Effect of Increasing Doses of Saw Palmetto Extract on Lower Urinary Tract Symptoms

A Randomized Trial

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Context Saw palmetto fruit extracts are widely used for treating lower urinary tract symptoms attributed to benign prostatic hyperplasia (BPH); however, recent clinical trials have questioned their efficacy, at least at standard doses (320 mg/d).

Objective To determine the effect of saw palmetto extract (*Serenoa repens*, from saw palmetto berries) at up to 3 times the standard dose on lower urinary tract symptoms attributed to BPH.

Design, Setting, and Participants A double-blind, multicenter, placebo-controlled randomized trial at 11 North American clinical sites conducted between June 5, 2008, and October 10, 2010, of 369 men aged 45 years or older, with a peak urinary flow rate of at least 4 mL/s, an American Urological Association Symptom Index (AUASI) score of between 8 and 24 at 2 screening visits, and no exclusions.

Interventions One, 2, and then 3 doses (320 mg/d) of saw palmetto extract or placebo, with dose increases at 24 and 48 weeks.

Main Outcome Measures Difference in AUASI score between baseline and 72 weeks. Secondary outcomes included measures of urinary bother, nocturia, peak uroflow, postvoid residual volume, prostate-specific antigen level, participants' global assessments, and indices of sexual function, continence, sleep quality, and prostatitis symptoms.

Results Between baseline and 72 weeks, mean AUASI scores decreased from 14.42 to 12.22 points (–2.20 points; 95% CI, –3.04 to –0.36) with saw palmetto extract and from 14.69 to 11.70 points (–2.99 points; 95% CI, –3.81 to –2.17) with placebo. The group mean difference in AUASI score change from baseline to 72 weeks between the saw palmetto extract and placebo groups was 0.79 points favoring placebo (upper bound of the 1-sided 95% CI most favorable to saw palmetto extract was 1.77 points, 1-sided $P = .91$). Saw palmetto extract was no more effective than placebo for any secondary outcome. No clearly attributable adverse effects were identified.

Conclusion Increasing doses of a saw palmetto fruit extract did not reduce lower urinary tract symptoms more than placebo.

Trial Registration clinicaltrials.gov Identifier: NCT00603304

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BENIGN PROSTATIC HYPERPLASIA (BPH) is a common cause of bothersome lower urinary tract symptoms (LUTS) among older men[1] and may be treated with medications, minimally invasive therapies, or surgery.[2,3] Plant extracts are also widely used for LUTS in the United States and Europe.[4] The most common are extracts of the fruit of the saw palmetto dwarf palm tree. In a 2007 US survey, 17.7% of adults reported use of a natural product in the last 30 days and 5.1% of users had taken saw palmetto[5]; undoubtedly, the frequency would be higher among older men. A variety of mechanisms for saw palmetto have been proposed including anti-androgenic, anti-inflammatory, and antiproliferative effects, but none have been conclusively proven.[6-9]

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In a 2002 Cochrane meta-analysis[10] of the efficacy of saw palmetto extracts for men with LUTS attributed to BPH, 21 clinical trials were identified. Compared with placebo, saw palmetto significantly reduced nocturia, increased self-rated improvement, and improved peak uroflow.[10] Adverse effects were infrequent.

However, subsequent more rigorous trials have yielded less positive results. In 2009, an updated Cochrane review[11] identified 9 new trials. Although the effect on nocturia remained significant, there was no significant effect on American Urological Association Symptom Index (AUASI) scores or peak uroflow.[11] The most common dose was 160 mg twice daily.

The largest trial was the Saw Palmetto Treatment for Enlarged Prostates (STEP) study.[12] Two hundred twenty-five men aged 50 years or older with baseline AUASI scores of 8 or higher were randomized at 1 center to saw palmetto extract (160 mg twice daily) or placebo. No improvement over placebo was found over 1 year in symptom scores or any secondary end points.[12] No important toxicity was observed.[13]

Following publication of the STEP study, we conducted a randomized clinical trial to determine if a standard daily dose of saw palmetto extract increased to a double and then a triple daily dose over 72 weeks would improve LUTS attributed to BPH.[14]

