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■ ■SUBSTANCE ABUSE AND TOBACCO (See also Chaps. 464 and 465) Substance abuse is more common in men than in women. However, nearly one-third of Americans who suf fer from alcoholism are women. Women are less likely to be diagnosed with alcoholism than men. A greater proportion of men than women seek help for alcohol and drug abuse. Men are more likely to go to an alcohol or drug treatment facility, whereas women tend to approach a primary care physician or mental health professional for help under the guise of a psychosocial problem. Blood alcohol levels are higher in women than in men after drinking equivalent amounts of alcohol, adjusted for body weight. This greater bioavailability of alcohol in women is due to both the smaller volume of distribution and the slower gastric metabolism of alcohol secondary to lower activity of gastric alcohol dehydrogenase than is the case in men. Women with alcohol ism have a higher mortality rate than do women and men without alcoholism. Women also appear to develop alcoholic liver disease and other alcohol-related diseases with shorter drinking histories and lower levels of alcohol consumption. Alcohol abuse also poses special risks to a woman, adversely affecting fertility and the health of the baby (fetal alcohol syndrome). Even moderate alcohol use increases the risk of breast cancer, hypertension, and stroke in women.

PART 12 Endocrinology and Metabolism More men than women smoke tobacco, but this sex difference continues to decrease. Women have a much larger burden of smokingrelated disease. Smoking markedly increases the risk of CVD in pre menopausal women and is also associated with a decrease in the age of menopause. Women who smoke are more likely to develop chronic obstructive pulmonary disease and lung cancer than men and at lower levels of tobacco exposure. Postmenopausal women who smoke have lower bone density than women who never smoked. Smoking during pregnancy increases the risk of preterm deliveries and low birth weight infants. ■ ■VIOLENCE AGAINST WOMEN Approximately 15% of women in the United States have experienced rape, physical violence, and/or stalking by an intimate partner, as compared to 4% of men with similar experiences. Adult women are much more likely to be raped by a spouse, ex-spouse, or acquaintance than by a stranger. Intimate partner violence (IPV) is a leading cause of death among young women. Rates of reported IPV in the United States increased dramatically amid stay-at-home orders during the COVID19 pandemic but have since declined again to prepandemic rates. IPV is an important risk factor for depression, substance abuse, and suicide in women. Screening instruments can identify women experiencing IPV and should be administered in settings that ensure adequate pri vacy and safety. SUMMARY Women’s health is now a mature discipline, and the importance of sex differences in biologic processes is well recognized. Nevertheless, ongoing misperceptions about disease risk, not only among women but also among their health care providers, result in insufficient attention to modifiable risk factors. Research into the fundamental mechanisms of sex differences will provide important biologic insights. Further, those insights will

have an impact on both women’s and men’s health. ■ ■FURTHER READING Howell E: Reducing disparities in severe maternal morbidity and mortality. Clin Obstet Gynecol 61:2, 2018. Lott N et al: Sex hormones in SARS-CoV-2 susceptibility: Key play ers or confounders? Nat Rev Endocrinol 19:217, 2023. Rich-Edwards J et al: Sex and gender differences research design for basic, clinical, and population studies: Essentials for investigators. Endocr Rev 39:4, 2018. Rubino D et al: Effect of continued weekly subcutaneous semaglu tide vs placebo on weight loss maintenance in adults with over weight or obesity: The STEP 4 randomized clinical trial. JAMA 325:14, 2021. Singh T et al: Takotsubo syndrome: Pathophysiology, emerging con cepts, and clinical implications. Circulation 145:13, 2022.

Shalender Bhasin

Men’s Health The emergence of men’s health as a distinct discipline within internal medicine is founded on the wide consensus that men and women dif fer across their life span in their susceptibility to disease, in the clinical manifestations of the disease, and in their response to treatment. Fur thermore, men and women weigh the health consequences of illness differently and have different motivation for seeking care. Men and women experience different types of disparities in access to health care services and in the manner in which health care is delivered to them because of a complex array of socioeconomic and cultural factors. Attitudinal and institutional barriers to accessing care, fear and embar rassment due to the perception that it is not manly to seek medical help, and reticence on the part of patients and physicians in discussing issues related to sexuality, substance use, and aging have heightened the need for programs tailored to address the specific health needs of men. The sex differences in disease prevalence, susceptibility, and clinical manifestations of the disease were discussed in Chap. 410 (Women’s Health) and will not be discussed here. It is notable that the two leading causes of death in both men and women—heart disease and cancer—are the same. However, men have higher prevalence of neu rodevelopmental and degenerative disorders; substance use disorders, including the use of performance-enhancing drugs and alcohol use disorder; diabetes; cardiovascular disease; liver cirrhosis; and some types of cancer such as prostate, melanoma, and pancreatic cancer; and women have a higher prevalence of autoimmune disorders, depression, rheumatologic disorders, and osteoporosis. Men are substantially more likely to die from accidents, suicides, and homicides than women. Among men 15–34 years of age, unintentional injuries, homicides, and suicides account for over three-fourths of all deaths. Among men 35–64 years of age, heart disease, cancer, and unintentional injuries are the leading causes of death. Among men ≥65 years of age, heart disease, cancer, lower respiratory tract infections, and stroke are the major causes of death. From 1999 to 2010, the mortality rates in the United States decreased for men and women of all age groups, largely due to reduced death rates from heart attacks, cancer, motor vehicle injuries, and HIV infection. However, since 2010, troubling disparities in sex-specific mortality rates have emerged among middle-aged men in the United States. From 2010 to 2017, the death rates have risen and life expec tancy has decreased for young and middle-aged men. The increase in mortality rates among people aged 25–64 was the highest in the Ohio Valley and Appalachia, and in the New England states of New Hampshire, Maine, and Vermont. The rising mortality rates in young and middleaged men have been attributed to an increase in deaths due to drug overdose, alcohol-related liver disease, and suicide. The rising rates of “deaths of despair” among young and middle-aged men, especially white non-Hispanics, have been associated with deterioration in eco nomic and social well-being, reduced rates of marriage and labor force participation, and poor physical

and mental health. The biologic bases of sex differences in disease susceptibility, pro gression, and manifestation remain incompletely understood and are likely multifactorial. Undoubtedly, sex-specific differences in the genetic architecture and circulating sex hormones influence disease phenotype; additionally, epigenetic effects of sex hormones during fetal life, infancy, and pubertal development may epigenetically imprint sexual and nonsexual behaviors, body composition, and disease sus ceptibility. The circulating and tissue concentrations of sex hormones differ substantially in men and women, and these hormonal differences may affect gene expression in cells of males and females in all parts of the body. The presence of only one X chromosome in men renders them more susceptible to X-linked disorders than women. Due to the X inactivation of one randomly chosen X chromosome, women's bod ies contain two epigenetically different cell populations. The genes that

