# Cernilton for benign prostatic hyperplasia (Review)

**Wilt T, MacDonald R, Ishani A, Rutks I, Stark G**

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 1998, Issue 3

http://www.thecochranelibrary.com

WILEY

## TABLE OF CONTENTS

[Intervention Review]

# Cernilton for benign prostatic hyperplasia

Timothy Wilt[1], Roderick MacDonald[1], Areef Ishani[2], Indy Rutks[3], Gerold Stark[4]

[1]General Internal Medicine (111-0), VAMC, Minneapolis, Minnesota, USA. [2]Department of Medicine (111), VA Medical Center, Minneapolis, Minnesota, USA. [3]Department of Internal Medicine (111-0), VAMC, Minneapolis, Minnesota, USA. [4]Corvallis Clinic, Corvallis, OR, USA

Contact address: Timothy Wilt, General Internal Medicine (111-0), VAMC, One Veterans Drive, Minneapolis, Minnesota, 55417, USA. Tim.Wilt@med.va.gov.

**Editorial group:** Cochrane Prostatic Diseases and Urologic Cancers Group.
**Publication status and date:** Edited (no change to conclusions), published in Issue 4, 2008.
**Review content assessed as up-to-date:** 30 March 1998.

**Citation:** Wilt T, MacDonald R, Ishani A, Rutks I, Stark G. Cernilton for benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews* 1998, Issue 3. Art. No.: CD001042. DOI: 10.1002/14651858.CD001042.



## ABSTRACT

### Background

Benign prostatic hyperplasia (BPH), nonmalignant enlargement of the prostate, can lead to obstructive and irritative lower urinary tract symptoms (LUTS). The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH has been growing steadily. Cernilton, prepared from the rye-grass pollen *Secale cereale*, is one of the several phytotherapeutic agents available for the treatment of BPH.

### Objectives

This systematic review aims to assess the effects of Cernilton on urinary symptoms and flow measures in men with benign prostatic hyperplasia (BPH).

### Search strategy

Trials were searched in computerized general and specialized databases (MEDLINE, EMBASE, Cochrane Library, Phytodok), by checking bibliographies, and by contacting manufacturers and researchers.

### Selection criteria

Trials were eligible if they were: (1) randomized controlled trials or controlled clinical trials comparing Cernilton with placebo or other BPH medications in men with BPH; and (2) included clinical outcomes such as urologic symptom scales, symptoms, or urodynamic measurements.

### Data collection and analysis

Information on patients, interventions, and outcomes was extracted by at least two independent reviewers using a standard form. Main outcome measure for comparing the effects of Cernilton with placebo and standard BPH medications were the change in urologic symptoms scales. Secondary outcomes included changes in nocturia as well as urodynamic measures (peak and mean urine flow, residual volume, prostate size). Main outcome measure for side effects was the number of men reporting side effects.

**Main results**

Four hundred forty-four men were enrolled in two placebo-controlled and two comparative trials lasting from 12 to 24 weeks. Three studies used a double-blind method although treatment allocation concealment was unclear in all. Cernilton improved "self rated urinary symptoms" (percent reporting satisfactory or improving symptoms) versus placebo and Tadenan. The weighted risk ratio (RR) for self-rated improvement versus placebo was 2.40 (95% CI = 1.21 to 4.75), and the weighted RR versus Tadenan was 1.42 (95% CI = 1.21 to 4.75). Cernilton reduced nocturia compared with placebo and Paraprost. Versus placebo, the weighted RR was 2.05 (95% CI = 1.41 to 3.00), and versus Paraprost, the WMD was -0.40 times per evening (95% CI = -0.73 to -0.07). Cernilton was not more effective than placebo or the comparative study agents in improving urinary flow rates, residual volume or prostate size. Adverse events were rare and mild. The withdrawal rate for Cernilton was 4.8% compared to 2.7% for placebo and 5.2% for Paraprost.

**Authors' conclusions**

The Cernilton trials analyzed were limited by short duration, limited number of enrollees, gaps in reported outcomes, and unknown quality of the preparations utilized. The comparative trials lacked a proven active control. The available evidence suggests Cernilton is well tolerated and modestly improves overall urologic symptoms including nocturia. Additional randomized placebo and active-controlled trials are needed to evaluate the long-term clinical effectiveness and safety of Cernilton.

## PLAIN LANGUAGE SUMMARY

**Cernilton, an extract from rye grass pollen, may help to relieve some urinary symptoms caused by an enlarged prostate gland, but more research is needed.**

Benign prostatic hyperplasia (BPH), enlargement of the prostate gland, is common in older men. An enlarged prostate can interfere with urination, increasing the frequency and urge, or causing problems emptying the bladder. Both surgery and drugs are used to try to treat BPH. However, using herbal medicines to try to relieve the symptoms of BPH is common. Cernilton is a popular herbal remedy used by men worldwide. The review found that cernilton was well-tolerated and modestly improved the urinary symptoms of BPH. However it did not improve measures of urine flow. More research is needed into long-term effects of cernilton.

## BACKGROUND

Benign prostatic hyperplasia (BPH), nonmalignant enlargement of the prostate, can lead to obstructive and irritative urinary tract symptoms. The majority of men over the age of 60 are considered to have urinary symptoms attributable to BPH. In the United States treatment of BPH accounts for approximately 1.7 million physician office visits (Guess 1992) and results in more than 300,000 prostatectomies annually (McConnell 1994). Several strategies have been utilized to reduce the symptoms of BPH, including pharmacologic therapies (Oesterling 1995).

