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TESTOSTERONE THERAPY IN MEN WITH SEXUAL DYSFUNCTION: REVIEW

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Sexual Function in Men Undergoing Androgen Deprivation Therapy

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Abstract

With an increase in the use of androgen deprivation therapy (ADT) in men diagnosed with prostate cancer, there are several adverse effects that accompany its utilization. Among these, sexual dysfunction has contributed to significant deleterious effects on quality of life (QoL) and overall satisfaction. This has prompted clinicians to pursue modalities of ADT that may mitigate these adverse sexual effects, which include continuous versus intermittent ADT, changes in the duration of ADT, and novel methods of cyclical androgen exposure during treatment. Importantly, this must not come at the expense of oncological outcomes. In addition, some men treated with ADT experience persistent hypogonadism and side effects from these medications that linger well after treatment is completed. In this systematic review we discuss the pharmaceutical, mechanical, and psychological methods that play an important role in the mitigation of these sexual side effects, including erectile dysfunction and decreased libido, and their uses and benefits are further discussed. Ultimately, the benefits of ADT and the possible morbidity that these men may experience from use of ADT, as well as options to minimize their side effects need to be discussed with the patient and their partner to make an informed decision and ensure patient autonomy while providing the most up-to-date evidence. Given the prevalence of prostate cancer in the aging male population, this systematic review aims to further explain the different ADT regimens and options for men, as well as discuss the sexual side effects that accompany these treatments and ways in which to mitigate these side effects to improve patient QoL.

Keywords: androgen deprivation therapy; erectile dysfunction; prostate cancer; sexual dysfunction; urology

Introduction

With an estimated 181,000 new cases diagnosed each year, prostate cancer is one of the most common types of cancer in men in the United States.¹ It accounts for 24% of all new cancer diagnoses in

men, and on average one in nine North American men will be diagnosed with prostate cancer in their lifetime. Of those men, 10–20% will develop castration resistant prostate cancer within 5 years after diagnosis.²

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Prostate cancer is diagnosed and staged through physical examination, transrectal guided prostate biopsy, imaging of the prostate such as with MRI, and measuring prostate-specific antigen (PSA) levels. Although radical prostatectomy (RP) is considered the gold standard for patients diagnosed with localized prostate cancer, androgen deprivation therapy (ADT) (Table 1) and radiation are integral to the treatment of intermediate to advanced prostate cancer.¹ The American Urological Association (AUA) guidelines on ADT state that for intermediate- or high-risk disease, clinicians should recommend RP or radiotherapy plus ADT for 24–36 months as standard treatment.³ For nonmetastatic castration-resistant prostate cancer (CRPC), the AUA recommends continued androgen deprivation with observation, or treatment with first-generation antiandrogens (flutamide, bicalutamide, and nilutamide) or first-generation androgen synthesis inhibitors (ketoconazole with a steroid) to select patients with nonmetastatic CRPC.³

ADT is the use of medical or surgical therapy to reduce the levels of serum testosterone and dihydrotestosterone (DHT). Testosterone and DHT are essential for prostate cell survival and function, and prostate cancer cells tend to exhibit excess activation of the androgen signaling pathway.⁴ It was first discovered in 1941 by Dr. Huggins and Dr. Hodges when they found that androgen deprivation through castration was beneficial to men with advanced prostate cancer.⁵ Since then, ADT has become an essential tool, resulting in remission in 80–90% of men with advanced prostate cancer and increasing the median progression-free survival from 12 to 33 months in those patients.²

The goal of ADT is to reduce circulating levels of testosterone to “castrate level,” recently redefined

as <20 ng/dL although historically was <50 ng/dL.⁶ ADT today consists of different modalities to achieve this goal: gonadotropin-releasing hormone (GnRH) agonists (e.g., leuprolide), GnRH antagonists (e.g., degarelix), CYP17 inhibitors (e.g., ketoconazole and abiraterone), and androgen receptor (AR) blockers (e.g., bicalutamide and enzalutamide).⁴

