Saw Palmetto Extracts for Treatment of Benign Prostatic Hyperplasia: A Systematic Review

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JAMA. 1998;280(18):1604-1609 (doi:10.1001/jama.280.18.1604)

http://jama.ama-assn.org/cgi/content/full/280/18/1604

Review

Saw Palmetto Extracts for Treatment of Benign Prostatic Hyperplasia

A Systematic Review

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Objective.—To conduct a systematic review and, where possible, quantitative meta-analysis of the existing evidence regarding the therapeutic efficacy and safety of the saw palmetto plant extract, *Serenoa repens*, in men with symptomatic benign prostatic hyperplasia (BPH).

Data Sources.—Studies were identified through the search of MEDLINE (1966-1997), EMBASE, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies.

Study Selection.—Randomized trials were included if participants had symptomatic BPH, the intervention was a preparation of *S repens* alone or in combination with other phytotherapeutic agents, a control group received placebo or other pharmacological therapies for BPH, and the treatment duration was at least 30 days.

Data Extraction.—Two investigators for each article (T.J.W., A.I., G.S., and R.M.) independently extracted key data on design features, subject characteristics, therapy allocation, and outcomes of the studies.

Data Synthesis.—A total of 18 randomized controlled trials involving 2939 men met inclusion criteria and were analyzed. Many studies did not report results in a method that permitted meta-analysis. Treatment allocation concealment was adequate in 9 studies; 16 were double-blinded. The mean study duration was 9 weeks (range, 4-48 weeks). As compared with men receiving placebo, men treated with *S repens* had decreased urinary tract symptom scores (weighted mean difference [WMD], −1.41 points [scale range, 0-19] [95% confidence interval (CI), −2.52 to −0.30] [n = 1 study]), nocturia (WMD, −0.76 times per evening [95% CI, −1.22 to −0.32] [n = 10 studies]), and improvement in self-rating of urinary tract symptoms; risk ratio for improvement (1.72 [95% CI, 1.21-2.44] [n = 6 studies]), and peak urine flow (WMD, 1.93 mL/s [95% CI, 0.72-3.14] [n = 8 studies]). Compared with men receiving finasteride, men treated with *S repens* had similar improvements in urinary tract symptom scores (WMD, 0.37 International Prostate Symptom Score points [scale range, 0-35] [95% CI, −0.45 to 1.19] [n = 2 studies]) and peak urine flow (WMD, −0.74 mL/s [95% CI, −1.66 to 0.18] [n = 2 studies]). Adverse effects due to *S repens* were mild and infrequent; erectile dysfunction was more frequent with finasteride (4.9%) than with *S repens* (1.1%; $P<.001$). Withdrawal rates in men assigned to placebo, *S repens*, or finasteride were 7%, 9%, and 11%, respectively.

Conclusions.—The existing literature on *S repens* for treatment of BPH is limited in terms of the short duration of studies and variability in study design, use of phytotherapeutic preparations, and reports of outcomes. However, the evidence suggests that *S repens* improves urologic symptoms and flow measures. Compared with finasteride, *S repens* produces similar improvement in urinary tract symptoms and urinary flow and was associated with fewer adverse treatment events. Further research is needed using standardized preparations of *S repens* to determine its long-term effectiveness and ability to prevent BPH complications.

JAMA. 1998;280:1604-1609

SYMPTOMATIC BENIGN prostatic hyperplasia (BPH) is one of the most common medical conditions in older men. As many as 40% of men aged 70 years or older have lower urinary tract symptoms consistent with BPH.[1] Treatment goals in the vast majority of men are to relieve irritative (urgency, frequency, and nocturia) and obstructive (weak stream, hesitancy, intermittency, and incomplete emptying) symptoms. In the United States, treatment of BPH exceeds $2 billion in costs, accounts for 1.7 million physician office visits,[2] and results in more than 300 000 prostatectomies annually.[3] Treatment options include lifestyle modification, device and surgical therapies, and pharmaceutical and phytotherapeutic preparations.[4,5]

Phytotherapy or the use of plant extracts for treating BPH symptoms was first described in Egypt in the 15th century BC. Currently, phytotherapy is common in Europe and is increasing in the western hemisphere. The sale of all botanical medications in the United States is $1.5 billion per year and the use of phytotherapies increased nearly 70% among US adults in the past year.[6,7] Phytotherapeutic agents represent nearly half the medications dispensed for treatment of BPH in Italy, compared with 5% for α-

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The authors have no commercial, proprietary, or financial interest in the products or companies in this article.

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blockers and 5% for 5 α-reductase inhibitors.[8] In Germany and Austria, phytotherapy is the first-line treatment for mild-to-moderate lower urinary tract symptoms and represents more than 90% of all drugs prescribed for the treatment of BPH.[9] In the United States, phytotherapies for BPH are readily available as nonprescription dietary supplements. Most of these compounds are unlicensed and often promoted to "maintain a healthy prostate" and as a natural and harmless treatment of BPH symptoms.

There are about 30 phytotherapeutic compounds used for the treatment of BPH.[10] The most widely used is the extract of the dried ripe fruit from the American dwarf saw palmetto plant *Serenoa repens* (also known by its botanical name *Sabal serrulata*). Berries from saw palmetto were first used by the American Indians in Florida in the early 1700s to treat testicular atrophy, erectile dysfunction, and prostate gland swelling or inflammation.[10] The medicinal value of *S repens* for relief of prostate gland swelling has been reported in medical literature since the 1800s. The mechanism of action of *S repens* is not known but may include alteration of cholesterol metabolism,[11] antiestrogenic, antiandrogenic, and anti-inflammatory effects,[12-14] and a decrease in available sex hormone–binding globulin.[15] Although *S repens* has been evaluated in several randomized trials its clinical efficacy has not been clearly demonstrated.

Our goal was to systematically review the existing evidence regarding the therapeutic efficacy and safety of the saw palmetto plant extract *S repens*. We specifically assessed whether *S repens* is more effective than placebo and as effective as other pharmacological therapies in improving symptoms and/or urodynamic measurements in men with BPH.

METHODS

Inclusion Criteria

Randomized controlled trials were included if participants had symptomatic BPH; the treatment intervention was a preparation of *S repens* (*S serrulata*, *Sabalis serrulata*, *Serenoa serrulata*, Permixon, PA109, Serendar, Talso, Curbicin, Prostagutt, Prostaselect, Prostagalen, Prostavigol, Strogen forte, and SPRO 160/120) alone or in combination with other phytotherapeutic agents; a control group received either placebo or other pharmacological therapies for BPH; and the treatment duration was at least 30 days.

