] These agents may further decrease testosterone or avoid the androgen effects in the prostate and brain tissue.

Initially, these agents were tested in patients with metastatic castration-resistant prostate cancer (CRPC), and subsequently for nonmetastatic CRPC and even for castration-sensitive prostate cancer (CSPC).[13,16] The anticipation of clinical use implies a progressively longer administration. Hence, the adverse events for these agents in cognitive function became paramount.

The aim of this systematic review and network meta-analysis was to investigate the risk of cognitive impairment among these four NHAs by evaluating data from randomized and nonrandomized controlled clinical trials (RCTs).

MATERIALS AND METHODS

Search strategy and selection criteria

This study followed the recommendations of the Preferred Reporting Items for Systematic Reviews and

Meta-analyses.[17] The method and analysis were prespecified in advance and registered on the PROSPERO website (CRD42021251520). To identify published and unpublished trials, we used electronic databases including PubMed, Embase, Scopus, Web of Science, and Clinicaltrial.gov (from inception to July 2021), without language or date restriction, as well as performing a manual literature search. We further searched relevant safety reports in the European Medical Agency (EMA) and the FDA websites. The detailed study protocol, search terms, and strategy are provided in Table S1. Randomized and nonrandomized controlled parallel-group design clinical trials comparing NHAs and placebo or standard of care were eligible for inclusion. NHAs include ABI, ENZA, APA, and DARO. Studies were included if they recorded the cognitive function change in the trials and were excluded if they did not report cognitive function change. Placebo and standard of care were in the same group. This is because when the clinical trial was conducted, the patients were not told or aware that NHAs would increase the cognitive impairment risk.

Outcome measures

Cognitive impairment data could be assessed by using investigator-assessed cognitive impairment or patient-reported outcome measurement instruments. Common Terminology Criteria for Adverse Events (CTCAE) is a standard tool for the investigator to report adverse events in the clinical trial. Cognitive impairment included terms of cognitive disturbance, amnesia, and memory impairment. For all these adverse events, grade 1 is mild, grade 2 is moderate, and grades 3 and 4 are severe. For patient-reported outcomes, the Montreal Cognitive Assessment (MoCA), and the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) were common tools to evaluate cognitive dysfunction. Clinically meaningful impairment was defined as cognitive impairment.

The primary outcome was the odds ratio (OR) and the secondary outcome was the incidence rate ratio (IRR) considering the different treatment duration. The incidence rate (time-adjusted rate) was defined as the occurrences of events divided by the total treatment-emergent period for each treatment group times 100.

Data extraction and quality assessment

One reviewer screened the titles and abstracts for eligibility and the other reviewer checked for correctness. The full articles were then assessed regarding eligibility criteria by two reviewers (authors H.S.W. and C.L.C.). The two reviewers then extracted data independently and cross-checked the data. We used the Cochrane Collaboration's Risk of Bias (ROB) tool and Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) to appraise randomized and nonrandomized studies' quality, respectively.[18,19] Any unresolved discrepancies in data extraction or appraisal of the results were evaluated by a third reviewer (author C.H.C.) who acted as an arbiter.

We attempted to contact authors about missing data, and several authors responded. When person-year data were not available, we calculated it from the articles' table or figure data.

Statistical methods

We conducted a pairwise random-effect meta-analysis. The OR and IRR were reported for binary data. Trials with zero events in all arms of each outcome were deleted during the analysis because they offered no valuable information and 0.5 was added in each cell for zero-cell correction by default. Heterogeneity was assessed by visual inspection of the forest plot and tested using I^2 statistics. A pairwise meta-analysis was performed using Review Manager version 5.3.[20]

Next, we undertook a frequentist network meta-analysis for each outcome separately. We performed a contrast-based network meta-analysis using Stata (version 17; Stata Corp) through a network module based on the "mvmeta" command for multiple treatment comparisons with the restricted maximum likelihood (REML) approach.[21] Between-study variances were equalized, correlations were set to 0.5, and confidence intervals (CIs) were estimated based on asymptotic error variance and normal distribution.

We evaluated potential inconsistencies between direct and indirect evidence within the network meta-analysis using the design-by-treatment interaction model and side-splitting method.[22,23] The design-by-treatment interaction model provides a global assessment of consistency across the entire network. The side-splitting method separated evidence on a particular comparison into direct and indirect evidence and then assessed their differences. Statistical significance was set at 5% for all analyses.

We also estimated the probabilities of each treatment being at each rank for each intervention and outcome. We obtained a treatment hierarchy using the surface under the cumulative ranking curve and mean ranks.[24]

Additional analysis and sensitivity analysis

Because disease status whether using hormone therapy before, patient age, and NHA treatment duration might affect cognitive function. We performed three meta-regression analyses according to the patient's disease status (CSPC vs.

