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Serenoa repens monotherapy for benign prostatic hyperplasia (BPH): an updated Cochrane systematic review

Roderick MacDonald[*], **James W. Tacklind**[*], **Indulis Rutks**[*], and **Timothy J. Wilt**[*,†]

[*]Center for Chronic Disease Outcomes Research (111-0), Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA

[†]Department of Medicine, University of Minnesota and Section of General Medicine Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA

Abstract

- To estimate the effectiveness and harms of *Serenoa repens* monotherapy in the treatment of lower urinary tract symptoms (LUTS) consistent with benign prostatic hyperplasia (BPH).
- We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and other sources through to January 2012 to identify randomised trials.
- Trials were eligible if they randomised men with symptomatic BPH to receive *Serenoa repens* extract monotherapy for at least 4 weeks in comparison with placebo, and assessed clinical outcomes and urodynamic measurements.
- Our primary outcome was improvement in LUTS, based on change in urological symptom-scale scores.
- In all, 17 randomised controlled trials (N = 2008) assessing *Serenoa repens* monotherapy (typically 320 mg/day) vs placebo met inclusion criteria, although only five reported American Urological Association Symptom Index (AUASI) or International Prostate Symptom Scores (IPSS). Trial lengths ranged from 4 to 72 weeks. The mean age of all enrolees was 64.3 years and most participants were of White race. The mean baseline total score was 14 points, indicating moderately severe symptoms. In all, 16 trials were double blinded and adequate treatment allocation concealment was reported in six trials.
- In a meta-analysis of three high quality long-to-moderate term trials (n = 661), *Serenoa repens* therapy was no better than placebo in reducing LUTS based on the AUASI/IPSS (weighted mean difference [WMD] −0.16 points, 95% confidence interval [CI] −1.45 to 1.14) or maximum urinary flow rate (Q_{max}; WMD 0.40 mL/s, 95% CI −0.30 to 1.09). Based on mostly short-term studies, Q_{max} measured at study endpoint were also not significantly different between treatment groups (WMD 1.15 mL/s, 95% CI −0.23 to 2.53) with evidence of substantial heterogeneity (I^2 58%).
- One long-term dose escalation trial (72 weeks) found double and triple doses of *Serenoa repens* extract did not improve AUASI compared with placebo and the proportions of clinical responders (≥ 3 point decrease in the AUASI) were nearly identical (43% vs 44% for *Serenoa repens* and placebo, respectively) with a corresponding risk ratio of 0.96 (95% CI 0.76–1.22).

Correspondence: Timothy J. Wilt, Minneapolis VA Center for Chronic Disease Outcomes Research, 1 Veterans Drive (111-0), Minneapolis, MN 55417, USA. tim.wilt@va.gov.

- Long-term, *Serenoa repens* therapy was no better than placebo in improving nocturia in one high-quality study ($P = 0.19$). Pooled analysis of nine short-term Permixon® trials showed a reduction in the frequency of nocturia (WMD −0.79 times/night, 95% CI−1.28 to −0.29), although there was evidence of heterogeneity (I^2 76%)
- Adverse events of *Serenoa repens* extracts were few and mild, and incidences were not statistically significantly different vs placebo. Study withdrawals occurred in ≈10% and did not differ between *Serenoa repens* and placebo.
- *Serenoa repens* therapy does not improve LUTS or Q_{max} compared with placebo in men with BPH, even at double and triple the usual dose.
- Adverse events were generally mild and comparable to placebo.

Keywords

Serenoa repens; benign prostatic hyperplasia; phytotherapy; systematic review

Introduction

Bothersome LUTS associated with BPH are common among ageing men and can interfere with daily activities and reduce quality of life. Phytotherapy is often used as a first-line treatment in Western countries [1,2]. In the USA use of phytotherapeutic agents has also markedly increased. In a 2002 survey, *Serenoa repens* was used by 2.5 million adults, 'often for BPH' [3]. One survey reported that one-third of men choosing non-surgical therapy for BPH were using herbal preparations alone or combined with prescription medications [4].

