Sildenafil for Male Erectile Dysfunction

A Systematic Review and Meta-analysis

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Objective: To determine the efficacy and safety of sildenafil citrate in the treatment of male erectile dysfunction.

Data Sources: The MEDLINE, HealthSTAR, Current Contents, and Cochrane Library databases (January 1, 1995, through December 31, 2000); bibliographies of retrieved articles and review articles; conference proceedings abstracts; the Food and Drug Administration Web site; and the manufacturer.

Study Selection: Trials were eligible if they included men with erectile dysfunction, compared sildenafil with control, were randomized, were of at least 7 days' duration, and assessed clinically relevant outcomes.

Data Extraction: Two reviewers independently evaluated study quality and extracted data in a standardized fashion.

Data Synthesis: Twenty-seven trials (6659 men) met the inclusion criteria. In results pooled from 14 parallel-group, flexible as-needed dosing trials, sildenafil was more likely than placebo to lead to successful sexual intercourse, with a higher percentage of successful intercourse attempts (57% vs 21%; weighted mean difference, 33.7; 95% confidence interval [CI], 29.2-38.2; 2283 men) and a greater percentage of men experiencing at least 1 intercourse success during treatment (83% vs 45%; relative benefit increase, 1.8; 95% CI, 1.7-1.9; 2205 men). In data pooled from 6 parallel-group, fixed-dose trials, efficacy appeared slightly greater at higher doses. Treatment response appeared to vary between patient subgroups, although relative to placebo, sildenafil significantly improved erectile function in all evaluated subgroups. In trials with parallel-group design and flexible dosing, men randomized to receive sildenafil were less likely than those receiving placebo to drop out for any reason and no more likely to drop out due to an adverse event or laboratory abnormality. Specific adverse events with sildenafil included flushing (12%), headache (11%), dyspepsia (5%), and visual disturbances (3%); all adverse events were significantly less likely to occur with placebo. Sildenafil was not significantly associated with serious cardiovascular events or death.

Conclusions: Sildenafil improves erectile function and is generally well tolerated. Treatment response seems to vary between patient subgroups, although sildenafil has greater efficacy than placebo in all evaluated subgroups.

Arch Intern Med. 2002;162:1349-1360

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ERECTILE DYSFUNCTION (ED) is defined as the persistent "inability to achieve or maintain an erection sufficient for satisfactory sexual performance."[1] While ED is not life threatening, it may result in withdrawal from sexual intimacy and reduced quality of life.[2-6] Although prevalence estimates for ED vary, up to 30 million men in the United States may be affected.[1] A recent study[6] found that 7% of men aged 18 to 29 years have trouble achieving or maintaining an erection, with prevalence rising to 18% for men aged 50 to 59 years. Elsewhere, half of all men aged 40 to 70 years were found to have some degree of ED, with nearly 10% of these men having complete ED.[7] Furthermore, the prevalence of ED increased with diabetes mellitus, heart disease, hypertension, smoking, and depression. Erectile dysfunction also may be caused by spinal cord injury, prostate surgery, and the use of certain medications.

Normal erectile function relies on the coordination of psychologic, neurologic, endocrine, vascular, and muscular factors. Problems with any of these elements—secondary to disease, psychogenic stress, or drug adverse effects—may contribute to ED. Most cases of ED are believed to be multifactorial.

Treatment options for ED include vacuum constriction devices, penile implants, vasoactive injection therapy,[8,9]

MATERIALS AND METHODS

LITERATURE SEARCH

Trials were identified by searching the MEDLINE, HealthSTAR, Current Contents, and Cochrane Library computer databases (January 1, 1995-December 31, 2000). The search strategy included the key terms "impotence" or "erectile dysfunction," combined with "sildenafil," "Viagra," and "UK-92,480," and limited by combination with the terms "clinical trial," "controlled trial," "randomized controlled trial," and "multicenter study." In addition, bibliographies of retrieved trials and review articles were reviewed, and urology journals and national meeting abstracts published through December 31, 2000, were hand searched. The Cochrane Controlled Trials Register also was screened for additional trials. All trials identified were written in English. Data for unpublished trials and supplemental data for published trials were obtained from the manufacturer and the Food and Drug Administration Web site.

SELECTION CRITERIA

Trials were eligible if they (1) included men with ED, (2) were randomized, (3) compared sildenafil with placebo or active control, (4) were at least 7 days in duration, and (5) assessed clinical outcomes related to ED (eg, success of sexual intercourse attempts and participant global assessment of treatment). For each trial, 2 reviewers (H.A.F., R.M., I.R.R.) independently assessed study eligibility. Differences in eligibility assessments were resolved by discussion.

OUTCOME MEASURES

Information on trial characteristics, patient demographics, inclusion and exclusion criteria, dropouts, treatment efficacy, and adverse events were extracted by 2 independent reviewers (H.A.F., R.M., I.R.R.) in a standardized fashion.

Because we judged successful sexual intercourse to be the most clinically relevant measure of treatment efficacy, our primary outcome was the percentage of all sexual intercourse attempts that were successful. Trials reporting this measure collected data on intercourse attempts and successes from participants' event logs. An intercourse attempt constituted each instance when a participant took the study medication and reported whether he subsequently had successful sexual intercourse. Sexual intercourse success was defined as vaginal penetration that the participant found satisfactory (ie, erection was sufficiently hard and long lasting).

Failure to achieve successful intercourse after use of sildenafil may not always have been due to failure of the drug to produce an adequate erection (eg, interruption of sexual activity and drug-associated adverse events). Therefore, data also were collected to estimate the percentage of successful intercourse attempts after excluding attempts reported by participants to have failed for reasons other than an insufficiently hard or long-lasting erection.

Additional outcomes were the percentage of participants achieving successful intercourse at least once during treatment; the percentage of participants reporting improvement in erectile function, with improvement possibly but not necessarily indicating the ability to reliably achieve

transurethral alprostadil therapy,[10,11] and oral therapies. Men have demonstrated a strong preference for oral treatments even if they have lower efficacy,[12,13] suggesting that efforts to optimize treatment of ED not only should target physiologic and clinical measures of improvement but also should address patient and partner satisfaction and preference.

Sildenafil citrate (Viagra; Pfizer, Inc, New York, NY) is an oral agent that is approved by the Food and Drug Administration for the treatment of ED. It affects erectile function by selectively inhibiting phosphodiesterase type 5, the enzyme responsible for degradation of cyclic guanosine 3′,5′-monophosphate in the corpora cavernosa. This enhances the effect of endogenous nitric oxide, producing penile smooth muscle relaxation, arterial dilation, and inflow of blood, leading to penile engorgement. Sildenafil use does not enhance libido or normal erectile function, and it rarely produces erections in the absence of sexual stimulation. The manufacturer's recommended treatment dose is 50 to 100 mg taken 30 to 60 minutes before desired sexual activity.

Many randomized controlled trials have evaluated sildenafil for the treatment of men with ED. However, we are unaware of any systematic review and quantitative meta-analysis that has formally evaluated the efficacy and safety of sildenafil therapy. Therefore, we conducted this systematic review and meta-analysis to estimate the magnitude of treatment benefits and adverse effects associated with sildenafil treatment in men with ED, overall and for those with comorbid conditions.

