Prevalence and predictive factors for the development of de novo psychiatric illness in patients receiving androgen deprivation therapy for prostate cancer

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Objective: *Androgen deprivation therapy (ADT) remains a widely utilized modality for treatment of localized and advanced prostate cancer. While ADT-induced alterations in testosterone have demonstrated impacts on quality of life, the effects on mental health remain ill-defined. We investigated the prevalence of de novo psychiatric illness and predictive factors following ADT induction for prostate cancer.*

Materials and methods: *We retrospectively reviewed patients receiving ADT for prostate cancer at our institution between 1/1989-7/2005, excluding men receiving only neoadjuvant ADT. Variables included age, race, body mass index, prostate-specific antigen (PSA), Gleason sum, clinical stage, ADT type (medical/surgical) and schedule (continuous/intermittent), and presence of pre-ADT and newly diagnosed psychiatric illness. The cohort was divided into three groups for analysis: pre-ADT psychiatric illness, de novo psychiatric illness, and no psychiatric illness. Data analysis utilized statistical software with $p < 0.05$ considered significant.*

Results: *Three-hundred and ninety-five patients with a mean age of 71.7 years at ADT initiation were analyzed. Thirty-four men (8.6%) were diagnosed with pre-ADT psychiatric illness. At mean follow-up of 87.4 months, 101 (27.9%) men were diagnosed with de novo psychiatric illness, most commonly including: depression (n = 57; 56.4%), dementia (n = 14; 13.9%), and anxiety (n = 9; 8.9%). On multivariate analysis, increasing pre-ADT PSA was predictive of post-ADT anxiety ($p = 0.01$). Overall and disease-specific survival outcomes were similar between groups.*

Conclusions: *De novo psychiatric illness was identified in 27.9% of men. While no predictive factors were identified for de novo psychiatric illness, increasing PSA was associated with de novo anxiety. Prospective investigation using validated instruments is requisite to further delineate the relationship between ADT and psychiatric health.*

Key Words: prostatic neoplasms, GnRH, castration, male, risk factors, diagnosis, psychiatric, oncology, cancer, substance-related disorders

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Introduction

With an expected 186,320 new cases and 28,660 deaths estimated in 2008, prostate cancer is the most common malignancy in men in the United States.[1] Androgen deprivation therapy (ADT) remains widely utilized for treatment of men with clinically localized or advanced stage disease, serving as both primary and salvage therapy in select patient populations.[2]

ADT-related morbidities including sexual dysfunction, osteoporosis, vasomotor flushing, fatigue, anemia, endocrine dysfunction, and altered body composition are widely reported in the literature.[2-8] Yet, despite increased recognition of ADT-associated morbidities and their impact on quality of life (QOL), there is a general paucity of studies investigating the psychological impact of long-term ADT.[9-11] Herein, we report our investigation into the prevalence, predictive factors, and oncologic outcomes in men diagnosed with pre-ADT and de novo psychiatric illness following ADT induction for prostate cancer.

Materials and methods

After obtaining institutional review board approval, we retrospectively reviewed all patients receiving ADT for prostate cancer treatment at a single center at our institution (Veterans Affairs Medical Center (VAMC), Memphis, Tennessee) between January 1989 and June 2005. Patients receiving only neoadjuvant ADT were excluded. Clinicopathologic variables examined included age at ADT induction, race, body mass index (BMI, kg/m^2), pre-ADT serum prostate-specific antigen (PSA, ng/ml), Gleason grades, American Joint Committee on Cancer (AJCC) 1992 clinical stage, type of ADT (medical versus surgical), primary or salvage ADT, type of prior prostate cancer-directed treatment, and ADT schedule (continuous versus intermittent). Patient charts were reviewed for the presence of pre-existing psychiatric illness and targeted therapy, and post-ADT diagnosis of de novo psychiatric illness requiring medical therapy. Clinically-significant psychiatric illness was confirmed based on fulfilment of the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria and subsequent initiation of directed therapy. Further, charts were reviewed for the diagnosis and/or treatment initiation for substance abuse, and the type of substance abused (tobacco, alcohol, narcotics). ADT was defined as receipt of a gonadotropin-releasing hormone agonist (GnRH, Goserelin acetate depot, AstraZeneca PLC, London, UK), combined androgen blockade (CAB, GnRH agonist and anti-androgen), or bilateral orchiectomy.