METHODS

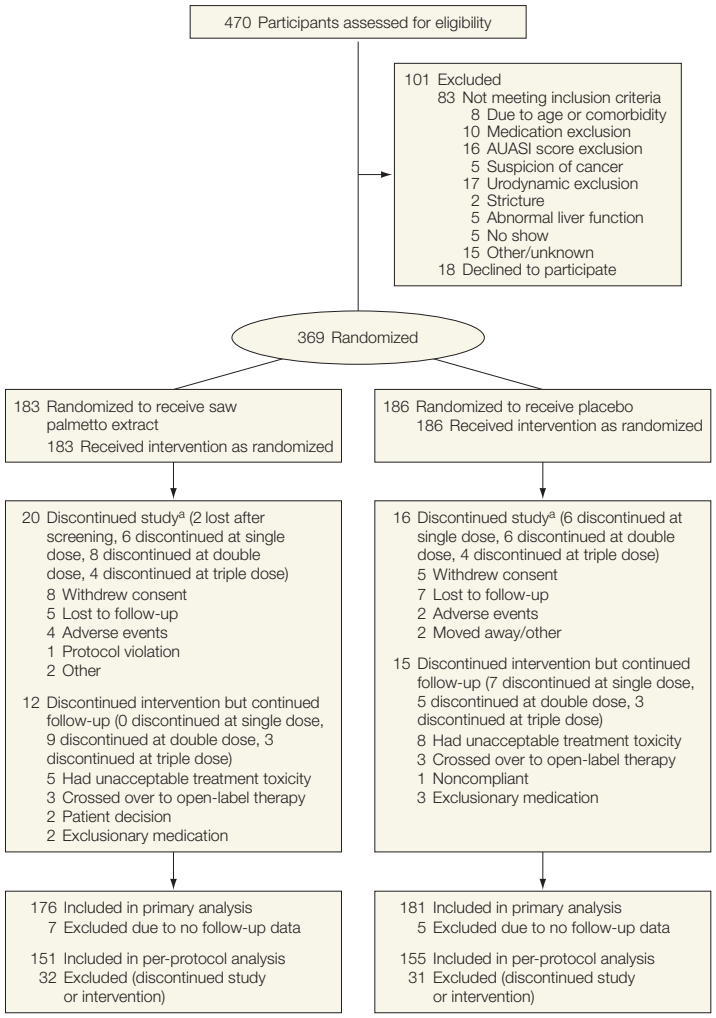
Trial Design

Our study was a double-blind, multicenter, placebo-controlled randomized trial of increasing doses of saw palmetto fruit extract. Enrollment began on June 5, 2008, with follow-up complete on October 10, 2010 (FIGURE 1).

Participants

We purposefully recruited a broad spectrum of men into the trial, because in the United States men do not need an evaluation by a health care professional or a prescription to buy and take a saw palmetto extract for LUTS. Men were eligible for enrollment if they were aged 45 years or older, had a peak uroflow rate of at least 4 mL/s, an AUASI score of between 8 and 24 at 2 screening visits, and signed written informed consent. Men were ineligible if they had prior invasive treatment for BPH; recent treatment with an α blocker (within 1 month), 5α-reductase inhibitor (within 3 months), or phytotherapy including saw palmetto extract (within 3 months); recent treatment with other medications affecting LUTS; creatinine level higher than 2.0 mg/dL (to convert to μmol/L, multiply by 88.4); liver function test results more than 3 times normal; coagulopathy or anticoagulation; recent unstable medical conditions; neurological conditions affecting urination; recent prostatitis or repeated urinary tract infections; prostate or bladder cancer or a prostate-specific antigen (PSA) level of more than 10 μg/L; recent or planned genitourinary instrumentation; severe incontinence; recent diuretic initiation or dose change; or medical conditions likely to prevent completion.[14] Participants were nonpaid volunteers recruited at 11 North American sites (California, Colorado, Connecticut,

Figure 1. CONSORT Diagram for the Trial



AUASI indicates American Urological Association Symptom Index.
[a] Seven participants in the saw palmetto extract group and 5 participants in the placebo group who discontinued the protocol provided no follow-up data.

Illinois, Iowa, Maryland, Missouri, New York [2 sites], Texas, and Ontario, Canada); the study was approved by each site's and the data coordinating center's institutional review boards. An independent data and safety monitoring board established by the National Institutes of Health periodically reviewed the progress and safety of the study.

