Serenoa repens extract for benign prostate hyperplasia: a randomized controlled trial

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OBJECTIVE

To compare the effect of a *Serenoa repens* extract with placebo for symptoms of benign prostatic hyperplasia (BPH).

PATIENTS AND METHODS

In a double-blind placebo-controlled randomized trial between January 1999 and March 2000, 100 men with symptoms of BPH, aged <80 years, with a maximum urinary flow rate of 5–15 mL/s for a voiding volume of 150 mL, were randomly and equally allocated to 320 mg *S. repens* extract or placebo (paraffin oil). The main outcome measures were the International Prostate Symptom Score (IPSS), peak urinary flow rate, and the Rosen International Index of Erectile Function (IIEF) questionnaire.

RESULTS

There was no significant difference between the treatments over the 12 weeks of the study in the IPSS, peak urinary flow rate or for the IIEF questionnaire.

CONCLUSIONS

During the trial all participants had some improvement in their symptoms of BPH but there was no significant beneficial effect of this *S. repens* extract over placebo in this 12-week trial.

KEYWORDS

benign prostatic hyperplasia, *Serenoa repens*, phytotherapy, randomized trial, outcome

INTRODUCTION

BPH can restrict the urinary outlet, resulting in dysuria, nocturia, increased frequency of urination and poor urinary flow [1]. BPH is a common complaint that increases with ageing [2]; it is androgen-dependent and thus drugs such as finasteride (a 5α-reductase blocker) are effective treatments for BPH [3]. However, these drugs are expensive and have significant side-effects, e.g. impotence and decreased libido. The most common treatment offered to men with BPH is either TURP or open prostatectomy. While surgery is effective it is associated with complications such as blood loss, UTI, urethral stenosis, incontinence and impotence [4]. A plant extract such as *Serenoa repens* may provide a more acceptable alternative treatment for relieving the symptoms of BPH.

S. repens or *Sabal serrulata* is a dwarf palm indigenous to Florida; at least two different extracts of the berries have been tested in clinical trials. Both a hexane extract, Permixon® [5,6] and a carbon-dioxide extract, Prostaserene® [7], have been shown to be better than placebo for treating BPH. In addition, the hexane extract has been shown to be equivalent to finasteride, but with fewer side-effects [8].

There have been few investigations of the effect of this herb on sexual function. There was no difference in treatment on libido in one study [9], and in another it was noted that sexual function was measured, but no results were presented [10]. There were fewer complaints of libido and impotence in subjects treated with Permixon than in those treated with finasteride in a sexual function questionnaire [8]. Thus we included sexual function as part of the present study to assess the effect of an extract of *S. repens* compared with placebo.

Most of the studies so far have been conducted in Europe [5–8] and herein we report a study in an Australian population, describing a double-blind randomized placebo-controlled trial of a carbon-dioxide extract of *S. repens* on symptoms of BPH, peak urinary flow and sexual function.

PATIENTS AND METHODS

This double-blind, placebo-controlled randomized trial was carried out at the Natural Therapies Unit at the Royal Hospital for Women, Sydney, and was approved by the South-eastern Sydney Area Health Research Ethics Committee. Participants were screened for eligibility by a telephone interview, and at the first visit, and the randomized at the second. The main part of the trial encompassed 12 weeks of randomized treatment during which there were three further visits, every 4 weeks.

Between January 1999 and March 2000, 560 men were screened and 100 randomized (Fig. 1). The sample size was chosen to detect a change of ≥2.5 units in the IPSS between treatment and placebo, with a SD of 4, 80% power and at $\alpha = 0.05$ significance level. Men who had at least three symptoms of prostatism, e.g. increased frequency of urination, nocturia, hesitancy, dribbling and poor stream, were invited to participate. They were required to be aged <80 years and to have no significant medical condition. Men with insulin-dependent diabetes, severe cardiopulmonary disease or significant CNS disease were excluded. Also, men were not permitted to have used the following in the previous 4 weeks: androgens, 5α-reductase inhibitors, α-blockers or herbal preparations for urinary problems. Men with a history of prostate cancer or adenomas, urethral, bladder, ureteric or renal abnormalities, urogenital surgery, renal stones, strictures or scarring, acute urinary retention or allergy to study treatment were excluded. The

participants were required to have a maximum urinary flow rate of 5–15 mL/s for a voided volume of 150 mL, and a normal serum PSA level (< 4 ng/mL) within the previous 3 months.