The study cohort was divided into three groups for analysis as follows: 1) men with pre-ADT psychiatric illness, 2) patients with de novo psychiatric illness following ADT induction, and 3) patients without psychiatric illness. Data analysis utilized Chi square and Kruskal-Wallis analysis of variance (where appropriate), as well as univariate and multivariate logistic regression, with all potential explanatory covariates incorporated into models. Variables demonstrating an association with psychiatric illness were considered for multivariate analysis. Independent variables were modeled as both continuous and categorical variables as follows: age ≥ 70 versus < 70 years, Gleason grade sum ≥ 7 versus < 7, PSA ≥ 10 versus < 10 ng/ml, and BMI ≥ 30 versus < 30 kg/m^2. All p-values were based on two-sided tests of significance, with $p < 0.05$ considered statistically significant. The Hosmer-Lemeshow test eliminated models that fit poorly. Kaplan-Meier analysis was utilized to compare survival outcomes between patient groups. Statistical analysis utilized SAS computerized software, version 9.1 (SAS Institute Inc., Cary, NC).

Results

Demographic data and disease characteristics for the entire study cohort are outlined in Table 1. After exclusions, 395 patients were analyzed with a mean age at ADT initiation of 71.7 years (range: 46.7-89.3) and with a mean follow-up of 87.4 months (range: 4.8-445.0). Of these, 233 (59.0%) were African-American while 162 (41.0%) were Caucasian/other. Three-hundred and seventy-five (94.9%) men received medical ADT while 20 (5.1%) underwent bilateral orchiectomy. In total, 264 (66.8%) men underwent salvage ADT for rising PSA after primary treatment while 131 (33.2%) received primary ADT, and 359 (90.9%) received continuous ADT (surgical or medical) while 36 (9.1%) received intermittent ADT.

Clinicopathologic and demographic data comparisons between the three patient groups are demonstrated in Table 2. Thirty-four (8.6%) patients had a pre-ADT diagnosis of psychiatric illness requiring therapy. At mean follow-up of 87.4 months, 119 psychiatric illnesses were newly diagnosed in 101 patients (27.9%). Thus, the rate of de novo psychiatric illness development was 3.8% per year following ADT induction. Psychiatric illness diagnosed during the study period were comprised of: depression only (n = 57; 56.4%), dementia only (n = 14; 13.9%), anxiety only (n = 9; 8.9%), psychosis only (n = 1; 1.0%), insomnia only (n = 2; 2.0%), depression/dementia (n = 5, 4.9%), depression/anxiety (n = 8, 7.9%), depression/insomnia (n = 2, 2.0%), depression/psychosis (n = 2, 2.0%), and anxiety/dementia (n = 1, 1.0%).

Comparison analysis between patient groups were similar except that patients with de novo psychiatric illness demonstrated a higher percentage of primary ADT (68.3%) compared to patients with pre-ADT psychiatric illness (58.8%) and no psychiatric illness (16.2%, p = 0.03). Further, men

TABLE 1. **Clinicopathologic and demographic data for patients with prostate cancer treated with ADT**

