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# Adverse Events Associated with Hormonal Therapy for Prostate Cancer

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## Abstract

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With expanding indications for androgen deprivation therapy for the treatment of prostate cancer, it is imperative that health care providers be cognizant of the possible adverse effects of therapy, as well as their prevention and treatment. Neurologic and psychiatric effects include depression and declines in cognitive function. Musculoskeletal effects of hormonal therapy include osteoporosis, decrease in muscle mass, and fatigue. Gynecomastia, weight gain, and erectile dysfunction are also seen, as are hematologic effects. Further research is needed to evaluate alternative forms of therapy, such as intermittent hormonal deprivation and antiandrogen monotherapy.

**Key words:** Prostate cancer, Hormonal therapy, Adverse effects, Prevention

Prostate cancer is the second leading cause of cancer-related mortality in men in the United States.[1] Hormonal blockade is widely used for controlling prostate cancer, but it has been indicated mainly for advanced disease. Recent data have indicated, though not conclusively, the early use of hormonal blockade after diagnosis in certain high-risk groups, thus expanding its indication. The concept of hormonal manipulation in prostate cancer was first introduced in 1941 by Huggins and Hodges.[2] Since then, different approaches for the reduction of androgen activity have included bilateral orchiectomy, use of estrogenic compounds, and, more recently, medical castration in the form of luteinizing hormone-releasing hormone (LHRH) analogues and androgen blockade with antiandrogens. A significant rise in the use of hormonal manipulation has been seen over the past decade. The main concern when choosing a form of hormonal blockade in men with prostate cancer is the risk of adverse events. Although current urologic practice has overwhelmingly shifted to the use LHRH analogues, some form of antiandrogen, or the combination of both, the rate of side effects is still alarming high, affecting the well-being and the overall quality of life in patients diagnosed with prostate cancer. Different regimens of androgen activity reduction have been extensively studied and include continuous or intermittent hormonal therapy, monotherapy with antiandrogen and maximal androgen blockade, and the use of antiandrogen with 5-α reductase inhibitor.[3] As yet, none of these regimens has proved superior in terms of long-term survival, and the impact of these regimens on the incidence of side effects and health-related quality of life is hotly debated.

This article reviews the known adverse effects associated with hormonal manipulation in men with prostate cancer (Table 1). Prevention and treatment of these effects are also discussed.

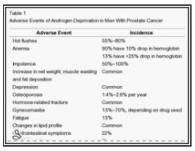

Table 1

Adverse Events of Androgen Deprivation in Men With Prostate Can

## Neurologic and Psychiatric Effects

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Impaired memory, concentration, verbal skills, and other cognitive dysfunctions in patients receiving hormonal deprivation regimens have been documented.[4] Hormonal deprivation also has emotional effects, including moodiness and short temper, crying with minimal provocation, and feeling depressed and anxious. The correlation between these effects and low testosterone levels has been mixed in the literature. Several studies failed to find a significant relationship between the level of testosterone and the incidence of depression,[5] whereas others reported that such a relationship, although weak, does exist.[6] Studies addressing the effect of hormonal deprivation in prostate cancer patients have been limited. Rosenblatt and Mellow[7] reported on 3 patients who developed refractory severe depression after androgen therapy, which was only reversed by discontinuation of therapy. Exercise, especially resistance exercise, has helped to improve psychological side effects in patients receiving hormonal manipulation.

## Hot Flushes

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Vasomotor hot flushes are a frequent complaint for men receiving an androgen deprivation regimen. The typical manifestation of hot flushes is a sudden perceived increase in temperature, specifically a feeling of warmth in the face, neck, upper chest, and back, which might be associated with reddening of the skin and profuse sweating. The exact etiopathology is not defined, but it is thought that stimulation of the hypothalamic thermoregulatory center secondary to the lack of increase in endogenous testosterone secretion results in a feeling of warmth.[8] The duration of hot flushes can vary from a few seconds to 1 hour. Hot flushes can occur spontaneously, but patients report their frequent association with hot weather, stress, or disturbed sleep. The intensity of hot flushes can vary from mild to severe; severe flushes can be incapacitating and usually do not resolve over time.

Available treatment of hot flushes includes the use of hormonal (estrogens, megestrol acetate, medroxy-progesterone acetate, and cyproterone acetate) and nonhormonal preparations (antidepressants and alternative therapies, such as herbal preparations, acupuncture, soy, and vitamin E). Estrogens are usually given as low-dose oral or transdermal diethylstilbestrol, which was shown to improve symptoms in the majority of men suffering from hot flushes, with minimal adverse effects.[9] Low-dose megestrol acetate[10] and steroidal antiandrogens, such as cyproterone,[11] were also shown to be very effective in reducing hot flushes. Nonetheless, increased cardiovascular risk and altered lipid profiles are serious side effects of the hormonal approach, and a risk/benefit ratio should be evaluated individually.

