AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- DESCRIBE current diagnostic methods and classifications for prostate cancer
- LIST new treatment options for prostate cancer and their monitoring parameters
- RECALL supportive care interventions for patients experiencing troubling symptoms
- APPLY the principles of motivational interviewing to patients who have prostate cancer to improve medication adherence

After participating in this activity pharmacy technicians will be able to:

- RECALL common symptoms of prostate cancer and the typical medications used to treat them
- IDENTIFY medications that are typically appropriate for symptom management in patients with prostate cancer
- RECOGNIZE when to refer patients to the pharmacist for recommendations

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission.

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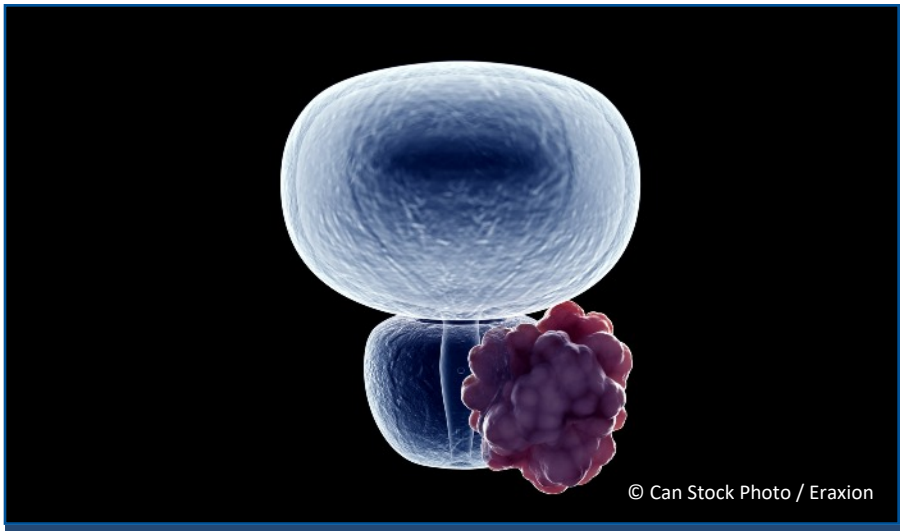

PSA (Prostate Specific Advancements): Understanding Supportive Care, Updated Guidelines, and Novel Medications

ABSTRACT: Prostate cancer is the most common cancer diagnosed in men. Most men are diagnosed with localized prostate cancer. Treatment varies depending on men's risk factors for developing advanced disease. Recently the classification for localized prostate cancer has been updated to categorize patients who may benefit from additional diagnostic testing and treatment options. Surgery, radiation, and androgen deprivation therapy (i.e., hormonal therapy) are the mainstays of localized prostate cancer treatment. Those with very high risk disease now may also benefit from the addition of chemotherapy with docetaxel. Men whose cancer has progressed also have new therapeutic options. Second-generation antiandrogens including apalutamide, darolutamide, and enzalutamide can be used for non-metastatic castrate-resistant prostate cancer. In those with newly diagnosed metastatic disease, apalutamide and enzalutamide are also now options. To date, targeted therapy has not been useful in prostate cancer. However, a small number of patients may have mutations that will respond to targeted therapy. Olaparib may now be considered for a select group of patients with DNA repair gene mutations. These new treatment advancements in prostate cancer require the pharmacy team to be familiar with common side effects and methods to mitigate them. Appropriate monitoring and supportive care therapies that facilitate patient adherence and tolerance of therapy should be included as part of the continuum of care.

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INTRODUCTION

Prostate cancer is the most common cancer diagnosed in men and the second leading cause of cancer-related deaths.[1] It arises in the prostate gland, which is a solid, round, heart-shaped organ positioned between the bladder and urogenital diaphragm. It is comprised of secretory cells. Its main function is secreting fluid that nourishes and protects sperm. Normal growth and differentiation of the

prostate gland depends on presence of androgens, specifically dihydrotestosterone.[2] Both the testes and adrenal glands are major sources of circulating androgens, such as dihydrotestosterone.

When prostate cancer develops, the size, shape, and cells in the prostate gland change. The most common type of cancer is adenocarcinoma, although neuroendocrine, sarcoma, or transitional cell types can occur rarely. Prostate cancer in some men can be very slow growing and in others it can progress rapidly.[3] The risk of developing prostate cancer increases with age, family history of prostate cancer, and African American ethnicity. Most men (70%) are diagnosed after age 65.[4] Because this is a chronic cancer of elderly, there's opportunity for pharmacy intervention with screening for potential drug interactions, managing comorbidities, and medication management.

Symptoms of prostate cancer depend upon extent of disease.[2] Those with localized disease are often diagnosed with a prostate cancer screening test and may be asymptomatic or experience urinary symptoms, such as increased frequency, hesitancy, dribbling after urination, or impotence. With advanced disease, back or other bone pain, weight loss, lower extremity edema, and anemia are the most common symptoms. Approximately 80% of men will be diagnosed with localized prostate cancer. These men have a high likelihood of treatment success; 99% are alive at 5 years.[1] Those diagnosed with advanced disease that has metastasized to other parts of the body have a 5-year overall survival rate of approximately 30%.

Treatment of prostate cancer depends on the disease's extent and aggressiveness, likely survival time, and presence of symptoms. Additionally, selection of a treatment will depend upon the patient's comorbidities. During treatment, patients are likely to experience side effects. The pharmacy team can play a key role in preventing and managing side effects and educating patients about how to quickly identify and treat side effects to optimize care. Thus understanding the current diagnostic and classification methods, available treatments, and supportive care therapies summarized below is crucial.

Prostate Cancer Diagnosis

Normal growth and differentiation of the prostate gland depends on presence of androgens, specifically dihydrotestosterone.[2] Both the testes and adrenal glands are major sources of circulating androgens, such as dihydrotestosterone. In early stage prostate cancer, the presence of androgens promotes aberrant tumor cell proliferation. Advanced disease, however, is often heterogenous, containing both androgen-dependent and -independent malignant cells. Essentially this allows the cancer to grown even when treatment depletes androgen sources. Progression of prostate cancer is likely due to genetic abnormalities that affect the androgen receptor and regulation of cell survival and apoptosis (cell death), leading to invasive neoplasia and disease that progresses despite androgen depletion (i.e., castrate resistance).

Technician Talk: When is a PSA "Normal"?[7]

Experts have not established a definitive prostate specific antigen (PSA) level that is "normal." A PSA test of a certain level is not diagnostic proof of cancer; clinicians can only confirmed prostate cancer using a biopsy.

Physicians consider several factors when they assess PSA and decide if they need to pursue a biopsy or other testing: race, age, current medications, and concurrent disease. For example, research indicates that using NSAIDS, statins, and thiazide diuretics over months to years reduces PSA by clinically relevant amounts.