The men were randomized off-site using a balanced-blocks procedure, where each block was for six men. Randomization codes were concealed in sealed envelopes and opened only after the last man had completed treatment. Fifty men were treated with *S. repens* extract (2 × 160 mg of CO_2 extract; Blackmores Ltd, Sydney, Australia) and 50 with the placebo (paraffin oil), given in identical capsules; the men in each treatment group took two capsules per day.

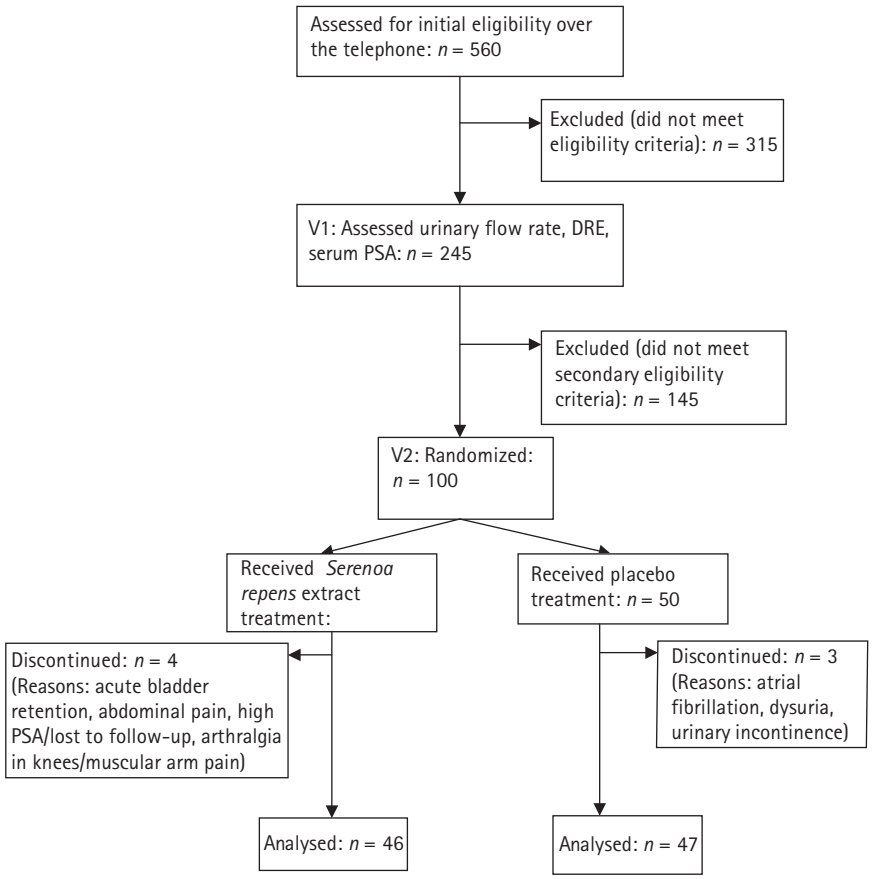
MAIN OUTCOME MEASURES

The IPSS [11] was used to assess the symptoms of BPH, and comprises a set of seven questions on urinary function, each measured on a 5-point scale, resulting in a total score of 35. There is one quality-of-life (QoL) question, which asks 'If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about this?', for which the answers range from 'delighted' (0) to 'terrible' (6). The peak urinary flow rate was assessed using a uroflowmeter (Urodyn 1000, Type 22G02, Dantec, Denmark), for which a voided volume of >150 mL is required for an accurate reading [12]. Sexual function was assessed using the Rosen International Index of Erectile Function (IIEF) sexual questionnaire [13] which measures erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction.

