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Hormonal Testing and Pharmacologic Treatment of Erectile Dysfunction: A Clinical Practice Guideline From the American College of Physicians

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Description: The American College of Physicians developed this guideline to present the available evidence on hormonal testing in and pharmacologic management of erectile dysfunction. Current pharmacologic therapies include phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil, vardenafil, tadalafil, mirodenafil, and udenafil, and hormonal treatment.

Methods: Published literature on this topic was identified by using MEDLINE (1966 to May 2007), EMBASE (1980 to week 22 of 2007), Cochrane Central Register of Controlled Trials (second quarter of 2007), PsycINFO (1985 to June 2007), AMED (1985 to June 2007), and SCOPUS (2006). The literature search was updated by searching for articles in MEDLINE and EMBASE published between May 2007 and April 2009. Searches were limited to English-language publications. This guideline grades the evidence and recommendations by using the American College of Physicians' clinical practice guidelines grading system.

Recommendation 1: The American College of Physicians recommends that clinicians initiate therapy with a PDE-5 inhibitor in men who seek treatment for erectile dysfunction and who do not have a contraindication to PDE-5 inhibitor use (Grade: strong recommendation; high-quality evidence).

Recommendation 2: The American College of Physicians recommends that clinicians base the choice of a specific PDE-5 inhibitor on the individual preferences of men with erectile dysfunction, including ease of use, cost of medication, and adverse effects profile (Grade: weak recommendation; low-quality evidence).

Recommendation 3: The American College of Physicians does not recommend for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with erectile dysfunction (Grade: insufficient evidence to determine net benefits and harms).

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Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance (1). Erectile dysfunction lasting for 3 months is considered a reasonable length of time to warrant evaluation and consideration of treatment. Erectile dysfunction is a common disorder of male sexual function and affects all age groups, especially people with advanced age, diabetes, vascular diseases, psychiatric disorders, and possibly hypogonadism (1–4). With the aging general population and increased life expectancy, combined with the high prevalence of diabetes and cardiovascular disease, the health care burden and quality-of-life issues associated with ED are projected to be substantial (5). In 1995, more than 152 million men worldwide were estimated to have experienced ED. The prevalence of ED is predicted to be approximately 322 million worldwide by the year 2025 (6). Estimates from the National Health and Nutrition Examination Survey suggested that the cost of treatment of ED in the United States could reach $15 billion if all affected men sought care (7).

The purpose of this guideline is to present the available evidence on the hormonal testing and pharmacologic management of ED. The target audience for this guideline is all clinicians, and the target population is all men with ED. Recommendations are based on the systematic evidence review by Tsertsvadze and colleagues (8) and the

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evidence report by the Agency for Healthcare Research and Quality–sponsored University of Ottawa Evidence-based Practice Center (5). Erectile dysfunction may be caused by chronic diseases, such as obesity, hypertension, dyslipidemia, and cardiovascular disease, or smoking; medications; psychosocial factors; and hormonal abnormalities. This guideline addresses only the utility of hormonal testing and treatment of ED. Such treatments as vacuum constriction devices, intraurethral suppositories, intracavernosal injections, and psychotherapy were not included in the evidence review and are not addressed in this guideline.

METHODS

The databases used for the literature search included MEDLINE (1966 to May 2007), EMBASE (1980 to week 22 of 2007), Cochrane Central Register of Controlled Trials (second quarter of 2007), PsycINFO (1985 to June 2007), AMED (1985 to June 2007), and SCOPUS (2006). The literature search was limited to studies published in English and scanning of reference lists of retrieved publications. The literature search was updated by searching for articles on MEDLINE and EMBASE published between May 2007 and April 2009.

