CME CREDIT

ALEXANDER CHAITOFF, MPH
Medical Student, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

T. COLIN KILLEEN, DO
Department of Internal Medicine, Cleveland Clinic; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

CRAIG NIELSEN, MD
Department of Internal Medicine, Cleveland Clinic; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH; Deputy Editor, *Cleveland Clinic Journal of Medicine*

Men's health 2018: BPH, prostate cancer, erectile dysfunction, supplements

ABSTRACT

This review describes the latest research and guidelines for 4 topics in men's health commonly addressed by primary care physicians: the diagnosis and treatment of benign prostatic hyperplasia (BPH), prostate cancer, and erectile dysfunction and the evidence concerning the use of dietary supplements in men.

KEY POINTS

The combination of an alpha-blocker and a 5-alpha reductase inhibitor is an effective regimen for BPH. Withdrawing the alpha-blocker from the combination can be considered if symptoms have been well controlled after 1 year of combination therapy.

A new look at 2 large trials of prostate-specific antigen screening strengthened evidence that testing in the right patient population can reduce deaths from prostate cancer, but a third recently published trial found no benefit to 1-time screening.

Magnetic resonance imaging offers a better method than ultrasonography-guided biopsy to triage patients thought to be at high risk of prostate cancer and tends to limit costly overtreatment of disease that likely would not cause death.

Erectile dysfunction is often associated with chronic disease and may suggest the need to screen for cardiovascular disease.

doi:10.3949/ccjm.85a.18011

PRIMARY CARE PHYSICIANS are tasked with a wide variety of issues affecting men. This article reviews the latest research in 4 areas of men's health commonly addressed in primary care:

- Medical management of benign prostatic hyperplasia (BPH)
- Prostate cancer screening and treatment
- Medical management of erectile dysfunction
- Use of supplements.

See related commentary, page 881

MEDICAL MANAGEMENT OF BPH

An 84-year-old man with a history of hypertension, type 2 diabetes, hyperlipidemia, BPH, mild cognitive impairment, and osteoarthritis presents for a 6-month follow-up, accompanied by his son.

Two years ago he was started on a 5-alpha reductase inhibitor and an alpha-blocker for worsening BPH symptoms. His BPH symptoms are currently under control, with an American Urological Association (AUA) symptom index score of 7 of a possible 35 (higher scores being worse).

However, both the patient and son are concerned about the number of medications he is on and wonder if some could be eliminated.

Assessment tools

BPH is a common cause of lower urinary tract symptoms in older men. Evidence-based tools to help the clinician and patient decide on when to consider treatment for symptoms are:

- The AUA symptom index[1]
- The International Prostate Symptom Score (IPSS).[2]

An AUA symptom index score or IPSS score of 8 through 19 of a possible 35 is consistent with moderate symptoms, while a score of 20 or higher indicates severe symptoms.

Combination therapy or monotherapy?

Monotherapy with an alpha-blocker or a 5-alpha reductase inhibitor is often the first-line treatment for BPH-related lower urinary tract symptoms.[3] However, combination therapy with both an alpha-blocker and a 5-alpha reductase inhibitor is another evidence-based option.

The Medical Therapy of Prostatic Symptoms study,[4] a randomized controlled trial, reported that long-term combination therapy reduced the risk of BPH clinical progression better than monotherapy. The same trial also found that either combination therapy or finasteride alone (a 5-alpha reductase inhibitor) reduced the risk of acute urinary retention and the future need for invasive therapy.

Monotherapy after a period of combination therapy?

There is also evidence to support switching from combination to monotherapy after an initial treatment period.

An alpha-blocker plus a 5-alpha reductase inhibitor is an effective regimen for BPH

Matsukawa et al[5] examined the effects of withdrawing the alpha-blocker from BPH combination therapy in a study in 140 patients. For 12 months, all patients received the alpha-blocker silodosin and the 5-alpha reductase inhibitor dutasteride. At 12 months, the remaining 132 patients (8 patients had been lost to follow-up) were randomized to continue combination therapy or to take dutasteride alone for another 12 months. They were evaluated at 0, 12, and 24 months by questionnaires (the IPSS and Overactive Bladder Symptom Score) and urodynamic testing (uroflowmetry, cystometrography, and pressure-flow studies).

There were no significant differences in subjective symptoms and bladder outlet obstruction between patients who continued combination therapy and those who switched to dutasteride monotherapy. In the monotherapy group, those whose symptoms worsened weighed more (68.8 kg vs 62.6 kg, P =.002) and had a higher body mass index (BMI) (26.2 kg/m^2 vs 22.8 kg/m^2, P < .001) than those whose symptoms stayed the same or got better.

These findings of successful alpha-blocker withdrawal were consistent with those of other studies.

The Symptom Management After Reducing Therapy study[6] showed that 80% of men with an IPSS score less than 20 who changed to dutasteride monotherapy did not have a noticeable worsening of their symptoms.

Baldwin et al[7] noted similar success after withdrawing the alpha-blocker doxazosin in patients on finasteride.

Review all medications

The National Health and Nutrition Examination Survey noted that the estimated prevalence of polypharmacy increased from 8% in 1999 to 15% in 2011.[8] Many commonly used medications, such as decongestants, antihistamines, and anticholinergic agents, can worsen BPH symptoms,[9] so it is reasonable to consistently review the patient's medications to weigh the risks and benefits and determine which ones align with the patient's personal care goals.