STATISTICS

Data were entered into a database and then analysed using commercial software (SPSS for Windows. Statistical package for the social sciences. Release 10.0.5 (c) SPSS Inc. 1989–99; SAS/STAT Software. Changes and Enhancements through Release 6.11; 1996 Cary, NC. SAS Institute Inc). The mean (SEM) is reported for continuous variables and they were compared using Mann–Whitney *U*-tests (for data not normally distributed) and Student's *t*-tests (for normally distributed data). The Kolmogorov-Smirnov statistic was used as a conservative test for normality. Analysis of the treatment effect across all visits involved a repeated measures ANOVA approach, using linear mixed models, of all data in the dataset. The models included effects for differences between groups at baseline, differences over time, and interactions between treatment group and time for the treatment effect. For comparisons between pairs of visits, only individuals who completed both visits were included. Multivariate techniques were also applied to investigate the effect of various exposure factors, selecting models using Akaike's information criterion. The repeated measures analysis was conducted using the SAS procedure PROC MIXED. All analyses were conducted on an intention-to-treat basis. No adjustment was made for multiple comparisons. A level of 0.05 was used to determine statistical significance.

FIG. 1. A flow diagram showing the distribution of participants at each stage.



RESULTS

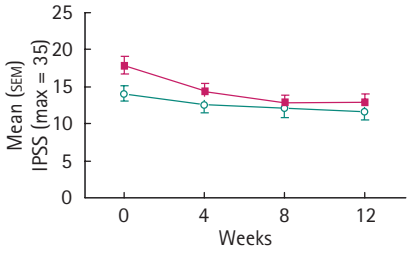
Of the 245 men invited to attend an initial visit to measure peak flow rate, 100 qualified to be randomized, 50 to each arm (Fig. 1); of these, 46 in the *S. repens* and 47 in the placebo group completed the study. The analysis of IPSS used data from these 93 men. The demographic characteristics were similar in both groups, including age, smoking status, exercise status, body mass index (BMI), and PSA (free and total) (Table 1). Similarly, there were no significant differences in the number of men with baseline symptoms (nocturia, poor stream, increased frequency, urgency, difficulty starting, difficulty stopping and dysuria) except for incontinence, where there were significantly more in the placebo group ($P = 0.021$).

At baseline the mean overall IPSS was significantly different between the groups ($P = 0.028$, *t*-test; Fig. 2); after 12 weeks of treatment the IPSS decreased in both groups. A multivariate regression analysis applying age and BMI to the model again showed a significant difference between the groups at baseline of −3.96 (− 7.05 to − 0.87; $P = 0.014$). The IPSS was significantly affected by age ($P = 0.049$) but not by BMI. There was a significant difference over time for both

Characteristic	*S. repens*	Placebo
Mean (SEM) or N:		
age, years	62.1 (1.2)	63.9 (1.3)
BMI, kg/m^2	27.8 (0.6)	26.4 (0.4)
PSA, ng/mL		
free	0.81 (0.10)	0.74 (0.09)
total	3.4 (0.6)	2.4 (0.3)
Smokers	1	2
Subjects who exercised	39	42
Times of exercise/week	4.0 (0.4)	4.0 (0.4)

TABLE 1
The baseline characteristics of the participants

FIG. 2. The mean (SEM) IPSS for each visit. Serenoa extract, green open circles. Placebo, red closed squares.



treatment groups of −3.62 (− 5.23 to −2.01; $P < 0.001$) but there was no significant difference in the decrease in IPSS over time between the groups, with a treatment effect of 1.74 (− 0.54 to 4.03; $P = 0.131$).

For the QoL score, the *S. repens* group had an initial score of 3.66 (3.35–3.97), which decreased to 3.17 (2.76–3.58) after 12 weeks; the placebo group initial score was 4.0 (3.58–4.42), which decreased to 3.31 (2.85–3.77) after 12 weeks. Regression analysis indicated no significant difference at baseline, no influence by treatment, with a treatment effect of 0.18 (− 0.16 to 0.53; $P = 0.292$), but men in both groups had a significantly lower score after the trial, by − 0.45 (− 0.69 to − 0.21; $P < 0.001$).