PSA levels tend to rise with age, and some people have advocated for age-specific levels. Unfortunately, researchers have not accumulated enough evidence to provide those levels. Usually, a physician's index of suspicion rises if men's PSA levels exceed 3-4 ng/mL, although it is possible for a man to have a lower number and still have prostate cancer.

Most often patients are evaluated for prostate cancer based upon an elevated prostate specific antigen (PSA) or an abnormality found upon digital rectal exams (DRE) conducted during a prostate cancer screening examination.[5] The **Sidebar** provides additional information about PSA levels. PSA is a protein that the prostate releases into the bloodstream; it is often (but not always) found in high concentrations in prostate cancer. Providers perform DREs during physical examination of the prostate by inserting their finger into the patient's rectum and inspecting the prostate for irregularities (e.g., nodule, induration [tissue hardening or thickening], or asymmetry). Although PSA testing can help detect prostate cancer early, it is not a specific marker of prostate cancer due to the fact that other conditions such as benign prostatic hyperplasia (BPH) and prostatitis (inflammation) can elevate PSA as well.[3] In men between the ages of 45-75 years, PSA readings exceeding 3 ng/mL or an abnormal finding on a DRE are worthy of further evaluation. In patients older than 75 years, a PSA level is 4 ng/mL or higher will suggest further evaluation.[6]

In some cases, it might be helpful to know when the elevated PSA may be related to another cause such as BPH. One such evaluative tool is the PSA density (PSAD). Clinicians calculate PSAD by measuring the prostate volume using a trans-urethral ultrasound (TRUS) and then dividing the PSA value (in ng/mL) by the prostate volume (in cc). BPH is most likely with lower PSADs. Other tests are being evaluated to improve upon the PSAD and include the circulating PSA (cPSA) and the unbound or free PSA (fPSA), but their clinical utility remains unclear. Additionally, some practitioners will also evaluate the PSA doubling time if more than one PSA level is recorded. The doubling time is the time it takes the PSA to double and can be a marker of the cancer's aggressiveness. The PSAD and PSA doubling time may help if the oncologist performs a biopsy in determining the patient's treatment.

The first step in evaluating an abnormal PSA level or DRE is to repeat and/or order a PSA to confirm the level remains elevated. Several blood and urine-based molecular and genomic tests are available to help guide the decision to biopsy the prostate; however these are not considered routine yet.[8] A TRUS-guided biopsy of the prostate is the gold standard method of diagnosing prostate cancer. The prostate cancer biopsy will provide the histology (the type of cancer present) and architectural features (Gleason score), which closely correlate with clinical outcomes. The Gleason grading system assesses the prostate gland tumor's growth pattern and degree of differentiation.[9] They are graded from 1 to 5, with 1 being the most differentiated. The Gleason score is a composite score derived by adding the numeric values of the biopsy's most prevalent differentiation patterns. A higher score indicates a greater likelihood of having more aggressive disease and a worse outcome. Additional information from the biopsy that helps inform the diagnosis is if the tumor involves both sides of the prostate gland, has extended beyond the prostate gland (extraprostatic), invades the perineural areas, or is affixed to adjacent structures such as rectum or bladder.

Based on these clinical and pathologic features, the oncologist will then stratify the patient into a risk group (very low to very high).[4] The risk group is based upon the likely chance that the patient

1) has disease that has spread outside of the prostate gland;
2) likelihood of disease progression after initial treatment; and
3) how likely additional therapy would control disease if primary treatment was unsuccessful.

The healthcare team will consider the assigned risk group and may order more diagnostic testing (imaging test such as CT and bone scans), molecular and biomolecular tumor analysis, and initial therapy.

PAUSE AND PONDER: If a patient has an elevated prostate specific antigen (PSA) level, what factors need to be considered?

If upon more diagnostic testing, it is determine the patient has disease that has spread outside of the prostate, then he would be classified as having regional disease (disease that has spread to a regionally located lymph node) or metastatic disease (disease that has spread beyond the regional area to a distant site [e.g., bone, liver]).[4] Newly diagnosed patients are often described

Table 1. First-Line Treatment for Localized Prostate Cancer[1,4]

Risk Group	Expected Survival & Recommended Treatment	
Very low risk	≥ 20 years • Active surveillance • Radiation therapy • Surgery + radiation therapy +/- ADT[a] or observation • Surgery	10-19 years • Active surveillance < 10 years • Observation
Low risk	≥ 10 years • Active surveillance • Radiation therapy • Surgery • Surgery + radiation therapy ± ADT or observation	< 10 years • Observation
Favorable intermediate risk	≥ 10 years • Active surveillance • Radiation therapy • Surgery ± radiation therapy ± ADT (6 months)	< 10 years • Observation • Radiation therapy
Unfavorable intermediate risk	≥ 10 years • Surgery ± radiation therapy ± ADT (6 months) • Surgery	< 10 years • Observation • Radiation therapy ± ADT (4 months) • Radiation therapy ± ADT (4 months)
High or very high risk	> 5 years or symptomatic • Radiation therapy + ADT (1-3 years) ± docetaxel • Surgery • Surgery ± radiation therapy ± ADT (6 months)	≤ 5 years and asymptomatic • Observation • ADT • Radiation therapy

[a]ADT (androgen deprivation therapy) includes luteinizing hormone-releasing hormone (LHRH) agonist ± antiandrogen, LHRH antagonist, or orchiectomy (note only option in regional and metastatic disease).

as hormone-sensitive or castrate-naïve because their tumors often respond well to treatment with hormonal agents that decrease testosterone levels.

Treatment of Prostate Cancer

Initial Treatment

Most patients with prostate cancer (80%) have localized disease (that is, disease has not spread to lymph nodes or distant sites within the body at diagnosis).[1] Treatment options will depend on their risk group and life expectancy (see **Table 1**) and can range from observation to multi-modal therapies (e.g., surgery ± radiation therapy ± system hormonal therapy).[4] Regional disease is defined as one positive regional lymph node.[9] Patients with regional disease will require radiation therapy + hormonal therapy. The goal of therapy for both localized and regional prostate cancer is cure. In patients with advanced or metastatic disease—that is, prostate cancer that has spread to non-regional lymph nodes, bone, or any other site within the body—cure is not possible. However, extending overall survival has now become possible with up-front combination systemic therapies, which often include a combination of hormonal therapies or hormonal therapy combined with chemotherapy.

In localized prostate cancer only, both observation and active surveillance are possible (see **Table 1**).[4] Observation is monitoring the disease for symptom development and then treating those symptoms. Active surveillance, on the other hand, involves monitoring the course of the disease using PSA and repeat biopsies as needed, but not too frequently. The therapeutic intent of active surveillance is to initiate curative treatment if cancer progresses.

