

Review Article**Effect of androgen deprivation therapy on cognitive functioning in men with prostate cancer: A systematic review**Cornelie D Andela,¹ Rafil Matte,¹ Ingrid M Jazet,¹ Willemijn CG Zonneveld,² Jan W Schoones³ and A Edo Meinders¹¹Division of Endocrinology, Department of Medicine, Leiden University Medical Center, ²Department of Urology, Leiden University Medical Center, and ³Walaeus Library, Leiden University Medical Center, Leiden, The Netherlands**Abbreviations & Acronyms**

ADT = androgen deprivation therapy
AVLT = Auditory Verbal Learning Test
BVMTR-R = Brief Visual Memory Test–Revised
CCT = computerized cognitive training
CNS = central nervous system
COWAT = Controlled Oral Word Association Test
CVLT = California Verbal Learning Test
D-KEFS = Delis–Kaplan Executive Function System
DSST = Digit Symbol Substitution Test
EBPM = Event-Based Prospective Memory
fMRI = functional magnetic resonance imaging
GMV = grey matter volume
HVLT-R = Hopkins Verbal Learning Test–Revised
HVOT = Hooper Visual Orientation Test
JLOT = Judgement of Line Orientation Test
LHRH = luteinizing hormone-releasing hormone
MMSE = Mini-Mental State Examination
MoCA = Montreal Cognitive Assessment
NA = not applicable
NART = National Adult Reading Test
NPA = neuropsychological assessment
PI = proactive interference
RAVLT = Rey Auditory Verbal Learning Test
RCFT = Rey Complex Figure Test
RCT = randomized controlled trial
SCWT = Stroop Color Word Task
SDMT = Symbol Digit Modalities Test
SOPT = Subject Ordered Pointing Task
TAVEC = Auditive Verbal Spanish Complitense Test
TBPM = Time-Based Prospective Memory
TMT = Trail-Making Test
WAIS-R = Wechsler Adult Intelligence Scale–Revised
WML = white matter lesion
WMS-R = Wechsler Memory Scale–Revised
WMV = white matter volume

Abstract: The objective of this study was to review publications assessing cognitive functioning in patients with prostate cancer treated with androgen deprivation therapy. We conducted a systematic review of the literature published in PubMed, Embase, Web of Science, Cochrane Library, and PsycINFO up to February 2020. A total of 31 studies were included. Half of the studies ($n = 16$) demonstrated that androgen deprivation therapy in patients with prostate carcinoma did not result in a negative effect on cognitive functioning, however, still a substantial proportion of the studies ($n = 11$) reported a negative effect on cognitive functioning. In four studies the results were inconclusive. In the three studies using additional functional magnetic resonance imaging, no significant effect on neuropsychological tests was found, but grey matter volume, brain activity, and brain connectivity were affected. Given the substantial number of studies showing a significant negative effect of androgen deprivation therapy on cognitive functioning, clinicians should be aware of this side effect. Furthermore, future research should focus on the further examination of brain characteristics using functional magnetic resonance imaging, since these techniques might be more sensitive in detecting brain abnormalities as a result of androgen deprivation therapy.

Key words: androgen deprivation therapy, cognitive functioning.

Introduction

Prostate cancer is the second most common cancer worldwide, with 1.3 million cases in 2018 and a yearly death rate of approximately 300 000.¹ Prostate adenocarcinoma cells are, in general, initially testosterone-sensitive. Consequently, approximately 50% of all patients are treated with ADT, predominantly by the use of LHRH. The majority of men undergo chemical castration with LHRH agonists or antagonists with or without antiandrogens.² The testicular production of testosterone is suppressed, as is the hypophyseal production of gonadotropins, especially luteinizing hormone, which stimulates testosterone production. ADT is usually given for many years or even lifelong. Several different side effects may occur during this therapy, for example, cardiovascular disease, osteoporosis, anemia, hot flushes, metabolic diseases such as insulin resistance, hyperlipoproteinemia, (central) adiposity, symptoms of a disturbed sexual life, loss of muscular tissue, and gynecomastia.^{3,4}

In the last two decades, attention has also been paid to potential disturbances in cognitive functioning in patients treated with ADT.^{5,6} “Free” testosterone, and especially its more potent metabolite dihydrotestosterone (fourfold), as well as estradiol (which is formed by conversion from testosterone by the enzyme aromatase) and their receptors are found throughout the male brain. The receptors for these hormones are especially present in areas that are involved in cognition such as the thalamus, the hippocampus and the cerebral cortex. Their action follows several different pathways, such as activation of calcium channels, modulating neurotransmitters and decreased production of beta-amyloid.⁷ In animal studies, a positive effect of substitution with androgens or estrogens on cognitive functioning was found after castration.⁸ In older men, testosterone levels decrease and a positive relationship was found between free testosterone levels and several different cognitive functions, such as working memory, verbal memory, and visuospatial abilities.^{9–11} Of interest is the recent hypothesis that it is not the

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Received 25 October 2020; accepted 14 April 2021.

Online publication 14 June 2021

decrease of testosterone and estradiol in elderly men and women that is an etiological factor for the cognitive decline (especially in Alzheimer's disease), but the elevated gonadotropins and their releasing hormone, because of the loss of negative feedback of the sex steroids. In that case, hormonal therapy with LHRH agonists or antagonists in prostate cancer could be a factor that slows down cognitive decline.^{3,12,13}