Identification of Relevant Trials

We searched MEDLINE for studies from 1966 to 1997 by crossing an optimally sensitive search strategy for trials from the Cochrane Collaboration with the medical subject headings *prostatic hyperplasia*, *phytosterols*, *plant extracts*, *sitosterols*, *Serenoa repens*, or *Sabal serrulata*, including all subheadings.[16] EMBASE, (1974-July 1997), Phytodok (Munich, Germany), and the Cochrane Library, including the database of the Cochrane Prostatic Diseases and Urologic Malignancies Group and the Cochrane Field for Complementary Medicine, were searched in a similar fashion. Reference lists of all identified trials and previous reviews were searched for additional trials. Expert relevant trialists and pharmaceutical companies were asked to identify additional published or unpublished trials. There were no language restrictions.

Data Extraction and Study Appraisal

Study characteristics, demographic information, enrollment criteria, therapy allocation, adverse effects, outcomes and numbers, and reasons for dropouts were extracted independently by 2 reviewers. Missing information was sought from authors and/or sponsors. Extracted data were reviewed by the principal reviewer and discrepancies resolved by discussion.

The main outcome was the efficacy of *S repens* vs placebo or active control in improving urologic symptom scale scores or global report of urinary tract symptoms (improved vs stable or worsened). Secondary outcomes included peak and mean urine flow, residual urine volume, prostate size, and nocturia.

As a measure of overall methodological study quality, we assessed the quality of concealment of treatment allocation according to a scale developed by Schulz et al,[17] assigning 1 as poorest quality and 3 as best quality. The treatment allocation included (1) trials in which concealment was inadequate (eg, such as alternation or reference to case record numbers or to dates of birth); (2) trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories; and (3) trials deemed to have taken adequate measures to conceal allocation (eg, central randomization; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes, etc, that contained elements convincing of concealment). Additionally, we assessed whether study participants and investigators were blinded to the treatment provided.

Statistical Methods

A random-effects model was used to combine data for all outcomes. For continuous variables weighted mean differences and their 95% confidence intervals (CIs) were calculated using RevMan 3.0 software.[18] For categorical variables weighted risk ratios (RRs) and 95% CIs were calculated.[19] For continuous measurements, a difference between treatment means and its correlated SE of the difference were calculated using the methods of Lau[19] and Laird and Mosteller.[20] Because studies did not report the SE of the difference between the means (*S repens* and control), analyses were carried out for 3 different assumed values of correlation (0.25, 0.50, 0.75). This approach was taken to test the sensitivity of the results to this unknown parameter. Because there were no statistically significant differences in the outcomes, according to the different correlation coefficients, we used SEMs calculated with a correlation coefficient of 0.50. χ^2 Tests were used for analysis of bivariate comparisons. To assess the percentage of patients having improvement in urologic symptoms, a modified intention-to-treat analysis was performed (ie, men who dropped out or were lost to follow-up were considered to have had worsening symptoms).[21] The denominator for the modified intention-to-treat analysis included the number randomized to treatment at baseline, and the numerator included the number completing the trial and showing improvement.

RESULTS

The combined search strategies identified 24 reports of trials; 18 met inclusion criteria.[22-39] Reasons for exclusion included duration unknown or less than 30 days (n = 2 trials)[40,41]; no clinical outcomes (examining enzyme or tissue effects (n = 3)[15,42,43]; and no indication of randomization (n = 1).[44] Main comparisons in the remaining studies were *S repens* alone vs placebo (n = 10); *S repens* in combination with other phytotherapeutic agents vs placebo (n = 3); *S repens* alone vs active control (n = 2); *S repens* vs another phytotherapeutic agent and vs placebo (n = 1); *S repens* in combination with other phytotherapeutic agents vs active control (n = 1); and *S repens* orally vs a rectal suppository form of *S repens*, a therapeutic bioequivalence study (n = 1). A total of 2939 participants were randomized in the 18 trials (1118 in trials of *S repens* alone or in combination vs placebo and 1821 in trials of *S repens* alone or in combination vs active control).

A description of the individual studies is available from the authors on request. The mean age of enrollees was 65 years (range, 40-88 years). The mean study duration was 9 weeks (range, 4-48 weeks). The percentage of men who dropped out

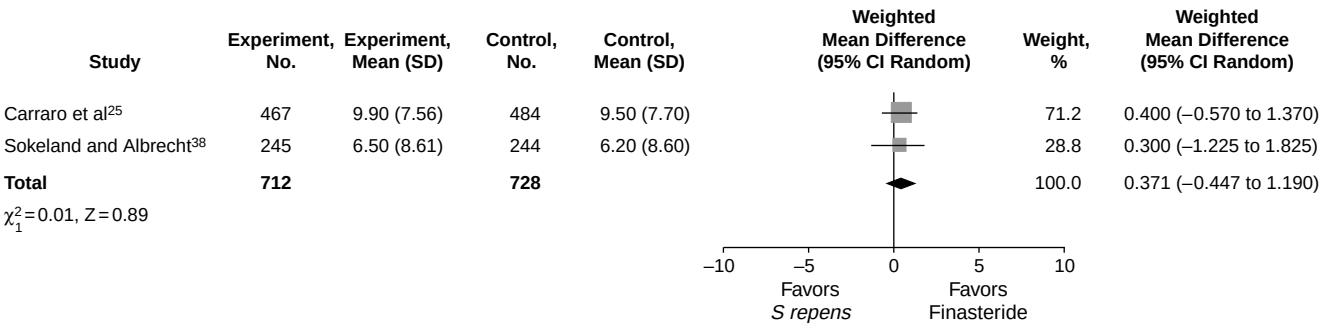

Figure 1.—Weighted mean differences in International Prostate Symptom Scale scores for men treated with *Serenoa repens* vs finasteride. CI indicates confidence interval.

