

Androgen deprivation therapy's impact on the mood of prostate cancer patients as perceived by patients and the partners of patients

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Abstract

Objective: To assess the relationship between of androgen deprivation therapy (ADT) and the mood of prostate cancer (PCa) patients and partners of PCa patients.

Methods: PCa patients ($n=295$) and partners of patients ($n=84$) completed an online survey assessing the patients' current mood and mood prior to treatment, relationship adjustment, and sexual function. We compared men on ADT to men who received non-hormonal treatments for their PCa.

Results: Patients currently treated with ADT ($n=82$) reported worsened mood as measured by the Profile of Mood States compared to those not on ADT ($n=213$). The negative impact of ADT on mood, however, was reduced in older patients. Partners of patients on ADT ($n=42$) reported similar declines in the patient's mood that patients reported, but to a greater degree than patient-reported levels.

Conclusions: Our data support ADT's impact on PCa patients' mood and verify that partners concurrently see the effects. The psychological changes related to ADT can impact relationships and affect the quality of life of both PCa patients and partners. Patients and their partners are likely to benefit from being well informed about the psychological effects of androgen deprivation on men beginning ADT.

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Background

Approximately half of all men treated for prostate cancer (PCa) will be offered androgen deprivation therapy (ADT) sometime during their life. At any one time in North America, approximately 600 000 men are on ADT [1]. ADT has been linked to anxiety and depression in patients [2–4]. Conspicuous to patients are not just physical changes (e.g., hot flashes, gynecomastia, loss of body hair, and weight gain), but sexual (lost libido and erection dysfunction), and emotional changes (depression, tearfulness, and fatigue), all of which negatively impact on patients' quality of life of and indirectly on their partners [5–8]. Men on intermittent ADT report lower physical and psychological quality of life when on ADT compared to off periods [9].

Higano was among the first to note that it is often the patients' partners who report increased moodiness, emotionality, and depression in ADT patients [10]. Anecdotal evidence has accumulated that patients using ADT experience greater adverse effects on mood than PCa patients in general.

Studies of hormones and mood have demonstrated correlations between mood and various hormone titers in

different populations. Relevant to our sample, low testosterone levels have been linked to depression and fatigue in several studies of men who were not PCa patients (reviewed by [11]), although the findings have been somewhat mixed [12]. Testosterone supplementation has been shown to improve mood, particularly for those with sub-threshold depressive symptoms [13]. In nonclinical populations, lower levels of salivary testosterone have been linked to higher levels of negative mood, as reported on the Profile of Mood States (e.g., [14]). Based on these correlational and experimental findings in healthy populations, we would expect that the mood of patients on ADT, who have extremely low levels of testosterone, to be more negatively affected compared to patients not on ADT.

Most studies on the relationship between ADT and mood in PCa patients have measured depression. Men undergoing ADT have increased levels of depression compared with: (a) the general population [15,16], (b) themselves when not on ADT [17], and (c) other PCa patients not on ADT [2,15,18,19]. A large scale study of over 3000 patients found that prostate patients on ADT had more emotional and mental health problems than men who had other PCa treatments for PCa [18].

Although there is growing evidence that ADT has negative psychological effects, some studies have not found significant differences in depression between PCa patients on ADT longitudinally [20] or compared to those who were not undergoing ADT [21–24]. Timilshina *et al.*, in particular, did not find any significant differences in depression when they assessed symptoms in three groups: PCa patients on ADT, PCa patients not taking ADT, and healthy controls [23]. Nor were there significant differences between the groups in depressive symptoms over time. However, the ADT group scored higher in depression and had noticeably greater variability than the non-ADT patient group. This suggests that some of the ADT patients were showing large increases in depression and some were showing decreases, while the non-ADT group was staying fairly stable over time. It is also possible that age is a factor in the mood effects seen in men on ADT. Older men—who are less sexually active with reduced testosterone levels—may react less dramatically to ADT. This idea is consistent with previous studies assessing age as a predictor of depression [2].