CRPC), mean patient age (≤70 years old vs. >70 years) and median treatment duration in the NHA arm (≤12 months vs. >12 months) provided in each trial report. Because RCT and non-RCT trials may give different results. We also performed a network meta-analysis only including RCTs.

We further compared the difference between interim and final reports and patient-reported outcomes with investigator-assessed outcomes by using meta-analysis, respectively. Because falls are reported to be associated with cognitive impairment, we also conducted a network meta-analysis to investigate the fall event.

Patient and public involvement declaration

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

The flow chart in Figure 1 shows the literature search process to obtain eligible trials. We identified 10,928 and 709 records from the database and clinical.gov registry, respectively. After eliminating 5415 duplicate articles, the total number of records was 6222. Of those, 5934 records were excluded on the basis of the abstract and title reviews. Of the remaining 288 reports wherein, the full texts were reviewed, and 118 and 95 reports were excluded because these reports were conference abstracts and post hoc analyses without cognitive impairment data. Among 34 registered clinical trials, 10 trials are still ongoing with mainly APA and DARO trials. Nine trials did not report any cognitive impairment data and mainly with ABI trials. At last, 25 reports in 15 trials met our inclusion criteria for the systematic review and meta-analysis.[11–14,16,25–44]

The 15 eligible trials enrolled a total of 14,743 participants and evaluated five treatments (4 NHAs with 1 placebo/standard care) for patients with advanced prostate cancer with five direct comparisons. Among them, 1809, 4372, 1331, and 955 were treated with ABI, ENZA, APA, and DARO, respectively. Amid those 15 trials, the majority of comparisons included ENZA, ABI, and placebo /standard care (Figure 2). There were only two and one trial comparing APA and DARO with placebo, respectively. The clinical and methodological characteristics and the studied outcomes of each trial are summarized in Table 1 and Table 2. Among 15 trials, 10, three, and two trials were phase III RCT, phase II RCT, and non-RCTs, respectively. Three trials involved patients with metastatic CSPC