BPH: Take-home points

- Combination therapy with an alpha-blocker and a 5-alpha reductase inhibitor is an effective regimen for BPH.
- Polypharmacy is a significant problem in the elderly.
- Withdrawing the alpha-blocker component from BPH combination therapy can be considered after 1 year of combination therapy in patients whose symptoms have been well controlled.

PROSTATE CANCER SCREENING AND TREATMENT

A 60-year-old patient calls you after receiving his laboratory testing report from his insurance physical. His prostate-specific antigen (PSA) level is 5.1 ng/mL, and he has several questions:

- Should he have agreed to the screening?
- How effective is the screening?
- What are the next steps?

Is PSA screening useful?

Over the last few years, there has been great debate as to the utility of screening for prostate cancer.

The US Centers for Disease Control and Prevention[10] reported that in 2014, an estimated 172,258 men in the United States were diagnosed with prostate cancer, but only 28,343 men died of it. These statistics support the notion that screening programs may be detecting what might otherwise be a silent disease.

The US Preventive Services Task Force (USPSTF)[11] recommends against blanket PSA screening, in view of the low probability that it reduces the risk of death from prostate cancer. For men ages 55 through 69, current guidelines give a grade C recommendation to PSA screening, meaning there is moderate agreement that the benefit is likely small, and screening should be selectively offered based on professional judgment and patient preference. In men ages 70 and older who are not at high risk, the guideline gives screening a grade D recommendation, meaning there is moderate evidence that there is no benefit from the practice. This is a change from the 2012 USPSTF guidelines,[12] which gave a grade D recommendation to PSA screening for all ages.

The American Urological Association[13] recommends against PSA screening in men under age 40 or ages 70 and older. It does not recommend routine screening in those ages 40 to 54 at average risk, but it says the decision should be individualized in this age group in those at higher risk (eg, with a positive family history, African American). At ages 55 through 69, it recommends shared decision-making, taking into account cancer risk and life expectancy. In those who opt for screening, an interval of 2 years or more may be preferred over annual screening to reduce the risk of overdiagnosis.

The USPSTF recommendations rely heavily on data from 2 trials: the European Randomized Study of Screening for Prostate Cancer (ERSPC)[14] and the Prostate, Lung, Colorectal, and Ovarian Screening (PLCO) trial.[15]

The ERSPC[14] demonstrated that screening for prostate cancer reduced deaths from prostate cancer by 20%, with an absolute risk difference of 0.71 deaths per 1,000 men; 1,410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent 1 death from prostate cancer. Screening also decreased the risk of developing metastatic disease by 30%.[16] On the negative side, screening increased the risk of overdiagnosis and other harms such as bleeding, sepsis, and incontinence.

The PLCO trial,[15] in contrast, found no difference in death rates between men randomly assigned to annual screening and those assigned to usual care. Differences between the trial results were thought to be due to different practice settings as well as study implementation and compliance.

Tsodikov et al[17] reanalyzed data from the ERSPC and the PLCO trial using 3 different mathematical models to estimate the effects of screening in both trials compared with no screening. The analysis found no evidence that the effects of screening vs not screening differed between the 2 trials, ultimately concluding that PSA screening reduced prostate cancer deaths by 25% to 32%, which the authors inferred was primarily a result of earlier detection of cancer.

The Cluster Randomized Trial of PSA Testing for Prostate Cancer,[18] published in March 2018, explored the effect of single PSA screening vs no screening on prostate cancer mortality rates in 419,582 men ages 50 through 69. Although screening detected more cases of low-risk prostate cancer, there was no significant difference in prostate cancer mortality rates after a median follow-up of 10 years. However, 10% to 15% of the control group was estimated to have also been screened, and these results do not directly speak to the efficacy of serial PSA screening.

Extended follow-up of this trial is planned to report on long-term survival benefits and whether screening lowers the risk of metastasis.

Imaging-guided prostate biopsy

Once a patient is found to have an elevated PSA level, standard practice has been to perform transrectal ultrasonography to obtain 12 core biopsy samples. The results indicate whether the prostate contains cancer, how aggressive the cancer is (Gleason score), and whether there is extracapsular extension.

In the past, magnetic resonance imaging (MRI) of the prostate before biopsy was thought to be too costly, and many insurance plans do not currently cover it.

Consider stopping the alpha-blocker from the BPH combination regimen if symptoms are well controlled at 1 year

Pahwa et al,[19] however, in a cost-effectiveness study using a decision-analysis model, found that using MRI to detect lesions and then guide biopsy by triaging patients into proper treatment pathways added health benefits in a cost-effective manner in 94.05% of simulations. These benefits were found across all age groups.

This study demonstrated that doctors could use MRI to better evaluate patients for potentially harmful lesions. If a focus of cancer is found, it can be biopsied; if no cancer is seen on MRI, the patient can avoid biopsy completely. Additionally, though MRI tended to miss low-risk cancers, these cancers are thought to disproportionately lead to higher healthcare costs through unnecessary treatment. Therefore, a negative MRI study was believed to be an excellent sign that the patient does not have aggressive prostate cancer. This approach led to a net gain of 0.251 additional quality-adjusted life years compared with the standard biopsy strategy.