Surgery using a radical prostatectomy is appropriate for any patient with clinically localized prostate cancer who has no serious comorbid conditions.[4] It is considered the gold standard treatment of prostate cancer. However, it is associated with perioperative morbidity, thus is reserved for those with a life expectancy of 10 years or more. It is typically done either laparoscopically or using robot-assisted techniques. Radiation therapy may be given in addition to surgery to improve the overall outcome, or administered alone in lower risk patients as the main treatment option. It is typically either photon or proton external beam radiation therapy that delivers a beam of high energy x-rays to the prostate tumor itself. Radiologists use various fractionation and dose regimens and no comparative studies have been performed. A boost of radiation therapy (an extra radiation dose given after the regular sessions of radiation are complete) is sometimes used in patients with high or very high-risk disease, using brachytherapy. Brachytherapy is the insertion of radioactive implants directly into the prostate gland.

Oncologists use androgen-deprivation therapy as the primary systemic therapy for treatment of regional or advanced/metastatic prostate cancer but it is also used in localized prostate cancer either before (neoadjuvant), during (concomitantly), or after (adjuvant) prostatectomy or radiation therapy to improve outcomes.[4] ADT's goal is to reduce circulating testosterone levels to that of castration (< 50 ng/mL). The rationale is to reduce this cancer's primary driver: testosterone. This can be accomplished by performing an orchiectomy (surgically removing both testicles); however, oncologists recommend and surgeons perform this procedure only rarely. Instead luteinizing hormone-releasing hormone (LHRH) agonists alone (goserelin, histerlin, leuprolide, triptorelin) or combined with first-generation antiandrogens (e.g., bicalutamide) or an LHRH antagonists (degarelix) are used most often. In localized disease, they are given short-term (four to six months) or long-term (two to three years). In regional and advanced disease they are given throughout the course of disease. Other therapies may be added initially and if the disease progresses.

Docetaxel, a taxane-based chemotherapy that has been used in combination with prednisone in the metastatic setting for years, was recently shown to provide additional benefit to patients with very-high risk localized prostate cancer. This advancement is discussed in more detail below in *New Treatment Options.*

In regional disease, treatment selection depends on life expectancy as well.[4] If the patient's life expectancy is greater than five years or the patient is symptomatic from the prostate cancer, guidelines recommend treatment. Treatment consists of external beam radiation therapy combined with ADT. The addition of the cytochrome P450 (CYP)17 enzyme inhibitor abiraterone + corticosteroid may provide some additional benefit to overall disease outcomes. In patients with a life expectancy of five years or fewer, observation or ADT alone is recommended. Abiraterone acetate selectively inhibits the enzymes C17, 20-lyase, and 17 alfa-hydroxylase on CYP17, which is essential for synthesis of androgen and glucocorticoids.[11] CYP17 is present on the testes, prostate, and adrenal gland. Abiraterone acetate irreversibly inhibits CYP17, decreasing testosterone and cortisol biosynthesis. A negative feedback loop will increase production of adrenocorticotropic hormone (ACTH) in the pituitary gland, ultimately leading to a mineralocorticoid excess syndrome manifested by hypokalemia, peripheral edema, and hypertension. This, however, can be mitigated by administration of a low-dose corticosteroid. Thus abiraterone acetate is administered with prednisone 5 mg by mouth daily or methylprednisolone 4 mg by mouth twice daily if the fine-particle formulation is used.[4]

In patients initially diagnosed with advanced prostate cancer, ADT is the gold standard initial treatment regardless of anticipated life expectancy. The goal of ADT therapy is to extend survival and if the PSA value decreases to less than 4 ng/mL after seven months of therapy, an improved survival time is expected.[12] In patients who have bone metastases and are symptomatic, LHRH-agonist therapy causes an initial increase in testosterone for seven days to a few weeks and can cause a tumor "flare" (tumor

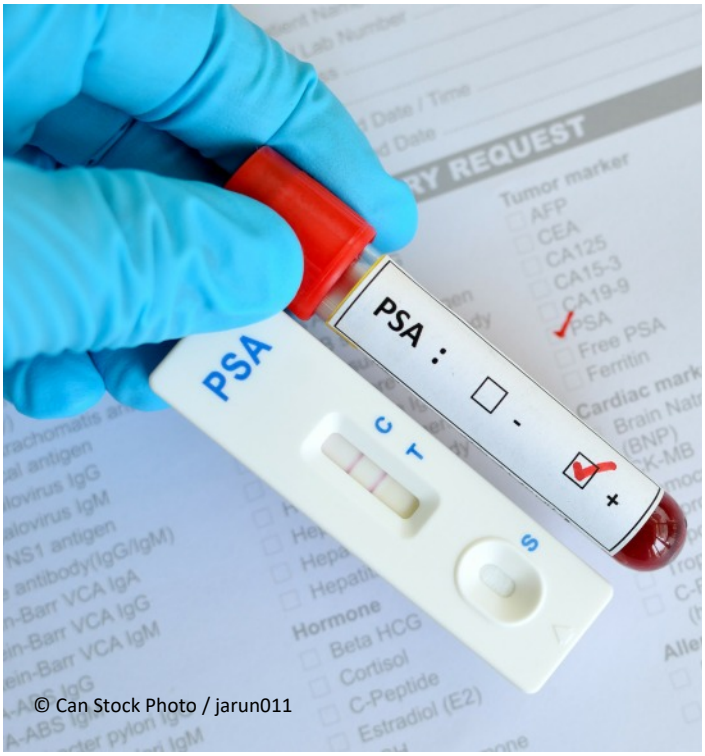
growth accelerates acutely until the testosterone peak subsides causing a significant increase in bone pain). The oncology team should start a first-generation anti-androgen therapy to block the flare *before* starting the LHRH-agonist therapy. After a few weeks, a negative feedback loop suppresses LHRH-agonist-associated testosterone surges and the team can discontinue the anti-androgen. LHRH antagonists rapidly decrease testosterone levels, and thus do not need co-administration with an antiandrogen. Adding abiraterone, docetaxel, or a second-generation antiandrogen (apalutamide or enzalutamide) to ADT at the diagnosis of metastatic prostate cancer has been shown to extend overall survival compared to ADT alone.[4]

Treatment Upon Progression

In patients with localized prostate cancer, the expectation is that the PSA level will fall to an undetectable level following completion of the treatment.[4] Rarely, some patients' PSA levels remain detectable. Regardless, the oncology team will follow patients closely using PSA levels every six to 12 months for five years and then annually. Patients will also have a digital rectal exam annually unless their PSA is undetectable, then it can be omitted. If the PSA rises, then the team will calculate the doubling time and consider imaging (bone scan, CT scans of abdomen/pelvis and chest) to determine if disease has spread to distant sites. If they find no distant sites of disease, they typically initiate ADT with more frequent PSA monitoring (every three to six months). If a rise in PSA occurs again, which typically it will over time, then the disease has probably become resistant to androgen deprivation therapy (ADT). This is called castration-resistant disease. Castration-resistant disease can occur in in men who have or do not have metastases. The key is that patients develop progression (either detected by rising PSA or presence of metastases on imaging) while receiving ADT that is maintaining a castrate-level of testosterone.