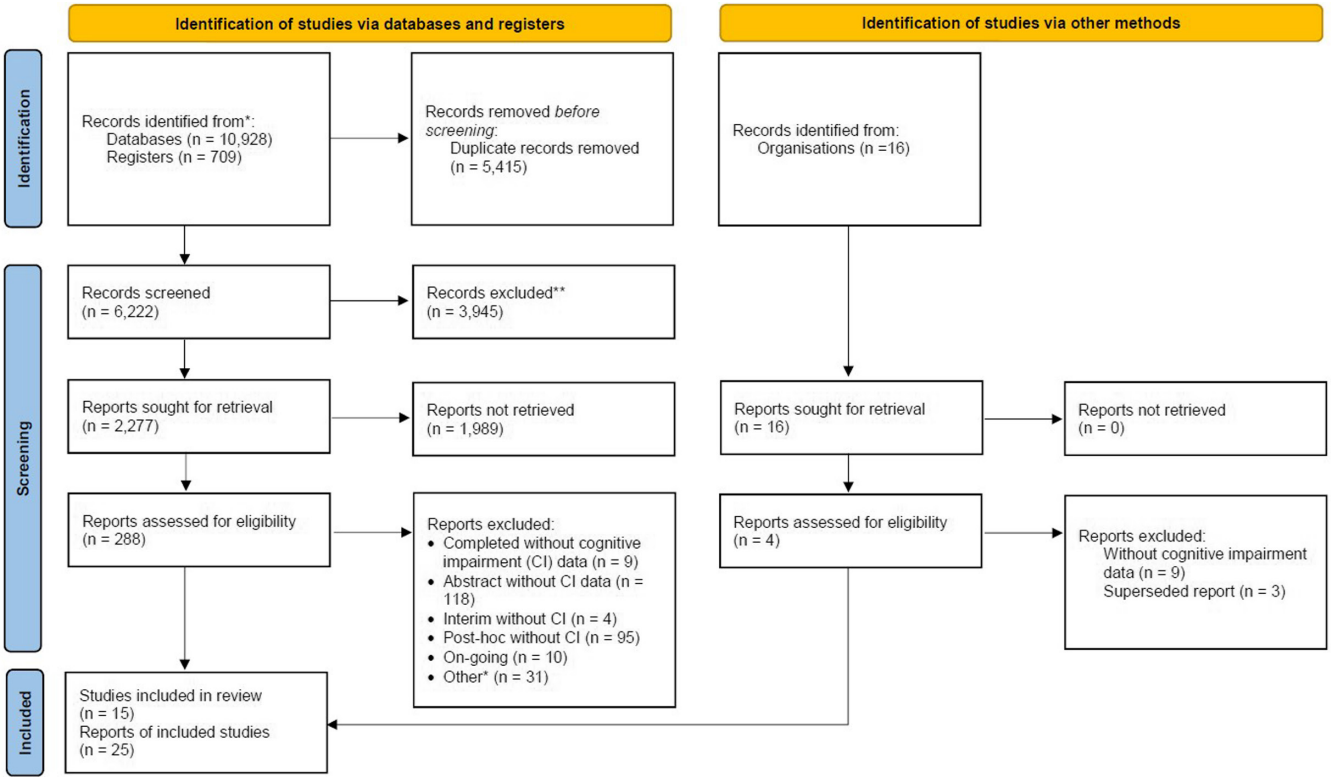

FIGURE 1 The Preferred Reporting Items for systematic review and Meta-analysis (PRISMA) flowchart

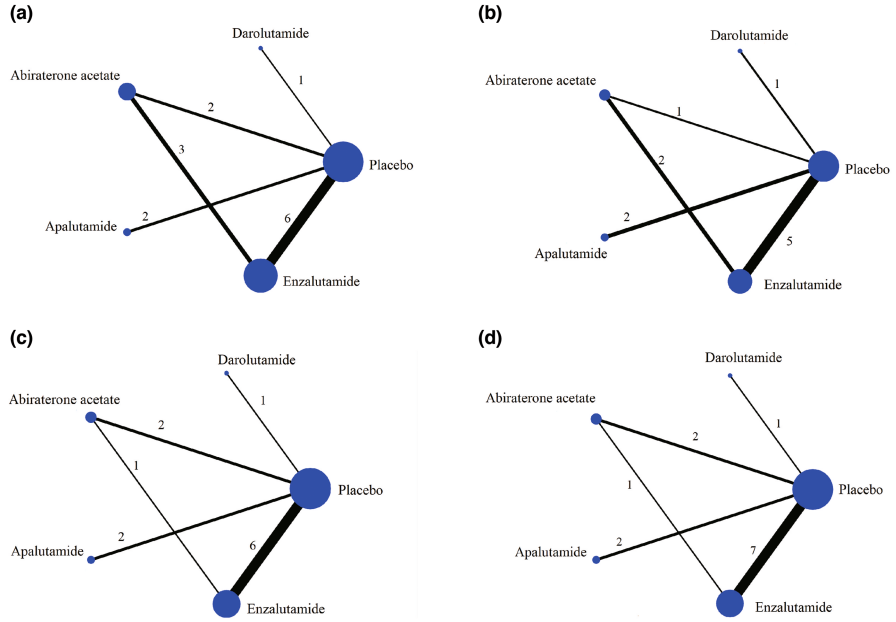

FIGURE 2 Network treatments comparisons for cognitive impairment and falls of the novel hormonal agents compared with placebo/standard care. (a) Studies with reports of event rate ratio of cognitive impairment; (b) studies with reports of incidence rate ratio of cognitive impairment; (c) studies only included randomized controlled trials; and (d) studies with reports of any grade of falls. The size of the nodes corresponds to the number of trials in which the treatments were studied. The interventions that are compared directly are joined with a line, the thickness of which corresponds to the number of trials that assessed the comparisons, and the number is shown on the line.

(mCSPC) and 12 trials involved patients with metastatic CRPC (mCRPC) and non-metastatic CRPC (nmCRPC). The median treatment duration was more than 12 months in eight trials and less than 12 months in seven trials in the treatment arm.

The ROB assessment is shown in Table S2. ROB was low in any domain because a majority of RCTs were pharmaceutical company-issued clinical trials with standard protocol. In non-RCTs, we judged a moderate risk overall in these two trials. The baseline characteristic was similar and the care provided was not different in the two treatment arms in these two trials. The participants were all patients with CRPC with new-user designs, and missing data were few. However nondifferential misclassification might exist when categorizing cognitive impairment.

Primary and secondary outcomes

A network of eligible comparisons for the primary and secondary outcomes is presented in Figure 2. We summarized our random-effects network meta-analysis and pairwise comparison of primary and secondary outcomes in Figures 3 and 4, Figure S1, and Table S3. In a pairwise meta-analysis, the use of NHAs increased the risk of cognitive impairment by 115% more than the placebo.

Among the four medications, ENZA, APA, and ABI had a higher risk of cognitive impairment than placebo with an OR of 3.60 (95% CI, 2.78 to 4.67, I^2 =0%), 1.76 (95% CI, 1.08 to 2.87, I^2 =0%), 1.74 (95% CI, 1.15 to 2.65, I^2 =0%), respectively (Figure 3). On the other hand, DARO was not associated with increased risk than placebo (1.11; 95% CI, 0.51 to 2.39). Besides, ENZA yields a greater risk than ABI for cognitive impairment with an OR of 5.23 (95% CI, 1.11 to 24.61, I^2 = 0%).