do not undergo X inactivation exhibit dosage differences between male and female cells. Expression of the Y chromosome genes in men may affect the function of somatic cells containing the Y chromosome. The loss of Y chromosome with aging in men is associated with increased risk of heart disease, especially heart failure, certain types of cancers, and shortened life span. The differences in the imprinting of maternally and paternally derived genes may also contribute to sex differences in the expression of disease. Reproductive load and physiologic changes during pregnancy, including profound hormonal and metabolic shifts and microchimerism (transfer of cells from the mother to the fetus and from the fetus to the mother), may affect disease susceptibility and disease severity in women. Sociocultural norms of child-rearing prac tices, societal expectations of gender roles, and the long-term economic impact of these practices and gender roles influence health behaviors and disease risk. Furthermore, the trajectories of age-related changes in sex hormones during the reproductive and postreproductive years vary substantially between men and women and influence the sex-specific patterns of the temporal evolution of age-related conditions such as osteoporosis, breast cancer, and autoimmune disease. In a reflection of the growing attention on issues related to men's health, men's health clinics have mushroomed all over the country. Although the major threats to men's health have not changed—heart disease, cancer, and unintentional injury continue to dominate the list of major medical causes of morbidity and mortality in men—the men who attend men's health clinics do so largely for sexual, reproductive, and urologic health concerns involving common conditions, such as testosterone deficiency syndromes, age-related decline in testos terone levels, sexual dysfunction, muscle dysmorphia and anabolicandrogenic steroid (AAS) use, lower urinary tract symptoms (LUTS), and medical complications of prostate cancer therapy, which are the subjects of this chapter. Additionally, we are witnessing the emergence of new categories of body image disorders in men that had not been recognized until the 1980s, such as the body dysmorphia syndrome and the use of performance-enhancing drugs to increase muscularity and lean appearance. Although menopause and women's health have been the subject of intense investigation for more than five decades, these issues that are specific to men's health are just beginning to gain the attention that they deserve because of their high prevalence and impact on overall health, well-being, and quality of life. AGING-RELATED CHANGES IN MALE REPRODUCTIVE FUNCTION A number of cross-sectional and longitudinal studies (e.g., the Bal timore Longitudinal Study of Aging, the Framingham Heart Study [FHS], the Massachusetts Male Aging Study, and the European Male Aging Study [EMAS]) have established that testosterone concentrations decrease with advancing age. This age-related decline starts in the third decade of life and progresses slowly (Fig. 411-1); the magnitude and trajectory of age-related decline in testosterone levels are affected by adiposity and weight

change, comorbid conditions, and genetic factors. Because sex hormone–binding globulin (SHBG) concentrations are higher in older men than in younger men, free or bioavailable testos terone concentrations decline with aging to a greater extent than total testosterone concentrations. In the EMAS, 2.1% of community-dwelling men aged 40–70 years had total testosterone levels <317 ng/dL and a free testosterone level of <64 pg/mL, as well as sexual symptoms. The age-related decline in testosterone is due to defects at all levels of the hypothalamic-pituitary-testicular (HPT) axis. Pulsatile gonadotropinreleasing hormone (GnRH) secretion is attenuated, luteinizing hormone (LH) response to GnRH is reduced, and the frequency, amplitude, and area of LH pulses are reduced in older men. Leydig cell number is reduced and testicular response to LH is impaired. The gradual rise of LH with aging suggests that testis dysfunction is the main cause of declining androgen levels. In epidemiologic surveys, low total and bioavailable testosterone concentrations in middle-aged and older men are associated with decreased sexual desire, poor erections, and diminished early morning erections; lower appendicular skeletal muscle mass, muscle strength,

Total testosterone (ng/dL) vs. age (y) FHS EMAS MrOS Testosterone level (ng/dL)

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20–29 50–59 Age (y) 60–69 70–79 80+ 30–39 40–49 FIGURE 411-1 Age-related decline in total testosterone levels. Total testosterone levels measured using liquid chromatography–tandem mass spectrometry in men of the Framingham Heart Study (FHS), the European Male Aging Study (EMAS), and the Osteoporotic Fractures in Men Study (MrOS). (Reproduced with permission from S Bhasin et al: Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the Framingham Heart Study and applied to three geographically distinct cohorts. J Clin Endocrinol Metab 96:2430, 2011.) and self-reported physical function; increased risk of mobility limitation and falls; higher visceral fat mass, insulin resistance, and type 2 diabetes; reduced telomere length and increased all-cause and cardiovascular mor tality; lower areal and volumetric bone mineral density and bone quality; and higher rates of bone fractures (Table 411-1). Middle-aged and older men with hypogonadism report a high frequency of depressive symp toms. However, testosterone levels have not been consistently associated with major depressive disorder. An analysis of signs and symptoms in older men in the EMAS revealed a syndromic association of sexual symp toms with total testosterone levels <320 ng/dL and free testosterone levels <64 pg/mL in community-dwelling older men. Men with hypogonadism or Klinefelter’s syndrome have reduced prostate cancer mortality. Mendelian randomization studies using data from the United Kingdom Biobank Study found a sexual dimorphic relation between genetically determined testosterone levels and the risk of type 2 dia betes; in men, lower genetically determined testosterone levels were associated with higher risk of type 2 diabetes, but in women, higher genetically determined testosterone levels were associated with higher risk of type 2 diabetes. Higher genetically determined testosterone levels were also associated with increased risk of prostate cancer in men in this study. TABLE 411-1 Association of Testosterone Levels with Outcomes in Older Men

1. Positively associated with: • Muscle mass and muscle strength • Self-reported and performance-based measures of physical function • Sexual desire • Bone mineral density, bone geometry and quality, and volumetric bone mineral density

2. Negatively associated with risk of: • Coronary artery disease • Type 2 diabetes mellitus • Metabolic syndrome • All-cause mortality • Falls and fracture risk • Dementia and Alzheimer’s disease • Frailty • Late-onset low-grade persistent depressive disorder (dysthymia)
3. Not associated with: • Lower urinary tract symptoms • Erectile dysfunction • Major depressive disorder

■ ■EFFICACY OF TESTOSTERONE REPLACEMENT THERAPY IN MIDDLE-AGED AND OLDER MEN WITH HYPOGONADISM Two large, randomized trials—the Testosterone Trials (TTrials) and the Testosterone Replacement Therapy for Assessment of LongTerm Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial—have provided the most comprehensive data on the efficacy and safety of testosterone treatment in middle-aged and older men with hypogonadism. The TTrials, a set of seven coordi nated placebo-controlled efficacy trials of testosterone replacement therapy, enrolled 788 men, aged 65 years or older, with an average of two morning, fasting total testosterone levels <275 ng/dL and one or more of the following: low sexual desire, mobility limitation, and/or fatigue. The primary aim of the TRAVERSE trial was to compare the effects of testosterone replacement therapy and placebo treatment on major adverse cardiovascular events in middle-aged and older men, 45–80 years, with two fasting, morning testosterone concentrations <300 ng/dL, one or more symptoms of hypogonadism, and preexisting coronary artery disease (CAD) or increased risk of CAD. The eligible participants were randomized with stratification for preexisting CAD to receive either 1.62% transdermal testosterone gel or a placebo gel daily for up to 5 years. Because of its large sample size and long dura tion, the TRAVERSE trial has provided important data on the efficacy and long-term safety of testosterone replacement therapy. In these and other trials, testosterone treatment was associated with greater improvement in overall sexual activity, sexual desire, and hypogonadal symptoms than placebo (Table 411-2). The effects of testosterone alone on erectile function were small and inconsistent across stud ies. Nearly 15% of men enrolled in the TRAVERSE trial had anemia; among men with anemia, a greater proportion of testosterone-treated men than placebo-treated men experienced correction of anemia. Tes tosterone treatment also reduced the incidence of anemia in men who were not anemic at baseline. Fifty percent of men with hypogonadism reported significant depressive symptoms at baseline; however, only 1.5% of men in the TRAVERSE trial met the rigorous definition of latelife-onset, low-grade persistent depressive disorder (previously called dysthymia). Testosterone treatment was more efficacious in improving

PART 12 Endocrinology and Metabolism TABLE 411-2 The Potential Benefits of Testosterone Replacement Therapy in Middle-Aged and Older Men with Hypogonadism Strong Evidence of Efficacy