RESULTS

CHARACTERISTICS OF TRIALS

Twenty-seven trials involving 6659 men met all eligibility criteria and are included in this systematic review (**Table 1**). Eleven trials were published in peer-reviewed journals,[17-26] 4 as abstracts,[27-30] and 2 in conference symposiums,[31,32] while 3 were available on the Food and Drug Administration Web site as part of the manufacturer's new drug application.[33] Data from the remaining unpublished trials were available only from the manufacturer. Supplemental data were obtained from the manufacturer for all published trials except for 1 conducted independently of their sponsorship.[23] Although all published trials reported that they were randomized, double blind, and placebo controlled, just two[20,25] detailed a clearly adequate method of random allocation and concealment of treatment assignment. Study protocols, obtained from the manufacturer, documented adequate measures to conceal allocation for 26 trials. In no trial was sildenafil compared with another active treatment. The most frequent trial design involved parallel treatment groups and flexible PRN dosing (n=14). Twenty-six trials indicated treatment duration (range, 1-26 weeks).

successful intercourse; and responses to questions 3 and 4 of the previously validated International Index of Erectile Function (IIEF).[14]

For adverse effects, we examined the percentage of men reporting adverse effects and the percentage of men withdrawing from the trial. Missing or additional information was sought from authors and sponsors.

ASSESSMENT OF METHODOLOGIC QUALITY

We assessed the quality of concealment of randomized treatment allocation according to a scale developed by Schulz et al,[15] assigning 1 to poorest quality and 3 to best quality. In addition, we assessed whether trial participants and investigators were aware of treatment provided, whether trials used an intention-to-treat analysis, and the percentage of participants who dropped out or were lost to follow-up.

STATISTICAL ANALYSIS

For assessment of categorical treatment outcomes, we determined the percentage of men achieving each outcome according to treatment assignment. For measures of efficacy, we calculated weighted relative benefit increases (RBIs) and their 95% confidence intervals (CIs) using RevMan 4.0 software.[16] For adverse events and withdrawals, we determined the percentage of men achieving each outcome according to treatment assignment and the weighted relative risk increases (RRIs) and their 95% CIs. For assessment of continuous outcomes, we determined the mean value (ie, percentage of successful attempts and IIEF value) for men in each treatment group and calculated weighted mean differences (WMDs) and their 95% CIs. Weighted RBIs, weighted RRIs, and WMDs were estimated using random effects meta-analyses.

Results presented for each outcome measure are those directly available from articles reviewed and from the manufacturer. However, because available results excluded randomized participants not reporting data for a particular outcome, sensitivity analyses were performed for all efficacy outcome measures. In these analyses, men with missing data were assumed, on average, to have experienced no change in erectile function between baseline and the end of treatment. Specifically, the distributions of missing baseline and end-of-treatment values were assumed to be equivalent to the distribution of baseline values for men assigned to the same treatment group who provided baseline data. These imputed outcome distributions for men with no data were then pooled with the outcome distributions for men with data, and the analyses described in this subsection were repeated.

Data from fixed-dose studies suggested the presence of a meaningful dose-response effect for at least some treatment outcomes. Therefore, different fixed doses were not pooled in meta-analyses. In addition, a clinical decision was made to perform meta-analysis between trials of similar design only. Trials that used a parallel-group design, flexible dosing, and administration on an as-needed basis (PRN) are emphasized in the text primarily because this is the manner in which sildenafil is used in clinical practice. Efficacy data for specific subgroups also are derived from parallel-group, flexible-dose PRN studies. Results were tested for heterogeneity at a significance level of $P<.10$.

Common trial inclusion criteria were age 18 years and older; ED of at least 3 to 6 months' duration; and involvement in a stable heterosexual relationship for 6 months or longer. Exclusion criteria used in most trials included genital anatomic deformity; primary nonerectile sexual disorder (eg, hypoactive sexual disorder); hyperprolactinemia; hypogonadism; major psychiatric disorders not well controlled with therapy (including schizophrenia and major depression); alcohol or substance abuse; major hematologic, renal, or hepatic abnormalities; spinal cord injury; poorly controlled diabetes mellitus; recent cardiovascular events (stroke, myocardial infarction, congestive heart failure exacerbation, unstable angina, or life-threatening arrhythmia within 6 months); uncontrolled hypertension or hypotension (eg, blood pressure >170/100 or <90/50 mm Hg, respectively); active peptic ulcer disease; history of bleeding disorder; current treatment with nitrates, trazodone hydrochloride, or androgens; retinitis pigmentosa; intention to donate blood products during or within 1 month of treatment; and unwillingness to discontinue use of other treatments for ED.

DEMOGRAPHICS OF PATIENTS

Men in these trials had a mean age of 55 years, with 21% aged 65 years or older (**Table 2**). Mean ED duration was 4.8 years. Baseline ED severity was estimated in 20 trials from scores of enrolled participants (n=6161) on the IIEF erectile function domain (range, 0-30). Men scoring 0 to 10 were rated as having severe ED (47%), those scoring 11 to 25 were rated as having mild to moderate ED (45%), and those scoring 26 to 30 were considered to have no ED (3%). Based on their weighted mean baseline scores for IIEF questions 3 and 4, on average, men were able to achieve or maintain erections much less than half of the time (IIEF question 3 mean score, 1.99; IIEF question 4 mean score, 1.68). Approximately half of the men had purely organic ED, whereas 19% had purely psychogenic ED and nearly 30% had a mixed cause (ie, organic plus psychogenic). The most common comorbid conditions in men participating in these trials were hypertension (28%), diabetes mellitus (22%), and ischemic heart disease (10%).

EFFICACY OUTCOMES

Overall Efficacy

Use of sildenafil produced a large and statistically significant improvement in erectile function compared with use of placebo. Treatment benefit was found for all outcome measures in all patient subgroups evaluated and across all studies.

For the primary efficacy outcome measure, results indicated that in the 4 weeks before the end-of-treat-