In network meta-analysis, compared with placebo, ENZA had the highest risk of cognitive impairment; OR 3.66 (95% CI 2.84 to 4.73), followed by APA (1.76; 95% CI, 1.08 to 2.87), ABI (1.64; 95% CI, 1.01–2.45), and DARO (1.11; 95% CI, 0.51–2.39) had the lowest risk (Figure S2, Table S4). After adjustment of treatment time duration, ENZA still had the highest risk of cognitive impairment with an IRR of 2.17 (95% CI, 1.69 to 2.78), followed by APA (1.30; 95% CI, 0.80 to 2.10), ABI (1.18; 95% CI, 0.79–1.77), and DARO (0.81; 95% CI, 0.38–1.75).

Additional analysis, sensitivity analysis, and inconsistency

Regarding disease status, age, and treatment duration effect, the meta-regression showed that these parameters were not effective modifiers and did not change the results with a p value for the interaction of 0.93, 0.73, and 0.10 (Figure S5).

After excluding non-RCTs, compared with placebo, ENZA still had the highest risk of cognitive impairment;

TABLE 1 Baseline characteristics of included studies

Trial name	Author	Pub year	Phase study design	Disease status	Intervention	Number	Age (median)	Follow-up duration (months)	Treatment duration (months)
AQUARiUS[25,26]	Antoine Thiery-Vuillemin	2020	NRS design	mCRPC	ABI/ENZA	105/106	76/76	12	8.8/8.9
ARAMIS[14,27,28]	Karim Fizazi	2020	III, RCT, DB	nmCRPC	DARO/placebo	955/554	74/74	29	25.8/11.6
ARCHES[29,30]	Andrew J. Armstrong	2019	III, RCT, DB	mCSPC	ENZA/placebo	574/576	70/70	14.4	12.8/11.6
ENZAMET[31]	Ian Davis	2019	III, RCT, open	mCSPC	ENZA/SoC	563/562	69.2/69	34	>12[b]
LATITUDE[12]	Karim Fizazi	2019	III, RCT, DB	mCSPC	ABI/placebo	597/602	68/67	51.8	25.8/14.4
PROSPER[13,32,33]	Cora N. Sternberg	2020	III, RCT, DB	nmCRPC	ENZA/placebo	933/468	74/73	48	33.9/14.2
REAAcT[34]	Neal D. Shore	2019	NRS	mCRPC	ABI/ENZA	50/50	75/74	2	2.1/2.0
SPARTAN[35,36]	Matthew R. Smith	2018	III, RCT, DB	nmCRPC	APA/placebo	806/401	74/74	20.3	18/11
STAMPEDE – G[37]	N.D. James	2017	II/III, RCT, open	CRPC	ABI/SoC	960/957	67/67	40	>12[b]
TITAN[11,36]	Kim N. Chi	2019	III, RCT, DB	mCSPC	APA/placebo	525/527	69/68	22.7	20/18
AFFIRM[16,29,38]	Howard I. Scher	2012	III, RCT, DB	mCRPC	ENZA/placebo	800/399	69/69	14.4	8.3/3
PREVAIL[29,38,39]	Tomasz M. Beer	2014	III, RCT, DB	mCRPC	ENZA/placebo	872/845	72/71	22	16.6/4.6
STRIVE[29,40]	David F. Penson	2016	II, RCT, DB	CRPC	ENZA/Bicalutamide	198/198	72/74	NA	14.7/8.4
TERRIN[29,41]	Neal D Shore	2016	II, RCT, DB	mCRPC	ENZA/Bicalutamide	184/191	71/71	20	11.6/5.8
NCT02125357[42–44]	Daniel J Khalaf	2019	II, RCT, open	mCRPC	ABI/ENZA	101/101	72.9/77.6	30.7[a]	<12[a]

Abbreviations: ABI, abiraterone; APA, apalutamide; CRPC, castration-resistant prostate cancer; DARO, darolutamide; DB, double blind; ENZA, enzalutamide; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration sensitive prostate cancer; NA, not available; nmCRPC, non-metastatic castration-resistant prostate cancer; NRS, non-randomized interventional studies; Pub, publication; RCT, randomized controlled trial; Soc, standard of care.

[a]We only adopted data <12 months.

[b]No reported median treatment duration and median progression-free survival not reached.