Although ADT is an important part of treatment of prostate cancer, it is not without significant side effects. The most common side effect is erectile dysfunction (ED), which has been seen in 70–90% of patients receiving therapy.¹ Other common side effects include decreased sexual desire, inability to achieve orgasm, decreased penile length, and reduced testicular size. Unlike men treated exclusively with RP, most men treated additionally with ADT likely do not fully recover their baseline sexual function with an estimated <20% of men undergoing the therapy maintaining any sexual activity.⁷

In addition, the efficacy of treatments such as phosphodiesterase inhibitors (e.g., sildenafil) is often poor in patients receiving ADT as the tissue’s androgenization is required for an optimal response to the medication. With the advent of PSA testing, men are remaining on ADT for much longer than originally anticipated on average, further exacerbating its side effects as longer durations of therapy results in decreased likelihood of testosterone level recovery.

Reduced sexual interest can result in withdrawal of physical and emotional intimacy, partner distress, and overall reduced quality of life (QoL).⁷ As a result, interventions should be put in place to help manage the expectations for post-treatment outcomes.¹ These interventions should focus on mitigating the sexual effects associated with ADT and involve both patient and partner. The goal of this article was to conduct a review of the literature to identify long-term sexual side effects of ADT, as well as to investigate methods of treating the sexual side effects of ADT.

Methods

This is a systematic review that was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist. A comprehensive literature search of electronic databases was performed by two observers independently. A search strategy was implemented with bibliographic databases, including PubMed, Google Scholar, and Medline, to uncover English language

Table 1. Most Common Androgen Deprivation Therapy Side Effects

Most common ADT side effects	
Sexual side effects	Other side effects
ED	Hot flashes
Low libido	Loss of bone density
Penile shrinkage	Loss of muscle mass/sarcopenia
Testicular atrophy	Dyslipidemia
Hypogonadism	Fatigue
Delayed/anorgasmia	Decreased energy
	Cardiovascular effects
	Weight gain
	Gynecomastia
	Psychiatric symptoms
	Cognitive symptoms

ADT, androgen deprivation therapy; ED, erectile dysfunction.



articles published through 2021. Search terms included but were not limited to ADT, sexual function, side effects of ADT, treatment for ED.

Testosterone and Sexual Function

Testosterone and DHT are the targets of ADT with regard to treating prostate cancer, but this inhibition is also the main source of unwanted side effects. To better understand this process, it is important to fully grasp the physiology of androgens in the sexual function of men. Testosterone exerts its effects centrally and peripherally; libido is thought to be effects by testosterone's role within the central nervous system (CNS). Libido, or sexual drive, is difficult to isolate as there are numerous physiological, environmental, and psychological factors that may influence it.

However, some explanations of testosterone's role are based on increased dopamine release within the CNS.⁸ Dopamine may directly influence libido, but it has also been postulated that it can act on oxytocinergic neurons within the brain and the pro-erectile sacral parasympathetic nucleus.⁹ However, it has been questioned whether this increased level of dopamine within the brain is directly related to sexual function or if it is mainly involved in reward-seeking processes. Studies using positron emission tomography scans have demonstrated that sexual arousal is associated with paralimbic zone activation.¹⁰ The paralimbic zone is primarily involved with emotional functioning and motivation, which supports the idea that dopamine plays a vital role in sexual function.

Testosterone also has peripheral implications regarding sexual function and erections. Mechanistically, erection is primarily driven by the parasympathetic nervous system through production of nitric oxide (NO) by NO synthase (NOS), which then promotes formation of cyclic GMP (cGMP), and ultimately results in relaxation of cavernous smooth muscle and subsequent penile engorgement (Corona). Phosphodiesterase 5 (PDE5) is responsible for breaking down cGMP and functions with NOS to control levels of the pro-erectile molecules. It is postulated that testosterone contributes to smooth muscle integrity within the corpora cavernosa as well as regulation of NO production by NOS.¹¹

A review by Traish et al. postulates that androgens may also upregulate NOS through transcriptional regulation after binding to the AR.¹² Animal studies have also shown that testosterone plays a critical role in not smooth muscle integrity, but also proper structure

of the tunica albuginea. In an animal study looking at rats, there was a significant difference in the structure of the tunica albuginea and corpora cavernosa 4 weeks after castration.¹³ In a human study done with 52 eugonadal males with ED, there was a direct relationship between serum testosterone and cavernous vasodilation.¹⁴ It was also found that there was a significant increase in serum testosterone during erections after sexual arousal in men with and without ED.¹⁵ Interestingly, the increase in testosterone was more prominent in men without ED.

