Benign Prostate Hypertrophy (BPH)

Author(s): Kristi Hough, PharmD, Chad Thury, DO

Executive Summary

Benign Prostate Hypertrophy (BPH) is the most common benign neoplasm in men who are 40 years old and older. After age 40, the prostate undergoes a growth spurt which progresses over time. Urinary symptoms include frequency, nocturia, hesitancy, urgency, and weak urine flow. Treatment options include medications and surgery. Approximately 20-30% of men with BPH require some form of treatment by age 80.

BPH Treatment Diagram

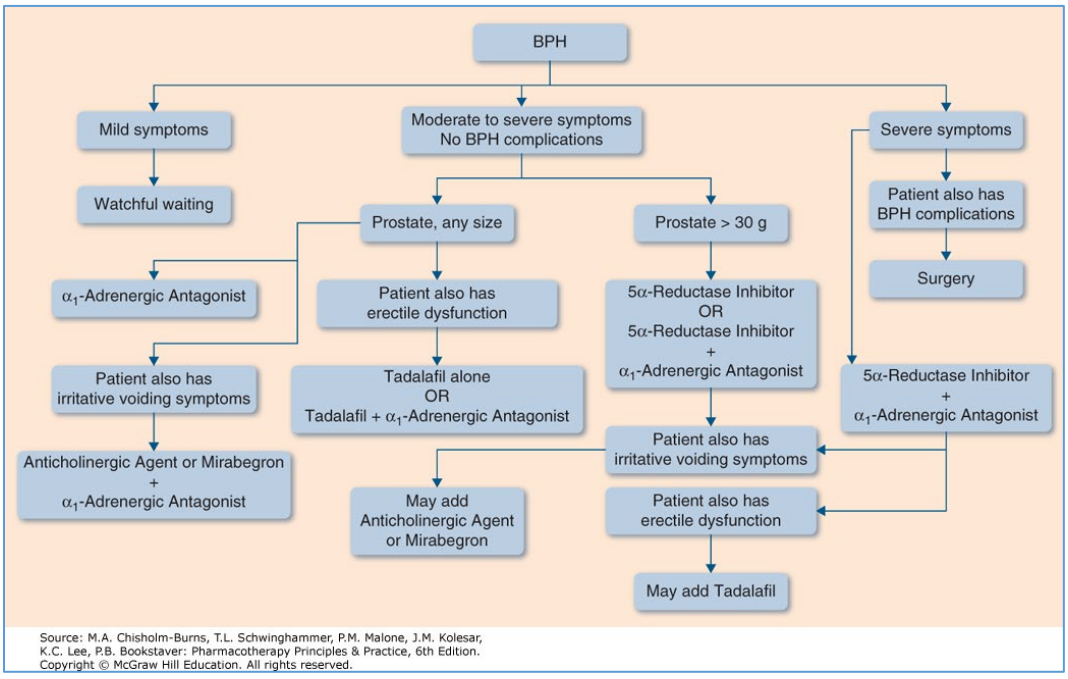

Table 1.1 - BPH Progression Prevention - 5α-Reductase Inhibitors (5ARIs)

Medication	Finasteride	Dutasteride
Dose	5 mg daily	0.5 mg daily
Maximum Effect	6-12 months	6-12 months
Renal Impairment	No adjustment	No adjustment
Hepatic Impairment	No adjustment; use with caution	No adjustment
Adverse Effects	Sexual dysfunction & gynecomastia likely	Sexual dysfunction & gynecomastia MORE likely

Finasteride and Dutasteride have equal clinical efficacy. The 5ARIs prevent BPH-related complications and disease progression, however are less effective than α1-adrenergic receptor antagonists in improving symptoms.

Baseline and annual PSA levels and digital rectal exam are recommended during treatment with these agents. 5ARIs can lower the PSA by 50% and thus PSA values should be doubled for patients on 5ARIs when trending PSA levels.

Randomized trials have shown a reduced risk of prostate cancer compared to placebo. However, they showed a potential concern of increased risk of high-grade prostate cancer which may be due to detection bias.

The FDA recommends urologic evaluation for patients being considered for 5ARI therapy, especially in those with elevated baseline PSA, to rule out prostate cancer. May use 5ARIs alone or in combination with α1-blockers.

