Psychological Effects of Androgen Deprivation Therapy on Men with Prostate Cancer and their Partners

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Keywords: prostate cancer, androgen deprivation therapy, sexual function, depression, cognition
Response to Reviewers

Reviewer 1

Comment 1: One weakness is the relative short shrift given to the treatment of more severe major depressive disorder with antidepressants on page 20. It is worth mentioning that not all antidepressants cause sexual dysfunction, e.g. mirtazapine and bupropion and to emphasize the importance of effective treatment for depression with SSRIs or other agents which may increase overall sexual function as psychological function improves.

Response 1: We have now revised the first paragraph of Interventions (page 20) to highlight the efficacy of pharmacologic therapy, specifically antidepressant therapy, in cases of more severe depression. We have also noted that not all antidepressants are associated with sexual dysfunction and that frequently, effective therapy may increase overall sexual function as psychological function and symptom control improve.

Comment 2: Some antidepressants e.g. venlafaxine have been used for the hot flashes associated with ADT.

Response 2: We have included text to this effect in the discussion of antidepressant therapy for depression (paragraph 1, page 20).

Comment 3: p.28 line 6 “ethnical” should be “ethical.”

Response 3: We apologize for the typographical error and have corrected the mistake.

Comment 4: The role of exercise should be restated in the conclusion as it is reflected in the abstract.

Response 4: As suggested, we have now stated in the Conclusions section (line 16 of the section) the role of exercise in mitigating the effects of ADT:

With respect to plausible interventions to mitigate the effects of ADT, physical exercise appears to have the greatest potential to address the psychological effects of ADT in both the man with PC and his partner.

Reviewer 2

Comment (General): This is a review of the impact of ADT on psychosexual function of men.

Response (General): We thank the reviewer for his thoughtful review. We also note that approximately one third of the manuscript entails a discussion of the various dimensions of sexual function as it relates to men on ADT. The remainder of the manuscript highlights the range of ADT-related adverse effects. Attention is specifically focused on mood-related effects and cognitive function. We hope the reviewer
agrees that this is a fairly comprehensive review of the psychological effects of ADT on men and their partners.

**Comment 1:** This is a narrative review. The methods by which the literature search was conducted are not described. The authors should use the PRISMA guidelines.

**Response 1:** While we appreciate the PRISMA guidelines, they are intended for systematic review and meta-analysis protocols. Our intent, indeed our charge, was to increase awareness of the psychological effects of ADT for prostate cancer on men and their partners via a clinically oriented narrative. We do not claim to have conducted an exhaustive literature search to support, for example, the development of clinical practice guidelines (i.e. one purpose of a systematic review), but believe our manuscript is both well-balanced and comprehensive.

**Comment 2:** Intermittent ADT is described as typically dosing with LHRH agonists for 24 months before a drug holiday. In general, the dosing period is shorter and some also use testosterone levels to trigger re-dosing. The cited study of Ng et al. also indicates a shorter dosing period of 9 months.

**Response 2:** We agree that intermittent ADT protocols are not standardized. Indeed, on-treatment intervals of 6, 8, 9, 18 and 24 months have been reported. We have revised the text on page 7 (paragraph 2) to reflect this. We also agree that re-dosing may be triggered by either PSA or testosterone levels, although the standard is PSA. We have revised the text on page 7 (paragraph 2) to reflect the use of testosterone to trigger re-dosing.

**Comment 3:** The discussion around the use of estradiol is one sided. It has been used in the past and abandoned because of high risk of VTE.

**Response 3:** Langley and Abel in the United Kingdom have shown that the thromboembolic risk with estrogens is specific to oral administration and the first pass of ingested chemicals through the liver, where clotting factors are up-regulated. The problem does not occur with transdermal application. Nevertheless, we have included text relevant to the discussion in paragraph 1, page 28.

*Estrogen taken orally increases the risk of thromboembolic events and gynecomastia. However, the risk of thromboembolic events from estrogen is greatly reduced with parenteral administration.*
Psychological Effects of Androgen Deprivation Therapy
on Men with Prostate Cancer and their Partners

Running Title: Psychological Effects of ADT

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Abstract

The clinical benefits of androgen deprivation therapy (ADT) for men with prostate cancer (PC) have been well-documented and include living free of symptoms of metastases for longer periods and improved quality of life. However, ADT comes with a host of its own serious side effects. There is considerable evidence of the adverse cardiovascular, metabolic and musculoskeletal effects of ADT. Far less has been written about the psychological effects of ADT. This review highlights several adverse psychological effects of ADT. We provide evidence for the effect of ADT on men’s sexual function, his partner and their sexual relationship. We also present evidence of increased emotional lability and depressed mood in men on ADT and comment on the risk of depression in the patient’s partner. The evidence for adverse cognitive effects with ADT is still emerging but suggests that ADT is associated with impairment in multiple cognitive domains. Finally, we review the available literature on interventions to mitigate the psychological effects of ADT. Across the array of adverse effects, physical exercise appears to have the greatest potential to address the psychological effects of ADT, in both men on ADT and their partner.