Table 1. Characteristics of Included Sildenafil Citrate Trials*

Study and Year	Men Randomized (Dropouts), No.†	Design	Treatment Regimen (Sildenafil, mg)‡	Treatment Duration, wk	Characteristics of Participants
Boolell et al,[18] 1996	12 (0)	Crossover	Once daily, fixed dose (25)	1	No organic cause of ED; mean age, 48 y
Goldstein et al,[17] 1998 (A)	532 (67)	Parallel	PRN, fixed dose (25, 50, 100)	24	Mean age, 58 y
Goldstein et al,[17] 1998 (B)	329 (22)	Parallel	PRN, flexible dose (25-100)	12	Mean age, 59 y
Price et al,[24] 1998	21 (1)	Crossover	Once daily, fixed dose (25, 50)	10 days	Diabetic men; mean age, 51 y
Dinsmore et al,[19] 1999	111 (14)	Parallel	PRN, flexible dose (25-50)	12	Mean age, 55 y
Giuliano et al,[20] 1999	178 (7)	Crossover	PRN, flexible dose (25-100)	6	ED due to spinal cord injury; mean age, 38 y
Hartmann et al,[31] 1999	315 (8)	Parallel	PRN, flexible dose (25-100)	26	Mean age, 55 y
Maytom et al,[21] 1999	27 (3)	Parallel	PRN, fixed dose (50)	4	ED due to spinal cord injury; mean age, 33 y
Montorsi et al,[22] 1999	514 (30)	Parallel	PRN, fixed dose (25, 50, 100)	12	Mean age, 56 y
Rendell et al,[25] 1999	268 (16)	Parallel	PRN, flexible dose (25-100)	12	Diabetic men; mean age, 57 y
Palmer et al,[23] 2000	17 (2)	Crossover	PRN, fixed dose (25, 50)	5 doses per arm§	Men with spina bifida; age range, 19-35 y
Tan et al,[26] 2000	255 (12)	Parallel	PRN, flexible dose (25-100)	12	Asian men; mean age, 51 y
Eardley et al,[27] 1996 (abstract)	44 (6)	Crossover	PRN, flexible dose (25-75)	4	No organic cause of ED; mean age, 53 y
Gingell et al,[28] 1996 (abstract)	351 (34)	Parallel	Once daily, fixed dose (10, 25, 50)	4	No organic cause of ED; mean age, 53 y
Lue,[29] 1997 (abstract)	416 (57)	Parallel	PRN, fixed dose (5, 25, 50, 100)	8	Mean age, 58 y
Menza et al,[32] 1999 (abstract)	152 (27)	Parallel	PRN, flexible dose (25-100)	12	Men with depression; mean age, 56 y
Olsson et al,[30] 2000 (abstract)	224 (18)	Parallel	PRN, flexible dose (25-100)	12	Men with HTN or CVD not treated with nitrates; mean age, 62 y
Unpublished trials‖					
148-106	497 (61)	Parallel	PRN, fixed dose (50, 100, 200)	12	Mean age, 58 y
148-350	16 (1)	Crossover	3 Times daily, fixed dose (25)	1	Mean age, 49 y
148-361	254 (13)	Parallel	PRN, fixed dose (50, 100, 200)	12	Mean age, 58 y
148-803	628 (14)	Parallel	PRN, flexible dose (25-100)	12	Asian men; mean age, 46 y
R-0530	249 (21)	Parallel	PRN, flexible dose (25-100)	12	Mean age, 59 y
R-0539	254 (37)	Parallel	PRN, flexible dose (25-100)	12	Diabetic men; mean age, 57 y
96-003	259 (8)	Parallel	PRN, flexible dose (25-100)	12	Asian men; mean age, 54 y
96-004	245 (31)	Parallel	PRN, flexible dose (25-100)	12	Mean age, 57 y
96-005	254 (30)	Parallel	PRN, flexible dose (25-100)	12	Mean age, 52 y
96-006	237 (17)	Parallel	PRN, flexible dose (25-100)	12	Asian men; mean age, 60 y

*PRN indicates taken as needed, no more often than once per day; ED, erectile dysfunction; HTN, hypertension; and CVD, cardiovascular disease.

†Dropouts are all randomized participants who did not complete the trial, including those excluded after randomization (n = 15 postrandomization exclusions for all trials combined). Number of dropouts for crossover studies represents number of treatment arms that were not completed.

‡In flexible-dose trials, participants began with either placebo or a 50-mg sildenafil dose. Dose was adjusted as determined by treatment response and participant tolerance, with an allowable sildenafil range of 25 to 100 mg. Fixed-dose trials compared participants in the placebo arm with those receiving a fixed sildenafil dose of 25, 50, or 100 mg.

§This trial was included because preliminary review of data from other sildenafil trials suggests that 5 doses scheduled PRN last approximately 2 weeks (data not shown).

‖Manufacturer study numbers are indicated for unpublished trials.

ment assessment, the mean percentage of participants' sexual intercourse attempts that were successful was 57% for men receiving sildenafil compared with 21% for men receiving placebo (WMD, 33.7; 95% CI, 29.2-38.2) (**Table 3** and **Figure 1**). For secondary efficacy outcome measures, during the 4 weeks before the end-of-treatment assessment, 83% of men in the sildenafil group reported at least 1 successful sexual intercourse attempt compared with 45% of those receiving placebo (RBI, 1.8; 95% CI, 1.7-1.9) (Table 3 and **Figure 2**), and 78% of men receiving sildenafil reported that treatment "improved" their erections compared with 25% of men allocated to the placebo group (RBI, 3.1; 95% CI, 2.7-3.5) (Table 3 and **Figure 3**).

In analyses excluding sexual intercourse attempts reported by the participant to have failed for reasons other than an insufficiently hard or long-lasting erection, the percentage of successful attempts was 66% in men receiving sildenafil and 25% in those receiving placebo (WMD, 39.4; 95% CI, 35.6-43.2) (Table 3). Analyses in which men with missing end-of-treatment data were assumed, on average, to have experienced no change from baseline erectile function, and were included with men reporting end-of-treatment data, produced results similar to the main results for the mean percentage of successful intercourse attempts and for improvement in erections.

Participants' weighted mean end-of-treatment scores for IIEF question 3 (n=3291) were 3.8 in men randomized to receive sildenafil vs 2.3 for those allocated to receive placebo (WMD, 1.4; 95% CI, 1.3-1.5). These scores indicate that, on average, sildenafil use provided "erections sufficient to penetrate one's partner" much more than half of the time (compared with much less than half of the time for the placebo group). For IIEF question 4, mean closeout scores were 3.6 for men randomized to receive sildenafil vs 2.1 for men allocated to the placebo group (WMD, 1.5; 95% CI, 1.4-1.6), indicating that "maintenance of erections during intercourse" was possible more than half of the time for men receiving sildenafil and much less than half of the time for those receiving placebo.

Efficacy by Treatment Dose

In data from trials that used a parallel design with fixed PRN dosing, efficacy of sildenafil across the dosing range used in clinical practice (25-100 mg) appeared slightly greater at higher doses for some efficacy measures (**Table 4**). The mean percentage per participant of intercourse attempts that were successful appeared greater at 50 or 100 mg compared with at 25 mg but no different between the 2 higher doses. In contrast, the percentage of men that reported at least 1 successful sexual intercourse attempt in the 4 weeks preceding the end-of-treatment assessment appeared the same with each sildenafil dose. Improvement in erections was reported more frequently with each increase in treatment dose.

Efficacy in Patient Subgroups

Subgroup efficacy data are derived mainly from 14 trials that used a parallel-group design with flexible PRN dosing (Table 3). Data on the likelihood of successful sexual intercourse attempts are available from 9 of the 14 trials, whereas improvement in erections was assessed in all 14 trials. Subgroup data for IIEF questions 3 and 4 were assessed in all 14 trials and are available on request from the authors. Not all subgroups were represented in every trial. Data for men with spinal cord injury and men with spina bifida are available only from crossover or fixed-dose trials. All subgroup data for intercourse success outcomes are presented using the primary analysis method that considered all intercourse attempts. Analyses in examined subgroups that excluded intercourse attempts reported to have failed for reasons other than an insufficiently hard or long-lasting erection generated WMDs for the percentage of successful attempts that were increased in favor of sildenafil treatment by 4% to 11% compared with the primary method (data not shown).

