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Depressive Symptomatology in Men Receiving Androgen Deprivation Therapy for Prostate Cancer: A Controlled Comparison

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Abstract

Objective—Prostate cancer patients who receive androgen deprivation therapy (ADT) often experience many physical and psychological side effects. ADT may be associated with increased risk for depression, but the relationship between ADT and depression is not fully understood. This study used a longitudinal design to assess depressive symptomatology in patients receiving ADT compared to two groups of matched controls.

Methods—Participants were men initiating ADT treatment (ADT+ group; n = 61) and their matched controls: prostate cancer patients treated with radical prostatectomy (ADT− group; n = 61) and no-cancer controls (CA− group; n = 61). Depressive symptomatology was assessed using the Center for Epidemiological Studies Depression Scale at ADT initiation and again six months later. Differences in depressive symptomatology and rates of clinically-significant depressive symptomatology were analyzed between groups at each time point and within groups over time. Results: Between baseline and follow-up, ADT+ participants demonstrated increased depressive symptomatology and increased rates of clinically-significant depressive symptomatology (*p*s < .05). ADT+ participants also reported greater depressive symptomatology than both control groups at follow-up (*p*s < .001). Rates of clinically-significant depressive symptomatology were higher in the ADT+ group than the ADT− and CA− groups at both time points (baseline: 28%, 5%, 12%; follow-up: 39%, 9%, 11%).

Conclusions—Findings support the hypothesis that ADT administration yields increases in depression and suggest that the mechanism behind ADT's association with depression should be explored and that prostate cancer patients treated with ADT should receive particular focus in depression screening and intervention.

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Keywords

prostate cancer; oncology; androgen deprivation therapy; depression; quality of life

Background

Prostate cancer is the most common malignancy among men in the United States, with approximately 240,000 new cases diagnosed in 2012 [1]. Several forms of treatment are available for prostate cancer including radiation therapy, brachytherapy, prostatectomy, and androgen deprivation therapy (ADT). In the past, ADT was used primarily in advanced-stage cases. In 2007, the American Society of Clinical Oncology issued guidelines suggesting ADT was also appropriate for prostate cancer patients (1) whose prostate-specific antigen (PSA) levels rise after prostatectomy or radiation therapy, (2) who are asymptomatic for metastasis and have node positive disease, and (3) who have evidence of metastasis on imaging studies despite being asymptomatic for metastasis [2]. Over time, the number of men undergoing ADT and the average length of treatment have increased [3,4]. At any given time, over 500,000 prostate cancer patients are receiving ADT in the United States [5].

ADT has been linked to many side effects including osteopenia, sarcopenia, loss of libido, hot flashes, fatigue, and cognitive difficulties [6–8]. Furthermore, ADT is often associated with reduced quality of life and may increase risk for depression [8]. ADT results in testosterone suppression; this hormonal change is the hypothesized mechanism linking ADT to depression. Support for this mechanism comes from evidence demonstrating increased risk for depression in healthy aging men with declining testosterone levels [9].

Previous research on depression in men undergoing ADT yielded mixed results. After an initial case report suggested a link between ADT and depression [10], several studies explored this relationship. While some studies found ADT was associated with depression [11–14], others found no association [15–19]. The lack of consistent findings may be due to methodological limitations that characterized many of these studies. Limitations included lack of appropriate control groups, small sample sizes, and use of cross-sectional or retrospective study designs.

Two recent studies addressed several of these concerns. Hervouet, Savard, Ivers, & Savard [20] compared depression in men receiving ADT and radiation (n = 28) and men receiving only radiation (n = 32) over 16 months using semi-structured interviews, the Hospital Anxiety and Depression Scale (HADS), and the Beck Depression Inventory-II (BDI-II). Results revealed no significant increases in depressive symptoms related to initiation of ADT. However, this study's small sample size resulted in limited statistical power to detect significant between-groups differences. Additionally, this study lacked a comparison group of men with no history of cancer. Since depression in prostate cancer patients receiving ADT and prostate cancer patients receiving other treatments may differ from depression in men who have not been diagnosed with cancer, the inclusion of a no-cancer control group is important. The other study, conducted by Timilshina, Breunis, and Alibhai [21], compared men receiving ADT (n = 85) to both prostate cancer patients not receiving ADT (n = 86) and healthy controls (n = 86) over 12 months using the Geriatric Depression Scale (GDS).