Key words: prostate cancer, androgen deprivation therapy, sexual function, depression, cognition
Condensed Abstract

The clinical benefits of androgen deprivation therapy (ADT) for men with prostate cancer (PC) have been well-documented and include living free of symptoms of metastases for longer periods and improved quality of life. This review highlights the adverse psychological effects of ADT on men with prostate cancer and their partners and makes recommendations for the management of those effects.
Conflict of Interest Disclosures: The authors have no conflicts to disclose.
Introduction

Androgen deprivation therapy (ADT) in the form of surgical or more commonly, medical, castration is the most common form of treatment for metastatic prostate cancer (PC).\textsuperscript{1-3} The clinical benefits of ADT for men with metastatic disease have been well documented and include living free of symptoms of metastases for longer periods and improved quality of life.\textsuperscript{3, 4} ADT use has increased over time based on clinical trial evidence of improved outcomes. This is especially the case for high-risk localized PC treated with radiotherapy and for lymph node-positive PC treated with radical prostatectomy.\textsuperscript{1, 5, 6} In industrialized nations, 50\% of men with PC can anticipate being prescribed ADT at some point in the course of their disease.\textsuperscript{2} In North America, ADT is currently prescribed to more than 600,000 men with PC.\textsuperscript{7} Furthermore, men are being exposed to ADT for longer periods of time; as many as five to ten years compared to a median duration of two to five years for patients with metastatic disease.\textsuperscript{8}

The goal of ADT in men with PC is to reduce levels of androgens, the hormones responsible for stimulating PC cells to grow. The principal androgen, testosterone, plays a significant role in male morphology and is the primary determinant of men’s sexual behavior, most notably their instinctual sex drive. Testosterone also has been described as a social hormone.\textsuperscript{9} Thus, testosterone not only regulates men’s desire for sex, but also their tendency toward competiveness, dominance, reactive aggression and stoic emotional presentation.\textsuperscript{10-12} Descriptive studies of men with PC report that many men feel less energetic and less decisive while also feeling more emotionally responsive while on ADT.\textsuperscript{13-15}
Although ADT is not considered curative, it effectively enables many men with PC to live for years without the symptoms of metastatic disease. The relative 10-year survival rate for PC at any stage is 99%. However, castrate levels of testosterone and the secondary loss of estrogen, which is normally derived from testosterone in men, are associated with a number of significant physical and psychological adverse effects. These include increased risk of cardiovascular disease, increased insulin resistance and incident diabetes, osteoporosis and fractures, anemia, fatigue, sarcopenic obesity, kidney disease, sexual dysfunction, breast growth, hot flashes and affective and cognitive symptoms. The incidence and severity of these effects depend largely on the duration of therapy yet each is known to adversely affect men’s health and quality of life. To date, a considerable literature exists regarding management of the adverse cardiovascular, metabolic and musculoskeletal effects of ADT in PC (see, for example, Isbarn et al., Smith, Grossman and Zajac). This is, however, much less the case for the psychological effects of ADT. The purpose of this review is to present evidence of the psychological effects of ADT on men with PC and their partners, and to make recommendations for the management of these effects.

**Sexual Function**

ADT has been shown to adversely affect men’s self-image, sexual desire, erectile function, ability to become aroused, and ability to achieve orgasm, all of which may hinder a man’s sexual function and disrupt sexual relations. Some contexts for the use and administration of ADT are likely to affect sexual function more than others. For example, short-term administration of ADT, in the context of adjuvant external beam radiation therapy, may only temporarily affect a man’s sexual function. Men may receive
adjuvant ADT in the form of luteinizing-hormone-releasing hormone (LHRH) agonists for as little as six months, though high-risk patients may be placed on an adjuvant LHRH agonist for up to three years. Typically, the longer the duration of ADT, the more adverse effects they may be.\textsuperscript{21} Patients undergoing short-term ADT are not spared sexual dysfunction; sexual function has been found to be adversely affected as early as two months after initiating ADT.\textsuperscript{22} While sexual function was observed to be similar between men treated with combined ADT and EBRT versus those treated with ADT alone, worse sexual bother was observed in the combined treatment group. Fortunately, the shorter the duration of ADT, the more likely it is that testosterone levels will recover with time.\textsuperscript{23}

There is some evidence to support intermittent administration of ADT over continuous administration of ADT when possible, in helping to alleviate adverse effects, in particular, libido.\textsuperscript{24} In this context, patients are administered an LHRH agonist for a specific period of time (the duration of this “on-treatment” period varies\textsuperscript{25, 26}) and then are given a drug holiday (the “off-treatment” period). During the off-treatment period, androgen titer in the body start to recover. For about 70\% of men, recovery of testosterone to 10 ng/ml occurs by 24 months (median = 10.4 months) off ADT.\textsuperscript{13} When the prostate specific antigen reaches a threshold level (testosterone level also may be monitored), the LHRH agonist is reinstated. It is worth noting that the longer the “on-treatment” period, the longer the “off-treatment” period needed for sexual recovery.\textsuperscript{13, 24}

\textsuperscript{\text{-}} For example, Ng et al.\textsuperscript{13} reported that 46\% of men on ADT for PC were sexually active at the time ADT was initiated. The proportion of sexually active men declined to 24\% after nine months on ADT. After nine months, ADT was halted and half of the men who were sexually active at the time ADT was initiated resumed sexual activity by 12 months.
off-treatment. Finally, some patients may be treated with anti-androgen monotherapy (via administration of non-steroidal anti-androgen, without LHRH agonists). In these patients, smaller declines in sexual desire and function are observed. ADT is commonly used in the context of biochemical failure (i.e. rising prostate specific antigen after primary curative treatment) or locally advanced disease. Men who have already undergone radical prostatectomy or radiation therapy are likely experiencing some degree of erectile dysfunction (ED) prior to starting on ADT. Androgen suppression with ADT further impairs erectile function. Thus, the effect of ADT on men’s sexual function may be additive, based on the patient’s treatment history.

