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Efficacy and safety of a hexanic extract of *Serenoa repens* (Permixon®) for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH): systematic review and meta-analysis of randomised controlled trials and observational studies

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Objectives

To comprehensively evaluate the efficacy and safety of the hexanic extract of *Serenoa repens* (HESr, Permixon®; Pierre Fabre Médicament, Castres, France), at a dose of 320 mg daily, as monotherapy for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH).

Materials and methods

We conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) and prospective observational studies in patients with LUTS/BPH identified through searches in Medline, Web of Knowledge (Institute for Scientific Information), Scopus, the Cochrane Library, and bibliographic references up to March 2017. Articles studying *S. repens* extracts other than Permixon were excluded. Data were collected on International Prostate Symptom Score (IPSS), maximum urinary flow rate (Q_{max}), nocturia, quality of life, prostate volume, sexual function, and adverse drug reactions (ADRs). Data obtained from RCTs and observational studies were analysed jointly and separately using a random effects model. A sub-group analysis was performed of studies that included patients on longer-term treatment (≥1 year).

Results

Data from 27 studies (15 RCTs and 12 observational studies) were included for meta-analysis (total $N = 5\,800$). Compared with placebo, the HESr was associated with 0.64 (95% confidence interval [CI] −0.98 to −0.31) fewer voids/night ($P < 0.001$) and an additional mean increase in Q_{max}

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of 2.75 mL/s (95% CI 0.57 to 4.93; $P = 0.01$). When compared with α-blockers, the HESr showed similar improvements on IPSS (weighted mean difference [WMD] 0.57, 95% CI −0.27 to 1.42; $P = 0.18$) and a comparable increase in Q_{max} to tamsulosin (WMD −0.02, 95% CI −0.71 to 0.66; $P = 0.95$). Efficacy assessed using the IPSS was similar after 6 months of treatment between the HESr and 5α-reductase inhibitors (5ARIs). Analysis of all available published data for the HESr showed a mean improvement in IPSS from baseline of −5.73 points (95% CI −6.91 to −4.54; $P < 0.001$). HESr did not negatively affect sexual function and no clinically relevant effect was observed on prostate-specific antigen. Prostate volume decreased slightly. Similar efficacy results were seen in patients treated for ≥1 year ($n = 447$). The HESr had a favourable safety profile, with gastrointestinal disorders being the most frequent ADR (mean incidence of 3.8%).

Conclusion

The present meta-analysis, which includes all available RCTs and observational studies, shows that the HESr (Permixon) reduced nocturia and improved Q_{max} compared with placebo and had a similar efficacy to tamsulosin and short-term 5-ARI in relieving LUTS. HESr (Permixon) appears to be an efficacious and well-tolerated therapeutic option for the long-term medical treatment of LUTS/BPH.

Keywords

systematic review, meta-analysis, LUTS/BPH, hexanic extract, *Serenoa repens*, Permixon

Introduction

LUTS are prevalent in adult men and are often associated with the presence of BPH [1]. LUTS associated with BPH (LUTS/BPH) is a troublesome condition that can have a significant negative impact on patients' quality of life (QOL) [2].

A range of treatment options are currently available for LUTS/BPH, including medical treatment and surgical interventions; watchful waiting might also be considered a management option in men whose symptoms are not overly bothersome and who are considered at low risk of clinical progression [3]. Medical therapies used to treat LUTS/BPH include α_1-blockers, 5α-reductase inhibitors (5ARIs), muscarinic receptor antagonists, phosphodiesterase 5 inhibitors, and phytotherapy [3], several of which can be used in combination.

Serenoa repens (*S. repens*) is the phytotherapeutic agent most commonly used to treat LUTS/BPH and is the most thoroughly studied, although systematic reviews and meta-analyses of *S. repens* data from RCTs have reported somewhat contrasting results. In a Cochrane meta-analysis, Tacklind et al. [4] concluded that *S. repens* does not improve LUTS or maximum urinary flow rate (Q_{max}) compared with placebo in men with BPH. However, a previous meta-analysis from the same group of researchers showed that *S. repens* improves urological symptoms and flow measures compared to placebo and that it produces similar improvement in urinary tract symptoms and urinary flow to finasteride, with fewer adverse events (AEs) [5,6]. One explanation for these apparently contradictory results is that the earlier meta-analysis mainly included randomised controlled trials (RCTs) investigating a specific brand of *S. repens* (Permixon®; Pierre Fabre Médicament, Castres, France) whilst the subsequent meta-analysis included several brands. As the composition of *S. repens* extracts varies significantly between manufacturers [7] and as different extraction techniques may affect the composition and biological activity of different brands of *S. repens* [8], it is possible that the greater focus on Permixon® in the earlier meta-analysis and the inclusion of a broader range of products in the second led to the different results.

Meta-analysis on plant extracts should therefore only include phytotherapeutic agents that have used the same validated extraction technique and/or have the same level of active ingredients as the pharmacokinetic properties can vary significantly, a fact which is clearly reflected in the 2017 European Association of Urology (EAU) Guidelines [3]. The two systematic reviews and meta-analyses that have focused exclusively on the hexanic extract of *S. repens* (HESr, Permixon) [9,10] are examples of this approach. The earlier review by Boyle et al. [9] showed significant improvements in Q_{max}, nocturia, and IPSS with the HESr, whilst the more recent meta-analysis of RCTs, which included the latest publications, came to similar conclusions [10]. However, both meta-analyses drew primarily on results from RCTs. The inclusion of data from observational studies, which are more often performed under conditions of usual practice and that include a wide range of patients, can provide relevant, complementary information in systematic reviews [11–15].