Two persons independently reviewed abstracts and relevant full-text articles regarding study, study population, and treatment characteristics. Disagreements were discussed and resolved by consensus. The reviewers excluded reviews, pooled analysis, editorials, commentaries, and letters. To assess the relative benefits and harms of pharmacologic treatments for ED, eligible studies included randomized, controlled trials (RCTs) of pharmacologic ED treatments in men aged 18 years or older with ED. To assess the clinical value of routine hormonal blood tests in men with ED, eligible studies were those reporting prevalence of hypogonadism, hyperprolactinemia, or both in men with ED and RCTs comparing hormone treatment alone or in combination versus control in men with ED. For adverse events, data abstracted included the number of patients with any adverse event, specific adverse events, withdrawals due to adverse events, serious adverse events, and serious cardiovascular adverse events. To assess the risks for nonarteritic anterior ischemic optic neuropathy (NAION) in men receiving phosphodiesterase-5 (PDE-5) inhibitors, eligible studies included RCTs; nonrandomized, controlled trials; and observational studies. Treatments not generally prescribed by primary care physicians, such as vacuum constriction devices, intraurethral suppositories, intracavernosal injections, or psychotherapy, were considered beyond the scope of this guideline.

This guideline rates the evidence and recommendations by using the American College of Physicians' guideline grading system, which is a slightly modified version of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (**Table**).

Table. **The American College of Physicians' Guideline Grading System***

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden OR Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

The objective of this guideline is to synthesize the evidence for the following key questions:

Key question 1: What is the clinical utility of routine hormonal blood tests—testosterone and prolactin—in identifying and affecting therapeutic outcomes for treatable causes of ED?

Key question 2: What are the benefits of pharmaceutical treatments for patients with ED?

Key question 3: What are the harms of the pharmaceutical treatments for patients with ED?

CLINICAL UTILITY OF ROUTINE HORMONAL DIAGNOSTIC TESTS

Evidence was gathered from 29 studies, of which 28 reported measurement of testosterone (9–37) and 10 reported measurement of prolactin (9, 10, 12, 14, 15, 20, 22, 27, 28, 38). Mean age of participants ranged from 47 to 60 years. The overall quality of evidence was rated as low because of between-study variability in study populations, varying hormone measurement methods, and prevalence rates of hormonal abnormalities.

The prevalence of low total testosterone levels (12, 23, 34, 35), low free testosterone levels (21, 29), and hyperprolactinemia (14, 27, 28) in men with ED varied widely across studies. The prevalence of low testosterone levels (defined in the studies as <288 ng/dL [<9.9 nmol/L] or <9.0 pg/mL [<31.2 pmol/L]) in men with ED varied from 12.5% to 35% in different studies (20, 21, 31). This variability may be due to between-study differences in study population characteristics, hormonal measurement methods, diagnostic criteria for ED or hormonal abnormalities, or a combination of these factors. Because evidence was insufficient to determine whether men with ED had a higher prevalence of hypogonadism or hyperprolactinemia than men without ED (31, 32), the value of routine hormonal testing for the evaluation of ED is unclear.

BENEFITS OF PHARMACOLOGIC TREATMENT

Oral PDE-5 Inhibitors

Evidence was gathered from 130 RCTs that evaluated oral PDE-5 inhibitors, alone or combination (72 RCTs of sildenafil [39–107], 27 RCTs of vardenafil [13, 108–133], 28 RCTs of tadalafil [134–161], 2 RCTs of mirodenafil [156, 157], and 1 RCT of udenafil [162]), and 4 RCTs with head-to-head comparisons of PDE-5 inhibitors (163–166). Treatment duration for most trials was 12 months, and 85% of the trials did not report treatment allocation concealment.

PDE-5 Inhibitor Versus Placebo

Successful Sexual Intercourse. High-quality evidence from RCTs showed that PDE-5 inhibitors improved successful sexual intercourse. The weighted mean percentage of successful sexual intercourse attempts was 69% (range, 52% to 85%) for sildenafil versus 35.5% (range, 19% to 68%) for placebo (41, 43, 44, 47, 48, 57, 66, 69, 78, 83, 84, 90, 93, 100, 102, 103), 68% (range, 50% to 88%) for vardenafil versus 35% (range, 20% to 40%) for placebo (13, 108, 110, 112, 115, 116, 121, 123, 124, 126, 127, 130, 132), and 69% (range, 50% to 85%) for tadalafil versus 33% (range, 23% to 52%) for placebo (136, 137, 139–141, 143, 144, 147, 149, 153–157, 159). In trials enrolling men with a wide spectrum of diseases, corresponding values were 69% versus 36% (41, 43, 44, 47, 48, 57, 66, 69, 78, 83, 84, 90, 93, 100, 102, 103, 108), 68% versus 35% (13, 110, 112, 115, 116, 121, 123, 124, 126, 127, 130–132), and 69% versus 33% (136, 137, 139–141, 143, 144, 147, 149, 153–157, 159).