To the best of our knowledge, six review articles have appeared on the subject of cognitive function in patients with prostate carcinoma treated with ADT. The first review was by Nelson *et al.*⁷ This review included nine relevant (small) studies and concluded that between 47% and 69% of men treated with ADT declined in at least one cognitive area, most often in visuospatial abilities and executive functioning.⁷ In 2012, Jamadar *et al.*¹⁴ selected 11 studies and reported that most of these had important limitations (e.g. small sample sizes, suboptimal control groups and baseline group differences in confounding factors). Nevertheless, it was concluded that the studies with the best controls suggested a potential negative impact of ADT on spatial memory and perhaps verbal memory.¹⁴ McGinty *et al.*¹⁵ conducted a systematic review and meta-analysis in 2014, including 14 studies, and analyzing seven cognitive domains. Patients on ADT performed worse on visuomotor ability tasks compared to controls as well as their own baseline measurements. No significant effects were detected in the other domains (i.e. attention/working memory, executive functioning, language, verbal memory, visual memory, visuospatial ability). Mundell *et al.*¹⁶ included 13 prospective studies in their review, and in five of these studies no effect on cognitive function was observed. In the other seven studies the evidence indicates that ADT adversely affects several different cognitive domains.¹⁶ Treanor *et al.*¹⁷ conducted a "review of reviews" including 28 reviews describing 20 primary studies published between 2003 and 2013. They found a prevalence rate of cognitive dysfunction varying from 10% to 69%. The domains impaired by ADT in prostate cancer patients included verbal memory, visuospatial abilities and executive functioning.¹⁷ The most recent systematic review and meta-analysis was conducted by Sun *et al.*,¹⁸ who reviewed 26 articles. Because of quality characteristics, only two prospective cohort studies and four retrospective cohort studies could be included in the meta-analysis. The overall results on cognitive tests following ADT in prostate cancer patients were inconclusive in the two prospective cohort studies, and nonsignificant in the other four retrospective studies.¹⁸

Considering the observation that the outcomes of the increasing number of studies on cognitive functioning in patients with prostate cancer treated with ADT are rather inconclusive, the aim of the present systematic review was to provide an overview of studies examining cognitive functioning in prostate cancer patients treated with ADT, including articles published up to 2020. Based on previous literature, we hypothesized that treatment with ADT using LHRH agonists or antagonists, and therefore exposure to low gonadotropins, might have a protective effect on cognitive functioning. Furthermore, we were interested in studies combining neuropsychological tests with modern techniques to detect

abnormalities in the brain (i.e. structural, functional, metabolic) in patients with prostate cancer on ADT.^{19–24}

Methods

Search strategy and data extraction

The following electronic databases were searched: PubMed, Embase, Web of Science, Cochrane Library, and PsycINFO. The search was performed on 6 February 2020. A search strategy was composed focusing on patients with prostate cancer and the effect of LHRH treatment on their cognitive functioning. All relevant keyword variations were used, including free text. All duplicates were excluded. See Appendix S1 for the complete search strategy. Only original studies were included. Studies were eligible if: (i) patients with prostate cancer were addressed; (ii) treatment with LHRH agonists or antagonists was involved; (iii) cognitive functioning was assessed and reported; (iv) sample size was >10 patients; and (v) they were written in English. Case reports, letters, and reviews were excluded. Data extraction and eligibility were assessed by three independent investigators (IM Jazet, AE Meinders, and CD Andela). Inconsistencies were resolved by reaching consensus. All references were checked for additional papers. The following data were extracted: (i) sample size; (ii) age; (iii) design; (iv) treatment; (v) potential inclusion of controls; (vi) procedure; (vii) cognitive measures used; (viii) cognitive domains assessed; and (ix) outcome of the study.

Quality assessment

A quality assessment was performed on all included studies. Eleven items were identified: clear research objective, inclusion/exclusion criteria, population demographics, duration of treatment, sample size, design, control group included, cognitive domains assessed, validation of measures, test instruction described and discussion of limitations (Appendix S2). The total individual quality score ranged from 0 to 23 points (Table 1). The quality of the studies was assessed by two reviewers independently (AE Meinders and CD Andela), discrepancies were discussed and resolved by reaching consensus. The total scores were calculated as percentages (individual score/23 × 100%). The median of the scores was 70 and was used as a cut-off point. Studies with a quality score 70 were considered high-quality papers ($n = 17$ studies). Given the low number of studies, studies were not excluded based on their quality assessment score.

Results

Literature overview

The literature search identified 1111 single publications, of which 33 were eligible for inclusion (Fig. 1). One study was found to be a duplicate²⁵ and was excluded. Another study referred to data described in a previous study²⁶ and was therefore also excluded. A final number of 31 studies was included, covering a total number of 1526 unique patients treated with ADT. Of these studies, 18 studies were prospective studies, nine studies were case-control/cross-sectional studies and four studies were RCTs (Table 2).