The proportion of men on ADT who remain sexually active is relatively small. Between 73% and 95% of men on ADT report ED. Rates of cessation of sexual activity are higher and range from 80% to 93%. Capturing accurate rates of cessation of sexual activity is challenging. Standard measures used to assess this factor are actually measures that assess erectile function and frequency of penetrative intercourse rather than the broader “sexual activity.” Consequently, these measures miss non-penetrative sexual activity and may underestimate the number of men who are sexually active in ways other than penetrative sex. Between 58% and 94% of men on ADT report a loss of sexual desire. Some men report reduced sensitivity of skin to physical touch, or changes in the kinds of touch that induce arousal. Though prevalence rates are unavailable, many men experience difficulty in becoming sufficiently aroused during sexual activity, such that anorgasmia, or difficulty achieving orgasm, is also common. For patients who have not already experienced a loss of ejaculate due to radical prostatectomy, ejaculatory
volume diminishes with time until orgasms become dry entirely, the impact of which is particularly profound in the gay community.  

In the literature, what is becoming increasingly clear is that a loss of sexual desire does not equate to a loss of interest in maintaining a sexual relationship. There have been many documented ‘motivators’ for engaging in sexual activity, beyond spontaneous sexual desire. For many couples adapting to ADT, maintaining a sexual relationship is an important conduit of closeness and connection, and helps the couple stave off a shift to a platonic relationship wherein the partners feel more like roommates, a feeling which may accompany a loss of intimacy in the relationship overall. Still, the loss of sexual desire is perhaps the biggest barrier to maintaining sexual activity. Men with the best of intentions to remain sexually active for the benefit of their partner, struggle to remember to initiate sexual activity when they are no longer cued by spontaneous sexual urges. 

For the clinician, there is a delicate balance between offering hope to couples that sex is still possible while on ADT, and helping them anticipate what challenges they will face should they choose to continue to remain sexually active. In contrast, well-meaning healthcare professionals wishing to prepare a couple may tell their patients that their sex lives are over. This view is consistent with the relatively nihilistic representation of androgen-deprived men’s sexual capacity presented in a recent paper by Mazolla and Mulhall. In the traditional sense, penetrative intercourse may be particularly challenging to maintain, but consistent with the growing opinion on sexual recovery after PC, healthcare professionals should encourage patients on ADT to think more flexibly about the kinds of activities they include in their sexual repertoire. Unfortunately, many
patients who are told that maintaining sexual activity while on ADT is impossible, go on to fulfill this prophecy and stop being sexual. These patients (and their partners) may have benefited from modifying and/or redefining their sexual practices to maintain satisfying sexual activity.\textsuperscript{39}

Sexuality is greatly influenced by contextual factors, including how a person feels about him or herself, as well as what is occurring in the context of the relationship. For many men, the male body is a strong source of their perceived masculinity and bodily changes may adversely affect men’s sexuality.\textsuperscript{15} Indeed, in a recent study, 60\% of men on ADT had negative changes in body image.\textsuperscript{32} Given the bodily feminization that can occur, including hot flashes, breast growth, loss of lean muscles mass, genital shrinkage and weight gain around hips,\textsuperscript{43} men on ADT commonly report experiencing a loss of masculinity.\textsuperscript{15}

Given that these studies document ‘changes in perceived masculinity” but have rarely defined or objectively measured masculinity, it is challenging to draw conclusions about the nature of these changes. Still, men continue to report a change in the way they see themselves as having experienced a “loss of masculinity” in their own right. In one study, after only 3 months on ADT, 50\% of men reported feeling less masculine, compared to 26\% at baseline.\textsuperscript{13} Furthermore, the sense of loss in some aspects of masculinity has been shown to increase as time on ADT increases. In a longitudinal study, this perceived emasculation increased continuously over the course of 36 months (most drastically increasing between 24 and 36 months) and did not show signs of leveling off.\textsuperscript{44}
A patient’s sense of his masculinity may be impacted in different ways by ADT. Some patients may conceptualize their masculinity in a more physical sense and therefore may be more affected by changes such as bodily feminization, infertility, or loss of muscle mass. For other men, masculinity may be more impacted by social factors including changes in relationships and roles, or psychological factors including changes in body image, loss of sexual function, and emotional lability.

It is important to note that there may be other potential explanations for changes in a man’s sense of his own masculinity while on ADT. The same study documented an increase in loss of masculinity over time also demonstrated that depressive and anxious symptomatology were predictive of lower perceived masculinity. As well, lowered sexual desire may be symptomatic of depression and depression is also strongly associated with ED. Pharmacologic therapies for depression, such as the use of selective serotonin re-uptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) may also negatively affect sexual function. To the extent that the erosion of a man’s sense of his manhood may strain his intimate relationship, this can affect a couple’s ability and motivation to engage in sexual activity.