1. Improves overall sexual activity and sexual desire in men with low libido
2. Relieves hypogonadal symptoms
3. Improves depressive symptoms in men with significant depressive symptoms
4. Improves energy level
5. Corrects unexplained anemia and prevents the development of anemia
6. Increases skeletal muscle mass, reduces whole-body and abdominal fat mass
7. Increases areal and volumetric bone mineral density and estimated bone strength Suggestive Evidence of Efficacy

8. Modestly improves mobility in older men with mobility limitation Evidence of Lack of Efficacy
9. Improves cognitive function in older men without cognitive deficit
10. Improves depressive symptoms with major depressive disorder Note: The Testosterone Trials (TTrials) and the TRAVERSE trial have provided robust evidence of efficacy of testosterone replacement therapy in middle-aged and older men with hypogonadism. The TTrials were a set of seven coordinated placebocontrolled trials whose primary aim was to determine whether testosterone treatment for 1 year of men aged 65 years or older with an average of two fasting morning testosterone levels <275 ng/dL plus one or more of low sexual desire, mobility limitation, and/or low vitality was more efficacious than placebo in improving sexual function, mobility, and/or vitality. The primary aim of the TRAVERSE trial was to compare the effect of testosterone replacement therapy with placebo on major adverse cardiovascular events in middle-aged and older men, 45–80 years of age, with at least two fasting morning testosterone level <300 ng/dL and preexisting coronary artery disease or increased risk of coronary artery disease. Because of its large sample size and longer treatment duration, the TRAVERSE trial has provided some of the most comprehensive evidence of the efficacy and safety of testosterone replacement therapy.

depressive symptoms and energy level than placebo. Testosterone treat ment improved volumetric as well as areal bone mineral density and estimated bone strength; the improvement in volumetric bone density in the spine was greater than in the hip and greater in the trabecular than the peripheral bone. Testosterone treatment also increased lean body mass, muscle strength, and some measures of physical function (Fig. 411-2). In the TTrials, testosterone treatment of older men with mobility limitation improved self-reported walking ability and mod estly improved 6-min walking distance but did not affect falls. In TRAVERSE trial participants who had prediabetes, the incidence of progression from prediabetes to diabetes was similar between testosterone- and placebo-treated groups. Testosterone treatment did not improve glycemic control in men with hypogonadism and predia betes or diabetes at baseline. Thus, testosterone treatment should not be used alone to improve glycemic control in men with diabetes or prediabetes. These findings of the TRAVERSE trial are in contrast to those of the Testosterone for Diabetes Mellitus (T4DM) trial in men, aged 50–74 years without hypogonadism who had a newly diagnosed type 2 diabetes or were at increased risk for type 2 diabetes. Testos terone treatment in conjunction with a lifestyle program for 2 years reduced the proportion of participants with type 2 diabetes more than Body composition and muscle strength Grip strength Fat mass Lean body mass –2

A Difference between change in testosterone and placebo (kg) Bone health Lumbar spine Femoral neck

Difference between testosterone and placebo change in bone mineral density (%) B Sexual function Sexual thoughts Sexual satisfaction Morning erections Intercourse Erectile function

Standardized mean difference between testosterone and placebo C FIGURE 411-2 The effects of testosterone therapy on body composition, muscle strength, bone mineral density (BMD), and sexual function in intervention trials. The point estimates and the associated 95% confidence intervals are shown. A. The effects of testosterone therapy on lean body mass, grip strength, and fat mass in a meta-analysis of randomized trials. B. The effects of testosterone therapy on lumbar

and femoral BMD in a meta-analysis of randomized trials. C. The effects of testosterone therapy on measures of sexual function in men with baseline testosterone <10 nmol/L (290 ng/dL). (A. Data from S Bhasin et al: Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. Nat Clin Pract Endocrinol Metab 2:146, 2006. B. Data from MJ Tracz et al: Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. J Clin Endocrinol Metab 91:2011, 2006. C. Data from AM Isidori et al: Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol (Oxf) 63:381, 2005.)

TABLE 411-3 Adverse Events Associated with Testosterone Replacement Therapy in Middle-Aged and Older Men Adverse Events for Which There Is Strong Evidence Erythrocytosis Venous thromboembolic events Growth of metastatic prostate cancer Reduced sperm production and fertility Acne Increased risk of detection of low-grade prostate cancer Adverse Events for Which There Is Strong Evidence That Testosterone Treatment Does NOT Increase Risk Major adverse cardiovascular events Lower urinary tract symptoms Adverse Events for Which There Is Weak Evidence Atrial fibrillation Bone fractures Acute kidney injury Male pattern balding Adverse Events for Which There Is Insufficient Evidence to Assess Risk Gynecomastia Growth of breast cancer placebo plus lifestyle program. Testosterone therapy has not been shown to improve cognitive function in men who do not have cogni tive dysfunction. ■ ■SAFETY OF TESTOSTERONE REPLACEMENT THERAPY IN MIDDLE-AGED AND OLDER MEN WITH HYPOGONADISM Erythrocytosis is the most frequent adverse event associated with tes tosterone treatment (Table 411-3). In two placebo-controlled trials, the rates of atherosclerosis progression did not differ significantly between the testosterone and placebo groups. In the Cardiovascular Trial of the TTrials, testosterone treatment was associated with a greater increase in the volume of the noncalcified plaque than placebo. In the TRA VERSE trial, which was designed and powered specifically to assess the cardiovascular safety of testosterone, the incidence of major adverse cardiovascular events, which included nonfatal myocardial infarction, cardiovascular death, and nonfatal stroke, was similar between the testosterone- and placebo-treated men. The incidences of high-grade prostate cancer or any prostate cancer, acute urinary retention, inva sive surgical procedures for benign prostatic hyperplasia, or initiation of new pharmacologic treatment for benign prostatic hyperplasia were low and did not differ significantly between the testosterone and placebo groups. Testosterone treatment did not worsen lower urinary tract symptoms but was associated with a higher incidence of venous thromboembolic events, atrial fibrillation, and acute kidney injury. The number of clinical bone fractures was greater in the testosterone group than in the placebo group; this finding was surprising because testos terone treatment increases areal and volumetric bone mineral density and estimated bone strength. APPROACH TO THE PATIENT Older Men with Age-Related Decline in Testosterone Population screening of all older men for low testosterone levels is not recommended; testing should be restricted to men who have symptoms or physical features suggestive of hypogonadism. Tes tosterone treatment of older men with hypogonadism offers some clinical benefits (e.g., improvement of sexual symptoms in men with low libido, improvements in mood and energy, correction of anemia), but also has some potential for adverse effects (e.g., increased risk of venous thromboembolism and atrial fibrillation). An expert panel of the Endocrine Society recommended against

testosterone treatment of all older men with low testosterone levels. Instead, the expert panel recommended that “testosterone therapy should be offered on an individualized basis … in men