The Prostate MRI Imaging Study[20] also found MRI to be effective in the prostate cancer workup. In this trial, 576 men who had never undergone biopsy underwent multiparametric MRI, transrectal ultrasonography-guided biopsy, and the reference standard, ie, transperineal template prostate mapping biopsy. Of those who underwent biopsy, 71% received a diagnosis of prostate cancer, and 40% had clinically significant disease. In patients with clinically significant disease, MRI was more sensitive than ultrasonography-guided biopsy (93% vs 48%, $P < .0001$) but less specific (41% vs 96%, $P < .0001$).

1,410 men need to be screened to prevent 1 death from prostate cancer

Based on these findings, if biopsy were performed only in those who had suspicious lesions on MRI, 27% of men with elevated PSA could avoid biopsy and its potential complications such as bleeding and sepsis, which occurred in 5.9% of the biopsy group.

The Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not? trial[21] more recently studied MRI with or without targeted biopsy vs standard transrectal ultrasonography-guided biopsy in 500 men who had not undergone biopsy before, and reported similar results. MRI with or without biopsy led to fewer biopsies and less overdetection of clinically insignificant prostate cancers compared with the standard approach. Furthermore, those in the MRI-targeted biopsy group were 13% less likely to receive a diagnosis of clinically insignificant cancer than those who received the standard biopsy (adjusted difference −13 percentage points, 95% confidence interval [CI] −19 to −7, $P < .001$).

Together, these data provide another argument for adding multiparametric MRI to the workup of men with an elevated PSA level.

Surveillance vs treatment for prostate cancer

Once prostate cancer is diagnosed, surveillance is becoming an increasingly common management strategy.

The Prostate Cancer Intervention Versus Observation Trial (PIVOT),[22] one of the largest and longest trials involving cancer patients, offered further evidence that active surveillance and less intervention for men with prostate cancer is a better approach in many cases. This trial compared prostatectomy and observation alone in a randomized fashion. Inclusion for the study required men to be medically fit for radical prostatectomy, along with having histologically confirmed localized prostate cancer (stage T1-T2NxM0 in the tumor-node-metastasis classification system) of any grade diagnosed within the last 12 months.

During 19.5 years of follow-up, 223 (61.3%) of the 364 men randomly assigned to radical prostatectomy died, compared with 245 (66.8%) of 367 men in the observation group; the difference was not statistically different ($P = .06$). Only 9.4% of the deaths were due to prostate cancer, 7.4% in the surgery group and 11.4% in the observation group ($P = .06$).

Surgery was associated with a lower all-cause mortality rate than observation in the subgroup of patients with intermediate-risk prostate cancer (defined as PSA 10–20 ng/mL and a Gleason score of 7). Surgery was also associated with less disease progression.[22]

This finding is in line with previous data from the **Scandinavian Prostate Cancer Group Study Number 4,**[23] as well as the much larger **Prostate Testing for Cancer and Treatment (ProtecT) trial,**[24] both of which

reported that metastasis was 1.5 and 2.6 times as common, respectively, in participants in the active surveillance groups. However, in the PIVOT trial, those in the surgery group were significantly more likely than those in the observation group to have erectile dysfunction and urinary incontinence at 10 years.

Therefore, in men with localized disease and in those with low-risk PSA levels, both the PIVOT and ProtecT trials suggest that death from prostate cancer is uncommon and that observation may be more appropriate.

Prostate cancer: Take-home points

- A new look at 2 large trials of PSA screening strengthened evidence that testing in the right patient population can reduce deaths from prostate cancer, but a third recently published trial that found no benefit from 1-time screening may reopen debate on the topic.
- MRI offers a better method than ultrasonography-guided biopsy to triage patients thought to be at high risk of prostate cancer and tends to limit costly overtreatment of disease that likely would not cause death.
- Surgery for prostate cancer may not prolong life but could reduce disease progression, at the risk of more adverse effects.
- Shared decision-making should be practiced when deciding whether to use active surveillance or active treatment of diagnosed prostate cancer.

MANAGEMENT OF ERECTILE DYSFUNCTION

A 62-year-old man with hypertension, hyperlipidemia, peripheral artery disease, and type 2 diabetes presents for a 6-month follow-up. His medications include aspirin, metformin, lisinopril, and atorvastatin, all of which he takes without problems. Over the past several months, he has noticed that his erections are not adequate for sexual intercourse. He recently heard that a generic version of sildenafil has just become available, and he wonders if it might benefit him.

Erectile dysfunction is common, associated with chronic diseases

Erectile dysfunction, ie, persistent inability to obtain and maintain an erection sufficient to permit satisfactory sexual intercourse,[25,26] is estimated to affect nearly 20% of men over the age of 20 and 75% of men over the age of 75.[27]

In age-adjusted models, erectile dysfunction has been shown[28] to be associated with:

- History of cardiovascular disease (odds ratio [OR] 1.63, 95% CI 1.02–2.63)
- Diabetes (OR 3.90, 95% CI 2.16–7.04)
- Treated hypertension vs no hypertension (OR 2.22, 95% CI 1.30–3.80)
- Current smoking vs never smoking (OR 1.63, 95% CI 1.01–2.62)
- BMI greater than 30 kg/m^2 vs less than 25 kg/m^2 (OR 1.80, 95% CI 1.03–3.14).