Table 2.1 - Symptom Relief - α1 Adrenergic Receptor Antagonists

	Terazosin*	Doxazosin*	Alfuzosin	Tamsulosin	Silodosin
Dosing & Administration	1mg QHS days 1-3, 2mg QHS days 4-14, 5mg QHS wks 2-6, 10mg QHS wk7 & on; May increase to 20mg QHS after 4-6wks at 10mg dose	Immediate Release 1mg QHS days 1-3, 2mg QHS days 4-14, 4mg QHS wks 2-6, 8mg QHS wk 7 & on. Extended Release 4mg Q AM days 1-21, 8mg Q AM wk 4 & on; Take with meal.	Extended Release 10 mg daily immediately after meal	0.4 mg daily; Increase to 0.8mg daily after 2-4 wks if need for response. Take 30 minutes after meal.	8 mg daily with meal
Renal Impairment	No adjustment	No adjustment	Use with caution	No adjustment; Not studied CrCl<10ml/min	Contraindicated CrCl<30ml/min
Hepatic Impairment	Use with caution	Avoid in severe impairment	Contraindicated if mod-severe	No adjustment	Contraindicated if severe
Uroselective	No	No	Yes	Yes	Yes
Hypotensive	Most likely	Most likely	Likely	Least likely	Least likely
Ejaculation Disorder	Likely	Likely	Likely	Most likely	Most likely

*Titrate to reduce orthostatic effects; advance if patient remains symptomatic & tolerating current dose.

Alpha1-adrenergic receptor antagonists have a fast onset of clinical effect in days to weeks, and are considered equally effective in relieving symptoms. If take with a phosphodiesterase type 5 inhibitor (PDE5), such as Tadalafil 5mg daily, the patient should be on a fixed stable dose first. Uroselective alpha1-adranergic medications have a higher risk of retrograde or anejaculation which should be discussed with the patient. There is some association with alpha-1 antagonists with intraoperative floppy iris syndrome. However, patients on these medications do not need to stop the medication prior to cataract surgery.

Table 3.1 - Other Medication Options For Lower Urinary Tract Symptoms

Class	Medication	Initial Dose*	Dose Titration	Maximum Dose*
PDE-5 inhibitor	Tadalafil	5 mg daily	None	5 mg daily
β3-adrenergic Agonists	Mirabegron	25 mg daily	↑ if need, if tolerated ≥ 4 wks	50 mg daily
	Vibegron	75 mg daily	None	75 mg daily

Anticholinergic Agents	Fesoterodine	4 mg daily	↑ if need, if tolerated ≥ 2 wks	8 mg daily
	Tolterodine IR	1to 2 mg BID	None	2 mg BID
	Tolterodine ER	2 to 4 mg daily		4 mg daily
	Oxybutynin IR	5 mg BID to TID	↑ if need, if tolerated in 5mg increments Q 1 to 2wks	5 mg 4x/day
	Oxybutynin ER	5 to 10 mg daily		30 mg daily
	Darifenacin	7.5 mg daily	↑ if need, if tolerated ≥2 wks	15 mg daily
	Solifenacin	5 mg daily		10 mg dail
	Trospium	20 mg BID; daily if ≥ 75 yo	None	20mg BID
	Trospium ER	60 mg daily		60 mg daily

*****_Adult dosing recommendations for normal organ function; consult clinical resource if impairment present._

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Erectile Dysfunction

Author(s): Amelia Koster, PharmD Candidate 2022, Emily Van Klompenburg, PharmD, BCACP

Executive Summary:
Erectile dysfunction (ED) is an early risk marker for underlying cardiovascular disease and other health conditions that may warrant evaluation and treatment. Risk factors and predictors of ED include cardiovascular disease (CVD), diabetes, hypertension, obesity, dyslipidemia, smoking, depression, hypogonadism, substance use, and peripheral arterial disease. Treatment of ED should include treating the underlying causes and risk factors of ED in addition to pharmacologic therapies for ED. Treatment should be a shared decision and include a discussion with the patient to determine the best course of therapy based on risks, benefits, and desired outcome.