The pharmacologic use of plants and herbs (phytotherapy) for the treatment of BPH symptoms has been growing steadily in most countries. Because of limited information regarding the efficacy and safety of plant extracts, they are rarely recommended in the United States for the treatment of symptomatic BPH. Phytotherapeutic agents represent nearly half of the medications dispensed for BPH in Italy (Di Silverio 1993). In Germany and Austria phytotherapies represent over 90% of all drugs prescribed for the treatment of BPH (Buck 1996). Use of phytotherapies in the United States have markedly increased (Gerber 1998). They are readily available as nonprescription dietary supplements and are often recommended in "natural health food stores or books" for self treatment of BPH symptoms.

Cernilton, prepared from the rye-grass pollen *Secale cereale*, is one of several phytotherapeutic agents available for the treatment of BPH. Cernilton is used by millions of men worldwide and is a registered pharmaceutical throughout Western Europe, Japan, Korea and Argentina (AB Cernelle). In the United States, Cernilton is used as a nutritional supplement by approximately 5,000 men (Ruyan 1999). One dose of Cernilton contains 60 mg of Cernitin T60, a water soluble pollen extract fraction, and 3 mg of Cernitin GBX, an acetone soluble pollen extract fraction (AB Cernelle). The acetone soluble fraction was found to contain ß-sterols (Buck 1996). Several in vitro studies undertaken to investigate the mech-

anism of action suggest Cernilton has anti-androgenic effects (Ito 1986), may relax urethral smooth muscle tone and increase bladder muscle contraction (Kimura 1986), or may act on the alpha-adrenergic receptors and relax the internal and external sphincter muscles (Nakase 1988). Despite these multiple studies demonstrating in vitro activity, the clinical effectiveness of Cernilton for the treatment of BPH remains unclear. Therefore, we wished to assess whether Cernilton is more effective than placebo or as effective as other pharmacologic therapies in improving the obstructive and irritative urinary symptoms associated with BPH.

## OBJECTIVES

To evaluate the effects of Cernilton versus placebo or active control on urinary symptoms in men with BPH. The main outcome was improvement in urologic symptom scale scores. Secondary outcomes included changes in peak and mean urine flow, residual urine volume, prostate size and side effects associated with the use of Cernilton.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized or controlled clinical trials

#### Types of participants

Men with symptomatic benign prostatic hyperplasia.

#### Types of interventions

Comparison of preparations of Cernilton with placebo or medical therapies for BPH with a treatment duration of at least 30 days

#### Types of outcome measures

Urologic symptom scores (Boyarsky, American Urologic Association Score, International Prostate Symptom Score (IPSS); Urodynamic measures (defined as change in peak urine flow (measured in mL/s), mean urine flow (measured in mL/s), residual urine volume (measured in ml), nocturia (measured in times per evening) and changes in prostate size (measured in cc).

### Search methods for identification of studies

We searched MEDLINE for 1966-1998 using a combination of the March 1996 update of the optimally sensitive search strategy for trials from the Cochrane Collaboration with the MeSH headings “prostatic hyperplasia,” “phytosterols,” “plant extracts,” “pollen,” “Cernilton.tw,” “Cernitin.tw,” and “Secale cereale” including all subheadings (Dickersin 1994). A search of EMBASE, years 1974 to 1998 (performed in July 1998) was done by using a similar approach. We also searched the private database Phytodok, Munich Germany, and the Cochrane Library, including the database of the Cochrane Prostate Review Group and the Cochrane Field for Complementary Medicine. Reference lists of identified trials and reviews were searched and expert relevant trialists were asked to identify additional published or unpublished trials. There were no language restrictions.

### Data collection and analysis

Eligibility:
At least two reviews independently decided on eligibility.
Extraction:
Extraction of study characteristics and data was performed independently by two reviewers. Missing or additional information was sought from authors/sponsors. Extracted data was reviewed by the principal reviewer and discrepancies resolved by discussion.
Assessment of methodological quality:
As a measure of overall methodologic study quality we assessed the quality of concealment of treatment allocation according to a scale developed by Schulz (1995) assigning 1 to poorest quality and 3 to best quality: 1 = trials in which concealment was inadequate (e.g. 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 (e.g. 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.
Summarizing results of primary studies:
Outcomes:
The mean urologic symptom scale scores (IPSS and Boyarsky), peak and mean urine flow (mL/s), residual urine volume (mL), nocturia (times per evening) and prostate size (cc). The number and percent of men reporting specific side effects and/or withdrawing from the study.
Meta-analysis:
A random effects model was used to combine data for all outcomes. For continuous variables, weighted mean differences and their 95% confidence intervals were calculated. The difference be-

tween treatment means and their correlated standard error of the difference were calculated using the methods of Lau and Laird (Lau 1996; Laird 1990). Papers reported only the mean values before and after Cernilton and control as well as the corresponding standard error of the mean. Because the standard error of the difference between the means (Cernilton and control) was not reported, analyses were carried out for 3 different assumed values of correlation (0.25, 0.50, 0.75). This approach was taken in order 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 utilized standard errors of the mean calculated with a correlation coefficient of 0.50. Chi-square tests were used for analysis of bivariate comparisons.

# RESULTS

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Four studies (Maekawa 1990; Becker 1988; Buck 1990; Dutkiewicz 1996) met inclusion criteria out of a total of six studies identified through the combined search strategy. Two trials were excluded based upon no control groups (Hayashi 1986; Yasumoto 1995). Three trials reported using a double-blind method (Maekawa 1990; Becker 1988; Buck 1990). Two studies were placebo-controlled (Becker 1988; Buck 1990) and two were "active-controlled" trials. The "active-controlled" trials included Tadenan, a phytotherapeutic extract from the African plum plant, *Pygeum africanum* (Dutkiewicz 1996), and Paraprost (Nikken Kagakusha), a pharmacologic treatment for benign prostatic hyperplasia used primarily in Japan containing 265 mg of L-glutamic acid, 100 mg of L-alanine and 45 mg of aminoacetic acid (Maekawa 1990). A total of 444 participants were enrolled in the 4 trials (163 in the placebo-controlled trials and 281 in the "active-controlled" trials). The mean age of enrollees was 69 years and ranged from 42 to 89 years. The duration of the trials ranged from 12 to 24 weeks. The overall rate of reported dropouts or losses to follow-up was 6.3% (n = 28) and ranged from 0% to 11.7%.