The objective of the present study was to carry out an exhaustive systematic review and meta-analysis of all available RCTs and prospective observational studies performed with the HESr (Permixon®) and to provide a comprehensive overview of its efficacy and tolerability for the medical treatment of LUTS/BPH.

Materials and Methods

Search Strategy

The meta-analysis was performed according to a pre-specified protocol guided by standards established for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [16]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [17] were used to guide reporting of the study.

Data searches were carried out up to April 2017 in four electronic databases (Medline, Web of Knowledge [Institute for Scientific Information], Scopus, and The Cochrane Library) to identify eligible studies published from inception through to March 2017.

Search terms included '*Serenoa repens*', 'saw palmetto', '*Sabal serrulata*', 'Permixon', 'benign prostatic hyperplasia', 'BPH', 'prostatic adenoma', 'prostatic hypertrophy', 'lower urinary tract symptom', and 'LUTS', which were combined with terms such as 'efficacy', 'tolerability', and 'outcome'. Reference lists of identified articles and published reviews were also hand searched.

Eligibility Criteria

We included studies that assessed the efficacy and/or safety of the HESr (Permixon) at a daily dosage of 320 mg in patients with LUTS/BPH. Articles were included for review if it was clearly indicated that the product studied was the HESr (Permixon®) or if that information could be easily deduced from the content. Study designs considered eligible for review included RCTs, non-randomised controlled trials, case-control studies, and prospective observational studies if they included data on the selected outcomes. There were no limitations on publication language. Theses, governmental reports and clinical surveys were excluded, as were clinical cases, studies on corpses, *in vitro* studies, or studies in populations other than human adult males.

Study Selection and Data Extraction

Two independent reviewers examined the results of the literature search and classified studies as being potentially suitable for inclusion based first on titles and abstracts, then on full texts. Disagreements about the relevance of individual studies were resolved in discussion with a third reviewer. The final list of articles for data extraction was agreed upon in discussions amongst the study team.

Two reviewers working independently and using a standardised form extracted data from the articles. The two sets of extracted data were then compared by one of the reviewers and discrepancies were resolved by either referring to the original source text and/or by discussion amongst the reviewers, with the assistance of a third reviewer if necessary. Data were extracted on study setting and design, study population, treatment characteristics (dose and duration), and outcomes, as described below. In the case of one observational study [18], only sub-groups of patients with comparable baseline characteristics in terms of LUTS severity were included when comparing results between the HESr and α-blockers or 5ARIs, to ensure comparability of results.

Outcomes Assessed

Data were extracted on the following outcomes: IPSS, Q_{max} (mL/s), nocturia, QOL (IPSS item 8, on a 0–6 scale), prostate volume, and sexual function. A decrease of ≥3.1 points on the IPSS was considered to represent a clinically relevant difference, as previously reported [19]. A subgroup analysis of studies reporting data for ≥1 year of treatment was also carried out to explore longer-term effects of treatment. A sub-group analysis was also performed by using a random effects model to test results for observational studies and RCTs separately. Results for the two types of study were then compared using a chi-squared test for subgroup differences.

In the case of safety data, we differentiated between adverse drug reactions (ADR) and AEs based on how the outcome was reported by the original study. An ADR was defined as a response to a drug that is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function. An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment [20].

Quality Assessment

As both observational studies and RCTs were included in the review, a quality indicator was sought which was suitable for both study types. The Quality Index (QI) was developed by Downs and Black [21], and is appropriate for assessing randomised and non-randomised studies. It consists of 26 items covering reporting, external validity, bias, confounding, and sample size, and has been shown to have good internal consistency, test–retest and inter-rater reliability. The score range for the QI is 0–27, with higher scores indicating better quality. Assessment of study quality was carried out by one reviewer with support from another reviewer if needed.

Statistical Methods

Continuous outcomes (IPSS, nocturia, QOL and Q_{max}) were expressed as mean pre–post treatment differences when assessing the effect of the HESr alone or as the difference between pre- and post-treatment values when comparing the

HESr with placebo or other active treatments. For dichotomous outcomes (ADR), proportions were used to assess the effect of the HESr. Meta-analysis was performed using a random effects model to summarise outcomes from the studies included [22]. When standard deviations (SDs) or standard errors (SEs) for mean differences were not provided in the original publication, they were imputed from other studies included in the analysis. For all outcomes studied, sensitivity analysis was performed by excluding studies that did not provide either SDs or SEs.

The Woolf statistic [23], from which we calculated the I^2 statistic, was used to analyse the degree of heterogeneity amongst studies. If significant heterogeneity due to outliers was found, secondary analysis was performed by sequentially removing studies considered as outliers (standardised residual absolute value >2) and meta-analyses refitted until no studies were considered outliers. When assessing the size of effect attributable to the HESr, we distinguished between observational studies and RCTs by performing a random effects model meta-analysis within each group. Summarised results were then compared using a *Z*-test.

Results are displayed as forest plots, while the presence of publication bias was explored using funnel plots [24]. If publication bias was suspected, additional sensitivity analysis was performed by removing the studies potentially associated with this bias and repeating the analysis. The results of the analysis were reviewed and interpreted independently by all authors.