Table 1 Quality assessment of the included studies

	1	2	3	4	5	6	7	8	9	10	12	Score	Quality score, %
Stone <i>et al.</i> ³⁸	1	2	1	1	1	1	0	1	2	1	0	11	48
Green <i>et al.</i> ⁵¹	1	2	1	1	1	2	2	2	2	0	0	14	61
Cherrier <i>et al.</i> ⁴⁴	1	2	1	2	0	1	2	2	1	1	1	14	61
Salminen <i>et al.</i> ⁵⁰	1	2	1	3	0	1	3	3	2	0	1	17	74
Almeida <i>et al.</i> ⁴¹	1	2	2	3	0	1	0	3	2	1	1	16	70
Green <i>et al.</i> ⁵²	1	2	1	3	1	1	2	2	2	0	1	16	70
Bussiere <i>et al.</i> ³²	1	2	1	4	2	1	3	1	2	1	0	18	78
Jenkins <i>et al.</i> ⁴⁵	1	1	1	2	0	1	3	2	2	1	1	15	65
Salminen <i>et al.</i> ⁴³	1	2	2	3	0	1	0	3	2	1	1	16	70
Joly <i>et al.</i> ²⁸	1	2	2	4	1	1	2	3	2	0	1	19	83
Clay <i>et al.</i> ³⁴	1	1	0	4	2	1	2	1	1	1	1	15	65
Cherrier <i>et al.</i> ⁴²	1	2	1	2	0	1	3	2	2	1	1	16	70
Alibhai <i>et al.</i> ⁴⁹	1	2	2	3	1	1	3	3	2	0	1	19	83
Jim <i>et al.</i> ²⁷	1	2	2	2	0	1	3	2	2	1	1	17	74
Matousek <i>et al.</i> ⁵³	1	2	2	1	0	2	2	2	2	1	1	16	70
Mohile <i>et al.</i> ⁴⁰	1	2	2	1	0	1	0	2	2	1	1	13	57
Chao <i>et al.</i> ¹⁹	1	2	1	1	0	1	3	2	2	1	1	15	65
Chao <i>et al.</i> ²¹	1	2	1	1	0	1	2	1	2	1	1	13	57
Tan <i>et al.</i> ³⁷	1	1	0	3	0	1	0	1	2	0	1	10	43
Wiechno <i>et al.</i> ³¹	1	2	1	0	1	1	2	1	2	0	1	12	52
Gonzalez <i>et al.</i> ⁴⁷	1	2	2	3	2	1	3	2	2	0	1	19	83
Okamoto <i>et al.</i> ³⁶	1	1	0	3	0	1	0	1	2	0	1	10	43
Yang <i>et al.</i> ²⁹	1	2	2	1	1	1	3	3	2	0	1	17	74
Yang <i>et al.</i> ³⁰	1	2	2	1	0	1	3	3	1	1	1	16	70
Alibhai <i>et al.</i> ³⁹	1	2	2	4	2	1	3	3	2	0	1	21	91
Gunlusoy <i>et al.</i> ⁴⁸	1	2	2	3	2	1	2	3	2	0	1	19	83
Morote <i>et al.</i> ³⁵	1	2	0	1	2	1	0	2	1	0	0	10	43
Ali Shah <i>et al.</i> ³³	1	2	0	3	0	1	0	1	2	1	1	12	52
Wu <i>et al.</i> ⁵⁴	1	2	1	4	1	2	2	3	2	0	1	19	83
Ceylan <i>et al.</i> ⁴⁶	1	2	2	3	2	1	2	3	2	0	1	19	83
Plata-Bello <i>et al.</i> ²⁴	1	2	1	2	1	1	2	2	2	0	1	15	65

Bold text indicates a high-quality paper: score ≥ 70 .



Fig. 1 Flowchart literature selection process.

Cognitive measures

In the 31 included studies, 17 different cognitive domains were examined using 61 different neuropsychological tests

(Tables 2 and 3). The most frequently examined cognitive domain was memory ($n = 26$), followed by attention ($n = 19$), and visuospatial abilities ($n = 18$). The most frequently used test was Digit span ($n = 10$), followed by the

Table 2 Literature table (N = 31)

Reference	N†	Age, years‡	Design	Treatment	Controls	Procedure	Cognitive measures	Cognitive domains	Outcome
Case-control/cross-sectional (n = 9) Jim et al. ²⁷	48	Mean 69 (51–87)	Case-control	Continuously treated with LHRH agonist alone or combined antiandrogen/LHRH agonist therapy for at least 6 months	48 age- and education-matched controls	Single visit for NPA	HVLT-R COWAT BVMTR Card Rotations test SDMT	Memory Verbal fluency Visuospatial abilities Executive functioning	Significantly more overall impairment (i.e. impairment in two or more tests) in patients compared to controls. Prior prostatectomy was associated with impairment in immediate and delayed verbal memory in patients
Joly et al. ²⁸	57	Median 73, range 52–87	Case-control	≥3 months of ADT	51 healthy age-matched controls	Single visit for NPA	High-Sensitivity Cognitive Screen	Memory Attention/concentration Spatial ability Visual motor skills Language skills Self-regulation/planning	No difference in cognitive functioning between patients and controls
Yang et al. ²⁹	33	68.85 ± 4.61	Case-control	6 months of ADT consisting of 50 mg bicalutamide once daily with an additional subcutaneous injection of 3.6 mg goserelin acetate once every 28 days following 2 weeks of bicalutamide therapy	32 non-ADT patients and 25 age- and education-matched healthy controls	Single visit for NPA	AVLT Digit span (WAIS-III) SCWT TMT Verbal fluency MoCA	Attention Concentration Executive functioning Visuospatial functions Memory Language Abstract thinking Naming Orientation Information processing Verbal fluency	Patients on ADT performed worse on recognition, digit span forward, TMT B and the Stroop test compared to control groups
Yang et al. ³⁰	43	69.28 ± 4.38	Case-control	6 months of ADT consisting of 50 mg bicalutamide once daily with an additional subcutaneous injection of 3.6 mg goserelin acetate once every 28 days following 2 weeks of bicalutamide therapy	35 non-ADT patients and 40 age- and education-matched healthy controls	Single visit for NPA	AVLT Digit span (WAIS-III) SCWT TMT Verbal fluency MoCA EBPM TBPM	Attention Concentration Executive functioning Visuospatial functions Memory Language Abstract thinking Naming Orientation Information processing Verbal fluency	Patients on ADT performed worse on EBPM compared to control groups, with no significant differences in TBPM. Patients on ADT performed worse on attention, memory, information processing compared to control groups
Wiechno et al. ³¹	88	Median 67, range 50–80	Case-control	LHRH analogue, gosereline, 12 injections every 3 months. Was initiated within 3 months of radiotherapy completion	61 with prostate cancer without hormone therapy	Single visit for NPA	MMSE	General cognitive screening	No significant differences in cognitive functioning between patients on hormone therapy and patients without hormone therapy
Clay et al. ³⁴	55	ST-ADT: 74.4 ± 6.1, range 70.3–78.0 LT-ADT: 73.1 ± 6.8, range 71.0–75.2	Cross-sectional/ case-control	ADT by orchiectomy, gonadotrophin-releasing hormone agonists, antiandrogens, or a combination	20 control subjects 25 non-ADT patients	Single visit for NPA in patients on short-term ADT (<6 months) and patients on long-term ADT (>6 months), non-ADT patients, and controls	DSST (WAIS-R)	Visuomotor skills	ADT did not have a significant effect on visuomotor function

Table 2 (Continued)