While there have been a number of studies assessing depression specifically, few studies have examined the relationship between ADT and subclinical mood disturbances. A small qualitative study of men on ADT reported increased irritability, anger, tearfulness, and mood fluctuations [25]. A similarly small quantitative study comparing 18 PCa patients on ADT to 17 healthy controls found that men on ADT reported higher levels of fatigue and confusion, and less vigor on the Profile of Mood States [26]. Cherrier, Aubin, & Higano, in a quantitative study of 20 PCa patients on ADT and 20 healthy controls, showed evidence for more negative mood in patients compared to controls, with some increases in negative mood over time for the patients compared to their baseline measures [27]. Most of the changes, however, were not statistically significant, which may be an artifact of the small sample size. In studies of the psychological impact of ADT that did not look specifically at mood, a commonly reported non-controversial adverse psychological effect of ADT is fatigue [9,20,28,29].

Although there are data suggesting ADT-specific effects on mood, studies on subclinical mood disturbances and ADT thus far have used small sample sizes and compared patients on ADT to healthy controls. In order to isolate the specific relationship between ADT and mood, we investigated the emotional changes in PCa patients currently undergoing ADT compared to those not on ADT. We assessed mood using the Profile of Mood States-Short form (POMS), which parses psychological distress more extensively than assessing just depression [30,31]. We felt it important to study mood beyond depression recognizing that, especially for partners, living with someone who is moody may be more challenging than living with someone with stable depression simply

because changes in mood may be unpredictable. Additionally, the POMS is very common in cancer research because it exclusively assesses mood without reference to the somatic symptoms of depression, which may be the result of cancer or its treatments [32]. Data were also gathered from a sample of individuals, who were partners of PCa patients but not necessarily of the specific PCa patients in our sample. Evidence suggests that partners of PCa patients in general may be more aware than the patients themselves of the patients' emotional changes [10], and report higher levels of distress in themselves and their partners [33].

Hypotheses for this study included the following: (1) Both patients and partners of patients on ADT will report worse current moods in those patients than in patients not on ADT. (2) Patients and partners of patients on ADT will also report greater negative perceived change in patients' mood compared to pre-ADT treatment. (3) Severity of mood-related changes will correlate inversely with age, such that younger men will experience more negative mood related to the side effects of ADT.

Method

Participants

Participants for this online survey were recruited through PCa related email listservs and social media (e.g. ads on Facebook). The online survey invited participation from both PCa patients (patients) and the partners of patients (partners) and required the patients to have been diagnosed and treated for localized prostate cancer. The partners of patients could participate regardless of whether their own partner (i.e. the patient) elected to be in the study. All invitations to participate provided a brief outline of the study topic. Participants were 295 (ADT $n=82$, Non-ADT $n=213$) men who had a diagnosis of and been treated for PCa and 84 partners of men with PCa (Partners of men on ADT $n=42$, partners of men not on ADT, $n=42$). Participants were asked their gender with an open-ended response option. All of the patients self-identified as male; Ninety-four percent of partners were female and 6% were male. The sample was 94% white, 90% heterosexual, and 90% in long-term relationships. Mean relationship length was 28 years for patients and 25 years for partners. There were no differences in demographic variables between the ADT and Non-ADT groups.

Patients were considered to be on ADT if they were actively taking LHRH agonists or antagonists, an anti-androgen, or some combination of the two at the time of the survey. Participants taking a 5-alpha-reductase inhibitor were included if they were taking it in combination with another androgen-suppressing drug. Participants reported being on ADT for a median of 24 months. At

survey completion, both partners and patients were asked to invite their partners to complete the survey; however, the majority of participants were recruited as individuals, and not as patient–partner dyads. Thus most patients and partners for this study are unrelated.

