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Cognitive impairment in prostate cancer patients receiving androgen deprivation therapy: A scoping review

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202570053

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 July 2025 and was last updated on 12 July 2025.

INTRODUCTION

Review question / Objective Review Question: What is the current evidence on the effects of androgen deprivation therapy (ADT), specifically luteinizing hormone-releasing hormone (LH-RH) analogues, on cognitive performance in men with prostate cancer?
Objective: The objective of this scoping review is to systematically map and summarize the existing literature on the relationship between androgen deprivation therapy (ADT)—particularly the use of LH-RH agonists and antagonists—and cognitive performance in patients with prostate cancer. This review aims to identify:
The cognitive domains assessed across studies;
The tools and methods used to measure cognitive change;
The nature and direction of reported cognitive outcomes;
Gaps in the literature that require further investigation;
The findings will inform clinicians, researchers, and policymakers about the potential cognitive risks associated with ADT and guide future research priorities in this area.

Background Prostate cancer (PCa) is the second most commonly diagnosed cancer in men worldwide, with over 1.4 million new cases and 375,000 deaths reported in 2020. The widespread use of prostate-specific antigen (PSA) testing has led to earlier detection and a rise in the number of men receiving treatment. Among systemic treatment options, androgen deprivation therapy (ADT) plays a central role, particularly in advanced and metastatic cases. ADT aims to suppress testosterone—an essential hormone for PCa growth—either surgically or pharmacologically, using luteinizing hormone-releasing hormone (LH-RH) agonists or antagonists.

Initially reserved for metastatic disease, ADT is now used more broadly, including in combination with radiotherapy for locally advanced PCa. This expansion has led to a growing number of men receiving ADT for longer durations. While effective in controlling disease progression, ADT is

associated with a range of adverse effects, including increased cardiovascular risk, metabolic disturbances, reduced bone density, muscle loss, and sexual dysfunction.

Emerging evidence also suggests a potential link between ADT and cognitive impairment. Testosterone and its metabolites play a role in maintaining brain function through androgen receptors located in key cognitive regions such as the hippocampus and amygdala. Some studies have reported domain-specific cognitive decline in men undergoing ADT, particularly in memory, executive function, and visuospatial skills. However, findings remain inconsistent across studies, with others reporting no significant cognitive effects.

Given the increasing use of ADT and the rising number of long-term PCa survivors, understanding the potential cognitive consequences of this treatment is clinically important. This scoping review aims to systematically synthesize the existing literature on the cognitive effects of ADT in PCa patients, identify knowledge gaps, and inform future research and clinical practice.

Rationale As the use of androgen deprivation therapy (ADT) continues to expand in the management of prostate cancer (PCa), there is growing concern about its long-term side effects, particularly its potential impact on cognitive function. Testosterone and its metabolites play critical roles in maintaining brain health, and the pharmacological suppression of androgens through ADT may disrupt neural pathways involved in memory, attention, and executive functioning.

While numerous studies have examined this relationship, the findings are inconsistent. Some report significant cognitive impairments associated with ADT, while others find no meaningful effects. This variation may stem from differences in study design, cognitive assessment tools, treatment duration, and patient populations. Moreover, most existing evidence is scattered across small clinical studies or observational cohorts, often with limited methodological rigor or inconsistent endpoints.

Given the increasing number of men undergoing long-term ADT and the anticipated growth in prostate cancer survivorship, it is essential to clarify whether and how ADT affects cognitive function. A comprehensive synthesis of current evidence is needed to better understand the scope, quality, and gaps in existing research. A scoping review is an ideal method to map the breadth of available literature, categorize cognitive outcomes studied, and inform both clinical decision-making and future research priorities.

This review will provide clinicians, researchers, and patients with a clearer understanding of the potential cognitive risks of ADT, supporting informed treatment decisions and highlighting areas where further investigation is needed.

METHODS

Strategy of data synthesis The findings from the included studies will be synthesized using a descriptive and narrative approach, as recommended for scoping reviews. Data will first be charted in a standardized extraction form to capture key information on study characteristics, population details, interventions, cognitive domains assessed, and outcomes.