## Risk of bias in included studies

Treatment allocation concealment was rated unclear in all studies reviewed although 2 indicated randomization (Maekawa 1990; Becker 1988). One trial did not report blinding for either the observers or patients (Dutkiewicz 1996). The two "active-controlled" or comparison trials include interventions that have not been shown to be clinically effective (Maekawa 1990; Dutkiewicz 1996).

## Effects of interventions

Urinary symptoms and Nocturia:

Versus Paraprost , the mean difference (MD) for the IPSS was 0.90 points (95% CI = -0.43 to 2.23) (% improvement from baseline: Cernilton 55%; Paraprost 62%) (Maekawa 1990). For the trial comparing Tadenan 2 undefined symptom scales were utilized to evaluate obstructive or irritative symptoms. The MD for the obstructive scale score was -0.70 points (95% CI = -1.78 to 0.40) (% improvement from baseline: Cernilton 63%; Tadenan 46%) and -0.90 points for the irritative scale score (95% CI = -2.26 to 0.46) (percent improvement from baseline: Cernilton 68%; Tadenan 40%) (Dutkiewicz 1996).

The risk ratio (RR) for self-reported improvement of symptoms versus placebo was 2.40 (95% CI = 1.21 to 4.75) (% of men who reported improvement: Cernilton 69%; placebo 29%) (Buck 1990). The RR versus Tadenan for positive overall therapeutic response was 1.42 (95% CI = 1.21 to 4.75) (% of patients who reported improvement: Cernilton 78%; Tadenan 55%) (Dutkiewicz 1996).

Nocturia results were reported in three studies. Versus placebo, the weighted RR was 2.05 (95% CI = 1.41 to 3.00) (30.8% absolute improvement) (Becker 1988; Buck 1990). Versus Paraprost, the MD was -0.40 times per evening (95% CI = -0.73 to -0.07) (Maekawa 1981Maekawa 1990).

Urinary flow measures and prostate size:

The MDs for peak urine flow and the Uroflow-Index were -1.60 mL/s (95% CI = -5.77 to 2.59) and 0.04 (95% CI = -0.11 to 0.19), respectively (Becker 1988; Buck 1990). Versus Paraprost, the MD was 0.37 mL/s for peak urine flow (95% CI = -1.90, 2.64) (4.6% absolute improvement) and 0.39 mL/s for mean flow rate (95% CI = -0.80 to 1.58) (Maekawa 1981). Versus Tadenan, the MD = 0.33 mL/s (95% CI = -2.00 to 2.66) (8.7% absolute improvement) (Dutkiewicz 1996Dutkiewicz 1996).

The weighted mean difference for residual volume in the two placebo-controlled studies was -14.35 mLs (95% CI -30.35 to 1.66) (36.5% absolute improvement) (Becker 1988; Buck 1990). Versus Tadenan, the MD was -5.00 mL (95% CI -14.98 to 4.98) (Dutkiewicz 1996) and 1.40 mL versus Paraprost (95% CI -20.00 to 22.80) (Maekawa 1990).

The MDs for reduction in prostate size for Tadenan and Paraprost were -2.09 cc (95% CI = -10.21 to 7.97) and -1.12 cc (95% CI = -10.21 to 7.97), respectively (Maekawa 1990; Dutkiewicz 1996).

One placebo-controlled study, reporting changes for three parameters (circumference, transverse diameter, anteroposterior diameter) of prostate volume, found a "statistically significant reduction in the anteroposterior diameter" following treatment with Cernilton (Buck 1990).

Adverse effects:

Cernilton was well tolerated in the short term. The only reported adverse effect associated with the use of Cernilton was one case of mild nausea (Buck 1990). Withdrawal rates were: Cernilton 4.8%; Placebo 2.7%; and Paraprost 5.2% (P = 0.26 for Cernilton versus placebo and P = 0.33 versus Paraprost).

## DISCUSSION

The evidence suggests Cernilton improved subjective symptoms and nocturia in comparison to placebo, Paraprost, and Tadenan. Cernilton was similar to the comparative study agents in improving urinary symptoms when evaluated by symptom scores. Only one adverse effect was reported indicating Cernilton was well tolerated. The dropout rate was less than 5%. In contrast to the modest improvement in subjective symptom outcomes, Cernilton did not significantly improve objective measures such as peak and mean urinary flow rates in comparison with placebo and the control study agents. Although Cernilton was analogous to Paraprost and Tadenan in improving peak flow rates and reducing residual volume and prostate size, these results are limited by the lack of proven efficacy of these agents.

Although the results suggest Cernilton provides modest benefit to men with BPH, the studies assessed for this review were limited by several factors. Treatment allocation concealment was deemed unclear in all four trials and may be indicative of questionable methodological quality of the studies meeting inclusion criteria. Two of the studies reported random allocation without detail of concealment method and 3 reported using a double-blind method. One trial did not report random allocation or a double-blind method (Dutkiewicz 1996). Inadequate concealment of randomization and blinding are known to affect effect sizes of the outcomes (Bero 1995). The treatment duration was short with no studies lasting longer than 24 weeks. Cernilton dosages were not reported in three studies and whether a standardized preparation was utilized is not known. Additionally, fewer than 500 men have been evaluated. Therefore, the long term efficacy and safety of Cernilton as well as their effectiveness in preventing complications of BPH such as acute urinary retention or the need for surgical interventions is not known. Only one study reported results from standardized and validated urologic symptom scale, the IPSS (Maekawa 1990), although a modified Boyarsky Scale was used for one study (Buck 1990). Nocturia was reported in three studies, peak urine flow, including the Uroflow index was reported in four studies, residual volume was reported in four studies, and prostate size was reported in three studies.