ADT Sexual Side Effects

ADT, regardless of intermittent or continuous, is capable of causing a multitude of debilitating side effects. This list includes decreased libido, ED, hot flashes similarly seen in women going through menopause, loss of bone density with possible subsequent fractures, weight gain, loss of muscle mass/sarcopenia, dyslipidemia, insulin resistance, fatigue, gynecomastia, testicular and penile shrinkage, and psychiatric symptoms mostly seen as mood swings and depression (Table 2).⁴ The antiandrogens may additionally, and rarely, cause liver damage and seizures as well. Considering ADT is employed in many patients diagnosed with prostate cancer who are relatively young and still interested in sexual function, it is particularly important that health care providers and their patients have extensive conversations regarding what side effects to expect and possible methods to mitigate them.

Broadly speaking, the side effects seen in men on ADT are due to the decrease in circulating androgens and/or the binding of these androgens to their receptors, and there is evidence supporting the notion that

Table 2. Androgen Deprivation Therapy Modalities

ADT modalities	
Drug class	Drugs
GnRH agonists	Leuprolide Goserelin Histrelin
GnRH antagonists	Abarelix Degarelix
Adrenal ablating drugs	Ketoconazole
Androgen receptor antagonists	Flutamide Enzalutamide Nilutamide Apalutamide Bicalutamide
5 alpha reductase inhibitors	Finasteride
Androgen synthesis inhibition	Abiraterone

GnRH, gonadotropin-releasing hormone.



this signaling is essential for the regulation of erections and sexual function peripherally.¹⁶ In addition, an important predictor of sexual function post-ADT is pretreatment function.¹⁷ Reviews and randomized trials have found that healthy men with lower levels of testosterone have worse erectile function.¹⁸ It has also been well documented that ADT can significantly impact erectile, ejaculatory, and orgasmic function.¹⁹ The lowered testosterone levels result in ED due to combination of venous leakage, blunted arterial inflow, and lower overall levels of NO.²⁰ Donovan et al. looked at the effects of ADT versus RP without ADT in men with prostate cancer.¹

They found that ADT resulted in worsening sexual function over 1 year of treatment when compared with non-ADT group. The ADT group also had worse self-reported sexual desire, ability to have an erection, and ability to orgasm. In addition, men in the RP group without ADT had overall improvement of sexual function over the 1-year period. These findings echoed others that found although RP resulted in immediate worsened sexual function, patient-reported satisfaction and sexual function improve with time.^{21,22} A study looking at men with prostate cancer who received brachytherapy with or without neoadjuvant ADT aimed to look at their ability to have an erection strong enough for penetrative intercourse.²³ They found that erectile function in these men, without medical or device assistance, was significantly worse in the ADT group (52% vs. 76%).

Interestingly, erections are still functionally possible in the absence of circulating androgens.¹⁹ An additional important finding is that men were able to achieve supracastrate levels of testosterone after long-term ADT and external beam radiotherapy (EBRT), although only a small portion of them fully recover their pretreatment potency and libido.²⁴ Many men on ADT are suppressed indefinitely even after suspension of therapy. This concept is usually not considered by many ADT prescribers. In a study by Nascimento et al., at 24 months after cessation of ADT, 8% of men remained at castrate level, 76% returned to TT >300 ng/dL, and only 51% had returned back to baseline levels of testosterone.²⁵ Lower baseline T levels (TT <400 ng/dL) and ADT duration >6 months were associated with a lower likelihood of recovery to normal TT at 24 months. Age >65 years and receiving ADT for >6 months were also significantly associated with a slower T recovery. These findings should be discussed with patients.