Effect on Partners

Many couples adjusting to ADT have already had to deal with the effects of the cancer diagnosis and primary treatments administered with curative intent. For example, in many relationships there is a shift in roles at diagnosis away from husband and wife toward patient and caregiver roles during treatment. However, given the wide ranging effects of ADT, it is not surprising that ADT can transform intimate relationships in some unique ways. Navon and Morag were the first to draw attention to the fact ADT,
because it reduces sexual desire and erectile function, may erode the spousal relationship and make the relationship more platonic in nature. Indeed, maintaining intimacy has been documented as the most difficult challenge of ADT.

It has been well-documented that female partners of men with PC may be more distressed (e.g. worry, depression, anxiety, experiencing cancer-related intrusive thoughts) than the men with PC. Predictors of greater distress in the female partners include: 1) greater patient distress, 2) less support from their partner who is the patient, 3) lower marital quality, 4) low levels of positive reappraisal coping, 5) searching for, but not finding, meaning in the illness experience, and 6) uncertainty about the patient’s health. Some have suggested the greater distress may have more to do with the partners being female than their being partners. This is because research on couples coping with cancer has found that females are more distressed than males regardless of whether they are the patient or partner. Kornblith et al., have suggested female partners are more distressed than patients because of a “discordance in communication” between partners. Specifically, the female partner may feel a need to discuss disease-related feelings and concerns, whereas the patient may wish to minimize the effects of his disease and has minimal desire to openly discuss the changes he is experiencing. Other research about couples coping with illness indicates that both partners may suppress emotions, worries and concerns to protect the other. Given the difficulties couples have in effectively communicating about cancer, there is little wonder that open communication is associated with better partner adjustment. In fact, improving communication between patients and their partners is an element of intervention shown to be effective in improving female partners’ mental health.
Finally, there are mixed findings about how significantly partners of men on ADT are affected by the loss of their sexual relationship. Some reports indicate men believe their partners are unaffected by the loss of sexuality.\textsuperscript{56} In support of this are partners who explain they can forego sexual activity because they feel it is a small price to pay for the patient’s potentially life-extending treatment. That said, some partners attempt to accept the loss of their sexual relationship, only to discover over time that the loss is more significant than they had anticipated.\textsuperscript{39} In fact, one of the most significant predictors of quality of life for partners after PC treatment is the quality of their sexual relationship.\textsuperscript{59} Little has been written about the partners of gay men with PC, even less on gay men treated with ADT. One qualitative study of gay patients not treated with ADT showed strains and changes in the romantic relationship for gay men when dealing with the side effects of the disease.\textsuperscript{60} Although findings are mixed about the degree to which partners are affected by the loss of the sexual relationship, partners suffer most when this loss leads to emotional withdrawal and loss of affection. In short, partners appear to adjust more easily to the loss of the sexual relationship, than to feeling abandoned.\textsuperscript{40}

\textit{Interventions}

Recent studies of sexual bother in men on ADT for advanced PC, found that contrary to expectations, greater sexual bother was significantly associated with greater marital satisfaction (as well as with younger age and shorter duration of ADT).\textsuperscript{61,62} This suggests that couples bothered by ADT-related changes in sexual function, who are in accord about the problem, can work together to address these changes and this, in turn, may increase marital satisfaction. This was borne out in a recent intervention trial in which couples who participated in an educational intervention to help couples adjust to
changes associated with ADT, showed less declines in intimacy and dyadic adjustment than those couples in the control group. A similar intervention, founded on the book: Androgen Deprivation Therapy: An essential guide for men with prostate cancer and their loved ones, contains a self-directed program to help patients manage all side effects associated with ADT, not just sexual changes. This unique psycho-educational program is currently being disseminated nationally in Canada. To date, this program is the only PC-related intervention targeted specifically at couples dealing with ADT. Even if couples elect not to maintain a sexual relationship, they should be counseled about ways to maintain good relational intimacy. Efforts to prevent emotional withdrawal and cessation of general affection are likely to help couples remain intimately connected, even if sexual activity ceases. Strategies that incorporate couple-based coping in PC are promising and indicate that a similar approach would be valuable in the ADT population.

For men on ADT interested in finding treatments to restore erectile function, recommending typical first line treatments such as phosphodiesterase inhibitors (PDE5is) are likely insufficient. These medications are often ineffective, especially if there is nerve damage from primary treatments such as radical prostatectomy or radiation therapy. As such, men on ADT may have better success starting with intracavernous injections, rather than with PDE5is. Patients must also understand that erectile aids, such as PDE5is, intracavernous injections, and vacuum erection devices, have no direct effect on libido. Patients should be coached not to wait for spontaneous sexual desire to initiate sexual activity, and taught that sexual stimulation is needed to facilitate arousal. Those couples that persist in sexual activity will likely have to make a conscious choice to engage in sex.
as men can no longer rely on a physiological urge to motivate them to be sexual.