Interventions

Participants were randomly assigned equally to receive 1, 2, and then 3 chocolate-colored gelcaps (320 mg/d) containing a standardized saw palmetto fruit extract with dose escalations at 24 and 48 weeks, or an identical number of placebo gelcaps escalated similarly. The 2 batches of saw palmetto extract used were standardized to a reference chromatogram (with 85%-95% fatty acids as marker substances), 30 mg of glycerol, 25 mg of sorbitol, 10 mg of purified water, and 90 mg of gelatin. The placebo contained 375 mg of polyethylene glycol, 25 mg of glycerol, and 75 mg of gelatin (matched weight of 475 mg). Participants were asked to take the gelcaps together at a convenient time. Participants with unacceptable adverse effects could split the dose or be maintained with lower doses. The phytotherapy used in this trial was a proprietary lipidic ethanolic extract of ripe, dried saw palmetto berries, *Serenoa repens* (W. Bartram) Small (Arecaceae), manufactured by Rottapharm/Madaus, Cologne, Germany, and sold as PROSTA-URGENIN UNO capsules (eAppendix, available at http://www.jama.com). Identification, extraction, and phytochemical content are described in the saw palmetto extract monograph published in USP33-NF28 S1 Reissue.[15]

Main Outcome Measures

The primary outcome measure was the change in AUASI score from baseline to 72 weeks. The AUASI is a self-administered 7-item index assessing frequency of LUTS (range, 0-35 points).[16] Secondary analyses on the AUASI were a comparison of the proportion of participants achieving a 3-point score decrease and a repeated measures analysis of scores over time. Secondary outcome measures included participants' global assessments of improvement and satisfaction at the end of the study (both Likert scales), as well as change from baseline to 72 weeks in the BPH Impact Index,[17] the quality of life item from the International Prostate Symptom Score,[18] the nocturia item from the AUASI,[16] peak uroflow, postvoid residual volume, PSA level, indices of erectile and ejaculatory function,[19,20] the International Continence Society male Incontinence Scale (ICSmaleIS),[21] the Jenkins Sleep Dysfunction Scale,[22] and the National Institutes of Health Chronic Prostatitis Symptom Index.[23] All questionnaires were available in English and Spanish.

Participants were observed at baseline and 12, 24, 36, 48, 60, and 72 weeks for outcome assessments. Participants were assessed for adverse effects, including blood cell counts, basic blood chemistries, coagulation tests, electrocardiograms, and urinalyses 4 weeks after each dose increase and at end of study (including a query about adverse effects occurring within 30 days of treatment discontinuation). Adherence was estimated by pill counts at each visit and attendance at protocol-specified visits was tracked.

Sample Size

To detect a hypothetical 2-point group mean difference in AUASI score change between saw palmetto extract and placebo groups with a 2-sample *t* test at a 1-sided significance level of .05 assuming a common SD of 6 points, a sample size of 157 participants per group was estimated to provide 90% power. A 2-point difference approximates the mean drop in AUASI score among men with baseline scores of 8 to 19 points who report "slight" improvement.[24] To allow for 10% dropouts, a total sample size of 350 participants was planned. During recruitment, the sample size was increased to 369 to allow for dilution of any therapeutic effect among participants unable to take the triple dose. Given that the clinical implications for use of the extract in the "real world" would be the same whether it proved no better or worse than placebo, an a priori decision was made to use 1-sided statistical testing.[25]

Randomization

Randomization was performed centrally using an Internet-accessible, password-protected, computer-based system that generated group assignments. Randomization was stratified by baseline AUASI score (8-15 or 16-24 points) and clinical center with randomly permuted blocks in each stratum.

Blinding

Study staff and participants were blinded to treatment assignment. Because of a mild odor of the saw palmetto extract, gelcaps were blister packaged to avoid unblinding during adherence assessments. To test the blindness, participants were asked to guess their treatment assignment at the end of the study.