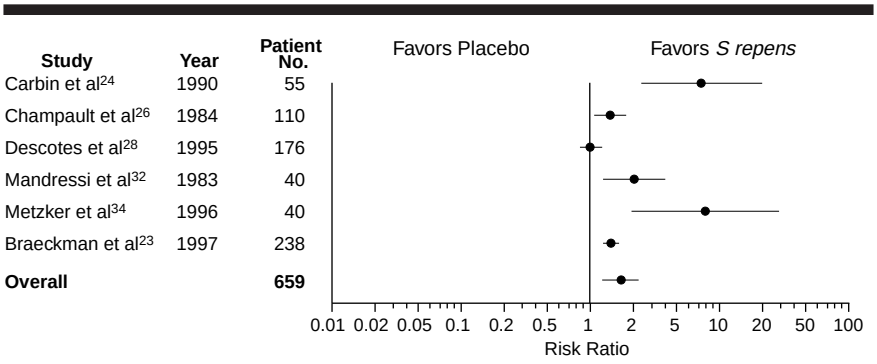

Figure 2.—Weighted risk ratios for self-rating of improvement in urinary tract symptoms for men treated with *Serenoa repens* vs placebo.

or were lost to follow-up was 9.6% (n = 283) and ranged from 4% to 15%. Treatment allocation concealment was adequate in 9 studies (50%) and 16 studies (89%) were double-blinded.

Baseline and outcome data from individual studies for urologic symptoms, nocturia, peak urine flow, and residual urine volume are available from the authors on request. These results indicate that on average, participating men had urinary tract symptoms and urinary flow measures consistent with moderate BPH. The mean (SD) baseline values for these variables did not differ by treatment group and included urologic symptom scale score (International Prostate Symptom Scale [IPSS]) in 2 studies with active control (14.4 [5.9] points; scale range, 0-35; moderate BPH symptoms, 8-19); urologic symptom scale score in 1 study with placebo (7.0 [2.8] points; scale range, 0-19, based on an addition of subscores for 6 variables: pollakiuria, nocturia, dysuria, hesitancy, urgency, and perineal heaviness); nocturia (2.5 [1.47] times per night; peak urine flow, 11.2 [3.9] mL/s; and residual urine volume, 55.8 [41.5] mL). Baseline values (SD) for mean urine flow (5.7 [2.1] mL/s) and prostate volume (43.9 [21.6] cc) also did not differ by treatment group. Symptom score results were reported in 10 studies, nocturia results in 12 studies, peak urine flow in 13 studies, and residual volume in 12 studies. Many studies did not report results in a method that permitted data to be combined in a meta-analysis.

Weighted Summary Differences in Outcomes

Urinary Tract Symptoms.—Summary treatment effect sizes were determined for *S repens* alone or in combination vs placebo and vs active controls. Results from participant and physician assessment indicated that *S repens* was superior to placebo and comparable with finasteride in improving urologic symptoms. The weighted mean difference for urinary symptom scale scores for *S repens* vs placebo was –1.41 points (scale range, 0-19) (28% absolute improvement vs placebo) (95% CI, –2.52 to –0.30) (n = 1 study) and vs finasteride was 0.37 IPSS points (scale range, 0-35) (37% absolute improvement from baseline for *S repens* vs 40% absolute improvement from baseline for finasteride) (95% CI, –0.45 to 1.19) (n = 2 studies) (Figure 1). The weighted mean difference for the combination preparation *Sabal-Urtica* vs placebo was –3.50 IPSS points (scale range, 0-35) (17% absolute improvement vs placebo) (95% CI, –6.75 to –0.25) (n = 1 study).

Participants and their physicians were both more likely to report improvement in symptoms in men treated with *S repens* than with placebo. The weighted RR for participant self-rating of improvement in urinary tract symptoms for *S repens* vs placebo was 1.72 (95% CI, 1.21-2.44) (n = 6 studies) (Figure 2). The weighted RR for physician rating of improved urologic symptoms for *S repens* vs placebo was 1.72 (95% CI, 1.11-2.65) (n = 3 studies). Overall, 242 (74%) of 329 men (6 studies) taking *S repens* reported an improvement of urologic symptoms compared with 168 (51%) of 330 men taking placebo ($P<.001$). Physician-assessed improvement of symptoms was reported in 165 (63%) of 262 men taking *S repens* and 101 (38%) of 262 men taking placebo ($P<.001$) (3 studies).

Serenoa repens reduced nocturia 25% (absolute difference) compared with placebo. The weighted mean difference was –0.76 times per evening vs placebo (95% CI, –1.21 to –0.32) (n = 10 studies) (Figure 3). *Serenoa repens* was comparable with active controls regarding nocturia. The weighted mean difference was –0.05 (95% CI, –0.49 to 0.39) (n = 1 study) vs finasteride and –0.20 (95% CI, –1.69 to 1.29) (n = 1 study) vs *Pygeum africanum*.

Urinary Flow Measures and Prostate Size.—*Serenoa repens* was superior to placebo and comparable with finasteride in improving peak and mean urine flow rates and residual urine volume. The weighted mean differences for peak urine flow were 1.93 mL/s vs placebo (24% absolute improvement vs placebo) (95% CI, 0.72-3.14) (n = 8 studies) (Figure 4), –0.74 mL/s vs finasteride (95% CI, –1.66 to 0.18) (n = 2 studies), 2.0 mL/s vs gestonorone caproate (95% CI, 1.36-2.64) (n = 1 study), and 1.6 mL/s for *Sabal-Urtica* vs placebo (95% CI, –0.67 to 3.87) (n = 1 study). The weighted mean differences for mean urine flow were 2.22 mL/s vs placebo (28% absolute improvement vs placebo) (95% CI, 1.17-3.27) (n = 4 studies) and –0.40 mL/s vs finasteride (95% CI, 0.15-0.95) (n = 1 study).