Although there is some evidence for the use of parental estrogen as a treatment for libido preservation,^{43, 67} further studies are needed. If erectile aids are not pursued, men should be encouraged to maintain a variety of sexual activities that are not dependent on erections.^{42} Couples who are motivated to maintain a sexual relationship may benefit from learning what other couples have done to promote recovery; to this end, more detail about couples’ struggles and recovery strategies used can be found in Walker and Robinson.^{34}

There is increasing support for the role of exercise in promoting sexual activity maintenance. A recent study of men on ADT found that men engaging in a group-based exercise protocol exhibited higher rates of sexual activity.^{68} Another study by Ng et al.,^{69} demonstrated that men on ADT with greater quadricep strength were also more likely to maintain sexual activity. Thus, the same efforts to preserve lean muscle mass may also promote sexuality. Hamilton et al.^{68} have published qualitative data suggesting that exercise also may help to mitigate men’s perceived loss of masculinity associated with ADT.

**Emotional Lability**

Exaggerated changes in mood, or emotional lability, have been reported by men on ADT for PC.^{18} This lability may be manifested differently, with some men reporting becoming more sensitive or sentimental while others may find they are more irritable and angry.^{14, 33, 70, 71} The most marked change for some men is to become more spontaneously tearful,^{14} particularly in situations where previously they would not. Some men find this confusing and difficult to understand; others may be embarrassed by their increased
tearfulness. This conspicuous increase in emotional expression may affect patients’ interpersonal interactions depending on whether they perceive this as “unmanly” or shameful, in contrast to being indicative of heightened empathy and an improved sensitivity to others. Ultimately, how men perceive this increase in emotionality and whether they accept it or not, may influence how well they adapt to ADT specifically and to PC generally.14, 15, 72, 73

Depression

Testosterone levels decline naturally with age, and low testosterone has been associated with depression in middle-age and older men who are not cancer patients.74, 75 The fact that this depression seems to remit when these non-cancer patients are initiated on testosterone replacement therapy76, 77 suggests that depression in men on ADT may be the direct result of androgen deprivation.78 Similarly, depression may persist in men who have been on ADT because of persistently low testosterone levels even after ADT treatment ends. Indeed, in many men, post-ADT levels of testosterone do not return to pre-ADT levels for a very long time, if at all.70, 79-81

Rates of depressive symptoms and/or diagnosable depression in men with PC have been described as relatively high, with estimates ranging from 8% to 25% and rates of depression in men on ADT even higher.82-85 In spite of the well-known association between depression and diminished quality of life in cancer, including PC,86 there is a paucity of research examining the relationship between ADT and depression in PC patients. This is particularly troubling when studies have demonstrated the significance of depression and the risk of suicide in PC.87 Relevant to this, in one of the larger studies published to date, DiBlasio et al.88 conducted a retrospective review of nearly 400 PC
patients receiving ADT over several years. Included in the review were men with pre-
ADT psychiatric illnesses, including depression, \textit{de novo} psychiatric illness and no
psychiatric illness. At mean follow up of 87 months, 28% of men were diagnosed with \textit{de
novo} psychiatric illness, most commonly depression. This was a three-fold increase from
a pre-ADT rate of 8.6%. Results also suggested that receipt of primary ADT and the
duration of ADT may be factors contributing to the development of \textit{de novo} psychiatry
illness. Although limited by its retrospective design, the findings of the DiBlasio et al.
study are intriguing and strongly support the need for well-designed, large scale
prospective studies of depressive symptomatology in men on ADT.

Although relatively few in number, there are as many studies with findings that do
not support a link between ADT and depression as there are studies that do.\textsuperscript{89} This
ambiguity may stem in part from methodological shortcomings that limit the
interpretation of findings and generalizability of results.\textsuperscript{89, 90} The majority of studies, for
example, have been cross-sectional or retrospective, not prospective, in design. Most
studies have utilized self-report measures of depressive symptoms rather than the gold
standard diagnostic interview for depression. Further, few have assessed history of
depression, a known risk factor for subsequent depression, both in the general population
and among PC patients, including those on ADT.\textsuperscript{82, 84, 85} Most studies have not included a
control group. Among those that have, the choice of an appropriate control group may be
debated. Finally, studies have been characterized by small sample sizes with limited
statistical power to detect between group differences.

Most recently, in an effort to address many of these methodological limitations,
Lee et al.\textsuperscript{78} used a longitudinal design with a sample of PC patients receiving ADT to
assess the effects of ADT on depression. Two control groups were included: men treated for PC with radical prostatectomy and men from the general population. Both of those groups were matched with the men on ADT by age and education. The radical prostatectomy patients were also matched on time since diagnosis within six months. In men on ADT, the rate of clinically significant depressive symptoms, measured by the Center for Epidemiologic Studies-Depression scale (CES-D) increased significantly (and their testosterone levels dropped dramatically from the beginning of ADT treatment to six months later). There was no increase in symptomatology in either of the control groups over time. At the six-month follow-up, rates of clinically significant depressive symptoms were significantly higher in men on ADT compared to the radical prostatectomy control group and the non-cancer control group (39% versus 9% versus 11%). The study utilized a self-report assessment of depressive symptoms, not a diagnostic interview, but the CES-D contains fewer somatic symptoms of depressive and thus, may be less likely to reflect the effects of cancer and cancer treatment. The six-month follow-up was too short to reveal long-term effects of ADT although the study’s short timeframe was not dissimilar to the timeframe of the majority of studies to date. Despite these limitations, findings affirm the relationship between ADT and depression.