AGE

Although men younger than 65 years appeared to be more likely than older men to experience improved erections and successful sexual intercourse when compared within treatment groups, in both age categories, sildenafil treatment resulted in significantly better outcomes than placebo use. Of men younger than 65 years, those receiving sildenafil had successful sexual intercourse during 60% of their attempts (vs 23% for the placebo group; WMD, 34.5; 95% CI, 29.5-39.5; n=1836), 85% had at least 1 successful sexual intercourse attempt during treatment (vs 47% for the placebo group; RBI, 1.7; 95% CI, 1.6-1.9, n=1779), and 80% reported improved erections with treatment (vs 27% for the placebo group; RBI, 2.9; 95% CI, 2.5-3.3; n=2777). In comparison, older men receiving sildenafil had successful intercourse during 46% of attempts (vs 14% for the placebo group), 74% had at least 1 successful intercourse attempt during treatment (vs 36% for the placebo group), and 69% reported improved erections (vs 18% for the placebo group); all differences were statistically significant (Table 3).

Table 2. Baseline Characteristics of 6659 Participants*

Characteristic	Sildenafil Group (n = 4240)†	Placebo Group (n = 2707)†
Age, mean ± SD, y	55 ± 10	54 ± 10
Ethnicity, %‡		
White	71	68
Asian	21	21
Black	4	5
Other	4	7
ED duration, mean, y	4.7	4.9
ED severity, %§		
Severe	47	47
Mild to moderate	46	44
None	2	3
ED cause, %		
Organic only	51	56
Psychogenic only	20	18
Mixed	29	26
Comorbid conditions, %		
Hypertension	26	29
Diabetes mellitus	19	24
Ischemic heart disease	10	9
Depression	6	4
Spinal cord injury‖	4	7
Radical prostatectomy	3	4
Peripheral vascular disease	3	3

*Not all trials provided data for each demographic characteristic. ED indicates erectile dysfunction.

†Sum of sildenafil citrate patients and placebo subjects (n = 6947) exceeds the total number of men randomized (n = 6659) because of men in crossover trials.

‡Numbers may not sum to 100% because of rounding.

§Men reporting clinical ED during screening were eligible for trial entry; ED severity was graded for enrollees by their baseline score in the International Index of Erectile Function erectile function domain. Numbers do not sum to 100% because of men with missing ED severity data.

‖Two trials (n = 205) were limited to men with ED due to spinal cord injury. Twenty-four trials excluded such men.

ETHNICITY

Compared with placebo treatment, sildenafil treatment significantly enhanced intercourse success and improved erections in all ethnic groups evaluated, with treatment response seeming to be roughly comparable between different ethnic groups. Among white men, those randomized to receive sildenafil had successful sexual intercourse during 45% of attempts vs 15% of attempts for those allocated to the placebo group (WMD, 29.3; 95% CI, 23.3-35.3; n=755). Also, 75% of white men receiving sildenafil reported 1 or more successful attempts at intercourse during treatment (vs 40% for the placebo group; RBI, 1.8; 95% CI, 1.5-2.3; n=731), and 70% reported improved erections with treatment (vs 17% for the placebo group).

Asian men receiving sildenafil had successful sexual intercourse during 61% of attempts vs 24% of attempts in those allocated to the placebo group, with nearly 90% of Asian men in the sildenafil group reporting 1 or more successful attempts at intercourse during treatment (vs 49% in men receiving placebo) (Table 3).

Data on intercourse success were available for few black men because black participants constitute fewer

Table 3. Efficacy Outcomes for Parallel-Group, Flexible-Dose PRN Trials According to Participant Subgroup*

	Successful Sexual Intercourse, Mean % of Attempts per Participant				Men With ≥1 Successful Sexual Intercourse Attempt During Treatment				Men With Self-reported Improvement in Erections			
	Sildenafil Group, %	Placebo Group, %	WMD (95% CI)	Men Analyzed, No.	Sildenafil Group, %	Placebo Group, %	RBI (95% CI)	Men Analyzed, No.	Sildenafil Group, %	Placebo Group, %	RBI (95% CI)	Men Analyzed, No.
All participants												
Primary method†	57	21	34 (29-38)	2283	83	45	1.8 (1.7-1.9)	2205	78	25	3.1 (2.7-3.5)	3535
Alternate method†	66	25	39 (36-43)	2205	NA	NA	NA	NA	NA	NA	NA	NA
Age ≥65 y	46	14	31 (24-38)	447	74	36	2.0 (1.6-2.4)	426	69	18	3.4 (2.7-4.2)	758
Asian men	61	24	37 (31-42)	1220	87	49	1.7 (1.6-1.9)	1170	86	34	2.5 (2.2-2.8)	1363
Black men	53	19	34 (16-51)	49	78	31	2.3 (1.3-3.9)	47	67	28	1.9 (1.3-2.8)	143
Severe ED	47	11	34 (26-42)	844	74	26	2.8 (2.1-3.7)	798	67	15	4.2 (3.5-5.1)	1654
HTN	50	16	33 (27-40)	628	75	39	1.9 (1.6-2.2)	604	68	21	3.1 (2.6-3.7)	1100
Diabetes mellitus	44	16	27 (20-34)	551	70	34	2.0 (1.6-2.3)	534	63	19	3.0 (2.5-3.7)	1019
Psychogenic ED	66	29	38 (32-44)	453	91	61	1.4 (1.2-1.6)	440	87	38	2.1 (1.7-2.5)	622
IHD	42	14	24 (2-46)	202	69	32	1.9 (1.3-2.7)	198	63	20	2.6 (1.8-3.8)	376
Depression	58	24	25 (4-47)	51	86	43	1.8 (1.1-2.9)	49	79	20	3.4 (2.4-4.7)	273
PVD	57	13	39 (18-59)	49	88	38	1.8 (0.9-3.6)	48	70	14	3.0 (1.7-5.5)	107
RP	25	3	24 (5-43)	42	47	14	2.9 (1.1-7.3)	37	48	10	3.8 (1.6-9.5)	116
SCI	53	8	45 (39-51)	332‡	81	26	3.2 (2.4-4.2)	308‡	83	12	7.2 (4.7-10.9)	345‡

*No spinal cord injury (SCI) data are available from parallel-group, flexible-dose trials; SCI data presented are derived from a crossover, flexible-dose trial (178 men). PRN indicates as needed; WMD, weighted mean difference; CI, confidence interval; RBI, relative benefit increase; NA, not applicable; ED, erectile dysfunction; HTN, history of hypertension; IHD, ischemic heart disease; PVD, peripheral vascular disease; and RP, history of radical prostatectomy.

†The primary method of analysis considered all sildenafil citrate doses taken and all intercourse attempts. The alternate method excluded from analyses intercourse attempts reported by the participant to have failed for reasons other than a sufficiently hard or long-lasting erection. Subgroup results were derived using the primary method.

‡Number of treatment arms.