If the disease has not spread to distant sites, these patients have progression only noted by a rising PSA (non-metastatic castration resistant disease). In these patients, ADT is continued to maintain a serum testosterone concentration below 50 ng/dL.[4] Historically, patients continued ADT and the oncology team would follow them closely for symptoms of metastatic disease. In 2019, however, several new therapies were proven to be beneficial in slowing the time to development of metastatic disease. This group of drugs is known as second-generation antiandrogens (apalutamide, darolutamide, enzalutamide; discussed in more detail in *New Treatment Options* below). Now, guidelines recommend adding a second generation antiandrogen to ADT if the PSA doubling time is fast (less than or equal to 10 months). For those whose PSA doubling time is slower, the clinical team will continue ADT and close observation.

In patients whose prostate cancer has spread to distant sites while on ADT (metastatic castrate-resistant disease) or those who were initially diagnosed with metastatic disease and progressed



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while receiving ADT, the treatment options are the same. Guidelines recommend biopsying the metastatic lesion to confirm that the metastases isn't from another cancer. Additionally, the lab will test the tumor for mutations that may direct therapy. The team will continue ADT to maintain a serum testosterone concentration below 50 ng/dL and add another therapy.[4]

The first-line treatment options (if they haven't been used previously) include abiraterone acetate, docetaxel, enzalutamide, sipuleucel-T, and radium 223 (only in those with symptomatic bone metastases). Sipuleucel-T is an autologous vaccine that has been available since 2010. This drug exposes the patient's own antigen-presenting cells to prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor and then re-infuses the cells into the patient. It is only recommended for patients who are asymptomatic or minimally symptomatic since their disease burden is low and immune function is likely fully intact.[4] Radium-223 dichloride is an alfa-particle emitting radioactive agent approved in 2013 for patients with symptomatic bone metastases. It is associated with improved survival and improved or slower decline of quality of life.[13]

Second- and subsequent-line options include

- one of the first-line options not already used
- cabazitaxel (a semi-synthetic taxane derivative)
- mitoxantrone (cytotoxic agent that intercalates DNA)
- pembrolizumab (a checkpoint inhibitor effective in those with a mismatch repair gene deficiency or high amounts of microsatellite instability), or
- olaparib (a poly-ADP ribose polymerase [PARP] inhibitor for patients with homologous recombination DNA repair gene (HRR) mutations.

NEW TREATMENT OPTIONS

Docetaxel + Radiation Therapy + ADT in Very High-Risk Localized Prostate Cancer

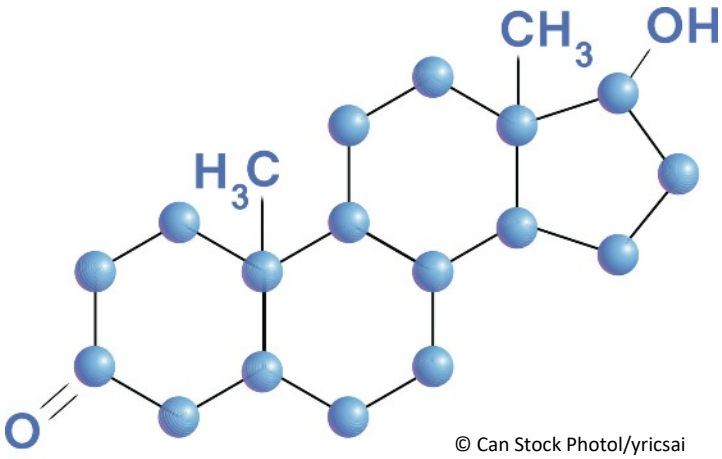
Several new treatment options for prostate cancer emerged over the last year. Unlike in other solid tumors, adjuvant chemotherapy has not been a standard of care.[14] Patients with localized prostate cancer who are categorized as high-risk or very-high risk have 5-year survival rates of 75% to 98%.[4] Thus, finding an adjuvant therapy that could improve cancer-free survival in these men is critical. Several studies have evaluated the addition of adjuvant chemotherapy to primary local therapies but have produced mixed results.[14] Recently, however, the Radiation Therapy Oncology Group (RTOG) 0521 trial demonstrated the benefit of adjuvant chemotherapy.[15]

Now, for the first time, adjuvant docetaxel-based chemotherapy following radiation therapy and long-term ADT has become standard of care for patients with very-high risk, localized prostate cancer. The RTOG 0521 trial randomized patients with high-risk or very-high risk localized prostate cancer to receive radiation therapy and ADT, with or without docetaxel.[15] Overall survival time improved from 83% to 93% four years after therapy (hazard ratio [HR], 0.69; 95% confidence interval [95% CI], 0.49-0.97; *P*=0.034). Additionally 6-year disease-free survival (DFS) rates and time to development of metastases within six years were significantly improved (55% versus 65%, *P*=0.44; 14% versus 9.1%; *P*=0.43). Patients tolerated treatment well with no unexpected side effects. For this small subset of patients with localized therapy, adjuvant chemotherapy combined with radiation therapy and ADT can improve long-term outcomes.

Second-Generation Antiandrogens in Castrate-Resistant Prostate Cancer (CRPC)

First-generation antiandrogens (bicalutamide, flutamide, nilutamide) are steroidal analogs that block androgen receptor ligand activation.[16] Resistance to these drugs—caused by androgen receptor amplification, point mutations and expression of androgen receptor splice variants, intratumor androgen production, or downstream mechanisms—develops relatively quickly. This renders these drugs ineffective after resistance develops. When resistance develops and the prescriber discontinues the first-generation antiandrogen, an androgen withdrawal syndrome occurs in tumors, producing a temporary disease regression.

The second-generation antiandrogens (apalutamide, darolutamide, enzalutamide) posess increased specificity to the androgen receptor, act with a higher affinity, and are antagonistic to the androgen receptor. This in turn prevents nuclear translocation and subsequent signaling to androgen receptor target genes. Because second-generation antiandrogens are antagonistic, they do not have the ability to cause an androgen withdrawal syndrome upon discontinuation.



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Testosterone

Enzalutamide was the first approved second-generation antiandrogen. It has been shown to be effective in metastatic CRPC cancer since 2012. It improves overall survival from 13.6% to 18.4% in patients who have relapsed following docetaxel therapy.[17] Most recently, enzalutamide has been shown to be effective in men with non-metastatic CRPC. The phase III PROSPER trial demonstrated improved metastasis-free survival when compared with placebo in men with nonmetastatic CRPC and a PSA double-timing of < 10 months (36.6 mo versus 14.7 mo; HR, 0.29; 95% CI, 0.24-0.35: *P*<0.001).[18] Generally, enzalutamide is well tolerated, with fatigue (33%), hot flush (13%), hypertension (12%), nausea (11%), and falls (11%) being its most common side effects. Enzalutamide is associated with an increased risk of seizures, albeit low. It is thought to be due to binding the gamma-aminobutyric acid receptor ($GABA_A$).