The peak urinary flow rates for the first two visits were averaged to give the baseline rate. For the *S. repens* group the mean at baseline was 11.1 (10.3–11.8) mL/s and for the placebo group was 11.2 (10.5–11.9) mL/s. After 12 weeks of treatment the respective flows were 12.6 (11.0–14.2) and 15.6 (13.2–18.1) mL/s. These results are for the 62 men who attended the initial and final visits, and who had a voided volume of > 150 mL at these visits. In summary, men in each group had similar flow rates at baseline and these improved in each group during the trial (*t*-test, $P < 0.001$).

In the multivariate regression analysis the urinary flow rate increased significantly in each group over the time of the trial by 2.35 (1.48–3.22; $P < 0.001$) but the difference between groups was not significant ($P = 0.098$). Urinary flow rates were significantly affected by voided volume ($P < 0.001$) but not by age or BMI.

The IIEF scores for the 74 men who were sexually active were initially 51.5 (43.9–59.1) and 49.4 (43.3–55.4) for the *S. repens* and placebo groups, respectively. After 12 weeks of treatment the respective scores did not change significantly, at 55.11 (48.4–61.8) and 48.7 (41.9–55.4). The regression analysis showed that age contributed significantly ($P = 0.008$), with no significant differences between the groups.

Only seven men withdrew from the trial, four from the *S. repens* and three from the placebo group. Three of these were serious adverse events, i.e. acute urinary retention (*S. repens*), atrial fibrillation (placebo) and abdominal pain (*S. repens*). The other adverse events resulting in withdrawal were a high PSA and loss to follow-up, and arthralgia in the knees and muscular arm pain (both *S. repens* group), and dysuria and urinary incontinence (placebo). Other adverse events not resulting in withdrawal included headache, constipation and photosensitivity in one each, and diarrhoea reflux and penile discomfort in two each.

DISCUSSION

The main hypotheses for this study were that in patients treated with *S. repens* extract, but not with placebo, the IPSS would decrease and peak urinary flow rate and sexual function would not decline. The results are partly unexpected, particularly for the IPSS and urine flow, which apparently improved with *S. repens* treatment, as assessed in a meta-analysis by the Cochrane Library [14]. In favour of the present results, the study used randomization and blinding, had a high compliance and low withdrawal rate (7%) and the dosage was also comparable to that in other studies.

Using a different urinary symptom score to that used in the present study, a weighted mean difference of −1.41 points (95% CI, −2.52, 0.30; scale range 0–19) was reported, indicating a clear treatment effect [14]. This is in contrast to the present result, i.e. no treatment effect. There are several possible explanations for the present IPSS results. The possibility of any significant decrease in symptoms might have been limited by the relatively low mean baseline IPSS in this study, at 14.1 for the *S. repens and* 17.9 for the placebo group, compared with means of 19.0 [15], 19.5 [16], 17.4 [10] and 15.7 [8]. In other study designs, a minimum IPSS could be used as an eligibility criteria [10,16]; this would be a desirable change if the study were to be repeated. Further explanations for the present results could be that there were too few patients, or the study was biased, or that the duration was insufficient to detect any change. In summary, the design of the present study might have limited the ability to detect a treatment difference.

For the peak urinary flow rate, the data summarized in the meta-analysis [14] indicated a weighted mean (95% CI) improvement of 1.93 (0.72–3.14), again indicating a clear treatment effect, in contrast to the present result. Obtaining flow rates from men when they had a full bladder was a challenging requirement. In the present study there was a significant number of men for whom the minimum voided volume of 150 mL posed some difficulty. Consequently the limited data might have reduced the possibility of detecting a treatment effect. The apparently more favourable effect on the placebo group is difficult to explain, and might be attributable to sample variability with too few patients.

The IIEF scores in the present study indicated that there was no significant change during treatment, consistent with the only study

where libido was compared in Permixon® and placebo treatment groups [9]. The apparent minor decrease in scores in the placebo group during the trial can be largely explained by the few men who became sexually inactive during the trial. It was noted by at least one patient that his decrease in sexual activity was because his wife was absent. Generally, towards the end of the trial, it was remarked that the patients felt less inclined to spend time completing the questionnaires accurately. Overall, there was no significant effect of *S. repens* extract on sexual function; this is a favourable outcome considering the less desirable effect of a treatments like finasteride [8].