Similar to the Hervouet et al. study, ADT initiation was not associated with worsening depressive symptoms. Nonetheless, there are challenges in drawing generalizable conclusions from this study because the primary analyses excluded participants who were suffering from depression and/or taking an antidepressant medication. Given the ongoing uncertainty regarding the effects of ADT on depression in prostate cancer patients, the current study aimed to address limitations of previous research by using a longitudinal design featuring a representative sample of patients receiving ADT and both a prostate cancer control group and a no-cancer control group.

Methods

Participant Eligibility and Recruitment

Participants included in the current analyses were recruited between September 2008 and October 2012 as part of a larger institutional review board-approved study examining quality of life, including cognitive outcomes, in prostate cancer patients treated with ADT. Participants with prostate cancer treated with ADT (ADT+) were matched on a 1:1 basis to both participants with prostate cancer treated with prostatectomy only (ADT−) and participants with no history of cancer (CA−). The study's eligibility criteria required all participants to (1) be older than 18 years of age, (2) be able to speak and read English, (3) have at least a sixth grade education, (4) have no history of stroke, (5) score in the normal range of mental functioning on the Short Portable Mental Status Questionnaire (score < 3), and (6) be willing to provide informed consent. Group-specific eligibility criteria and recruitment strategies are described as follows.

ADT+ participants—Patients in the ADT+ group were required to meet the following additional eligibility criteria: (1) be diagnosed with nonmetastatic prostate cancer, (2) have not received treatment for any other cancer within the past 12 months and have no clinical evidence of another cancer at the most recent follow-up visit, (3) have never been diagnosed with primary brain cancer and/or received cranial radiation, (4) be scheduled for treatment with ADT (e.g., goserelin or leuprolide) continuously for at least six months, and (5) have not been treated with ADT within the 12 months or anti-androgen within the 6 months prior to initiating the current ADT treatment. ADT+ participants were identified using computerized appointment systems, screened for eligibility via medical record review, and recruited during outpatient appointments at Moffitt Cancer Center (MCC) or James A. Haley VAMC (JAHVAMC) prior to or within one month of initiating ADT treatment.

ADT− participants—Patients in the ADT− group were required to meet the following additional eligibility criteria: (1) be diagnosed with nonmetastatic prostate cancer, (2) have not been diagnosed with any other cancer (except nonmelanoma skin cancer), (3) have undergone prostatectomy with no evidence of recurrent disease, (4) have not undergone or be scheduled to undergo other forms of prostate cancer treatment, and (5) not be receiving testosterone supplementation. Each ADT− participant was matched to his corresponding ADT+ participant on time since diagnosis (within 6 months), age (within 5 years), and education (≤ 12 years; 13–16 years, or ≥ 17 years). ADT− patients were identified using the

MCC tumor registry, screened for eligibility via medical record review, and recruited via mail and telephone following recruitment of each ADT group participant.

CA− participants—Men in the no-cancer control group (CA− group) were required to meet the following additional eligibility criteria: (1) have not been diagnosed with any cancer (except nonmelanoma skin cancer), and (2) not be receiving testosterone supplementation. CA− participants were matched to the corresponding ADT+ participant on age (within 5 years) and education (≤ 12 years; 13–16 years, or ≥ 17 years). Following recruitment of each ADT+ participant, matching CA− participants were identified using a commercially available marketing database (Marketing Systems Group, Fort Washington, PA, USA) and recruited via mail and telephone using procedures mirroring those for the ADT− group.

Procedure

Participants in the current analyses completed self-report questionnaires at study recruitment (i.e., Time 1) and six months later (i.e., Time 2). The Time 1 assessment for ADT+ participants occurred before or within one month of ADT initiation. ADT+ participants were included in the current analyses if they had completed both assessments and had both an ADT− and a CA− matched control.

Measures

Demographic and clinical characteristics—Participants' sociodemographic and clinical information was collected via self-report at Time 1 (i.e., age, race, ethnicity, marital status, annual household income, years of education, and medication use) and Time 2 (i.e., medication use). Disease-related information (i.e., time since diagnosis, Gleason score, and type and length of current and past prostate cancer treatments) was collected via medical chart review for ADT+ and ADT− participants.

Depressive symptomatology—Depressive symptomatology was assessed at both time points using the Center for Epidemiological Studies Depression Scale (CES-D) [22]. The CES-D is a 20-item measure that asks participants to rate the frequency of various symptoms of depression in the past week using a 4-point scale (0 = rarely or none of the time; 3 = most or all of the time). Total CES-D scores can range from 0–60; higher scores indicate greater depressive symptomatology. Clinically-significant depressive symptoms are considered present if the total score is ≥ 16 [22,23]. Validity of the CES-D has been demonstrated with many populations, including cancer patients [24,25].

