

# Oral Phosphodiesterase-5 Inhibitors and Hormonal Treatments for Erectile Dysfunction: A Systematic Review and Meta-analysis

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**Background:** Erectile dysfunction (ED) is a common male sexual disorder. The relative benefits and harms of pharmacologic therapies for ED, as well as the value of hormonal testing in men with ED, are uncertain.

**Purpose:** To evaluate the efficacy and harms of oral phosphodiesterase-5 (PDE-5) inhibitors and hormonal treatments for ED and assess the effect of measuring serum hormone levels on treatment outcomes for ED.

**Data Sources:** English-language studies from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, PsycINFO, AMED, and SCOPUS through April 2009. Trial reference lists also were scanned.

**Study Selection:** Randomized, controlled trials (RCTs) of oral PDE-5 inhibitors and hormonal treatment for ED, and observational studies reporting measurement of serum hormone levels, prevalence of hormonal abnormalities, or both in men with ED.

**Data Extraction:** Two independent reviewers abstracted data on study, participant, and treatment characteristics; efficacy and harms outcomes; and prevalence of hormonal abnormalities.

**Data Synthesis:** Data, primarily from short-term trials ( $\leq 12$  weeks), indicate that PDE-5 inhibitors were more effective than placebo in improving sexual intercourse success (69.0% vs. 35.0%). The proportion of men with improved erections was significantly greater

among those treated with PDE-5 inhibitors (range, 67.0% to 89.0%) than with placebo (range, 27.0% to 35.0%). The PDE-5 inhibitors were associated with increased risk for any adverse events compared with placebo (for example, relative risk with sildenafil, 1.72 [95% CI, 1.53 to 1.93]). In 4 head-to-head RCTs comparing sildenafil, vardenafil, and tadalafil, improvement of ED and adverse events did not differ among treatments. Results from 15 RCTs evaluating hormonal treatment of ED were inconsistent on whether treatment improved outcomes. Evidence was insufficient regarding whether men with ED had a higher prevalence of hypogonadism than men without ED.

**Limitations:** Many RCTs were of low methodological and reporting quality, particularly those involving hormonal treatments or directly comparing different PDE-5 inhibitors. Most RCTs provided only short-term efficacy and harms data.

**Conclusion:** Oral PDE-5 inhibitors improved erectile functioning and had similar efficacy and safety profiles. Results on the efficacy of hormonal treatments and the value of hormone testing in men with ED were inconclusive.

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Erectile dysfunction (ED) is a common male sexual disorder and is defined as the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance (1). Advanced age, diabetes, vascular diseases, psychiatric disorders, and possibly hypogonadism are associated with increased prevalence of ED (1–4). According to data from the Massachusetts Male Aging Study (2), the prevalence of ED in men aged 40 to 70 years is about 50%.

Unless contraindicated, oral phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil, tadalafil, or vardenafil, are currently first-line treatments of ED (5). Alternative treatments include hormones, vacuum constriction devices, intraurethral suppositories, intracavernosal injections, or surgery (for example, penile prosthesis implants) (5–7). Direct comparisons between treatments have been limited, and the relative long-term efficacy and safety profiles of different therapies have not been adequately explored.

Estimates from the National Health and Nutrition Examination Survey suggested that annual U.S. treatment costs of ED could reach \$15 billion if all affected men

sought care (8). In the past decade, the use of diagnostic tests for underlying causes of ED markedly decreased and use of pharmacologic therapy, especially with oral PDE-5 inhibitors, increased (8). In 2005, sales of sildenafil, tadalafil, and vardenafil were \$1.6 billion, \$747 million, and \$327 million, respectively (9–11).

The value of hormonal blood tests (such as testosterone) in routine evaluation of men with ED is uncertain (12–15). The European Association of Urology and the British Society for Sexual Medicine guidelines recommend

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Summary for Patients. . . . . I-44

## Web-Only

Appendixes

Appendix Figures

References

Conversion of graphics into slides

endocrinologic screening in the initial evaluation of all men with ED (15–20). In contrast, the American Urological Association recommends that hormone testing in men with ED be based on initial clinical assessment (for example, decreased libido, small testes, and reduced body hair) or failure of initial PDE-5 therapy management (5). Whether this targeted approach for identifying and treating hormonal disorders as underlying causes of ED is appropriate has not been rigorously evaluated (13, 15, 20, 21).

The aims of our review were to systematically identify and synthesize the published evidence to determine 1) the relative benefits and harms of oral PDE-5 inhibitors and hormonal treatments of ED, including the effect of patient characteristics and comorbid conditions on the likelihood of treatment success and 2) the clinical value of hormonal blood testing for identifying treatable causes of ED (for example, hypogonadism) and improving its outcomes.

We summarized and updated evidence from a technical review prepared for the Agency for Healthcare Research and Quality (22) and adapted the article in collaboration with the American College of Physicians' Clinical Efficacy Assessment Subcommittee to inform the development of its clinical practice guideline on this topic. The article focuses more specifically than the Agency for Healthcare Research and Quality technical review on treatments likely to be prescribed by primary care physicians. The topic of diagnosis and treatment of ED, as a subject for systematic review, was originally nominated by the American College of Physicians.

## METHODS

### Data Sources and Searches

We searched for English-language articles in 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). Search terms were *impotence; erectile dysfunction; randomized, controlled trial; and controlled clinical trial*. We also scanned reference lists of retrieved publications. We updated the review by searching MEDLINE and EMBASE (May 2007 to April 2009).

### Study Selection

To assess the relative benefits and harms of pharmacologic treatments for ED, we selected randomized, controlled trials (RCTs) of pharmacologic treatments in men aged 18 years or older with ED. 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 review and are addressed in the technical report.

To assess the risks for nonarteritic anterior ischemic optic neuropathy (NAION) in PDE-5 inhibitor users, we selected RCTs; nonrandomized, controlled trials; and observational studies. To assess the clinical value of routine hormonal blood tests in men with ED, we selected studies that reported prevalence of hypogonadism, hyperprolactinemia, or both in men with ED and all RCTs comparing hormone treatment alone or in combination versus control in men with ED.

We excluded reviews, pooled analyses, editorials, commentaries, and letters. Two independent reviewers screened all identified titles and abstracts and, for articles considered potentially eligible, abstracted their full-text reports. Discrepancies were discussed and resolved by consensus. **Appendix Figure 1** (available at [www.annals.org](http://www.annals.org)) shows the literature selection process.

### Data Extraction and Quality Assessment

Two reviewers independently abstracted data on study, population, and treatment characteristics. Treatment efficacy outcomes were the proportion of successful sexual intercourse attempts based on either participants' diaries or event logs (erection sufficiently hard and long-lasting for satisfactory intercourse) or participants' responses to question 3 of the Sexual Encounter Profile (SEP) (erection lasted long enough for successful intercourse) (23); the improvement in erectile function based on either participants' self-reports of improved erections (global assessment or efficacy question 1) or the mean Erectile Function domain score of the International Index of Erectile Function (IIEF) (24); and participants' responses to IIEF questions 3 (successful penile penetration) and 4 (maintenance of erection after penetration) (24).

Abstracted adverse events data were the number of patients with any adverse event, specific adverse events, withdrawals due to adverse events, serious adverse events, and serious cardiovascular adverse events. We assessed the prevalence of hypogonadism or hyperprolactinemia by using the definitions provided by study authors, even though these may have differed between studies.

We evaluated the overall strength of evidence by using a method developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group (25). We used the Jadad scale to assess the methodological and reporting quality of RCTs (score range, 0 to 5; higher score indicates better quality) (26). We judged the adequacy of allocation concealment to be adequate, inadequate, or unclear by using the approach proposed by Schulz and Grimes (27). We assessed the quality of studies reporting serum hormonal levels by using a subset of the Quality Assessment Tool of Diagnostic Accuracy Studies (questions 1, 2, 8, 12, and 14) (28). To explore the overall risk for bias, we generated risk-for-bias graphs (29). **Appendix A** (available at [www.annals.org](http://www.annals.org)) includes all evidence and quality

assessment tables and risk-for-bias graphs for the included studies.