It is possible that factors other than ADT actually account for the depressive symptoms documented in the study by Lee et al. Depression in men on ADT may be secondary to uncontrolled pain or fatigue or may be the result of functional impairments such as sexual dysfunction or urinary incontinence after radical prostatectomy. This depression may reflect a composite of the physical and emotional toll of a cancer diagnosis that combine with reduced testosterone to induce depression. Finally, a
cascade pattern of symptoms may link ADT to depression. For examples, hot flashes resulting from ADT may exacerbate sleep problems and may lead to insomnia,\textsuperscript{92} which then leads to depression. Similarly, weight gain, gynecomastia and breast tenderness, loss of body hair, hot flashes and/or genital shrinkage may lead to strongly negative perceptions of body image,\textsuperscript{18} thus increasing the risk of depressive symptoms in men on ADT.

\textit{Effect on Partners}

Many of the risk factors associated with depression in men on ADT are consistent with the risk factors associated with depression in men with PC in general.\textsuperscript{90} Thus, we know that being married or living in a marriage-like relationship reduces the risk of depression\textsuperscript{50, 54, 91, 93} and that depression impairs relationships.\textsuperscript{90} Often, a partner becomes aware of the patient’s depressive symptomatology before the patient is aware. This awareness may either facilitate early intervention or create conflict within the couple when there is disagreement about the severity of the symptoms or how to cope with them.\textsuperscript{94} Effective couple and self-management strategies are therefore crucial to overcoming the effects of depression on men and their families.\textsuperscript{95, 96} We also know that in PC, as in other cancers, the female partners’ risk for depression is as high as or higher than the male patients’ risk.\textsuperscript{51, 84, 97, 98} More research is needed about the impact on same-sex couples. Although some might argue the psychological well-being of the partner is outside the scope of standard oncologic practice, recent research suggests that ignoring the impact of ADT on the partner and the relationship may adversely affect the physical and psychological health and well-being of the patient himself.\textsuperscript{99, 100}

\textit{Interventions}
The complex relationship between depression and ADT for PC remains to be fully elucidated. Nevertheless, men (and their partners) should be informed of the possibility of ADT-related emotional lability and depression. They should be encouraged to report any symptoms that arise and advised of the interventions available to mitigate these effects. In many men on ADT, symptoms of depression often are severe enough to warrant clinical intervention. Thus, it is reasonable to screen all men on ADT for depression and, if they screen positive, to more fully assess and intervene accordingly. Antidepressant medications and psychotherapy, especially cognitive behavior therapy, are widely accepted treatments for depression in the general population and in cancer populations. As such, they are likely to be efficacious for men on ADT. Antidepressant medications are most effective for patients with more severe depression, while psychotherapy, cognitive behavior therapy in particular, has been found to be effective across the spectrum from milder to moderately severe depression. Currently, there are no evidence-based recommendations regarding the superiority of any antidepressant over another in cancer patients (or in other populations). The choice of which antidepressant medication to prescribe requires the clinician to consider a number of factors, including the current symptom profile, medical comorbidities, potential drug interactions and the potential side effect profile of the medication. As previously noted, SSRIs and SNRIs may negatively affect sexual function but certain of these (venlafaxine, for example) are also effective in reducing hot flashes. Certain antidepressants, mirtazapine and bupropion, specifically, are not typically associated with sexual dysfunction and bupropion in particular may have positive sexual effects. In any case, the effective treatment of depression with SSRIs, SNRIs or other agents may actually increase overall
sexual function and/or sexual desire as psychological function and symptom control improve. This may be especially true when depression arises along with pain, fatigue and sleep disturbance, from the disease and its treatment. To date, psychosocial interventions for men with PC (and their partners) are relatively few. A recent Cochrane review identified 19 studies comparing psychosocial interventions versus usual care in more than 3,200 PC patients. The interventions included cognitive behavioral, psycho-educational and supportive therapies. Six of 19 studies included depression as an outcome. Across studies, there were no significant differences in self-reported depressive symptomatology between the intervention groups and usual care at any of the time points observed. Notably, the specific effect of the psychosocial interventions on depression in men on ADT was not examined as there were no data regarding treatment with ADT that could be extracted from the studies.

Developing interventions to mitigate the psychological as well as physical effects of ADT is crucial to improving the health and well-being of men on ADT for PC. To this end, a recent cross-sectional study found that in men on ADT for PC, greater adherence to national exercise guidelines was associated with lower levels of depression and better quality of life. More recently, a systematic review of exercise interventions in men on ADT for PC found that supervised or unsupervised structured exercise interventions improved the quality of life of men on ADT. Only one study examined the benefits of exercise for depression per se. Culos-Reed et al. conducted a randomized controlled trial of a 16 week unsupervised exercise program consisting of three to five times weekly exercise program with moderate intensity compared to a once weekly 90 minute group session. Depression scores on the CES-D decreased in the intervention group and
increased in the control group over time but the changes from baseline were not statistically significant. This null finding, combined with several identified limitations of the evidence base to date, suggests more research is necessary to establish the most effective exercise program for reducing depression in men on ADT.

**Cognition**

Many neural centers in the brain have both androgen and estrogen receptors that are involved in information storage and learning (e.g., the hippocampus), as well as the consolidation of memory (e.g., the amygdala). From a neuroendocrinological perspective then, ADT may impair memory and other cognitive processes in PC patients simply because it suppresses the ligands that bind to those receptors. Indeed, men on ADT commonly complain about lapses in memory and declines in their problem-solving skills. Other cognitive complaints include changes in verbal memory, spatial memory and visuospatial processing.