We will summarize the data both quantitatively (e.g., through frequency counts of study designs, sample sizes, cognitive domains assessed) and qualitatively (e.g., through thematic analysis of cognitive changes reported across studies). Where possible, cognitive outcomes will be categorized into specific domains such as memory, executive function, attention, processing speed, visuospatial ability, and language. We will also document the type of cognitive assessment tools used and the duration of ADT exposure.

Results will be presented in tabular and narrative formats to provide an overview of the existing evidence. This will allow identification of key themes, patterns, and gaps in the literature. No formal meta-analysis or critical appraisal will be conducted, as this is beyond the scope of a scoping review.

The synthesis will aim to map the breadth and depth of the available literature, describe how cognitive effects of ADT have been studied, and inform recommendations for future research and clinical awareness.

Eligibility criteria Participants
We will include studies involving adult men (≥18 years) with a histologically confirmed diagnosis of adenocarcinoma of the prostate. All stages of prostate cancer—localized, locally advanced, or metastatic—will be considered.

Concept
Eligible studies must investigate cognitive performance or cognitive change as an outcome. This includes any domain of cognitive function (e.g., memory, executive function, attention,

processing speed), assessed using standardized neuropsychological tools or validated questionnaires.

Context
We will include studies examining the use of androgen deprivation therapy (ADT) with a specific focus on luteinizing hormone-releasing hormone (LH-RH) analogues or agonists/antagonists (e.g., leuprorelin, goserelin, triptorelin). Studies that evaluate other ADT modalities such as estradiol or orchiectomy will also be considered if cognitive outcomes are reported.

Types of Studies
We will include:
Randomized controlled trials (RCTs)
Cohort studies (prospective or retrospective)
Case-control studies
Cross-sectional studies

Only full-text articles published in English will be considered. Studies from any geographical region or healthcare setting will be eligible.

Exclusion Criteria
Studies not reporting on cognitive outcomes
Non-original research (e.g., reviews, editorials, commentaries, protocols)
Animal or preclinical studies
Conference abstracts without full-text availability.

Source of evidence screening and selection All records identified through database searches will be imported into reference management software (EndNote version 21.01.1, Build 17232) to facilitate duplicate removal. After deduplication, two independent reviewers (JVB and GF) will screen the titles and abstracts of the remaining records against the predefined inclusion and exclusion criteria.

Articles deemed potentially relevant will be retrieved in full text and further assessed for eligibility by the same two reviewers (JVB and PB) independently. Reasons for exclusion at the full-text stage will be documented in detail. Any discrepancies between reviewers during either stage of the screening process will be resolved through discussion or, if necessary, consultation with a third reviewer (DG).

To ensure comprehensiveness, we will also screen the reference lists of all included studies to identify any additional relevant sources of evidence.

The study selection process will be reported using the PRISMA flow diagram, outlining the number of records identified, screened, assessed for eligibility, and included in the final review.

Data management All references retrieved from the electronic database searches will be imported into EndNote (version 21.01.1, Build 17232) for reference management and duplicate removal. After deduplication, the remaining records will be exported into Microsoft Excel, where a structured data charting form will be developed to manage and extract relevant information from included studies.

Two reviewers (JVB and PB) will independently extract data using this standardized form. Extracted information will include:

Study characteristics (author, year, country)
Study design
Population details (sample size, age, prostate cancer stage)
Type and duration of ADT (specifically LH-RH analogues)
Cognitive domains assessed
Assessment tools used
Main findings related to cognitive performance

The data extraction form will be pilot tested on a subset of studies and refined if necessary to ensure clarity and consistency. Discrepancies between reviewers will be resolved through discussion or consultation with a third reviewer (DG).

All extracted data will be stored securely in password-protected institutional storage, and only authorized members of the review team will have access.

Reporting results / Analysis of the evidence The findings of this scoping review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. The results will be presented using a combination of descriptive statistics and narrative synthesis.