TABLE 2 Events numbers and relative information of included studies

Trial name	Author	Pub year	Intervention	Numbers	Cognitive impairment							Falls	
					amnesia	Cognitive disturbance	Concentration impairment	Memory impairment	Dementia	Any grade	Incidence rate	Any grade	Evaluation methods
AQUARiUS	Antoine Thiery-Vuillemin	2020	APA/ENZA	105/106						0/5	0.56/6.32	NA	FACT-Cog, CTCAE 4.03
ARAMIS	Karim Fizazi	2020	DARO/placebo	954/554				19/10		19/10	1.3/1.6	50/27	CTCAE V4.03
ARCHES	Andrew J. Armstrong	2019	ENZA/placebo	572/574						26/12	4.26/2.19	21/15	CTCAE V4.03
ENZAMET	Ian Davis	2019	ENZA/SoC	563/558						110/32	9.17/3.56	54/20	CTCAE V4.03
LATITUDE	Karim Fizazi	2019	APA/placebo	597/602						1/1		1/0	CTCAE V4.0
PROSPER	Cora N. Sternberg	2020	ENZA/placebo	930/465	6/2	7/1	15/1	18/4	6/1	73/10	3.35/1.76	164/25	CTCAE V4.0
REAAcT	Neal D. Shore	2019	APA/ENZA	50/50						1/4		NA	Cogstate battery
SPARTAN	Matthew R. Smith	2018	APA/placebo	803/398	15/4	7/3	10/1	14/6		46/14	3.5/3.1	135/37	CTCAE V4.03
STAMPEDE - G	N.D. James	2017	APA/SoC	948/960						61/36	2.34/1.9	0/0	CTCAE V4.0
TITAN	Kim N. Chi	2019	APA/placebo	524/527	4/1	5/1	1/1	7/6		17/9	2/1.2	39/37	CTCAE V4.03
AFFIRM	Howard I. Scher	2012	ENZA/placebo	800/399	27/4	16/3	18/4	31/8	3/2	34/7	4.19/2.47	37/5	CTCAE V4.0
PREVAIL	Tomasz M. Beer	2014	ENZA/placebo	871/844						50/11		113/45	CTCAE V4.0
NCT02125357	Daniel J Khalaf	2019	APA/ENZA	101/101						0/1	0.65/2.04	1/0	CTCAE V4.0; MoCA
STRIVE	David F. Penson	2016	ENZA/ Bicalutamide	197/198	11/0	1/0	1/1	7/3	1/1	19/5[a]	4.06/1.53[a]	27/16	CTCAE V4.0
TERRIN	Neal D Shore	2016	ENZA/ Bicalutamide	183/189						19/5[a]	4.06/1.53[a]	12/7	

Abbreviations: APA, apalutamide; CTCAE, Common Terminology Criteria for Adverse Events; DARO, darolutamide; ENZA, enzalutamide; FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive; MoCA, Montreal Cognitive Assessment; NA, not applicable; Pub, publication; SoC, standard of care.

[a]The data combined STRIVE and TERRIN results.