### Data Synthesis and Analysis

We qualitatively summarized data on study (design, reporting quality, and sample size), population (age, severity of ED, and comorbid conditions), and treatment characteristics (dose, frequency, and duration). We considered studies suitable for pooling if they used the same design (RCT), enrolled similar populations (trials restricted to participants with a specific comorbid condition vs. those enrolling participants with a heterogeneous profile of comorbid conditions), evaluated the same type of treatment (for example, sildenafil), and reported the same efficacy or safety outcomes. We used DerSimonian and Laird random-effects models to generate pooled estimates of relative risks (RRs) and weighted mean differences (WMDs) with 95% CIs (30). To avoid double-counting during pooling of a trial with several PDE-5 dose groups versus placebo, we used a generic inverse variance method to combine data from these groups for a single estimate of mean response rate versus placebo. Statistical heterogeneity was evaluated using a chi-square test and the  $I^2$  statistic (low = 25.0%; moderate = 50.0%; high = 75.0%) and was explored through subgroup and sensitivity analyses (for example, study quality and random- or fixed-effects model) (31). We defined the subgroups a priori with respect to severity (mild, severe, or moderate) and cause (psychogenic, mixed, or organic) of ED, treatment (for example, dose [50 mg or 100 mg], dosing [fixed or flexible], type [sildenafil, tadalafil, or vardenafil], and duration [ $\leq 12$  weeks vs.  $> 12$  weeks]), and underlying or concurrent condition (for example, diabetes, cardiovascular disease, depression, or prostatectomy).

When studies did not adequately report summary statistics (such as treatment group mean score and SD), we calculated the needed variables if data for individual patients were reported. If a study reported only an SE of the mean response, we converted it to an SD. Trials were not incorporated into meta-analyses if the needed data (means [SDs]) could not be derived, and crossover trials did not report precrossover data. We included trials with no events for harms in the meta-analyses.

We examined the extent of publication bias through visual inspection of funnel plot asymmetry (32) and linear regression-based tests proposed by Egger and colleagues (33). We performed analyses with R software, version 2.4.0 ([www.r-project.org](http://www.r-project.org)), and STATA software, version 11 (StataCorp, College Station, Texas).

### Role of the Funding Source

The Agency for Healthcare Research and Quality provided funding. The funding source suggested the initial research questions and provided copyright release for this manuscript but had no role in the design, conduct, analysis, or reporting of the data or in the decision to submit the manuscript for publication.

## RESULTS

### Literature Flow

Our literature search (**Appendix Figure 1**, available at [www.annals.org](http://www.annals.org)) identified 10 882 publications, of which 191 unique studies (222 publications) were included in the review. Of these included studies, 32 (23 PDE-5 inhibitor trials, 1 trial of hormonal treatment, 5 prevalence studies, and 3 NAION case reports) were identified through the updated EMBASE and MEDLINE search (May 2007 to April 2009).

### Oral PDE-5 Inhibitors

#### Study and Population Characteristics

In total, 130 RCTs (160 main and secondary publications) evaluating oral PDE-5 inhibitors met eligibility criteria. These included 72 RCTs of sildenafil (34–102), 27 RCTs of vardenafil (23, 103–128), 28 RCTs of tadalafil (129–156), 2 RCTs of mirodenafil (157, 158), and 1 RCT of udenafil (159). In addition, 4 RCTs directly compared PDE-5 inhibitors (160–163).

Most trials ( $> 70.0\%$ ) were parallel-group and placebo-controlled and had only short-term follow-up ( $\leq 12$  weeks). Most were conducted in North America or Europe and were funded by the pharmaceutical industry. Trials enrolled heterosexual adult men with ED of various causes. Exclusion criteria common to most trials were penile or testicular deformity, cardiovascular conditions, use of nitrates, prostate cancer, HIV/AIDS, major hepatic or renal disease, spinal cord injury, and major psychiatric disorder. Nearly half of vardenafil trials and one third of tadalafil trials excluded men with ED that did not respond to previous PDE-5 inhibitor therapy or those who had discontinued PDE-5 inhibitor therapy because of adverse events. The efficacy and harms for 2 novel PDE-5 inhibitors, mirodenafil (157, 158) and udenafil (159), were evaluated only in Asian men. The PDE-5 inhibitors were administered at flexible doses (initial dose could be titrated up or down on the basis of individual participant response, with the following dose ranges: sildenafil, 25 to 100 mg/d; vardenafil, 5 to 20 mg/d; and tadalafil, 5 to 20 mg/d) or fixed (sildenafil, 25 to 100 mg/d; vardenafil, 5 to 40 mg/d; tadalafil, 5 to 20 mg/d; and mirodenafil, 50 to 150 mg/d) doses. About 80.0% of the trials were double-blind, and 30.0% used an appropriate randomization method. The adequacy of allocation concealment and blinding method was not clear for a high proportion of trials (85.0% and 60.0%, respectively) (**Appendix A: Figure 1**).

Among 4 RCTs that directly compared PDE-5 inhibitors, all had a crossover design and reported patient treatment preference as their primary outcome measure (160–163). It was not clear whether these trials used an appropriate randomization method, 2 trials were not described as double-blind (160, 163), and 2 restricted sildenafil to less than the standard maximum dosing (161, 162). All 4 trials reported reasons for and proportions of withdrawals or dropouts. Three trials were sponsored by

the manufacturer of tadalafil (**Appendix A: Figure 2**) (160–162).

### Efficacy

*PDE-5 Inhibitor Versus Placebo.* In 116 RCTs, all PDE-5 inhibitors consistently improved erectile functioning more than placebo. The mean scores for the Erectile Function domain and questions 3 and 4 of the IIEF were statistically significantly greater in PDE-5 inhibitor–treated men than in placebo recipients (data not shown).

On the basis of participants' diaries or event logs in 16 trials that enrolled men with a wide spectrum of comorbid conditions, the mean per-patient percentage of successful sexual intercourse attempts for sildenafil-treated patients was 69.0% (range, 52.0% to 85.0%) versus 35.5% (range, 19.0% to 68.0%) for placebo recipients (**Table 1**). In 4 trials from which data pooling was possible (**Appendix B: Figure 1**, available at [www.annals.org](http://www.annals.org)), the WMD in improvement from baseline in the percentage of successful intercourse attempts was 34.3 (95% CI, 25.8 to 42.8) in favor of sildenafil (85, 88, 97, 98).

In 13 trials of vardenafil that enrolled men with a wide spectrum of comorbid conditions, the percentages of successful sexual intercourse attempts based on SEP question 3 in vardenafil and placebo groups were 68.0% (range, 50.0% to 88.0%) and 35.0% (range, 20.0% to 49.0%), respectively (23, 104, 106, 109, 110, 115, 117–119, 121, 122, 125, 127). The diary or event log–based, weighted mean per-patient percentage of successful sexual intercourse attempts for vardenafil-treated patients was 73.0% versus 38.0% for placebo recipients (107, 112) (**Table 1**). In 2 trials from which data pooling was possible (**Appendix B: Figure 2**), the WMD in improvement from baseline in the percentage of successful intercourse attempts was 33.2 (CI, 26.0 to 40.3) in favor of vardenafil (106, 117).

In 15 trials of tadalafil that enrolled men with a wide spectrum of comorbid conditions, the percentages of successful sexual intercourse attempts based on SEP question 3 were 69% (range, 50.0% to 85.0%) for tadalafil versus 33% (range, 23.0% to 52.0%) for placebo (131, 132, 134–136, 138, 139, 142, 144, 148–152, 154). The mean per-patient percentage of successful intercourse attempts was 48.0% for tadalafil-treated patients and 9.0% for placebo recipients, based on diary or event logs (1 trial) (**Table 1**) (153). In 5 trials from which data pooling was possible (**Appendix B: Figure 3**), the WMD in improvement from baseline in the percentage of successful intercourse attempts was 35.1 (CI, 26.9 to 43.3) in favor of tadalafil (132, 135, 139, 142, 148).

All 5 agents (sildenafil, vardenafil, tadalafil, mirodenafil, and udenafil) consistently increased the proportion of men with improved erections (range, 73.0% to 88.0%)

more than placebo (range, 26.0% to 32.0%) (see overall grade of evidence in **Table 1**). **Appendix Figures 2 to 4** (available at [www.annals.org](http://www.annals.org)) provide the corresponding pooled RR estimates and studies.

Men with specific medical conditions were significantly more likely to experience improved erections with PDE-5 inhibitors relative to placebo, on the basis of trials limited to men with diabetes (37, 48, 49, 53, 55, 99, 102, 103, 121, 122, 141, 156), depression (35, 47, 61, 86, 116), cardiovascular disease (40, 56, 59, 69, 75, 77, 90, 114, 128), prostate cancer (68, 91, 96, 105, 126, 137, 153, 164), multiple sclerosis (57, 101), colorectal cancer (66), schizophrenia (87), liver failure (58), and renal failure (84, 123) (**Appendix Figures 2 to 4**).