Because of the strong association between cardiovascular disease and erectile dysfunction, the presence of one often suggests the need to screen for the other.[29] While tools such as the International Index of Erectile Function (IIEF-5) have been developed to evaluate erectile dysfunction, it is most often diagnosed on the basis of clinical impression, while validated assessment methods are reserved for clinical trials.[28]

Multiple causes of erectile dysfunction

Erectile dysfunction arises from inadequate penile tissue response to a sexual signal. The response can be disrupted at several points. For example, damage to vascular smooth muscle cells (eg, from age or obesity) and endothelial cells (from smoking or diabetes) and narrowing of the vascular lumen (from atherosclerosis or hypertension) have all been shown to impair engorgement of the corpus cavernosum.[30] In addition, denervation from prostate surgery or spinal trauma and psychogenic causes should be recognized in discussions with patients.

Once prostate cancer is diagnosed, surveillance is becoming an increasingly common management strategy

Drugs for erectile dysfunction

Pharmacologic management of erectile dysfunction includes oral, sublingual, intracavernosal, and intraurethral therapies.[31] Treatment in primary care settings usually includes addressing underlying chronic diseases[32] and prescribing phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil, and avanafil). These drugs work by increasing local concentrations of cyclic guanosine monophosphate in the corpus cavernosum to induce vasodilation.[33]

While these 4 drugs are still patent-pro-

tected, a manufacturer has been allowed to introduce a generic version of sildenafil into US markets, and a generic version of tadalafil is expected to be available soon.

Sildenafil, tadalafil, and vardenafil have been studied and found to have some degree of effectiveness in erectile dysfunction caused by damage to the penile vasculature, denervation, and spinal cord injury.[34] All drugs of this class have adverse effects including headache, facial flushing, and nasal congestion, but the drugs are generally well tolerated.[35]

Sildenafil and tadalafil improve IIEF-5 scores by a similar margin, raising scores on the erectile domain subsection from approximately 14 of a possible 30 to approximately 24 of 30 in a trial of both drugs.[36] However, multiple crossover studies comparing the 2 drugs have shown that nearly 75% of patients prefer tadalafil to sildenafil,[36,37] perhaps because of tadalafil's longer duration of action.[34]

There is little evidence to suggest that vardenafil is more effective or more often preferred by patients than tadalafil or sidenafil.[34,38] And though data on the newest drug on the market, avanafil, are limited, a meta-analysis concluded that it may be less effective than tadalafil and without significant differences in terms of safety.[39]

Erectile dysfunction may affect 20% of men over age 20, and 75% of men over age 75

Other treatments

Lifestyle modifications, especially smoking cessation and exercise, have been shown to reduce the risk of erectile dysfunction with varying effect sizes across studies.[40–42] Moreover, factors such as obesity, alcohol use, and smoking may cause irreversible harm, and thus a healthy lifestyle should be encouraged.[41]

While there is only weak evidence for the use of psychological interventions alone for treating most types of erectile dysfunction, one meta-analysis found that the combination of psychological intervention and a phosphodiesterase-5 inhibitor improved sexual satisfaction more than drug therapy alone.[43]

Erectile dysfunction: Take-home points

- Erectile dysfunction is common, affecting nearly 20% of men over the age of 20 and over 75% of men over the age of 75.
- Erectile dysfunction is often associated with chronic disease and may suggest the need to screen for cardiovascular disease.
- Treating underlying chronic diseases may help, and phosphodiesterase-5 inhibitors are effective; tadalafil may be most often preferred.

SUPPLEMENT USE AND MEN'S HEALTH

A 68-year-old man with a history of hypertension, BPH, and erectile dysfunction presents for a 6-month follow-up. His medication use includes lisinopril, which he takes without problems. He denies any new physical symptoms. His physical examination is unremarkable. He says he has heard about supplements that might help with his sexual performance and hopes to discuss recommendations during the visit.

A burgeoning, unregulated industry

Since the passage of the Dietary Supplement and Health Education Act in 1994, a law that decreased oversight of the supplement industry, spending on supplements has skyrocketed to over $41.1 billion each year.[44] Advertisements for these products typically claim that they improve general mental and physical health, sexual and romantic performance, leanness, and muscularity.[45] A national survey of men ages 57 and older reported that the most popular products were aimed at nutrition (such as multivitamins), cardiovascular health (such as omega-3 fatty acids), and chronic conditions (such as saw palmetto for BPH).[46]

Little evidence of efficacy

There is little evidence to support the use of most supplements to improve men's health. For example, a study in 82,405 men found no association between mortality rates and multivitamin use (hazard ratio [HR] 1.07, 95% CI 0.96–1.19).[47] Even for specific uses, such as cognitive performance, randomized trials exploring the effects of multivitamins in men have been largely negative.[48]

The positive trials that have been reported are often of low quality and are funded by supplement manufacturers. For example, one of the few trials that reported a positive association between multivitamin supplementation and cognition in men was underpowered (N = 51) and found improvement in only 1 of 19 cognitive domains.[49] Despite the poor design and results to the contrary, this industry-funded study nevertheless concluded that multivi-

tamins may play a role in improving elements of memory.