Not only does it impact erections, but libido can also be decreased as testosterone actions within the CNS is also affected.²⁶ An important difference seen in men treated for prostate cancer with ADT versus without is that libido may be preserved utilizing RP without ADT. A study by Le et al. looking at 620 men who underwent RP found that sexual desire was not significantly affected.²⁷ A study attempted to identify certain threshold levels of testosterone that may result in sexual dysfunction in men receiving ADT.²⁸

It was found that libido was affected when testosterone levels dropped <15 nmol/L, whereas erectile function declined as the testosterone levels dipped <8 nmol/L. Although, historically the relationship between ADT and libido has been difficult to establish due to the complexity of sexual desire, as there are physical and psychological interplay. Considering men are still able to have sexual desire while on ADT, it raises the question of whether there are other important hormones that sustain their libido and if better psychological practices may be able to compensate for lower testosterone to a degree.²⁹

When compared with GnRH medications, AR blockers have shown to have fewer sexual side effects. One study comparing bicalutamide, an AR blocker, with leuprolide found that monotherapy with the former resulted in lower levels of fatigue, higher libido, and less flushing.³⁰ This, however, cannot completely support the use of antiandrogens as monotherapy over GnRH agonists or antagonists as they have not been found to be noninferior with regard to oncological outcomes particularly in men with metastatic disease.²⁰ However, additionally, there is a higher incidence of gynecomastia with antiandrogens.¹⁷ This is primarily due to buildup of androgens with subsequent conversion to estrogens which directly interact with breast tissue in these men. Tamoxifen may be a consideration before starting antiandrogen therapy if this is a significant concern as gynecomastia can be effectively reduced by using estrogen receptor modulators such as tamoxifen or through prophylactic radiation of the tissues.²⁰

Options for ADT

Castration may be achieved surgically (i.e., bilateral orchiectomy) or pharmaceutically with the discussed medications. The Prostate Cancer Outcomes Study looked at sexual function following through ADT with GnRH agonists versus bilateral orchiectomy in 431 men with prostate cancer.³¹ About 73% of the



patients stopped engaging in sexual activity after treatment and 69% of those who had intact sexual function pretreatment were impotent after their ADT; no differences were noted between method of ADT. The overall rate of sexual inactivity increased from 45% to 80% with ADT and 48% to 83% after orchiectomy.

However, men who received GnRH agonists had a higher reported rate of dissatisfaction with their sexual function (38.4% vs. 25.6% in men who had orchiectomies).³¹ This study highlighted that GnRH agonists and orchiectomy have overall similar sexual function and the decision will be dependent on the patient's preference of type of therapy (medicine vs. surgery), frequency (routine medicine administration vs. one-time surgery), and reversibility (possible with medications vs. not possible with surgery).

Regarding pharmaceutical castration, there are different classes of medications as well as timing protocols that are utilized. The GnRH agonists and antagonists serve to decrease circulating androgens by either downregulation of the GnRH receptor (agonists) or direct inhibition of the receptor (antagonists). The other classes of ADT medications, the antiandrogens, block synthesis of androgen precursors in the adrenal gland (CYP17 inhibitors) or directly block the AR.⁴ Androgen synthesis inhibitors are utilized because they are able to prevent production of androgens and their precursors by the adrenal gland and cancer cells within the prostate, which is not achieved with orchiectomy or the other classes of ADT medications.³² These medications are typically administered along with a steroid to prevent mineralocorticoid-related side effects.³³

AR blockers are not typically used as monotherapy for prostate cancer since they do not block the production of androgens; they selectively block the action of androgens on their receptor.³² Because of this, they will typically be combined with GnRH agonists/antagonists or in patients who underwent orchiectomies to achieve complete androgen blockade. Importantly, antiandrogens have been associated with high risk of treatment resistance when compared with GnRH agonists and have been overall ineffective in treating CRPC.² There have been questions into whether high dose bicalutamide may be used as monotherapy in selective cases, depending on patient disease severity and other baseline health issues.³⁴ Although there does not seem to be a recommendation for bicalutamide monotherapy for initial management, a study by Okubo et al. focused on using this regimen as salvage therapy on men with biochemical relapse after RP over a 2-year period.³⁵