	Entire cohort
Number of patients	395
Age at ADT initiation (years)	
Mean	71.7
Median (range)	73.1 (46.7-89.3)
Pretreatment serum PSA level (ng/ml)	
Mean	130.8
Median (range)	15.4 (0.4-6031.0)
Gleason grade sum (mean (median, range))	6.9 (7.0, 3.0-10.0)
Primary Gleason grade	3.4 (3.0, 2.0-5.0)
Secondary Gleason grade	3.5 (3.0, 1.0-5.0)
BMI (kg/m^2)	
Mean	26.9
Median (range)	26.7 (12.5-52.4)
Race (n/%)	
African-American	233 (59.0)
Caucasian/other	162 (41.0)
Castration type (n/%)	
Medical	375 (94.9)
Surgical	20 (5.1)
ADT type (n/%)	
Primary	131 (33.2)
Salvage	264 (66.8)
EBRT/brachytherapy	199 (50.3)
RRP	32 (8.1)
TCAP	13 (3.3)
EBRT/TCAP	2 (0.5)
RRP/EBRT	18 (4.6)
ADT schedule (n/%)	
Continuous	359 (90.9)
Intermittent	36 (9.1)
Clinical stage (n/%)	
T1	178 (45.1)
T2	64 (16.2)
T3	7 (1.8)
N+	8 (2.0)
M+	14 (3.5)
Unknown	124 (31.4)
Death event (n/%)	
Yes	69 (17.5)
DOD	16 (4.1)
DOC	35 (8.9)
DUC	18 (4.6)
No	326 (82.5)
Substance abuse (n/%)	
Yes	78 (19.8)
No	317 (80.2)
Substance abuse type (n/%)	
Tobacco	43 (10.9)
Alcohol	27 (6.8)
Narcotic	8 (2.0)
Time on ADT (months)	
Mean	63.4
Median (range)	56.7 (2.9-208.3)
Follow-up time (months)	
Mean	87.4
Median (range)	80.5 (4.8-445.0)

ADT = androgen deprivation therapy;
PSA = prostate-specific antigen; BMI = body mass index;
EBRT = external-beam radiotherapy;
RRP = radical retropubic prostatectomy;
TCAP = targeted cryoablation of the prostate
DOD = death of disease (prostate cancer);
DOC = death from other cause,
DUC = death from unknown cause

with de novo psychiatric illness also demonstrated a significantly longer mean duration of ADT (76.9 months) compared to the pre-ADT (43.1 months) and no psychiatric illness groups (60.9 months; $p < 0.0001$). On the other hand, men with no psychiatric illness demonstrated a significantly longer mean duration of follow-up ($p = .007$; Table 2). Analyzing the patterns of substance abuse between groups, while the distribution of substance abuse type demonstrated a trend towards significance ($p = 0.05$), the overall rates of substance abuse were similar ($p = 0.76$). Groups were similar with respect to the remainder of variables, Table 2.

Logistic regression analysis was performed to identify factors predictive for or protective against reporting post-ADT psychiatric illness in this cohort. Variables incorporated into the models included age, race, BMI, pre-ADT serum PSA, castration type and schedule, Gleason grade sum, clinical stage, primary/salvage ADT, and history of substance abuse (data not shown). When adjusting for other variables, univariate and multivariate analysis did not demonstrate any significant predictors for developing de novo post-ADT psychiatric illness. Further logistic regression was then utilized to identify predictors of specific psychiatric illnesses (e.g. depression, anxiety,

TABLE 2. **Comparison of clinicopathologic data between patients with de novo psychiatric illness, pre-ADT psychiatric illness and no psychiatric illness**