>65 years who have symptoms or conditions suggestive of testosterone defi ciency (e.g., low libido, significant depressive symptoms, fatigue, or unexplained anemia) and consistently low testosterone.” The decision to offer testosterone treatment to older men with hypo gonadism should be a shared decision, guided by an individualized assessment of potential benefits and risks and careful weighing of the burden of symptoms/conditions against the potential benefits and risks (Fig. 411-3). Evaluate whether the patient has clear evi dence of testosterone deficiency confirmed by two or more early morning, fasting testosterone levels below the lower limit of normal for healthy young men plus the presence of symptoms. Weigh the burden of symptoms/conditions against the known benefits and the uncertainty of long-term harm. Ascertain whether the patient has any conditions that might increase the risk of harm, such as prostate cancer, severe LUTS, erythrocytosis, or a hypercoagulable condition. Older men considering testosterone treatment should undergo baseline evaluation of prostate cancer risk. The initiation of prostate screening and monitoring should be a shared decision because prostate cancer screening has some risks. A shared decision to treat should be accompanied by a standardized monitoring plan to optimize the benefit-to-risk ratio. Men’s Health CHAPTER 411 AGE-RELATED CHANGES IN FECUNDITY Although testicular morphology, semen production, and fertility are maintained up to a very old age in men, advanced paternal age is a risk factor for reduced fertility. Compared to men aged 21–25 years, men >50 years have lower sperm motility and sperm morphology, a higher frequency of sperm tail defects, and lower fecundity. The fecundity is reduced when both parents are >40 years old. Increased workforce participation and changing career expectations of women, a higher age at reproductive union, and the availability of contraceptives that enable couples to separate their sexual and procreative lives have underpinned powerful secular trends toward postponement of child bearing to an older age. The median age at first childbirth has been increasing steadily across the world; postponement of childbirth to an older age increases the risk of involuntary childlessness because of the adverse effects of advanced maternal and paternal age on fecundity, increased risk of comorbidities that may indirectly affect fecundity, and the age-related changes in reproductive behaviors. Increased paternal age is associated with increased risk of germline mutations in the FGFR2, FGFR3, and RET genes and the associated autosomal dominant diseases, such as achondroplasia, Pfeiffer’s syndrome, thana tophoric dysplasia, Crouzon’s syndrome, Apert’s syndrome, multiple endocrine neoplasia (MEN) 2A, and MEN 2B. Advanced paternal age also increases the offspring’s risk of Klinefelter’s syndrome, trisomy 13 and 18, neurodevelopmental disorders such as schizophrenia, autism, bipolar disorders, and cardiac malformations such as ventricular septal defects, atrial septal defects, and patent ductus arteriosus. Sexual Dysfunction Various forms of sexual dysfunction are a major motivating factor for men seeking care at men’s health clinics. The landmark descriptions of the human sexual response cycle by Masters and Johnson demonstrating that men and women display predictable physiologic responses after sexual stimulation provided the basis for rational classification of human sexual disorders. Subsequently, this model was expanded to include sexual desire, resulting in a three-stage model comprising of desire, arousal, and orgasm. Whipple and BrashMcGreer later proposed a circular model of sexual response whereby a positive sexual experience reinforces desire. The classification of sexual disorders in men has been revised in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the eleventh revision of the International Classification of Diseases and Related Health Problems (ICD-11). DSM-5 includes three major categories of male sexual disorders: sexual desire disorders, sexual arousal disorders, and orgasmic disorders. The DSM-5 also

The Approach to Individualized Decision-Making

1. Establish that the patient has testosterone deficiency – consider the diagnostic imprecision.
2. Weigh the burden of symptoms.
3. Ascertain conditions that might increase the risk of harm.
4. Share the burden of decision-making with the patient. Balancing the Potential for Benefits and Risks and Patient's and Clinician's Values The severity of testosterone deficiency and symptoms Potential benefits in context of the burden of symptoms PART 12 Endocrinology and Metabolism The strength of the evidence of testosterone deficiency Patient's values and risk tolerance FIGURE 411-3. An approach to individualized, shared treatment decision-making in older men with testosterone deficiency. Testosterone treatment is not indicated in all older men with testosterone deficiency. Consider the diagnostic imprecision in establishing the diagnosis, the burden of symptoms, and the presence of comorbid conditions that might increase the risk of harm. Weigh the potential benefits against the burden of symptoms, the potential of harm from treatment and monitoring in the context of other comorbid conditions, and the feasibility of alternate strategies such as weight loss, improved glycemic control, and the use of selective phosphodiesterase-5 inhibitors (PDE5Is). A shared treatment decision takes into consideration the patient's and clinician's values. ED, erectile dysfunction. includes an additional category of "other specified sexual dysfunction" due to causes other than those included in the above three categories. Male erectile dysfunction is now referred to as erectile disorder. Classification of the patient's disorder into these categories is important as the etiologic factors, diagnostic tests, and therapeutic strategies vary for each class of sexual disorder. Historically, the clas sification and nomenclature for sexual disorders were based on the DSM, based on the erroneous belief that sexual disorders in men are largely psychogenic in origin. However, the recognition of erectile disorder as a manifestation of systemic disease and the availability of easy-to-use oral selective phosphodiesterase-5 (PDE5) inhibitors have placed sexual disorders in men within the purview of the primary care provider. These disorders have been discussed in Chap. 409 (Sexual Dysfunction). ■ ■MUSCLE DYSMORPHIA SYNDROME IN MEN—A FORM OF BODY IMAGE DISORDER Muscle dysmorphia is a form of body image disorder characterized by a pathologic preoccupation with muscularity and leanness. The men with muscle dysmorphia express a strong desire to be more muscular and lean and report dissatisfaction and embarrassment about their body size and shape, preoccupation with bodybuilding and muscular ity, and impairment of social and occupational functioning. Patients with muscle dysmorphia also report higher rates of mood and anxiety disorders and obsessive and compulsive behaviors than individuals without muscle dysmorphia. Patients with muscle dysmorphia syndrome—nearly all men—are almost always engaged in weightlifting and body building and are more likely to use performance-enhancing drugs, especially AASs, than men in the general population or even weightlifters without body dysmorphia. Muscle dysmorphia disorder exposes men to an increased risk of disease due to the combined interactive effects of the intensity of physical exercise, the use of performance-enhancing drugs, and other lifestyle factors associated with weightlifting and the use of performance-enhancing drugs. No randomized trials of any treatment modalities have been conducted; anecdotally, behavioral and cognitive therapies have been tried with varying degrees of success. AAS Abuse by Athletes and Recreational Bodybuilders The illicit use of AASs to enhance athletic performance first surfaced in the 1950s among powerlifters and spread

rapidly to other sports, profes sional as well as high school athletes, and recreational bodybuilders. In

The feasibility of alternate strategies (weight loss, glycemic control, PDE5Is for ED) The comorbid conditions that might increase the risk of adverse events Potential adverse effects of treatment and risks of monitoring Clinician’s the early 1980s, the use of AAS spread beyond the athletic community into the general population. Most AAS users are not athletes, but rather recreational weightlifters who use these drugs to look lean and more muscular. The most commonly used AASs include testosterone esters, nandro lone, stanozolol, methandienone, trenbolone, boldenone, and oxandro lone. AAS users generally use increasing doses of multiple steroids in a practice known as stacking. The adverse effects of long-term AAS abuse remain poorly under stood. Most of the information about the adverse effects of AAS has emerged from case reports, uncontrolled studies, or clinical trials that used replacement doses of testosterone (Table 411-4). The adverse event data from clinical trials using physiologic replacement doses of testosterone have been extrapolated unjustifiably to AAS users who may administer 10–100 times the replacement doses of testosterone over many years and to support the claim that AAS use is safe. A sub stantial fraction of AAS users also use other drugs that are perceived to be muscle-building or performance-enhancing, such as growth hormone; erythropoiesis-stimulating agents; insulin; stimulants such as amphetamine, clenbuterol, cocaine, ephedrine, and thyroxine; and drugs perceived to reduce adverse effects such as human chorionic gonadotropin (hCG), aromatase inhibitors, or estrogen antagonists. Men who abuse AAS are more likely to engage in other high-risk behaviors than nonusers. The adverse events associated with AAS use may be due to AAS themselves, concomitant use of other drugs, or high-risk behaviors. The high rates of mortality and morbidities observed in AAS users are alarming. One Finnish study reported 4.6 times the risk of death among elite power lifters than in age-matched men from the general population. The causes of death among power lifters included sui cides, myocardial infarction, hepatocellular failure, and non-Hodgkin’s lymphoma. A retrospective review of patient records in Sweden also reported higher standardized mortality ratios for AAS users than for nonusers. Studies indicate that 32% of deaths among AAS users were suicidal, 26% homicidal, and 35% accidental. The median age of death among AAS users in this study—24 years—was even lower than that for heroin or amphetamine users. Numerous reports of cardiac death among young AAS users raise concerns about the adverse cardiovascular effects of AAS. High doses of AAS may induce proatherogenic dyslipidemia, increase thrombosis risk via effects on clotting factors and platelets, induce vasospasm