Evidence of possible harm from antioxidants

While not always specific to men, many meta-analyses have explored the effects of antioxidant supplements on cardiovascular and mortality risk. Most of them concluded that antioxidant supplements have no benefit and that some may actually be harmful.

For example, multiple meta-analyses of vitamin E supplementation found no cardiovascular benefit but possible increases in all-cause mortality rates in those taking high doses (risk ratio 1.04, 95% CI 1.01–1.07).[50,51]

Another meta-analysis of 180,938 participants in high-quality studies found an increased risk of all-cause mortality associated with independent intake of several antioxidant vitamins, including beta-carotene (risk ratio 1.07, 95% CI 1.02–1.11) and vitamin A (risk ratio 1.16, 95% CI 1.10–1.24), while intake of vitamin C and selenium had no impact on mortality.[52]

Similarly, although nearly 10% of US adults report taking omega-3 fatty acid supplements, a review of 24 randomized controlled trials and meta-analyses published between 2005 and 2012 concluded that only 2 supported the use of these supplements for any health benefit.[53]

Can supplements improve sexual function, prostate health?

To improve sexual function. A 2015 narrative review of the ingredients in General Nutrition Center's top 30 best-selling products targeted at improving men's sexual performance (including improving libido and erectile dysfunction) found only poor evidence for any efficacy.[54] The few studies that did support the use of select supplements, including B vitamins in people with diabetes, L-arginine, and yohimbine, were deemed to be of poor quality or showed a smaller effect size compared with standard medical therapy.

To prevent prostate cancer. Studies of supplement use to improve prostate health have had mixed results. For example, multiple large case-control studies have suggested that taking vitamin D[55,56] or vitamin C[57] is not associated with prostate cancer risk, while increased vitamin A[58,59] and E[60,61] intake is associated with inconsistent increases in prostate cancer risk.

In the Selenium and Vitamin E Cancer Prevention Trial,[62] a randomized controlled trial in 35,533 men, those assigned to receive vitamin E supplementation were 17% more likely to get prostate cancer than were those assigned to placebo (HR 1.17, 99% CI 1.004–1.36, $P = .008$).

However, there are plausible biologic links between nutraceuticals and prostate cancer. For example, studies have linked genetic polymorphisms in vitamin D receptors[63] as well as intake of natural androgen receptor modulators, such as the most active polyphenol in green tea,[64] to prostate cancer risk and aggressiveness in certain populations. This led a recent review to conclude that there is some biologic plausibility, but at present little epidemiologic evidence, to support any dietary supplement's ability to broadly affect prostate cancer risk.[65]

Interest continues in exploring the targeted use of nutraceuticals as adjuvant therapy in specific populations at risk of prostate cancer.[66,67]

To treat BPH. There is a similar dearth of clinical or population-based evidence that supplements can broadly affect BPH symptoms. For example, in a 2012 Cochrane review of *Serenoa repens* (saw palmetto) utilizing only high-quality evidence, there was no evidence that supplement use significantly reduced lower urinary tract symptoms, nocturia, or peak urine flow in BPH patients, and this was true even when the supplement was taken at triple-strength doses.[68]

There is little evidence to support the use of most supplements to improve men's health

For other diseases. There is also limited evidence that supplements can affect other chronic diseases. For example, a meta-analysis of 3,803 patients found that glucosamine, chondroitin, and their combination had no impact on joint pain or joint space narrowing in patients with osteoarthritis of the knee or hip.[69]

Even when there is some evidence to suggest benefit from supplementation, study heterogeneity and varying evidence quality limit confidence in the conclusions. For example, meta-analyses suggest garlic may improve blood pressure control in those with hyper-

tension[70] and improve lipid and blood glucose control in type 2 diabetes.[71] However, most of the trials included in those systematic reviews were underpowered, with samples as low as 10 patients, and many suffered from improper design, such as inadequate blinding of researchers. In addition, these meta-analyses often do not report adverse events, suggesting that higher quality studies would be needed to adequately measure event rates. As such, there is need for caution and a case-by-case review before recommending even a seemingly benign supplement like garlic to patients.

In total, there is only limited evidence to support the efficacy of supplements across many diseases and concerns common to men in primary care. This includes improving general health, cardiovascular health, sexual functioning, or other chronic diseases. While a supplement's placebo effect may at times provide some benefit, supplements are much less strictly regulated since the passing of the 1994 act, and even vitamin supplementation has been shown to be associated with negative health outcomes. As such, a patient's use of supplements requires careful consideration and shared decision-making.

Supplements: Take-home points

- Supplements are only loosely regulated by the federal government.
- There is some biologic but limited epidemiologic evidence for the use of multivitamins to improve cognition or mortality rates; for the use of antioxidant vitamins or omega-3 fatty acids to improve cardiovascular health; for the use of any of the top-selling sexual enhancement supplements to improve libido or erectile function; and for the use of vitamins or other supplements for improving BPH or reducing prostate cancer risk. Using supplements may in some cases be harmful.
- Given the heterogeneity of studies of supplements to manage chronic diseases and a lack of reporting of adverse events, careful consideration is needed when recommending supplements to patients.