They concluded, similar to other authors, that bicalutamide monotherapy should be recommended for routine management of relapse after RP; however, postulated that it may be considered in patients without high-risk disease or quick progression to biochemical relapse. Patients would need to be carefully selected as bicalutamide monotherapy resulted in a likely significant risk of cancer progression and had relatively poor relapse-free survival of 82.3% at 2 years and 37.2% at 5 years.³⁵ An important limitation to this study was that it used a single-arm design and had a relatively small sample size of 62 patients who were able to complete the full 2 years of treatment.

In addition, a prospective study looking at men with well or moderately well differentiated prostate cancer treated with either bicalutamide monotherapy or combined androgen blockade found that there was no detectable difference in cause-specific survival (CSS) or overall survival (OS) between the groups, despite the monotherapy group having a higher risk of disease progression.³⁶ Tyrrell et al. also found that bicalutamide monotherapy was as effective in men with nonmetastatic prostate cancer when compared with castration.³⁷ Also, the difference in median survival in patients with metastatic disease was roughly 6 weeks, which suggests that antiandrogen therapy may still be suggested for this demographic given the superior side effect and tolerability profiles.

Another important consideration is duration of ADT. This should involve an extensive discussion between patients and their physicians regarding the balance between oncological outcomes and mitigation of detrimental sexual side effects. Regarding duration, a study by Bong et al. found that 53% of men who received 4 or more years of GnRH agonist therapy remained castrated, whereas those who received 3 years or less were more likely to return to their baseline testosterone levels.³⁸ In patients with PSA levels >20 who had already received EBRT, another study found that those who received ADT for at least 12 months had significantly higher CSS and OS compared with those who received 6 months or less of treatment.³⁹

After RP and adjuvant radiotherapy, ADT for >12 months had lower rates of biochemical failure as well as instances of distant metastases.⁴⁰ However, it is also important to highlight that a longer duration does not always produce clinically significant benefits. A randomized trial including men with high-risk prostate cancer who received radiotherapy found that there was no difference in survival between those



who received 18 months of ADT when compared with those who received ADT for 36 months.⁴¹ Importantly, the group that received 18 months had a better reported QoL.

An important component to take into consideration is that clinicians may lean toward using longer courses of ADT in patients with more aggressive disease, and the rates of long-term ADT use has increased for the past decade.⁴² It may not always be beneficial, especially in patients with low- or intermediate-risk prostate cancer as described by Dong et al.⁴³ This retrospective study including >1000 men with prostate cancer treated with EBRT demonstrated that the addition of ADT did not show improved rate of biochemical failure, rate of distant metastases, or OS. These instances may spare men from the side effects seen with short- and long-term ADT use.

Another aspect of duration is the use of continuous ADT versus implementing an intermittent treatment plan. The controversy here is based on the benefits of intermittent androgen deprivation (IAD) by possibly improving QoL versus the risk of not receiving continuous androgen deprivation (CAD). A randomized trial with >500 men with advanced prostate cancer compared a group that received IAD with another that received ADT; the IAD group was only administered a GnRH agonist when their PSA went above a threshold of 20 ng/mL.⁴⁴ Although men who received IAD had significantly better QoL measures, including sexual functioning, activity limitation, and physical capacity, there was no difference in reported adverse events when compared with the CAD group.

There was some discrepancy seen when assessing for sexuality, which was surprisingly better in the CAD group, but the authors postulate this may be due to relatively low response rates on this portion of the questionnaire. It is also important to note that this study focused on QoL and adverse events, but did not report on disease-specific outcomes of the groups. A large review looking at seven trials aimed to assess not only QoL measures, but also oncological outcomes.⁴⁵ Although there were important technical variations between the reviewed studies (e.g., PSA threshold to discontinue ADT, induction periods, and follow-up time), it was overall demonstrated that IAD produced noninferior oncological results with arguably better tolerability when compared with ADT.