TABLE 411-4 Potential Adverse Effects Associated with the Use of Anabolic-Androgenic Steroids A. Four Major Categories of Serious Adverse Effects Associated with the Use of Anabolic-Androgenic Steroids

1. Cardiovascular a. Hypertension b. Sudden death c. Cardiomyopathy d. Diastolic dysfunction e. Accelerated atherosclerosis f. Dyslipidemia
2. Endocrine a. Suppression of the hypothalamic-pituitary-testicular axis i. Anabolic steroid withdrawal hypogonadism ii. Infertility iii. Testicular atrophy b. Gynecomastia
3. Neuropsychiatric a. Major mood disorders i. Hypomania and mania during periods of high-dose anabolicandrogenic steroids use ii. Depression and even suicidality during anabolic steroid withdrawal b. Other behavioral disorders i. Rage reactions ii. Aggressive responding and violence c. Dependence and addiction behaviors d. Cognitive deficits

4. Musculoskeletal Injuries a. Tendon injuries b. Other musculoskeletal injuries B. Other Adverse Events
5. Hematologic a. Erythrocytosis b. Venous thromboembolic events
6. Hepatotoxicity a. Inflammatory or cholestatic hepatic damage with the use of 17α-alkylsubstituted steroids b. Peliosis hepatis c. Hepatic adenoma d. Hepatocellular carcinoma
7. Hair and skin a. Acne b. Scalp hair loss in genetically predisposed men c. Increased body hair d. Striae
8. Renal a. Acute kidney injury due to rhabdomyolysis b. Focal glomerulosclerosis through their effects on vascular nitric oxide, and induce myocardial hypertrophy and fibrosis. The supraphysiologic doses of testosterone and orally administered, 17-α-alkylated, nonaromatizable AAS are associated with marked reductions in high-density lipoprotein (HDL) cholesterol and increases in low-density lipoprotein (LDL) cholesterol. Studies using tissue Doppler and strain imaging and magnetic resonance imaging (MRI) have reported diastolic and systolic dysfunc tion, including lower early and late diastolic tissue velocities, reduced E/A ratio, and reduced peak systolic strain in AAS users than in nonusers. Power athletes using AAS often have short QT intervals but increased QT dispersion, which may predispose them to ventricular arrhythmias. Long-term AAS use may be associated with myocardial hypertrophy and fibrosis. Myocardial tissue of power lifters using AAS has been shown to be infiltrated with fibrous tissue and fat droplets. AAS users demonstrate higher coronary artery plaque volume than

nonusers, and lifetime AAS dose is associated with coronary athero sclerotic burden.

Long-term AAS use suppresses LH and follicle-stimulating hormone (FSH) secretion and inhibits endogenous testosterone production and spermatogenesis. Men who have used AAS for more than a few months experience marked suppression of the HPT axis after stopping AAS that may be associated with sexual dysfunction, fatigue, infertility, and depressive symptoms. In some long-term AAS users, HPT suppression may last more than a year, and in a few individuals, complete recovery may not occur. The symptoms of androgen deficiency during AAS withdrawal may cause some men to revert back to using AAS, leading to continued use and AAS dependence. As many as 30% of AAS users develop a syndrome of AAS dependence, characterized by long-term AAS use despite adverse medical and psychiatric effects. In some men’s health clinics, as many as 25% of young men receiving testosterone replacement therapy have anabolic steroid withdrawal hypogonadism. Men’s Health CHAPTER 411 Supraphysiologic doses of testosterone may also impair insulin sensitivity. Orally administered androgens have been associated with insulin resistance and diabetes. Unsafe injection practices, high-risk behaviors, and increased rates of incarceration render AAS users at increased risk of HIV and hepati tis B and C. In one survey, nearly 1 in 10 gay men had injected AAS or other substances, and AAS users were more likely to report high-risk unprotected anal sex than other men. Surveys of male prisoners find high rates of AAS use. Some AAS users develop hypomanic and manic symptoms dur ing AAS exposure (irritability, aggressiveness, reckless behavior, and psychotic symptoms, sometimes associated with violence) and major depression (sometimes associated with suicidality) during AAS with drawal. Users may also develop other forms of illicit drug use. AAS use has been associated with difficulties with spatial as well as working memory, problem solving, and attention, and structural and functional changes in many brain regions involved in inhibitory control and emotional regulation. A structural

MRI study of users of high doses of AAS reported smaller cortical, gray matter, putamen, and corpus callosum volumes. Both low and high androgen levels have been associated with increased Aβ and tau-P levels and Aβ toxicity. These data have raised concern that long-term AAS use may increase the risk of Alzheimer's disease and related dementias. Elevated liver enzymes, cholestatic jaundice, hepatic neoplasms, and peliosis hepatis have been reported with oral, 17-α-alkylated AAS. AAS use may cause muscle hypertrophy without compensatory adaptations in tendons, ligaments, and joints, thus increasing the risk of tendon and joint injuries. AAS use is associated with acne, baldness, and increased body hair. APPROACH TO THE PATIENT Detection of AAS Use AAS users generally mistrust physicians and seek medical help infrequently; when they do seek medical help, it is often for the treatment of AAS withdrawal syndrome, infertility, gynecomastia, or other medical or psychiatric complications of AAS use. The suspicion of AAS use should be raised by the increased hemoglobin and hematocrit levels; suppressed LH, FSH, SHBG and testosterone levels; low HDL cholesterol; and low testicular volume and sperm density in a person who looks highly muscular (Table 411-5). A combination of these findings along with self-report of their use by the patient—which usually can be elicited by a tactful interview— are often sufficient to establish a diagnosis in clinical practice. Accredited laboratories use gas chromatography and mass spec trometry or liquid chromatography and mass spectrometry to detect AAS abuse. Illicit testosterone use is detected generally by the measurement of the urinary testosterone-to-epitestosterone ratio and confirmed by the use of the 13C:12C ratio in testosterone by the use of isotope ratio combustion mass spectrometry. Exogenous testosterone administration increases urinary testosterone glucuro nide excretion and consequently the testosterone-to-epitestosterone

TABLE 411-5 Detection of the Use of Anabolic-Androgenic Steroids Clinical indicators that should raise suspicion of anabolic-androgenic steroid use