DRUGS ASSOCIATED WITH ERECTILE DYSFUNCTION

Proposed Mechanism	Medications
Decreased penile blood flow	B-blockers, diuretics, central sympathomimetics (clonidine, methyldopa)
Inhibition of prolactin inhibitory factory thereby increasing prolactin levels which decrease testosterone production	Dopamine antagonists (metoclopramide, phenothiazines)
Antiandrogen effects of suppressed testosterone medicated stimulation of libido	Spironolactone, finasteride, dutasteride, cimetidine, ketoconazole, digoxin
Anticholinergic activity through reduced parasympathetic induced vasodilation	Antihistamines, tricyclic antidepressants (TCAs), phenothiazine, antipsychotics
5-HT2 stimulation	Selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, TCAs, mirtazapine

Treatment

Non-Pharmacologic Therapy

- Consider a referral to a mental health professional to promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship.
- Lifestyle modifications including changes in diet, increased physical activity, smoking cessation, and discontinuation of alcohol should be made.
- Improve control of chronic disease states that are known risk factors for ED including diabetes, hypertension, dyslipidemia, thyroid disorders, hormonal imbalances, depression, and anxiety.

Pharmacologic therapy

- First line therapy: phosphodiesterase-5 Inhibitors, testosterone (only for patients with testosterone deficiency).
- Second line therapy: intraurethral alprostadil, vacuum constriction device.
- Third line therapy: Injected vasodilators.

Phosphodiesterase-5 Inhibitors (PDE-5 inhibitors)

- Mechanism of action: Inhibit PDE-5 which prevents the breakdown of cyclic guanosine monophosphate (cGMP) increasing nitric oxide, thereby increasing smooth muscle relaxation, and enhancing blood flow to the penis.
- Doses of PDE-5 inhibitors should be titrated for response and efficacy.
- All four options are equally effective, but treatment can be ineffective for 30-40% of patients.
- Patients should complete an adequate trial of at least 5-8 doses before treatment failure is declared; after completing adequate trial, it is reasonable to try another PDE-5 agent.
- Tadalafil may be preferred by some patients due to the longer duration of action and daily dosing.
- Contraindications and precautions
    - Men with underlying CVD should be assessed before use with a PDE-5 inhibitor.
    - All PDE-5 inhibitors are contraindicated with use of any nitrates due to risk of severe hypotension.
    - Concomitant use with alpha-1 blockers (terazosin, doxazosin) increases risk of hypotension. Patients should be stable on dose of alpha-1 blocker before initiating treatment with a PDE-5 with a lower starting dose.
    - Use with alcohol should be avoided due to increased hypotension, drowsiness, and worsening of ED.
    - Vardenafil can cause QT prolongation and should be used cautiously in patients who are at increased risk.

PDE-5 Inhibitors for ED

	Sildenafil	**Vardenafil**	**Avanafil**	**Tadalafil**
Starting Dose	50 mg 1 hour prior to sexual activity	10 mg 1 hour prior to sexual activity ODT: 10 mg	100 mg at least 15-30 minutes prior to sexual activity	As needed: 10 mg at least 30 minutes before sexual activity Daily: 2.5-5 mg once daily
Max	100 mg	20 mg	200 mg	As needed: 20 mg Daily: 5 mg
Dose adjustments	Hepatic Impairment Renal Impairment (sildenafil, tadalafil) >65 years (Sildenafil, vardenafil)			
Onset of Action	30-60 minutes	30-60 minutes	15-30 minutes	60 minutes
Duration	4 hours	4 hours	5 hours	Up to 36 hours
Effect of food	High fat meal decreases efficacy – take on empty stomach	High fat meal decreases efficacy – take on empty stomach	None	None

Testosterone

- Therapy with testosterone is only indicated in patients with ED who are also diagnosed with hypogonadism to help increase libido.
- Optimum efficacy of PDE-5 inhibitor is most likely to be achieved when testosterone levels are normalized, although the data behind this is lacking.
- Testosterone should be in addition to a PDE-5 inhibitor as monotherapy with testosterone is not effective.

Alprostadil

- Mechanism of action: alprostadil is prostaglandin E1 which causes smooth muscle relaxation and vasodilation allowing increased blood floor to penis and entrapment of blood.
- Contraindicated with sickle cell disease.
- Comes as an intraurethral suppository and has an intracavernosal injection.

Intraurethral pellet (Muse®)

- Dose: 125-1000 mcg intraurethral suppository inserted 5-10 minutes prior to sexual activity.
- Max of 2 doses per day
- Duration: 30-60 minutes
- Less invasive than intracavernosal injection, but less effective.
- Use not recommended with pregnant partners.