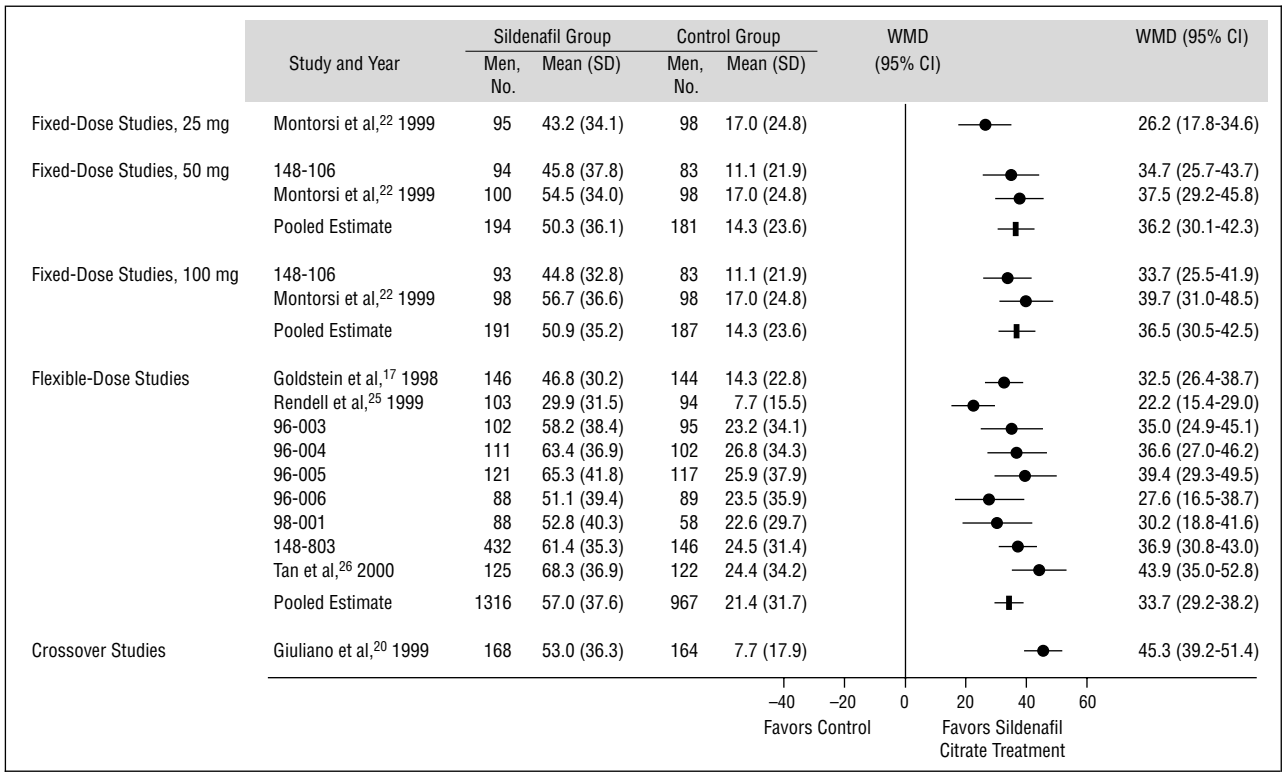

Figure 1. Weighted mean differences (WMDs) in the percentage of sexual intercourse attempts that were successful per participant. CI indicates confidence interval.

than 5% of all participants in completed sildenafil trials. Consequently, for all outcome measures, CIs around the point estimates for the difference in results for black men receiving sildenafil vs those receiving placebo are wide. Nevertheless, results indicate that black men randomized to sildenafil use had significantly greater intercourse success and improvement in erections than did those randomized to placebo use (Table 3).

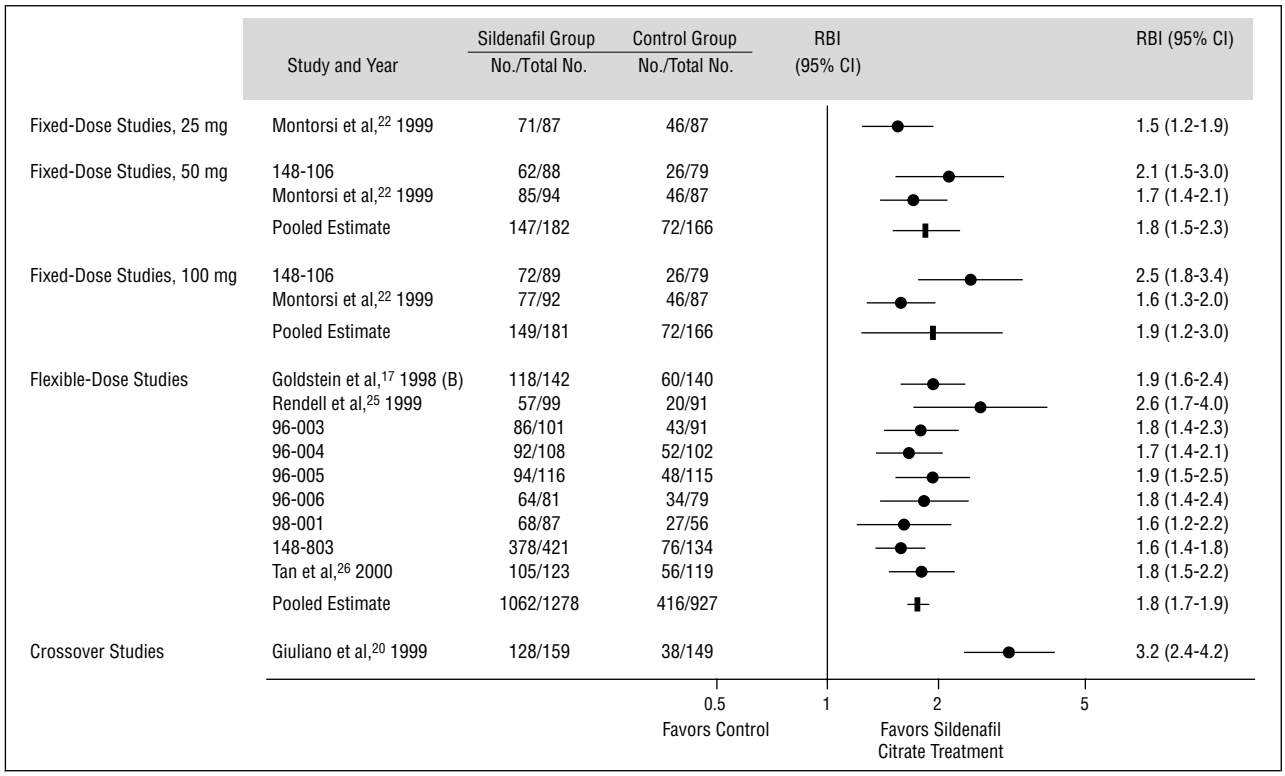

Figure 2. Relative benefit increases (RBIs) in the percentage of men reporting at least 1 successful sexual intercourse attempt during treatment. CI indicates confidence interval.

SEVERITY

Men categorized at baseline as having severe ED appeared less likely than those with mild to moderate ED to experience improved erections and successful sexual intercourse when compared within treatment groups. However, for men in both categories of ED severity, sildenafil treatment produced significantly better results than placebo treatment for all efficacy outcomes. Men with mild to moderate ED at baseline who received sildenafil had successful sexual intercourse during 63% of attempts (vs 28% for the placebo group; WMD, 35.3; 95% CI, 31.7-38.9; n=1359), with 88% having at least 1 successful intercourse attempt during treatment (vs 56% for the placebo group) and 87% reporting improved erections with treatment (vs 36% receiving placebo). Men with severe ED who received sildenafil had successful sexual intercourse during 47% of their attempts vs 11% of attempts for men receiving placebo, and they were more likely to experience at least 1 successful intercourse attempt during treatment (74% vs 26% for the placebo group) (Table 3). Men with severe ED receiving sildenafil also were more than 4-fold more likely to report improved erections compared with such men receiving placebo (RBI, 4.2; 95% CI, 3.5-5.1).