Improvement in sexual intercourse success and erectile function was greater with higher versus lower doses of 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 tadalafil (20 mg vs. 10 mg vs. 5 mg) or mirodenafil (50 mg vs. 100 mg vs. 150 mg) (42, 48, 51, 72, 103, 107, 108, 110, 112, 122, 156–159). In 1 trial, men preferred tadalafil on-demand therapy rather than scheduled dosing 3 times per week, although the mean per-patient proportion of successful intercourse attempts or mean IIEF Erectile Function domain score did not differ (129). In another trial, on-demand and once-daily vardenafil, 10 mg, produced similar treatment effects on the mean Erectile Function domain score in men with mild to moderate ED (124).

Among men assigned to PDE-5 inhibitors, those with severe baseline ED experienced significantly greater absolute improvements in the IIEF scores than did those with mild baseline ED. However, men with severe ED still had worse end-of-treatment Erectile Function domain scores than did men with mild baseline ED (37, 46, 66, 110, 112, 131, 149, 151, 152). There was no obvious treatment effect modification by the duration or cause of ED (42, 44, 51, 70, 74, 112).

*PDE-5 Inhibitor Versus PDE-5 Inhibitor.* In 4 trials (160–163), improvements in outcomes between PDE-5 inhibitors were inconsistent. Between-group differences in the mean IIEF Erectile Function domain scores were either statistically nonsignificant or significant but of small magnitude. In 1 trial (160), the use of 10- to 20-mg tadalafil was associated with a small but statistically significantly greater improvement in the mean proportion of successful sexual intercourse attempts compared with 25- to 100-mg sildenafil (76.9% vs. 72.2%;  $P = 0.003$ ). In the same trial, mean change in Erectile Function domain scores did not differ between groups. In a second trial, mean Erectile Function domain scores were similar between men receiving 100-mg sildenafil and men receiving 20-mg tadalafil (163) (**Table 1**). More men preferred 20-mg tadalafil (range, 52.2% to 73.0%) to 50-mg sildenafil (range, 27.0% to 33.7%) or 20-mg vardenafil (20.0%).

Table 1. Summary of Findings of Effectiveness

Intervention and Outcome of Interest	Strength of Evidence and Study Characteristics*	Findings	References
<b>Oral PDE-5 inhibitors</b>			
<b>Sildenafil vs. placebo</b>			
Successful sexual intercourse	High Design: RCT DB: 85.0% AAC: 21.0% Directness: yes Consistency: yes Precision: yes	<ol style="list-style-type: none"> <li>1. Consistent results from 24 mostly fair-quality RCTs indicated that sildenafil was more effective than placebo in improving the mean per-patient proportion of successful sexual intercourse attempts.</li> <li>2. In 16 trials enrolling men with a wide spectrum of diseases, the WMs were 69% for sildenafil vs. 36% for placebo.</li> <li>3. The frequency of successful sexual intercourse attempts was greater with sildenafil vs. placebo (4 trials).</li> </ol>	<ol style="list-style-type: none"> <li>1. 36–40, 42, 43, 52, 53, 59, 61, 64, 73, 75, 77–79, 85, 86, 88, 95, 97, 98, 101</li> <li>2. 36, 38, 39, 42, 43, 52, 61, 64, 73, 78, 79, 85, 88, 95, 97, 98</li> <li>3. 35, 49, 55, 72</li> </ol>
Improvement in erections	High Design: RCT DB: 85.0% AAC: 21.0% Directness: yes Consistency: yes Precision: yes	Consistent results from 35 trials indicated higher rates of improved erection in men receiving sildenafil than in men receiving placebo. A pooled analysis of 19 trials ( <b>Appendix Figure 2</b> ) enrolling men with a wide spectrum of diseases showed more men with improved erection with sildenafil vs. placebo (79% vs. 31%; RR, 2.50 [95% CI, 2.27–2.76]).	35–40, 42–44, 46, 49–53, 55, 57, 59, 61, 64–66, 69, 72–75, 77–79, 86, 90, 94, 95, 101
<b>Vardenafil vs. placebo</b>			
Successful sexual intercourse	High Design: RCT DB: 90.0% AAC: 9.5% Directness: yes Consistency: yes Precision: yes	<ol style="list-style-type: none"> <li>1. Consistent results from 19 fair-quality RCTs indicated that vardenafil was more effective than placebo in improving the mean per-patient proportion of successful sexual intercourse attempts.</li> <li>2. In 13 trials enrolling men with a wide spectrum of diseases, the WMs were 68% for vardenafil vs. 35% for placebo.</li> <li>3. Vardenafil improved the frequency of successful sexual intercourse attempts more than placebo (2 trials).</li> </ol>	<ol style="list-style-type: none"> <li>1. 23, 103–106, 109, 110, 114–119, 121, 122, 125–128</li> <li>2. 23, 104, 106, 109, 110, 115, 117–119, 121, 122, 125, 127</li> <li>3. 107, 112</li> </ol>
Improvement in erections	High Design: RCT DB: 90.0% AAC: 6.6% Directness: yes Consistency: yes Precision: yes	Consistent results from 15 mostly fair-quality RCTs indicated that vardenafil was more effective than placebo in improving erections. A pooled analysis of 11 RCTs ( <b>Appendix Figure 3</b> ) enrolling men with a wide spectrum of comorbid conditions indicated that more vardenafil-treated men had improved erections vs. placebo-treated men (77% vs. 27%; RR, 2.73 [CI, 2.46–3.04]).	103–107, 109, 110, 112, 114, 116–119, 125, 127
<b>Tadalafil vs. placebo</b>			
Successful sexual intercourse	High Design: RCT DB: 78.0% AAC: 28.0% Directness: yes Consistency: yes Precision: yes	<ol style="list-style-type: none"> <li>1. Consistent results from 17 mostly fair-quality RCTs indicated that tadalafil was more effective than placebo in improving the mean per-patient proportion of successful sexual intercourse attempts.</li> <li>2. In 15 trials enrolling men with a wide spectrum of diseases, the WMs were 69% for tadalafil vs. 33% for placebo.</li> <li>3. Tadalafil improved frequency of successful sexual intercourse attempts more than placebo (1 trial).</li> </ol>	<ol style="list-style-type: none"> <li>1. 131, 132, 134–139, 142, 144, 148–152, 154, 156</li> <li>2. 131, 132, 134–136, 138, 139, 142, 144, 148–152, 154</li> <li>3. 153</li> </ol>
Improvement in erections	High Design: RCT DB: 78.0% AAC: 28.0% Directness: yes Consistency: yes Precision: yes	Consistent results from 17 mostly fair-quality RCTs indicated that tadalafil was more effective than placebo in improving erections. A pooled analysis of 13 RCTs ( <b>Appendix Figure 4</b> ) enrolling men with a wide spectrum of comorbid conditions indicated that more men had improved erections with tadalafil than with placebo (80% vs. 32%; RR, 2.62 [CI, 2.15–3.18]).	131–133, 135, 137–139, 141, 142, 144, 148–152, 154, 156
<b>Mirodenafil vs. placebo</b>			
Successful sexual intercourse	Low Design: RCT DB: 100.0% AAC: 0% Directness: yes Consistency: no Precision: no	Two fair-quality trials indicated that mirodenafil was more effective than placebo in improving mean per-patient proportion of successful sexual intercourse attempts (SEP question 3) (45.0%–67.3% vs. 18.6%–20.2%).	157, 158