Statistical Methods

The treatment groups were compared with respect to demographic and baseline measures using Pearson χ^2 test, *t* test for independent samples, and Wilcoxon rank sum test. The primary analysis was based on the modified intention-to-treat population that included all eligible participants who took at least 1 dose of study drug and had at least 1 follow-up assessment. For participants who discontinued before 72 weeks, multiple imputations were used to estimate their AUASI score at week 72 and other secondary outcome measures. There were 23 participants (12 in the saw palmetto extract group and 11 in the placebo group) who had all secondary outcome measures for week 72 imputed. For an additional 14 participants (4 in the saw palmetto extract group and 10 in the placebo group), 1 to 2 secondary outcomes at week 72 were imputed. At baseline, secondary measures were missing for 7 participants (2 in the saw palmetto extract group and 5 in the placebo group)

and were estimated using multiple imputation. Baseline measures for AUASI were obtained from all participants.

Results of the modified intention-to-treat analysis were confirmed in the per-protocol population, which included all participants who received treatment for 72 weeks. An unpaired *t* test was used to compare the 2 treatment groups with respect to change in AUASI score from baseline to 72 weeks, using 1-sided $P \leq .05$ as the threshold for statistical significance. Prespecified secondary analyses on the primary outcome included a comparison of the proportion of participants achieving at least a 3-point AUASI score decrease at 72 weeks using Fisher exact test, and a mixed models repeated measures analysis comparing change in AUASI scores from baseline between the 2 groups over time. A single prespecified subgroup analysis was based on participants' self-reported race/ethnicity; post hoc subgroup analyses were also conducted by dichotomizing baseline age, AUASI score, BPH Impact Index score, peak uroflow, postvoid residual volume, and PSA level at the medians of their distributions; and education was dichotomized as college graduate or less. The interaction term of the 2-way analysis of variance was used to determine the effect of subgroups on the primary outcome measure. Statistical testing in secondary analyses was not adjusted for multiple comparisons to avoid sacrificing sensitivity for specificity. Analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

To explore for any dose-response, the changes in AUASI score between baseline and 24 weeks, 24 and 48 weeks, and 48 and 72 weeks were compared, with plans to use the Hochberg step-up method to deal with multiple comparisons, if necessary. Secondary outcome measures were assessed using 2-sample *t* tests with 1-sided .05 significance levels. Rates of occurrence of adverse events and abnormal laboratory values were estimated using the Poisson distribution and compared using a normal approximation.

RESULTS

A total of 1032 men were interested and prescreened, usually by telephone, and preliminarily eligible men were invited to a screening visit.[26] Figure 1 provides a CONSORT diagram for the 470 men attending a first screening visit. A total of 369 men were randomized, between 19 and 52 men per site. TABLE 1 compares the baseline characteristics of the 357 participants randomized and included in the modified intention-to-treat analysis. Participants had a mean (SD) age of 61 (8.4) years and were predominantly well-educated non-Hispanic white men, with a mean (SD) AUASI score of 14.6 (4.5) points.

Adherence with scheduled visits excluding visits after dropouts was 97.0%. Median pill count across attended visits was 98.2%. Of the 306 participants who completed 72 weeks of treatment, all were successfully increased to triple dose and included in the per-protocol analysis. At the end of the study, out of participants randomized

Table 1. Baseline Characteristics of Participants Included in the Modified Intention-to-Treat Analysis[a]