Improvement in Erections. High-quality evidence indicated that all 5 agents (sildenafil, vardenafil, tadalafil, mirodenafil, and udenafil) improved erections (range, 73% to 88%) compared with placebo (range, 26% to 32%) (13, 40–43, 47–49, 51, 54–58, 60, 62, 64, 66, 69–71, 74, 77–80, 82–84, 91, 95, 99, 100, 106, 109–113, 115, 116, 118, 120, 122–124, 130, 132, 136–144, 146, 147, 149, 153–157, 161, 162, 167, 168). Men assigned to PDE-5 inhibitors experienced improved erections compared with placebo in trials limited to patients with specific medical conditions, such as diabetes (42, 53, 54, 58, 60, 104, 107, 109, 126, 127, 146, 161), depression (40, 52, 66, 91, 122), cardiovascular disease (45, 61, 64, 74, 80, 82, 95, 120, 133), prostate cancer (73, 96, 101, 111, 131, 142, 158, 169), multiple sclerosis (62, 106), colorectal cancer (71), schizophrenia (92), liver failure (63), and renal failure (89, 128).

Dose. Improvement in erectile functioning was related to higher dose for sildenafil (50 mg vs. 25 mg but not 100 mg vs. 50 mg) and vardenafil (20 mg vs. 10 mg vs. 5 mg) but not for tadalafil (20 mg vs. 10 mg vs. 5 mg) (53, 57, 74, 77, 109, 113, 114, 116, 118, 127, 161, 162, 167, 168).

PDE-5 Inhibitor Versus Non–PDE-5 Inhibitor

Sildenafil was more effective than non–PDE-5 inhibitor treatments, such as sublingual apomorphine, psychotherapy, continuous positive airway pressure, phentolamine, and alfuzosin, in improving erectile function (170–174), frequency of penile penetration or erectile maintenance, and percentage of successful intercourse attempts (175–179).

PDE-5 Inhibitor Plus Non–PDE-5 Inhibitor Versus PDE-5 Inhibitor

Sildenafil combined with other ED therapies (such as psychotherapy, dihydroergotamine, cabergoline, atorvastatin, quinapril, and alfuzosin) resulted in greater improvements in erectile function and frequency of penile penetration or maintenance of erection than did sildenafil alone (169, 175, 179–185).

PDE-5 Inhibitor Versus PDE-5 Inhibitor

Successful Sexual Intercourse. Low-quality studies comparing tadalafil and sildenafil provided insufficient evidence to determine whether 1 treatment was more effective than the other (163).

Improvement in Erections. Evidence from 2 low-quality RCTs comparing tadalafil and sildenafil was insufficient to determine the effectiveness of 1 drug over the other (163, 166).

Hormonal Treatments

Evidence was gathered from 15 RCTs that evaluated the efficacy of hormonal therapy (oral, intramuscular, gel, cream, or patch testosterone) on ED outcomes in hypogonadal men (186–200).

Hormonal Therapy Versus Placebo

Successful Sexual Intercourse. Low-quality evidence was insufficient to show whether testosterone was more effective than placebo (193, 200). In 1 low-quality trial, gel testosterone (50 to 100 mg) but not patch testosterone modestly improved the frequency of successful sexual intercourse compared with placebo (187).

Improvement in Erections. Low-quality evidence was insufficient to determine whether testosterone was more effective than placebo (186, 189, 191, 193, 195, 197).

Hormonal Therapy Plus PDE-5 Inhibitor Versus PDE-5 Inhibitor

Successful Sexual Intercourse. Low-quality evidence was insufficient to determine whether testosterone plus a PDE-5 inhibitor (sildenafil) was more effective than a PDE-5 inhibitor (sildenafil) and placebo in improving frequency or percentage of successful sexual intercourse attempts (188, 190).

Improvement in Erections. Low-quality evidence was insufficient to determine whether testosterone plus a

PDE-5 inhibitor (sildenafil) was more effective than a PDE-5 inhibitor (sildenafil) and placebo (188, 190, 194).