Study	Experiment, No.	Experiment, Mean (SD)	Control, No.	Control, Mean (SD)	Weighted Mean Difference (95% CI Random)	Weight, %	Weighted Mean Difference (95% CI Random)
Boccafoschi and Annoscia[22]	11	1.80 (2.01)	11	2.10 (1.79)		5.4	−0.300 (−1.891 to 1.291)
Carbin et al[24]	26	1.40 (1.02)	27	2.00 (1.04)		13.8	−0.600 (−1.155 to −0.045)
Champault et al[26]	47	1.70 (1.16)	41	2.70 (1.09)		14.6	−1.000 (−1.470 to −0.530)
Cukier et al[27]	43	2.20 (1.97)	47	2.90 (1.99)		11.0	−0.700 (−1.519 to 0.119)
Descotes et al[28]	82	1.40 (1.81)	94	1.50 (1.94)		13.8	−0.100 (−0.654 to 0.454)
Emili et al[29]	15	1.70 (1.90)	15	2.30 (1.90)		6.7	−0.600 (−1.960 to 0.760)
Mandressi et al[32]	20	1.70 (2.41)	20	3.10 (2.46)		5.8	−1.400 (−2.909 to 0.109)
Mattei et al[33]	19	1.50 (1.48)	19	4.00 (1.48)		9.8	−2.500 (−3.441 to −1.559)
Reece Smith et al[36]	33	1.90 (1.20)	37	1.90 (1.40)		13.2	0.000 (−0.609 to 0.609)
Tasca et al[39]	14	0.90 (2.02)	13	1.90 (1.99)		5.8	−1.000 (−2.513 to 0.513)
Total	**310**		**324**			100.0	−0.762 (−1.210 to −0.315)

$\chi^2_9 = 26.49$, $Z = 3.34$

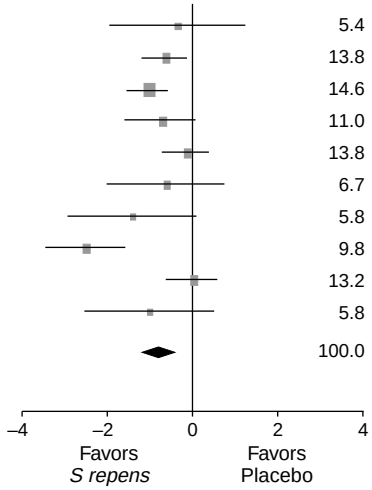

Figure 3.—Weighted means differences in nocturia for men treated with *Serenoa repens* vs placebo. CI indicates confidence interval.

Study	Experiment, No.	Experiment, Mean (SD)	Control, No.	Control, Mean (SD)	Weighted Mean Difference (95% CI Random)	Weight, %	Weighted Mean Difference (95% CI Random)
Boccafoschi and Annoscia[22]	11	13.70 (7.03)	11	12.20 (7.03)		4.1	1.500 (−4.375 to 7.375)
Braeckman et al[23]	106	13.20 (5.76)	99	12.20 (5.60)		45.1	1.000 (−0.555 to 2.555)
Champault et al[26]	46	16.10 (19.19)	39	10.60 (17.67)		2.3	5.500 (−2.343 to13.343)
Descotes et al[28]	82	15.30 (13.04)	94	13.50 (13.96)		8.7	1.800 (−2.191 to 5.791)
Emili et al[29]	15	13.70 (4.37)	15	9.40 (4.37)		13.8	4.300 (1.172 to 7.428)
Gabric and Miskic[30]	15	14.60 (5.57)	14	10.80 (5.39)		8.7	3.800 (−0.190 to 7.790)
Reece Smith et al[36]	33	8.50 (7.12)	37	8.60 (7.12)		12.2	−0.100 (−3.441 to 3.241)
Tasca et al[39]	14	16.20 (7.03)	13	11.80 (7.03)		5.0	4.400 (−0.907 to 9.707)
Total	**322**		**322**			100.0	1.932 (0.724 to 3.140)

$\chi^2_7 = 7.46$, $Z = 3.13$

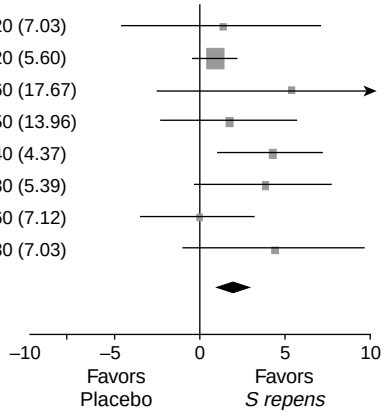

Figure 4.—Weighted mean differences in peak urinary flow rates for men treated with *Serenoa repens* vs placebo. CI indicates confidence interval.

For residual volume the weighted mean difference was −22.05 mL vs placebo (43% absolute decrease vs placebo) (95% CI, −40.78 to −3.32) (n = 6 studies) and 5.70 mL vs finasteride (95% CI, −5.42 to 16.82) (n = 1 study). *Serenoa repens* did not reduce prostate size; the weighted mean differences for prostate size were −2.14 cc (95% CI, −10.92 to 6.65) (n = 2 studies) vs placebo, and 4.08 cc (95% CI, 1.42-8.18) (n = 1 study) vs finasteride.

Adverse Effects

Adverse effects due to *S repens* were generally mild and comparable with placebo. Withdrawal rates were *S repens*, 9.1%; placebo, 7.0%; and finasteride, 11.2% ($P = .02$ for *S repens* vs placebo and $P = .87$ vs finasteride). Erectile dysfunction was reported in 1.1% of men taking *S repens*; placebo, 0.7%; and finasteride, 4.9% ($P = .58$ for *S repens* vs placebo and $P < .001$ vs finasteride). Gastrointestinal adverse effects were reported in 1.3% of men taking *S repens*, placebo, 0.9%; and finasteride, 1.5% ($P > .50$ vs placebo and finasteride).

COMMENT

This systematic review summarizes the evidence from randomized controlled trials regarding the efficacy and safety of extracts from the saw palmetto berry *S repens* in men with lower urinary tract symptoms attributable to BPH. The available data indicate that *S repens* (alone or in combination with other phytotherapeutic agents) improves urinary tract symptoms and urinary tract flow measures. Compared with placebo, *S repens* improved urinary tract symptoms by 28%, nocturia by 25%, peak urine flow by 24%, mean urine flow by 28%, and residual urine volume by 43%. Men taking *S repens* were nearly twice as likely to report improvement in symptoms than men taking placebo. When compared with finasteride, *S repens* provided similar responses in urologic symptoms and flow measures and was associated with a lower rate of erectile dysfunction.

Participant baseline characteristics regarding age, prostate volume, peak urine flow, and symptom scale scores were comparable with previous trials and meta-analyses involving pharmaco-

logical management of BPH.[45-48] Therefore, our results are generalizable. They did not substantially change when we restricted our analysis to studies that had adequate treatment allocation concealment (level 3) or were double-blinded. Furthermore, the treatment effect sizes with regard to symptom scale scores, peak and mean urinary flow, nocturia, and residual volume are considered clinically important and similar to effects reported with other pharmacological agents.[45-48]

METHODOLOGICAL ISSUES

Previous reviews of phytotherapy in the treatment of BPH were not structured systematic reviews or quantitative meta-analyses.[9,10] They included information from nonrandomized or uncontrolled studies and, therefore, may have overestimated treatment effectiveness. The number of randomized trials included in these previous studies was less than we identified. The inclusion of an EMBASE and Phytodok search identified 5 studies not listed in MEDLINE. If our search had been restricted to English-language journals, we would have missed 12 trials (67%).