Reference	N†	Age, years‡	Design	Treatment	Controls	Procedure	Cognitive measures	Cognitive domains	Outcome
Bussiere et al. ³²	14	Mean 66.9, range 50–80	Case-control	Continuous ADT with leuprolide acetate in 12 men and with orchiectomy in two men without other concurrent adjuvant therapies, including chemotherapy	16 healthy control men, matched for age, years of education and intelligence test (WAIS-R vocabulary subtest)	NPA in patients on ADT for on average 1991 days	Word list-learning test	Memory	Patients on ADT showed impairment in retention but normal encoding and retrieval processes
Ali Shah et al. ³³	20	Mean 72.1, range 57–85	Cross-sectional	ADT with LHRH agonist	NA	NPA in patients on early ADT (<4 months) and patients on late ADT (>4 months)	MMSE	General cognitive screening	No difference in cognitive functioning between early vs late ADT
Plata-Bello et al. ²⁴	50	78.3 ± 7.5	Case-control	≥6 months of ADT	15 non-ADT patients	NPA and MRI to examine GMV and WMV	Word List Generation COWAT JLOT HVOT TMT BVMT TAVEC	Verbal fluency Visuospatial ability Processing speed Memory	No significant differences in cognitive functioning, GMV and WMV between patients and controls, but there was a negative relationship between ADT period and GMV
Prospective (n = 18) Morote et al. ³⁵	308	71.2 ± 8.1, range 46–100	Prospective, observational, multicenter, open-label	LHRH analogue treatment, with bicalutamide 50 mg/day 2 weeks before and 2 weeks after the first LHRH administration	NA	NPA at baseline and after 6 months of treatment	2-part ad hoc test Digit Span (WAIS-III) Benton Judgment of Line Orientation test Mental Rotation test Matrix Reasoning test (WAIS-III) MMSE	Memory Visuospatial ability Nonverbal analytical reasoning	No significant change in cognitive functioning after LHRH analogues
Okamoto et al. ³⁶	45	67.5 ± 3.5	Prospective	6-month neoadjuvant ADT (i.e. leuprolide) with radiation therapy, followed by adjuvant ADT	NA	NPA before treatment, after 6 months and 12 months	MMSE	General cognitive screening	Treatment had no effect of MMSE scores. Lower MMSE scores were associated with low estradiol and cortisol and high androstenedione levels at 6 months
Tan et al. ³⁷	50	71 (59–89)	Prospective	Leuprolide injection 30 mg every 4 months	NA	NPA before the first leuprolide injection and at 2, 4, 12 months	MMSE CVLT	General cognitive screening Memory	No change from baseline to follow-up on the MMSE. Verbal memory improved slightly, which was indicative of a practice effect
Almeida et al. ⁴¹	40	72.4 ± 7.5, range 44–83	Prospective	Androgen blockade therapy (flutamide and leuprolide) for 36 weeks and followed-up for another 18 weeks	NA	NPA at baseline and at week 4, 12, 24, 36, 42, 48 and 54	Cambridge Examination for Mental Disorders of the Elderly (CAMCOG) Word lists (WMS-III) Verbal paired associations (WMS-III) Visual reproduction (WMS-III) Block design (WAIS-III) Digit-span (reverse)	Orientation Language Memory Attention Praxis Abstract thinking Perception Calculation Executive functioning Visuospatial ability	Discontinuation of treatment is associated with better cognitive functioning, especially in verbal memory
Stone et al. ³⁸	62	Median 69 (55–80)	Prospective	First-line hormone therapy cyproterone acetate 100 mg	NA	NPA before the first leuprolide injection and at 2, 4, 12 months	MMSE CVLT	Attention	No significant effects on the reverse digit span

Table 2 (Continued)

Reference	N†	Age, years‡	Design	Treatment	Controls	Procedure	Cognitive measures	Cognitive domains	Outcome
Alibhai et al. ^{§49}	77	69.3 ± 6.9	Prospective Case-control	three times daily for 3 weeks followed by monthly injections with zoledex ADT not further specified	82 patients not receiving ADT 82 healthy controls	NPA prior to and following 3 months of treatment NPA at baseline, 6 months and at 12 months	Digit span (WAIS) Spatial span (WMS) TMT COWAT Card rotations test JLOT CVLT BVMT Conditional associative learning test Spatial working memory task D-KEFS	Attention Processing speed Verbal fluency Visuospatial ability Memory Executive functioning	One test in immediate memory, working memory, and visuospatial ability were worse at 12 months in ADT users compared to control groups, while other test in these domain were not significantly different
Alibhai et al. ^{§49}	77	Mean 68.9, median 16 (all included participants)	Prospective Case-control	73 patients used LHRH agonists alone, whereas four were receiving combined LHRH agonists and nonsteroidal antiandrogens	82 non-ADT patients and 82 healthy controls	NPA at baseline and on five occasions over 36 months	Digit span (WAIS) Spatial span (WMS) TMT COWAT Card rotations test JLOT CVLT BVMT Conditional associative learning test Spatial working memory task D-KEFS	Attention Processing speed Verbal fluency Visuospatial ability Memory Executive functioning	In patients ADT use was not associated with significant changes over time in any cognitive test compared with healthy controls
Cherrier et al. ^{‡42}	20	62.05 ± 7.19	Prospective Case-control	Intermittent ADT consisting of 9 months treatment with combined leuproliide and flutamide, followed by an off-treatment period	20 healthy controls matched for age and education	NPA at baseline and at 3 months and 9 months of ADT, and after 3 months of no treatment	Puget sound route learning test Block design (WAIS-R) Mental rotation test PI Story recall (WMS-R) Verbal fluency test SCWT SOPT	Memory Spatial ability Verbal fluency Executive functioning	In ADT patients there was a significant decline at 3 months in spatial abilities (block design, mental rotation) and visual working memory (SOPT)
Mohile et al. ⁴⁰	32	Median 71.0, range 51–87	Prospective	ADT with or without the addition of antiandrogen	NA	NPA at baseline and after 6 months of ADT	TMT Digit span (WAIS-III) COWAT RCFT HVLTR BVMTR Grooved pegboard and finger tapping test	Attention Cognitive flexibility Verbal fluency Visuospatial abilities Memory Motor speed	High prevalence of lower than expected cognitive performance at baseline. There was no significant difference in cognitive performance at baseline and at 6-month follow-up
Salminen et al. ⁵⁰	25	64.4 ± 6.5, range 49–75	Prospective Case-control	ADT was started with flutamide for 4 weeks, and LHRH analogue (s.c. 3 months four	52 healthy control subjects	NPA at baseline, at 6 months and at 12 months	Similarities (WAIS) Digit span (WAIS) DSST (WAIS)	Language skills Verbal fluency Visuomotor skills	During follow-up there was improvement in object recall and semantic memory.