Harms of Pharmacologic Treatment

Oral PDE-5 Inhibitors

PDE-5 Inhibitor Versus Placebo

High-quality evidence showed that men receiving PDE-5 inhibitors are more likely to have at least 1 adverse event compared with placebo. However, the incidence for more serious adverse events was less than 2%, with no difference between PDE-5 inhibitors and placebo. The most common adverse effects were headache, flushing, rhinitis, and dyspepsia. Less common adverse effects were visual disturbances, myalgia, nausea, diarrhea, vomiting, dizziness, and chest pain.

PDE-5 Inhibitor Versus Non–PDE-5 Inhibitor

Sildenafil was associated with fewer adverse events than non–PDE-5 inhibitors (170–179).

PDE-5 Inhibitor Plus Non–PDE-5 Inhibitor Versus PDE-5 Inhibitor

Sildenafil was associated with fewer adverse events than PDE-5 inhibitors combined with non–PDE-5 inhibitors (169, 175, 179, 181–185).

PDE-5 Inhibitor Versus PDE-5 Inhibitor

Very-low-quality evidence showed that adverse events did not statistically significantly differ among men taking sildenafil, tadalafil, and vardenafil (163–166).

NAION

Nonarteritic anterior ischemic optic neuropathy is defined as ischemic optic neuropathy in the absence of temporal arteritis and polymyalgia rheumatica, and "possible" NAION is defined as papillitis, optic neuritis, or both in the absence of temporal arteritis, polymyalgia rheumatica, and previous optic neuropathies. Very-low-quality evidence evaluating the association of NAION with the use of PDE-5 inhibitors showed that among 4 million veterans aged 50 years or older, PDE-5 inhibitors were not associated with an increased risk for NAION (absolute risk, 4.6 cases per 10 000 men per year; relative risk, 1.02 [95% CI, 0.92 to 1.12]); however, PDE-5 inhibitors were associated with an increased risk for possible NAION (absolute risk, 2.4 cases per 10 000 men per year; relative risk, 1.34 [CI, 1.17 to 1.55]) (201).

Priapism

Trials evaluated for this guideline did not report priapism. Prolonged erection and priapism were reported infrequently during postmarketing surveillance (202).

Contraindications

Concurrent use, regularly or intermittently, of nitrates in any form (for example, nitroglycerin and isosorbide dinitrate) is a contraindication for oral PDE-5 inhibitor therapy.

Hormonal Treatments

Hormonal Therapy Versus Placebo

Very-low-quality evidence showed that adverse events did not differ between oral or gel testosterone and placebo (187, 193, 200). The levels of prostate-specific antigen were similar in testosterone and placebo groups in 3 trials reporting these data (189, 198, 199).

Hormonal Therapy Plus PDE-5 Inhibitor Versus PDE-5 Inhibitor

Low-quality evidence showed that the incidence of adverse events was low and did not differ between sildenafil alone versus sildenafil plus patch, gel, or oral testosterone (188, 190, 194). Prostate-specific antigen levels were not significantly higher in the sildenafil plus testosterone groups than in sildenafil groups in 2 trials reporting these data (190, 194).

Summary

The evidence regarding the utility of hormonal blood tests in identifying and affecting therapeutic outcomes for treatable causes of ED was inconclusive. The evidence demonstrated clinical benefit associated with the use of PDE-5 inhibitors regardless of the cause (such as diabetes, depression, or prostate cancer) or baseline severity of ED. The magnitude of benefit increased with severity of ED. Higher doses of sildenafil and vardenafil were associated with a modestly greater magnitude of benefit with respect to erectile function; however, this was not true for tadalafil. Overall, PDE-5 inhibitors were relatively well tolerated and were associated with mild or moderate adverse events. The incidence of adverse events did not significantly differ among the various PDE-5 inhibitors. Evidence was insufficient to determine whether PDE-5 inhibitors are associated with an increased risk for NAION.

Future Research

The quality of reporting primary studies should be improved. authors reporting trials in journals that publish ED-related research should consider using the CONSORT (Consolidated Standards of Reporting Trials) Statement as a reporting guide. Some studies evaluated the dose–response effect of PDE-5 inhibitors with respect to efficacy and harms; however, more high-quality studies are needed. The evidence regarding the incidence of adverse events was limited and inconclusive, and more high-quality head-to-head trials are needed to explore differences in adverse events, especially severe adverse events. The evidence regarding the utility of routine hormonal blood tests was inconclusive given the limited number of studies and various methodological issues and needs to be further developed.