## AUTHORS' CONCLUSIONS

### Implications for practice

The available evidence suggests that Cernilton is well tolerated and modestly improves subjective urologic symptoms for up to 24 weeks. Cernilton was not demonstrated to improve urinary flow measures compared to placebo. The long-term effectiveness and safety of Cernilton and its ability to prevent complications from BPH are not known.

### Implications for research

Future trials should be of sufficient size and duration to detect important differences in outcomes including urologic symptom scale scores (e.g., IPSS), mean and peak urine flow, voided volume, prostate size, residual urine volume, development of acute urinary retention or need for surgical intervention. Studies are needed to compare Cernilton, a-blockers, 5a-reductase inhibitors and other phytotherapeutic agents such as *Serenoa repens*. Studies should also use standardized doses of Cernilton products that have been analyzed for purity and potency by an independent laboratory to ensure the quality of the product.

## REFERENCES

### References to studies included in this review


**Becker 1988** *{published data only}*
Becker H, Ebeling L. Konservative therapie der benignen prostata-hyperplasie (BPH) mit Cernilton N. *Urologe B* 1988;**28**:301–306.

**Buck 1990** *{published data only}*
Buck AC, Cox R, Rees RW, Ebeling L, John A. Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, cernilton. a double-blind, placebo-controlled study. *Br J Urol* 1990;**66**(4): 398–404. [MEDLINE: 1991028603]

**Dutkiewicz 1996** *{published data only}*
Dutkiewicz S. Usefulness of Cernilton in the treatment of benign prostatic hyperplasia. *Int Urol Nephrol* 1996;**28**(1): 49–53. [MEDLINE: 1996331567]

**Maekawa 1990** *{published data only}*
Maekawa M, Kishimoto T, Yasumoto R, Wada S, Harada T, Ohara T, Okajima E, Hirao Y, Ohzono S, Shimada K, et al.Clinical evaluation of Cernilton on benign prostatic hypertrophy:a multiple center double-blind study with Paraprost. *Hinyokika Kiyo* 1990;**36**(4):495–516. [MEDLINE: 1990334079]


### References to studies excluded from this review

**Hayashi 1986** *{published data only}*

Hayashi J, Mitsui H, Yamakawa G, et al.Clinical evaluation of Cernilton in benign prostatic hypertrophy. *Hinyo Kiyo* 1986;**32**(1):135–41.

**Yasumoto 1995** *{published data only}*

Yasumoto R, Kawanishi H, Tsujino T, Tsujita M, Nishisaka N, Horii A, Kishimoto T. Clinical evaluation of long-term treatment using Cernitin pollen extract in patients with benign prostatic hyperplasia. *Clin Ther* 1995;**17**(1):82–87. [MEDLINE: 1995277792]

## Additional references

**AB Cernelle**

AB Cernelle. Engelholm, Sweden.

**Bero 1995**

Bero L, Drummond R. The Cochrane Collaboration: preparing, maintaining, and disseminating systematic reviews of the effects of health care. *JAMA* 1995;**274**: 1935–8.

**Berry 1984**

Berry SL, Coffey, DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1984;**132**:474–9. [MEDLINE: 1984292487]

**Buck 1996**

Buck AC. Phytotherapy for the prostate. *Br J Urol* 1996;**78** (3):325–36. [MEDLINE: 1997036289]

**Di Silverio 1993**

Di Silverio F, Flammia GP, Sciarra A, Caponera M, Mauro M, Buscarini M, Tavani M, D'Eramo G. Plant extracts in benign prostatic hyperplasia. *Minerva Urol Nefrol* 1993;**45**: 143–9. [MEDLINE: 1994294881]

**Dickersin 1994**

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**312**:944–7.

**Gerber 1998**

Gerber GS, Zagaja GP, Bales GT, Chodak GW, Contreras BA. Saw palmetto (Serenoa repens) in men with lower urinary tract symptoms: effects on urodynamic parameters and voiding symptoms. *Urology* 1998;**51**(6):1003–7.

**Guess 1992**

Guess HA. Benign prostatic hyperplasia antecedents and natural history. *Epidemiol Rev* 1992;**14**:131–53. [MEDLINE: 1993170433]

**Ito 1986**

Ito R, Ishii M, Yamashita S. Cernitin pollen extract (Cernilton); antiprostatic hypertrophic action of Cernitin pollen extract (Cernilton). *Pharmacometrics* 1986;**31**:1–11.

**Kimura 1986**

Kimura M, Kimura I, Nakase K, Sonobe T, Mori E. Micturition activity of pollen extract: contractile effects on bladder and inhibitory effects on urethral smooth muscle of mouse and pig. *Planta medica* 1986;**2**:148–51.

**Laird 1990**

Laird N, Mosteller F. Some statistical methods for combining experiment results. *Int J Tech Assess Health Care* 1990;**6**:5–30.

**Lau 1996**

Lau J. Meta-Analyst version 0.99. 1996:New England Medical Center.

**McConnell 1994**

McConnell JD, Barry MJ, Bruskewitz RC. Benign prostatic hyperplasia: Diagnosis and treatment. Clinical Practice Guideline No. 8, AHCPR Publication No. 94-0582. 1994: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services. [MEDLINE: 1994122755]

**Nakase 1988**

Nakase S, Takenaka K, Hamanaka T, Kimura M. Effects of Cernilton pollen-extract on the urethral smooth muscle and diaphragmatic neuromuscular specimen. *Folio Pharmacol Japan* 1988;**91**:385–92.