Although IAD produced relatively modest QoL benefits, the authors highlight that there was insufficient evidence of improved long-term prevention of ADT

complications with IAD. Kratiras et al. also argue that results from trials comparing IAD with CAD indicate that intermittent therapy is a suitable option considering its superior cost and QoL benefits.⁴⁶ It is noted, however, that IAD likely benefits a specific group of patients, particularly men with biochemical recurrence without evidence of bony metastases. The authors also state that IAD should be avoided in patients who were unable to achieve a low PSA nadir after induction treatment, men with bulky tumors, significant bone and nodal metastases, PSA levels >100 ng/mL, rapid PSA elevation, or severe pain.

A prospective study by Crook et al. including ~1400 men with prostate cancer status postlocal radiotherapy also found that IAD was noninferior to CAD regarding OS, whereas intermittent therapy was associated with better reports of hot flashes, urinary symptoms, and sexual drive.⁴⁷ However, not all studies have concluded similar findings of comparable oncological outcomes. In a randomized trial looking at 3040 men with metastatic hormone-sensitive prostate cancer, Hussain et al. reported statistically inconclusive results.⁴⁸ Although IAD produced better QoL measures over CAD, specifically erectile function and mental health, the authors were unable to conclude that intermittent ADT was noninferior regarding the risk of death because of their predetermined threshold for noninferiority.

A more novel approach to medical management involves cyclically exposing prostatic cells to physiological and supraphysiological levels of androgens, and this technique is known as bipolar androgen therapy (BAT).⁴⁹ It was found that cells adaptively increased their expression of AR during ADT; however, these cells also became highly vulnerable to apoptosis when exposed to supraphysiological levels of androgens. Schweizer et al. found that in men with recurrent or advanced prostate cancer, treating with alternating cycles of ADT and BAT resulted in a >40% rate of PSA suppression <4 ng/mL.⁴⁹ There have been other small clinical trials that have shown similar oncological outcomes with incorporating BAT; importantly, the treatment course was well tolerated and did not have any deaths in the treatment arms.⁵⁰ However, there is a paucity for larger studies to further confirm its clinical benefit.

Pharmacotherapy and Mechanical Assistance

Decisions to improve erectile function after starting ADT depends largely on if the couple desires to be sexually active and if the patient had adequate



pretreatment function. Patients and their partners should know that men can still achieve orgasm even if their erections are not firm.⁵¹ Patients who were able to achieve a functional erection before ADT may consider using PDE5 inhibitors, intracavernosal injections using medications that promote vasodilation, vacuum devices, or implantation of an inflatable penile prosthesis—all of which have been found to be effective in treating ED in men on ADT.^{17,51} The use of phosphodiesterase inhibitors has become first-line treatment for ED after ADT. It has been rated the most cost-effective first-line strategy for ED with evaluation after 3 months of therapy.⁷

A review by DiBlasio et al. found that there was a wide range of response to medical therapy in men who received ADT, from 33% to 85%.⁵² PDE5 inhibitors had a response rate of 44% as monotherapy, whereas multimodal management yielded the best results. PDE5 inhibitors are also relatively inexpensive and easy to use, which may result in more compliance with patients. However, intracavernosal injections have been shown in certain studies to have better results than PDE5 inhibitors, and this provides patients with multiple options in case one of them fails.⁷ The response to pharmacotherapy was more robust in younger healthier men who had better baseline erectile function.⁵²

Testosterone replacement therapy (TRT) is another route of attempting to manage sexual adverse effects after treatment for prostate cancer through ADT. Natale et al. summarized that TRT has been safely utilized in managing hypogonadal symptoms of patients who received surgical or radiotherapy with or without ADT.⁵⁰ It was found that administration of testosterone improved response rates to PDE5 inhibitors. Importantly, it was emphasized that even though there may be a rise in PSA in patients who underwent ADT and later receive TRT, this does not directly indicate biochemical recurrence.⁵⁰ When considering therapy to improve adverse effects from life-saving treatment such as ADT, it is paramount that it will not affect oncological outcomes.