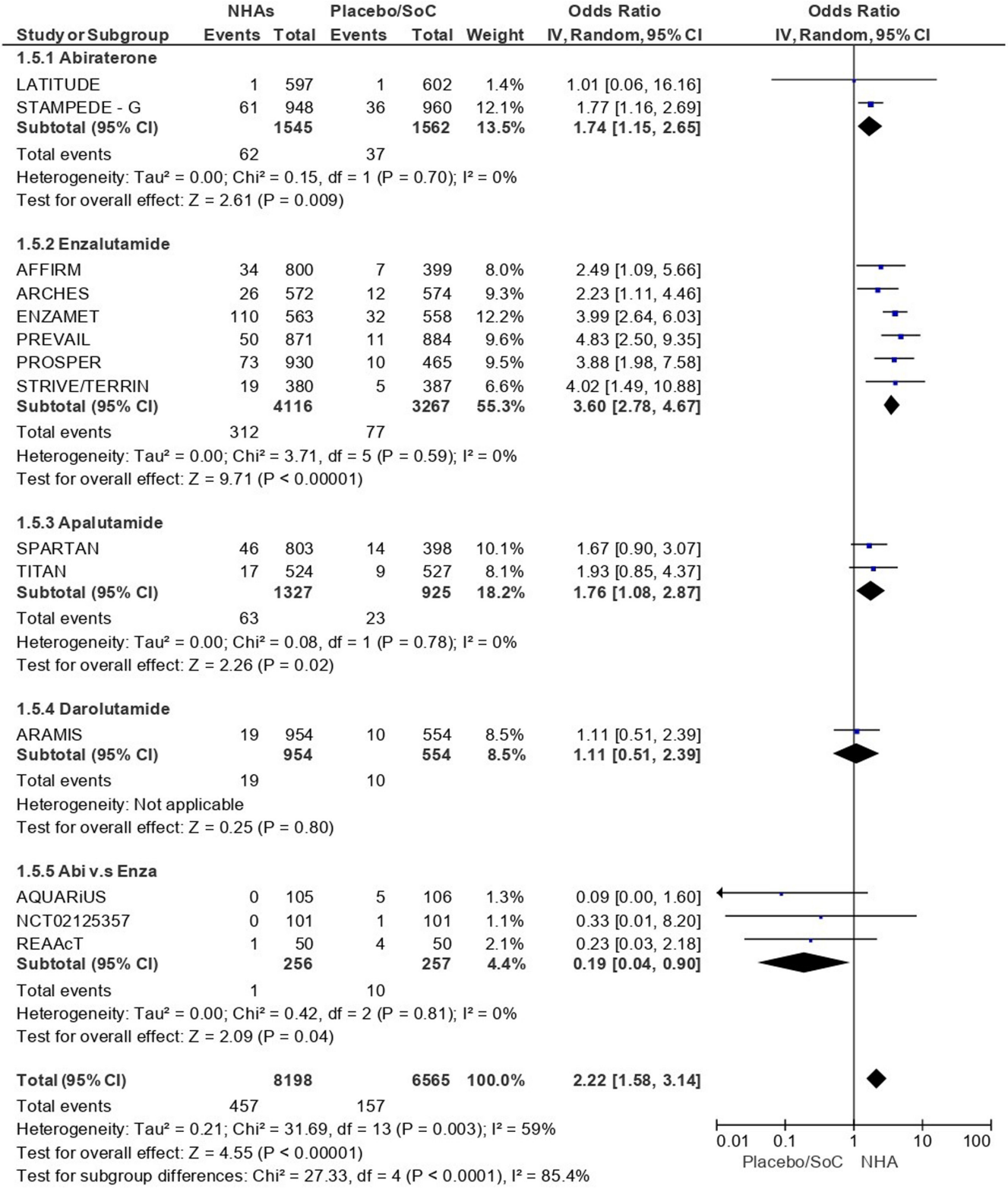

FIGURE 3 Pairwise meta-analysis of event rate ratio for cognitive impairment of the novel hormonal agents compared with placebo/standard care. CI, confidence interval; NHA, novel hormonal agent

OR 3.60 (2.78 to 4.66), followed by APA (1.76; 95% CI, 1.08 to 2.87), ABI (1.73; 95% CI, 1.14–2.62), and DARO (1.10; 95% CI, 0.51–2.39).

Regarding falls, ENZA still had the highest risk; OR, 2.55 (1.90 to 3.41) compared with placebo, followed by APA (1.49, 95% CI, 0.94 to 2.35), ABI (1.42, 95% CI,

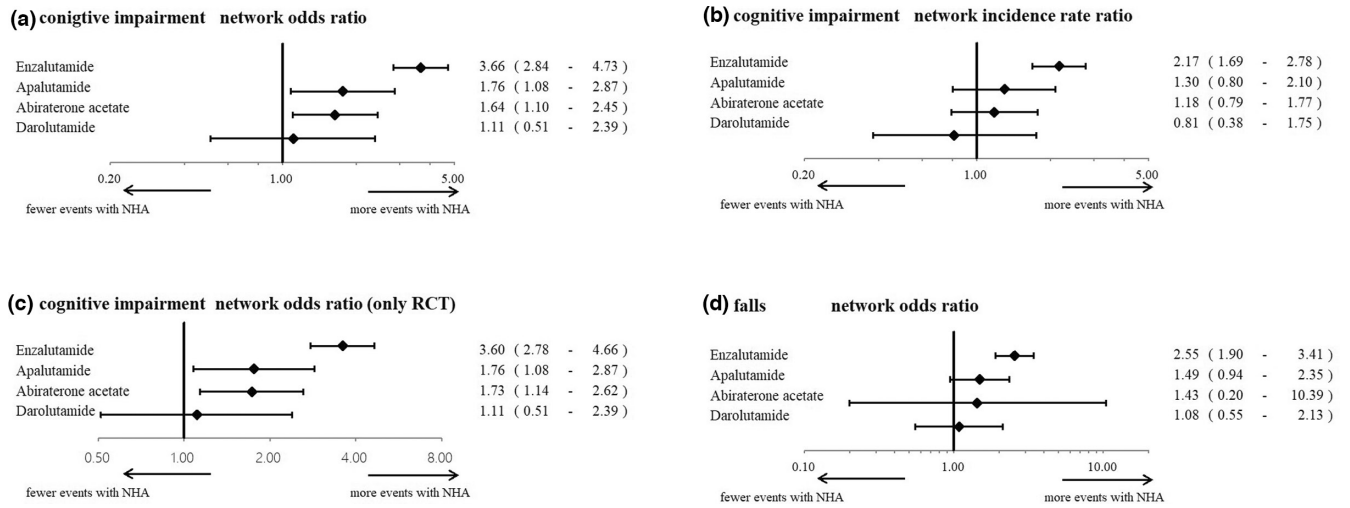

FIGURE 4 Network meta-analysis of the cognitive impairment and falls of the novel hormonal agents compared with placebo/standard care. Common heterogeneity variables for all comparisons in this network meta-analysis included: $\tau = 0, 0, 0$, and 0.06, with reference to odds ratio (OR) of cognitive impairment, incidence rate ratio of cognitive impairment, OR of cognitive impairment only including RCT, and OR of falls, respectively. Treatments are ranked according to the SUCRA values. RCT, randomized controlled trials; SUCRA, surface under the cumulative ranking

0.20–10.39), and DARO (1.08, 95% CI, 0.55–2.13) had the lowest risk.