Our results should be viewed with caution. Despite abstracting and analyzing 18 randomized trials that included nearly 3000 participants, many studies did not report outcomes data in a consistent fashion. Several did not report means and SDs making completion of a quantitative systematic review difficult. Funnel plot analysis for urinary tract symptoms comparing study weight with weighted mean difference revealed no publication bias.[49] Multiple attempts to contact the trialists enabled us to obtain information from additional studies.[50]

Only 3 studies reported results from standardized and validated urologic symptom scales.[25,34,38] One trial reported results from a scale that had not been standardized or validated.[23] All these studies were rated as having adequate treatment allocation concealment. Most studies were conducted prior to the development of validated urologic symptom scale scores. Results from these scales have been demonstrated to be the most valid and clinically relevant end points for assessing treatment effectiveness in men with mild to moderate symptoms of BPH.[3] Secondary outcomes were combined in only a minority of trials: mean urine flow (5 trials), peak urine flow (12 trials), residual volume (6 trials), nocturia (11 trials), and prostate size (3 trials). The treatment duration was short with only 2 studies having follow-up of at least 6 months' duration. Studies used different doses and preparations of *S repens* or were performed in combination with other phytotherapeutic compounds. The most frequently reported dosage was 160 mg of *S repens* twice per day.

Several statistical issues in combining the data in our analysis need to be mentioned. For the "self-rating of symptom improvement" outcome, there was significant heterogeneity in the treatment effects. Ideally, when significant heterogeneity of treatment effect is present, meta-regression should be explored to understand reasons for the differences. However, this was not possible here because of an insufficient number of studies and lack of standardized reporting of meaningful clinical covariates. Nonetheless, if an overall quantitative estimate is deemed to be useful, then a random-effects model that incorporates between-studies heterogeneity would be more appropriate as we have done. The random-effects model typically produces wider CIs compared with the fixed-effects model. Five of 6 studies[23,24,26,32,34] had significant treatment effects and the second largest study also had trends in the same direction, thus reducing the likelihood that the pooling produced a false-positive result.

Because of the high baseline response rate in the control groups and the wide range of the baseline rates of several studies, the choice of treatment effect metric used to combine outcomes may also affect the results. Compared with the pooled random-effects RR (RR, 1.71; 95% CI, 1.22-2.39), the pooled odds ratio (OR) is much higher (OR, 5.74; 95% CI, 2.14-15.35). The OR is frequently used to approximate the RR in the clinical trial setting. In this case, the high pooled OR creates a false impression that *S repens* is far more efficacious. We chose the more conservative metric provided by the RR in our analysis.

We were not able to determine if *S repens* prevented long-term complications of BPH, such as acute urinary retention or the need for surgical interventions. Previous studies have demonstrated that, in men with large prostates (ie, >40 cc) producing moderate to severe symptoms, finasteride is effective in relieving BPH symptoms and reducing the development of acute urinary retention and the need for surgical intervention.[45,46] However, fewer than one third of men with BPH have prostate glands more than 40 cc in size.[51] In men with "large prostates," the absolute rate of acute urinary retention or symptomatic progression requiring surgical intervention is less than 3% per year. In our review, the mean prostate volume in studies reporting prostate size was 44 cc. The available data did not allow us to determine if prostate volume was an important predictor of outcomes. Additionally, there were no reported studies comparing *S repens* with α-adrenergic blockers that met criteria. One study compared *S repens* with alfuzosin, but the duration of follow-up was only 3 weeks.[41]

The medication charges of *S repens* are less than other pharmacological therapies. A 90-day supply of saw palmetto berry (320 mg/d of *S repens*) is between $10 and $50. However, available dosages and preparations frequently vary from those used in the published trials. The pharmacy charges for a 90-day supply of finasteride or terazosin (5 mg/d) are approximately $200 and $120, respectively.[4]

Additional placebo-controlled trials are needed as well as studies that compare *S repens* with α-antagonists.[47,48] Future trials should be of sufficient size and duration to detect important differences in clinically relevant end points. At a minimum, these studies should assess and report the means and SDs at baseline and conclusion for the following variables: age, number enrolled and completing the study, standardized urologic symptom scale scores, mean and peak urine flow, voided volume, prostate size, residual urine volume, complications from BPH, need for subsequent therapy, and long-term adverse effects of *S repens*. Until then, this systematic review provides the most complete assessment regarding the efficacy and safety of *S repens* for treatment of symptomatic BPH.

In conclusion, the available evidence suggests that extracts from the saw palmetto plant, *S repens*, improve urinary tract symptoms and flow measures in men with BPH. Compared with finasteride, *S repens* produces similar improvements in urinary tract symptoms and flow measures, has fewer adverse treatment effects, and costs less. The long-term effectiveness and safety of *S repens* and its ability to prevent complications from BPH are not known.

This study was funded by the Department of Veterans Affairs Health Services Research and Development Service, Washington, DC.

We thank Maurizio Tiso, MS, Margaret Haugh, and Rich Crawford, MD, for their work in translating and abstracting data from the non–English-language studies.

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Table 1.—Description of Individual Studies*