Table 2 (Continued)

Reference	N†	Age, years‡	Design	Treatment	Controls	Procedure	Cognitive measures	Cognitive domains	Outcome
Salminen et al. ⁴³	23	65.0 ± 6.7, range 49–75	Prospective	ADT started with flutamide 250 mg three times a day for 4 weeks, and LHRH analog (leuprolid 11, 25 mg subcutaneously, four times a year every 3 months) was added after 2 weeks	NA	NPA at baseline and at 6 and 12 months on ADT	CogniSpeed software Similarities (WAIS) Digit span (WAIS) DSST (WAIS) Block design (WAIS) Object naming/recall Verbal fluency test Word list recall Benton visual recognition task Visual span (WMS) MMSE	Memory Attention Visuospatial abilities Language skills Verbal fluency Visuomotor skills Memory Attention Visuospatial abilities	During longitudinal testing no impairment in cognitive functioning was found Visual memory and recognition speed were declined at 6 months. This decline was associated with a decline in estradiol during ADT Verbal fluency improved at 12 months
Chao et al. ¹⁹	15	69.0 ± 5.3	Prospective Case-control	Receiving ADT for 6 months	15 patients not receiving ADT, matched for age and education	NPA at baseline and after 6 months of treatment	CogniSpeed software N-back task Stop signal task MMSE	Memory Cognitive control General screening	No effect of treatment on cognitive functioning, but brain activation during cognitive control and functional brain connectivity (fMR) were diminished after 6 months of treatment
Cherrier et al. ⁴⁴	19	Mean 65, range 51–81 (all included participants)	Prospective Case-control	9 months of leuprolide and flutamide followed by an off-treatment period	15 healthy community dwelling controls.	NPA at baseline, after 9 months of androgen suppression and after 3 months off-treatment.	Route test Block design Mental rotation test PI Story recall Verbal fluency test SCWT Grid arrays	Memory Visuospatial abilities Verbal fluency Executive functioning Attention	Patients declined on a measure of spatial rotation after 9 months of treatment. During off-treatment period patients improved on a measure of verbal memory
Jenkins et al. ⁴⁵ (pilot study)	32	67.5 ± 4.7	Prospective Case-control	LHRH agonist	18 controls without prostate cancer	Before treatment, after 3 months or after completing drug treatment but before RT, and 9 months later	NART Verbal fluency test RAVLT RCFT Mental rotation test Digit span (WMS-III) Spatial span (WMS-III) Kendrick assessment of cognitive ageing battery MoCA	Intelligence Verbal fluency Memory Visuospatial ability Attention Processing speed	After 3 months, LHRH therapy resulted in cognitive decline on at least one test (most frequently spatial memory and ability) in more patients compared to controls. There was no significant difference at 9-month follow-up
Ceylan et al. ⁴⁶	72	67.27 ± 5.06	Prospective Case-control	Complete ADT continuously for 12 months	72 control patients who underwent radical prostatectomy	NPA at baseline and after 6 and 12 months		Attention Concentration Executive functioning Visuospatial functions Memory Language Abstract thinking	Patients and controls had worse post-treatment scores. There were no differences between patients and controls

Table 2 (Continued)

Reference	N†	Age, years‡	Design	Treatment	Controls	Procedure	Cognitive measures	Cognitive domains	Outcome
Chao <i>et al.</i> ²¹	12	69.1 ± 5.6	Prospective Case-control	ADT consisted of LHRH agonist (Goserelin 10.8 mg subcutaneously every 90 days) after a lead-in period for 2 weeks with bicalutamide 50 mg daily ADT for 12 months	12 demographically matched controls	NPA and MRI of the brain at baseline and after 6 months of ADT	N-back task MMSE	Naming Orientation Memory General screening	A decrease in GMV of the primary motor cortex was correlated with longer reaction time to target detection in the working memory task. There was no difference in working memory between patients and controls
Gonzalez <i>et al.</i> ⁴⁷	58	67.31 ± 8.87	Prospective Case-control	ADT for 12 months	84 patient controls treated with prostatectomy and 88 healthy controls. Both age and education matched	NPA at baseline and 6 and 12 months later	HVLT-R Logical memory (WMS-III) Digit span (WMS-III) Spatial span (WMS-III) BVMTR Color trials SDMT COWA TIADL NART MoCA Frontal assessment battery	Intelligence Memory Attention Executive function	ADT patients were more likely to demonstrate impaired cognitive performance within 6 and 12 months after starting ADT compared to controls
Gunlusoy <i>et al.</i> ⁴⁸	78	67.12 ± 5.12	Prospective Case-control	ADT treatment was an oral dose of 50 mg bicalutamide once daily with an additional subcutaneous injection of 10.8 mg goserelin acetate or 22.5 mg leuprolide acetate once every 3 months	78 patients controls treated with radical prostatectomy	NPA at baseline and after 6 and 12 months	WMS AVLT RCFT Digit-symbol (WAIS-R) TMT COWAT SCWT WAIS-R	Attention Concentration Executive functioning Visuospatial functions Memory Language Abstract thinking Naming Orientation Conceptualization Mental flexibility Programming Sensitivity of interference Inhibitory control Environmental autonomy	Patients on ADT performed worse on post treatment test compared to patient controls, especially on language ability and short-term memory capacity
RCT (n = 4) Green <i>et al.</i> ⁵¹	65	73.3 ± 6.4, range 56–86	RCT	Leuprorelin or goserelin or cyproterone acetate	15 patients in close clinical monitoring	Patients were randomly assigned to continuous leuprorelin or goserelin or cyproterone acetate or close clinical monitoring. NPA at baseline and before starting treatment, and 6 months later	WMS AVLT RCFT Digit-symbol (WAIS-R) TMT COWAT SCWT WAIS-R	Memory Attention Executive functioning Intelligence	24 of the 50 men randomized to active treatment demonstrated a significant decline in one or more tests. In the close clinical monitoring group no one demonstrated a decline
Green <i>et al.</i> ⁵²	62	73.5 ± 6.4	RCT	Leuprorelin Goserelin Cyproterone acetate	Close clinical monitoring group Community comparison group	Before treatment and after 6 months and after 12 months	WMS AVLT RCFT Digit-symbol (WAIS-R) TMT	Memory Attention Executive functions	Patients with pharmacologic treatment showed worse performance on verbal memory, coding and inhibitory tasks compared to the comparison groups