For all analyses, 95% CIs are reported and test results are considered significant for $P < 0.05$. All analyses were performed in R (version 3.2.2) [25] using the 'meta' [26] and 'metafor' [27] packages (R, R Foundation for Statistical Computing, Vienna, Austria).

Results

Data for meta-analysis were extracted from a total of 27 studies, of which 15 [28–42] were RCTs and 12 [18,43–53] were observational studies. The selected studies included 5 800 patients corresponding to: Permixon (*n* = 3 926); α-blockers (*n* = 775; tamsulosin [*n* = 377], unspecified [*n* = 398]); 5ARIs (*n* = 578; finasteride [*n* = 484], unspecified [*n* = 94]); placebo (*n* = 301); control group (*n* = 190); and gestonorone caproate (*n* = 30). The subgroup analysis of studies reporting ≥1 year of treatment included three clinical trials [40, 50, 51] with data from 447 patients. The PRISMA trial flow diagram for the systematic review is presented in Fig. 1.

The key characteristics of the studies included in the meta-analysis are shown in Tables 1 and 2. Of the 27 studies included, one RCT [35] and one observational study [45] were used solely for information on ADR due to a lack of precision in the efficacy data. Articles were published between 1983 [28] and 2016 [18] with sample sizes ranging from 10 [43] to 1 713 [18]. Study duration ranged from 1 month [36] to 60 months [50], although the most frequent duration was 3 months (10 studies). In most of the comparative studies, the comparator used was placebo [28–32,34,36], although some studies compared the HESr to 5ARIs [18,37] or α-blockers [18,40,42], whilst two studies [38,39] compared different forms of administration of the HESr. Scores on the Downs and Black QI (DBQI) ranged from 3 [46] to 25 [40], with a mean of 15 for the RCTs and 11 for the observational studies.

Supporting information for the most relevant outcomes, including funnel plots of all analysed outcomes and, where appropriate, the results of sensitivity analysis, is shown in Figs S1–S11.

Permixon Compared to Placebo

All studies included in this analysis were RCTs and of moderate quality, according to the DBQI (score between 6 and 17).

Figure 2 shows the forest plots for efficacy data of the HESr in comparison with placebo for nocturia and Q_{max}. The meta-analysis (Fig. 2a) shows a benefit of 0.64 (95% CI −0.98 to −0.31) fewer voids/night for the HESr ($P < 0.001$). Data on Q_{max} were available from four studies [28,29,32,36], with the HESr providing an additional benefit over placebo of 2.75 mL/s (95% CI 0.57 to 4.93; $P = 0.014$; Fig. 2b). No heterogeneity was observed. Funnel plots of the nocturia and Q_{max} analysis suggest no publication bias (Figs S1 and S2, respectively).