In the last two decades, several reviews have refined our understanding of the impact of ADT on various domains of cognition. The domains explored to date include working memory, attention, executive function, language, verbal memory, visual memory, visuomotor ability and visuospatial ability. While some studies support the adverse effect of ADT on various cognitive domains, others have failed to document any cognitive effects of ADT. Others have reported mixed results across a wide range of domains and some have even suggested improvement in at least one domain. Consider, for example, the effects of ADT on verbal memory. In the earliest studies, ADT was reported to adversely affect this domain and that result has been
widely cited by clinicians.\textsuperscript{114,115} However, larger and more recent studies failed to find evidence that ADT is associated with impairment in verbal memory.\textsuperscript{118,122}

The diversity in cognitive domains that have been reported to be affected (or not) by ADT may be a function of methodological differences in the studies. These include differences in study designs (whether a control group is included and the nature of this control group, for example), learning and practice effects in patients who serve as their own controls, sample sizes and the assessment procedures utilized. The diversity in findings also may reflect differences in the age, education, health status, and baseline cognitive abilities of participants.\textsuperscript{116,125} Nevertheless, a review by Nelson et al.\textsuperscript{116} estimated that between 47\% and 69\% of men on ADT experience some degree of impairment in at least one cognitive domain.

To date, the best controlled studies point to negative effects of ADT on verbal and spatial memory. These effects makes intuitive sense in that spatial processing is known from many studies in other populations to be sensitive to gonadal hormone titers.\textsuperscript{117,126} Furthermore, a few recent, small pilot studies using fMRI, endorse the conclusions drawn from the most recent reviews. The first, by Cherrier et al.,\textsuperscript{127} presents preliminary data that ADT reduces activity in the right parietal-occipital region of the brain, a region associated with spatial representation of objects and mental rotation. The other fMRI studies, by Chao et al.\textsuperscript{126,128} report changes in the frontal and prefrontal cortical areas, which are known to be active in cognitive control and executive functioning. Those authors point out that ADT "may have a deleterious impact on cerebral structures and functions that are not evident using traditional behavioral tests," such as the assessment instruments used in any number of descriptive neurocognitive studies.
One of the most compelling arguments to date for adverse cognitive effects of ADT derives from a recent and fairly definitive meta-analysis by McGinty et al. The authors included 14 studies that recruited 417 patients treated with ADT and concluded that the strongest demonstrable cognitive effect is on visuospatial tasks involving coordinated visual perception and motor skills (i.e., visuomotor ability). That finding is perhaps not surprising in that the sex differences in visuospatial processing, as assessed by tests of mental rotation (i.e., manipulating an image of an object in one’s mind), consistently show a large effect size (Cohen’s $d = .57$). Visuospatial ability is also a cognitive domain where testosterone titers in males have been linked directly to performance superiority. Notably, the findings in this recent meta-analysis are consistent with the review by Jamadar et al. and the results of Cherrier et al. fMRI study. In general, however, it is premature to conclude that visuospatial processing is the only area where ADT impairs cognitive function. There may well be other cognitive domains, such as verbal memory and executive function, which involve cortical areas that are adversely affected by androgen-deprivation. In one of the more recent studies to date, Yang et al. found ADT negatively affected attention, memory and information processing. These results, combined with existing studies, suggest defects in verbal memory and executive function. Interestingly, Yang et al. point out that performance in these cognitive domains, as they assessed them, correlate with neural activity in the prefrontal areas that Chao et al. found altered by ADT. As McGinty et al. point out, however, the effect sizes for studies of cognitive domains outside of visuospatial processing are small (all $d < 0.22$). The fact is there simply have not been investigations
with large enough samples and with rigorous enough study designs to rule out
impairment in other cognitive domains.

**A Yet to be Investigated Cognitive Domain**

An area that particularly warrants investigation is the impact of ADT on social
signaling, awareness, sensitivity, and attention. Testosterone, as noted above, is first and
foremost a social hormone (and we are an obligatory social species). How individuals
“read” and react to each other in general—i.e., their tendency toward empathy, egotism,
competition, cooperation, dominance, fair play, team play, etc.—are known to be
influenced by testosterone and thus these social abilities and interactions
typically show measurable sexual differences. All of these aspects of neuro-
processing and behavior fall under the broad area of “social cognition.” Although there
are a variety of assessment instruments that measure aspects of social cognition, we
know of no studies that have used them to advance our understanding of ADT’s impact
on men with PC. One notes, however, that social cognition involves (among other neural
centers) the cortical areas that the Chao et al. fMRI studies identified as being
affected by ADT. The absence of research on this cognitive domain is somewhat
surprising given the burden that ADT often places on partners of men with PC. Often,
changes in social cognition for patients materialize as changes in sociality that others
must deal with. A better understanding of ADT’s effect on social cognition might raise
awareness for the need to assist men with PC and their partners in adapting to the effects
of ADT on their lives as a couple.