Study	Details of Participants	Intervention	Follow-up Period, wk	Total Randomized (No. Dropped Out Following Randomization)	Quality of Concealment of Allocation	Double-blind Method
Boccafoschi and Annoscia[22]	Symptomatic BPH Not in need of surgery Age range, 54-79 y Mean age, 68.0 y	(1) *S repens*, 160 mg twice daily (Permixon) (2) Placebo	8.5	22 (0)	2	Yes
Braeckman et al[23]	Symptomatic BPH Peak urine flow of 5-15 mL/s (± 750 mL) Residual urine volume ≤60 mL Age range, 57-73 y Mean age, 65.0 y	(1) *S repens*, 160 mg twice daily (Serendar) (2) Placebo	12	238 (12)	3	Yes
Carbin et al[24]	BPH on the basis of history Acid phosphatase Prostate examination Age range, 51-72 y Mean age, 61.6 y	(1) *S serrulata* and *C pepo L*, 160 mg twice daily (Curbicin) (2) Placebo	12	55 (2)	3	Yes
Carraro et al[25]	BPH diagnosed by digital rectal examination International Prostate Symptom Score, >6 Maximum urinary flow 4-15 mL/s (urine volume ≥150 mL, post void residual <200 mL) Prostate size >25 mL PSA <10 ng/mL (prostates ≤60 mL) or 15 ng/mL (prostates >60 mL) Age range, 49-88 y Mean age, 64.5 y	(1) *S repens*, 160 mg plus placebo twice daily (Permixon) (2) Finasteride, 5 mg (Proscar) plus placebo (morning) and 2 placebos evening	26	1098 (147)	3	Yes
Champault et al[26]	Symptomatic BPH Age range, not reported Mean age, not reported	(1) *S repens*, 80 mg twice daily (PA109/Permixon) (2) Placebo	4	110 (16)	2	Yes
Cukier et al[27]	Men with BPH for whom surgery was not indicated (no mechanical or infectious complications). Age range, not reported Mean age, 69.0 y	(1) *S repens*, 160 mg twice daily (Permixon) (2) Placebo	10	168 (22)	3	Yes
Descotes et al[28]	Mild-moderate BPH Dysuria, daytime and nocturnal urinary frequency (>2 nocturnal micturitions, of at least 8 wk) Maximum urinary flow ≥5 mL/s Age range, not reported Mean age, 66.3 y	(1) *S repens*, 160 mg twice daily (Permixon) (2) Placebo	4	215 (39)	2	Yes
Emili et al[29]	Men with manageable BPH Age range, 44-78 y Mean age, not reported	(1) *S repens*, 160 mg twice daily (Permixon) (2) Placebo	4	30 (0)	2	Yes
Gabric and Miskic[30]	Mild-moderate BPH Age range, 40-82 y Mean age, not reported	(1) *S serrulata* and *U dioica* extracts, 20 drops 3 times daily (Prostagutt) (2) Placebo	6	30 (0)	2	Yes
Löbelenz[31]	Mild-moderate BPH Peak urine flow <20 mL/s Age range, 40-82 Mean age, not reported	(1) *S serrulata*, 100 mg 4 times daily (2) Placebo	6	60 (0)	3	Yes
Mandressi et al[32]	BPH diagnosed by digital rectal examination Age range, 50-80 y Mean age, not reported	(1) *S repens*, 320 mg 4 times daily (Permixon) (2) *P africanum* (3) Placebo	4	60 (0)	2	Yes
Mattei et al[33]	Manageable BPH Age range, 45-72 y Mean age, not reported	(1) *S repens*, 160 mg twice daily (Talso) (2) Placebo	13	40 (2)	2	Yes
Metzker et al[34]	Mild-moderate BPH Age range, 52-84 y Mean age, 65.5 y	(1) *S serrulata*, 160 mg , and *U dioica*, 120 mg extracts 1 capsule twice daily (Prostagutt) (2) Placebo	48	40 (3)	3	Yes
Pannunzio et al[35]	BPH without prior treatment Bladder residual volume <150 mL Age range, 44-78 y Mean age, not reported	(1) *S repens*, 160 mg twice daily (Permixon) (2) Gestonorone caproate, 200 mg (Depostat) intramuscularly 4 times per wk	8	60 (0)	2	No
Reece Smith et al[36]	Symptomatic BPH Age range, 55-80 y Mean age, 66.6 y	(1) *S repens*, 160 mg twice daily (Permixon) (2) Placebo	12	80 (10)	3	Yes

Table 1.—Description of Individual Studies* (cont)

Study	Details of Participants	Intervention	Follow-up Period, wk	Total Randomized (No. Dropped Out Following Randomization)	Quality of Concealment of Allocation	Double-blind Method
Roveda and Colombo[37]	Symptomatic BPH Age range, 55-76 y Mean age, 62.9 y	(1) *S repens*, 160 mg 4 times daily (2) *S repens*, 640 mg rectal capsule 4 times daily	4	30 (0)	3	No
Sokeland and Albrecht[38]	Mild-moderate BPH Age range, 50-88 y Mean age, not reported	(1) Sabal-Urtica-Extract, four times daily (PRO 160/120) (2) Finasteride, 5 mg plus placebo ("double-dummy design")	12	543 (54)†	3	Yes
Tasca et al[38]	Mild-moderate BPH Prostatic adenomas Age range, 49-81 y Mean age, 61.5 y	(1) *S repens*, 160 mg twice daily (PA109/Permixon) (2) Placebo	8	30 (3)	2	Yes

*BPH indicates benign prostatic hyperplasia; PSA, prostate-specific antigen.
†Data from 516 subjects were included in the adverse effects analysis and 489 subjects were included in the therapy effect analysis.

Table 2.—Summary of Outcome Data For Symptom Scores, Nocturia, Peak Urine Flow, and Residual Volume: *Serenoa repens* vs Control[a]