Characteristics	Total Score Range	Participants			*P* Value
		Total (N = 357)	Saw Palmetto Extract (n = 176)	Placebo (n = 181)	
Age, y		60.97 (8.40)	61.25 (8.72)	60.7 (8.08)	.54
Race/ethnicity, No. (%)					
Non-Hispanic white		284 (79.6)	145 (82.4)	139 (76.8)	.42
Black		41 (11.5)	17 (9.7)	24 (13.3)	
Hispanic, Latino, or other[b]		32 (9.0)	14 (8.0)	18 (9.9)	
Education, No. (%)					
<High school		13 (3.6)	6 (3.4)	7 (3.9)	.64[c]
High school graduate		38 (10.6)	20 (11.4)	18 (9.9)	
Some college		60 (16.8)	26 (14.8)	34 (18.8)	
College graduate		99 (27.7)	48 (27.3)	51 (28.2)	
Postcollege		142 (39.8)	75 (42.6)	67 (37.0)	
No response		5 (1.4)	1 (0.6)	4 (2.2)	
AUASI score	8-24	14.55 (4.52)	14.42 (4.29)	14.69 (4.75)	.58
BPH Impact Index score	0-13	3.55 (2.51)	3.39 (2.24)	3.71 (2.72)	.30
IPSS QOL score	0-6	3.21 (1.20)	3.2 (1.2)	3.23 (1.21)	.83
AUA nocturia item	0-5	2.17 (1.11)	2.09 (1.08)	2.26 (1.13)	.14
Peak uroflow, mL/s		14.90 (6.92)	15.03 (7.15)	14.78 (6.71)	.74
Postvoid residual, median (IQR), mL		41.0 (13.0-90.0)	37.5 (13.5-88.0)	43.0 (12.0-92.0)	.88
PSA level, ng/mL		2.07 (1.78)	2.20 (1.95)	1.93 (1.59)	.16
IIEF scale[d]	1-30	19.38 (9.87)	18.79 (10.36)	19.93 (9.43)	.29
MSHQ-EjD scale[d]	1-20	10.87 (4.16)	10.56 (4.27)	11.18 (4.03)	.16
ICSmaleIS score[d]	0-24	3.81 (2.75)	3.44 (2.3)	4.17 (3.08)	.01
Jenkins Sleep Dysfunction Scale score	0-20	7.36 (4.62)	6.95 (4.28)	7.72 (4.93)	.11
NIH CPSI					
Pain scale, median (IQR)	0-21	0 (0-2)	0 (0-2)	0 (0-30)	.17
Urinary symptom scale	0-10	4.15 (2.20)	4.02 (2.31)	4.27 (2.08)	.28
QOL scale	0-12	4.51 (2.13)	4.45 (2.00)	4.57 (2.24)	.61

Abbreviations: AUASI, American Urological Association Symptom Index; BPH, benign prostatic hyperplasia; ICSmaleIS, International Continence Society male Incontinence Scale; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; IQR, interquartile range; MSHQ-EjD, Male Sexual Health Questionnaire-Ejaculatory Dysfunction; NIH CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; PSA, prostate-specific antigen; QOL, quality of life.

[a] Data are presented as mean (SD) unless otherwise specified. For all scales except as noted, higher scores indicate greater dysfunction (*P* values from 2-sample *t* tests).

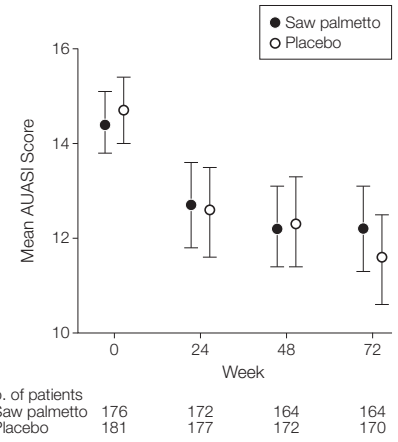
[b] Other included American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, or unknown or not reported.

[c] *P* value based on Wilcoxon rank sum test.

[d] Higher scores on these scales indicate less dysfunction.

to saw palmetto extract who were still taking study drug and responded, 45 of 149 (30.2%) thought they were taking saw palmetto extract, 67 of 149 (45.0%) thought they were taking placebo, and 37 of 149 (24.8%) said they were not sure. Of similar participants randomized to placebo, 66 of 154 (42.9%) thought they were taking placebo, 39 of 154 (25.3%) thought they were taking saw palmetto extract, and 49 of 154 (31.8%) said they were not sure. The responses were not significantly different from each other ($P = .36$).

Figure 2. Mean AUASI Scores for Saw Palmetto and Placebo Groups From Baseline to 72 Weeks



AUASI indicates American Urological Association Symptom Index. Error bars indicate 95% CI.