REFERENCES

1. **Barry MJ, Fowler FJ Jr, O'Leary MP, et al**. The American Urological Association symptom index for benign prostatic hyperplasia. J Urol 2017; 197(2S):S189–S197. doi:10.1016/j.juro.2016.10.071
2. **Urological Sciences Research Foundation**. International Prostate Symptom Score (IPSS). http://www.usrf.org/questionnaires/AUA_SymptomScore.html. Accessed October 16, 2018.
3. **McVary KT, Roehrborn CG, Avins AL, et al**. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 2011; 185(5):1793–1803. doi:10.1016/j.juro.2011.01.074
4. **McConnell JD, Roehrborn CG, Bautista OM, et al**. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 2003; 349(25):2387–2398. doi:10.1056/NEJMoa030656
5. **Matsukawa Y, Takai S, Funahashi Y, et al**. Effects of withdrawing alpha-1 blocker from the combination therapy with alpha-1 blocker and 5-alpha-reductase inhibitor in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a prospective and comparative trial using urodynamics. J Urol 2017; 198(4):905–912. doi:10.1016/j.juro.2017.05.031
6. **Barkin J, Guimaraes M, Jacobi G, Pushkar D, Taylor S, van Vierssen Trip OB**. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5a-reductase inhibitor dutasteride. Eur Urol 2003; 44(4):461–466. pmid:14499682
7. **Baldwin KC, Ginsberg PC, Roehrborn CG, Harkaway RC**. Discontinuation of alpha-blockade after initial treatment with finasteride and doxazosin in men with lower urinary tract symptoms and clinical evidence of benign prostatic hyperplasia. Urology 2001; 58(2):203–209. pmid:11489700
8. **Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL**. Trends in prescription drug use among adults in the United States from 1999-2012. JAMA 2015; 314(17):1818–1831. doi:10.1001/jama.2015.13766
9. **DuBeau CE, Yalla SV, Resnick NM**. Improving the utility of urine flow rate to exclude outlet obstruction in men with voiding symptoms. J Am Geriatr Soc 1998; 46(9):1118–1124. pmid:9736105
10. **US Department of Health and Human Services Health Resources and Services Administration**. United States Cancer Statistics: 1999-2014 Incidence and Mortality Web-Based Report. Atlanta; 2017. https://nccd.cdc.gov/uscs/. Accessed October 17, 2018.
11. **US Preventive Services Task Force**. Final recommendation statement. Prostate cancer: screening. www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening1. Accessed October 16, 2018.
12. **US Preventive Services Task Force**. Archived: prostate cancer: screening. Original release date: May 2012. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/prostate-cancer-screening. Accessed October 16, 2018.
13. **Carter HB, Albertsen PC, Barry MJ, et al**. Early detection of prostate cancer: AUA guideline. J Urol 2013; 190(2):419–426. doi:10.1016/j.juro.2013.04.119
14. **Schröder FH, Hugosson J, Roobol MJ, et al**. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360(13):1320–1328. doi:10.1056/NEJMoa0810084
15. **Andriole GL, Crawford ED, Grubb RL, et al**. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009; 360(13):1310–1319. doi:10.1056/NEJMoa0810696
16. **Schröder FH, Hugosson J, Carlsson S, et al**. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012; 62(5):745–752. doi:10.1016/j.eururo.2012.05.068
17. **Tsodikov A, Gulati R, Heijnsdijk EAM, et al**. Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. Ann Intern Med 2017; 167(7):449–455. doi:10.7326/M16-2586
18. **Martin RM, Donovan JL, Turner EL, et al**. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. JAMA 2018; 319(9):883–895. doi:10.1001/jama.2018.0154