We found no evidence of global inconsistency in any outcomes by using the design-by-treatment interaction models, respectively. Applying side-splitting methods, there was also no substantial inconsistency between direct and indirect estimates in Table S5. Comparison-adjusted funnel plots also showed no small study bias in Figure S3. Heterogeneity was low in various pairwise comparisons of any outcomes. The event rates in the placebo arm were similar and yielded no transitivity problem (Figure S4).

Two trials had interim reports (Aramis and Prosper), and the event rates increased from 0.9% to 2.0% ($p = 0.03$) and 5.16% to 7.85% ($p = 0.01$) from interim to the final report in the treatment arm of the Aramis and Prosper trials, respectively. However, there was no difference in events rate in the controlled arm in the interim and final reports. Two trials reported patient-reported outcomes and investigator-reported outcomes simultaneously, and both showed that ENZA had a greater risk of cognitive impairment than ABI. Nonetheless, the event rate was 44.5% and 15.8% in the patient-reported outcome and 4.7% and 1.0% in the investigator-reported outcome in AQUARiUS and NCT02125357 trials, respectively (Figure S5).

DISCUSSION

In our study, ENZA, APA, and ABI yielded a greater risk of cognitive impairment than placebo and DARO. After adjusting for treatment duration, ENZA still had the greatest risk of developing cognitive impairment. The risk remained significant nonmatter in different disease statuses (CRPC or CSPC), different treatment duration (≥12 month and <12 months), or different age groups (≥70 years old and <70 years old). The risk of falls was the same with cognitive impairment, ENZA yielded the greatest risk, followed by APA, ABI, and DARO which had the lowest risk. Our findings support that NHAs may increase the risk of cognitive impairment and cognitive function should be monitored in patients with advanced prostate cancer especially treated with ENZA.

Because ARs are highly expressed in the prefrontal cortex, parietal lobe, and hippocampus, any influences from androgen deprivation therapy may result in cognitive impairment.[45–47] Among NHAs, ENZA, APA and DARO, are AR antagonists. ENZA and APA share similar chemical structures, whereas DARO is structurally unique with a polar group. The difference between these agents is the permeability of the blood–brain barrier (BBB) leading to different drug concentrations in the brain. ENZA had 46-fold and two-fold higher brain concentrations than were observed with DARO and APA, respectively.[48] In addition, in nude mice bearing orthotopic VCaP tumor models, brain/plasma ratios (%) were 1.9–3.9%, 27%, and 62% after the oral dosing of DARO (25–100 mg/kg, b.i.d. for 7 days), ENZA (20 mg/kg, q.d. for 7 days) or APA (a single dose of 10 mg/kg), respectively. DARO and its main metabolite showed a very low brain/plasma ratio with no dose response. Furthermore, DARO did not affect the testosterone level in serum compared with other anti-androgen therapy, implying that DARO did not stimulate central nervous systems of luteinizing hormone signaling.[49] Clinical evidence

from other central nervous system (CNS) adverse events showed that ENZA and APA had a higher chance of BBB penetration which would lead to inhibition of the y-aminobutyric acid receptor to cause epilepsy.[15] ENZA and APA also caused fatigue, mental disorders, and dizziness at a higher rate than placebo.[13,35] Relatively speaking, DARO has shown low BBB penetration, resulting in a lower chance of epilepsy.[50]

Cognitive impairment has been identified as a risk factor for falls in the older population. Impaired executive/attention function and visuomotor task, but not memory impairment, may account for the increased incidence of falls.[51] Furthermore, falls have been reported to be associated with fatigue, age, poor performance statutes, history of neuropathy, and a-blocker prescription in patients with advanced prostate cancer treated with ADT.[52,53] Whether falls are related to cognitive impairment in NHA treatment in advanced prostate cancer needs further research.

To our knowledge, this is the first study to compare four NHA side effects in cognitive function by using meta-analysis. Previous studies failed to perform meta-analysis because cognition function change was not viewed as a frequent adverse event, and published articles usually lack useful and important relevant data.[54,55] We found these data in the EMA, the FDA, and clinical.gov safety reports. Besides, we used network meta-analysis to compare four NHA simultaneously. Network meta-analysis is a meta-analytic method that integrates results of direct comparison within trials, and indirect comparison between trials into a single effect size and gives a ranking under the same statistical model.