There are ≈30 phytotherapeutic compounds available for the treatment of symptomatic BPH, and some of the most widely used are extracts from the fruit of the American saw palmetto *Serenoa repens*. We have updated a previous a systematic review to address the effects and harms of monotherapeutic preparations of *Serenoa repens* in the treatment of LUTS associated with BPH [5].

Materials and methods

We electronically searched MEDLINE, the Cochrane Central Register of Controlled trials (CENTRAL), EMBASE, Web of Science®, Scopus, BIOSIS Previews®, LILACS, http://clinicaltrial.gov/, http://www.controlled-trials.com/, http://www.who.int/ictrp/en/, and http://www.clinicalstudyresults.org/. Systematic reviews, references, clinical-practice guidelines, and conference abstracts were also hand-searched. We included studies that were:

1. randomised
2. enrolled men with LUTS consistent with BPH
3. compared monotherapeutic preparations of *Serenoa repens* with placebo
4. treatment duration was ≥ 30 days

As a measure of overall methodological study quality we used criteria developed by Schulz and The Cochrane Collaboration [6,7]. Trials were considered of 'high quality' if they reported adequate treatment allocation concealment, double-blinding, and addressed incomplete data (used intention-to-treat analysis and adequately described reasons for study withdrawal).

Our primary outcome was mean change in validated urological symptom scores, such as the AUA Symptom Index (AUASI) and the IPSS. Both scale scores use an identical scale of 0–

35, with mild symptoms scored 1–8, moderate 9–18, and severe ≥ 19. Secondary outcomes included change in maximum urinary flow rate (Q_{max}; mL/s), nocturia (times/night), change in prostate size (mL), and adverse events. We also assessed the percentage of men who had a clinically important improvement (≥ 3 points) on the AUASI/IPSS.

Analyses were performed using RevMan 5.1 software [8]. Relative risks (RR) and weighted mean differences (WMD) with 95% CIs were calculated using a random effects model. To minimise the uncertainty of the pooled-effect estimate, we used an inverse variance method, which allows larger trials with a smaller standard error of the mean more weight over smaller trials with larger standard error of the mean. Heterogeneity between studies was assessed using and the I^2 test (50% or greater indicates substantial heterogeneity) [9] and the chi-squared test for heterogeneity (present if $P < 0.1$).

Results

Literature search and trial characteristics

The combined search strategies identified 17 trials enrolling 2008 participants meeting inclusion criteria (Table 1) [10–26]. Overall the mean age of the participants was 64.3 years (10–14,16,17,19,24–26) and most were White race (94%). The mean baseline AUASI/IPSS score was 14 points indicating moderate symptoms [10–12,19]. The mean baseline values for Q_{max} and nocturia were 11.5 mL/s and 2.7 times/night, respectively. Eight of the included trials used Permixon®, a commercialized extract, and all were conducted in Europe [13,15–18,21,24,25]. The standard daily dose was 320 mg. One trial used a 100 mg dose of *Serenoa repens* extract [20] and one trial increased the standard dose up to three times (960 mg) [10]. Most of the included studies had a short-term study duration, ≤ 3 months. Only two trials were considered long-term, a minimum trial duration of 1 year [10,12]. The most recent trials were conducted in the USA [10,12,19] and Australia [26].

Study quality

Six trials reported adequate treatment allocation concealment [10,12,14,16,19,20]. Nearly all trials indicated subjects and investigators were ‘blinded’ to treatment assignment [10–12,14–26]. Most of the trials adequately addressed incomplete data indicating low risk for attrition bias. Studies considered ‘high quality’ included Barry *et al.* [10] 2011, Bent *et al.* [12] 2006, Gerber *et al.* [19] 2001, and Löbelenz *et al.* [20] 1992.