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Table 1—Continued

Intervention and Outcome of Interest	Strength of Evidence and Study Characteristics*	Findings	References
Improvement in erections	Low Design: RCT DB: 100.0% AAC: 0% Directness: yes Consistency: no Precision: no	The proportion of men with improved erection in 2 trials was greater in mirodenafil groups (67.0%–89.0%) than in placebo groups (31.5%–34.5%).	157, 158
Udenafil vs. placebo			
Successful sexual intercourse	Low Design: RCT DB: 100.0% AAC: 0% Directness: yes Consistency: no Precision: no	In 1 RCT, udenafil improved the mean per-patient proportion of successful sexual intercourse attempts (SEP question 3) more than placebo (70.1%–75.7% vs. 15.4%).	159
Improvement in erections	Low Design: RCT DB: 100.0% AAC: 0% Directness: yes Consistency: no Precision: no	The proportion of men with improved erection was greater in the udenafil group (81.5%–88.5%) than in the placebo group (26.0%).	159
Direct comparisons of oral PDE-5 inhibitors			
Successful sexual intercourse	Low Design: RCT DB: 0% AAC: 0% Directness: yes Consistency: no Precision: no	Evidence from 1 low-quality RCT comparing tadalafil and sildenafil was insufficient to determine whether 1 treatment was more effective than the other in improving successful sexual intercourse attempts.	160
Improvement in erections	Low Design: RCT DB: 0% AAC: 0% Directness: yes Consistency: no Precision: no	Evidence from 2 low-quality RCTs comparing tadalafil and sildenafil was insufficient to determine whether 1 treatment was more effective than the other in improving erectile function.	160, 163
<b>Hormonal treatments†</b>			
Hormonal treatments vs. placebo			
Successful sexual intercourse	Low Design: RCT DB: 67.0% AAC: 0% Directness: yes Consistency: no Precision: no	1. Evidence from 2 low- to fair-quality trials indicated no difference between testosterone vs. placebo. 2. Evidence from 1 low-quality RCT indicated that gel testosterone (but not patch) modestly improved the frequency of successful sexual intercourse compared with placebo.	1. 186, 193 2. 180
Improvement in erections	Low Design: RCT DB: 67.0% AAC: 17.0% Directness: yes Consistency: no Precision: no	1. Evidence from 4 low-quality RCTs was insufficient to determine whether intramuscular testosterone was more effective than placebo in improving erections. There was heterogeneity across study designs, study populations, and study results. 2. Evidence from 2 low-quality RCTs was insufficient to determine whether oral testosterone was more effective than placebo in improving erections. There was heterogeneity across study designs, study populations, and study results.	1. 184, 186, 188, 190 2. 179, 182
Hormonal treatments + PDE-5 inhibitors vs. PDE-5 inhibitors alone			
Successful sexual intercourse	Low Design: RCT DB: 50.0% AAC: 0% Directness: yes Consistency: no Precision: no	Evidence from 2 low-quality RCTs was insufficient to determine whether testosterone (gel, 1 trial; patch, 1 trial) + PDE-5 inhibitor was more effective than placebo + PDE-5 inhibitor in improving the frequency or percentage of successful sexual intercourse attempts.	181, 183

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Table 1—Continued

Intervention and Outcome of Interest	Strength of Evidence and Study Characteristics*	Findings	References
Improvement in erections	Low Design: RCT DB: 33.3% AAC: 0% Directness: yes Consistency: no Precision: no	Evidence from 1 high- and 2 low-quality RCTs was insufficient to determine whether testosterone (gel, 1 trial; patch, 1 trial; oral, 1 trial) + PDE-5 inhibitor was more effective than placebo + PDE-5 inhibitor in improving erections.	181, 183, 187

Appendix figures mentioned in the table can be found at [www.annals.org](http://www.annals.org). AAC = adequate allocation concealment; DB = double blind; PDE-5 = phosphodiesterase-5; RCT = randomized, controlled trial; RR = relative risk; SEP = Sexual Encounter Profile; WM = weighted mean.

\* Criteria for assigning grade: study design, study quality (DB, AAC), consistency in results, precision around an effect estimate, and directness. Based on the approach of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group (25): high = further research is unlikely to change our confidence in the estimate of effect; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

† Hormonal treatments include oral, intramuscular, gel, cream, or patch testosterone.

### Extent of Publication Bias

Visual inspection suggested asymmetry in the sildenafil, vardenafil, and tadalafil funnel plots for the rates of improved erection (Appendix C, available at [www.annals.org](http://www.annals.org)). The linear regression test confirmed statistically significant asymmetry for all 3 funnel plots: sildenafil ( $P < 0.001$ ), vardenafil ( $P = 0.003$ ), and tadalafil ( $P < 0.001$ ).

### Harms

**PDE-5 Inhibitor Versus Placebo.** A greater proportion of men treated with PDE-5 inhibitors than men who received placebo had at least 1 adverse event (Table 2). The most commonly reported adverse events were headache, flushing, rhinitis, and dyspepsia (Appendix D, available at [www.annals.org](http://www.annals.org)). Other reported events were visual disturbances, myalgia, nausea, diarrhea, vomiting, dizziness, and chest pain. In general, these events were mild to moderate and were transient. Serious adverse events were reported in fewer than 2.0% of participants, and incidence did not differ between PDE-5 inhibitor recipients and placebo recipients. In 58 placebo-controlled trials reporting data, risk for a serious cardiovascular event (such as fatal or nonfatal myocardial infarction, stroke, or severe angina) seemed higher in men treated with sildenafil (0.5%) than in men receiving placebo (0.1%). The risk for serious cardiovascular events was similar in men treated with vardenafil (0.2%) or tadalafil (0.3%) compared with placebo (range, 0.1% to 0.2%). Because many PDE-5 inhibitor trials were unbalanced with respect to the number of men randomly assigned in each treatment group, the estimated Peto odds ratios may have been prone to bias (29) and therefore are not presented here.

**PDE-5 Inhibitor Versus PDE-5 Inhibitor.** Differences in the incidence of any adverse events among men treated with sildenafil (range, 24.0% to 34.0%), tadalafil (range, 28.0% to 35.0%), and vardenafil (27.0%) were not statistically significant (Table 2) (160–163). Discontinuation due to adverse effects ranged from 0.5% to 3.8% during tadalafil treatment, 0.5% to 3.8% during sildenafil treat-

ment, and 1.0% during vardenafil treatment. The frequency of specific adverse events (headache, flushing, dyspepsia, and nasal congestion) seemed similar among treatments. Tadalafil may have been associated with more frequent myalgia (range, 2.3% to 4.4%) than sildenafil or vardenafil (range, 0% to 0.5%).

**NAION or Priapism.** Evidence on the incidence of NAION associated with use of PDE-5 inhibitors was limited to 10 case reports (165–174), 2 case series (175, 176), and 1 retrospective cohort study (177). In the cohort study, NAION and “possible” optic neuropathy were identified by using medical diagnostic codes, with NAION defined as ischemic nonarteritic optic neuropathy in the absence of temporal arteritis and polymyalgia rheumatica and “possible” NAION defined as papillitis, optic neuritis, or both in the absence of temporal arteritis, polymyalgia rheumatica, and previous optic neuropathies. Among more than 4 million male veterans aged 50 years or older, those prescribed PDE-5 inhibitors (11.5% of the cohort) had a risk for NAION similar to that of those who were not prescribed PDE-5 inhibitors (absolute rates of 4.6 and 4.5 cases per 10 000 men per year, respectively; RR, 1.02 [95% CI, 0.92 to 1.12]), but they had an increased risk for “possible” NAION (RR, 1.34 [CI, 1.17 to 1.55]) (177). Trials did not report the incidence of priapism, although the incidence of prolonged erection and priapism has been reported infrequently in PDE-5 inhibitor users during postmarketing surveillance (178).

### Hormonal Treatments

#### Study and Population Characteristics

Fifteen RCTs evaluated the efficacy of hormonal therapy (oral, intramuscular, gel, cream, or patch testosterone) in hypogonadal men with ED (179–193). The criteria for defining men as hypogonadal varied widely across the trials, and some trials enrolled men both with and without ED (187–189, 191). Three trials were restricted to men with HIV (186), major depressive disorder (190), or dia-