Dementia is the fifth leading cause of death among older adults and one of the major causes of disability and dependency among older people globally. The prevalence doubles with every 5-year increase in age after 65 years.[56] Moreover, dementia, very mild dementia, and mild cognitive impairment affect 20% of men more than 65 years old.[57] These patients might be more vulnerable to exposure to NHAs. DARO may be more suitable for these patients due to the lower risk of cognitive impairment.

Cognitive impairment is frequently underdiagnosed in geriatric patients with cancer.[58] Because age, cancer-related discomfort, and patients' comorbidities may account for cognitive function change during cancer treatment, treatment-related cognitive impairment is easily ignored. Our data show a large discrepancy in cognitive impairment incidence between patient-reported outcomes and investigator-assessed outcomes. It implied that under-reported is severe in patients with advanced prostate cancer if using investigator assessment. Patient-reported outcome measurement with a validated questionnaire may be more suitable to identify subtle but clinically meaningful cognitive impairment.

There are only two trials that reported cognitive impairment adverse events in the interim report, other trials did not report them because the event rate was usually under 4% in the treatment arm in the interim trial. The continually increasing events rate between the interim and final report indicated that the risk of cognitive impairment was stably cumulated. In the AQUARiUS trial, patients with mCRPC treated with ENZA consistently reported greater cognitive decline over the course of 12 months than those receiving ABI. The trend of NHAs is to be used in patients with an earlier stage of advanced prostate cancer which results in a longer duration of exposure. Cognitive impairment in patients with cancer can affect patient decision making in treatment choice, and participation in occupational or leisure activity, and markedly affect both subjective and objective QOL.[58,59] Otherwise, patients with prostate cancer experienced CNS adverse events increasing the economic burden and therapy discontinuation.[60] As patients with prostate cancer live longer, diminishing treatment-related toxicity in order to improve QOL became a paramount of importance.

There are six domains in neurocognitive function, poor cognitive performance which affects visuomotor skills, executive function, and verbal memory in patients with prostate cancer who underwent chemical castration.[8,10] However, which neurocognitive domain may be affected by NHA was unclear. The majority of trials in our review only had a global evaluation of cognitive impairment, further research using the validated instruments is needed.

Clinicians rarely apply validated assessment tools for cognition function in patients with advanced prostate cancer because of the lengthy questionnaire. Recently, the International Society of Geriatric Oncology recommended using mini-cog as a brief screening tool to evaluate the cognitive function of elderly patients with prostate cancer.[61] Our results also suggested that baseline screening and routine follow-up of cognition function are needed. A brief validated questionnaire is more suitable owing to under-reported cognitive impairment events in these patients. A neuropsychologist referral may be warranted when cognitive impairment is identified. Otherwise, a multidisciplinary approach, collaborating with pharmacists, geriatricians, and neuropsychiatrists, in treating patients with advanced prostate cancer may reduce the potential detrimental effect. Moreover, cognitive function evaluation should be included in future clinical trials in reporting side effects of new medication treatment in patients with advanced prostate cancer.

Our network meta-analysis has some limitations. First, because this is aggregated data, not individual data, we cannot find out the risk factor of cognitive impairment except for medication. Besides, we cannot

access personal medical history, including how many lines of treatment were received prior to treatment, what type of treatment was received, etc. Moreover, we also cannot establish the correlation between falls and cognition function in our study. The over-inference may contribute to ecological bias. Second, meta-regression is a low-power estimation. Whether age, disease status, and treatment duration are mediators of cognitive impairment in NHAs needs further research. Third, the majority of trials in our review only had a global evaluation of cognitive impairment, which neurocognitive domain was affected by NHAs needs further research. Fourth, because the cognitive function was not emphasized in the earlier trials, we lack cognitive function data in some early abiraterone trials, such as the COU-AA-301, COU-AA-301, and LATITUDE trials that only reported side effects more than grade 3. Besides, there was only a single study of DARO reporting cognitive function enrolled in this analysis, so interpretation of any findings for this drug will require additional data.

CONCLUSION

NHAs, especially ENZA, may increase the risk of cognitive impairment in patients with advanced prostate cancer. The potential negative impact of NHAs should be assessed and highlighted while preparing for the prescription because prevention of cognitive impairment is a core pillar of prostate cancer treatment.

AUTHOR CONTRIBUTIONS

S.-W.H. and C.-S.T. wrote the manuscript. S.-W.H., L.-C.C., and Y.-S.P. designed the research. S.-W.H. and L.-C.C. performed the research. S.-W.H., L.-C.C., and C.-H.C. analyzed the data. W.-Y.S. and L.-H.Y. contributed new reagents/analytical tools.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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