Table 2 (Continued)

Reference	N†	Age, years‡	Design	Treatment	Controls	Procedure	Cognitive measures	Cognitive domains	Outcome
Matousek et al. ⁵³	25	71.0 ± 8.8	Prospective/RCT	Phase 1: gonadotropin-releasing hormone analogue + bicalutamide Phase 2: added micronized E2 1 mg/day	Phase 2: added placebo	Prior to and after 3 months and after 6 months	COWAT SCWT MMSE Mental rotations test Paper folding test Block design (WAIS-III) Logical memory (WMSR) Verbal paired associations (WMSR) Verbal fluency test Digit symbol (WAIS-III) Letter number sequencing task CNS vital signs	General cognitive screening Visuospatial abilities Memory Visuomotor skills Attention Verbal fluency	No difference in cognitive functioning after 3 months of combined ADT. Added estradiol did not result into improvement of cognitive functioning
Wu et al. ⁵⁴	60	66.6 ± 8.5	RCT	≥3 months of ADT	Usual care	Prior (T1) and directly after the home-based CCT (T2), and after 8 weeks' follow-up (T3)		Attention Processing speed Motor speed Memory Cognitive flexibility	CCT resulted in better reaction time, but worse verbal and visual memory. Memory was temporarily suppressed in the CCT group at T2, but normalized by T3

†Number of patients with prostate carcinoma on ADT. ‡Mean ± standard deviation, or otherwise mentioned. §Duplicate sample.

MMSE ($n = 9$) which is a general cognitive screening, the COWAT ($n = 7$; assesses verbal fluency), as well as other verbal fluency tests (using letters or animal names; $n = 6$).

Single measurement of cognitive functioning of patients treated with ADT compared to control groups (case-control/cross-sectional studies)

Nine studies examined cognitive functioning during a single measurement compared to other/control groups. These studies included a total of 408 unique patients. Their average age ranged from 66.9 to 78.3 years. They received treatment for at least 3–6 months. Of the included studies, seven were case-control studies,^{24,27–32} one performed a cross-sectional analysis (i.e. short-term ADT vs long-term ADT),³³ and one study used both.³⁴ Of the studies using a case-control design, three studies used a healthy matched control group, two studies included a patient control group, and three studies included a healthy matched control group, as well as a patient control group.

In five of the nine studies no significant differences were found in cognitive functioning between the patients on ADT and the specific control groups.^{24,28,31,33,34} Clay *et al.*³⁴ did not find a difference in visuomotor performance between treated patients (ADT or orchiectomy) and healthy controls, as well as no difference between shorter treatment (<6 months) and longer treatment (>6 months) in patients. An unknown number of patients treated with orchiectomy was included, but no difference was found in visuomotor performance between patients with or without orchiectomy.³⁴ Interestingly, Plata-Bello *et al.*²⁴ did not observe differences in cognitive functioning between prostate carcinoma patients on ADT and healthy controls, but they did observe a negative relationship between ADT period and GMV using MRI in 50 prostate cancer patients treated with ADT for 6 months. Also a positive association was found between age and WML burden in the ADT patients, but not in the control subjects. There were no significant differences in GMV and WML between patients and controls.²⁴

Four studies did observe a negative effect of ADT on cognitive functioning.^{27,29,30,32} The study by Bussiere *et al.*³² demonstrated that patients receiving ADT have impairment in retention, but normal encoding and retrieving processes in the memory domain. Two of the 14 included patients underwent orchiectomy as ADT. However, the results of the data remained the same after excluding the data of the patients who underwent orchiectomy.³² In the study by Jim *et al.*²⁷ the patients on LHRH therapy displayed lower scores and higher rates of impairment on five of seven individual tests and a greater number of impaired tests, but the difference compared to the control subjects was not significant. However, the patient group displayed significantly greater overall impairment (defined as the percentage of individuals with impaired performance on two or more tests) than the control group. Prior prostatectomy was associated with impairment in immediate and delayed verbal memory in the ADT patients.²⁷ In the study by Yang *et al.*, patients in the ADT group obtained significantly worse scores on several tests compared to the non-ADT group and the healthy control group. No

difference between the two control groups was found for the test results.²⁹ In the other study by Yang *et al.*, patients on LHRH therapy performed worse on “EBPM,” on attention and memory and information processing, but not on “TBPM” compared to patient controls, as well as healthy controls.³⁰

Cognitive functioning during treatment with ADT (prospective studies)

Eighteen studies used a prospective design to evaluate the effect of ADT on cognitive functioning. These studies included a total of 968 unique patients. Their average age ranged from 64.4 to 72.4 years. Eleven of the 18 prospective studies included a control group (three studies included healthy controls as well as patients with prostate carcinoma not receiving ADT, five studies only included patient controls, and three studies only included healthy controls). The time to the last follow-up measurement moment in these studies ranged from 3 to 36 months.