Intracavernosal injection (Caverject®)

- Dose: 2.5-60 mcg injected 5-10 minutes prior to sexual activity.
- Dose needs to be titrated in providers office.
- No more than 1 injection per 24 hours and no more than 3 injections per week.
- Duration: 60 minutes
- Higher efficacy than intraurethral pellet, but also higher incidence of priapism.
- Bleeding risk for patients taking anticoagulants or with thrombocytopenia.

Vacuum Erection Device (VED)

- Mechanism of action: increases blood flow to the penis and maintained with occlusive ring.
- Should not be used for more than 30 minutes at a time and may interfere with ejaculation.
- Can be used with PDE-5 inhibitors or intraurethral/intracavernosal alprostadil.
- Use with caution in patients taking anticoagulants.
- Contraindicated with sickle cell disease.

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Hypogonadism

Author(s): Sean Grosklags, PharmD Candidate 2022, Emily Van Klompenburg, PharmD, BCACP, Chad Thury, DO

Executive Summary:

Male hypogonadism can result from a normal age-related decline in testosterone or secondary to a surgical procedure, other medical condition and/or certain medications.

Routine screening for low testosterone is not recommended unless patients have high risk medical conditions for hypogonadism or have characteristic symptoms associated hypogonadism.

It is important to ensure proper workup for hypogonadism, including labs as well as imaging if necessary. Once the diagnosis is confirmed there should be a shared-decision making conversation with patients related to the risks and benefits of testosterone replacement in general as well as the various treatment options.

Diagnosing Male Hypogonadism

1. Obtain measurements from two separate early morning fasting testosterone levels (between 8 to 10 a.m.).
2. If the testosterone levels are unclear, consider obtaining free and bioavailable testosterone levels.
    a. For males who are considered morbid obesed or of older age, consider free and bioavailable testosterone and SHBG levels.
3. The lower end of normal for total testosterone level is 300. Based on results, if a patient has low testosterone levels, consider obtaining Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) levels to guide subsequent workup.

Low Testosterone Levels + LH and FSH Levels Elevated → **Likely Primary Hypogonadism**

- If the LH and FSH are elevated, then obtain a karyotype.

Low Testosterone Levels + LH and FSH Levels Not Elevated → **Likely Secondary Hypogonadism**

- If LH and FSH are not elevated, then it is likely secondary hypogonadism. Then obtain prolactin, TSH and free T4, 8 AM cortisol, plus iron and transferrin levels.
- Abnormal thyroid, prolactin or cortisol levels, consider MRI of the pituitary gland.

Treatment

Treatment for hypogonadism should be administered in men who have low testosterone levels as above and have clear clinical symptoms of androgen deficiency: low libido, decreased morning erections, loss of body hair, low bone mineral density, gynecomastia and small testes. However, treatment of older men without identifiable pituitary or hypothalamic disease is less clear. Furthermore, middle aged men with vague symptoms of decreased energy and sexual interest with low normal testosterone levels should not be treated. Prior to initiating treatment a hemoglobin and hematocrit should be obtained, and in older men a PSA as well.

Understanding Risks Prior to Treatment

The risks of testosterone replacement should be discussed with patients prior to initiating treatment, especially for young men. Young men should be educated that long term treatment can lead to suppression of spermatogenesis, thus virility. If they desire fertility, other treatment options should be entertained.

Contraindications	Adverse Effects
Prostate Cancer	Elevation in PSA
Breast Cancer	Worsening of BPH symptoms
Severe lower urinary tract symptoms (LUTS) symptoms	Elevation in hemoglobin/hematocrit
Erythrocytosis (eg Hct >50%)	Venous Thromboembolism
Severe untreated sleep apnea	Cardiovascular risk – potential increase in myocardial infarction and strokes
Uncontrolled heart failure	Skin irritation

Testosterone Injections or Topical Testosterone Agents

Hypogonadism treatment is obtained through testosterone injections or topical testosterone agents. This is because oral testosterone is rapidly metabolized by the liver and thus hard to maintain normal serum levels. Testosterone replacement can help counter the signs and symptoms of male hypogonadism, such as decreased sexual desire, energy, facial and body hair, and loss of muscle mass and bone density. Topical products are generally recommended due to the fact they provide relatively stable serum testosterone concentrations and patient preference compared to injections. Topical formulations, such as gels and patches, are typically applied to the upper arms, shoulders, or torso, depending on the manufacturer's recommendation. There are certain gels and patches that can be applied to the thigh instead. These dosage forms are typically used daily. There is a risk for transfer to others through skin-to-skin contact.