Figure. **The American College of Physicians guideline on hormonal testing and pharmacologic treatment of erectile dysfunction.**

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Summary of the American College of Physicians Guideline on Hormonal Testing and Pharmacologic Treatment of Erectile Dysfunction	
Disease/condition	Erectile dysfunction
Target audience	Internists, family physicians, other clinicians
Target patient population	Men with erectile dysfunction
Interventions	Hormonal testing; oral PDE-5 inhibitors; hormonal therapy
Outcomes	Successful sexual intercourse and improvement in erections
Recommendations	***Recommendation 1: The American College of Physicians recommends that clinicians initiate therapy with a PDE-5 inhibitor in men who seek treatment for erectile dysfunction and who do not have a contraindication to PDE-5 inhibitor use (Grade: strong recommendation; high-quality evidence).*** ***Recommendation 2: The American College of Physicians recommends that clinicians base the choice of a specific PDE-5 inhibitor on the individual preferences of men with erectile dysfunction, including ease of use, cost of medication, and adverse effects profile (Grade: weak recommendation; low-quality evidence).*** ***Recommendation 3: The American College of Physicians does not recommend for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with erectile dysfunction (Grade: insufficient evidence to determine net benefits and harms).***
Clinical considerations	This guideline refers to patients with erectile dysfunction. There may be other reasons to perform hormonal testing. Clinicians should be aware of the cautions related to PDE-5 inhibitor use when prescribing these agents. Nonpharmacologic treatment of erectile dysfunction is beyond the scope of this guideline.

PDE-5 = phosphodiesterase-5.

RECOMMENDATIONS

Recommendation 1: The American College of Physicians recommends that clinicians initiate therapy with a PDE-5 inhibitor in men who seek treatment for erectile dysfunction and who do not have a contraindication to PDE-5 inhibitor use (Grade: strong recommendation; high-quality evidence).

Treatment with an oral PDE-5 inhibitor demonstrated statistically significant and clinically relevant improvements in sexual intercourse and erectile function in patients with ED. Improvement in erectile functioning was related to higher doses for sildenafil and vardenafil. However, higher doses were associated with a greater risk for an adverse effect. Nitrate therapy is a contraindication for therapy with oral PDE-5 inhibitors.

Recommendation 2: The American College of Physicians recommends that clinicians base the choice of a specific PDE-5 inhibitor on the individual preferences of men with erectile dysfunction, including ease of use, cost of medication, and adverse effects profile (Grade: weak recommendation; low-quality evidence).

The evidence is insufficient to compare the efficacy and adverse effects of different PDE-5 inhibitors for the treatment of ED because only few head-to-head trials are available. Therefore, individual preferences, ease of use, and cost of medication are reasonable criteria to help select a treatment.

Recommendation 3: The American College of Physicians does not recommend for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with erectile dysfunction (Grade: insufficient evidence to determine net benefits and harms).

The prevalence of low testosterone varies from 12.5% to 36% in studies of men with ED. However, the evidence is inconclusive about the effectiveness of hormonal treatment in the management of patients with ED, even in patients with low testosterone levels. Trials comparing testosterone (in oral, injection, gel, patch, and cream forms) with placebo in hypogonadal men with ED were small, were of low quality, or reported inconsistent effects on erectile function. Clinicians should individualize decisions to measure hormone levels on the basis of the clinical presentation (for example, decreased libido, premature ejaculation, and fatigue) and physical findings (for example, testicular atrophy and muscle atrophy) that suggest hormonal abnormality.

SUMMARY OF RECOMMENDATIONS AND EVIDENCE

See the **Figure** for a summary of the recommendations and clinical considerations. The **Table** describes the American College of Physicians' guideline grading system.

From the American College of Physicians and University of Pennsylvania, Philadelphia, Pennsylvania; University of Colorado, Aurora, Colorado; Atlantic Health, Morristown, New Jersey; Veterans Affairs Palo Alto Health Care System and Stanford University, Stanford, California; and Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California.

Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

Disclaimer: The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

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