There was a low withdrawal rate (7%) in the present trial; the three serious adverse events were more likely to be connected with the condition than the treatment. Headache, nausea and diarrhoea have been reported previously [5,17], and in general, the treatment was well tolerated.

In conclusion, there was an improvement in BPH symptoms over time for all participants in this 12-week trial, but there was no detectable significant difference between the treatment groups. This result is consistent with some studies [9,10] but not with others [5–7]. As suggested previously [9], it appears that simply having some attention and talking about their condition was therapeutic for these men. Further research needs to address the efficacy of *S. repens* extract on a larger sample and for longer. This will enable health professionals to be confident in their treatment of an Australian population with BPH using this product.

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REFERENCES

1 Christensen MM, Bruskewitz RC. Clinical manifestations of benign prostatic hyperplasia and indications for therapeutic intervention. *Urol Clin North Am* 1990; **17**: 509–16
2 Berry SJ, Coffey DS, Walsh PC *et al.* The development of human benign prostatic hyperplasia with age. *J Urol* 1984; **132**: 474–9
3 McConnell JD, Bruskewitz R, Walsh P *et al.* The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia; *N Engl J Med* 1998; **338**: 557–63
4 Mebust WK, Holtgrewe HL, Cockett AT *et al.* Transurethral prostatectomy: immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3885 patients. *J Urol* 1989; **141**: 243–7
5 Champault G, Patel JC, Bonnard AM. A double-blind trial of an extract of the plant *Serenoa repens* in benign prostatic hyperplasia. *Br J Clin Pharmacol* 1984; **18**: 461–2
6 Descotes JL, Rambeaud JJ, Deschaseaux P *et al.* Placebo-controlled evaluation of the efficacy and tolerability of Permixon in benign prostatic hyperplasia after exclusion of placebo responders. *Clin Drug Invest* 1995; **9**: 291–7
7 Braeckman J, Denis L, de Leval J *et al.* A double-blind, placebo-controlled study of the plant extract *Serenoa repens* in the treatment of benign hyperplasia of the prostate. *Eur J Clin Res* 1997; **9**: 247–59
8 Carraro J-C, Raynaud J-P, Koch G *et al.* Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomised international study of 1,098 patients. *Prostate* 1996; **29**: 231–40
9 Reece Smith H, Memon A, Smart CJ *et al.* The value of Permixon in benign prostatic hypertrophy. *Br J Urol* 1986; **58**: 36–40
10 Marks LS, Partin AW, Epstein JI *et al.* Effects of a saw palmetto herbal blend in men with symptomatic benign prostatic hyperplasia. *J Urol* 2000; **163**: 1451–6
11 Mebust W, Roizo R, Schroder F *et al.* Correlations between pathology, clinical symptoms and the course of the disease. In Cockett ATK, Aso Y, Chatelain C *et al.* eds, *Recommendations of the International Consultation on Benign Hyperplasia*. Geneva: WHO, 1991: 51–62
12 Kirby RS. The clinical assessment of benign prostatic hyperplasia. *Cancer* (*Suppl*) 1992; **70**: 284–90
13 Anonymous. The process of care consensus panel. The process of core model for evaluation and treatment of erectile dysfunction. *Int J Impot Res* 1999; **11**: 59–70
14 Wilt T, Ishani A, Stark G *et al.* Serenoa repens for treatment of benign prostatic hyperplasia (Cochrane Review). In: *The Cochrane Library, Issue 1* 1999. Oxford: Update Software
15 Braeckman J. The extract of Serenoa repens in the treatment of benign prostatic hyperplasia: a multicenter open study. *Curr Therap Res*; 1994; **55**: 776–85
16 Gerber GS, Zagaja GP, Bales GT *et al.* Saw palmetto (Serenoa repens) in men with lower urinary tract symptoms. effects on urodynamic parameters and voiding symptoms. *Urology*; 1998; **51**: 1003–7
17 Drew A. An alternative stream: Serenoa repens for benign prostatic hypertrophy? *Aust Prescr* 2000; **23**: 79

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Abbreviations: **QoL**, quality-of-life (score); **IIEF**, International Index of Erectile Function; **BMI**, body mass index.