Nine of the 18 prospective studies did not find a significant effect of ADT on cognitive functioning.^{19,21,35–41} Although Mohile *et al.*⁴⁰ did not observe a decline in cognitive performance after 6 months of ADT, they did observe a high prevalence of lower than expected cognitive performance at baseline in patients with prostate cancer. Interestingly, Chao *et al.*¹⁹ evaluated the effect of ADT on cognitive functioning, as well as on brain characteristics by using fMRI. They prospectively followed 15 patients with nonmetastatic prostate cancer treated with ADT and 15 patients with nonmetastatic prostate cancer without ADT; the patient groups were comparable in age and educational level. Patients were tested before and 6 months after starting ADT, and controls were tested twice with an interval of 6 months. The N-back task (assessing working memory) and the stop-signal task (assessing cognitive control) were used. The results for the N-back task and the stop-signal task were similar after 6 months compared with baseline in each group. However, significant associations were found between ADT use (*vs* nonuse) and decreased medial prefrontal cortical activation during cognitive control. This was also found for decreased connectivity between the medial prefrontal cortex and other regions involved in cognitive control. Thus, ADT for 6 months did not affect the selected tests for cognition, however, fMRI showed abnormalities in brain activations and brain connectivity during testing.¹⁹ In 2013 the same research group reported the results of a structural MRI study of cerebral morphology in 12 prostate cancer patients before and after 6 months of ADT compared with 12 comparable patients not treated with ADT. The ADT group showed a decreased GMV in the frontopolar cortex, the dorsolateral prefrontal cortex and the primary motor cortex. These changes were not found in the control subjects. The decrease in GMV of the primary motor cortex related significantly to a longer reaction time to target detection in a working memory task, suggesting processing insufficiency.²¹ Almeida *et al.*⁴¹ assessed the effect of ADT and evaluated cognitive functioning for 36 weeks during treatment (on-treatment period). Then ADT was stopped and cognitive functioning was evaluated during the following 18 weeks (off-treatment period).

Table 3 Neuropsychological tests used

Memory	
PI	Verbal memory
Word lists (WMS-III)	Verbal memory
Logical memory (WMS-III)	Verbal memory
Verbal paired associations (WMS-III)	Verbal memory
Story recall (WMS-R)	Verbal memory
HVLT-R	Verbal memory
Object naming/recall	Verbal memory
Word list recall	Verbal memory
CVLT	Verbal memory
Word list-learning test	Verbal memory
PI	Verbal memory
RAVLT	Verbal memory
AVLT	Verbal memory
TAVEC	Verbal memory
BVMT-R	Visual memory
Benton visual recognition task	Visual memory
Visual span (WMS)	Visual memory
Visual reproduction (WMS-III)	Visual memory
Two-part ad hoc test	Visual memory
Puget sound route learning test, route test	Spatial memory
Spatial working memory task	Spatial working memory
Conditional associative learning test	Working memory
N-back task	Working memory
Letter–Number sequencing task	Working memory
EBPM	Event-based memory
TBPM	Time-based memory
Visuospatial ability	
Block design (WAIS-R)	Visuospatial ability
Mental rotations test	Visuospatial ability
Card rotations test (Benton) JLOT	Visuospatial ability
HVOT	Visuospatial ability
Paper folding test	Visuospatial ability
Verbal fluency	
Verbal fluency test	Verbal fluency, executive functioning, attention
COWAT	Verbal fluency, executive functioning, attention
Word List Generation	Verbal fluency
Executive functions	
SCWT	Executive functioning, information processing
SOPT	Executive functioning, working memory
TMT	Attention, cognitive flexibility, processing speed
RCFT	Executive visuospatial planning abilities, visual memory
D-KEFS color-word interference test	Cognitive flexibility
Stop signal task	Cognitive control
Timed instrumental activities of daily living test	Executive functioning
Color trials	Executive functioning
Attention	
Digit span (WAIS-III)	Attention, working memory
Spatial span (WMS-R)	Attention, working memory
Grid arrays	Attention

Table 3 (Continued)

Visuomotor skills	
Grooved pegboard and finger tapping test	Motor speed
DSST (WAIS)	Visuomotor skills, attention, executive functioning
SDMT	Visuomotor skills, attention, executive functioning
Language skills	
Similarities (WAIS)	Language skills
Intelligence	
Matrix reasoning test (WAIS-III)	Nonverbal analytical reasoning
NART	General intelligence
WAIS-R	General intelligence
Neuropsychological batteries	
Cambridge Examination for Mental Disorders of the Elderly (CAMCOG)	Cognitive screening
MMSE	Cognitive screening
Kendrick assessment of cognitive ageing battery	Processing speed
MoCA	Cognitive screening
Frontal assessment battery	Screening for frontal lobe function
High-Sensitivity Cognitive Screen	Cognitive screening
WMS-R	Memory assessment
CNS vital signs	Computer-administered NPA tool
CogniSpeed software	Cognitive processing

During the on-treatment period there were no clinically meaningful changes in cognitive functioning. However, after discontinuing ADT, performances on the verbal memory test improved while there were no differences on visuospatial tasks. The authors reported that the improvement in cognitive functioning after discontinuing ADT might be explained by the fact that, during the on-treatment period, the potential learning effect of multiple testing was counterbalanced by the potential negative cognitive effect of a lack of sex hormones. After stopping ADT this learning effect dissipated.⁴¹