AUASI/IPSS symptom scores

In all, 11 trials (two long-term (> 1 year), two moderate-term (6–12 months), 13 short-term (< 6 months) reported outcomes for urinary symptom-scale scores comparing *Serenoa repens* monotherapy with placebo but only five studies used the validated AUASI/IPSS indexes [10–12,19,26]. Shown in Table 2 [10,12,19], long- or moderate-term treatment with *Serenoa repens* did not improve LUTS compared with placebo based on mean changes from baseline in the AUASI/IPSS (WMD −0.16 points, 95% CI −1.45 to 1.14) [10,12,19]. There was substantial heterogeneity between studies (I^2 52%) but this was removed when the moderate-term trial of 6 months was removed from the analysis [19]. Clinically meaningful improvements (≥ 3 points in the AUASI) did not differ between the *Serenoa repens* treatment and placebo groups in the longest trial, 43% vs 44%, respectively (RR 0.96, 95% CI 0.76–1.22) [10]. Two trials compared IPSS total scores at study endpoint [11,26]. The moderate-term study (6 months) by Bauer *et al.* [11] reported statistically significant improvement ($P < 0.01$) with *Serenoa repens* therapy (37% improvement) vs placebo (14% improvement), although the mean baseline score was 9.2 indicating mild symptoms. The short-term trial of 12 weeks reported improved symptoms for both arms but the difference between groups was not statistically significant (WMD 1.74, 95% CI −0.54 to 4.03) and the

mean IPSS scores at baseline were significantly different between the two groups (P = 0.028) [26].

Q_{max} and secondary outcomes

Long- or moderate-term *Serenoa repens* therapy did not improve Q_{max} compared with placebo based on mean changes from baseline (WMD 0.40 mL/s, 95% CI −0.30 to 1.09; I^2 0%; Table 2) [10,12,19]. An analysis of mostly short-term studies also found Q_{max} values were not significantly different between treatment groups based on rates when measured at study endpoint (WMD 1.15 mL/s, 95% CI −0.23 to 2.53) with evidence of substantial heterogeneity (I^2 58%) [12,14,15,17–19,24,26]. Long-term, *Serenoa repens* therapy was no better than placebo in improving nocturia based on the AUA Nocturia score (P = 0.19) [10]. Pooled analysis of nine short-term Permixon trials found a significant reduction in the frequency of nocturia with a WMD of −0.79 times/night [95% CI −1.28 to −0.29], although there was evidence of profound heterogeneity (I^2 76%) [13,15–18,21,22,24,25]. One long-term trial reported no significant reduction in prostate volume after treatment with *Serenoa repens* vs placebo (WMD −1.22 mL, 95% CI −3.90 to 1.47) [12].

Study withdrawals and adverse events

The percentages of study withdrawals were comparable for the *Serenoa repens* therapy and placebo groups, 9.5% and 10.2%, respectively (P = 0.76). Adverse events of *Serenoa repens* therapy were few and mild, and compared with placebo, not statistically significantly different. The most common adverse events reported included gastrointestinal discomfort, upper respiratory tract infections, diarrhoea, and headache. In the two long-term trials, percentages of participants reporting at least one adverse event were also similar, 59% for *Serenoa repens* treatment group vs 57% for the placebo group (P = 0.71) [10,12]. The long-term trial by Barry *et al.* [10] reported that 136 men randomised to *Serenoa repens* therapy had at least one adverse event compared with 137 men randomised to placebo (P = 0.80) but none of the adverse events were deemed attributable to the treatment. In addition, < 2% of participants discontinued due to adverse events, four men in *Serenoa repens* therapy group and two men in the placebo arm.