**Oesterling 1995**

Oesterling JE. Benign prostatic hyperplasia. Medical and minimally invasive treatment options. *N Engl J Med* 1995; **332**(2):99–109. [MEDLINE: 1995082886]

**Ruyan 1999**

Ruyan D, Cernitin American. Personal communication. 1999.

**Schulz 1995**

Schulz KF, Chalmers I, Hayes RJ Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408–12.

## References to other published versions of this review

**MacDonald 2000**

MacDonald R, Ishani A, Rutks I, Wilt TJ. A systematic review of cernilton for the treatment of benign prostatic hyperplasia. *BJU Int* 2000;**85**:(in press).

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Becker 1988**

| | |
|---|---|
| Methods | Single-site study.<br>Randomization: noted<br>Patients blinded: Providers blinded:<br>Lost to follow-up: 7 (7%) |
| Participants | Geographic region: Germany<br>Study setting: community<br>n = 103<br>Age range: 42-85 mean: 66.6<br>Race: White<br>Diagnostic criteria: BPH, stage I-II (Vahlensieck). |
| Interventions | Control: matching placebo<br>Treatment: Cernilton 2 capsules three times daily<br>Average follow-up: 12 weeks. |
| Outcomes | Dysuria<br>"Uroflow Index"<br>Bladder residual volume<br>Nocturia<br>Dropouts due to side effects: none |
| Notes | Exclusions: residual volume > 150ml; prostatitis; diagnosed or suspicion of prostate cancer; urinary obstruction or urogenital surgery; neurogenic bladder; bladder stones; currently on other medication; persons with infections |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Buck 1990**

| | |
|---|---|
| Methods | Single-site study.<br>Randomization: unclear<br>Patients blinded: Providers blinded:<br>Lost to follow-up: 7 (11.6%) |
| Participants | Geographic region: UK<br>Study setting: community<br>n = 60<br>Age range: 56-89 mean: 68.6 |

**Buck 1990** (*Continued*)

| | |
|---|---|
| | Race: White<br>Diagnostic criteria: Men awaiting operative treatment for outflow obstruction due to BPH |
| Interventions | Control: matching placebo<br>Treatment: Cernilton 2 capsules two times daily<br>Average follow-up: 24 weeks. |
| Outcomes | "Subjective evaluation" (Improved response rates reported for daytime frequency, nocturia, hesitancy, urgency, intermittency, incomplete emptying, terminal dribble and dysuria)<br>Peak urine flow<br>Bladder residual volume<br>Voided volume<br>Prostate volume<br>Dropouts due to side effects: none |
| Notes | Exclusions: No details provided. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Dutkiewicz 1996**

| | |
|---|---|
| Methods | Single-site study.<br>Randomization: unclear<br>Patients not blinded: Providers not blinded:<br>Lost to follow-up: none |
| Participants | Geographic region: Poland<br>Study setting: community<br>n = 89<br>Age range: 50-68 mean: not reported<br>Race: White<br>Diagnostic criteria: Men with a short history of BPH (no longer than a few weeks duration) without complete urine retention |
| Interventions | Control: Tadenan 2 tablets twice daily.<br>Treatment: Cernilton 2 tablets three times daily x 2 weeks followed by 1 tablet three times daily up to 4 months.<br>Average follow-up: 24 weeks. |
| Outcomes | Obstructive symptom score<br>Irritative symptom score<br>Peak urine flow<br>Bladder residual volume<br>Prostate volume |

**Dutkiewicz 1996** (*Continued*)

| | |
|---|---|
| | Dropouts due to side effects: none |
| Notes | Exclusions: No details provided. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Maekawa 1990**

| | |
|---|---|
| Methods | Multisite study.<br>Randomization: noted<br>Patients blinded: Providers blinded:<br>Lost to follow-up: 14 (7%). Efficacy studied in 159 subjects |
| Participants | Geographic region: Japan<br>Study setting: community<br>n = 192<br>Age range: 54-86 mean: 70<br>Race: Asian<br>Diagnostic criteria: Symptom score; peak urine flow rate 10ml/s (over 150ml); mean urine flow 7ml/s; residual volume < 50ml |
| Interventions | Control: Paraprost 6g capsules twice daily<br>Treatment: Cernilton 63mg capsules twice daily<br>Average follow-up: 12 weeks. |
| Outcomes | Symptom score (not specified).<br>Peak urine flow<br>Mean urine flow<br>Total voided volume<br>Bladder residual volume<br>Prostate size (volume)<br>Nocturia<br>Dropouts due to side effects: |
| Notes | Exclusions: prostate cancer; other cancers;current/contraindicated medications; prior treatment |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Hayashi 1986 | No control group. |
| Yasumoto 1995 | No control group. |

## DATA AND ANALYSES

### Comparison 1. Cernilton versus Paraprost

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 IPSS (points) | 1 | 192 | Mean Difference (IV, Random, 95% CI) | 0.90 [-0.43, 2.23] |
| 2 Nocturia (times per evening) | 1 | 185 | Mean Difference (IV, Random, 95% CI) | -0.40 [-0.73, -0.07] |
| 3 Peak urine flow (mL/sec) | 1 | 123 | Mean Difference (IV, Random, 95% CI) | 0.37 [-1.90, 2.64] |
| 4 Residual volume (mL) | 1 | 120 | Mean Difference (IV, Random, 95% CI) | 1.40 [-18.00, 22.80] |
| 5 Mean urine flow (mL/sec) | 1 | 124 | Mean Difference (IV, Random, 95% CI) | 0.39 [-0.80, 1.58] |
| 6 Prostate size (cc) | 1 | 74 | Mean Difference (IV, Random, 95% CI) | -1.12 [-10.21, 7.97] |