Another common delivery for testosterone therapy is parenteral via IM injection given every one to three weeks. The higher the dose and longer the frequency between doses the greater the likelihood of supratherapeutic peak shortly after the injection and a subtherapeutic nadir before the next injection. Thus, shorter intervals like 50-100mg weekly or 100 to 200mg every 2 weeks are used.

Once therapy is initiated and when adjusting doses, an evaluation should be completed after two to three months. Once a stable dose is achieved, monitoring every 6 to 12 months is reasonable. Appropriate monitoring varies slightly with different formulations. For intramuscular (IM) injection formulations, measure a level at the midpoint between injections. With topical formulations timing for testosterone levels is less important, but should be taken at least 14 days after a dose adjustment.

Product	Delivery	Frequency	Availability
Androgel®	Topical Gel	Daily	Packets, pump
Testim®	Topical Gel	Daily	Tubes
Fortesta®	Topical Gel	Daily	Pump
Axiron®	Topical solution	Daily	Pump
Androderm®	Transdermal patch	Daily	Patch

Testosterone enanthate (Xyosted)	IM injection*	Every 1-3 weeks	Injection
Testosterone cypionate	IM injection*	Every 1-3 weeks	Injection
Aveed® (testosterone undecanoate)	IM Injection*	Initially, 3 weeks, 10 weeks thereafter	Injection
Jatenzo® (testosterone undecanoate)	Oral capsule	Twice daily	Capsule
Natesto®	Nasal Gel	Three times daily	Pump
Testopel®	SQ Implant	3-6 months	Pellet
*IM injections require an additional prescription for syringes. Generic versions of most gels and pumps are now available. Few adverse effects typically present that are unrelated to the mechanism of action of testosterone. Skin irritation from topical preparations and injection site reactions are possible.			

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Testosterone Boosting Supplements

Authors: Emily Van Klompenburg, PharmD, BCACP, Tominee Sorenson, PharmD Candidate 2024,

Executive Summary:

A natural process of aging in males is the continual decrease in testosterone levels after the age of 30. Other factors that can cause a decrease in testosterone levels may include medications, alcohol abuse, obesity, or illness. Low testosterone can result in a low sex drive, erectile dysfunction (ED), depression, fatigue, or difficulties concentrating.[12] Due to concerns of low testosterone levels there have been common over-the-counter supplement ingredients have been advertised and studied as "testosterone boosting". Among them, fenugreek, Vitamin D, and DHEA have been researched for their effectiveness to naturally increase testosterone levels. The results of these studies vary between the supplements making it prudent to only recommend them in specific patient populations.

FENUGREEK (*Trigonella forenum-groecum L.*)

Fenugreek is a herb from the Mediterranean region that is used both in cooking and natural medicine. The seed is the most common part used in supplements due its potency of saponins and sapogenins.[9] These steroidal compounds are precursors to sex hormones; additionally it is proposed that fenugreek blocks the conversion of testorone to estrogen via the inhibition of 5α reductase and aromatase.[12] A study of 60 healthy males aged 18-35 in good physical and cardiovascular health were placed on a four day-eight week resistance training program. A placebo group was compared to fenugreek 300mg by mouth twice daily. Free testosterone levels increased with significance in both groups from baseline and there was no reduction of total testosterone in either, while the fenugreek group just had a bigger increase in free testosterone.[12] A meta- analysis of four studies found that the mean total testosterone levels were higher in the intervention groups with a WMD= 0.85 95% CI [0.10, 1.60], p=.026. However, it was concluded that more studies would need to be conducted to specify the efficacy of fenugreek on testosterone levels.[7] Fenugreek is well tolerated with only minor gastrointestinal adverse effects such as diarrhea and bloating. Typical dosing of fenugreek used in studies that are evaluating increased testosterone ranges from 250mg to 600mg daily.