Discussion

In previous Cochrane reviews [5,27], first published in 1998, we reported that *Serenoa repens* extracts provided mild improvement of urological symptoms. However, the trials evaluated were mostly under-powered, short-term (< 6 months), had variable study designs, outcomes, and used unvalidated symptom-scale scores. Method of allocation concealment was unclear in most of these trials, which may have led to selection bias. Thus we urged caution in concluding effectiveness. Beginning in 2008, with the addition of rigorous, high quality, long-term trials, we reported that *Serenoa repens* therapy was no better than placebo in reducing LUTS in men with BPH. One high quality 12-month trial enrolling 225 participants reported that *Serenoa repens* therapy did not improve symptoms or urinary flow and other objective measures [12]. Another recent long-term (follow-up 72 weeks), adequately powered, dose-escalation trial (320, 640, and 960 mg/day) of high quality, also found *Serenoa repens* no better than placebo at 24, 48, and 72 weeks, respectively [10].

Of the 17 included trials in the present review, only six enrolled ≥ 100 men. The most recent trials included in this update have included at least 200 men [10,12] and these two larger studies were longer term and of higher methodological quality. Another problem in many studies was the use of unvalidated symptom scores. In our 1998 systematic review none of the *Serenoa repens* monotherapy, placebo-controlled trials used the AUASI/IPSS to assess LUTS [28]. All of the included trials published since 2001 included in the present review

have done so, although most of the older trials were conducted before the creation of the AUASI/IPSS. All of the *Serenoa repens* monotherapy, placebo-controlled trials included in the first review were considered short-term, < 6 months in duration, and none of these studies were > 3 months.

We do not know if the present conclusions are generalizable to proprietary products of *Serenoa repens* extracts, such as Permixon® or Prostagutt® forte. Lack of standardisation is a long-recognised problem of phytotherapeutic products, and that includes *Serenoa repens* [29,30]. A systematic review reported improvements in the IPSS for of Permixon and placebo but included only one direct comparison between the two arms [31]. Another analysis asserted Permixon appeared to as effective as α-blockers and 5α-reductase inhibitors, therefore as efficacious [32]. In the present review, there was no difference in reported improvements in the AUASI but none of the trials used Permixon. Future randomised studies using proprietary *Serenoa repens* preparations should be placebo-controlled, have a study duration of at least 1 year, be methodologically sound, well powered, and use validated symptom-scale scores, such as the AUASI/IPSS.

In conclusion, *Serenoa repens* extracts are widely used to treat symptomatic BPH. Based on high quality, long-term trials, treatment with *Serenoa repens*, even at escalating doses, did not improve LUTS or Q_{max} associated with BPH.

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Abbreviations

AUASI	AUA Symptom Index
Q_{max}	maximum urinary flow rate
RR	relative risk
WMD	weighted mean difference

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What's known on the subject? and What does the study add?

For the past 30 years *Serenoa repens* has become a widely used phytotherapy in the USA and in Europe, mostly because of positive comparisons to α-blockers and 5α-reductase inhibitors.

During the last 4 years we have seen two very high quality trials comparing *Serenoa repens* to placebo and up to 6 years duration. These trials found *Serenoa repens* no better than placebo, even (in one trial) at escalating doses.

Table 1

Baseline characteristics of the included placebo-controlled trials ($N = 17$)