We will summarize the characteristics of the included studies using frequencies and percentages where appropriate (e.g., study design, country, sample size, type of ADT, and cognitive domains assessed). Results will be organized thematically based on the cognitive domains evaluated (e.g., memory, executive function, attention, visuospatial skills), the assessment tools used, and comparative groups (e.g., ADT vs. non-ADT, ADT vs. healthy controls, pre-post comparisons).

We will map and describe the extent, range, and nature of available evidence regarding the cognitive effects of LH-RH analogues in prostate cancer patients. Key patterns, inconsistencies, and knowledge gaps will be highlighted.

Tables and visual summaries will be used to enhance the clarity and comparability of findings across studies. No meta-analysis or formal risk of bias assessment is planned, as this is outside the scope of a scoping review.

The synthesis will inform clinicians, researchers, and stakeholders about the current state of evidence and guide recommendations for future research priorities in this area.

Presentation of the results The results of this scoping review will be presented in both tabular and narrative formats to provide a clear and comprehensive overview of the evidence.
A PRISMA flow diagram will be used to illustrate the study selection process, including the number of records identified, screened, assessed for eligibility, and included in the final review, along with reasons for exclusions at the full-text stage.
Included studies will be summarized in descriptive tables detailing study characteristics (e.g., author, year, country, study design), population details, type and duration of androgen deprivation therapy (ADT), cognitive domains assessed, and tools used for cognitive evaluation.
Key findings related to the effects of LH-RH analogues on cognitive performance will be grouped by cognitive domain (e.g., memory, attention, executive function) and described narratively. When applicable, subgroup comparisons (e.g., ADT vs. non-ADT, short-term vs. long-term ADT, or ADT vs. healthy controls) will be reported.
Where appropriate, frequencies and proportions will be used to summarize the distribution of study types, cognitive domains evaluated, and directionality of findings (e.g., impairment, no change, or improvement).
This structured presentation will allow readers to easily identify patterns, inconsistencies, and research gaps in the literature regarding the cognitive impact of ADT in prostate cancer patients.

Language restriction English.

Country(ies) involved Portugal.

Other relevant information This scoping review will be conducted as part of a broader research project examining the long-term effects of androgen deprivation therapy (ADT) in prostate cancer patients.
No formal assessment of methodological quality or risk of bias will be performed, in accordance with JBI guidance for scoping reviews.
Ethical approval is not required for this review, as it involves analysis of data from already published studies.
Any protocol amendments during the course of the review will be documented and updated in the INPLASY record.
The review team includes multidisciplinary expertise in oncology, cognitive psychology, and evidence synthesis.

Keywords Prostate cancer; Androgen deprivation therapy; Luteinizing hormone-releasing hormone (LH-RH) analogues; Gonadotropin-releasing hormone (GnRH) agonists; GnRH antagonists; Cognitive function; Cognitive impairment.

Dissemination plans The findings of this scoping review will be disseminated through multiple channels to reach both academic and clinical audiences. Specifically, the results will be:
Submitted for publication in a peer-reviewed journal focused on oncology.
Presented at national and international conferences related to oncology, urology, or psycho-oncology.
Shared with relevant clinical and research networks to support evidence-based decision-making in the management of prostate cancer patients undergoing androgen deprivation therapy (ADT).
If appropriate, an infographic or plain-language summary will be developed to communicate the findings to patients, caregivers, and advocacy groups.

The goal of dissemination is to inform future research directions, clinical practice, and patient education on the potential cognitive effects of LH-RH analogue treatment in prostate cancer.

Contributions of each author
Author 1 - João Vasco Barreira - Lead the conceptualization and design of the review, develop the search strategy, coordinate the review process, extract and analyze data, draft the original manuscript, and contribute to the critical revision and final approval of the manuscript.
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Author 2 - Pedro Barreira - Contribute to study screening, full-text review, and data extraction. Participate in the analysis of findings and provide significant input during manuscript drafting and review.

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Author 4 - Daniela Garcez - Participate in resolving conflicts during screening and data extraction. Review the manuscript for clinical relevance and help with editing and final approval.
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