Procedure

Procedures were approved by the Research Ethics Board at Mount Allison University. Psych Data (www.psychdata.com), a secure, online survey-hosting site designed for researchers in the social sciences, hosted the survey. Once participants consented to the study, they were presented with a series of questionnaires related to demographic and health information, PCa treatments, and mood. Participants also completed additional questionnaires not reported in this paper. Patients and partners saw the same questionnaires. For demographics, partners reported for themselves. For the other questionnaires, they reported on their perceptions of the patient's (i.e. their partner's) experiences. For example, with the mood questionnaires, partners were asked, 'Please indicate how you

think your partner has felt, on average, over the past week using the following scale.' At the completion of the survey, all participants were debriefed with information about the study.

Measures

The demographics and health questionnaire was created by the researchers and included basic demographic information such as age, sexual orientation, and relationship status. Health measures included questions about PCa treatments and adverse effects. These included an open ended question in which participants' described their treatments, a question about current medications/treatments, and a question about duration of time on current treatment. The questionnaire also included a list of physical and sexual side effects that participants may be experiencing.

To assess mood, we used the Profile of Mood States-Short Form (POMS), which consists of 37 mood-related words [31]. Participants rate these words using a five-point scale from 1 (Not at all) to 5 (Extremely) over the past week. Six subscales are included within the POMS to gather information on participants' mood: Tension–Anxiety,

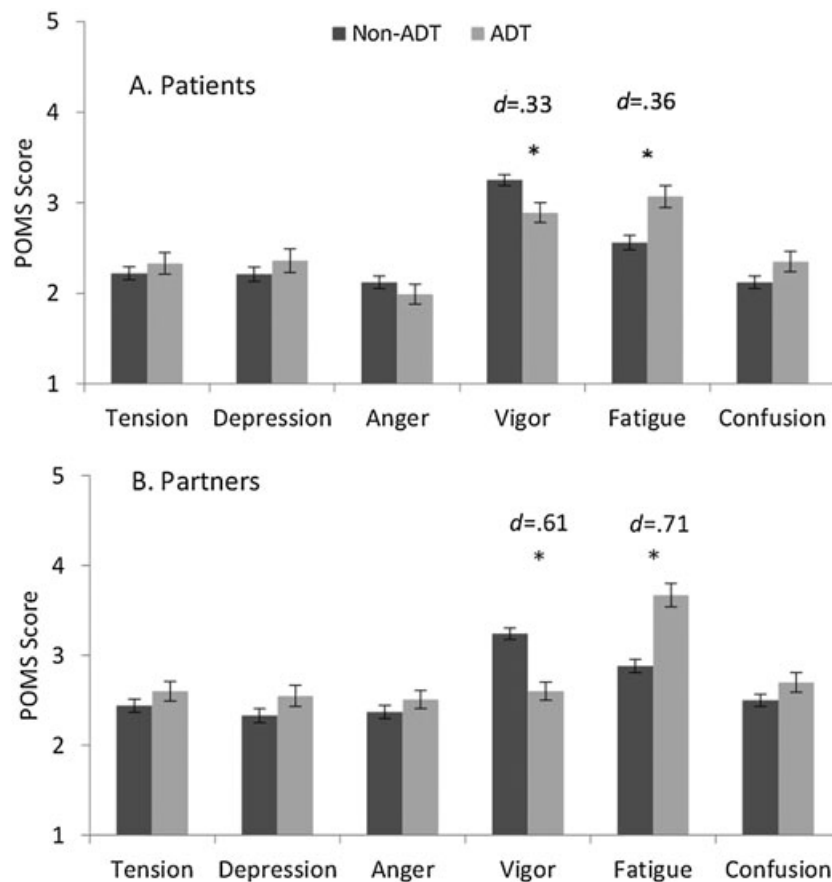


Figure 1. Between groups comparison of mood between Non-ADT and ADT groups of (A) PCa patients (controlling for age) and (B) partners of PCa patients. d = Cohen's d , calculated for both groups without controlling for age * indicates a significant difference at $p < .05$. Both men on ADT and the partners of men on ADT reported that patients had more negative and less positive moods than men not on ADT