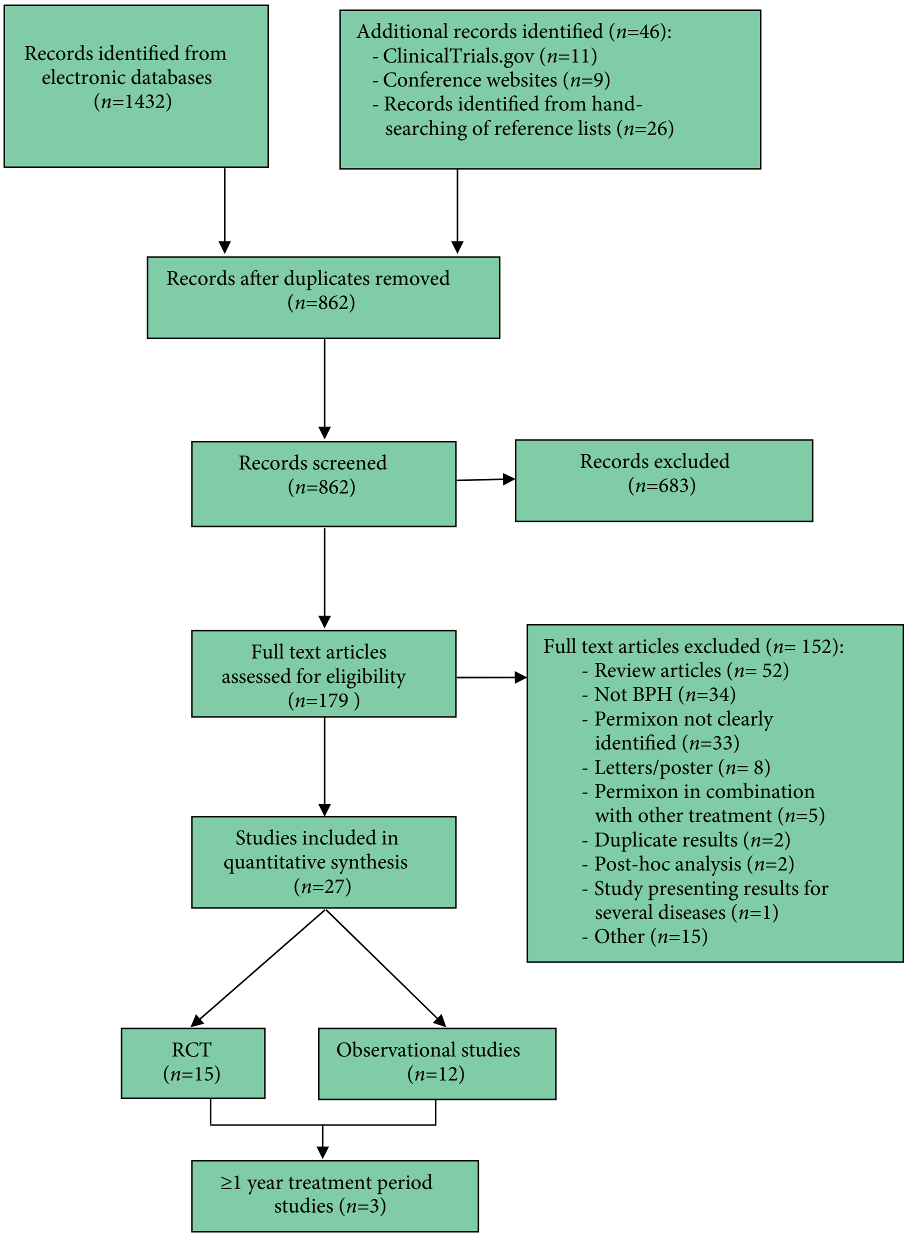
Permixon Compared to α-Blockers

Three studies [18,40,42], two RCTs and one observational study, reported data on IPSS; all were of high quality based on their DBQI scores (between 19 and 25).

Figure 3a shows a difference in effect between HESr and α-blockers on IPSS of 0.57 points, although the difference was not statistically significant (95% CI −0.27 to 1.42; $P = 0.18$). The result was almost identical when data from a study identified as an outlier was excluded (WMD 0.3, 95% CI −0.29 to 0.89; $P = 0.31$; Fig. S3). When only data from RCTs was used, the results were similar, with no statistically significant difference between arms ($P = 0.35$).

The effect of the HESr and tamsulosin on Q_{max} and prostate volume was compared using data from two RCTs [40,42]. No statistically significant differences were found for either endpoint ($P = 0.95$ for Q_{max}, Fig. 3b; and $P = 0.34$ for prostate volume, Fig. 3c). Likewise, no statistically significant differences were found between the HESr and α-blockers in terms of effect on PSA ($P = 0.60$, Fig. 3d).

Figure 1 PRISMA flow chart.



Permixon Compared to 5ARIs

Two studies [18,37], with a DBQI score of 19 and 21, respectively, compared the effects of 5ARIs and the HESr on IPSS outcomes. There was no statistically significant difference between the treatments at the 6-month follow-up (difference of 0.46 points, 95% CI −0.41 to 1.34; $P = 0.30$; Fig. 4a). In the same studies, PSA values showed a statistically significant reduction ($P < 0.001$) with 5ARIs compared with stable PSA values with the HESr (Fig. 4b). No heterogeneity was observed between the studies for either outcome ($I^2 = 0\%$, $P > 0.49$).

Permixon, Change from Baseline

Figure 5 shows change from baseline with the HESr over a range of outcomes. The mean IPSS (Fig. 5a) improved by −5.73 points (95% CI −6.91 to −4.54; $P < 0.001$), with symptom relief seen both in patients with moderate–severe symptoms and in those with mild symptoms [53]. Study quality varied widely with the DBQI score ranging between 5 and 25. There was no significant difference between the results obtained using data from RCTs (WMD −5.76, 95% CI −7.00 to −4.52; $P < 0.001$) and those obtained using data from observational studies (WMD −5.70; 95% CI

Table 1 Key features of studies included for quantitative analysis – RCTs (n = 15).