	De novo psychiatric illness	Pre-ADT psychiatric illness	No psychiatric illness	p-value
Number of patients (n/%)	101 (25.6)	34 (8.6)	260 (65.8)	-
Age at ADT initiation (years)				
Mean	71.7	71.6	71.7	0.99
Median (range)	73.1 (47.8-86.1)	72.0 (51.4-84.1)	73.2 (46.7-89.2)	
Pre-ADT PSA (ng/ml)				
Mean	83.2	37.3	156.5	0.39
Median (range)	16.5 (0.4-2321.0)	11.7 (1.0-331.0)	15.5 (0.4-6031.0)	
Gleason grade sum				
Mean	7.2	6.7	6.9	0.25
Median (range)	7.0 (5.0-10.0)	7.0 (5.0-9.0)	7.0 (3.0-10.0)	
BMI (kg/m^2)				
Mean	22.7	29.2	27.1	0.11
Median (range)	22.1 (14.8-35.9)	27.7 (18.3-52.4)	26.8 (12.6-47.7)	
Race (n/%)				
African-American	52 (51.5)	17 (50.0)	164 (67.5)	0.26
Caucasian/other	49 (48.5)	17 (50.0)	96 (32.5)	
Castration type (n/%)				
Medical	98 (97.0)	32 (94.1)	245 (94.2)	0.54
Surgical	3 (3.0)	2 (5.9)	15 (5.8)	
ADT type (n/%)				
Primary	69 (68.3)	20 (58.8)	42 (16.2)	0.03
Salvage	32 (31.7)	14 (41.2)	218 (83.8)	
ADT schedule (n/%)				
Continuous	87 (86.1)	32 (94.1)	240 (92.3)	0.15
Intermittent	14 (13.9)	2 (5.9)	20 (7.7)	
Clinical stage (n/%)				
T1	43 (42.6)	15 (44.1)	120 (46.2)	0.78
T2	12 (11.9)	4 (11.8)	48 (18.5)	
T3	3 (3.0)	0 (0)	4 (1.4)	
N+	4 (3.9)	1 (2.9)	3 (1.2)	
M+	3 (3.0)	0 (0)	11 (4.2)	
Unknown	36 (35.6)	14 (41.2)	74 (28.5)	
Death event (n/%)				
Yes	23 (22.8)	4 (11.8)	42 (16.2)	0.08
DOD	3 (2.9)	1 (2.9)	12 (4.6)	
DOC	17 (16.8)	1 (2.9)	17 (6.5)	
DUC	3 (2.9)	2 (5.9)	13 (5.0)	
No	78 (77.2)	30 (88.2)	218 (83.8)	
Substance abuse (n/%)				
Yes	21 (20.8)	10 (29.4)	47 (18.1)	0.28
No	80 (79.2)	24 (70.6)	213 (81.9)	

Substance abuse type (n/%)				
Tobacco	7 (6.9)	9 (26.5)	27 (10.4)	0.16
Alcohol	12 (11.9)	1 (2.9)	14 (5.4)	
Narcotic	2 (1.9)	0 (0)	6 (2.3)	
Time on ADT (months)				
Mean	76.9	43.1	60.9	< 0.0001
Median (range)	69.6 (11.6-184.8)	32.3 (3.1-101.7)	53.7 (2.9-208.3)	
Follow-up time (months)				
Mean	77.4	73.5	83.5	0.007
Median (range)	70.0 (4.5-185.9)	58.4 (5.7-206.5)	77.4 (4.8-364.9)	

ADT = androgen deprivation therapy; PSA = prostate-specific antigen, BMI = body mass index;
DOD = death of disease (prostate cancer); DOC = death from other cause, DUC = death from unknown cause

dementia, etc.). This analysis demonstrated that when adjusting for other variables, only pre-ADT PSA was associated with an increased risk for developing post-ADT anxiety (odds ratio (OR) 7.68, p = 0.01). No other significant predictors for the remaining psychiatric diagnoses were identified (data not shown).

Subset analysis was performed to identify differences in mortality events during the study period. See Tables 1 and 2. All patient groups were similar with respect to the number and distribution of mortality events (p = 0.08). Further, Kaplan-Meier analysis demonstrated similar overall (p = 0.88) and disease-specific (p = 0.48) survival outcomes. See Figures 1 and 2, respectively.

Discussion

ADT continues to play a substantial role in contemporary prostate cancer treatment. Survival advantages with primary ADT have led to significant increases in the utilization of this treatment application.[2,17] Subsequently, the adverse-effects of ADT continue to be elucidated, and attempts at recognizing and mitigating these treatment-associated morbidities have become increasingly important in order to maximize QOL in the contemporary prostate cancer patient.

ADT, whether via administration of GnRH agonists/antagonists or orchiectomy, results in reduced circulating serum testosterone and estradiol