**Interventions**
There is little doubt that ADT can affect some cognitive processes in a subset of men with PC, but the effect sizes are small and the cognitive domains are not fully defined. As such, it is premature to promote interventions to ameliorate the adverse effects of ADT on cognition in men with PC. There are, however, efforts underway to develop cognitive rehabilitation programs for cancer patients in general and these efforts are likely to inform efforts specific to ADT-related cognitive concerns. In the meantime, PC patients may be able to modify their lifestyles in advance of starting on ADT to limit subsequent problems in their lives by taking a prehabilitative or preventative approach. Consistent with the research to date, PC patients anecdotally often comment on the problems they have with tasks requiring good visuospatial memory and visuomotor ability. Skills in these areas are what we all use to order and organize objects in time and space. Thus, men starting ADT might be able to avoid future problems by pre-emptively reducing clutter in their living space. They might be able to mitigate some of the cognitive effects of ADT by thoroughly organizing their desks, closets, draws, and storage areas before ADT side effects emerge.

The positive physical, psychological and social benefits of physical exercise and the relationship of these to improved quality of life for persons with a variety of health conditions, including men on ADT for PC, have been well-documented. Whether a prehabilitative exercise program for men on ADT for PC has benefits for cognitive function remains to be determined. Nevertheless, exercise has long been endorsed as a means of alleviating a number of ADT side effects, including sarcopenic obesity and depression. Further, taking a prehabilitative approach may be
especially beneficial, as it may be particularly challenging to initiate an exercise program once any of the more common physiological side effects of ADT set in.

Another intervention with potentially positive effect is computerized cognitive training (CCT). In a recent meta-analysis of 52 studies of CCT encompassing 4,885 older adult participants without dementia or other cognitive impairments (and not on ADT), Lampit et al.\textsuperscript{156} reported statistically positive effects of CCT on verbal, non-verbal, and working memory. Although the effect sizes were small (Hedge’s g < 0.22), the benefits of CCT were greatest in processing speed and visuospatial skills (Hedge’s g = 0.031 and 0.30, respectively). As noted above, visuospatial skills is the cognitive domain wherein McGinty et al.’s recent meta-analysis\textsuperscript{129} found the strongest evidence for ADT-related cognitive impairment. This suggests CCT may have considerable potential as an intervention for men with ADT-related cognitive concerns. Lampit et al.\textsuperscript{156} also found that at-home, unsupervised CCT programs were not effective, suggesting that community- or hospital-based CCT may have the greatest potential for helping men maintain mental acuity while on ADT. Lampit et al.\textsuperscript{156} further suggested combining CCT with interventions such as physical exercise and memory strategy training to enhance executive functions\textsuperscript{148} and verbal memory, respectively.\textsuperscript{150}

Finally, researchers have suggested that the cognitive problems associated with ADT may be due to the lack of estradiol (E2), a metabolic product of testosterone, and not the lack of testosterone itself.\textsuperscript{110, 134, 157} Estrogen is well known for alleviating menopausal symptoms in women, and some have suggested that it may do the same for androgen-deprived men.\textsuperscript{67, 154, 158, 159} As we noted above, many neural centers in the brain, including those critical to cognitive processes, have estrogen receptors\textsuperscript{160-162} This
suggests that supplemental E2 may be of some benefit for men on ADT.\textsuperscript{110, 163, 164} Estrogen taken orally increases the risk of thromboembolic events and gynecomastia.\textsuperscript{67, 165} However, the risk of thromboembolic events from estrogen is greatly reduced with parenteral administration.\textsuperscript{166–168} E2 also promotes cancer cell growth in certain castrate-resistant, PC cell lines\textsuperscript{169–171} so it should not be recommended for patients with advanced PC. To date, there is evidence that E2 can help maintain bone mineral density, reduce hot flashes, and, as previously noted, help preserve libido above castrate levels in androgen-deprived males.\textsuperscript{67, 154, 158, 172} It remains to be determined whether E2 may mitigate the effects of ADT on cognition in men with PC.\textsuperscript{111, 119}

**Conclusions**

ADT is the most common form of treatment for metastatic and locally advanced PC. Although ADT is not curative, it effectively enables many men with PC to live for many years without the symptoms of metastatic disease. In addition to multiple adverse physical effects, ADT is associated with adverse psychological effects. These effects include difficulties in multiple sexual domains, emotional lability, depression and cognitive impairment. The strongest evidence exists for ADT’s effect on men’s sexual function and the sexual relationship. Less is known about the nature of the emotional or cognitive changes associated with ADT, but evidence increasingly suggests ADT-associated impairments in multiple cognitive domains and though causal mechanisms for depression are debatable, men on ADT are at increased risk of depression. Partners may also be negatively affected by ADT-related effects. The clinical implications of ADT’s adverse psychological effects include the ethical responsibility of clinicians who prescribe ADT to obtain informed consent from their patients. Knowledge of how ADT...
affects a man psychologically as well as physically may aid patients in making treatment decisions with their partners. Clinicians should monitor men on ADT for erectile dysfunction and counsel them regarding reduced libido. Men should also be monitored for significant depressive symptoms and cognitive decline. Clinicians should screen for these effects and offer treatment recommendations or make referrals as appropriate. With respect to plausible interventions to mitigate the effects of ADT, physical exercise appears to have the greatest potential to address the psychological effects of ADT in both the man with PC and his partner. This review also highlights the need for additional research assessing the natural history of these effects using well-designed prospective studies. Developing interventions to mitigate the psychological as well as physical effects of ADT based on results of such studies is crucial to improving the health and well-being of men on ADT.
References