RCTs										
References	Arms (n)	Randomised Y/N/blind	Withdrawals, n (%)	Study duration, months	Age, years mean or range	Change in IPSS from baseline, mean (SD)	Change in voids/night, mean (SD)	Change in QOL score*, mean (SD)	Change in Q_{max}, mL/s, mean (SD)	Study quality (DBQI score)†
Boccafoschi et al. (1983) [28]	Permixon (11) Placebo (11)	Y Single blind	0	2	68	–	Permixon: −2.20 (1.62) Placebo: −1.00 (1.62)	–	Permixon: 4.13 (8.62) Placebo: 1.96 (8.62)	12
Emile et al. (1983) [29]	Permixon (15) Placebo (15)	Y Double blind	0	1	–	–	Permixon: −1.66 (1.94) Placebo: −0.34 (1.75)	–	Permixon: 3.37 (4.94) Placebo: 0.20 (3.79)	6
Champault et al. (1984) [30]	Permixon (55) Placebo (55)	Y Double blind	16 (15)	1	–	–	Permixon: −1.43 (1.17) Placebo: −0.48 (1.26)	–	–	14
Cukier et al. (1985) [31]	Permixon (70) Placebo (76)	Y Double blind	22 (13)	3	69	–	Permixon: −1.10 (1.62) Placebo: −0.50 (1.56)	–	–	12
Tasca et al. (1985) [32]	Permixon (14) Placebo (13)	Y Double blind	3 (10)	2	61	–	Permixon: −2.60 (1.62) Placebo: −1.20 (1.68)	–	Permixon: 3.30 (5.72) Placebo: 0.60 (3.23)	9
Pannunzio et al. (1986) [33]	Permixon (30) OHPC (30)‡	Y NR	0	2	64	–	–	–	Permixon: 5.1 (13.66) OHPC: 2.2	10
Reece Smith et al. (1986) [34]	Permixon (33) Placebo (37)	Y Double blind	10 (13)	3	67	–	Permixon: −1.00 (1.59) Placebo: −1.00 (1.65)	–	–	10
Dathe and Schmid (1991) [35]	Permixon 320 mg/day (24) Permixon (960 mg/day) (25)	Y NR	–	6 (24 weeks)	–	–	–	–	–	11
Descotes et al. (1995) [36]	Permixon (82) Placebo (94)	Y Double blind	39 (18)	1	66	–	Permixon: −0.67 (1.05) Placebo: −0.32 (0.81)	–	Permixon: 3.40 (14.00) Placebo: 1.10 (11.2)	17
Carraro et al. (1996) [37]	Permixon (467) Finasteride (484)	Y Double blind	147 (14)	6	64	Permixon: −5.8 (8.0) 5ARI: −6.20 (7.78)	–	Permixon: – 1.38 (1.82)	Permixon: 2.68 (6.36) 5ARI: 3.20 (7.88)	21
Stepanov et al. (1999) [38]	Permixon BID (45) Permixon OD (47)	Y Double blind	5 (10) 3 (6)	3	67	BID: −6.40 (5.40) OD: −6.50 (5.90)	–	BID: −1.00 (8.31) OD: −1.10 (9.01)	BID: 1.80 (20.09) OD: 1.40 (18.99)	19
Giannakopoulos et al. (2002) [39]	Permixon BID (50) Permixon TID (50)	Y Double blind	–	6	64	BID: −7.60 (1.94) TID: −8.48 (2.15)	–	BID: −0.52 (0.86) TID: −0.62 (0.90)	BID: 2.80 (1.95) TID: 4.54 (1.80)	22
Debruyne et al. (2002) [40]	Permixon (269) Tamsulosin (273)	Y Double blind	54 (15.4) 56(15.8)	12	66	Permixon: −4.40 (5.50) Tamsulosin: −4.40 (5.06)	–	–	Permixon: 1.90 (4.80) Tamsulosin: 1.80 (4.82)	25
Vela Navarrete et al. (2003) [41]	Permixon (16) Control (19)	Y NR	–	3	50–75	−5.10 (6.38)	–	–	–	17
Latil et al. (2015) [42]	Permixon (102) Tamsulosin (104)	Y Double blind	Permixon: 19 (18) Tamsulosin: 18 (17)	3	45–85	Permixon: −4.28 (5.55) Tamsulosin: −6.56 (5.55)	–	Permixon: −0.87 (1.21) Tamsulosin: −1.29 (0.12)	Permixon: 1.77 (4.65) Tamsulosin: 2.09 (4.54)	24

*BID, twice daily (bis in die); NR, Not reported; OD, once daily; OHPC, hydroxyprogesterone caproate; TID, thrice daily (ter in die). *QOL question of the IPSS questionnaire. †Scores on the Quality Index range from 0 to 27, with higher scores indicating greater quality. ‡Results for the comparator arm with OHPC are provided in the table for completeness but are not included in the meta-analysis.*

Table 2 Key features of studies included for quantitative analysis – Observational studies (n = 12).

Observational studies										
Reference	**Arms (n)**	**Randomised Y/N/blind**	**Withdrawals, n (%)**	**Study duration months**	**Age, years mean or range**	**Change in IPSS from baseline, mean (SD)**	**Change in voids/night, mean (SD)**	**Change in QOL score*, mean (SD)**	**Change in Q_{max}, mL/s, mean (SD)**	**Study quality (DBQI score)†**
Martorana et al. (1986) [43]	Permixon (10)	N	–	6	69	–	–	–	11.00 (10.70)	7
Authie et al. (1987) [44]	Permixon (500)	N	–	3	68	–	−2.21 (1.69)	–	–	6
Ebbinghaus (1995) [45]	Permixon (99)	N		3	69	–	–	–	–	8
Gorilovsky and Lasebnik (1995) [46]	Permixon (23)	N	0	3	75	–	–	–	8.00 (9.30)	3
Foroutan (1997) [47]	Permixon (592)	N	–	3	67	−6.48 (47.68)	–	−1.49 (10.96)	2.93 (21.56)	11
Al-Shukri et al. (2000) [48]	Permixon (57) Control (18)	N	–	2	52–78	Permixon: −2.20 (5.90) Control: −0.10 (11.7)	–	−0.60 (1.69)	0.70 (4.83)	11
Praun et al. (2000) [49]	Permixon (142)	N	12	3	63	−6.54 (8.03)	–	−1.37 (1.97)	–	19
Aliaev et al. (2002) [50]	Permixon (26)	N	–	60	65	−8.80 (3.66)	–	−1.31 (0.84)	4.13 (4.47)	5
Pytel et al. (2002) [51]	Permixon (116)	N	14	24	65	−5.33 (4.53)	–	−1.31 (1.05)	1.13 (10.30)	17
El-Demiry (2004) [52]	Permixon (190)	N	10	6	62	−11.40 (6.68)	–	–	4.40 (9.30)	14
Djavan et al. (2005) [53]	Permixon (88)	N	–	24	67	Permixon: −1.00 (6.68) Control: 0.30 (6.07)	–	−0.40 (3.10)	1.80 (9.30)	8
Alcaraz et al. (2016) [18]	Control (153)‡ HESr (678) α-blockers [AB] (398) 5ARI (94) AB + 5ARI (93)‡ AB + HESr (219)‡	N	Control (10.3) HESr (6.6) AB (5.5) 5ARI (2.1) AB + 5ARI (3.2) AB + HESr (7.8)	6	Control: 63.1 HESr: 61.7 AB: 64.7 5ARI: 69.3 AB + 5ARI: 69.4 AB + HESr: 64.6	Control: −2.5 (4.4) HESr: −3.7 (4.4) AB: −5.00 (4.2) 5ARI: −6.50 (6.0) AB + 5ARI: −7.6 (6.6) AB + HESr: −6.6 (4.9)	–	Control: −0.5 (1.2) HESr: −1.0 (1.2) AB: −1.3 (1.2) 5ARI: −1.5 (1.3) AB + 5ARI: −1.7 (1.3) AB + HESr: −1.7 (1.2)	–	19