Apalutamide, another second-generation antiandrogen, is less likely to cross the blood-brain barrier than enzalutamide. This is thought to be a positive characteristic because it may potentially lower risk of seizure activity. In 2019, the FDA approved apalutamide for the use men with nonmetastatic CRPC based on the results of the SPARTAN trial.[19] In this phase III trial, researchers randomized more than 1200 nonmetastatic CRPC patients with a PSA doubling time of less than 10 months to receive apalutamide or placebo. The median metastasis-free survival was significantly improved: 40.5 mo versus 16.2 mo; HR, 0.28 (95% CI, 0.23-0.35: *P*<0.001). The most common side effects with apalutamide are fatigue, hypertension, rash, and diarrhea. Seizures still did occur but at a very low rate (0.2%). Additionally hypothyroidism (8%), falls (16%), and fractures (12%) were higher compared with those receiving placebo.

Darolutamide has increased potency over apalutamide and enzalutamide and has the ability to inhibit androgen receptor mutations that the other second-generation inhibitors cannot.[20] The FDA approved it in 2019. The ARAMIS trial evaluated darolutamide in men with nonmetastatic CRPC who had a PSA doubling time of 10 months or less. Darolutamide improved

metastasis-free survival (40.4 mo versus 18.4 mo; HR, 0.41; 95% CI, 0.34-0.5; *P*<0.001). At the first interim analysis, overall survival was also improved (HR, 0.71; 95%CI, 0.5-0.99; *P*=0.45). Darolutamide's most common side effects are fatigue (15.8%), dizziness (4.5%), and fractures/falls (4.2%). Rarely rash (2.9%), seizures (0.2%) and hypothyroidism (0.2%) occur.

Second-Generation Antiandrogens in Castration-Naive Metastatic Prostate Cancer

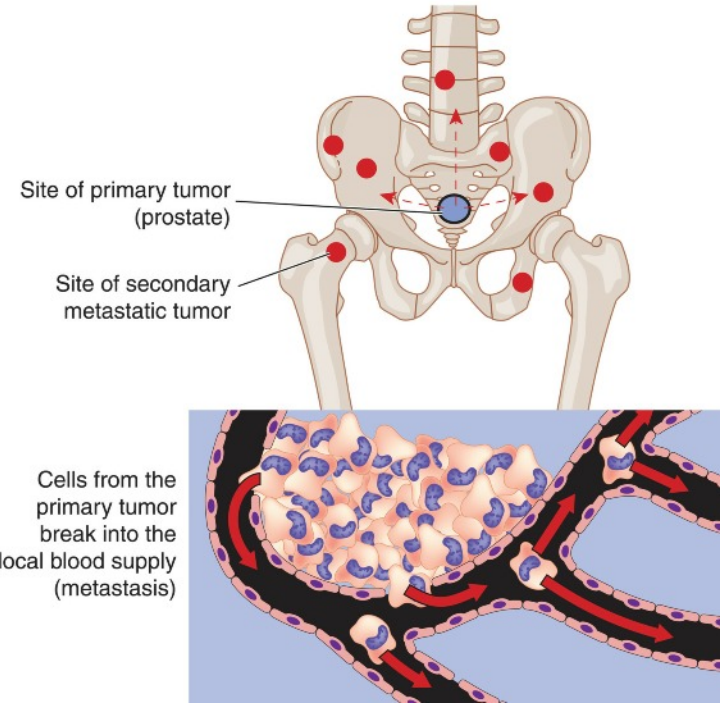
Both apalutamide and enzalutamide have been shown to be effective as initial therapies for men with newly diagnosed metastatic prostate cancer not previously receiving therapy (i.e., castration-naive). Apalutamide was evaluated in the phase III TITAN trial.[21] Men with newly diagnosed metastatic prostate cancer (one or more bone lesions or lymph node involvement) were randomized to apalutamide (+ADT) or placebo (+ADT). Apalutamide significantly improved radiographic progression free survival (PFS) and overall survival at 24 months. Radiographic PFS occurred in 68.2% of apalutamide-treated patients and 47.5% of those receiving placebo. (HR, 0.48; 95% CI, 0.39-0.6; *P*<0.001). Twenty-four month overall survivial (OS) was 82.4% versus 73.5% (HR, 0.67; 95% CI, 0.51-0.89; *P*=0.005). Hypertension, rash, fractures, and hypothyroidism were more common with apalutamide.

The ENZAMET and ARCHES studies demonstrated enzalutamide's effectiveness combined with ADT in men with newly-diagnosed castration-naïve metastatic prostate cancer.[22,23] The ENZAMET study improved overall survival at the interim analysis (82% versus 75%; HR, 0.67; 95% CI, 0.52-0.86; *P*=0.002) as well as clinical and PSA-related PFS times.[21] The ARCHES trial demonstrated an improved radiographic PFS time (19 mo versus not reached; HR, 0.39; 95% CI, 0.30-0.50; *P*<0.001).[23] Fatigue, nausea, hypertension and seizure risk (<1%) were noted in these trials.

PAUSE AND PONDER: What are the differences in monitoring guidelines among the second-generation antiandrogens?

PARP Inhibitors as Second- or Subsequent-Line Treatment in Metastatic CPRC

In men with metastatic prostate cancer or those with regional disease, the National Comprehensive Cancer Network (NCCN) evidence-based guidelines recommend evaluating the prostate tumor for alterations in the HRR genes.[4] These include genes such as *BRCA1, BRACA2, ATM, PALB2, FANCA, RAD51D, CHEK2,* and *CDK12*. This information may be useful for genetic counseling, whereby germline or testing for hereditary-based cancers may be recommended based on family history or the use of specific drug therapy.



The PARP inhibitor olaparib has been associated with clinical activity in men with CRPC and hereditary (i.e., germline) or acquired (i.e., somatic) DNA repair enzyme mutations. A phase II study conducted several years ago showed that patients with advanced cancer, including eight patients with prostate cancer and *BRCA1* or *BRCA2* mutations, benefited from olaparib.[24] Tumor response rates were observed in 50% of patients and stable disease in 25% of patients. The most common side effects were anemia, diarrhea, and nausea.

More recently, a small, phase II double-blind, placebo-controlled trial compared olaparib in combination with abiraterone acetate with abiraterone alone.[25] In this study, 15% of patients had a known HRR mutation and approximately 60% had a partially characterized mutation status. The results of this trial showed an improved PFS of 13.8 months with combination therapy compared with 8.2 months with abiraterone only (HR, 0.65; 95% CI, 0.44-0.97; *P*=0.34). Most common side effects with the combination of abiraterone and olaparib included nausea, constipation, back pain, and fatigue. Although these results are encouraging, olaparib is not FDA-approved for use in the treatment of prostate cancer patients.[4] More data is needed to recommend this routinely for all patients. Those with HRR mutations are encouraged to enroll in clinical trials. However, recently the NCCN prostate cancer evidence-based guidelines recommend consideration of olaparib for men with an HRR mutation who have progressed on prior treatment with enzalutamide or abiraterone, particularly if a clinical trial is not available.