(Tension), Depression–Dejection (Depression), Anger–Hostility (Anger), Vigor–Activity (Vigor), Fatigue–Inertia (Fatigue), and Confusion–Bewilderment (Confusion). Participants who completed the POMS were asked if their mood or their partner’s mood (if they were the partner of a patient) had changed since beginning treatment for PCa. If they said ‘yes’, they were asked to complete the POMS again with reference to the patient’s mood prior to his PCa treatment (retrospective POMS). Scores were averaged for each subscale.

Results

Previous research has noted differences in diagnoses and outcomes between heterosexual and non-heterosexual men with PCa [34,35]. Although our sample of men partnered with men was not large enough to test for differences, we did run the analyses with and without these participants, and there were no changes in the significance of

the outcomes. There were also 12 patient–partner dyads in the overall sample. To ensure these paired samples were not affecting the results, we ran the analyses with and without the patients from the partner–patient pairs. Again, there were no differences in the significance of the results. Because results were similar with and without these dyads included, the analyses reported below include all participants.

POMS scores for the ADT and non-ADT groups were entered into a multivariate ANOVA with group as the fixed factor and age as a covariate. The main effect of treatment was significant in the overall MANOVA, $F(6,282)=5.0$, $p<.001$, $\eta_p^2=.10$. There was also a significant effect of age for the overall MANOVA, $F(6,282)=4.7$, $p<.001$, $\eta_p^2=.09$. Age was a significant covariate for all of the univariate ANOVAs (all $ps<.001$), so all subsequent results include age as a covariate. Men on ADT reported significantly higher scores on Fatigue, $F(1,287)=12.5$, $p<.001$, and lower scores on Vigor, $F(1,287)=9.0$, $p=.003$. There were