Statistical Analyses

Means and frequencies were calculated for sociodemographic characteristics. Chi-square and t-tests were conducted with ADT+ participants and each of their matched controls (i.e., ADT+/ADT− and ADT+/CA− pairs) to examine differences in participant characteristics at Time 1; p-values < 0.10 were considered significant for these tests. Next, a series of ANCOVAs was performed to assess group differences between ADT+ participants and each of their matched controls in depression scores at each time point and changes within each group in depression between Time 1 and Time 2, controlling for significant between-groups

sociodemographic differences. Finally, logistic regression and McNemar's tests were used to compare proportions of clinically significant depression between groups at each time point and within groups between time points. Analyses were conducted using SAS version 9.3. P values < 0.05 were considered statistically significant for all analyses except those evaluating between group sociodemographic differences.

Results

Sixty-one ADT+ participants had completed the CES-D and had both an ADT− and a CA− control; thus, a total of 183 participants are included here. In the larger study from which this sample was drawn, participation rates were: ADT+ = 86%, ADT− = 41%, CA− = 20%. Demographic and clinical characteristics are presented in Table 1. Regarding sociodemographic differences between groups, three significant differences were apparent at baseline: CA− participants were more likely than ADT+ participants to be married ($X^2(1, N = 119) = 3.41$, $p = .06$) and to earn at least $40,000 per year ($X^2(1, N = 109) = 3.65$, $p = .06$). Additionally, ADT− participants were more likely than ADT+ participants to earn at least $40,000 per year ($X^2(1, N = 103) = 3.53$, $p = .06$). Consequently, ANCOVAs were conducted with income and marital status as covariates. No significant between-groups differences were observed for age, ethnicity, race, education, or antidepressant medication use. As would be expected, Gleason scores were higher among ADT+ participants compared to ADT− participants (Table 1). In the ADT+ group, 6 of 61 participants initiated ADT before completing the Time 1 assessment. Days between ADT initiation and the Time 1 assessment ranged from 1–24 (median = 13). Among ADT+ participants, those who initiated ADT prior to the first assessment had lower CESD scores at Time 1 ($t = -2.99$, $p < .01$). At Time 1, no significant between-groups differences were observed for antidepressant medication use. At Time 2, ADT+ participants were more likely to be taking antidepressant medication than ADT− participants ($X^2(1, N = 122) = 6.97$, $p = .001$).

Results of the ANCOVAs used to analyze differences between ADT+ participants and their matched controls in continuously measured depression controlling for significant sociodemographic variables are presented in Table 2. In these models, ADT+ participants reported significantly greater symptomatology then ADT− participants at both Time 1 ($F(1, 98) = 5.79$, $p = 0.02$) and Time 2 ($F(1, 84) = 9.27$, $p < 0.01$). Compared to CA− participants, ADT+ participants reported significantly greater symptomatology at Time 2 ($F(1, 93) = 13.43$, $p < 0.001$) but not at Time 1 ($F(1, 104) = 2.66$, $p = 0.11$). Excluding somatic items from the CES-D [22] yielded similar results, except that the difference in depressive symptomatology between ADT+ participants and ADT− participants at Time 1 was no longer significant ($F(1, 98) = 3.77$, $p = 0.06$). ADT+ participants experienced a significant increase in depressive symptomatology between Time 1 and Time 2, while ADT− and CA− participants' depressive symptomatology did not change significantly over time (Table 2).

Logistic regression was used to assess differences between ADT+ participants and their matched controls in rates of clinically-significant depressive symptomatology at each time point. At Time 1, rates were 28%, 5%, and 12% in the ADT+, ADT−, and CA− groups respectively. Controlling for significant sociodemographic variables, rates of clinically-significant depressive symptomatology were significantly higher in ADT+ participants

versus ADT− participants (X^2 = 4.63, p < .05) but not compared to CA− participants (X^2 = 0.95, p = .33) at Time 1.

At Time 2, rates of clinically-significant depressive symptomatology were 39%, 9%, and 11% in the ADT+, ADT−, and CA− groups respectively. Controlling for relevant sociodemographic variables, rates of clinically-significant depressive symptoms were significantly higher for ADT+ participants compared to both ADT− participants (X^2 = 7.93, p < .01) and CA− participants(X^2 = 6.43, p = .01) at Time 2. Between Time 1 and Time 2, rates of clinically-significant depressive symptomatology increased significantly in the ADT + group (X^2(1, N = 61) = 3.77, p < .05). At Time 1, 17 ADT+ participants reported clinically-significant depressive symptomatology; between Time 1 and Time 2, 10 ADT+ participants' scores increased to clinically-significant levels, and 3 decreased from clinically-significant levels. Within-group changes in the ADT− (X^2(1, N = 44) = 0.33, p = .56) and CA− (X^2(1, N = 46) = 2.00, p = .16) groups between Time 1 and Time 2 were non-significant.