### Comparison 2. Cernilton versus Tadenan

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Positive therapeutic response | 1 | 89 | Risk Ratio (M-H, Random, 95% CI) | 1.42 [1.03, 1.95] |
| 2 Peak urine flow (mL/sec) | 1 | 89 | Mean Difference (IV, Random, 95% CI) | 0.33 [0.00, 2.66] |
| 3 Residual volume (mL) | 1 | 89 | Mean Difference (IV, Random, 95% CI) | -5.0 [-14.98, 4.98] |
| 4 Obstructive symptom score (points) | 1 | 89 | Mean Difference (IV, Random, 95% CI) | -0.70 [-1.78, 0.38] |
| 5 Irritative symptom score (points) | 1 | 89 | Mean Difference (IV, Fixed, 95% CI) | -0.90 [-2.26, 0.46] |
| 6 Prostate size (cc) | 1 | 90 | Mean Difference (IV, Fixed, 95% CI) | -2.09 [-5.53, 1.35] |

### Comparison 3. Cernilton versus Placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Overall improvement-subjective symptoms: Boyarsky Scale | 1 | 57 | Risk Ratio (M-H, Random, 95% CI) | 2.40 [1.21, 4.75] |
| 2 Nocturia: reported improvement | 2 | 153 | Risk Ratio (M-H, Random, 95% CI) | 2.06 [1.41, 2.99] |
| 3 Peak urine flow (mL/sec) | 1 | 50 | Mean Difference (IV, Random, 95% CI) | -1.60 [-5.79, 2.59] |
| 4 Residual volume (mL) | 2 | 148 | Mean Difference (IV, Random, 95% CI) | -14.35 [-30.35, 1.66] |
| 5 Uroflow-Index | 1 | 96 | Mean Difference (IV, Random, 95% CI) | 0.04 [-0.11, 0.19] |

### Analysis 1.1. Comparison 1 Cernilton versus Paraprost, Outcome 1 IPSS (points).

Review: Cernilton for benign prostatic hyperplasia

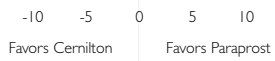
Comparison: 1 Cernilton versus Paraprost

Outcome: 1 IPSS (points)

| Study or subgroup | Cernilton N | Mean(SD) | Paraprost N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Maekawa 1990 | 96 | 5.2 (4.7) | 96 | 4.3 (4.7) | | 100.0 % | 0.90 [ -0.43, 2.23 ] |
| **Total (95% CI)** | **96** | | **96** | | | **100.0 %** | **0.90 [ -0.43, 2.23 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.33 (P = 0.18)




### Analysis 1.2. Comparison 1 Cernilton versus Paraprost, Outcome 2 Nocturia (times per evening).

Review: Cernilton for benign prostatic hyperplasia

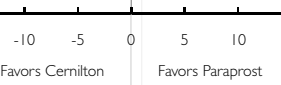
Comparison: 1 Cernilton versus Paraprost

Outcome: 2 Nocturia (times per evening)

| Study or subgroup | Cernilton N | Mean(SD) | Paraprost N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Maekawa 1990 | 92 | 2.8 (1.15) | 93 | 3.2 (1.16) | | 100.0 % | -0.40 [ -0.73, -0.07 ] |
| **Total (95% CI)** | **92** | | **93** | | | **100.0 %** | **-0.40 [ -0.73, -0.07 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 2.36 (P = 0.019)

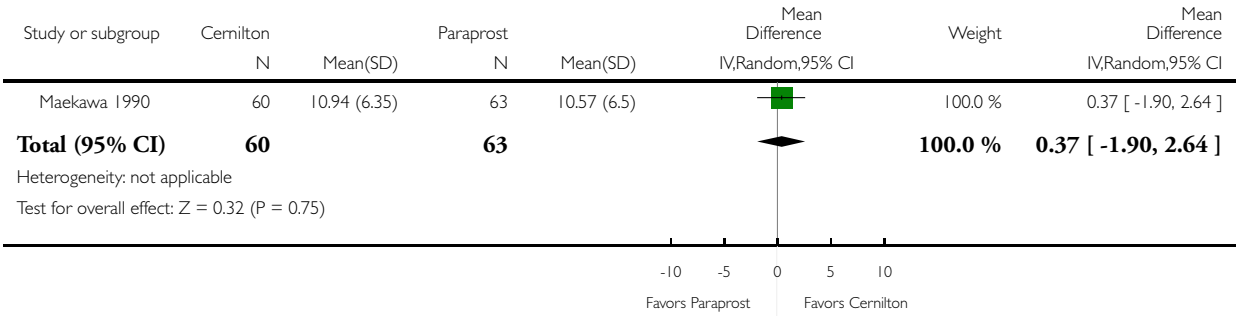


### Analysis 1.3. Comparison 1 Cernilton versus Paraprost, Outcome 3 Peak urine flow (mL/sec).

Review: Cernilton for benign prostatic hyperplasia

Comparison: 1 Cernilton versus Paraprost

Outcome: 3 Peak urine flow (mL/sec)