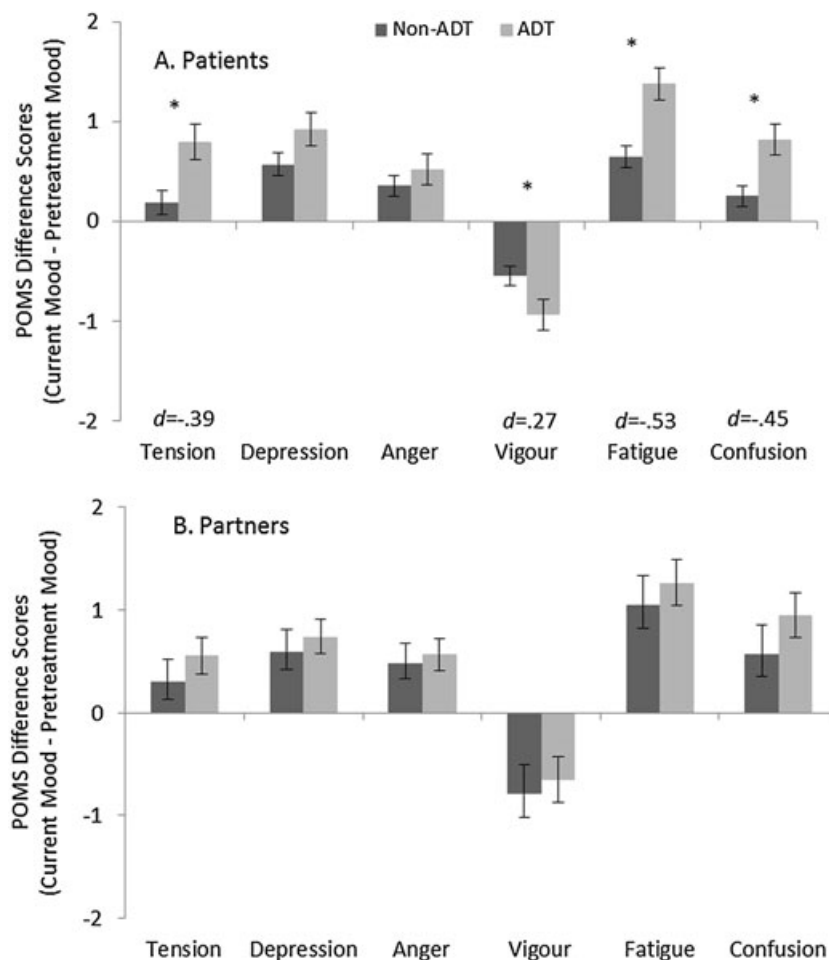


Figure 2. Difference scores for patients’ self-reported mood before (retrospective) beginning treatment for PCa and after/during (current) treatment for PCa. All patients reported worse mood, but men on ADT reported significantly more Tension, Fatigue, and Confusion, and less Vigor than men not on ADT. d = Cohen’s d , calculated without controlling for age * indicates a significant difference at $p < .05$

no significant differences between the groups on Tension, $F(1,287)=.62$, $p=.43$, Depression, $F(1,289)=1.02$, $p=.31$, Anger, $F(1,287)=.96$, $p=.32$, or Confusion, $F(1,287)=3.2$, $p=.08$ (Figure 1a).

Partners of men with PCa, who were and were not on ADT, reported a pattern of results for POMS scores that was similar to the patients. We did not ask the partners the age of the patient to which they were referring, so this analysis does not include age as a covariate. The overall MANOVA for the main effect of treatment was significant, $F(6,74)=3.5$, $p=.004$, $\eta_p^2=.09$. Partners of men on ADT reported that the patients had higher levels of Fatigue, $F(1,79)=10.07$, $p=.002$, and lower levels of Vigor, $F(1,79)=8.20$, $p=.006$. Similar to the patients, partners also reported no significant differences between ADT and non-ADT men on Tension, $F(1,79)=.33$, $p=.57$, Depression, $F(1,79)=.66$, $p=.42$, Anger, $F(1,79)=.27$, $p=.60$, or Confusion, $F(1,79)=.48$, $p=.49$ (Figure 1b).

Although the results for both patients and partners were similar, the effect size for differences when on and off ADT reported by partners of patients was greater than the differences between groups reported by patients themselves.

Upon completion of the POMS for their current mood, participants were asked if they thought their mood (if a patient) or their partner's moods (if a patient's partner) had changed since beginning treatment for PCa. Seventy-one percent ($n=57$) of men on ADT and 68% ($n=143$) of men not on ADT reported that their moods had changed since beginning their treatment for PCa. Of those who reported a change in mood, 52 men on ADT and 120 men not on ADT completed the retrospective POMS. We calculated difference scores for the reported change in mood by subtracting the patients' retrospective POMS scores from their current POMS scores for each subscale. Difference scores were then entered into a MANOVA with ADT