Conclusions

The current study evaluated the relationship between ADT administration and symptoms of depression using a longitudinal design featuring two matched control groups. Findings supported the hypothesis that ADT administration yields increases in depression. Specifically, depressive symptomatology and rates of clinically-significant depressive symptomatology were found to increase significantly from the beginning of treatment to six months later in participants receiving ADT but not in prostate cancer controls or non-cancer controls assessed over the same interval. Moreover, depressive symptomatology and rates of clinically-significant depressive symptomatology were significantly higher at follow-up in participants receiving ADT than in prostate cancer controls and non-cancer controls.

These findings stand in contrast to two recent studies that found little or no evidence indicating ADT administration exacerbated symptoms of depression [20,21]. Several methodological features may explain this discrepancy. First, each of the three studies used a different self-report instrument to measure depression. Depression is a complex, multidimensional construct that can be conceptualized and assessed in various ways; the measures used (CESD, BDI, and GDS) differ substantially in these respects. The measures contain different numbers of items that are rated on different scales and phrased in different ways. Furthermore, the measures' factor structures differ with respect to both the number of factors represented in the measure and the underlying dimensions reflected by the observed factors. The BDI employs a two-factor model of depression [26], while the CESD conceptualizes depression as a four-factor construct [22], and the GDS has been found to have five factors [27]. Examples of the differences in underlying dimensions reflected by the observed factors include the BDI's lack of items assessing positive affect (both the CESD and the GDS measure lack of positive affect) and the GDS's inclusion of items that are not specific to depression (e.g., boredom). Furthermore, the CESD may be preferable to the BDI because it contains fewer items about the somatic symptoms of depression, thereby providing an index that is less likely to reflect the effects of cancer and its treatments and more indicative of underlying dysphoria. The studies also differed with respect to participant

groups: While the current study and Timilshina et. al's study [21] included non-cancer control groups, healthy controls were not used in the Hervouet et al. [20] study. Another methodological feature that varied between studies was participant inclusion criteria. The Timilshina et al. [21] study excluded from the main analyses anyone who was suffering from depression or taking antidepressant medication at baseline, which limits the generalizability of the study's results, as patients may be prescribed antidepressants for many conditions other than depression. Finally, though all the studies included groups comprised of ADT recipients and groups of prostate cancer patients not receiving ADT, the prostate cancer control group differed somewhat between studies. The current study used a patient control group comprised of prostate cancer patients who had undergone radical prostatectomy but were not currently receiving treatment, while patients currently receiving radiation therapy served as patient controls in the Hervouet et al. study [20]. Timilshina et al. [21] did not specify any treatment-related inclusion criteria for patient controls.

Strengths of the current study include a rigorous matching process for ADT+ participants and their controls, a longitudinal research design, and a measure of depressive symptomatology that has been validated for use with cancer patients. However, the study also has limitations. First, participation rates varied considerably across the three study groups. The possibility that these differences may be associated with systematic biases cannot be ruled out. Second, the ADT+ group had a poorer prognosis than the ADT− group, as evidenced by the difference in Gleason scores. Although this difference would be expected based on indications for prescribing ADT, it raises the possibility that differences in depression are due to a patient's awareness of his prognosis rather than anything inherent in ADT. While disease severity may explain the differences between groups at Time 1, the patterns between Time 1 and Time 2 whereby depressive symptomatology increased in only the ADT+ group are more consistent with the view that ADT administration results in increases in depressive symptomatology. Third, some ADT+ participants initiated their treatment prior to completing the Time 1 assessment. Ideally, all Time 1 assessments would have occurred prior to or concurrent with the initiation of ADT+. Fourth, due to the relatively brief period of time between the two study assessments, the study cannot speak to the long-term impact of ADT on depressive symptomatology. Fifth, because self-report measures alone were used to assess depressive symptomatology, it is not possible to determine the proportion of participants in each group who would be diagnosed with a depressive disorder based on a structured diagnostic interview. However, it should be noted that in the Hervouet et al. study [20], no significant increases were observed in rates of clinical depression among patients receiving ADT. To address the main limitations, future research should explore the longer-term effects of ADT on depressive symptomatology using a measurement method that allows for formal evaluation of depressive disorders.