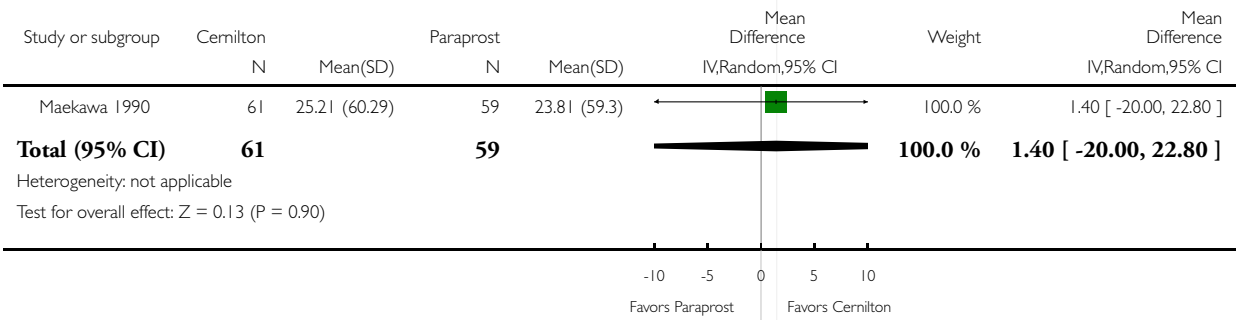



### Analysis 1.4. Comparison 1 Cernilton versus Paraprost, Outcome 4 Residual volume (mL).

Review: Cernilton for benign prostatic hyperplasia

Comparison: 1 Cernilton versus Paraprost

Outcome: 4 Residual volume (mL)



### Analysis 1.5. Comparison 1 Cernilton versus Paraprost, Outcome 5 Mean urine flow (mL/sec).

Review: Cernilton for benign prostatic hyperplasia

Comparison: 1 Cernilton versus Paraprost

Outcome: 5 Mean urine flow (mL/sec)

| Study or subgroup | Cernilton N | Mean(SD) | Paraprost N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Maekawa 1990 | 61 | 5.96 (3.36) | 63 | 5.57 (3.41) | | 100.0 % | 0.39 [ -0.80, 1.58 ] |
| **Total (95% CI)** | **61** | | **63** | | | **100.0 %** | **0.39 [ -0.80, 1.58 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.64 (P = 0.52)




### Analysis 1.6. Comparison 1 Cernilton versus Paraprost, Outcome 6 Prostate size (cc).

Review: Cernilton for benign prostatic hyperplasia

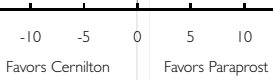
Comparison: 1 Cernilton versus Paraprost

Outcome: 6 Prostate size (cc)

| Study or subgroup | Cernilton N | Mean(SD) | Paraprost N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Maekawa 1990 | 39 | 30.97 (20.48) | 35 | 32.09 (19.4) | | 100.0 % | -1.12 [ -10.21, 7.97 ] |
| **Total (95% CI)** | **39** | | **35** | | | **100.0 %** | **-1.12 [ -10.21, 7.97 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.24 (P = 0.81)



### Analysis 2.1. Comparison 2 Cernilton versus Tadenan, Outcome 1 Positive therapeutic response.

Review: Cernilton for benign prostatic hyperplasia

Comparison: 2 Cernilton versus Tadenan

Outcome: 1 Positive therapeutic response

| Study or subgroup | Cernilton n/N | Tadenan n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Dutkiewicz 1996 | 40/51 | 21/38 | | 100.0 % | 1.42 [ 1.03, 1.95 ] |
| **Total (95% CI)** | **51** | **38** | | **100.0 %** | **1.42 [ 1.03, 1.95 ]** |
| Total events: 40 (Cernilton), 21 (Tadenan) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.14 (P = 0.032) | | | | | |


### Analysis 2.2. Comparison 2 Cernilton versus Tadenan, Outcome 2 Peak urine flow (mL/sec).

Review: Cernilton for benign prostatic hyperplasia

Comparison: 2 Cernilton versus Tadenan

Outcome: 2 Peak urine flow (mL/sec)

| Study or subgroup | Cernilton N | Mean(SD) | Tadenan N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Dutkiewicz 1996 | 51 | 15.51 (6) | 38 | 15.18 (5.18) | | 100.0 % | 0.33 [ -2.00, 2.66 ] |
| **Total (95% CI)** | **51** | | **38** | | | **100.0 %** | **0.33 [ -2.00, 2.66 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.28 (P = 0.78) | | | | | | | |

### Analysis 2.3. Comparison 2 Cernilton versus Tadenan, Outcome 3 Residual volume (mL).

Review: Cernilton for benign prostatic hyperplasia

Comparison: 2 Cernilton versus Tadenan

Outcome: 3 Residual volume (mL)

| Study or subgroup | Cernilton N | Mean(SD) | Tadenan N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Dutkiewicz 1996 | 51 | 45 (25.71) | 38 | 50 (22.19) | | 100.0 % | -5.00 [ -14.98, 4.98 ] |
| **Total (95% CI)** | **51** | | **38** | | | **100.0 %** | **-5.00 [ -14.98, 4.98 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.98 (P = 0.33)


### Analysis 2.4. Comparison 2 Cernilton versus Tadenan, Outcome 4 Obstructive symptom score (points).

Review: Cernilton for benign prostatic hyperplasia

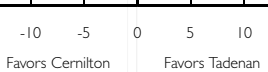
Comparison: 2 Cernilton versus Tadenan

Outcome: 4 Obstructive symptom score (points)

| Study or subgroup | Cernilton N | Mean(SD) | Tadenan N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Dutkiewicz 1996 | 51 | 1.9 (2.78) | 38 | 2.6 (2.4) | | 100.0 % | -0.70 [ -1.78, 0.38 ] |
| **Total (95% CI)** | **51** | | **38** | | | **100.0 %** | **-0.70 [ -1.78, 0.38 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.27 (P = 0.20)



### Analysis 2.5. Comparison 2 Cernilton versus Tadenan, Outcome 5 Irritative symptom score (points).

Review: Cernilton for benign prostatic hyperplasia

Comparison: 2 Cernilton versus Tadenan

Outcome: 5 Irritative symptom score (points)

| Study or subgroup | Cernilton N | Mean(SD) | Tadenan N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Dutkiewicz 1996 | 51 | 1.2 (3.5) | 38 | 2.1 (3.02) | | 100.0 % | -0.90 [ -2.26, 0.46 ] |
| **Total (95% CI)** | **51** | | **38** | | | **100.0 %** | **-0.90 [ -2.26, 0.46 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable


### Analysis 2.6. Comparison 2 Cernilton versus Tadenan, Outcome 6 Prostate size (cc).

Review: Cernilton for benign prostatic hyperplasia

Comparison: 2 Cernilton versus Tadenan

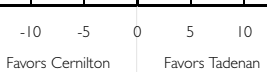
Outcome: 6 Prostate size (cc)

| Study or subgroup | Cernilton N | Mean(SD) | Tadenan N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Dutkiewicz 1996 | 51 | 48.58 (8.86) | 39 | 50.67 (7.74) | | 100.0 % | -2.09 [ -5.53, 1.35 ] |
| **Total (95% CI)** | **51** | | **39** | | | **100.0 %** | **-2.09 [ -5.53, 1.35 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.19 (P = 0.23)

Test for subgroup differences: Not applicable



### Analysis 3.1. Comparison 3 Cernilton versus Placebo, Outcome 1 Overall improvement-subjective symptoms: Boyarsky Scale.

Review: Cernilton for benign prostatic hyperplasia

Comparison: 3 Cernilton versus Placebo

Outcome: 1 Overall improvement-subjective symptoms: Boyarsky Scale

| Study or subgroup | Cernilton n/N | placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Buck 1990 | 20/31 | 7/26 | | 100.0 % | 2.40 [ 1.21, 4.75 ] |
| **Total (95% CI)** | **31** | **26** | | **100.0 %** | **2.40 [ 1.21, 4.75 ]** |

Total events: 20 (Cernilton), 7 (placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 2.50 (P = 0.012)


### Analysis 3.2. Comparison 3 Cernilton versus Placebo, Outcome 2 Nocturia: reported improvement.

Review: Cernilton for benign prostatic hyperplasia

Comparison: 3 Cernilton versus Placebo

Outcome: 2 Nocturia: reported improvement

| Study or subgroup | Cernilton n/N | Placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Becker 1988 | 33/48 | 16/48 | | 71.9 % | 2.06 [ 1.32, 3.21 ] |
| Buck 1990 | 17/31 | 7/26 | | 28.1 % | 2.04 [ 1.00, 4.14 ] |
| **Total (95% CI)** | **79** | **74** | | **100.0 %** | **2.06 [ 1.41, 2.99 ]** |

Total events: 50 (Cernilton), 23 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 3.76 (P = 0.00017)

### Analysis 3.3. Comparison 3 Cernilton versus Placebo, Outcome 3 Peak urine flow (mL/sec).

Review: Cernilton for benign prostatic hyperplasia

Comparison: 3 Cernilton versus Placebo

Outcome: 3 Peak urine flow (mL/sec)

| Study or subgroup | Cernilton N | Mean(SD) | placebo N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Buck 1990 | 26 | 10.5 (7.7) | 24 | 12.1 (7.4) | | 100.0 % | -1.60 [ -5.79, 2.59 ] |
| **Total (95% CI)** | **26** | | **24** | | | **100.0 %** | **-1.60 [ -5.79, 2.59 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.75 (P = 0.45)


### Analysis 3.4. Comparison 3 Cernilton versus Placebo, Outcome 4 Residual volume (mL).

Review: Cernilton for benign prostatic hyperplasia

Comparison: 3 Cernilton versus Placebo

Outcome: 4 Residual volume (mL)

| Study or subgroup | Cernilton N | Mean(SD) | Placebo N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Becker 1988 | 48 | 22.5 (41.08) | 48 | 37 (41.08) | | 94.8 % | -14.50 [ -30.94, 1.94 ] |
| Buck 1990 | 28 | 101.9 (134.46) | 24 | 113.4 (124.48) | | 5.2 % | -11.50 [ -81.93, 58.93 ] |
| **Total (95% CI)** | **76** | | **72** | | | **100.0 %** | **-14.35 [ -30.35, 1.66 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.94); $I^2 = 0.0\%$

Test for overall effect: Z = 1.76 (P = 0.079)

**Analysis 3.5. Comparison 3 Cernilton versus Placebo, Outcome 5 Uroflow-Index.**

Review: Cernilton for benign prostatic hyperplasia

Comparison: 3 Cernilton versus Placebo

Outcome: 5 Uroflow-Index

| Study or subgroup | Cernilton N | Mean(SD) | Placebo N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Becker 1988 | 48 | 0.86 (0.38) | 48 | 0.82 (0.38) | | 100.0 % | 0.04 [ -0.11, 0.19 ] |
| **Total (95% CI)** | **48** | | **48** | | | **100.0 %** | **0.04 [ -0.11, 0.19 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.52 (P = 0.61)


## WHAT'S NEW

Last assessed as up-to-date: 30 March 1998.

| Date | Event | Description |
|---|---|---|
| 13 May 2008 | Amended | Converted to new review format. |

## HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 2, 2000

| Date | Event | Description |
|---|---|---|
| 31 March 1998 | New citation required and conclusions have changed | Substantive amendment |

## DECLARATIONS OF INTEREST

None.

## SOURCES OF SUPPORT


### Internal sources

- Management Decision and Research Center-Department of Veterans Affairs HSRD, USA.
- Minneapolis/VISN-13 Center for Chronic Disease Outcomes Research, USA.

### External sources

- No sources of support supplied


## INDEX TERMS

### Medical Subject Headings (MeSH)

Phytotherapy; Plant Extracts [*therapeutic use]; Prostatic Hyperplasia [*drug therapy]; Secale cereale

### MeSH check words

Humans; Male