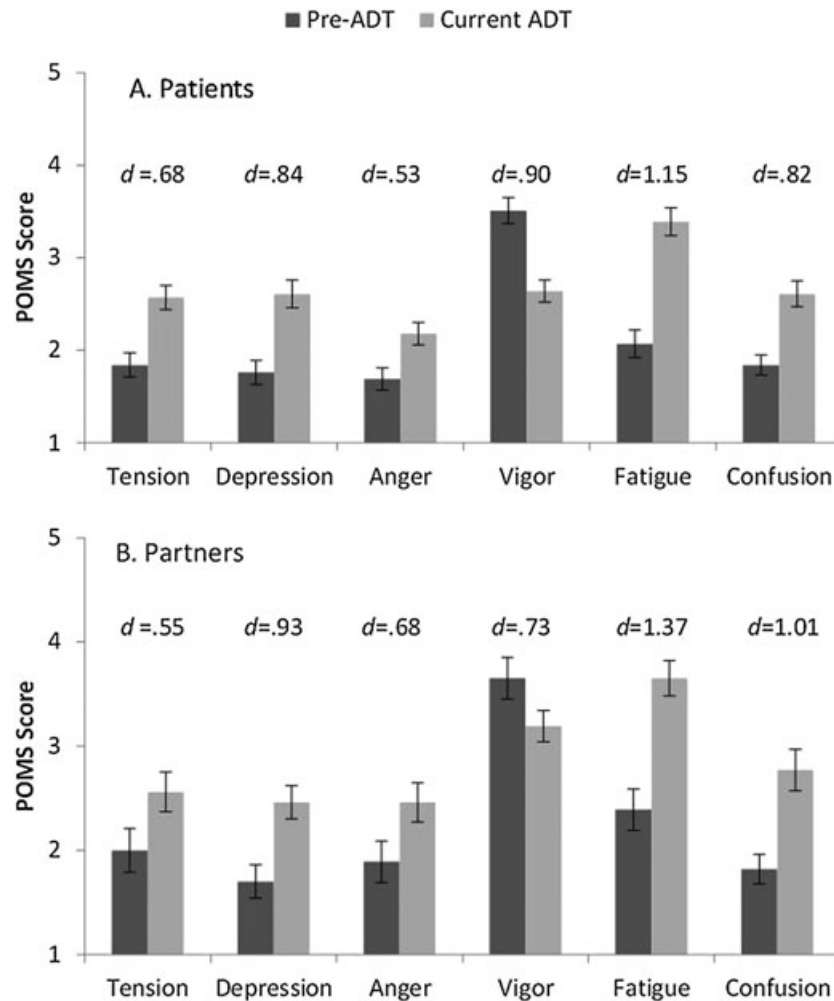


Figure 3. Within-person comparisons of mood before (retrospective) and during use of ADT treatment for (A) PCa patients (controlling for age) and (B) partners of PCa patients. All differences are significant at $p < .05$. Both patients and partners report that patients have had significantly worse mood since beginning ADT. Partners reported a larger difference in the patients' mood than did the patients themselves for all parameters except Vigor and Tension

group as the fixed factor and age as a covariate. Both men on and off ADT reported worse mood since treatment began, but the men on ADT reported greater increases in negative mood and decreases in positive mood. These differences were significant for Tension, $F(1,170)=5.42$, $p=.02$, Fatigue $F(1,170)=14.17$, $p<.001$, Confusion $F(1,170)=9.39$, $p=.003$, and Vigor, $F(1,170)=4.63$, $p=.03$ (Figure 2a).

For partners, 69% ($n=29$) of partners of men on ADT and 46% ($n=18$) of partners of men not on ADT reported that their partner's (i.e. the patients') mood had changed since beginning treatment. However, only 25 of the partners of ADT men and 16 of the partners of non-ADT men completed the POMS for a second time. The overall MANOVA was not significant, $F(6,34)=.49$, $p=.81$, and none of subscale analyses were significant. These numbers were too small to have adequate power to detect a difference between groups. The means of the Non-ADT and ADT groups were in a similar direction as the patients' (Figure 2b).

To look more in depth at the men on ADT and partners of men on ADT, we compared the pre-ADT POMS scores with the current mood scores. Patient data were entered into a repeated-measures ANOVA with time (pre-ADT, current) and POMS subscale as the within-subjects factors and age as a covariate. The MANOVA for Time was significant, indicating there was a perceived change in mood from pre-ADT to the current time, $F(1,51)=7.2$, $p=.01$. Age was also significant as a covariate, $F(1,51)=5.8$, $p=.02$. Posthoc repeated measures ANOVAs with age as a covariate found that men who perceived changes in their moods since using ADT indicated significant increases in self-reported Tension, $F(1,51)=5.82$, $p=.02$, Depression, $F(1,51)=8.23$, $p=.006$, Anger, $F(1,51)=15.43$, $p<.001$, Confusion, $F(1,51)=12.14$, $p=.001$, and Fatigue $F(1,51)=12.74$, $p=.001$, when on ADT. Not surprisingly, they also reported lower levels of Vigor, $t(56)=18.09$, $p<.001$ (Figure 3a).