Of the 18 prospective studies, a total of eight studies reported a decline in cognitive functioning after starting ADT.^{42–49} These studies observed a decline in cognitive functioning during a follow-up period of 3 months^{42,44,45} or 12 months compared to controls.^{43,46–49} Alibhai *et al.*⁴⁹ observed a decline in cognitive tests assessing immediate memory, working memory, and visuospatial ability after 12 months in patients treated with ADT compared to healthy controls; however, when comparing the percentage of participants that declined (>1 SD), there were no differences between patients and controls. Furthermore, Salminen *et al.*⁴³ observed a decline in cognitive functioning after 12 months of ADT (compared to baseline) which was also associated with a decline in estradiol. Interestingly, they observed an improvement in verbal fluency after 12 months of ADT.⁴³ Ceylan *et al.*⁴⁶ did observe a decline in cognitive functioning after a treatment period of 12 months compared to baseline, but this was not different from the control group. Cherrier *et al.* also evaluated the effect during off-treatment. They observed that cognitive functioning declined after 3 months of ADT, but that

there were no significant differences compared to baseline after 9 months of ADT or at 3 months after discontinuing ADT (at 12 months after the start of ADT).^{42,44}

Apparently one prospective study found improvement in cognitive functioning (i.e. object recall, semantic memory) after 12 months of ADT.⁵⁰

Effect of different treatment modalities on cognitive functioning (RCTs)

Four of the included studies were RCTs, of which three evaluated the effect of different ADT modalities,^{51–53} and one evaluated the effect of CCT on cognitive functioning in prostate cancer patients on ADT.⁵⁴ The number of included patients with prostate cancer in the three studies evaluating ADT modalities ranged between 25 and 65 patients. The average participant age in these studies ranged between 71.0 and 73.5 years. In these studies, the control groups were either patients with prostate carcinoma treated with cyproterone acetate, close monitoring, or healthy men without prostate carcinoma.

In the study by Matousek *et al.*,⁵³ after 3 months of combined ADT (ADT and bicalutamide), estradiol or placebo was added for 3 months. The authors did not observe any differences in cognitive test scores during the first 3 months of combined ADT. Furthermore, adding estradiol to the combined ADT in the following 3 months did not result in improvement of cognition.⁵³ In both studies by Green *et al.*,^{51,52} active hormonal therapy was accompanied by a decline of cognitive function (at 6 and 12 months) compared to the control groups.

The study by Wu *et al.*⁵⁴ did not show a consistent improvement of cognitive functioning after computerized neuropsychological training.

Discussion

The present systematic review demonstrates that half of the available studies in patients with prostate carcinoma treated with ADT using LHRH agonists or antagonists report a decline in cognitive functioning, while the other half did not show a negative effect on cognitive functioning, and only one study reported an improvement in cognitive functioning. Therefore, it can be postulated that the evidence for the hypothesis of a potential protective effect of ADT is not convincing.

Based on our quality assessment, it can be concluded that more than half of the included studies were of high quality. However, there was a large variety in the tests used (i.e. 61 different neuropsychological tests), making it difficult to compare the influence of ADT on specific cognitive function. Of the studies that observed impairment in cognitive functioning, memory was the most frequently impaired domain, followed by spatial abilities, executive functioning, language ability, attention, and information processing. The cognitive decline was observed after 3 months of ADT when such early measurements took place. Two studies also examined cognitive functioning during off-treatment periods (periods ranging from 3 to 4.5 months) and observed improvement/normalization of cognitive functioning after an initial decline after

starting ADT. One might argue that these are rather short periods of observation, knowing that the normalization of hormone levels after stopping treatment with LHRH agonists or antagonists can take considerably longer periods. Furthermore, for the examination of cognitive functioning during off-treatment, it is important to establish normalization of the hypothalamic–hypophysial–testicular axis.

Of the included studies, only three combined cognitive tests with fMRI.^{19,21,24} These studies showed that ADT for 6 months did not affect cognitive functioning (i.e. working memory, cognitive control); however, fMRI showed smaller GMVs in the frontopolar cortex, the dorsolateral prefrontal cortex, and the primary motor cortex, as well as impaired brain activation and brain connectivity during testing.^{19,21} Furthermore, a longer duration of ADT was associated with smaller GMVs (whole brain), and older age was associated with more WMLs in prostate carcinoma patients on ADT.²⁴ Although not included in the present review, Cherrier *et al.* reported a preliminary study of fMRI of the brain in combination with cognitive testing in five ADT-treated prostate cancer patients compared to seven healthy control subjects of the same age and education level. The tests were performed before and 9 months after ADT and twice with a 9-month time interval in the controls. Patients treated with ADT showed a reduced blood oxygenation level-dependent activation using fMRI, which was not found in the control subjects. Reduction in activation in the right parietal-occipital regions was observed during the recall of the spatial location of objects and mental rotation.²² In 2018, the same research group reported on the cerebral metabolic activity (using fluorine-18 fluorodeoxyglucose positron emission tomography) before and 9 months after ADT in eight patients with prostate cancer. They found a decreased regional cerebral glucose metabolism in the cerebellum, posterior cingulate and medial hypothalamus bilaterally. Cortical glucose metabolism was associated positively and negatively with select cognitive tests. While on ADT, positive correlations were found between the posterior cingulate, left inferior parietal lobule and left mid-temporal gyrus and spatial reasoning, and a negative correlation between the left inferior parietal lobule and verbal memory.²³ Considering these five publications using fMRI and positron emission tomography, it can be postulated that ADT can negatively influence characteristics of the brain (i.e. structure, function, metabolism).

In conclusion, there is no convincing evidence of the protective effect of treatment with LHRH agonists or antagonists on cognitive functioning in men with prostate cancer. Considering the substantial part of the studies reporting a decline in cognitive functioning after starting ADT, and the increasing number of studies showing that there might be a potential underlying substrate in the brain, it is important that clinicians are aware of this side effect. In the shared decision making when starting ADT, clinicians should discuss this potential side effect. This is in accordance with the recent updated guideline of the International Society of Geriatric Oncology on prostate cancer management in older patients.⁵⁵ When starting ADT this should be discussed with patients. Future (randomized) studies should focus on the effect of ADT on cognitive functioning in patients with prostate cancer

using a valid neuropsychological test battery, together with innovative techniques to examine brain function, structure and metabolism, and potentially take into account difference between LHRH antagonists and LHRH agonists.⁵⁶

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Search strategy.

Appendix S2. Quality assessment prostate cancer.