1. "V" muscular phenotype
2. Reduced testicular volume (<15 mL)
3. Excessive concern about leanness and muscularity. Laboratory indicators
4. Suppressed LH, FSH, and SHBG levels
5. Increased hematocrit Detection of anabolic-androgenic steroids
6. LC-MS/MS analysis of urine Detection of exogenous testosterone use
7. Urinary testosterone-to-epitestosterone ratio
8. Isotope ratio mass spectrometry analysis to detect differences in 13C:12C ratio PART 12 Endocrinology and Metabolism in exogenous and endogenous testosterone Note: In clinical settings, the use of anabolic-androgenic steroids can often be ascertained simply by direct questioning. Reduced testicular volume, suppressed LH and FSH, and increased hematocrit in an unusually muscular man should raise suspicion of anabolic-androgenic steroid use. Although rarely needed in clinical practice, recent use of anabolic-androgenic steroids can be confirmed by LC-MS/ MS analysis of urine. Exogenous testosterone use can be detected using the urinary testosterone-to-epitestosterone ratio and isotope ratio mass spectrometry analysis to detect differences in 13C:12C ratio in exogenous and endogenous testosterone. Abbreviations: FSH, follicle-stimulating hormone; LC-MS/MS, liquid chromatography–tandem mass spectrometry; LH, luteinizing hormone. ratio. Ratios >4 suggest exogenous testosterone use but can also reflect genetic variation. Genetic variations in the uridine diphos pho-glucuronyl transferase 2B17 (UGT2B17), the major enzyme for testosterone glucuronidation, CYP17 (the aromatase gene), SHBG, and 3', 5'

cyclic nucleotide phosphodiesterase (PDE7B) affect the testosterone-to-epitestosterone ratio and increase the risk of a false-negative test. Synthetic testosterone has a lower 13C:12C ratio than endogenously produced testosterone, and these differences in the 13C:12C ratio can be detected by isotope ratio combustion mass spectrometry and used to confirm exogenous testosterone use in individuals with a high testosterone-to-epitestosterone ratio. TREATMENT Integrated Management of Patients with AAS Use The nonathlete weightlifters who abuse AAS frequently do not seek medical treatment and often mistrust physicians. They also do not view these drugs and the associated lifestyle as deleterious to their health. Many clinicians erroneously view AAS abuse as largely a problem of cheating in competitive sports, while, in fact, most AAS users are not athletes at all. In addition to treating the underlying body dysmorphia disorder that motivates the use of these drugs and the addiction behaviors, the treatment should be directed at the symptoms or the condi tion for which the patient seeks therapy, such as infertility, sexual dysfunction, gynecomastia, or depressive symptoms. Accordingly, therapy may include some combination of cognitive and behavioral therapy for muscle dysmorphia syndrome, antidepressant therapy for depression, selective PDE5 inhibitors for erectile dysfunction, and/or use of selective estrogen receptor modulators, aromatase inhibitors, or hCG to restore testosterone levels. As discussed above, AASs suppress the male hypothalamicpituitary-gonadal axis, and men with long-term AAS use may expe rience symptoms of profound androgen deficiency such as sexual dysfunction, fatigue, and depressive symptoms during AAS with drawal. Some of these patients may resume AAS use or start using other drugs to combat the distressing withdrawal symptoms. There are no randomized trials of any therapies for AAS withdrawal. Case reports and clinical experience suggest that administration of selec tive estrogen receptor modulators, CYP19 aromatase inhibitors, or hCG may restore circulating testosterone levels. Clomiphene citrate, a partial estrogen receptor agonist, administered in a dose of 25–50 mg on alternate days, can increase LH and FSH levels and restore testosterone levels in a vast majority of men with AAS withdrawal syndrome. However, the recovery of sexual function during clomiphene administration is variable despite improvements in testosterone levels. Anecdotally, other aromatase inhibitors such as anastrozole have also been used. hCG, administered by intra muscular injections of 1500 to 2000 IU three times each week, can raise testosterone levels into the normal range. Some patients may not respond to either clomiphene or hCG therapy, raising the pos sibility of irreversible long-term toxic effects of AAS on Leydig cell function. Cognitive and behavioral therapy to address the body image dis order and addiction behaviors and antidepressants to treat depres sion may be needed. The opioid antagonist naltrexone blocks AAS dependence in animals. Therefore, treatments for human opioid dependence might also benefit AAS dependence. Many patients who abuse AAS suffer from body image disorder and require psy chiatric treatment for this underlying disorder. ■ ■LUTS IN MEN LUTS in men include storage symptoms (urgency, daytime as well as nighttime frequency, and urgency incontinence), voiding distur bances (slow or intermittent stream, difficulty in initiating micturi tion, straining to void, pain or discomfort during the passage of urine, and terminal dribbling), or postmicturition symptoms (a sense of incomplete voiding after passing urine and postmicturition dribble). The overactive bladder syndrome refers to urgency with or without urgency incontinence, usually with urinary frequency and nocturia, and is often due to detrusor muscle overactivity. A presumptive diag nosis of benign prostatic hyperplasia should be made only in men with LUTS, who have demonstrable evidence of prostate enlargement

and obstruction based on the size of the prostate. LUTS have historically been attributed to benign prostatic hyperplasia, although it has become apparent that the pathophysiologic mechanisms of LUTS are complex and multifactorial and may include structural or functional abnormali ties of the bladder, bladder neck, prostate, distal sphincter mechanism, and urethra, as well as abnormalities in the neural control of the lower urinary tract and autonomic dysfunction. Diuretics, antihistamines, antidepressants, and other medications that have anticholinergic prop erties can cause or exacerbate LUTS in older men. The intensity of LUTS tends to fluctuate over time. LUTS is highly prevalent in older men, affecting nearly 50% of men

> “ 65 and 70% of men >80 years old. LUTS adversely affect quality of life because of their impact on sleep, ability to perform activities of daily living, and depressive symptoms. LUTS are often associated with erectile dysfunction. APPROACH TO THE PATIENT Lower Urinary Tract Symptoms Medical evaluation should include assessment of potential causes of symptoms; medications including herbal and over-the-counter products that might contribute to symptoms; the symptom severity and bother using an International Prostate Symptom Score; and in some patients, a frequency-volume chart. The impact of LUTS on sleep, activities of daily living, and quality of life should be evaluated. Evaluation should also include digital prostate exami nation, neurologic examination focused on perineum and lower extremities, urinalysis, fasting blood glucose, electrolytes, creati nine, and prostate-specific antigen (PSA). Urodynamic studies are not required in most patients but are recommended when invasive surgical therapies are being considered. A urologic referral may be appropriate if the patient has hydronephrosis, renal insufficiency, recurrent urinary tract infections, hematuria, or history of acute urinary retention.

TREATMENT Patients with LUTS Considerations of the severity of symptoms; the impact of symp toms on sleep, activities of daily living, and quality of life; the natural history of the disease; and potential adverse effects of the intervention should guide the decision to intervene. In men with mild to moderately severe LUTS, the symptoms typically progress slowly over many years and may remain stable or even improve in some men. The men who have mild symptoms can usually be reas sured and followed. Several simple steps such as reducing caffeine and alcohol intake, especially late in the day, taking the diuretic medication early in the day, avoiding excessive water intake close to bedtime, bladder training, pelvic floor exercises including bio feedback to promote pelvic floor relaxation, and timed voiding regimens or double voiding to ensure complete emptying of the bladder may be helpful in reducing the severity of symptoms. Men with mild to moderate bothersome LUTS can be treated effectively using α-adrenergic antagonists, steroid 5α-reductase inhibitors, PDE5 inhibitors, or anticholinergic agents alone or in combina tion. Selective α-adrenergic antagonists are typically the first line of therapy; their side effects include hypotension, dizziness, nasal congestion, retrograde or delayed ejaculation, and rarely floppy iris syndrome. In men with probable benign prostate obstruction with gland enlargement and LUTS, therapy with steroid 5α-reductase inhibitors, finasteride or dutasteride, improves urinary symptoms and flow rate and reduces prostatic volume. Long-term treatment with 5α-reductase inhibitors can reduce the risk of acute urinary retention and need for prostate surgery. Combined administration of a