With these recent advances in management of prostate cancer, knowing the appropriate monitoring for these therapies is critical to achieving optimal outcomes. Docetaxel is not a new therapy. It was first approved in 1996 and has been used in the metastatic prostate cancer setting for decades.[25] For men receiving adjuvant docetaxel therapy, recommendations for dosing, monitoring, and supportive care can be found in **Table 2**.[27]

Table 3 provides recommendations for the pharmacy team to consider when caring for prostate cancer patients receiving the new oral treatment medications. Ischemic cardiac events have been observed with both apalutamide and enzalutamide.[28,29] Guidelines and prescribing information recommend managing hypertension, diabetes, dyslipidemia, and other cardiovascular risk factors. Similarly, falls and fractures can occur with these drugs. It is prudent to assess fall risk and evaluate bone mineral density (BMD) in these patients prior to initiating therapy and to monitor more closely. A small number of patients develop seizures. The onset has ranged from 13 days to more than 60 months after treatment starts. In some case predisposing factors were present (history of seizure, drugs known to decrease seizure threshold, brain metastases). It is not known whether anticonvulsants can prevent seizures. Therefore, educating patients about this risk is important and if a seizure should occur, discontinue the drug.

Maculopapular rashes have been reported in nearly 25% of patients taking apalutamide.[28] The median time to onset is 78 days; rash can be managed with oral antihistamines (e.g., diphenhydramine or similar OTC products) and topical corticosteroids. In some cases, patients may require systemic corticosteroids or treatment interruption or discontinuation. This would occur if the rash was grade 3 (> 30% of body covered or limiting activities of daily living).[30] Rash has reappeared in 50% of patients who take a treatment break. Hypothyroidism has been reported with apalutamide with a median onset of four months. Monitoring thyroid stimulating hormone levels at baseline and then every four months is recommended. If needed, thyroid replacement therapy should be initiated.

Rarely, posterior reversible encephalopathy syndrome has been reported in patients receiving enzalutamide.[29] It manifests with rapidly evolving symptoms such as headache, seizure, lethargy, confusion, and blindness with or without hypertension. The clinical team should evaluate patients immediately and must confirm diagnosis by magnetic resonance imaging. Hypersensitivity reactions with enzalutamide have rarely been reported as well, including facial, tongue, or lip edema. Enzalutamide should be permanently discontinued if either of these occur.

Darolutamide is very well tolerated.[31] It did cause neutropenia more often than in placebo, so although not routinely recommended, it may be prudent to monitor CBC occasionally. Dose reductions may be needed for hepatic and renal impairment (see **Table 3**). It needs to be taken twice daily with food.

Olaparib is associated with myelosuppression. Anemia, neutropenia, and thrombocytopenia can all occur.[32] Therefore, clinicians should monitor complete blood count with differential monthly and interrupt the dose, ordering weekly blood counts until recovery occurs. Nausea and vomiting is usually mild and may improve by administering olaparib with food. Hypersensitivity reactions (rash and dermatitis) and pneumonitis have rarely been reported. Clinicians should evaluate patients with new or worsening cough, dyspnea, fever, or any pulmonary radiologic changes for pneumonitis. Finally myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported in patients with BRCA mutations receiving olaparib for other cancers. Typically MDS or AML occurs between six months and two or more years after therapy and patients

Table 2. Monitoring Recommendations for Docetaxel in the Adjuvant Setting[28]

Monitoring Parameter	Clinical Pearls
Dose	Docetaxel 75 mg/m^2/dose IV over 1 hour every 21 days + prednisone 10 mg po daily[a] x 6 cycles
Pre-medications	Dexamethasone 8 mg po BID x 3 days, starting day before docetaxel *(to prevent peripheral edema and hypersensitivity reactions and because it has antiemetic effect on day of chemotherapy)*
Monitoring	• CBC with differential, bilirubin, alkaline phosphatase, ALT, AST, renal function, glucose within 3 days before each cycle • Blood pressure regularly • Hypersensitivity, peripheral neuropathy, fluid retention, GI toxicity (diarrhea, mucositis), changes in fingernails and toenails (color, texture, and shape changes)
Supportive care	• Administer prednisone with food to prevent gastritis; consider H_2 blocker (e.g., famotidine) or PPI (e.g., esomeprazole, pantoprazole) during therapy to prevent stress ulcers • Breakthrough antiemetic (e.g., prochlorperazine, ondansetron) in case nausea or vomiting occurs

[a]Daily prednisone is optional if dexamethasone is administered as a premedication.
ALT = alkaline aminotransaminase; AST = aspartate aminotransaminase; H_2, histamine-2; IV = intravenous; PPI = proton-pump inhibitor.

receiving other chemotherapy or radiation therapy, which may be responsible for the dysplasia, are at greatest risk. However, if prolonged cytopenias occur and do not recover with treatment interruption, a further evaluation for MDS and/or AML should occur.

Supportive Care in Men With Prostate Cancer

Supportive care during and after treatment of prostate cancer is important. ADT has numerous side effects that include menopausal-like symptoms, and bone- and cardiovascular-related effects.[4,33] A suggested link between ADT and cognitive decline has been reported but not proven yet.[4] Generally, ADT's side effects increase with its duration. As men with metastatic prostate cancer are living longer, the need to manage these effects will increase. **Table 3** summarizes recommended treatment strategies. Pharmacists should also remember that many men who have prostate cancer will have adherence barriers, and employ the principles of motivational interviewing (see **Sidebar**).

ADT increases bone turnover and decreases bone mineral density, thus increasing the risk of fracture.[36] Bone loss can occur as early as six months after initiating therapy. Thus, men who initiate ADT should be evaluated and treated for osteoporosis. The National Osteoporosis Foundation guidelines recommendation that all patients receive calcium (1000-1200 mg/day) from food sources and supplements and vitamin D_3 (400-1000 international units/day).[37] For men who are 50 and older, bone mass should be assessed by dual energy x-ray absorptiometry (DEXA) and a fracture risk evaluated using the World Health Organization's FRAX algorithm.[4] When calculating the FRAX score, ADT is considered secondary osteoporosis. In men who have a low bone mass (T-score between -1.0 and -2.5) at the femoral neck, total hip, or lumbar spine and a 10-year probability of fracture 3% or higher should receive additional bone health treatment.[37,38] Additionally, those who have a 10-year probability of a major osteoporosis-related fracture of 20% or higher regardless of BMD, should receive additional bone health treatment.[37] One year after initiating ADT, the care team should repeat the DEXA scan,

(Text continues on page 11)

Table 3. ADT-Related Supportive Care for Prostate Cancer Patients[4,36-39]