For partners, the results mirrored those of the patients on ADT. The MANOVA for Time was significant, indicating that there was a significant change in their reports of the patients' mood from before to during ADT usage, $F(1,24)=19.5$, $p<.001$. Posthoc paired samples t -tests found that partners who reported perceived changes in the moods of the patient since he began using ADT reported significant increases in Tension, $t(24)=2.81$, $p=.008$, Depression, $t(24)=3.83$, $p=.001$, Anger, $t(24)=3.58$, $p=.002$, Confusion, $t(24)=3.58$, $p=.002$, and Fatigue $t(24)=5.02$, $p<.001$. They also reported lower levels of Vigor for their partners when the men were on ADT, $t(24)=-1.16$, $p=.01$ (Figure 3b). Notably, similar to the between-groups effects, partners of patients on ADT reported larger changes in the patients' mood than did the patients themselves for all POMS subscales except Vigor and Tension.

Table 1. Correlations between changes in POMS scores from pre-treatment to during/post-treatment and age of the patient. Younger men reported more negative mood changes than older men, especially for those using ADT. * indicates a significant correlation at $p<.05$

		Tension	Depression	Anger	Vigor	Fatigue	Confusion
Age	Non-ADT	-.19*	-.19*	-.14	.11	-.14	-.09
	ADT	-.26*	-.28*	-.18	-.43*	-.32*	-.35*

To assess the hypothesis that the changes in mood would be more severe for younger patients, we ran Pearson correlations with age and the difference scores (Current – Retrospective) for each of the POMS subscales. Age was significantly negatively correlated with Tension and Depression for both groups. There was no significant correlation between age and anger for either group, but for patients on ADT, age was significantly negatively correlated with changes in Fatigue and Confusion and positively correlated with Vigor (Table 1). These results suggest that PCa treatments, and in particular, ADT have a more negative psychological effect on younger patients.

Conclusion

Dealing with PCa has both physical and emotional effects on patients. In particular, patients who are treated with ADT may experience more severe side effects than patients not on ADT. The present study was designed to assess the mood of patients with PCa, who were or were not currently using ADT. Anecdotal reports and qualitative data suggest that men become more moody, angry, and tearful on ADT, but there are few empirical data to support these claims. This can result in assumptions on the part of physicians, psychologists, patients, and their partners about how men experience ADT. But without rigorous studies of the effects of ADT, it is unclear how widespread these emotional changes are nor how to deal with them.

Our first hypothesis was that PCa patients on ADT and the partners of patients on ADT would report that patients had worse moods than patients not on ADT. This hypothesis was supported. This is the first comprehensive quantitative study of subclinical mood shifts in patients using ADT as a treatment for PCa, and the first to compare men on ADT to other PCa patients.

We were particularly interested in getting the perspectives of both patients and partners of patients. One of the most striking findings was the congruence in the patterns of response of the patients and the partners, especially given that few were actually partner–patient dyads. This similarity in results indicates that the observed patterns of change in this study are likely common for many

patients on ADT. Whether assessed internally by patients or externally by partners, these data add to the findings that ADT has a greater negative effect on mood than other treatments for PCa.

We also hypothesized that patients and partners of patients on ADT would report more severe changes in mood since beginning treatment. Patients did report more severe changes when on ADT, and partners of patients reported a similar pattern of mood changes, but these differences were not significant. Our data confirmed that the adverse changes in the mood of patients on ADT are perceived as more severe by partners of patients than by patients themselves, which echoes the findings of Winters-Stone *et al.* [36] on general symptom severity and of Movsas *et al.* [37] on perceptions of sexual dysfunction symptoms.