Table 2. Summary of Findings on AEs\*

Intervention and Outcome of Interest	Strength of Evidence†	Findings	References
<b>Oral PDE-5 inhibitors</b>			
<b>Sildenafil vs. placebo</b>			
Any AE	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 25 mostly fair-quality RCTs indicated that sildenafil recipients had an increased risk for any AEs (45.0% vs. 26.0%; RR, 1.72 [95% CI, 1.53–1.93]).	36–40, 43, 46, 52, 53, 57, 59, 61–66, 71, 72, 75, 77–79, 81, 101
Serious AEs	Low Design: RCT Directness: yes Consistency: no Precision: no	A pooled analysis of 29 mostly fair-quality RCTs indicated that sildenafil and placebo recipients had a similar risk for serious AEs (1.2% vs. 1.3%; RR, 0.99 [CI, 0.63–1.55]).	36–40, 43, 44, 46, 47, 52, 53, 57, 59, 63–66, 69, 71, 75, 77–79, 81, 85, 86, 88, 94, 101
Serious CV events	Low Design: RCT Directness: yes Consistency: no Precision: no	27 mostly fair-quality RCTs indicated that sildenafil recipients had a numerically slightly higher risk for serious CV events (fatal or nonfatal MI, stroke, severe angina) (0.5% vs. 0.1%).	36–40, 43, 44, 46, 47, 50, 53, 55, 57, 64–66, 69, 72, 75, 78, 79, 81, 85, 86, 88, 94, 101
Headache	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 43 mostly fair-quality RCTs indicated that sildenafil recipients had a higher risk for headache (14.2% vs. 4.3%; RR, 2.94 [CI, 2.52–3.42]).	35–40, 42–44, 46, 47, 49–53, 55, 57, 59, 61–66, 69, 71–75, 77–79, 81, 85, 86, 88, 94, 95, 97, 98, 101
Flushing	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 42 mostly fair-quality RCTs indicated that sildenafil recipients had a higher risk for flushing (11.4% vs. 1.6%; RR, 5.67 [CI, 4.24–7.60]).	35–40, 42–44, 46, 47, 49–53, 55, 57, 59, 61–66, 69, 71–75, 77–79, 81, 85, 88, 94, 95, 97, 98, 101
Dyspepsia	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 29 mostly fair-quality RCTs indicated that sildenafil recipients had a higher risk for dyspepsia (6.4% vs. 1.2%; RR, 3.86 [CI, 2.77–5.37]).	35, 37–40, 42–44, 47, 49–51, 53, 57, 63, 64, 69, 71–75, 77–79, 81, 85, 86, 88
Visual disturbances	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 35 mostly fair-quality RCTs indicated that sildenafil recipients had a higher incidence of visual disturbances (3.6% vs. 0.7%; RR, 3.81 [CI, 2.59–5.62]).	35–40, 42–44, 46, 47, 49–53, 57, 59, 61–65, 71–74, 77–79, 86, 88, 97, 98, 101
<b>Vardenafil vs. placebo</b>			
Any AE	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 13 mostly fair-quality RCTs indicated that vardenafil recipients had a higher risk for any AEs (41.5% vs. 23.7%; RR, 1.64 [95% CI, 1.39–1.92]).	104, 106, 107, 109, 114, 115, 117, 119, 121, 122, 125–127
Serious AEs	Low Design: RCT Directness: yes Consistency: no Precision: no	A pooled analysis of 18 mostly fair-quality RCTs indicated that vardenafil and placebo recipients had a similar risk for serious AEs (2.0% vs. 1.4%; RR, 1.16 [CI, 0.80–1.68]).	23, 103, 104, 106, 109, 110, 112, 114–119, 121, 122, 125, 127, 128
Serious CV events	Moderate Design: RCT Directness: yes Consistency: yes Precision: no	11 mostly fair-quality RCTs indicated that vardenafil and placebo recipients had a numerically similar risk for serious CV events (0.2% vs. 0.1%).	23, 104, 105, 107, 110, 115–119, 127
Headache	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 22 mostly fair-quality RCTs indicated that vardenafil recipients had a higher risk for headache (10.6% vs. 2.5%; RR, 3.52 [CI, 2.64–4.69]).	23, 103–107, 109, 110, 112, 114–119, 121–123, 125–128
Flushing	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 21 mostly fair-quality RCTs indicated that vardenafil recipients had a higher rate of flushing (10.0% vs. 0.8%; RR, 6.83 [CI, 4.73–9.86]).	23, 103–107, 109, 110, 112, 114–119, 121–123, 125–128
Dyspepsia	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 11 mostly fair-quality RCTs indicated that vardenafil recipients had a higher rate of dyspepsia (3.6% vs. 0.7%; RR, 3.55 [CI, 2.04–6.15]).	23, 103–107, 109, 110, 112, 114–119, 121–123, 125–127

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Table 2—Continued

Intervention and Outcome of Interest	Strength of Evidence <sup>c</sup>	Findings	References
Tadalafil vs. placebo Any AE	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 3 mostly fair-quality RCTs indicated that tadalafil recipients were at higher risk for any AEs (44.0% vs. 23.0%; RR, 1.75 [CI, 1.26–2.43]).	134, 137, 141
Serious AEs	Low Design: RCT Directness: yes Consistency: no Precision: no	18 mostly fair-quality RCTs indicated that tadalafil and placebo groups had similar rates of serious AEs (0.9% vs. 0.7%; RR, 1.05 [CI, 0.52–2.11]).	130–135, 137–139, 141, 147–152, 154, 156
Serious CV events	Low Design: RCT Directness: yes Consistency: no Precision: no	20 mostly fair-quality RCTs indicated that tadalafil and placebo groups had similar rates of serious CV events (0.3% vs. 0.2%).	130–135, 137–139, 141, 142, 144, 147–152, 154, 156
Headache	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 18 mostly fair-quality RCTs indicated that tadalafil recipients had a higher risk for headache (11.0% vs. 3.0%; RR, 2.78 [CI, 2.06–3.73]).	130, 131, 134, 135, 137–139, 141, 142, 144, 145, 147–152, 154
Flushing	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 9 mostly fair-quality RCTs indicated that tadalafil recipients had a higher incidence of flushing (4.0% vs. 1.0%; RR, 2.57 [CI, 1.25–5.30]).	131, 135, 137, 138, 141, 142, 145, 152, 154
Dyspepsia	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 15 mostly fair-quality RCTs indicated that tadalafil recipients had a higher incidence of dyspepsia (7.0% vs. 0.6%; RR, 6.13 [CI, 3.30–11.39]).	130, 131, 134, 135, 137, 139, 141, 142, 144, 145, 147, 149–152
Myalgia	High Design: RCT Directness: yes Consistency: yes Precision: yes	A pooled analysis of 12 mostly fair-quality RCTs indicated that tadalafil recipients had a higher incidence of myalgia (4.0% vs. 0.8%; RR, 2.82 [CI, 1.47–5.41]).	130, 131, 134, 135, 137, 141, 142, 144, 145, 149, 150, 154
Back pain	Moderate Design: RCT Directness: yes Consistency: no Precision: yes	A pooled analysis of 15 mostly fair-quality RCTs indicated that tadalafil recipients had a higher incidence of back pain (5.0% vs. 2.0%; RR, 1.61 [CI, 1.10–2.38]).	130, 131, 134, 135, 137–139, 141, 142, 145, 147, 149–152
Mirodenafil vs. placebo Any AE	Moderate Design: RCT Directness: yes Consistency: no Precision: no	For 2 RCTs, only treatment-related AEs were reported; incidence was higher in men receiving mirodenafil (range, 24.0%–28.0% vs. 6.7%). Higher dose (50 mg vs. 100 mg vs. 150 mg) corresponded to an increased incidence of any AEs. In both trials, the most common events were flushing ( $n = 32$ ), headache ( $n = 23$ ), nausea ( $n = 5$ ), eye redness ( $n = 8$ ), and dizziness ( $n = 2$ ).	157, 158
Udenafil vs. placebo Any AE	Very low Design: RCT Directness: no Consistency: no Precision: no	For 1 RCT, only treatment-related AEs were reported; incidence was greater in men receiving 100-mg (19.3%) and 200-mg (37.5%) udenafil vs. placebo (5.6%). The most frequent events in men receiving 200-mg udenafil were flushing (23.2%), headache (8.9%), and nasal congestion (7.1%).	159
Serious AE	Very low Design: RCT Directness: yes Consistency: no Precision: no	No serious AE occurred.	159
Direct comparisons of oral PDE-5 inhibitors Any AE	Very low Design: RCT Directness: no Consistency: no Precision: no	Evidence from 4 RCTs (2 low-quality RCTs) was insufficient to draw conclusions on risk for AEs. Incidence of headache, flushing, or dyspepsia was generally similar between groups.	160–163

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Table 2—Continued

Intervention and Outcome of Interest	Strength of Evidence†	Findings	References
Myalgia	Very low Design: RCT Directness: yes Consistency: no Precision: no	Four RCTs (2 low-quality RCTs) suggested that men receiving tadalafil had a higher incidence of myalgia (range, 2.0%–4.0%) than did those sildenafil (range, 0%–0.5%) and vardenafil (0%).	160–163
<b>Hormonal treatments‡</b>			
Hormonal treatments vs. placebo			
Any AE	Very low Design: RCT Directness: no Consistency: no Precision: no	1. Evidence from 3 RCTs reporting AEs were insufficient to draw conclusions about risk for AEs. One low-quality trial assessing intramuscular testosterone reported greater incidences of acne (21.0% vs. 0%) and testicular atrophy (5.0% vs. 0%) vs. placebo. 2. 1 low-quality trial found no significant difference in the incidence of at least 1 treatment-related AE between testosterone gel and placebo groups. 3. 1 fair-quality study (Jadad score, 3) reported no difference in the proportion of men with at least 1 AE between testosterone gel (8/20 patients [40.0%]) vs. placebo (8/18 patients [44.0%]). The reported events in men receiving testosterone gel were mostly transient (back pain, abdominal discomfort, constipation, hyperglycemia, and eye disorder).	1. 180 2. 186 3. 193
Skin irritation	Very low Design: RCT Directness: no Consistency: no Precision: no	One low-quality RCT indicated that patch testosterone was associated with an increased incidence of skin irritation vs. gel or placebo (data not reported).	180
Hormonal treatments + PDE-5 inhibitor vs. PDE-5 inhibitor alone			
Any and specific AEs	Low Design: RCT Directness: no Consistency: no Precision: no	Evidence from 3 existing RCTs was insufficient to assess risk for AEs.	181, 183, 187

AE = adverse event; CV = cardiovascular; MI = myocardial infarction; PDE-5 = phosphodiesterase-5; RCT = randomized, controlled trial; RR = relative risk.