Another analysis looking at ~150,000 men who were diagnosed with prostate cancer aimed to discern if TRT resulted in worse survival.⁵³ The authors found that those treated with TRT did not experience higher overall mortality, cancer-specific mortality, or requirement of salvage ADT, whereas having a beneficial effect on hypogonadal adverse effects. In addition, incorporating BAT with ADT was also found to have

beneficial effects on QoL after a 6-month course of ADT.⁴⁹ The AUA Guidelines on testosterone deficiency recommend that for patients with a history of prostate cancer, clinicians inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer and that there is inadequate evidence to quantify the risk–benefit ratio of testosterone therapy.

Another medical option for sexual dysfunction after ADT that has been considered is estrogen. With the consideration that estradiol has a known positive role in maintenance of libido and erectile function in men, supplementation of this estrogen has been considered a viable option to possibly decrease sexual hypogonadal symptoms.⁵⁴ Although there is a lack of studies looking at long-term benefits of estrogen in these patients, the available studies indicate that this may improve libido in castrated men.⁵⁵ However, no concrete evidence points to a similar beneficial effect on erectile function and overall sexual satisfaction.

Psychology and Partner Involvement

Understandably so, decline in sexual function leads to not only frustration of the men receiving ADT, but also their partners, which may lead to strain and loss of intimacy within their relationships. Oftentimes patients will withdraw from physical or emotional intimacy when their definition of sex is unable to be met, or their lack of interest creates a new void in the relationship. It is important that practitioners involve partners as part of the management of ED. In a recent survey conducted by Fode et al., the majority of men experiencing ED admitted that their interest in sex was not motivated by sexual desire, but instead by an interest in feeling an emotional connection with their partner, satisfying their partner, fear that the partner would leave, and achieving orgasm.⁵⁶

Unfortunately, this is often not done. Walker and Robinson highlight that couples will most likely have significant difficulties with finding a successful method to adjust to their relationships that may be devoid of sex while on ADT.⁵⁷ They postulate that there are three main aspects of couples making this adjustment: altering their understanding of what a sexual relationship may be defined as, prevention of physical and emotional withdrawal through open communication and understanding, and adjusting their attitudes and perceptions.

Ultimately, the authors assert that couples are capable of expressing affection and remaining sexually



active despite sexual dysfunction from ADT, and suggest that health care professionals may be particularly helpful if couples are having difficulty adjusting. In a survey of clinicians who manage treatment-induced ED, 89% of the experts agreed that partners should be involved when managing ADT-related ED.⁷ Unfortunately, only 36% of the respondents involved the partners in their clinical practice. This highlights another important aspect that we as physicians can implement to improve the sexual health of our patients. Expectation management and open communication led by physicians can help encourage engagement and development of new behaviors and sexual norms both during and after ADT.

Other Side Effects

The other nonsexual side effects of ADT are not trivial and should be extensively discussed with patients as well. Hot flashes can be debilitating and may affect up to 60% of men receiving ADT.⁵⁸ These can typically be managed with hormonal agents such as estrogens or gabapentin effectively.⁵⁹ ADT has also been linked to loss of bone density and there is an established increased risk of bone fractures when compared with controls.⁶⁰ It is recommended that patients undergo bone density evaluation before starting therapy with periodic reassessment depending on the initial findings.⁶¹

Although lacking concrete guidelines for management and prevention, this may include increase calcium and vitamin D intake, exercise, denosumab, selective estrogen receptor modulators (SERMs), estradiol, and bisphosphonates.^{61–63} Nguyen et al. looked at the decreased bone mineral density, weight gain, decreased muscle mass, increased insulin resistance, decreased libido, hot flashes, and gynecomastia associated with ADT. Through randomized trials they were able to find that bone loss can be improved by use of bisphosphonates (e.g., denosumab) and SERMs.⁶²