19. **Pahwa S, Schiltz NK, Ponsky LE, Lu Z, Griswold MA, Gulani V**. Cost-effectiveness of MR imaging–guided strategies for detection of prostate cancer in biopsy-naive men. Radiology 2017; 285(1):157–166. doi:10.1148/radiol.2017162181
20. **Ahmed HU, El-Shater Bosaily A, Brown LC, et al**. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017; 389(10071):815–822. doi:10.1016/S0140-6736(16)32401-1
21. **Kasivisvanathan V, Rannikko AS, Borghi M, et al**. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018; 378(19):1767–1777. doi:10.1056/NEJMoa1801993
22. **Wilt TJ, Jones KM, Barry MJ, et al**. Follow-up of prostatectomy versus observation for early prostate cancer. N Engl J Med 2017; 377(2):132–142. doi:10.1056/NEJMoa1615869
23. **Bill-Axelson A, Holmberg L, Garmo H, et al**. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 2014; 370(10):932–942. doi:10.1056/NEJMoa1311593
24. **Hamdy FC, Donovan JL, Lane JA, et al**. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016; 375(15):1415–1424. doi:10.1056/NEJMoa1606220.
25. **Morley JE**. Impotence. Am J Med 1986; 80(5):897–905. pmid:3518438
26. **NIH Consensus Development Panel on Impotence**. NIH Consensus Conference. Impotence. JAMA 1993; 270(1):83–90. pmid:8510302
27. **Selvin E, Burnett AL, Platz EA**. Prevalence and risk factors for erectile dysfunction in the US. Am J Med 2007; 120(2):151–157. doi:10.1016/j.amjmed.2006.06.010
28. **Rosen RC, Cappelleri JC, Gendrano N 3rd**. The International Index of Erectile Function (IIEF): a state-of-the-science review. Int J Impot Res 2002; 14(4):226–244. doi:10.1038/sj.ijir.3900857
29. **Gandaglia G, Briganti A, Jackson G, et al**. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol 2014; 65(5):968–978. doi:10.1016/j.eururo.2013.08.023
30. **Heaton JPW, Adams MA**. Causes of erectile dysfunction. Endocrine 2004; 23(2-3):119–123. doi:10.1385/ENDO:23:2-3:119
31. **Montorsi F, Salonia A, Deho F, et al**. Pharmacological management of erectile dysfunction. BJU Int 2003; 91(5):446–454. pmid:12603396
32. **Cai X, Tian Y, Wu T, Cao CX, Bu SY, Wang KJ**. The role of statins in erectile dysfunction: a systematic review and meta-analysis. Asian J Androl 2014; 16(3):461–466. doi:10.4103/1008-682X.123678
33. **Webb DJ, Freestone S, Allen MJ, Muirhead GJ**. Sildenafil citrate and blood-pressure–lowering drugs: results of drug interaction studies with an organic nitrate and a calcium antagonist. Am J Cardiol 1999; 83(5):21C–28C. pmid:10078539
34. **Doggrell SA**. Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. Expert Opin Pharmacother 2005; 6(1):75–84. doi:10.1517/14656566.6.1.75
35. **Gresser U, Gleiter CH**. Erectile dysfunction: comparison of efficacy and side effects of the PDE-5 inhibitors sildenafil, vardenafil and tadalafil—review of the literature. Eur J Med Res 2002; 7(10):435–446. pmid:12435622
36. **Eardley I, Mirone V, Montorsi F, et al**. An open-label, multicentre, randomized, crossover study comparing sildenafil citrate and tadalafil for treating erectile dysfunction in men naive to phosphodiesterase 5 inhibitor therapy. BJU Int 2005; 96(9):1323–1332. doi:10.1111/j.1464-410X.2005.05892.x
37. **von Keitz A, Rajfer J, Segal S, et al**. A multicenter, randomized, double-blind, crossover study to evaluate patient preference between tadalafil and sildenafil. Eur Urol 2004; 45(4):499–509. doi:10.1016/j.eururo.2003.11.030
38. **Martin-Morales A, Haro JM, Beardsworth A, Bertsch J, Kontodimas S; EDOS Group**. Therapeutic effectiveness and patient satisfaction after 6 months of treatment with tadalafil, sildenafil, and vardenafil: results from the erectile dysfunction observational study (EDOS). Eur Urol 2007; 51(2):541–550. doi:10.1016/j.eururo.2006.09.027
39. **Yuan J, Zhang R, Yang Z, et al**. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol 2013; 63(5):902–912. doi:10.1016/j.eururo.2013.01.012
40. **Cao S, Yin X, Wang Y, Zhou H, Song F, Lu Z**. Smoking and risk of erectile dysfunction: systematic review of observational studies with meta-analysis. PLoS One 2013; 8(4):e60443. doi:10.1371/journal.pone.0060443
41. **Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB**. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology 2000; 56(2):302–306. pmid:10925098
42. **Esposito K, Giugliano F, Di Palo C, et al**. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA 2004; 291(24):2978–2984. doi:10.1001/jama.291.24.2978
43. **Schmidt HM, Munder T, Gerger H, Frühauf S, Barth J**. Combination of psychological intervention and phosphodiesterase-5 inhibitors for erectile dysfunction: a narrative review and meta-analysis. J Sex Med 2014; 11(6):1376–1391. doi:10.1111/jsm.12520
44. **New Hope Network**. Supplement Business Report 2017. Boulder; 2017. http://images.info.newhope.com/Web/NewHopeNaturalMedia/%7B3a3f3b03-6130-41d4-9e66-84f29eeebe44%7D_2017_Supplement_Business_Report_-_Extended_TOC.pdf. Accessed October 16, 2018.
45. **Labre MP**. Burn fat, build muscle: a content analysis of men's health and men's fitness. Int J Mens Health 2005; 4(2):187–200.
46. **Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST**. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA 2008; 300(24):2867–2878. doi:10.1001/jama.2008.892
47. **Park SY, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN**. Multivitamin use and the risk of mortality and cancer incidence: the multiethnic cohort study. Am J Epidemiol 2011; 173(8):906–914. doi:10.1093/aje/kwq447
48. **McNeill G, Avenell A, Campbell MK, et al**. Effect of multivitamin and multimineral supplementation on cognitive function in men and women aged 65 years and over: a randomised controlled trial. Nutr J 2007; 6(1):10. doi:10.1186/1475-2891-6-10
49. **Harris E, Macpherson H, Vitetta L, Kirk J, Sali A, Pipingas A**. Effects of a multivitamin, mineral and herbal supplement on cognition and blood biomarkers in older men: a randomised, placebo-controlled trial. Hum Psychopharmacol Clin Exp 2012; 27(4):370–377. doi:10.1002/hup.2236
50. **Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ**. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. Lancet 2003; 361(9374):2017–2023. doi:10.1016/S0140-6736(03)13637-9
51. **Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E**. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005; 142(1):37–46. pmid:15537682
52. **Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C**. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 2007; 297(8):842–857. doi:10.1001/jama.297.8.842
53. **Grey A, Bolland M**. Clinical trial evidence and use of fish oil supplements. JAMA Intern Med 2014; 174(3):460–462. doi:10.1001/jamainternmed.2013.12765
54. **Cui T, Kovell RC, Brooks DC, Terlecki RP**. A urologist's guide to ingredients found in top-selling nutraceuticals for men's sexual health. J Sex Med 2015; 12(11):2105–2117. doi:10.1111/jsm.13013
55. **Schenk JM, Till CA, Tangen CM, et al**. Serum 25-hydroxyvitamin D concentrations and risk of prostate cancer: results from the Prostate Cancer Prevention Trial. Cancer Epidemiol Prev Biomarkers 2014; 23(8):1484–1493. doi:10.1158/1055-9965.EPI-13-1340
56. **Albanes D, Mondul AM, Yu K, et al**. Serum 25-hydroxy vitamin D and prostate cancer risk in a large nested case-control study. Cancer Epidemiol Prev Biomarkers 2011; 20(9):1850–1860. doi:10.1158/1055-9965.EPI-11-0403
57. **Roswall N, Larsen SB, Friis S, et al**. Micronutrient intake and risk of prostate cancer in a cohort of middle-aged, Danish men. Cancer Causes Control 2013; 24(6):1129–1135. doi:10.1007/s10552-013-0190-4
58. **Mondul AM, Watters JL, Männistö S, et al**. Serum retinol and risk of prostate cancer. Am J Epidemiol 2011; 173(7):813-821.