steroid 5α-reductase inhibitor and an α1-adrenergic blocker can rapidly improve urinary symptoms and reduce the relative risk of acute urinary retention and surgery. PDE5 inhibitors, when admin istered chronically alone or in combination with α-adrenergic blockers, are effective in improving LUTS and erectile dysfunction through their effects on nitric oxide–cyclic guanosine monophos phate (cGMP) in the bladder, urethra, and prostate. PDE5 inhibi tors do not improve uroflow parameters, and their hypotensive effect may be potentiated by α1-adrenergic blockers. Anticholiner gic drugs are used for the treatment of overactive bladder in men with prominent irritative symptoms, such as frequency, urgency, and incontinence, and no evidence of elevated postvoid residual urine. Containment products, such as pads, can help improve social life in men who have severe storage symptoms, including inconti nence. Surgery is indicated when medical therapy fails, symptoms progress despite medical therapy, or the patient develops acute urinary retention, hydronephrosis, renal insufficiency, or recurrent urinary tract infections, or if the patient has postvoid residual urine volume >25% of the urinary bladder volume. ■ ■MEDICAL COMPLICATIONS OF PROSTATE CANCER THERAPY Prostate cancer is the most common malignancy in American men. The majority of these men have low-grade, organ-confined prostate cancer; are treated with radical prostatectomy, radiation, or active sur veillance; and have excellent prospects of long-term survival. Substan tial improvement in survival in men with prostate cancer has focused attention on the high prevalence of sexual dysfunction, physical dys function, and low vitality in the men, which are important contribu tors to poor quality of life among patients treated for prostate cancer. The pathophysiology of these symptoms after radical prostatectomy or radiation therapy is multifactorial, but denervation and testosterone deficiency are important contributors to these symptoms. Testosterone deficiency is common in men with prostate cancer. Testosterone levels decline with age, and men with prostate cancer are at risk of having low testosterone levels simply by virtue of their age. However, total and free testosterone levels are even lower in men with prostate cancer who have undergone prostatectomy, when compared to noncancer age-matched controls. Testosterone deficiency in men with

prostate cancer is associated with fatigue, sexual dysfunction, mobility limitation, and decreased physical function. A majority of men treated with surgery or radiation therapy will develop sexual dysfunction and incontinence. Although there is some recovery of sexual function with passage of time, 40–50% of men undergoing radical prostatectomy find their sexual performance to be a moderate to large problem 18 months after surgery. Sexual problems are a source of psychosocial distress in men with localized prostate cancer. The men with locally advanced or metastatic prostate cancer who undergo androgen deprivation therapy (ADT) encounter even more distressing symptoms. In addition to fatigue, sexual dysfunction, and hot flushes, these men are at increased risk for diabetes, metabolic syndrome, coronary heart disease, and frailty.

Men’s Health CHAPTER 411 Testosterone Therapy in Men with a History of Prostate Cancer A history of prostate cancer has historically been consid ered a contraindication for testosterone therapy. This guidance is based on observations that testosterone promotes the growth of metastatic prostate cancer and metastatic prostate cancer generally regresses after orchiectomy and ADT. Androgen receptor signaling plays a central role in maintaining growth of normal prostate and prostate cancer. The role of testosterone in prostate cancer is complex. Epidemio logic studies and their meta-analyses have not revealed a consistent relationship between serum testosterone or dihydrotestosterone levels and prostate cancer. However, men with hypogonadism or Klinefelter’s syndrome have lower prostate cancer mortality than the general population. In a

Mendelian randomization analysis of men in the UK Biobank, higher genetically determined bioavailable testosterone levels were associated with increased risk of prostate cancer. Testosterone treatment of older men with low testosterone does not affect intra prostatic androgen levels or the expression of androgen-dependent prostatic genes. The suppression of circulating testosterone levels by a GnRH antagonist also does not affect intraprostatic androgen concen trations. Open-label trials and retrospective analyses of testosterone therapy in men with prostate cancer who have undergone radical pros tatectomy and have undetectable PSA levels after radical prostatectomy have found very low rates of PSA recurrence. A majority of men diagnosed with prostate cancer today have local ized disease that can be potentially cured by radical prostatectomy. The men with organ-confined prostate cancer (pT2, N0, M0) and Gleason score 6 or 7 (3+4) are at a very low risk of disease recurrence after radical prostatectomy, with 0.5% biochemical recurrence rate and 0.2% local recurrence rate at >10–15 years. Therefore, men with organ-confined prostate cancer (pT2), Gleason score 6 or 7 (3+4), and a preoperative PSA of <10 ng/mL, who have had undetectable PSA levels (<0.1 ng/mL) for >2 years after radical prostatectomy, have very low risk of disease recurrence (<0.5% at 10 years) and may be consid ered for testosterone therapy on an individualized basis. If testosterone therapy is instituted, it should be associated with careful monitoring of PSA levels and close consultation with a urologist. ■ ■MEDICAL COMPLICATIONS OF ADT In patients with prostate cancer and distant metastases, ADT improves survival. In patients with locally advanced disease, ADT in combina tion with external beam radiation or as an adjuvant therapy (post prostatectomy and pelvic lymphadenectomy) also has been shown to improve survival. However, ADT along with radiation is being increas ingly used as primary therapy in men with localized disease and in men encountering biochemical recurrence. The overall use of ADT in men with prostate cancer has increased in the past two decades, and its use in men with localized disease and biochemical recurrence accounts for a substantial fraction of this increase. Since most men with prostate cancer die of conditions other than their primary malignancy, recogni tion and management of these adverse effects are paramount. Profound hypogonadism resulting from ADT is associated with sexual dysfunction, vasomotor symptoms, gynecomastia, decreased muscle mass and strength, frailty, increased fat mass, anemia, fatigue, bone loss, loss of body hair, depressive symptoms, and reduced qual ity of life. Increased risk of diabetes and cardiovascular disease has

Thromboembolic Any fracture (1.54) Cardiovascular Metabolic Skeletal PART 12 Endocrinology and Metabolism Fracture requiring hospitalization (1.66) Diabetes (1.44) Myocardial infarction (1.11) Peripheral vascular disease (1.16) Coronary heart disease (1.16) Sudden death (1.16) FIGURE 411-4 Adverse cardiometabolic and skeletal effects of androgen deprivation therapy (ADT) in men receiving ADT for prostate cancer. Administration of ADT has been associated with increased risk of thromboembolic events, fractures, and diabetes. Some, but not all, studies have reported increased risk of cardiovascular events in men receiving ADT. (Data from VB Shahinian et al: N Engl J Med 352:154, 2005; NL Keating et al: J Clin Oncol 24:4448, 2006; JC Hu et al: Eur Urol 61:1119, 2012.) recently been added to the list of these complications (Fig. 411-4). Treatment with GnRH agonists in men with prostate cancer is associ ated with rapid induction of insulin resistance, hyperinsulinemia, and a significant increase in the risk of incident diabetes. Metabolic syn drome is prevalent in >50% of men undergoing long-term ADT when compared to age-matched men with prostate cancer not undergoing ADT and their age-matched eugonadal counterparts. Some but not all studies have reported an increased risk of cardiovascular events, death due to cardiovascular events, and peripheral vascular disease in men undergoing ADT. Some reports suggest that men