FIGURE 2 shows the mean AUASI scores during follow-up and TABLE 2 shows the group mean changes in AUASI scores between baseline and 72 weeks. The AUASI score decreased a mean of 2.20 points with saw palmetto extract and 2.99 points with placebo, a group mean difference of 0.79 points favoring placebo (upper bound of the 1-sided 95% CI most favorable to saw palmetto extract was 1.77 points, 1-sided $P = .91$). The per-protocol analysis comparing the mean decrease in AUASI score among 151 participants taking saw palmetto extract with 155 participants taking placebo who completed 72 weeks on triple dose yielded a group mean difference of 0.82 points favoring placebo (upper bound of the 1-sided 95% CI most favorable to saw palmetto extract was 1.91 points, 1-sided $P = .89$). The proportion of participants achieving a 3-point decrease in AUASI score at 72 weeks was 42.6% in the saw palmetto extract group and 44.2% in the placebo group (1-sided Fisher exact test, $P = .66$). The results of the mixed models repeated measures analysis showed no greater improvement with saw palmetto extract vs placebo ($P = .22$). In addition, the analysis of dose response also showed no greater improvement with saw palmetto extract vs placebo at any dose level. Saw palmetto extract was no better than placebo for any secondary outcome (Table 2).

FIGURE 3 shows the group mean difference in AUASI score decrease by treatment group stratified by race/ethnicity, as well as the exploratory subgroup analyses for other baseline parameters. These analyses did not reveal any subgroup with a clinically important differential response to saw palmetto extract compared with placebo. At week 72, the 2 subjective assessment measures did not differ significantly between the 2 treatment groups. Participant assessments of urinary symptoms compared with baseline averaged 3.6 and 3.5 for saw palmetto extract and placebo groups, respectively, which is between "a little bet-