Issue	Clinical Pearls
Bone Health	All men receiving ADT • Calcium (1000-1200 mg/day) + vitamin D3 (400-1000 international units/day) Osteopenia ± fracture risk: • Alendronate 70 mg po weekly • Densoumab 60 mg SC q 6 mo • Zoledronic acid 5 mg IV annually Prevent skeletal-related events in metastatic CRPC • Densoumab 120 mg SC q 4 wk • Zoledronic acid 4 mg IV q 4 wk
Diabetes and CV Health	• Screen patients for and intervene with typical treatment and risk reduction options as for general population • Encourage healthy eating, smoking cessation, appropriate alcohol consumption, exercise
Loss of muscle mass and fatigue	• Encourage regular resistance and weight-bearing exercise
Vasomotor symptoms	• Educate patient about use of layered clothing/bedding, avoidance of caffeine, alcohol, hot/spicy food, regular exercise/physical activity, weight loss if obese • Nonpharmacologic – acupuncture, cognitive behavioral therapy • Venlafaxine 25 mg po daily and increase to 75 mg po daily if needed • Gabapentin 100 mg po daily and increase to 300 mg po TID if needed • Referral to specialist for consideration of hormonal therapy (e.g., medroxyprogesterone)
Sexual health	Erectile dysfunction • Oral PDE5 (e.g., avanafil, sildenafil, tadalafil, vardenafil) PRN or low-dose daily (if not contraindicated) • Lifestyle modifications, pelvic physical therapy Ejaculatory problems • SSRIs daily (paroxetine, sertraline, citalopram, fluoxetine) or clomipramine on demand • Pelvic physical therapy • Climacturia: empty bladder before sex, pelvic physical therapy, imipramine Orgasm problems • PDE5 inhibitors if not contraindicated • Vibrator or clitoral stimulatory device – referral to specialist • Pelvic physical therapy

ADT = androgen deprivation therapy; CV = cardiovascular; PDE5 = phsophodiesterase type 5 inhibitors; SSRIs = selective serotonin receptor inhibitors

SIDEBAR: Motivational Interviewing in the Patient with Prostate Cancer[34,35]

Motivational interviewing (MI) is a counseling method that helps people change their behavior. Pharmacists can help patients develop internal motivation by resolving ambivalent feelings and insecurities. By employing empathy and well-constructed questions, skilled interviewers can let patients know that they understand how difficult it is to make life changes. They can also lead the patient to change. MI is best used when working with patients who are unprepared for change or unmotivated—this might be the man whose prostate cancer is progressing, and he is ambivalent about starting ADT.

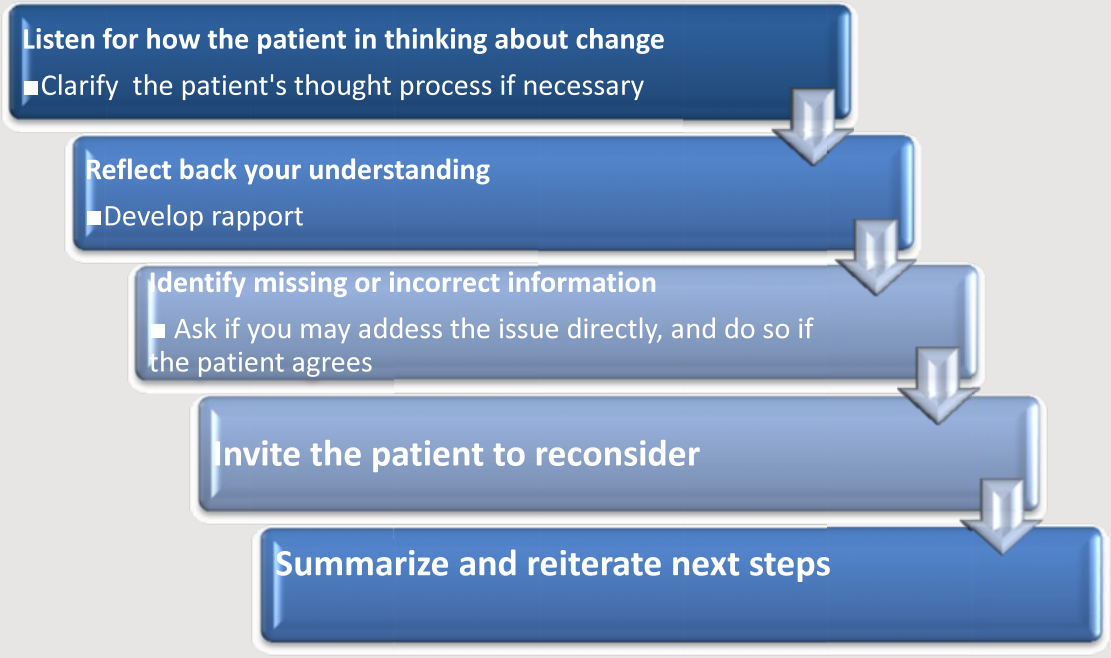
Pharmacists can encourage patients to talk about their need for change and their personal reasons for wanting to change. Pharmacist-interviewers listen empathetically and reflect the patient's thoughts back. Patients will often hear their own reasons and motivations and realize that they want to change. The goal is to increase the patient's motivation to change, and then to have the patient commit to the change. This theory is based on a simple fact: a patient's resistance to change is almost always related to conditions other than a character flaw or the desire to make a healthcare provider's life more difficult.

Patients who are in a state of high distress often resort to passive escape-avoidance coping behaviors (e.g., wishing things would get better, hoping for a miracle). Using MI, pharmacists can move them away from escape-avoidance, and toward higher self-efficacy and an improved sense of control. Patients who learn to manage their current side effects will also feel less distress when new side effects develop.

MI relies on four basic techniques:

- Open-ended questions. Some typical questions among men who are nonadherent to medications for prostate cancer or considering stopping ADT might be
    - What are the issues that trouble you, and how can I help you deal with those?
    - What goal would you like to set that you are willing to accomplish?
    - Would you mind if I share some thoughts with you, and then you can tell me what you think? (This is not open ended, but gives the patient situational control.)
- Affirmations (expressing empathy and celebrating even small successes)
    - "I understand how troubling hot flashes can be."
- Reflective listening (repeating words back to patients)
    - "I hear you saying that you are considering stopping your ADT because the hot flashes keep you awake."
    - "I can see that you want to pursue treatment so that you can be there for your family in the future."
- Summarizing
    - "You said that the hot flashes are very disruptive, and we talked about three things that might help—using a fan, wearing easily removable layers of clothing, and asking your oncologist if you might be a good candidate for venlafaxine or gabapentin. Which of those approaches might you be able to try before giving up?"

This is a basic graphic of how MI works:



and obtain vitamin D levels.[33] Men with CRPC and bone metastases are at higher risk of skeletal-related events, such as fractures, spinal cord compression, and the need for surgery or radiation therapy to treat significant bone pain or these types of bone effects.[4] Thus, they should receive a bone-modifying agent to prevent these skeletal-related events. Both denosumab and zoledronic acid can be used but the doses and schedules are different than that used for osteopenia (see **Table 3**).