The findings reported here suggest multiple avenues for further investigation. The mechanism underlying ADT's association with increased depressive symptomatology should be explored. As previously mentioned, the radical reduction in testosterone that results from ADT is proposed to be the mechanism linking this treatment to depression. The current results are consistent with this explanation since depressive symptomatology and rates of clinically-significant depressive symptomatology increased significantly in ADT+ participants in the months following the start of ADT (i.e., as their testosterone levels

dropped precipitously) but was unchanged over time in the other groups. While these findings support the testosterone explanation for ADT's link to depression, they do not preclude other potential explanations. It is possible that ADT+ participants' increased depressive symptomatology after the initiation of ADT resulted from psychological distress related to the treatment's other common side effects such as sarcopenia, hot flashes, and cognitive difficulties [6,8]. Alternatively, the mechanism may be one of the other physiological changes that can result from ADT. For example, ADT is known to impact the immune system [28], and a growing body of literature indicates a connection between immune parameters such as pro-inflammatory cytokines (e.g., IL-1 and IL-6) and depression [29]; ADT-induced changes in immunity might influence depressive symptomatology. Given the range of possible explanations, future research should directly assess a variety of potential mechanisms linking ADT to depression.

The current findings also have implications for clinical practice. To date, research on screening and interventions for psychological concerns in prostate cancer patients has been sparse, possibly due in part to the common misperception that older men are unlikely to experience significant psychological distress, even when facing cancer [30]. Though the results reported here should be viewed with some caution due to possible over-reporting in the self-report measure used to assess depressive symptomatology, the notably high rates of clinically-significant depressive symptomatology in men receiving ADT in this study (28% at Time 1 and escalating to 39% at Time 2) are concerning. These findings suggest particular focus should be given to the subgroup of prostate cancer patients treated with ADT. Antidepressant medications (e.g., selective serotonin reuptake inhibitors) and psychotherapy (e.g., cognitive behavioral therapy) are widely accepted treatments for depression in the general population and might also be efficacious for ADT recipients. Identifying and treating symptoms of depression in men receiving ADT should be a priority in both research and clinical domains. Though ADT may be a necessary and beneficial treatment for many prostate cancer patients, its impact on depressive symptomatology should not go unnoticed.

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Table 1

Demographic and clinical characteristics of ADT patients and two matched comparison groups.

	ADT (*n* = 61)	Surgery (*n* = 61)	Healthy Control (*n* = 61)	Between Groups *p* (ADT/Surgery)	Between Groups *p* (ADT/Healthy Control)
Age, M (range)	67 (49–83)	67 (50–84)	67 (47–84)	.94	.66
Ethnicity (% non-Hispanic)	58 (97%)	59 (97%)	58 (95%)	.99	.66
Race (% Caucasian)	52 (87%)	58 (95%)	57 (93%)	.11	.21
Marital Status (%married)	40 (67%)	49 (80%)	49 (83%)	.09	.04
Education (% college graduate)	22 (36%)	27 (44%)	21 (34%)	.36	.85
Annual household income (%≥$40k)	28 (50%)	33 (70%)	37 (70%)	.04	.04
Years since diagnosis, M (SD)	3.57 (4.85)	3.82 (4.15)	N/A	.76	N/A
Gleason score (% 7 or higher)	51 (89%)	26 (44%)	N/A	<.01	N/A
Antidepressant use – Time 1 (% on medication)	7 (11%)	3 (5%)	4 (7%)	.19	.34
Antidepressant use – Time 2	9 (15%)	1 (2%)	4 (7%)		

Table 2

Means, standard deviations, and ANCOVA results comparing depression in ADT patients and two groups of matched participants.

		ADT M(SD)	Surgery M(SD)	Healthy Control M(SD)	Between Groups *F* (ADT/Surgery)	Between Groups *F* (ADT/Healthy Control)	Within Groups *F* (ADT)	Within Groups *F* (Surgery)	Within Groups *F* (Healthy Control)
CES-D	T1	12.20 (11.48)	6.19 (5.75)	7.20 (7.00)	5.79*	2.66			
	T2	14.77 (11.68)	6.91 (6.56)	6.16 (5.91)	9.27**	13.43***			
	T1 - T2	−2.58 (7.91)	0.020 (3.80)	0.23 (4.79)			6.47*	0.00	0.11

* $p < .05$.

** $p < .01$.

*** $p < .001$