HYPERTENSION AND VASCULAR DISEASE

Men with a self-reported history of hypertension who received sildenafil had successful sexual intercourse during a mean of 50% of attempts vs 16% of attempts for men receiving placebo (WMD, 33.3; 95% CI, 26.6-40.0; n=628) (Table 3). Three quarters of men allocated to the sildenafil group experienced at least 1 successful intercourse attempt during treatment compared with 39% of those randomized to receive placebo.

Men with ischemic heart disease were significantly more likely to experience improved erectile function with sildenafil use compared with placebo use for all measured efficacy outcomes (Table 3). The mean percentage of sexual intercourse attempts that were successful was 42% for men with ischemic heart disease receiving sildenafil vs 14% in those receiving placebo (WMD, 23.8; 95% CI, 2.1-45.6; n=202).

Data on the efficacy of sildenafil treatment relative to placebo treatment are available for few men with peripheral vascular disease (Table 3). Nevertheless, compared with men receiving placebo, those receiving sildenafil reported a significantly higher mean percentage of successful sexual intercourse attempts (57% vs 13%; WMD, 38.8; 95% CI, 18.2-59.4; n=49) and more often reported improved erections with treatment (70% vs 14% for the placebo group). Men allocated to receive sildenafil were not significantly more likely to experience at least 1 successful intercourse attempt during treatment than were men receiving placebo, although the magnitude of treatment effect in this small sample was similar to that seen in men overall (86% for sildenafil vs 40% for placebo; RBI, 1.8; 95% CI, 0.9-3.6; n=44).

DIABETES MELLITUS

Two trials consisted entirely of men with diabetes mellitus,[24,25] whereas a total of 14 trials that used a parallel-

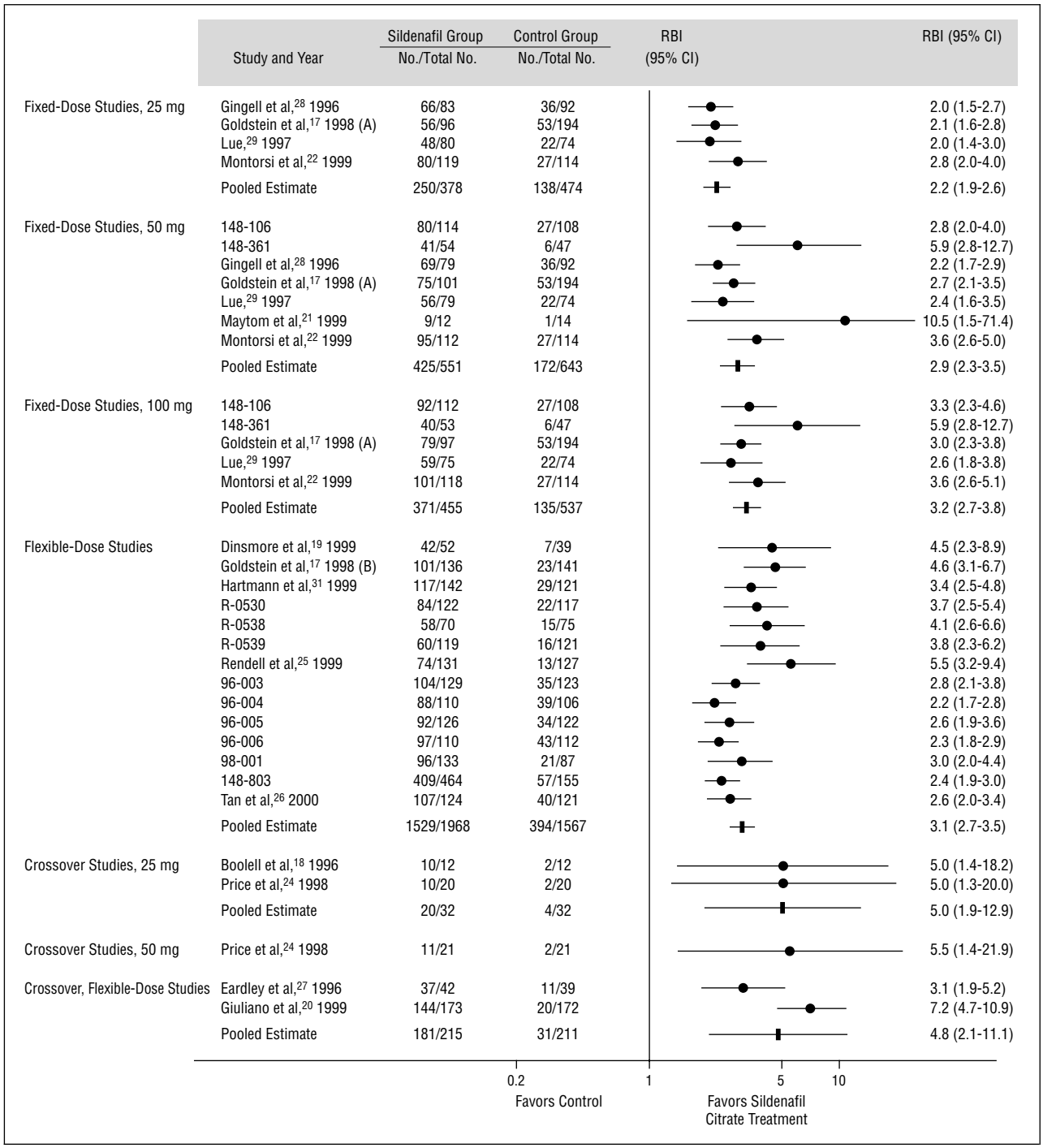

Figure 3. Relative benefit increases (RBIs) in the percentage of men reporting improvement in erections. CI indicates confidence interval.

group design and flexible PRN dosing provided subgroup data on men with diabetes mellitus. In pooled data from the larger group of trials (Table 3), men receiving sildenafil had a mean of 44% successful sexual intercourse attempts compared with 16% for men receiving placebo (WMD, 26.9; 95% CI, 19.9-33.9; n=551). Seventy percent of men receiving sildenafil were able to have successful intercourse at least once during treatment, significantly more than the 34% of men who received placebo. Men with diabetes mellitus receiving sildenafil also were significantly more likely to report improved erections than those treated with placebo (63% vs 19%; RBI, 3.0; 95% CI, 2.5-3.7).