\* See also Appendix D, available at [www.annals.org](http://www.annals.org).

† Criteria for assigning grade: study design, consistency in results, precision around an effect estimate, and directness. Based on the approach of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group (25): high = further research is unlikely to change our confidence in the estimate of effect; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

‡ Hormonal treatments include oral, intramuscular, gel, cream, or patch testosterone.

betes (185). Only 60.0% of the trials were described as double-blind. The appropriateness of randomization and blinding method was not clear for 87.0% and 93.0% of trials, respectively. Only 1 trial reported adequate allocation concealment (182). Given the uncertainty in these quality domains (randomization, blinding, and allocation concealment) and the differences among study populations, the overall strength of evidence was graded as low (Table 1 and Appendix A: Figure 3).

### Efficacy

**Hormonal Therapy Versus Placebo.** Results of trials comparing oral, intramuscular, or patch testosterone with placebo in hypogonadal men with ED were inconsistent regarding their effects on erectile function, degree of erection, or improved erection, with most indicating that testosterone was no more effective than placebo (Table 1). In 1 trial, gel testosterone (50 to 100 mg) but not patch testoster-

one modestly improved sexual intercourse frequency compared with placebo (180). In another trial (193), men treated with testosterone gel (50 mg/d) had slightly higher mean IIEF Erectile Function domain scores than did placebo recipients (21.6 vs. 18.1;  $P < 0.01$ ).

**Hormonal Therapy Plus PDE-5 Inhibitor Versus PDE-5 Inhibitor Alone.** Three small trials in hypogonadal men with ED refractory to previous PDE-5 inhibitor therapy yielded inconsistent results on whether oral PDE-5 inhibitor plus testosterone improved sexual function more than did PDE-5 inhibitor alone (Table 1). In the first trial, 100-mg sildenafil plus 5-mg/d patch testosterone improved several measures of sexual intercourse success and erectile function compared with sildenafil plus placebo (183). In the second trial, men randomly assigned to 100-mg sildenafil plus 1.0% gel testosterone had no greater frequency of sexual intercourse success than men randomly assigned to sildenafil plus placebo; they had small improvements on

IIEF scores that were statistically significant at 4 weeks but not at 8 or 12 weeks (181). In the third trial, sildenafil plus 120-mg/d oral testosterone was associated with a small improvement in the mean Erectile Function domain score compared with sildenafil plus placebo (187).

### Harms

**Hormonal Therapy Versus Placebo.** The incidence of any (or treatment-related) adverse events did not differ between oral or gel testosterone and placebo groups (179, 180, 193). Men receiving patch testosterone had a higher rate of application-site skin reactions and increased hematocrit than men receiving gel testosterone or placebo (180, 194, 195). In 1 trial (180), 2 men treated with patch testosterone developed prostate cancer (Table 2). Prostate-specific antigen levels were similar in testosterone and placebo groups in 3 trials reporting these data (182, 191, 192).

**Hormonal Therapy Plus PDE-5 Inhibitor Versus PDE-5 Inhibitor Alone.** In 3 trials, the incidence of adverse events was low and did not differ between sildenafil alone versus sildenafil plus patch, gel, or oral testosterone groups (Table 2) (181, 183, 187). Prostate-specific antigen levels were not significantly higher in the sildenafil plus testosterone groups than in the sildenafil-alone groups in 2 trials reporting these data (183, 187).

### Clinical Utility of Routine Hormonal Blood Tests in Men With Erectile Dysfunction

#### Study and Population Characteristics

Twenty-nine studies (30 publications) were included, of which 28 (13, 15, 196–222) and 10 (13, 15, 197, 199, 200, 205, 207, 212, 213, 223) reported measurements of testosterone and prolactin, respectively. Patients were recruited predominately from specialty clinics (for example, urology, sexual dysfunction, and endocrinology). Participants' mean age across studies ranged from 47 to 60 years.

About 80.0% of the studies reported at least some information on the hormonal test method. Most of the studies did not report on withdrawals or dropouts. Only 60.0% of studies described participant selection criteria clearly (Appendix A: Figure 4). Given between-study variability in populations, hormone measurement methods, and prevalence rates of hormonal abnormalities, we rated the overall quality of evidence for the association of hormonal abnormalities with ED as low.

#### Prevalence of Hypogonadism and Hyperprolactinemia in Men With ED

The prevalence of low total testosterone levels (197, 208, 219, 220), low free testosterone levels (206, 214), and hyperprolactinemia (199, 212, 213) in men with ED varied widely across studies, with limited data from U.S. primary care settings or U.S. population representative samples. In 1 primary care clinic study, 24.1% of men with ED had total testosterone levels less than 10 nmol/L (<288 ng/dL) (205). In a study of veterans recruited from an outpatient registry, 14.0%

with “inadequate” erectile function had free testosterone levels less than 9.0 pg/mL (206).

By comparison, in a study based in 1 ED specialty clinic, 36.0% of 157 consecutively referred men with ED had hypogonadism (total testosterone level <300 ng/dL) (219). In a retrospective chart review of 2794 men presenting to a Veterans Affairs ED specialty clinic between 1987 and 2002 with a symptom of ED, 654 (23.0%) had androgen deficiency (total testosterone level <300 ng/dL) (220).

In Boston Area Community Health Survey's population-based stratified random sample of men aged 30 to 79 years, the prevalence of total testosterone levels less than 300 ng/dL was 35.0% in men with ED and 22.7% in men without ED (216). In another population-based cohort of men aged 40 to 70 years, the Massachusetts Male Aging Study, there was no association between ED and total testosterone, bioavailable testosterone, or sex hormone-binding globulin after adjustment for potentially confounding variables (217).

Overall, these data suggest that variability in prevalence estimates may reflect between-study differences in population characteristics, hormonal measurement methods, or diagnostic criteria for ED or hormonal abnormalities. Studies were inconsistent regarding whether, among men with ED, those with and without hypogonadism differed in age, severity or duration of ED, or prevalence of chronic diseases (13, 15, 199, 201, 204, 207, 212, 218, 224). Among men with ED in specialty clinic populations, those with low sexual desire, premature ejaculation, or testicular atrophy tended to have low testosterone levels (13, 15, 204, 207, 218). In 1 of these studies, the men with low sexual desire also were more likely to have hyperprolactinemia (207). We could not identify studies examining the rate of hormonal abnormalities in men whose initial PDE-5 inhibitor treatment failed. Overall, evidence was insufficient to determine whether, in primary care clinics, men with ED (or specific subgroups of men with ED) had a higher prevalence of hypogonadism or hyperprolactinemia than did men without ED.

## DISCUSSION

In our systematic review, we found a large quantity of “high-grade” evidence indicating that sildenafil, vardenafil, and tadalafil are more effective than placebo in improving erectile function in men with ED over the short term ( $\leq 12$  weeks), both in mixed study populations and study populations of men with specific comorbid conditions. The observed between-treatment differences were of clinically meaningful and statistically significant (104, 115, 127). In trials that directly compared sildenafil, vardenafil, and tadalafil, the magnitude of improvement in erectile function from baseline was similar among the agents. Compared with lower doses, higher doses of sildenafil and vardenafil (but not tadalafil) were associated with modestly greater improvements in erectile function.

Evidence on whether 1 PDE-5 inhibitor was more or less harmful than another was inconclusive. All PDE-5 inhibitors were associated with increased risk for any or specific adverse events. The reporting of all serious adverse or cardiovascular adverse events was inconsistent and incomplete. The overall rate of serious adverse events in men randomly assigned to PDE-5 inhibitors was about 2.0% or lower and was similar to that in men randomly assigned to placebo. Evidence was insufficient to determine whether treatment with PDE-5 inhibitors increases risk for serious cardiovascular events or NAION in men not receiving nitrates.