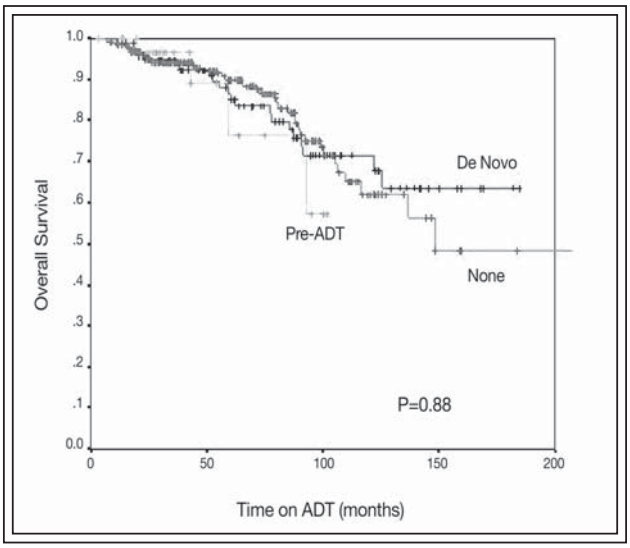

Figure 1. Overall survival comparisons between patients with pre-ADT psychiatric illness, de novo psychiatric illness, and no psychiatric illness.

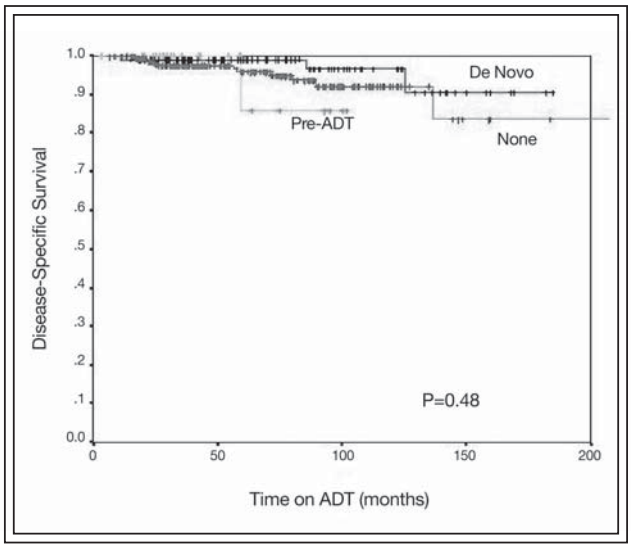

Figure 2. Disease-specific survival comparisons between patients with pre-ADT psychiatric illness, de novo psychiatric illness, and no psychiatric illness.

levels through down-regulation of the luteinizing hormone receptors at the anterior pituitary gland.[2] Castrate testosterone levels, whether age-related or due to ADT, have demonstrated well-documented associations with altered body composition, endocrine dysfunction, vasomotor flushing, sexual dysfunction, and osteoporosis.[2-8]

While the psychological impacts of newly diagnosed cancer have been reported, data remains scarce.[12] Changes in psychological well-being have been associated with hypogonadism, and in particular, men with prostate cancer.[10,11,13-18] Specific to the prostate cancer patient, however, elucidating this relationship has been difficult owing to the numerous confounders that exist in this older age group that can impact QOL and mental health.[10,11,15]

Hypogonadism has been linked to such psychological problems as depression, anxiety, cognitive impairment, and insomnia. Yet, studies analyzing the relationship between testosterone and these endpoints have been inconclusive.[13,15,17-19] Barrett-Connor et al reported on 856 men between 50-89 years of age to elucidate the relationship between testosterone and depression.[13] The authors found testosterone levels to be inversely correlated to scores on the Beck Depression Inventory (BDI), independent of other variables. Similarly, a large longitudinal study of 1456 men by Shores et al reported a two-to-three-fold increased risk of depression in hypogonadal men when compared to eugonadal controls.[18] Our data demonstrated similar findings, with a three-fold increase observed between rates of pre-ADT psychiatric illness and development of de novo illness during the study period (8.6% versus 27.9%, respectively; Table 2). On the other hand, Perry et al demonstrated lower levels of bioavailable testosterone to be associated with fewer depressive symptoms, less anxiety, and a greater emotional well-being.[17] Further, some series have demonstrated no relationship between hormone levels and depressive symptoms.[19]