DEPRESSION OR PSYCHOGENIC ED

In men with depression, those receiving sildenafil had a significantly higher mean percentage of intercourse successes than those randomized to receive placebo (58% vs 24%; n=51) and a greater likelihood of experiencing 1 or more successful intercourse attempts during treatment (86% vs 43%; RBI, 1.8; 95% CI, 1.1-2.9; n=49) (Table 3). Men

Table 4. Efficacy Outcomes by Dose for Parallel-Group, Fixed-Dose Studies*

Efficacy Measure	25 mg			50 mg			100 mg		
	Sildenafil Citrate Group, %	Placebo Group, %	WMD or RBI† (95% CI)	Sildenafil Citrate Group, %	Placebo Group, %	WMD or RBI† (95% CI)	Sildenafil Citrate Group, %	Placebo Group, %	WMD or RBI† (95% CI)
Successful sexual intercourse, mean % of attempts per participant	43	17	26 (18-35)	50	14	36 (30-42)	51	14	36 (31-42)
Men with ≥1 successful sexual intercourse attempt during treatment	82	53	1.5 (1.2-1.9)	81	43	1.8 (1.5-2.3)	82	43	1.9 (1.2-3.0)
Men with self-reported improvement in erections	66	29	2.2 (1.9-2.6)	76	27	2.8 (2.3-3.4)	82	25	3.2 (2.7-3.8)

*WMD indicates weighted mean difference; RBI, relative benefit increase; and CI, confidence interval.
†WMD is given for the first efficacy measure and RBI is given for the second and third efficacy measures.

receiving sildenafil also were more than 3-fold more likely to report that treatment improved their erections than were men receiving placebo (RBI, 3.4; 95% CI, 2.4-4.7).

Men with ED entirely attributed to a psychogenic cause appeared to more frequently experience improved erections and successful intercourse than did men with nonpsychogenic ED (ie, organic ED). Of men with psychogenic ED, those receiving sildenafil reported a significantly higher percentage of successful sexual intercourse attempts (66% vs 29% for the placebo group; n=453) and a greater likelihood of experiencing at least 1 successful intercourse attempt during treatment (91% vs 61% for the placebo group; RBI, 1.4; 95% CI,1.2-1.6) (Table 3). In comparison, men with organic ED receiving sildenafil had successful sexual intercourse during 50% of attempts (vs 17% for the placebo group; WMD, 31.9; 95% CI, 26.0-37.9), whereas 76% of these men who received sildenafil had at least 1 successful intercourse attempt during treatment (vs 37% for the placebo group; RBI, 2.0; 95% CI, 1.8-2.3), with both treatment group differences achieving statistical significance.

HISTORY OF RADICAL PROSTATECTOMY

Relatively little information is available regarding the efficacy of sildenafil treatment for men with a history of radical prostatectomy. These data indicate that although these men do significantly better with sildenafil use than with placebo use for all efficacy outcomes (Table 3), they seem considerably less likely to respond to either sildenafil or placebo use than all other groups of men with ED. Compared with men randomized to receive placebo, those who received sildenafil had a significantly higher mean percentage of successful intercourse attempts (25% vs 3%; n=42) and a greater likelihood of experiencing 1 or more successful intercourse attempts during treatment (47% vs 14%; n=37).

SPINAL CORD DISORDERS

Two trials[20,21] enrolled men with ED secondary to traumatic spinal cord injury, of which only one[20] provided data on the likelihood of successful sexual intercourse with treatment. In this crossover design, flexible PRN dosing trial, the mean percentage of successful intercourse attempts with sildenafil use was significantly greater than the mean percentage with placebo use (53% vs 8%; n=178 men randomized) (Table 3). Men receiving sildenafil also were significantly more likely to experience at least 1 successful intercourse attempt during treatment than were men receiving placebo (81% vs 26%). In data from both trials, 83% of men receiving sildenafil reported improved erections compared with 12% receiving placebo (RBI, 7.2; 95% CI, 4.7-10.9).

One trial[23] comprised young men with spina bifida and used a crossover design and fixed PRN dosing. Participants receiving sildenafil had a significant improvement in erectile function, as measured by "erectile score" ($P<.05$ vs placebo; n=17 men randomized). No data were reported regarding success of intercourse attempts.

ADVERSE EVENTS

In data from 14 parallel-group, flexible-dose PRN trials (n=3780), men randomized to sildenafil use were less likely than those allocated to placebo use to drop out of trials for any reason (7% vs 14%; RRI, 0.6; 95% CI, 0.5-0.9) and no more likely to drop out due to an adverse event or laboratory abnormality (1.3% vs 1.2%; RRI, 1.3; 95% CI, 0.7-2.3) (**Table 5**). In fixed-dose studies, dropouts also were reduced relative to placebo at each treatment dose (25-100 mg), with no substantial difference between the sildenafil doses or between the results for fixed-dose and flexible-dose studies.

Nearly half of the men (48%) randomized to sildenafil use reported at least 1 adverse event compared with 36% of men randomized to placebo use (RRI, 1.4; 95% CI, 1.3-1.6) (Table 5). The most commonly reported adverse events in men receiving sildenafil were headache (11% vs 4% for the placebo group), flushing (12% vs 2% for the placebo group), dyspepsia (5% vs 1% for the placebo group), and visual disturbances (3% vs 0.8% for the placebo group); all differences were statistically significant. Data from fixed-dose trials indicated that all of these adverse effects were more frequent at higher doses. Most adverse events were mild or moderate in severity. The incidence of these adverse events appeared comparable across different subgroups of patients (data not shown).

The incidence of death and serious cardiovascular events, such as angina pectoris and myocardial infarction, were infrequent in individuals enrolled in these randomized trials. In data available from 24 of 27 eligible trials,

Table 5. Discontinuations and Adverse Events by Treatment Dose*

	Sildenafil Group, %	Placebo Group, %	RRI (95% CI)
Discontinuations			
Flexible dose†	7	14	0.6 (0.5-0.9)
Fixed dose, 25 mg‡	10	14	0.8 (0.5-1.1)
Fixed dose, 50 mg	8	13	0.6 (0.4-0.96)
Fixed dose, 100 mg	9	14	0.7 (0.5-0.96)
Any adverse event			
Flexible dose	48	36	1.4 (1.3-1.6)
Fixed dose, 25 mg	61	45	1.4 (1.2-1.6)
Fixed dose, 50 mg	65	48	1.4 (1.2-1.5)
Fixed dose, 100 mg	79	50	1.5 (1.3-1.8)
Headache			
Flexible dose	11	4	2.6 (1.8-3.7)
Fixed dose, 25 mg	18	6	3.0 (2.0-4.6)
Fixed dose, 50 mg	20	7	2.9 (2.1-4.0)
Fixed dose, 100 mg	28	7	4.0 (2.9-5.6)
Vasodilation (flushing)			
Flexible dose	12	2	5.8 (3.4-10.0)
Fixed dose, 25 mg	9	1	7.1 (3.2-15.7)
Fixed dose, 50 mg	17	2	8.0 (4.7-13.9)
Fixed dose, 100 mg	18	2	7.6 (4.3-13.2)
Dyspepsia			
Flexible dose	5	1	3.8 (2.2-6.6)
Fixed dose, 25 mg	5	2	2.5 (1.1-5.6)
Fixed dose, 50 mg	8	2	3.9 (2.2-7.0)
Fixed dose, 100 mg	17	2	8.9 (4.8-16.5)
Abnormal vision			
Flexible dose	3	<1	3.1 (1.8-5.4)
Fixed dose, 25 mg	<1	<1	1.5 (0.2-10.3)
Fixed dose, 50 mg	2	<1	3.3 (0.7-15.5)
Fixed dose, 100 mg	11	<1	11.6 (4.4-30.5)

*RRI indicates relative risk increase; CI, confidence interval.