Study	Symptom Scores and Ratings (SD)		Nocturia, Times per Evening (SD)		Peak Urine Flow, mL/s (SD)		Residual Volume, mL (SD)	
	S repens	Control	*S repens*	Control	*S repens*	Control	*S repens*	Control
Boccafoschi and Annoscia[22]								
Baseline	. . .	4.0 . .		3.1	9.6	10.2	103.3	65.8
Follow-up	. . .	1.8 . .		2.1	13.7	12.2	55.0	36.6
Difference	. . .	−2.2 . .		−1.0 (*P* = >.50)	4.1	2.0 (*P*<.05)	−48.3	−29.2 (*P* = >.50)
Braeckman et al[23] [b]								
Baseline	7.5 (3.1)	6.6 (2.5)	. . .	. . .	10.4 (2.6)	11.0 (2.3)	33.0 (21.9)	32.1 (21.5)
Follow-up	3.7 (2.7)	5.1 (3.2)	. . .	. . .	13.2 (5.6)	12.2 (3.5)	22.7 (26.2)	24.0 (22.6)
Difference	−3.8	−1.5 (*P*<.01)	. . .	. . .	2.8	1.2 (*P* = >.50)	−10.3	−8.1 (*P* = >.50)
Carbin et al[24] [c]								
Baseline	. . .	1.9 (0.6)		2.1 (0.7)	. . .	. . .	135.0 (43.9)	127.6 (39.0)
Follow-up	. . .	1.4 (0.7)		2.0 (0.9)	. . .	. . .	92.5 (48.0)	120.0 (37.5)
Difference	85%	1[illegible]% (*P*<.001)		−0.1 (*P*<.01)	. . .	. . .	−42.5	−7.6 (*P*<.01)
Carraro et al[25] [d]								
Baseline	15.7 (5.9)	15.2 (5.7)		2.4 (1.4)	10.6 (2.8)	10.8 (3.1)	. . .	. . .
Follow-up	9.9 (5.4)	9.5 (5.5)		1.7	13.3 (6.7)	14.0 (7.4)	. . .	. . .
Difference	−5.8	−6.2 (*P* = .17)		−0.7 (*P* = >.50)	2.7	3.2 (*P* = .04)	. . .	. . .
Champault et al[26] [e]								
Baseline	. . .	3.1 (0.8)		3.2 (0.8)	10.7 (10.24)	10.1 (10.24)	94.7 (26.9)	91.3 (45.2)
Follow-up	. . .	1.7 (0.8)		2.7 (0.9)	16.1 (16.75)	10.6 (13.11)	55.1 (39.6)	100.0 (60.9)
Difference	88% 90%	68%[illegible] (*P*<.001) 36% (*P*<.001)		−0.5 (*P*<.001)	5.4	0.5 (*P*<.001)	−39.6	−8.7 (*P*<.001)
Cukier et al[27]								
Baseline	. . .	3.3 . .		3.4	. . .	. . .	110.7	103.3
Follow-up	. . .	2.2 . .		2.9	. . .	. . .	94.4	158.3
Difference	. . .	−1.1 . .		−0.5 (*P*<.001)	. . .	. . .	−16.3	55.0 (*P*<.05)
Descotes et al[28] [f]								
Baseline	. . .	2.1 (1.7)		1.8 (1.1)	11.8 (7.5)	12.4 (8.3)	. . .	. . .
Follow-up	. . .	1.4 (1.2)		1.5 (1.2)	15.3 (11.9)	13.5 (8.6)	. . .	. . .
Difference	71% 57%	6[illegible]% (*P* = >.50) 47% (*P* = >.50)		−0.3 (*P* = .03)	3.5	1.1 (*P* = .04)	. . .	. . .
Emili et al[29]								
Baseline	. . .	3.3 (1.7)		2.7 (1.4)	10.3 (3.4)	9.2 (2.6)	70.7 (41.1)	79.3 (55.8)
Follow-up	. . .	1.7 (1.0)		2.3 (1.1)	13.7 (3.6)	9.4 (2.7)	34.7 (26.4)	67.3 (47.9)
Difference	. . .	−1.7 . .		−0.3 (*P*<.05)	3.4	0.2 (*P*<.001)	−36.0	−12.0 (*P*<.05)
Gabric and Miskic[30] [g]								
Baseline	. . .	. . .	. . .	. . .	10.5 (3.1)	11.6 (3.5)	30.6 (22.3)	44.0 (18.0)
Follow-up	. . .	. . .	. . .	. . .	14.6 (4.5)	10.8 (4.0)	24.9 (20.0)	39.2 (33.0)
Difference	2.2	1.3 (*P*<.001)	. . .	. . .	4.1	−0.8 (*P* = .02)	−5.7	−4.8 (*P* = .27)
Löbelenz[31]								
Baseline	. . .	. . .	. . .	. . .	12.3	13.0	. . .	. . .
Follow-up	. . .	. . .	. . .	. . .	13.5	13.6	. . .	. . .
Difference	. . .	. . .	. . .	. . .	1.2	0.6 (*P* = >.50)	. . .	. . .
Mandressi et al[32] [h]								
Baseline	. . .	. . .	3.0	3.0 (Pbo) 3.0 (Pbo)	. . .	. . .	. . .	. . .
Follow-up	. . .	. . .	1.7	1.9 (Pa) 3.1 (Pbo)	. . .	. . .	. . .	. . .
Difference	90% 90%	63% (*P*<.05) 40% (*P*<.01)	−1.3	−1.1 0.1 (*P*<.05)	. . .	. . .	10% (*Sr*)	−4% (*Pa*) 0% (Pbo)
Mattei et al[33]								
Baseline	. . .	4.5 (0.7)		4.2 (0.8)	. . .	. . .	110.0 (105.0)	102.0 (110.0)
Follow-up	. . .	1.5 (1.3)		4.0 (1.1)	. . .	. . .	45.0 (87.0)	110.0 (101.0)
Difference	. . .	−3.0 . .		−0.2 (*P*<.01)	. . .	. . .	−65.0	8.0 (*P*<.01)
Metzker et al[34] [i]								
Baseline	18.6	19.0	. . .	. . .	14.4	15.0	25.5	26.0
Follow-up	9.8	13.3	. . .	. . .	19.1	17.5	17.0	22.5
Difference	−8.8	−5.7	. . .	. . .	4.7	2.5 (*P* = .03)	−8.5	−3.5 (*P* = >.50)
Pannunzio et al[35] [j]								
Baseline	. . .	. . .	. . .	. . .	6.9 (0.5)	7.8 (0.8)	. . .	. . .
Follow-up	. . .	. . .	. . .	. . .	12.0 (1.0)	10.0 (1.0)	. . .	. . .
Difference	. . .	57% . .		47% (*P* = >.50)	5.1	2.2 (*P*<.01)	. . .	. . .
Reece Smith et al[36] [k]								
Baseline	. . .	2.9 (1.2)		2.9 (1.4)	6.2	6.3	96.0	90.0
Follow-up	. . .	1.9 . .		1.9	8.5	8.6	112.0	109.0
Difference	All scores (*P*=1.0 >.50) All scores (*P* = >.50)			−1.0 (*P* = >.50)	2.3	2.3 (*P* = >.50)	16.0	19.0 (*P* = >.50)
Roveda and Colombo[37] [l]								
Baseline	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Follow-up	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Difference	O = 67%	RS = 77%	. . .	. . .	. . .	. . .	O = 67%	RS = 78% (*P* = >.50)

Table 2.—Summary of Outcome Data For Symptom Scores, Nocturia, Peak Urine Flow, and Residual Volume: *Serenoa repens* vs Control(cont)

Study	Symptom Scores and Ratings (SD)[b]		Nocturia, Times per Evening (SD)		Peak Urine Flow, mL/s (SD)		Residual Volume, mL (SD)	
	S repens	**Control**	***S repens***	**Control**	***S repens***	**Control**	***S repens***	**Control**
Sokeland and Albrecht[38] [d]								
Baseline	11.3 (6.5)	11.8 (6.6)	. . .	. . .	12.7 (4.4)	12.7 (4.5)	48.2	49.4
Follow-up	6.5 (5.8)	6.2 (5.2)	. . .	. . .	14.6 (6.4)	15.4 (6.8)	38.0	32.3
Difference	−4.8	−5.6 (*P* = .54)	. . .	. . .	1.9	2.7 (*P* = .19)	−10.2	−17.1
Tasca et al[39]								
Baseline	. . .	. . .	3.5	3.1	12.9	11.2	. . .	. . .
Follow-up	. . .	. . .	0.9	1.9	16.2	11.8	. . .	. . .
Difference	. . .	. . .	−2.6	−1.2 (*P* = >.50)	3.3	0.6 (*P*<.05)	. . .	. . .