Reference/country	N	Withdrawals, n (%)	Intervention daily dose, mg	Duration, months	Mean age, years*	AUASI/IPSS, points*	Q_{max}, mL/s*
Long-term trials (≥12 months)							
Barry *et al.* [10] 2011/USA	369	36 (10)	*Serenoa repens* extract 320–960 (x 1, 2, and then 3 doses)	18	61	14.6	14.9
Bent *et al.* [12] 2006/USA	225	19 (8)	*Serenoa repens* extract 320	12	63	15.4	11.5
Moderate-term trials (≥6 to <12 months)							
Gerber *et al.* [19] 2001/USA	85	6 (7)	*Serenoa repens* extract 320	6	65	16.2	11.9
Bauer *et al.* [11] 1999/Germany, Italy	101	3 (3)	Sabal extract (LG166/S) 320	6	66	9.2	12.3
Short-term trials (<6 months)							
Willetts *et al.* [26] 2003/Australia	100	7 (7)	*Serenoa repens* extract 320	3	63	*≈14–17***	11.2
Mohanty *et al.* [23] 1999/India	75	2 (3)	*Serenoa repens* extract	2	–	–	11.8
Descotes *et al.* [17] 1995/France	215	39 (18)	Permixon 320	2	–	–	12.1
Braeckman *et al.* [14] 1994/Belgium	238	33 (14)	Serendar 320	3	65	–	10.7
Löbelenz [20] 1992/Germany	60	0	Sabal extract 100	1.5		–	12.7
Mattei *et al.* [22] 1990/Italy	40	2 (5)	Talso 320	3	–	–	-
Reece-Smith *et al.* [24] 1986/UK	80	10 (13)	Permixon 320	2	67	–	*≈6.2*†
Cukier *et al.* [16] 1985/France	168	22 (13)	Permixon 320	2	69	–	–
Tasca *et al.* [25] 1985/Italy	30	3 (10)	Permixon 320	2	62	–	12.1
Champault *et al.* [15] 1984/France	110	16 (15)	Permixon 320	1	–	–	5.2
Boccafoschi and Annoscia [13] 1983/Italy	22	0	Permixon 320	2	68	–	9.9
Emili *et al.* [18] 1983/Italy	30	0	Permixon 320	2	–	–	9.8
Mandressi *et al.* [21] 1983/Italy	60††	0	Permixon 320	1	–	–	-

*Overall (*Serenoa repens* and placebo);

**from graph, there was a statistically significant difference between treatment groups;

†from graph;

††three-arm trial with *Pygeum africanum.*

Table 2

Changes in AUASI and Q_{max} for moderate-to-long-term trials

Reference	Treatments, n	Study duration, months	Baseline, mean (SD)*	Endpoint, mean (SD)*	Mean change (SD)	Difference between Groups (95% CI); I^{2**}
AUASI						
Barry *et al.* [10] 2011	*Serenoa repens,* 176 Placebo, 181	18	14.4 14.7	12.2 11.7	−2.20 (9.1) −2.99 (5.6)	0.79 (−0.78 to 2.36)
Bent *et al.* [12] 2006	*Serenoa repens,* 112 Placebo, 113	12	15.7 (5.7) 15.0 (5.3)	– –	−0.68 (3.7) −0.72 (3.7)	0.04 (−0.93 to 1.01)
Gerber *et al.* [19] 2001	*Serenoa repens,* 41 Placebo, 44	6	16.7 (4.9) 15.8 (4.8)	12.3 (5.5) 13.6 (6.6)	−4.4 (5.9) −2.2 (5.4)	−2.20 (−4.61 to 0.21)
WMD						−0.16 (−1.45, 1.14); 52%
Q_{max} (mL/s)						
Barry *et al.* [10] 2011	*Serenoa repens,* 176 Placebo, 181	18	15.0 14.8	14.8 14.0	−0.18 (6.0) −0.79 (5.4)	0.61 (−0.58 to 1.80)
Bent *et al.* [12] 2006	*Serenoa repens,* 112 Placebo, 113	12	11.4 (3.5) 11.6 (4.3)	– –	0.42 (3.6) −0.01 (3.6)	0.43 (−0.51 to 1.37)
Gerber *et al.* [19] 2001	*Serenoa repens,* 41 Placebo, 44	6	10.7 (4.7) 12.9 (6.8)	11.7 (5.8) 14.3 (17.5)	1.0 (4.9) 1.4 (4.9)	0.40 (−2.48 to 1.68)
WMD						0.40 (−0.30 to 1.09); 0%

*If reported;

**I^2 test for heterogeneity – 50% or greater indicates substantial heterogeneity.