receiving ADT are at an increased risk of thromboembolic events and cognitive dysfunction. The rates of acute kidney injury are higher in men currently receiving ADT than in men not receiving ADT; the increased risk appears to be particularly associated with the use of combined regimens of a GnRH agonist plus an antiandrogen. ADT also is associated with substantially increased risk of osteoporosis and bone fractures. APPROACH TO THE PATIENT Men Receiving ADT The benefits of ADT in treating nonmetastatic prostate cancer should be carefully weighed against the risks of ADT-induced adverse events (Table 411-6). If ADT is medically indicated, con sider whether intermittent ADT is a feasible option. Men being considered for ADT should undergo assessment of cardiovas cular, diabetes, and fracture risk; this assessment may include measurement of blood glucose, plasma lipids, and bone mineral density by dual energy x-ray absorptiometry. Institute measures to prevent bone loss, including physical activity, adequate calcium and vitamin D intake, and pharmacologic therapy in men with a previous minimal trauma fracture and those with 10-year risk of a major osteoporotic fracture >20%, unless contraindicated. Bisphos phonates and denosumab have been shown to reduce fracture risk in men undergoing ADT, and zoledronic acid and denosumab have been approved by the U.S. Food and Drug Administration for the prevention of metastasis-related skeletal-related events in

Shahinian et al 2005, NEJM Keating et al 2006, JCO Keating et al 2006, JCO Hu et al 2012, Eur Urol

this population. Men with prostate cancer who are receiving ADT should be monitored for weight gain and diabetes. Encourage life style interventions, including physical activity and exercise, and attention to weight, blood pressure, lipid profile, blood glucose, and smoking cessation to reduce the risk of cardiometabolic com plications. Metformin plus lifestyle intervention can prevent and improve metabolic dysregulation. In randomized trials, gabapentin, medroxyprogesterone, and the serotonin reuptake inhibitor venla faxine have been shown to be more efficacious than placebo in alle viating hot flushes. The side effects of these medications—increased appetite and weight gain with medroxyprogesterone, gynecomastia with estrogenic compounds, and dry mouth with venlafaxine— should be weighed against their relative efficacy. Acupuncture, soy products, vitamin E, herbal medicines, and transdermal estradiol have been used empirically for the treatment of vasomotor symp toms without clear evidence of efficacy. Gynecomastia can be TABLE 411-6 Checklist for Men Undergoing Androgen Deprivation Therapy (ADT)

1. Weigh the risks and benefits of ADT and whether intermittent ADT is a feasible and safe option.
2. Perform a baseline assessment including fasting glucose, plasma lipids, blood pressure, bone mineral density, and FRAX score.
3. Optimize calcium and vitamin D intake, encourage structured physical activity and exercise, and consider pharmacologic therapy in men with a previous minimal trauma fracture and those with a 10-year risk of a major osteoporotic fracture >20%, unless contraindicated.
4. Monitor body weight, fasting glucose, plasma lipids, blood pressure, and bone mineral density, and encourage smoking cessation and physical exercise. Consider metformin in those with metabolic disorder.
5. In men who are receiving ADT and who experience bothersome hot flushes, as indicated by sleep disturbance or interference with work or activities of daily living, consider initial therapy with venlafaxine. If ineffective, add medroxyprogesterone acetate or gabapentin.

6. In men who experience painful breast enlargement, consider therapy with an estrogen receptor antagonist, such as tamoxifen.

prevented by the use of an antiestrogen, an aromatase inhibitor, or local radiation therapy; these therapies are effective in alleviating pain and tenderness but are less effective in reducing established gynecomastia. For long-standing gynecomastia that persists after cessation of ADT and is bothersome, mammoplasty is an effective treatment option. Intermittent ADT can reduce the frequency of adverse effects associated with ADT, but its long-term efficacy and safety need further investigation. ■ ■PREVENTION OF SEXUALLY TRANSMITTED DISEASES Adolescent boys and young men aged 15–24 years; men who have sex with men, have multiple sex partners, have unprotected sex without condom, or have sex with sex workers; men who use illicit drugs; men who have a history of previous sexually transmitted infection (STI); and transgender men are at increased risk for STIs. STIs increase the risk of oropharyngeal and anogenital cancers, liver disease, pelvic pain, infertility, inadvertent transmission of infection to others, and emergency department visits and are a preventable cause of excess morbidity and mortality. HIV, hepatitis B and C infections, and syphilis can have additional disease-specific complications. The prevention and treatment of STIs are discussed in Chap. 141. Additionally, the Centers for Disease Control and Prevention (CDC) and U.S. Preventive Services Task Force (USPSTF) have published guidelines on the prevention, treatment, and pre- and postexposure prophylaxis of STIs. The approach to the prevention of STIs includes a structured risk assessment; counseling about safe sex practices including condom use; immunization of individuals at risk; diagnosis and treatment of infected individuals whether or not they are symptomatic; detection and treatment of sexual partners; and targeted sex education of adolescents and young men who are at high risk for STIs. The USPSTF recommends screening for HIV in all men aged 15–65 years, regardless of risk, and for hepatitis B virus and syphilis in men at increased risk. Because more than half of STIs occur in persons aged 15–24 years, the USPSTF also recommends behavioral counseling for all sexually active adolescents and adult men at increased risk of STIs to encourage condom use and other protective behaviors, including consideration of abstinence, reducing the number of sex partners, and avoidance of unsafe sex practices. Consistent and correct condom use is the most important method of preventing STIs. Effective immunizations are available against hepatitis B, human papillomavirus (HPV), and Neisseria meningitides. The CDC’s Advisory Committee on Immunization Practices (ACIP) recommends universal hepatitis B immunization for all unvaccinated adults presenting to an STI clinic, all HIV-infected adults, and health workers. Although ACIP recommends HPV vaccination in males aged 9–21 years and in men aged 9–26 if they have sex with men or have an immunocompromising condition, recent data suggest that the prevalence of HPV and its complications continue to increase until middle age, and some experts recommend extending the age limit for HPV vaccination. Meningococcal vaccination is indicated for men who have sex with men from an area of outbreak and for all HIV-infected men. Because men seeking care in men’s health clinics often do so for sexual and urogenital problems, these visits offer opportunities for counseling, screening, and treatment of STIs and institution of immunization and other preventive measures for STIs. ■ ■SEX DIFFERENCES IN COVID-19 DISEASE OUTCOMES The COVID-19 pandemic has highlighted sex differences in the susceptibility to respiratory viral infections. Men infected with SARSCoV-2 virus are more likely to have a more severe disease, require mechanical ventilation, have disease complications, and die of the disease than women. Somewhat similar sex differences in morbidity and mortality have been reported for influenza infection. In the United States, the incidence and rates of hospitalization for influenza

are higher in men than in women across all age groups. However, the sex-specific mortality rates associated with influenza vary substantially across countries and age groups. The sex differences in susceptibility to SARS-CoV-2 infection and morbidity have been attributed to behavioral factors, such as higher rates of smoking and alcohol use in men; biologic factors, such as higher rates of comorbid conditions in men than in women; sex differences in immune responses, including a poor T lymphocyte response to SARS-CoV-2 infection; and lower expression levels in men of X-linked genes that are involved in the innate detection of RNA viruses and that escape X inactivation in women, resulting in higher expression levels in women. Additionally, the expression of angiotensin-converting enzyme 2 (ACE2) and the cell surface transmembrane protease serine 2 (TMPRSS2), the two host proteins that facilitate the entry of SARS-CoV-2 into the alveolar cells, is regulated by androgens in subsets of lung epithelial cells, and it is possible that higher testosterone levels in men may contribute to increased susceptibility to the infection.

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