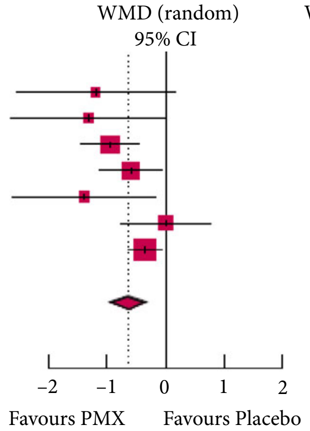
*AB, α-blocker. *QOL question of the IPSS questionnaire. †Scores on the Quality Index range from 0 to 27, with higher scores indicating greater quality. ‡Results for the arm with combined therapy and control group are provided exclusively for information but are not included in the meta-analysis.*

Figure 2 Forest plots of comparisons in studies with Permixon vs placebo for (**a**) nocturia and (**b**) Q_{max}. PMX, hexanic extract of *Serenoa repens* (Permixon).

a Nocturia

Study	N	Permixon Mean (SD)	N	Placebo Mean (SD)	Weights %	WMD (random)	95% CI
Boccafoschi 1983[28]	11	−2.20 (1.62)	11	−1.00 (1.62)	5.19	−1.20	[−2.56; 0.16]
Emili 1983[29]	15	−1.66 (1.94)	15	−0.34 (1.75)	5.41	−1.32	[−2.64; 0.00]
Champault 1984[30]	47	−1.43 (1.17)	41	−0.48 (1.18)	21.0	−0.95	[−1.44; −0.46]
Cukier 1985[31]	70	−1.10 (1.62)	76	−0.50 (1.62)	19.7	−0.60	[−1.13; −0.07]
Tasca 1985[32]	14	−2.60 (1.62)	13	−1.20 (1.62)	6.18	−1.40	[−2.62; −0.18]
Reece-Smith 1986[34]	33	−1.00 (1.59)	37	−1.00 (1.74)	12.4	0.00	[−0.78; 0.78]
Descotes 1995[36]	82	−0.67 (1.05)	94	−0.32 (0.87)	30.2	−0.35	[−0.64; −0.06]
Total (95% CI)	272		287			−0.64	[−0.98; −0.31]

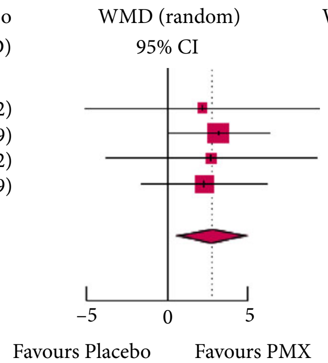
Test for heterogeneity: $I^2 = 42.2\%$, $Q = 10.37$, $df = 6$, $P = 0.010$
Test for Overall effect: $z = -3.80$, $P = 0.001$



b Qmax

Study	N	Permixon Mean (SD)	N	Placebo Mean (SD)	Weights %	WMD (random)	95% CI
Boccafoschi 1983[28]	11	4.13 (8.62)	11	1.96 (8.62)	9.16	2.17	[−5.04; 9.38]
Emili 1983[29]	15	3.37 (4.94)	15	0.20 (3.79)	47.9	3.17	[0.02; 6.32]
Tasca 1985[32]	14	3.30 (8.62)	13	0.60 (8.62)	11.2	2.70	[−3.81; 9.21]
Descotes 1995[36]	82	3.40 (14.0)	94	1.10 (11.9)	31.7	2.30	[−1.58; 6.18]
Total (95% CI)	122		133			2.75	[0.57; 4.93]

Test for heterogeneity: $I^2 = 0\%$, $Q = 0.15$, $df = 3$, $P = 0.986$
Test for Overall effect: $z = 2.47$, $P = 0.014$



−7.67 to −3.72; $P < 0.001$; [test for subgroup differences, $P = 0.96$]).

Funnel plot analysis suggested a potential publication bias (Fig. S4), although after excluding outliers the mean improvement in IPSS was −5.38 points (95% CI −6.36 to −4.39; $P < 0.001$; Fig. S5). The funnel plot for the latter analysis shows a symmetric distribution, although a potential publication bias cannot be completely discounted (Fig. S6).

Analysis of Q_{max} data (Fig. 5b) indicated that the HESr was associated with an increase of 2.89 mL/s (95% CI 1.92 to 3.85; $P < 0.001$) from baseline, although the funnel plot indicates possible publication bias (Fig. S7). When analysing the studies with complete data, an improvement of 2.26 mL/s (95% CI 1.80 to 2.71; $P < 0.001$) was seen with no heterogeneity (Fig. S8) or publication bias (Fig. S9).