VITAMIN D

An important function of Vitamin D is to aid in regulating calcium and phosphorus for bone growth; Vitamin D may be obtained from the diet, sunlight, and dietary supplements. Vitamin D may play a more prominent role in low testosterone than previously thought. Vitamin D receptors are widely distributed in tissues and organs, including the men's reproductive system: prostate, testes, and sperm.[5] There is a distinct correlation between low Vitamin D levels and low testosterone in men based on a meta analysis of 18 articles.[3] The standard Vitamin D3 (cholecalciferol) dosing range for healthy adults is 600 to 1000 IU daily.[6] The clinical studies of the use of Vitamin D supplementation in raising testosterone levels have produced mixed results. Three small studies that analyzed the short-term use of Vitamin D3

(600 IU, 1200 IU, or 2000 IU, respectively) daily for six to 16 weeks did not find a statistically significant correlation between Vitamin D supplementation and an increase in testosterone levels.[4] The median patient in the three short term studies did not become Vitamin D sufficient with their levels at the end of studies remaining below <30 ng/mL.[2] One study did find that a prescription-strength Vitamin D2 (Ergocalciferol) oral solution of 600,000 IU per month for 12 months in middle-aged patients with deficient Vitamin D levels did see an increase in testosterone levels.[2] One study suggested that in healthy males with sufficient or moderately low Vitamin D levels, there was no increase in serum testosterone after a once weekly high dose of 20,000 IU per week of Vitamin D treatment for 12 weeks.[5] Future studies are needed to see if a long term treatment regimen of OTC Vitamin D supplementation may increase testosterone levels. Vitamin D supplementation is well tolerated and relatively safe. Vitamin D toxicity is rare but could lead to hypercalcemia; monitoring symptoms are nausea, vomiting, anorexia, polydipsia, polyuria, and weakness.[6]

DHEA (Dehydroepiandrosterone)

DHEA is an adrenal sex hormone precursor. The body turns DHEA into estrogen and testosterone. It is made primarily by the adrenal glands and liver. Research has shown that DHEA levels decrease with age. Supplementation with DHEA may have benefits for depression, aging skin, and infertility, but more research is needed. DHEA is banned by the National Collegiate Athletic Association (NCAA), the International Olympic Committee, and the World Anti-Doping Agency (WADA).[11] Areas in which DHEA supplements may not be useful are aging, muscle strength, and physical performance in aging adults.[11] While results from some small studies have suggested that DHEA supplementation helps to stimulate testosterone production, other studies have concluded the opposite.[13] Typical DHEA dosing in studies is 50 mg per day, however doses as high as 1600 mg per day for 28 days have been studied. It should be noted that safety with long term use of DHEA has not been properly examined.[13]

A 2013 study found that middle-aged adults taking 50 mg per day raised their free testosterone levels when undergoing high intensity interval training.[10] The study concluded that at baseline, free testosterone levels were much lower in middle-aged men compared to young men.[10] Levels were rechecked 12 hours after oral supplementation of DHEA and the levels increased in both the middle aged and young men groups.[10] Use of DHEA should be avoided in those with liver dysfunction. Adverse effects linked to DHEA supplementation include reduced HDL levels, acne, mania, and heart palpitations. DHEA has many possible medication interactions including, but not limited to testosterone, estrogen, antipsychotics, triazolam, and selective serotonin reuptake inhibitors.[13] In addition, medications that are metabolized by CYP3A4 can interact with DHEA. Both the therapeutic effects and side effects of these medications may be affected. One food interaction to monitor while taking DHEA is foods containing glycyrrhetinic acid, such as licorice.[11] Glycyrrhetinic acid can increase circulating DHEA levels.[1]

TAKEAWAYS

Fenugreek supplementation can be considered in patients who may want an over the counter agent to increase testosterone. Other methods that may aid in increasing testosterone levels are resistance training, high protein diets,

minimizing stress, and adequate sleep hygiene.[13]

DHEA and Vitamin D supplementation could have a positive effect on testosterone production, but evidence to support these claims has not been well researched. Vitamin D is well tolerated and relatively safe supplement with the potential for raising testosterone levels but should only be considered if the patient has low Vitamin D levels. DHEA can potentially cause serious adverse side effects. Due to limited evidence that DHEA increases testosterone levels coupled with its ability to cause adverse effects, it is generally not recommended to use DHEA to boost testosterone.

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