Several sources of potential bias may have affected PDE-5 inhibitor trials. First, exclusion of men intolerant of or poorly responsive to previous sildenafil treatment from many tadalafil and vardenafil placebo-controlled trials may have resulted in overestimation of efficacy and underestimation of harms for these agents. Second, the design of head-to-head trials that compared PDE-5 inhibitors may have had biased results in favor of tadalafil through their funding by the manufacturer of tadalafil and their restriction of sildenafil doses. Furthermore, funnel-plot asymmetry and regression analyses suggested possible publication bias for PDE-5 inhibitor trials, although the asymmetry may be explained by methodological or clinical heterogeneity across published studies. Publication bias, if present, may have led to overestimation of the true effect size of clinical benefits associated with use of PDE-5 inhibitors.

Results of trials on the effectiveness and harms of hormonal treatments for ED were inconsistent, probably because of low methodological and reporting quality, differences in patient inclusion criteria, types and doses of testosterone treatment, and outcomes. Results for most trials suggested that testosterone was no more effective than placebo in improving erections or increasing frequency of sexual intercourse.

The evidence on the utility of hormonal blood tests in identifying and affecting therapeutic outcomes for treatable causes of ED is inconclusive. This is in part attributable to the high variability in prevalence of hormonal abnormalities in men with ED across studies and insufficient data on the comparative treatment effectiveness of hormones and PDE-5 inhibitors in men with ED and hormonal abnormalities. Furthermore, consistent evidence was lacking on whether specific clinical features (such as age, comorbid conditions, obesity, hyperlipidemia, and nonresponse to PDE-5 inhibitors) help identify men with hormonal abnormalities among those with ED in primary care settings.

Our review has several limitations. First, many trials had limited methodological and reporting quality, particularly those that directly compared PDE-5 inhibitors and those that evaluated hormonal therapies. Moreover, clinical or methodological heterogeneity and missing information limited the extent of statistical data pooling. Second, the low number and selective reporting of serious cardiovascular events should be interpreted with caution. Third, most RCTs were of short

duration ( $\leq 12$  weeks), and longer-term efficacy and safety data ( $\geq 6$  months) were unavailable.

It is striking that we identified a dearth of credible information on hormonal therapies used in the treatment of ED but an impressive amount of “high-grade” evidence on therapeutic effects of PDE-5 inhibitors compared with placebo for men with ED. This sharp contrast may be explained by the fact that more than 70% of the PDE-5 inhibitor trials in this review were industry funded. This gap in our research base is especially noteworthy in light of the growing popularity of androgen supplementation for various indications in aging men and controversial findings for hormone replacement therapies in women, which are far more extensively studied.

Future efforts are needed to help improve the reporting quality of primary studies. The CONSORT (Consolidated Standards of Reporting Trials) Statement could be considered as a guide for authors reporting trials and journals that publish research related to ED (225). The conduct of studies using standardized hormonal tests and those designed to identify subgroups of men with ED at increased risk for hormonal disorders would help to further determine the utility of routine hormonal blood tests (226). Well-designed, long-term PDE-5 inhibitor trials ( $\geq 6$  months) are also warranted. In the presence of comorbid conditions or specific causes of ED, the comparison of cause-specific therapies (those targeting underlying causes of ED) to empirical treatments (for example, PDE-5 inhibitors) is important. More direct comparison trials of PDE-5 inhibitor drugs are also needed.

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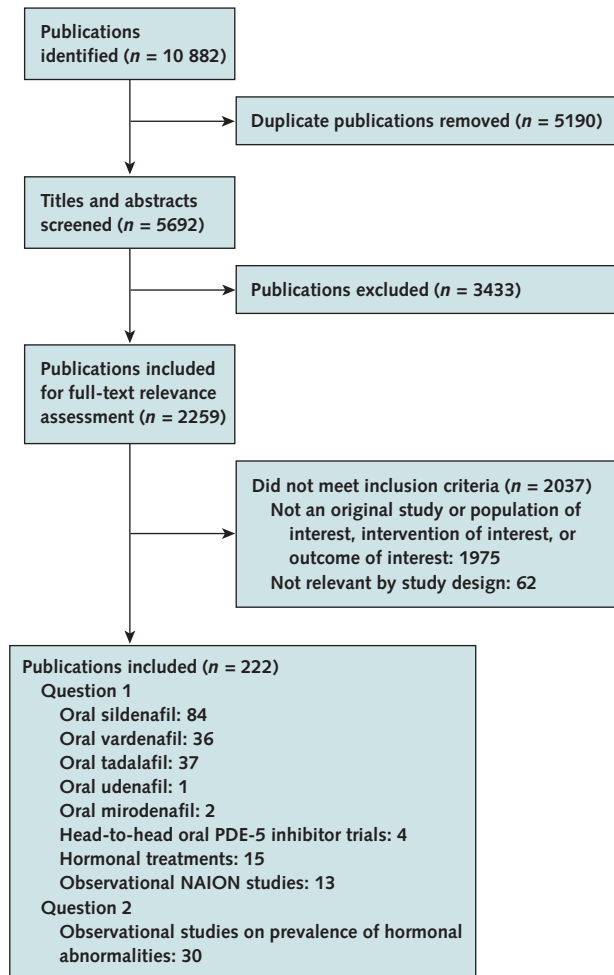
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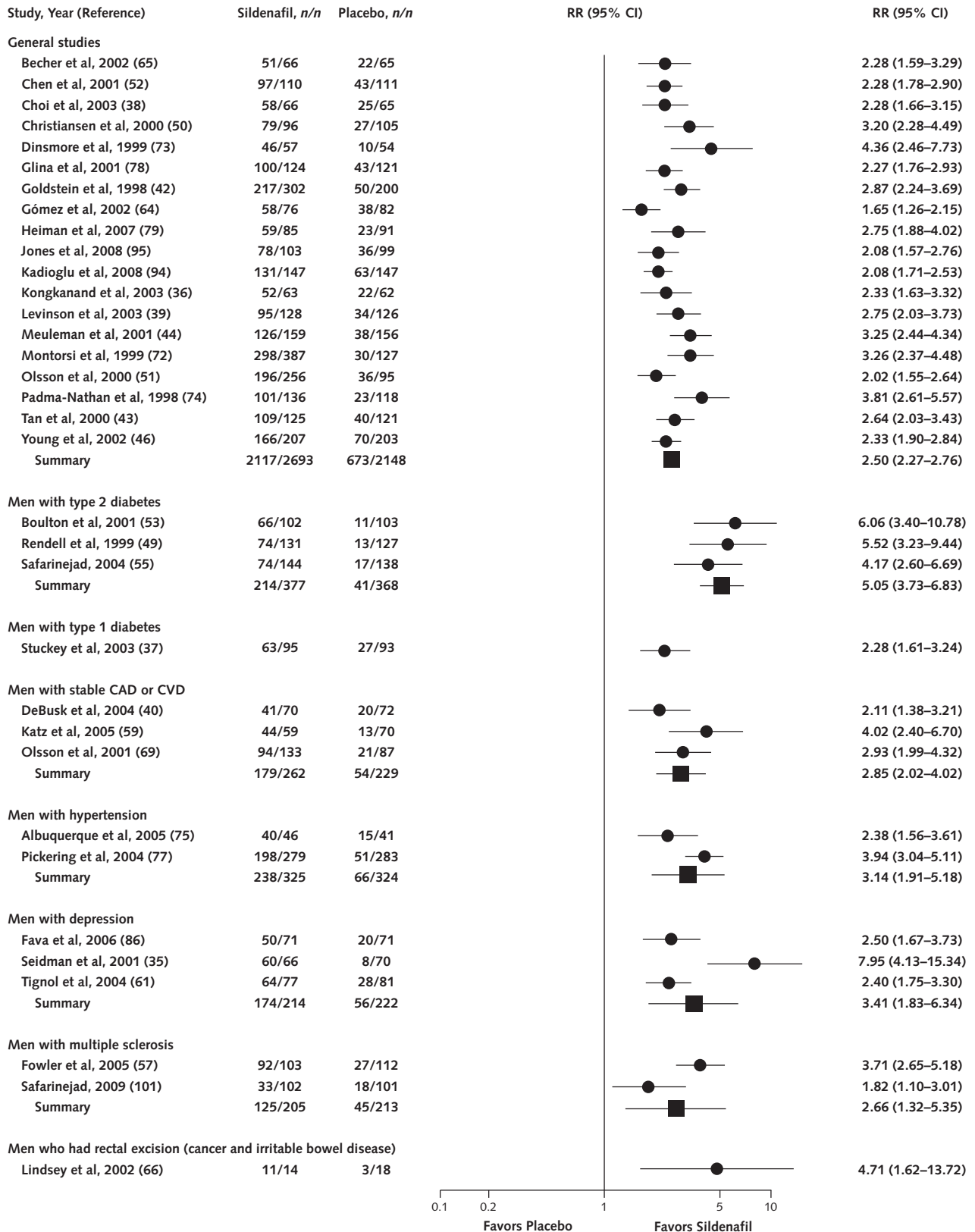
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*Appendix Figure 1. Literature search and selection.*