doi:10.1093/aje/kwq429
59. **Schenk JM, Riboli E, Chatterjee N, et al**. Serum retinol and prostate cancer risk: a nested case-control study in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Prev Biomarkers 2009; 18(4):1227–1231. doi:10.1158/1055-9965.EPI-08-0984
60. **Bidoli E, Talamini R, Zucchetto A, et al**. Dietary vitamins E and C and prostate cancer risk. Acta Oncol 2009; 48(6):890–894. doi:10.1080/02841860902946546
61. **Wright ME, Weinstein SJ, Lawson KA, et al**. Supplemental and dietary vitamin E intakes and risk of prostate cancer in a large prospective study. Cancer Epidemiol Prev Biomarkers 2007; 16(6):1128–1135. doi:10.1158/1055-9965.EPI-06-1071
62. **Klein EA, Thompson IM, Tangen CM, et al**. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2011; 306(14):1549–1556. doi:10.1001/jama.2011.1437
63. **Jingwi EY, Abbas M, Ricks-Santi L, et al**. Vitamin D receptor genetic polymorphisms are associated with PSA level, Gleason score and prostate cancer risk in African-American men. Anticancer Res 2015; 35(3):1549–1558. pmid:25750310
64. **Siddiqui IA, Asim M, Hafeez BB, Adhami VM, Tarapore RS, Mukhtar H**. Green tea polyphenol EGCG blunts androgen receptor function in prostate cancer. FASEB J 2011; 25(4):1198–1207. doi:10.1096/fj.10-167924
65. **Yacoubian A, Dargham RA, Khauli RB, Bachir BG**. Overview of dietary supplements in prostate cancer. Curr Urol Rep 2016; 17(11):78. doi:10.1007/s11934-016-0637-8
66. **Kallifatidis G, Hoy JJ, Lokeshwar BL**. Bioactive natural products for chemoprevention and treatment of castration-resistant prostate cancer. Semin Cancer Biol 2016; 40:160–169. doi:10.1016/j.semcancer.2016.06.003
67. **Shui IM, Mondul AM, Lindström S, et al**. Circulating vitamin D, vitamin D–related genetic variation, and risk of fatal prostate cancer in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. Cancer 2015; 121(12):1949–1956. doi:10.1002/cncr.29320
68. **Tacklind J, MacDonald R, Rutks I, Stanke JU, Wilt TJ**. Serenoa repens for benign prostatic hyperplasia. Cochrane Database Syst Rev 2012; 12:CD001423. doi:10.1002/14651858.CD001423.pub3
69. **Wandel S, Jüni P, Tendal B, et al**. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ 2010; 341:c4675. doi:10.1136/bmj.c4675
70. **Reinhart KM, Coleman CI, Teevan C, Vachhani P, White CM**. Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. Ann Pharmacother 2008; 42(12):1766–1771. doi:10.1345/aph.1L319
71. **Wang J, Zhang X, Lan H, Wang W**. Effect of garlic supplement in the management of type 2 diabetes mellitus (T2DM): a meta-analysis of randomized controlled trials. Food Nutr Res 2017; 61(1):1377571. doi:10.1080/16546628.2017.1377571

***ADDRESS**: Alexander Chaitoff, MPH, Department of Internal Medicine, G10, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; chaitoa@ccf.org*

CORRECTION

Men's health 2018

NOVEMBER 2018

In the article by Chaitoff et al (Men's health 2018: BPH, prostate cancer, erectile dysfunction, supplements. Cleve Clin J Med 2018; 85(11):871–880, doi:10.3949/ccjm.85a.18011), the prostate-specific antigen level of a 60-year-old man was given as 5.1 mg/dL. The unit of measure should have been 5.1 ng/mL. This has been corrected online.