Table 2. Change in Primary and Secondary Outcome Measures Between Baseline and Week 72

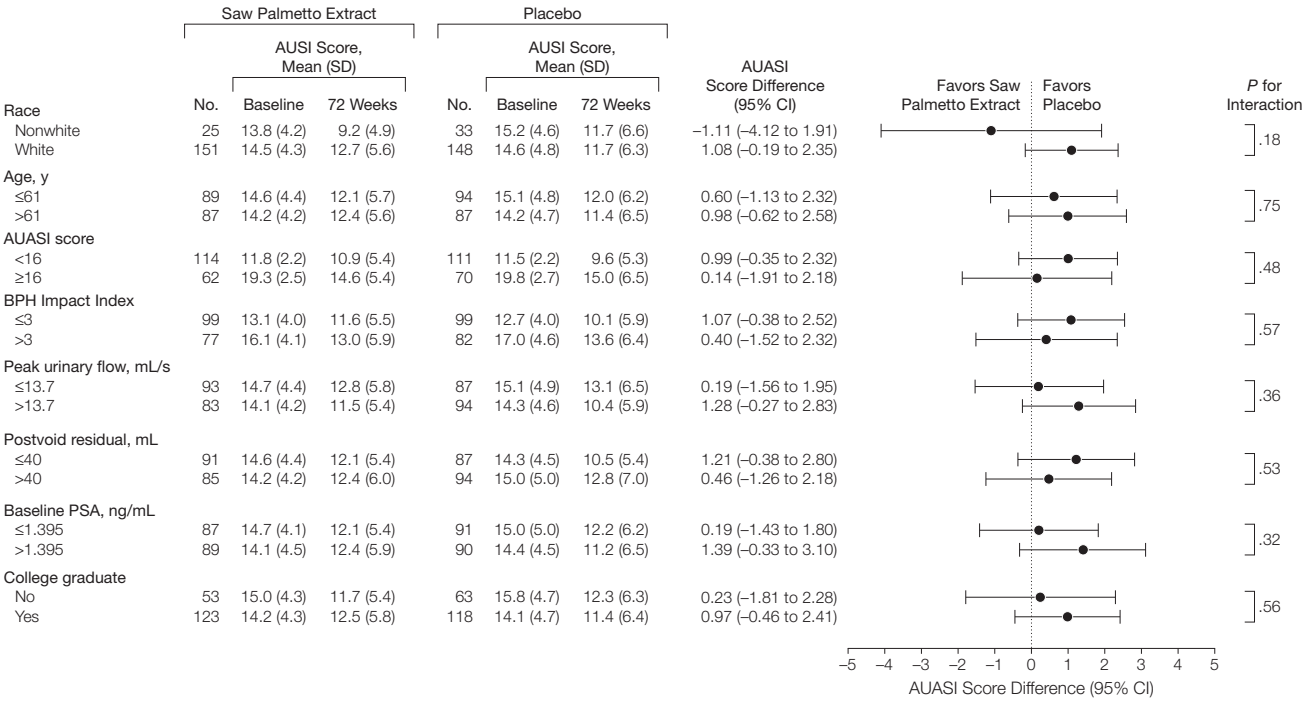
	Saw Palmetto Extract (n = 176)			Placebo (n = 181)			
Outcome Measure	Baseline Mean	Week 72 Mean	Mean Difference (95% CI)	Baseline Mean	Week 72 Mean	Mean Difference (95% CI)	1-Sided *P* Value
Primary							
AUASI score	14.42	12.22	–2.20 (–3.04 to –0.36)	14.69	11.70	–2.99 (–3.81 to –2.17)	.91
Secondary							
BPH Impact Index	3.43	2.62	–0.81 (–1.16. to –0.46)	3.70	2.47	–1.23 (–1.60 to –0.87)	.95
AUASI QOL	3.20	2.86	–0.34 (–0.52 to –0.16)	3.23	2.74	–0.49 (–0.67 to –0.31)	.87
AUA Nocturia	2.09	1.84	–0.36 (–0.72 to 0)	2.26	1.78	–0.15 (–0.44 to 0.13)	.19
Peak flow rate, mL/s	15.03	14.84	–0.18 (–1.07 to 0.70)	14.78	13.99	–0.79 (–1.58 to 0)	.84
Postvoid residual, mL[a]	37.5	44.5	4.78 (–30.00 to 52.00)	43.00	42.00	1.17 (–33.00 to 34.00)	.31[a]
PSA level, ng/ml	2.20	2.41	0.32 (–0.08 to 0.73)	1.93	2.07	–0.19 (–0.53 to 0.14)	.97
IIEF scale	18.81	18.29	–0.52 (–1.63 to 0.59)	19.92	18.86	–1.06 (–2.11 to –0.02)	.76
MSHQ-EjD scale	10.56	10.18	–0.38 (–1.04 to 0.28)	11.18	11.09	–0.09 (0.63 to 0.45)	.25
ICS male incontinence scale score	3.44	2.96	–0.48 (–0.80 to –0.16)	4.17	3.32	–0.84 (–1.17 to –0.51)	.94
Jenkins Sleep Dysfuction Scale score	6.96	6.15	–0.80 (–1.34 to –0.27)	7.75	6.12	–1.63 (–2.25 to –1.01)	.98
NIH CPSI							
Pain scale[a]	0	0	0 (–0.08 to 0)	0	0	0 (–1.00 to 0)	.20[a]
Urinary symptom scale	4.02	3.67	–0.35 (–0.67 to –0.03)	4.27	3.41	–0.86 (–1.22 to –0.49)	.98
QOL scale	4.45	3.61	–0.85 (–1.16 to –0.53)	4.57	3.49	–1.08 (–1.39 to –0.77)	.85