ADT also increases fat mass and decreases lean body mass; increases fasting plasma insulin; decreases insulin sensitivity; and increases serum cholesterol and triglyceride levels.[4] Thus, men receiving ADT are at higher risk of developing diabetes, cardiovascular disease, and hyperlipidemia and often experience weight gain. A median weight gain of 1 to 2 kilograms (2.2 to 4.4 pounds) after one year of treatment has been observed.[39] Typical nonpharmacologic strategies such as a heart-healthy diet and exercise are recommended for all patients, as is screening for diabetes and cardiovascular disease. Treatment of these should follow the same guidelines used in men without prostate cancer. Fatigue is also very common in these patients. Regular exercise has been shown to improve overall fatigue levels.

Due to the loss of testosterone caused by ADT, males receiving ADT often experience menopausal symptoms and sexual dysfunction.[33] Like women undergoing menopause, men can develop night sweats or hot flashes that can range from mild in nature to disruptive to quality of life. Guidelines recommend nonpharmacologic and pharmacologic treatments for men similar to those used in menopausal women. In no event should testosterone or products that contain testosterone-like substances be used as they would negate ADT's effects. Other hormonal agents (progesterone or estrogen-related products) should only be recommended by a specialist.

The two non-hormonal pharmacologic agents shown to be beneficial for hot flashes in men include venlafaxine and gabapentin.[36,39] Venlafaxine has been shown to decrease the number and intensity of hot flashes whereas gabapentin has been shown to decrease hot flashes moderately in a dose-dependent manner. When these agents are initiated, start with the lowest dose and titrate if needed.

All men receiving ADT will experience testicle shrinkage and in some cases penile shrinkage and/or gynecomastia. Sexual dysfunction can manifest as loss of libido, erectile dysfunction, or problems with ejaculation or orgasm. Lifestyle modifications and pelvic physical therapy can be beneficial. In some cases, pharmacologic therapy such as oral phosphodiesterase type 5 inhibitors or selective serotonin receptor inhibitors may be helpful as long as the patient has no contraindications.[36,39] If possible, referral to a sexual health specialist can be helpful in identifying the sexual dysfunction and appropriate therapy.

CONCLUSION

Advancements in diagnosing prostate cancer, stratifying risk of disease progression, and likelihood of responding to treatment in early stage prostate cancer have changed practice. By categorizing patients based on risk, treatment can be tailored to provide the most effective outcome while reducing the risk of long-term morbidity from treatment. For the first time in the history of prostate cancer, adjuvant chemotherapy with docetaxel is an option in those with very high-risk localized prostate cancer. In patients who progress or who have metastatic prostate cancer, new treatment advances, including the use of second-generation antiandrogens and PARP inhibitors in those with HRR mutations, have improved outcomes. These new treatment options, though, require close monitoring to prevent and/or mitigate toxicity. Furthermore, supportive care, particularly in those receiving ADT, is necessary. The pharmacy care team can play a vital role in educating patients, providing recommendations for the monitoring of new treatments, and providing patients with supportive care.

Figure 1 (next page) walks you through ways to maximize your role in caring for prostate cancer.

Figure 1. Maximizing the Pharmacy Team's Role in Prostate Cancer

Best

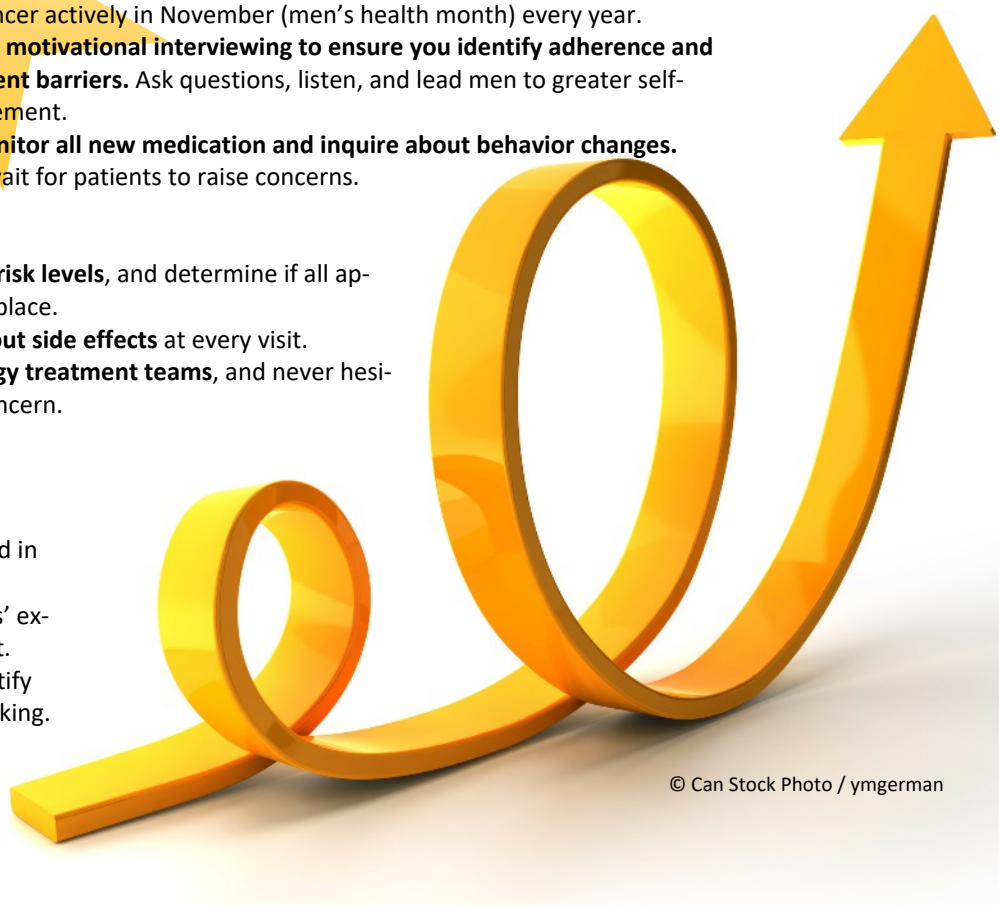
❶ **Be COMMUNITY CHAMPIONS.** Actively heighten awareness of prostate cancer actively in November (men's health month) every year.
❷ **Use motivational interviewing to ensure you identify adherence and treatment barriers.** Ask questions, listen, and lead men to greater self-management.
❸ **Monitor all new medication and inquire about behavior changes.** Don't wait for patients to raise concerns.

Better

❶ **Consider the patient's risk levels**, and determine if all appropriate therapies are in place.
❷ **Inquire proactively about side effects** at every visit.
❸ **Know patients' oncology treatment teams**, and never hesitate to call if you have a concern.

Good

❶ **Know the current medications** used in various stages of prostate cancer.
❷ **Ask a few questions** about patients' experiences and concerns with treatment.
❸ **Listen** to men's concerns, and identify areas of ambivalence or conflicted thinking.



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