Antidepressant agents, like venlafaxine and gabapentin, have been shown to be effective. In one study, a 25-mg dose of venlafaxine (a selective serotonin reuptake inhibitor) reduced hot flushes in more than 50% of men.[12] Gabapentin (an analogue of γ-aminobutyric acid) was also helpful in some case studies.[13] It is hypothesized that antidepressants acts by reducing noradrenergic overactivity, hence improving the vasomotor tone, but the mechanism of action is still largely unknown.

Some studies have suggested benefit from alternative and herbal medicines, which have been shown to be of benefit in alleviating postmenopausal symptoms in women.[14] These include black cohosh and red clover supplements,[15] ginseng, licorice, and turmeric,[16] but these show no proved efficacy in controlled studies. Other less-studied products, such as soy and vitamin E, and techniques such as acupuncture have not been studied for efficacy in men receiving androgen therapy; however, some benefit has been documents in postmenopausal women.

In summary, the effectiveness of a nonhormonal approach for the treatment of hot flushes is thought to be lower compared with the use of hormonal preparations.

## Gastrointestinal Side Effects

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Antiandrogens are reported to be commonly associated with gastrointestinal (GI) side effects like abdominal pain, diarrhea and constipation, nausea/vomiting, and anorexia. The exact mechanism is still unknown. A recent study of 106 patients receiving flutamide with or without prior radiation therapy for prostate cancer showed no difference in the incidence of GI side effects between the groups (approximately 22%).[17] On the basis of these findings, the investigators hypothesized that flutamide-induced local toxicity does not fully describe the GI disturbances.[17] GI symptoms are reported more frequently in association with combination therapy with LHRH when compared with antiandrogens alone.[18] Furthermore, flutamide and other antiandrogens have, to varying degrees, been linked with hepatotoxicity in the form of abnormal liver function test results and liver failure.

## Musculoskeletal Side Effects

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Musculoskeletal side effects of hormonal therapy include osteoporosis, decrease in muscle mass, and fatigue.

Studies over time have shown that bone density decreases by approximately 0.5% to 1% per year in healthy elderly men.[19] In healthy subjects, general bone loss as a normal part of aging is slower and less visible in men than in women.[19] The risk of fatal complications due to osteoporotic fractures, however, is higher in men than in women. Bone mineral density (BMD) is used to quantify osteoporosis. Osteoporosis is an important health problem in aging men, contributing to fracture risk and death. The relationship between androgen activity reduction and osteoporosis was first demonstrated in a study in which bone density in 12 men who underwent orchiectomy was compared with that of normal controls.[20] In another, larger study,[21] there was a 14% incidence of fractures in a group with orchiectomy compared with controls, who had an incidence of 1%. Another study has shown that androgen castration can cause 5% to 10% loss in BMD.[22] There is some evidence that hormone-naïve patients with prostate cancer have BMD lower than expected for their age,[23] suggesting a further risk in these men with the administration of hormonal treatment for prostate cancer, probably doubling the risk of osteoporotic fractures.

Sex hormones affect the metabolic activity of bone. However, antiandrogens seem to affect bone loss differently than would be expected from LHRH agonist use. In one cross-sectional study, the biochemical markers of bone turnover were elevated in men receiving LHRH agonist treatment but not in men receiving bicalutamide monotherapy for prostate cancer.[24] These observations suggest that bicalutamide monotherapy might maintain BMD and prevent fractures. Research has shown that when inhibition of estrogen or testosterone is followed by replacement therapy, estrogen is more important than testosterone in the maintenance of bone density.[25]

The current guidelines for the prevention of osteoporotic fractures in patients receiving hormonal manipulation mainly address issues of lifestyle modification, including smoking cessation, decreased alcohol intake, added resistance exercise, and adequate supplementation of calcium (up to 1200 mg per day) and vitamin D (up to 400 IU per day). Other treatment options include the use of bisphosphonates (Figure 1) and estrogens. Three different bisphosphonate preparations (alendronate, pamidronate, and zoledronate) have been used to prevent osteoporosis in androgen-deficient men. Alendronate was shown to increase BMD at lumbar spine and femoral neck in men with osteoporosis not receiving hormonal deprivation.[26] Alendronate, which can be given orally, should be taken in an erect position and on an empty stomach, and the patient's head should be elevated for half an hour. Side effects include