The results for nocturia (Fig. 5c) showed a mean reduction from baseline of 1.56 voids/night with the HESr (95% CI −2.16 to −0.97; $P < 0.001$). No publication bias was observed. The reduction in number of voids/night was 1.58 (95% CI −2.12 to −1.04; $P < 0.001$) when outliers were excluded.

For QOL (Fig. 5d), which was assessed using question 8 of the IPSS, the HESr was associated with an improvement of 1.07 points (95% CI 1.28 to 0.87; $P < 0.001$). A similar result was seen after exclusion of outliers (overall reduction of 1.03 points, 95% CI 1.25 to 0.80; $P < 0.001$).

For prostate volume (Fig. 5e), HESr was associated with a statistically significant reduction of −2.93 mL (95% CI −4.58 to −1.28; $P < 0.001$) corresponding to a mean reduction of 6.8% from baseline. Funnel plot analysis showed no publication bias. When outliers were excluded, the decrease was of −2.36 mL (95% CI −3.73 to −0.99; $P < 0.001$).

Change in PSA was assessed in five studies [18,37,40,49,51]. There was a clinically non-significant mean change of 0.17 ng/mL (95% CI 0.07 to 0.27) when analysing data that showed no heterogeneity ($I^2 = 1\%$, $P = 0.403$; Fig. S10).

Sexual function was assessed in four studies [37,40,42,51] using the Male Sexual Function four-item questionnaire, with meta-analysis showing no relevant effect of the HESr on sexual function ($P = 0.64$; Fig. S11).

Figure 3 Forest plots of studies comparing Permixon with α-blockers on (**a**) IPSS, (**b**) Q_{max}, (**c**) prostate volume, and (**d**) PSA. PMX, hexanic extract of *Serenoa repens* (Permixon); AB, α-blockers.

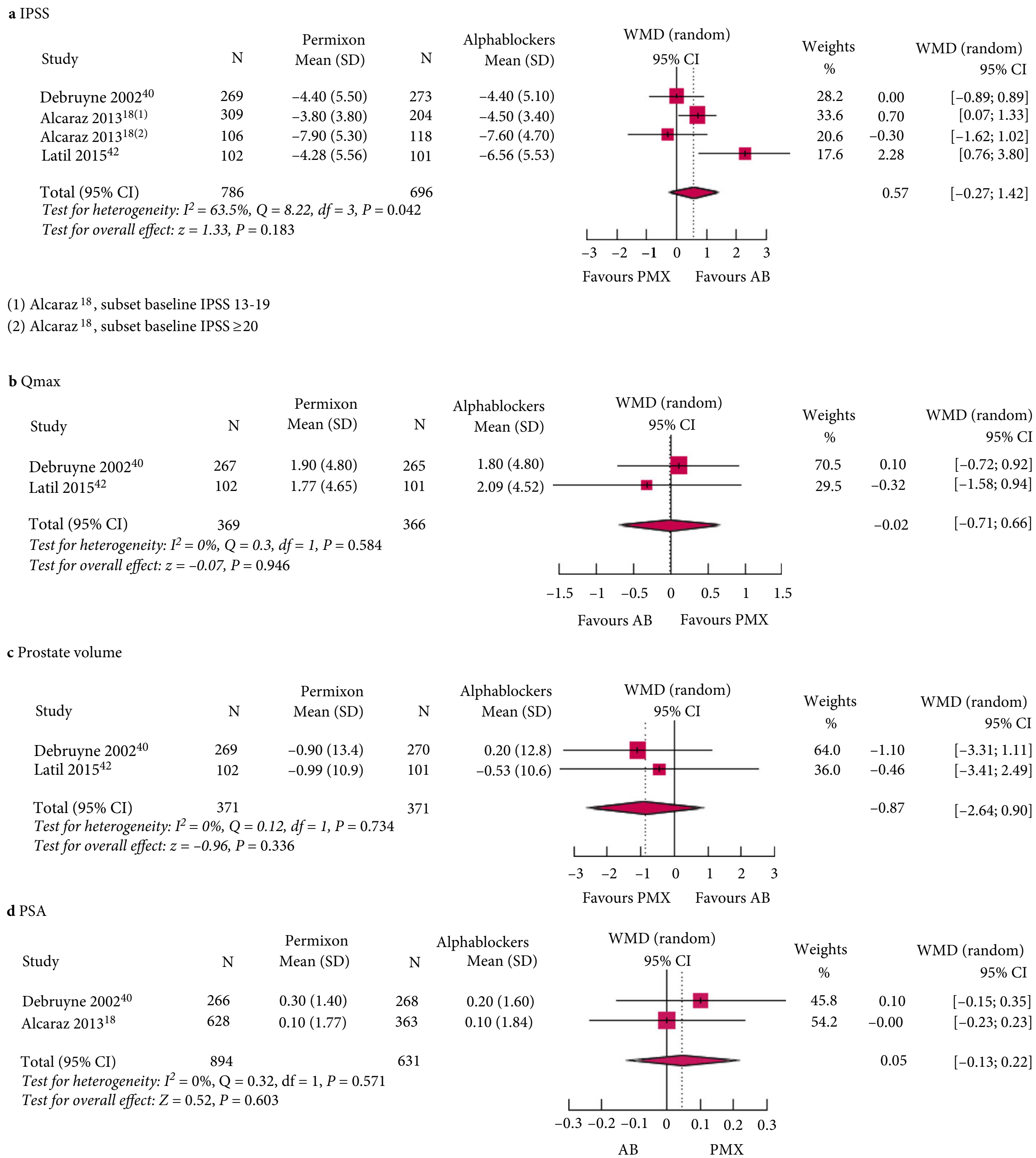
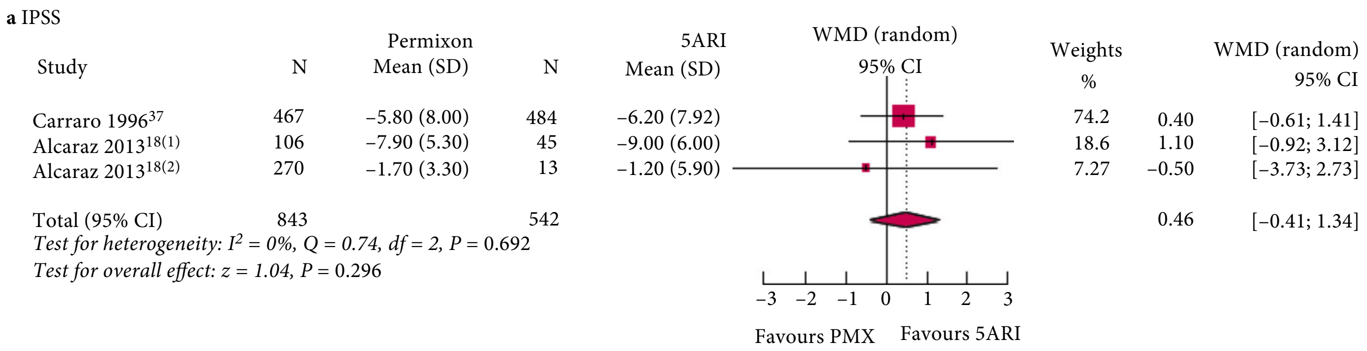
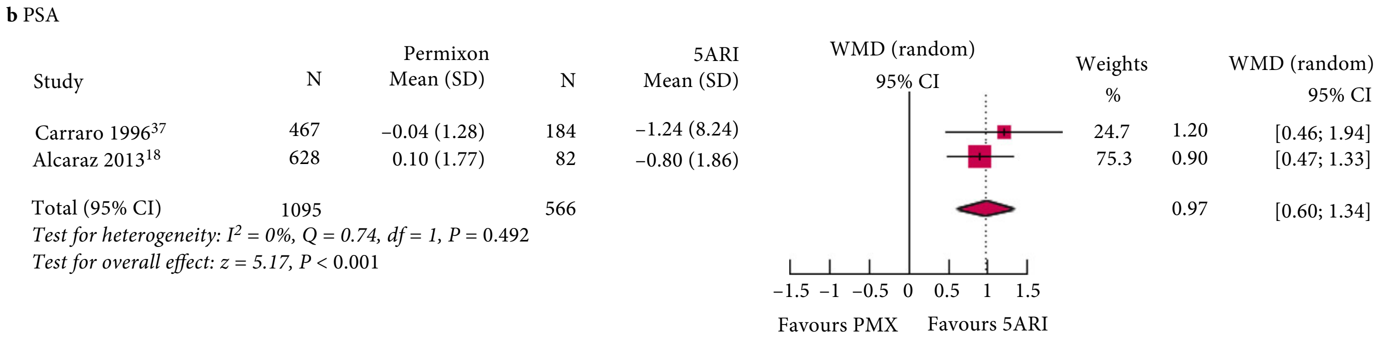