†In flexible-dose trials, participants began at a 50-mg dose, with adjustment between 25 and 100 mg as determined by treatment response and participant tolerance. Discontinuation and adverse events data are available for 3780 men from these trials.

‡Fixed-dose trials compared individuals in the placebo arm with those receiving a fixed sildenafil citrate dose of 25, 50, or 100 mg. For each fixed-dose comparison, discontinuation and adverse events data are available from the following number of men: 25 mg (n = 397) vs placebo (n = 521); 50 mg (n = 605) vs placebo (n = 716); and 100 mg (n = 506) vs placebo (n = 607).

the combined outcome of angina or chest pain of possible cardiac origin was reported by 0.8% of men receiving sildenafil compared with 0.5% of men receiving placebo (P=.08). In all 27 trials (4240 men in sildenafil treatment arms and 2707 in the placebo arm), myocardial infarction occurred in 0.1% of men receiving sildenafil (n=6) and 0.2% of men receiving placebo (n=6), and deaths occurred in 0.1% of men randomized to receive sildenafil (n=4) and 0.1% of men randomized to receive placebo (n=2). All deaths occurred more than 7 days after the last treatment dose. In results restricted to men with ischemic heart disease not taking nitrates (664 men from 24 of 27 eligible trials), angina was reported by 2.4% of men receiving sildenafil vs 0.4% of men receiving placebo (P=.06).

COMMENT

This systematic review and quantitative meta-analysis summarizes the evidence from randomized controlled clinical trials regarding the efficacy and safety of sildenafil for the treatment of ED. Overall, compared with men receiving placebo, those allocated to the sildenafil group had a higher percentage of successful sexual intercourse attempts, were more likely to have successful intercourse at least once during follow-up, and were more likely to report improved erections. Treatment benefit was found across all trials and for all evaluated patient subgroups. Although each of the sildenafil doses used in clinical practice (25, 50, and 100 mg) had significantly greater efficacy than placebo, the difference between these active treatment doses appeared modest and was not present for all outcomes.

When data were analyzed excluding intercourse attempts reported to have failed for reasons other than an insufficiently firm or long-lasting erection, overall and subgroup results appeared comparable to those derived using the primary analysis method, although with an apparent increase in the relative benefit of sildenafil use over placebo use. Additional analyses suggested that overall results change little when men without outcomes data are assumed to have had no change from baseline erectile function and are included in the analyses.

In data from trials that used a parallel-group design and flexible PRN dosing, the response to treatment, as measured by mean percentage of successful intercourse attempts per participant, in subgroups ranged from 42% to 66%, except in men with a history of radical prostatectomy (25%). Although the potential role of differences in the pathophysiologic characteristics of ED between subgroups in explaining variation in efficacy outcomes cannot be evaluated with meta-analytic techniques, other factors may be important. Some differences in treatment outcome may be related to the level of baseline erectile function. For example, men with a history of radical prostatectomy had among the lowest levels of intercourse success during the open run-in periods that preceded most trials (data not shown). Differences in treatment outcome also may be related to variation in placebo responsiveness. We estimated placebo effect for each subgroup by comparing its mean percentage of successful intercourse attempts during the run-in phase with its success rate during the double-blind phase among the men who received placebo. In these comparisons, men with depression and psychogenic ED achieved a 15% to 20% improvement in the intercourse success rate with placebo therapy, and men with a history of radical prostatectomy or peripheral vascular disease experienced essentially no improvement with placebo use. Finally, differences between specific subgroups also may be affected by confounding due to other patient variables, a possibility that could not be investigated in this trial-level meta-analysis.

Safety data from the trials in this meta-analysis suggest that sildenafil administration was generally well tolerated. Although adverse events were significantly more frequent with sildenafil use than with placebo use, they were mostly mild or moderate in severity, and dropout rates due to adverse events or to laboratory abnormalities occurred no more frequently with sildenafil use than with placebo use. All adverse effects were more fre-

quent at higher sildenafil doses. Differences in reports of angina or chest pain of cardiac origins between men receiving sildenafil and those allocated to placebo use did not reach statistical significance, and myocardial infarction and death were uncommon and appeared to be no more likely in men receiving sildenafil than in those receiving placebo.

Although even large meta-analyses such as the present one may have limited power to detect modest increases (eg, <2-fold) in relatively uncommon events such as myocardial infarction or death (eg, 0.1%-1.0%),[34] postmarketing data do not provide any conclusive evidence for an excess cardiovascular risk with sildenafil use as prescribed in the United States and England. Through January 14, 2000, the Adverse Event Reporting System of the Food and Drug Administration listed 635 US deaths possibly associated with sildenafil use.[35] However, because of limitations in data obtained from these types of postmarketing reports,[36] it cannot be determined whether these deaths are related to sildenafil use, sexual activity, patients' underlying disease, or a combination of these factors. Preliminary postmarketing surveillance data from the UK Drug Safety Research Unit[37] indicated that in nearly 6000 men prescribed sildenafil from whom questionnaires were returned, the mortality rate related to myocardial infarction or ischemic heart disease was not greater than expected for an age-adjusted population of English men. The authors caution that the possibility of differences between the cohort of sildenafil users and men in the general population of England limits the conclusions that may be drawn from these data.

Although these trials provide clinically meaningful information on the treatment efficacy and adverse events associated with sildenafil treatment, overall and for most important subgroups, only limited efficacy data are available for black or Hispanic men and for men with a history of radical prostatectomy, peripheral vascular disease, depression, or spina bifida. In addition, efficacy and safety results from this systematic review and meta-analysis should not be extrapolated to the categories of patients excluded from most evaluated trials with the probable exception of men with ED secondary to spinal cord injury for whom there are data from trials that enrolled only such individuals. In addition, none of these trials lasted longer than 26 weeks, so long-term efficacy and safety data from randomized controlled trials are not available.

In conclusion, the evidence from this systematic review and meta-analysis indicates that sildenafil use significantly improves erectile function and is well tolerated by men with ED. However, several questions remain. Longer-term trials would help clarify the degree to which efficacy and safety of sildenafil are maintained over time. Additional data are needed to more precisely determine the efficacy and safety of sildenafil treatment in black and Hispanic patients and in men with a history of radical prostatectomy, peripheral vascular disease, or depression. Appropriately, trials in black and Hispanic patients are ongoing. In addition, it is important to more fully elucidate the safety of sildenafil treatment in men possibly at increased risk for cardiovascular events, such as those with stable ischemic heart disease. Ongoing prescription adverse event monitoring[37] and other database surveillance may provide additional information that further evaluates the apparent safety of sildenafil use in appropriate populations of men. Randomized trials should compare sildenafil with other treatments for ED and sildenafil monotherapy vs combined therapy with sildenafil and other active treatment(s). End points should include intercourse success, patient and partner preference, sexual function–related quality of life, and adverse effects, including cardiovascular events.

Accepted for publication October 22, 2001.

This study was supported in part by a grant from the Technology Assessment Program of the Management Decision and Research Center, Health Services Research and Development Service of the Veterans Health Administration's Office of Research and Development, and by the Center for Chronic Disease Outcomes Research and the Cochrane Review Group in Prostate Diseases and Urologic Malignancies, Veterans Affairs Medical Center.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

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