esophagitis, abdominal pain, and gastroesophageal ulceration. Pamidronate and zoledronate are at present available as intravenous (IV) preparations only. In a randomized trial, two groups of patients without bone metastases were given leuprolide alone or leuprolide and pamidronate 60 mg IV every 12 weeks. The pamidronate group showed no change in bone density, whereas the other group had significant loss of density (3.3% at lumbar spine, 2.1% at trochanter, and 1.8% at hip).[23] Zoledronic acid (4 mg IV every 3 weeks) was shown to have similar efficacy in men with prostate cancer and bone metastases.[27] Zoledronic acid was also shown to increase bone density in a prospective randomized trial in patients receiving LHRH analogues.[28] Adverse effects of bisphosphonates include anemia, fever, reactions at injection sites, constipation, and hypophosphatemia. Furthermore, renal failure was observed in some patients receiving a higher dose and rapid administration of zoledronic acid, prompting close creatinine monitoring. A relatively new bisphosphonate, neridronate, was recently reported to maintain bone density in men with induced hypogonadism with LHRH analogue treatment, when compared with treatment with calcium and vitamin D supplements alone.[29]

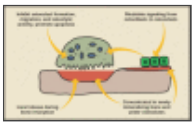

Figure 1
Mechanisms of bisphosphonate action.

Progressive loss of muscle mass is linked to the gradual decline in testosterone levels observed with advancing age. However, the etiology seems to be more complex and multifactorial. In a cross-sectional study performed to evaluate positive prognostic factors for maintenance of muscle mass, free testosterone level proved to be the most important factor.[30] Thus, in men with a low level of free testosterone, as seen in men with prostate cancer receiving androgen deprivation, this process is iatrogenically accelerated. Sarcopenia significantly increases morbidity and mortality and contributes to the increased risk of falls. Stone and colleagues[31] examined 62 men undergoing LHRH antagonist (goserelin) and cyproterone acetate treatment for prostate cancer and assessed the voluntary muscle strength and fatigability changes after 3 months of therapy. A significant increase in subjective fatigue measurements after 3 months and a small but significant increase in hand grip fatigability was reported.[31] There was also a significant decrease in muscle mass, with no overall weight change. Resistance exercise and psychological motivation are probably the most effective tools for reducing this debilitating symptom and improving quality of life.

## Endocrine Side Effects

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Changes in the hormonal balance induced by hormonal manipulation in men with prostate cancer can alter the ratio of circulating estrogens to androgens, thereby increasing the likelihood of developing gynecomastia. The incidence of gynecomastia varies with type of therapy: 40% to 70% with estrogens and antiandrogens, 13% with LHRH analogues and maximal androgen blockade.[32] Gynecomastia usually resolves spontaneously after cessation of hormonal manipulation during the first year. After that it tends to become permanent because of fibrosis and hyalinization in the breast tissue. Radiotherapy to the breast, subareolar mastectomy, and medical treatment are the main preventive and therapeutic options currently available, short of cessation of the androgen blockade.

Breast pain is another debilitating effect associated with androgen blockade in prostate cancer patients. Radiation is not as beneficial once gynecomastia is established (>12 months); however, it might alleviate the concurrent breast pain.[33] Aromatase inhibitors and short-term tamoxifen are also helpful in ameliorating breast pain.

## Cardiovascular Side Effects

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Patients receiving hormonal deprivation tend to gain weight, mainly by increases in subcutaneous fat deposition. In one prospective study of 40 men treated with LHRH analogue therapy, an average 9.7% increase in fat body mass and 2.6% decrease in lean body mass was observed.[34] Moorjani and colleagues[35] reported that significant hypertriglyceridemia and elevation of plasma high-density lipoprotein (HDL) cholesterol, phospholipid, and apolipoprotein A-I and A-II concentrations were associated with estrogen preparations. Orchidectomy, however, was associated with hypercholesterolemia and an increase in both total and low-density lipoprotein apolipoprotein B, all of which are strong risk factors of cardiovascular disease. The investigators suggested that the cardiovascular complications that occur during estrogen administration are mediated through the hypertriglyceridemic effect rather than through changes in the lipoprotein profile.[35] Moreover, combination therapy with orchidectomy and antiandrogens was more beneficial on the lipoprotein profile than single therapy.[35] In another prospective study, cyproterone acetate alone was associated with lower HDL and higher very-low-density lipoprotein triglyceride levels.[36] Furthermore, induced hypogonadism was reported to result in a rise in the augmentation of central arterial pressure, suggesting large artery stiffening.[37] Other changes observed in men receiving prolonged hormonal manipulation include increased insulin levels and abdominal girth.[38] However, direct correlation with the development of diabetes mellitus in these men has not been proved.