Specific to the prostate cancer patient receiving ADT, there remains a general paucity of data that examines these relationships.[9-11] Pirl et al studied 45 men with prostate cancer receiving ADT using the BDI and Structured Clinical Inventory for DSM-IV (SCID).[11] The authors identified a prevalence of 12.8% for major depressive disorder in the study cohort. Using the BDI, 13.3% reported mild-moderated depressive symptoms, while 86.7% were free from these complaints. Further, prostate cancer treatment-response to ADT did not demonstrate a relationship with rates of major depression (13.9% in stable prostate cancer versus 14.3% in progressive prostate cancer, $p = 0.8$) by SCID or BDI ($p = 0.2$). Further, the type of ADT (medical versus surgical) did not differ with respect to SCID ($p = 0.8$) or BDI ($p = 0.4$) scores. No patients without a history of previous depression were diagnosed with de novo psychiatric illness. In a recent study, Pirl et al examined differences in depressive symptoms between men receiving GnRH analogue therapy versus androgen-receptor blockers.[10] In this series, reports of depression (of any degree) were identified in 10.4% to 16.3% of men over the 12 month study period and no significant differences in depression rates were seen between the two types of hormone therapy.

In our series, de novo psychiatric illness was identified in 101 patients (27.9%), with 57 (56.4%) of these diagnosed with new-onset depression. Thus, we identified a prevalence of de novo depression in our cohort of 14.4%, which is comparable to findings of other series. Pirl et al reported a prevalence rate of 12.8% in their single-center series of 45 consecutive prostate cancer patients receiving ADT, though the authors did not report any de novo cases of major depression.[11] Comparisons between men with de novo psychiatric diagnoses versus pre-ADT or no psychiatric illness demonstrated no differences between ADT schedules ($p = 0.15$) or ADT type ($p = 0.54$), which is also consistent with the findings of Pirl et al.[11] However, men with de novo psychiatric illness were comprised of a greater percentage of men receiving primary ADT (68.3% versus 58.8% and 16.2%, $p = 0.03$) and had a significantly longer mean duration of ADT (76.9 months versus 43.1 and 60.9, $p < 0.0001$; Table 2). The higher rates of de novo psychiatric illness may in fact be related to these factors as men with newly diagnosed prostate cancer may be more troubled by their cancer diagnosis. In fact, Steginga et al reported on 111 men with newly diagnosed prostate cancer, finding that at 12 months follow-up, psychological and treatment decision-related distress decreased with time, regardless of the type of treatment rendered.[20] Thus, the higher percentage of newly-diagnosed patients (i.e. men receiving primary ADT) in the de novo psychiatric illness group may account for this finding. However, receipt of primary versus salvage ADT was not demonstrated to be predictive of de novo psychiatric illness on multivariate analysis ($p = 0.17$) when adjusting for other variables, so the significance of this finding remains unclear. However, the fact that this patient group was exposed to a longer mean duration of ADT may also be a contributing factor to these findings.

It is important to note that age was similar between both groups in our series, Table 2. Several series have found an inverse relationship between age and anxiety and depression, such that older men demonstrate

lower incidences of these endpoints.[14,16,21] Since our groups were similar with respect to age, it does not seem that this could explain the differences seen in our series.

Substance abuse-induced alterations in testosterone levels have also been implicated in development of depression and other psychiatric illnesses.[15] For this reason, we incorporated not only the presence of substance abuse, but the type of substance abuse into our analysis. While patient groups demonstrated a trend towards differences between types of substance abuse ($p = 0.05$), overall presence of substance abuse was similar between all groups ($p = 0.28$; Table 2).

Disease stage has also been associated with psychopathology in prostate cancer patients.[9] In a series of 172 men with prostate cancer, Kornblith et al found 29% of patients to report diagnosis-related "worry", and 21% to report symptoms of depression.[9] In men with advanced stage disease, the authors identified a significantly greater rate of psychological illness when compared to men with early-stage disease. Our series, on the other hand, did not demonstrate a relationship between de novo psychiatric illness and tumor stage at ADT induction ($p = 0.78$).

We attempted to identify factors that would predict the development of post-ADT psychiatric illness in this cohort. In fact, only pre-ADT PSA was identified as a predictor, and as such, only predicted the development of post-ADT anxiety and not the development of post-ADT psychiatric illness in general. With regards to overall and disease-specific survival, outcomes were not impacted by the presence of psychiatric illness, neither de novo nor pre-existing prior to ADT induction, Table 2; Figures 1 and 2.