In a study of PCa patients' stress responses, the higher degree of stress reported by the partner was thought to be an inaccurate reflection of the actual stress experienced by the patient [38]. Based on past patient interactions, we believe, that many patients, who are uninformed of the potential impact on ADT on their personality and mood, may feel that they must try to hide the emotional changes they experience in order to preserve normality. Efforts by patients to suppress or deny the psychological effects of ADT may lead to disagreement between partners and patients about the patient's emotional state. Of course, patients may have different responses to the emotional changes they are experiencing. Differences in response to displays of increased emotionality, have been noted elsewhere as in patients' responses to ADT [39]. One patient on ADT recounted how ashamed he was, then angry, at being seen as tearful by his daughter, while another ADT patient proudly announced that he now shares tissue with his wife when they go out for a movie. Such examples typify the range of emotional responses that may be accentuated by ADT.

Previous research suggested that age may be an important factor to consider when deciding on a treatment path for patients [2]. We hypothesized that younger men would be more affected by their treatment, and we found that this was the case, especially for men taking ADT. Correlational data indicated that younger patients had more negative and less positive self-reported moods. Older patients are likely to have lower testosterone levels because of aging so the change they experience with ADT may be less dramatic for them. These findings suggest that younger men are more negatively affected by ADT, which can be taken into consideration by physicians and patients when deciding upon a treatment path.

This study was not without its limitations. We used a convenience sample recruited primarily from Internet sources. As we recruited specifically from PCa support groups and websites, the sample was biased toward those who saw themselves in need of support. Patients using online support groups are likely more educated and, as

shown by our demographics, predominantly white and reasonably well-off financially.

For some of our analyses, we used the POMS in new ways. Using the POMS as a tool to report on other's moods has not previously been validated, to our knowledge. We would argue that the similarity in responses between unrelated partners of patients and patients themselves demonstrates that the POMS is a valid tool to use when assessing the moods of others. Although the POMS is often used retrospectively, it is usually a concrete time frame (e.g. past week, past month). Our retrospective use of the POMS to a time before beginning treatment may not be as accurate as a more recent past time-point. However, we believe that perception of worsened mood (whether or not it is accurate) is a valid assessment, especially because we found a difference in reported mood change when comparing between ADT and non-ADT participants.

Recruiting partners proved more difficult, and the sample size was smaller than we would have liked. As pointed out recently by Dagan and Hagedoorn [40] and others cited by them, accruing couples in cancer research is particularly challenging. When mood is affected for patient or partner, often couples are at odds with each other and cannot agree to participate jointly in studies. Past research has found negative effects on patients' partners because of cancer and more specifically PCa [41–43]. Additionally, the partners we did recruit may also be a biased toward ones exceptionally concerned about the patients' health and on the internet on search for cancer-related information. Alternatively, they could be partners, who are having a more difficult time with the effects of PCa treatment on their partners and seeking online support for themselves.

Last, some older participants may not have felt comfortable using computers or completing online studies and we may have received a higher response rate if we had circulated the study in paper form. Our sample would have a selection bias towards those who felt comfortable accessing the internet.

Summary

We have confirmed the negative relationship between ADT and mood of PCa patients. We have further demonstrated that partners of patients on ADT are cognizant of the changes in the patient's personality and rate them as severe, if not more severe, than the patients do themselves.

With these findings we can make the following recommendations for clinical practice: As an ethical issue around informed consent, patients should be made aware of the potentially negative psychological impact of ADT, particularly if they are younger (and sexually active). Second, because ADT affects both patients (directly) and partners (indirectly), prescribing physicians and

psychologists working with PCa patients have an ethical responsibility to inform not just the patients, but their partner, about how ADT might affect the patient's mood and personality. Last, in assessing the quality of life of patients on ADT, healthcare providers need to listen to

both the patients and the partners. The partners' observations of the impact of ADT upon patients' mood are potentially as pertinent and clinically relevant as the patients' own perception of treatment affect upon their mood and quality of life.

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