## Erectile Dysfunction

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Loss of sexual desire and erectile dysfunction (ED) are common side effects of hormonal deprivation therapy. Preservation of libido in a proportion of patients receiving hormonal treatment suggests that testosterone alone might not be the sole factor. Factors affecting variation in libido include the patient's age, physical fitness, and testosterone levels before treatment. Loss of penile volume and fibrosis is another adverse effect, which can be ameliorated by maintaining sexual activity. Other ED manifestations observed after prolonged hormonal deprivation therapy (>3 months) include decrease in nocturnal penile tumescence in terms of frequency, degree of rigidity, duration, and volume of erection.[39] Therapy for sexual dysfunction includes phosphodiesterase (PDE)-5 inhibitors, intracavernosal injections, vacuum constriction devices, and penile prostheses. PDE-5 inhibitors are recognized as the first line of therapy for men with ED. Their efficacy, if any, in men treated with hormonal deprivation with or without radical surgery or radiation therapy is thought to be mild. Long-term randomized studies are still awaited.

## Hematologic Adverse Effects

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Normocytic normochromic anemia is commonly encountered in men receiving hormonal deprivation therapy. The cause is thought to be deficiency of erythropoietin and the lack of stimulation of erythroid stem cells by testosterone and dihydrotestosterone. A study by Strum and colleagues[40] showed that hemoglobin levels can fall within 1 month after starting therapy and that nadir hemoglobin levels were reached by 6 months. In this study, anemia was symptomatic in 13% of patients and was worse in combined androgen blockade compared with the use of LHRH analogues alone. This side effect is reversible upon cessation of hormonal blockade. Recombinant human erythropoietin has been used to correct this form of anemia.

## Biological Adverse Effects

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The occurrence of the “flare” phenomenon—the initial burst of testosterone release when LHRH analogues are used alone—is still controversial. In men with symptomatic bone metastasis or at risk for cord compression, this can be devastating. Although it is usually avoided by combining an antiandrogen for first month with LHRH analogues in most cases, this does not totally eliminate the risk of flare responses in all patients.

In addition to the above-mentioned adverse events, other less frequently reported symptoms, including body hair loss, dry eyes, and vertigo are also associated with hormonal deprivation in prostate cancer.

## Therapy Modifications

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Therapy modification is an important tool for alleviating the debilitating symptoms associated with androgen manipulation in prostate cancer patients; however, these modifications should be evaluated carefully by the treating physician and the patient alike for risk/benefit ratio. The use of intermittent androgen deprivation therapy, monotherapy, and combination with finasteride has been suggested to lessen the side effects associated with hormonal manipulation in prostate cancer and improve the quality of life in these men. For example, the use of bicalutamide monotherapy is thought to have a less detrimental effect on bone loss,[24] and the use of a combination of flutamide and finasteride has been reported to preserve erectile function in 55% of patients.[41] The use of alternative castration therapy—switching to polyestradiol phosphate from complete androgen deprivation—was shown to reduce hot flushes by more than 50%.[42]

## Conclusions

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Prostate cancer is a major health care issue in the United States. With expanding indications for androgen deprivation therapy, it is imperative that health care providers be cognizant of the possible side effects of therapy, to counsel patients, decrease morbidity, and improve patients' quality of life. Further research is needed to evaluate alternative forms of therapy, such as intermittent hormonal deprivation and antiandrogen monotherapy.

### Main Points

- Recent data have indicated, though not conclusively, the early use of hormonal blockade after a diagnosis of prostate cancer in certain high-risk groups; the main concern when choosing a form of hormonal blockade is the risk of adverse events.
- Hot flushes are a common side effect of hormonal manipulation; treatments are similar to those for postmenopausal symptoms in women and include estrogens, progestins, antidepressants, cyproterone acetate, and alternative therapies, such as acupuncture, soy, and vitamin E.
- Osteoporotic fractures in patients receiving hormonal manipulation are prevented mainly by lifestyle modifications (smoking cessation, decreased alcohol intake, resistance exercise, and adequate supplementation with calcium and vitamin D); other treatment options include the use of bisphosphonates and estrogens.
- Loss of muscle mass is accelerated in men with low levels of free testosterone; resistance exercise and psychological motivation are probably the most effective tools for reducing this debilitating symptom.
- Changes in the hormonal balance induced by hormonal manipulation in men with prostate cancer can increase the likelihood of gynecomastia; gynecomastia usually resolves spontaneously after cessation of hormonal manipulation during the first year.
- Loss of sexual desire and erectile dysfunction are common side effects of hormonal deprivation therapy; the efficacy, if any, of phosphodiesterase-5 inhibitors in men treated with hormonal deprivation with or without radical surgery or radiation therapy is thought to be mild.
- Therapy modifications to reduce adverse side effects associated with hormonal manipulation in prostate cancer might include the use of intermittent androgen deprivation.

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