Lower levels of an estrogenic metabolite of testosterone have been found to directly contribute to these symptoms, and this physiology is targeted through the use of SERMs and estradiol.⁶² Decreased muscle loss has also been linked with lowered levels of testosterone, and this can lead to significant fatigue and overall weakness.⁶⁴ There is also a proposed increased risk of diabetes mellitus and cardiovascular disease (CVD), as well as risk of death from CVD.^{65–68} Cormie et al. found that combined aerobic and resistance exer-

cise prevented weight gain; improved cardiovascular fitness, muscular strength, and lower body function; improved high density lipoprotein to cholesterol ratios; and improved sexual, psychological, and social functioning.⁶⁹ They advised the initiation of supervised exercise programs to all patients receiving ADT to minimize the morbidity associated with the potential severe hypogonadism.

Many of these nonsexual side effects play a significant role in sexual health and QoL. Sarcopenia, low bone density, and worsened cardiovascular status may make sexual activity more difficult or challenging for patients. Couples may require assistive devices to comfortably allow sexual activity. Fatigue and lack of energy may inhibit sexual engagement resulting in patients' withdrawal and becoming avoidant. These are important topics to discuss and counsel with patients before starting ADT.

Once treatment is started, early and close monitoring should be followed as data suggest metabolic sequelae occur most commonly within 3–6 months after beginning therapy.⁷⁰ These metabolic complications should be managed with appropriate lifestyle (e.g., cardiovascular exercise, weight bearing exercises, health dietary intake, minimizing complex carbohydrates and high sugar foods, and smoking cessation) and medical (e.g., antihypertensive, cardioprotective, statin, and antidiabetic) interventions. Statins in particular have shown improved CSS and OS in men with prostate cancer receiving ADT.⁷¹ If a patient has established, underlying cardiac disease, including a cardiologist in follow-up could also be beneficial.²⁶ Another well-established effect of ADT on men is psychiatric derangements.

Cherrier et al. highlighted how ADT resulted in decreased energy and mood, irritability, and a decline in working memory and spatial ability.⁷² Although it has also been postulated that ADT could contribute to cognitive impair, this relationship is yet to be concretely established.²⁶ If patients meet diagnostic criteria for depression, pharmacotherapy and cognitive behavioral therapy have shown positive outcomes in mood, QoL, and stress levels in men undergoing ADT. These alterations tend to peak a few months after initiating ADT and returned to baseline when therapy was stopped. Depression and psychological impacts of ADT should not be minimized, nor their impacts of the sexual health of a couple. If suspected, patients should be encouraged to seek therapy or treatment.



Conclusion

After a review of the literature, we found that adequate counseling about ADT timing, duration, and regimen is paramount. This should include a detailed discussion with the patient about potential sexual side effects of ADT and its impact on the overall QoL, as well as setting realistic expectations for the management of the sexual side effects. Future direction should include the development of a risk assessment tool to predict likelihood of developing side effects. In addition, studies should be done to compare the newer generation antiandrogens side effect profile with the traditional ADT.

Authors' Contributions

H.L.B., G.M.G., J.F., and O.A.R. contributed to the design, idea, literature search, and drafting of the article. H.L.B. and G.M.G. completed revisions and final editing.

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Abbreviations Used

- ADT = androgen deprivation therapy
- AR = androgen receptor
- AUA = American Urological Association
- BAT = bipolar androgen therapy
- CAD = continuous androgen deprivation
- cGMP = cyclic GMP
- CNS = central nervous system
- CRPC = castration-resistant prostate cancer
- CVD = cardiovascular disease
- CSS = cause-specific survival
- DHT = dihydrotestosterone
- EBRT = external beam radiotherapy
- ED = erectile dysfunction
- GnRH = gonadotropin-releasing hormone
- IAD = intermittent androgen deprivation
- NO = nitric oxide
- NOS = NO synthase
- OS = overall survival
- PDE5 = phosphodiesterase 5
- PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis)
- PSA = prostate-specific antigen
- QoL = quality of life
- RP = radical prostatectomy
- SERMs = selective estrogen receptor modulators
- TRT = testosterone replacement therapy