There are several limitations to this study. Firstly, we report a retrospective review of our findings at a single center and thus, our observations are subject to the inherent biases of this type of analysis. Further, we did not attempt to compare this patient population to a control group (i.e., patients undergoing surveillance protocols) and therefore report on a single cohort of patients. Additionally, while comprised of 395 patients, the number of patients reporting post-ADT psychiatric illness ($n = 101$) was relatively small. As such, our analysis may be limited in its ability to demonstrate all potential relationships between variables and the study end points. Furthermore, patients were not routinely evaluated in a uniform and prospective manner throughout their prostate cancer treatment and we only studied patients with psychiatric illness considered to be clinically significant, i.e. requiring medical therapy. Therefore, we suspect that it is possible that a greater number of patients may have had pre-ADT psychiatric illness and/or developed de novo psychiatric illness that went undetected. We also did not attempt to compare surgical versus medical ADT and their respective impact on post-ADT mental health due to the diminutive size of the number of patients in the surgical ADT group. Additionally, our patient cohort was comprised of patients treated solely at the VAMC. As veteran status has shown increased associations with psychopathology,[22] it is possible that the rates of psychiatric illness, pre-existing or de novo, are not comparable to those of non-veterans.

Thus, it is uncertain whether these study limitations potentially underestimate the effects of long-term ADT on mental health. Nonetheless, we feel the results of this investigation are strengthened by the size of the study cohort and the duration of follow-up. To our knowledge, this is the largest single-center series of patients evaluated for psychiatric illness in patients receiving ADT for prostate cancer reported to date. The mean follow-up period of 87.4 months at an equal access health care facility remains considerable. Age and prostate cancer characteristics in our cohort appear similar to the general United States prostate cancer population, while race, lifestyle, and comorbid illnesses may be dependent on regional demographics.[23] Thus, in order to truly define the relationship between ADT and the endpoints of our study, prospective analysis using validated mental health-directed instruments with direct comparison to matched controls is requisite.

Despite these limitations, we feel these findings should at least prompt physicians administering ADT to patients with prostate cancer to actively inquire into a patients' emotional and mental health, and to adopt a regimen of close, serial monitoring of emotional and mental health with prompt referral if any alterations are noted.

In conclusion, de novo psychiatric illness was identified in 27.9% of men post-ADT, representing a three-fold increase from pre-ADT rates (8.6%). No predictive factors for development of general psychiatric illness were identified. However, increasing PSA at ADT induction was associated with de novo anxiety requiring treatment. The presence of psychiatric illness does not appear to affect survival outcomes. Receipt of primary ADT as well as the duration of ADT may be factors contributing to the development of de novo psychiatric illness. Prospective investigation using validated instruments is requisite to further delineate the psychiatric impact of prolonged ADT on patients treated for prostate cancer. □

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EDITORIAL COMMENT

Testosterone deficiency (TD) is increasingly recognized as an important negative factor in the general health in older men, independent from multiple risk factors.1 It does not take a great leap to imagine the consequences of the profound deficiency experienced by patients with prostate cancer receiving ADT, aside from the cancer itself . Since these men are already victims of an advanced cancer, little attention has been paid, until recently, to the detrimental effects of ADT. After all, ADT is recognized as an effective and well tolerated means of suppressing the growth of prostate cancer.

Most of the efforts to counteract the adverse effects of ADT have been oriented toward bone health and progress has been made in this direction. Although it is well documented that depression is a frequent manifestation of TD, in the particular instance of men with metastatic prostate cancer, it is easier to attribute it to the emotional and physical upheaval of the diagnosis and the dire prognosis. This paper is both timely and important and the authors are to be congratulated for their effort. As in most retrospective studies, it carries some deficiencies but points to a relevant but largely neglected area of oncology research. The finding that almost a third of men receiving ADT developed de novo psychiatric illness is significant but not surprising. It should alert us to a possible effect of ADT in those with a long life expectancy. Hopefully this report and a few others in the same vein will spur interest in prospective investigations. The need for studies that include cohorts of men with cancer not receiving ADT and those on intermittent ADT would be of obvious significance. For the latter group, a correlation with androgenic status would be essential since most of them never recover adequate gonadal function.

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