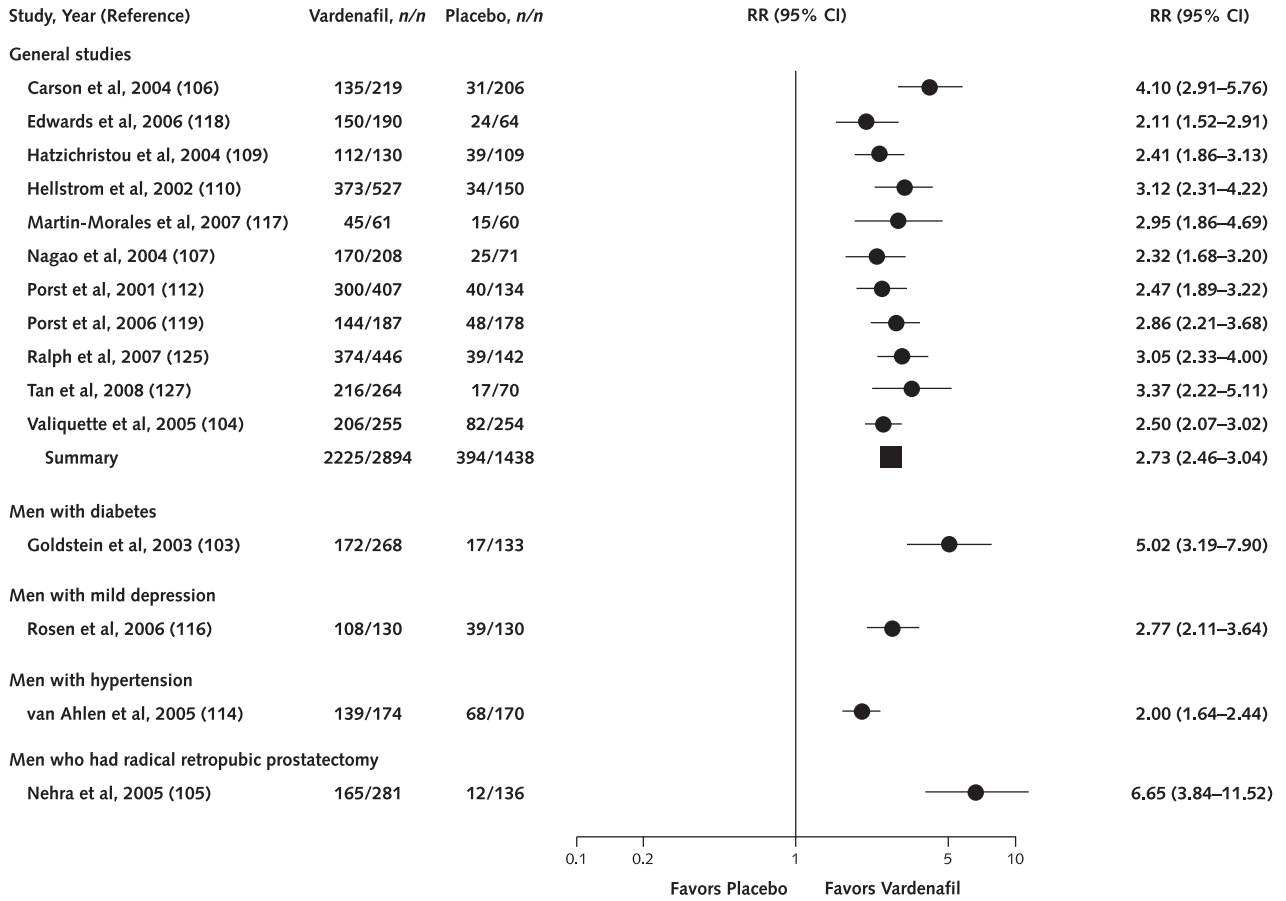
NAION = nonarteritic anterior ischemic optic neuropathy; PDE-5 = phosphodiesterase-5.

Appendix Figure 2. Improvement in erections: sildenafil versus placebo.



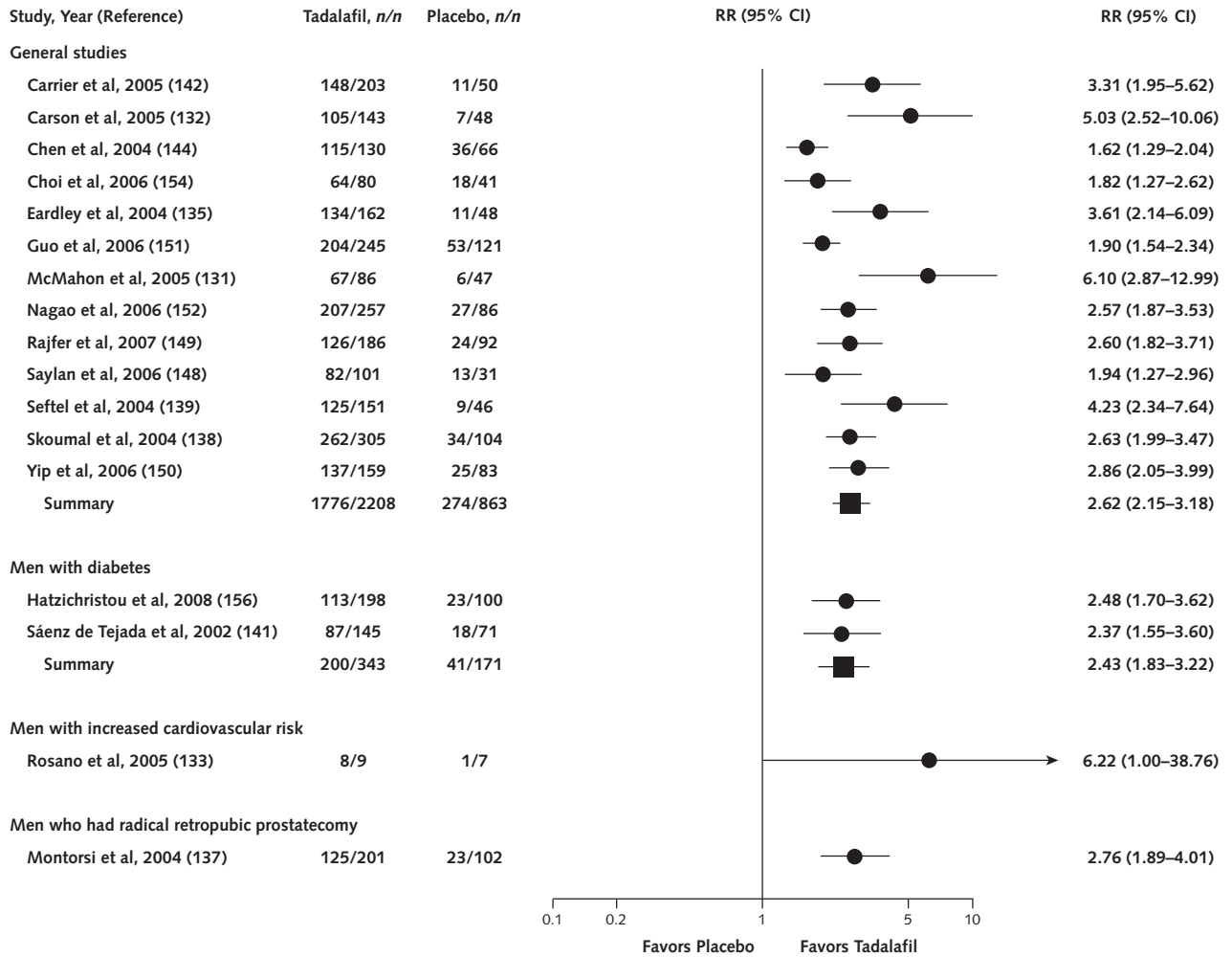
CAD = coronary artery disease; CVD = cardiovascular disease; RR = relative risk.

Appendix Figure 3. Improvement in erections: vardenafil versus placebo.



RR = relative risk.

Appendix Figure 4. Improvement in erections: tadalafil versus placebo.



RR = relative risk.