[a]All *P* values are for *S repens*; vs control. Not all studies provided SDs. Ellipses indicate data not available.
[b]Scal is not identified.
[c]Percentage of patients who are self-rating their improvement.
[d]Outcomes vs finasteride. The score is based on the International Prostate Symptom Scale.
[e]For the *S repens* group, 88% of patients self-rated their improvement, while of physicians rated that 90% of the patients improved. For the control group, 68% of patients self-rated improvement, while physicians rated that 36% of the patients improved.
[f]For the *S repens* group, 71% of patients self-rated their improvement, while physicians rated that 57% of the patients improved. For the control group, 68% of patients self-rated their improvement, while of physicians rated that 47% of the patients improved.
[g]Physician rating score was based on a 3-level scale: 1, no success, to 3, most success.
[h]Symptoms and rating outcome data are for *S repens* vs *Pygeum africanum* (Pa). For the Sr group, 90% of patients self-rated improvement, while physicians rated that 90% of the patients improved. For the Pa group, 63% of patients self-rated improvement, while physicians rated that 40% of the patients improved. Residual volume is measured as the percent decrease. For the Sr group, the decrease in residual volume is 10%; for the Pa group, −4% (residual volume increased); and for the placebo (Pbo) group, 0%.
[i]The score is based on the International Prostate Symptom Scale.
[j]Outcomes vs gestonorone caproate vs active control. For the nocturia outcome data, the *S repens* group reported a 57% decrease, while the gestonorone caproate group reported a 57% decrease.
[k]Mean score for all 9 symptoms. For both groups, patient self-reported scores, and the physician rated scores.
[l]*Serenoa repens* administered as oral capsules (O) vs *S repens* administered as rectal suppositories (RS). For the O group, 67% of the patients self-rated their improvement, while 77% who received RS self-rated improvement. Residual volume outcome data are the percentage of those who indicated improvement based on improvement scores with a range of 0 to 4. For the O group, 67% improved, while 78% receiving RS improved.

parent groups, school boards, and local officials to develop legislation requiring chlamydia screening for entry into each year of high school.

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2. Howell MR, Quinn TC, Brathwaite W, Gaydos CA. Screening women for *Chlamydia trachomatis* in family planning clinics. *Sex Transm Dis*. 1998;25:108-117.

In Reply: Choice of treatment regimen, either doxycycline, 100 mg twice daily for 7 days, or a 1-g dose of azithromycin, was based on local clinic policy, which reflects standard treatment in most clinic settings serving adolescents at risk. We agree that analyzing our data on repeat chlamydia infections by treatment modality or compliance or both may have provided interesting information on efficacy. Although data on treatment regimen were not collected in our study, 2 recent reports compared the efficacy of doxycycline vs azithromycin and found them to be comparable, with treatment failures of less than 5% at 2 to 4 weeks after therapy.[1,2] Therefore, we do not believe differentiation of results by treatment regimen or reported patient compliance would have altered our findings.

Although our study population was homogeneous and Baltimore is known to have high sexually transmitted disease rates, we believe sufficient evidence exists supporting our recommendation of chlamydia screening every 6 months for sexually active adolescent females. Chlamydia screening in most adolescent female populations yields prevalences of more than 10%, except in areas with long-standing chlamydia control programs such as the Pacific Northwest.[3-6] Dr Klausner presents recommendations based on prevalence rates calculated with small numbers of patients and does not provide information on frequency of infection or reinfection. Our recommendation is based on incidence rates calculated from prospective data collected over 33 months on 3202 adolescent females.

Klausner advocates for screening practices to be dictated by local disease prevalences. We agree in concept. However, the chlamydia burden in other parts of the country has not been well described, and most health care infrastructures currently do not have the resources, technology, or impetus to generate these data. In addition, many chlamydia prevalence rates are determined with less-sensitive tests than were used in our study and may underestimate the disease burden.[3]

Wherever we look for chlamydia we find it, especially among adolescents.[3-6] Since chlamydia is mostly an asymptomatic infection with serious consequences, as Klausner points out, and since the risk of pelvic inflammatory disease and its sequelae increases with the duration of untreated infection, we feel it is cavalier to assume without supporting evidence that chlamydia is not a problem in any given adolescent population. Therefore, we recommend screening all sexually active adolescent females for chlamydia infection, regardless of history or symptoms, until evidence to the contrary is generated.

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3. Schacter J. *Chlamydia trachomatis*: the more you look, the more you find–how much is there? *Sex Transm Dis*. 1998;25:229-231.
4. Division of STD Prevention. *Sexually Transmitted Disease Surveillance, 1996*. Atlanta, Ga: Centers for Disease Control and Prevention; 1997.
5. Winter L, Goldy AS, Baer C. Prevalence and epidemiologic correlates of *Chlamydia trachomatis* in rural and urban populations. *Sex Transm Dis*. 1990;17:30-36.
6. Fisher M, Swenson PD, Risucci D, Kaplan MH. *Chlamydia trachomatis* in suburban adolescents. *J Pediatr*. 1987;111:617-620.

CORRECTION

Errors in Figures: In the Review entitled "Saw Palmetto Extracts for Treatment of Benign Prostatic Hyperplasia: A Systematic Review," published in the November 11, 1998, issue of THE JOURNAL (1998;280:1604-1609), there were several errors in the figures. In the column headings for Figures 1, 3, and 4, the word "expected" should have read "experiment." In Figure 2, the number of patients for Braeckman et al should have been 238, bringing the overall total to 659 patients. In Figure 4, the overall confidence interval for peak urinary flow should have read 0.724, not –0.724.

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