Abbreviations: AUASI, American Urological Association Symptom Index; BPH, benign prostatic hyperplasia; ICS, International Continence Society; IIEF, International Index of Erectile Function; MSHQ-EjD, Male Sexual Health Questionnaire-Ejaculatory Dysfunction; NIH CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; PSA, prostate-specific antigen; QOL, quality of life.
[a]Median (interquartile range) are shown; *P* value based on Wilcoxon rank sum test.

ter" and "about the same." Satisfaction with current status of urinary symptoms averaged 3.1 and 3.0 for saw palmetto extract and placebo groups, respectively, which corresponds with "neither satisfied nor dissatisfied."

TABLE 3 presents the number of adverse events by treatment group for those adverse events that occurred in

Figure 3. Difference Between Group Mean AUASI Score Changes From Baseline to 72 Weeks for the Saw Palmetto and Placebo Groups Stratified by Select Baseline Variables



AUASI indicates American Urological Association Symptom Index; BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen. Continuous variables were dichotomized at the median. The subgroup analysis by race was prespecified in the study protocol; the rest are exploratory post hoc analyses. *P* values are based on a test for interaction in the primary analysis.

Table 3. Number of Adverse Events by Treatment Group in the Modified Intention-to-Treat Population

	No. of Adverse Events			No. of Participants		
Type of Adverse Event	Saw Palmetto Extract	Placebo	*P* Value[a]	Saw Palmetto Extract	Placebo	*P* Value[b]
All adverse events	530	476	.17	136	137	.80
Musculoskeletal	81	72	.46	53	46	.35
Genitourinary	58	59	.96	41	42	>.99
Upper respiratory tract	54	60	.72	39	34	.43
Gastrointestinal	52	58	.71	38	39	>.99
Physical injury or trauma	28	11	.11	24	10	.01
Oral or dental	26	14	.19	21	12	.10
Flu-like symptoms	19	15	.77	16	12	.43
Dermatological	17	26	.33	12	20	.20
Increased PSA	15	15	.95	14	13	.84
Increased blood pressure	14	6	.21	13	6	.10
Ophthalmic	11	11	.95	8	9	>.99
Abnormal serum chemistry	11	10	.80	11	7	.34
Arrhythmia	8	10	.72	8	10	.81

Abbreviation: PSA, prostate-specific antigen.
[a] Based on comparison of Poisson rates.
[b] Based on Fisher exact test.

at least 5% of study participants, and the eTable describes all serious adverse events reported among participants. Only the number of participants with physical injury or trauma was significantly higher in the saw palmetto extract group (24 vs 10 participants; $P = .01$).

COMMENT

Saw palmetto extracts have been widely used by men with LUTS, but more recent rigorously conducted trials, particularly the STEP trial,[12] have not proven better responses than placebo at standard doses of 320 mg/d. We designed our trial to determine whether saw palmetto extract at daily doses up to 960 mg would prove better than placebo at improving LUTS and other BPH-related outcomes. We found that the saw palmetto extract had no greater effect than placebo on LUTS attributed to BPH or a broad range of secondary outcomes, although small decreases in AUASI scores were observed in both groups. Better responses than placebo were not demonstrated despite using a saw palmetto preparation prepared with an ethanolic extraction procedure as opposed to the carbon dioxide extraction procedure used in preparing the STEP product and increasing to 3 times the standard dose. Even at these higher doses, the only adverse effect observed among significantly more participants in the saw palmetto extract group were physical injuries or trauma. Only one in the saw palmetto extract group was a serious adverse event; the rest were minor.

The strengths of our trial, which distinguish it from earlier studies, included the use of a well-characterized saw palmetto extract, an adequate sample size (our 1-sided 95% CIs make any clinically important benefit relative to placebo extremely unlikely), recruitment from multiple centers to increase generalizability, an adequate dose of the extract, an adequate duration of treatment (24 weeks at each dose level), excellent adherence with study medication and visits, a comprehensive set of outcome measures, and documentation of adequate blinding of participants.

Do our findings apply to other saw palmetto extract preparations? We studied only 1 extract and because the potential active ingredients and mechanisms are unknown, our findings may not be generalizable. Nevertheless, a recent series of negative trials using different saw palmetto extract preparations makes it increasingly unlikely a dose of some preparation will be identified that is better than placebo.[11,12]

Our study eligibility criteria were intentionally broader than for many previous trials of prescription medications for LUTS attributed to BPH, such as the Medical Therapy of Prostatic Symptoms (MTOPS) study[3] comparing doxazosin, finasteride, and combination therapy with placebo; in part because of our desire to recruit men who might typically chose to take phytotherapy for LUTS. As a result, our participants were slightly younger (mean age, 61 vs 63 years), less symptomatic (mean AUASI score, 14.6 vs 17.0 points), had lower PSA levels (mean PSA, 2.1 vs 2.4 ng/mL), and substantially higher peak uroflow rates (14.9 vs 10.5 mL/s) than men enrolled in the MTOPS study.[3] As a result, a greater percentage of men in our study compared with the MTOPS study may have had LUTS due to causes other than BPH.[27,28] Nevertheless, the exploratory subgroup analyses did not suggest a differential effect of saw palmetto extract on men more likely to have LUTS due to BPH, such as men with higher PSA levels or lower peak uroflow. Not surprisingly, our study population was demographically and clinically more similar to the STEP population.[12]

In conclusion, we found that saw palmetto extract used at up to 3 times the standard daily dose had no greater effect than placebo on improving lower urinary symptoms or other outcomes related to BPH.

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Online-Only Material: The eAppendix, eTable, and Author Interview are available at http://www.jama.com.

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