Figure 4 Forest plots of studies comparing Permixon with 5ARIs on (**a**) IPSS and (**b**) PSA. PMX, hexanic extract of *Serenoa repens* (Permixon).



(1) Alcaraz[18], subset baseline IPSS ≥20

(2) Alcaraz[18], subset baseline IPSS 8-13



When comparing the results between observational studies and RCTs, it was confirmed that there were no statistically significant differences between the two types of study when analysing IPSS, Q_{max} and QOL outcomes. Statistically significant differences between study types were found for nocturia and prostate volume.

Change from Baseline to End of Treatment with Permixon in Studies with ≥1 Year of Treatment

Figure 6 shows the forest plots for change from baseline with HESr treatment for patients treated for ≥1 year. The studies selected for this analysis had treatment and follow-up periods of 1 [40], 2 [51,53] and 5 [50] years, with DBQI scores between 5 and 25. However, the Djavan et al. [53] study only included patients with mild IPSS, who do not usually receive medical treatment [3]. As that meant it investigated a clinically different population from the other studies, it was excluded from this sub-group analysis.

Meta-analysis of change in outcomes from baseline showed a mean improvement in IPSS (Fig. 6a) of −6.06 points (95% CI −8.00 to −4.13; $P < 0.001$), or −4.85 points (95% CI −5.76 to −3.94; $P < 0.01$) after exclusion of outliers. There was an increase in Q_{max} (Fig. 6b) of 2.29 mL/s (95% CI 0.89 to 3.69; $P < 0.001$), or 1.81 mL/s (95% CI 1.27 to 2.36; $P < 0.01$) after excluding outliers, and an improvement in QOL, measured using IPSS item 8, of 1.31 points (95% CI 1.46 to 1.16; $P < 0.001$; Fig. 6c), with no heterogeneity. Prostate volume decreased by −5.37 mL (95% CI −10.34 to −0.41; $P = 0.034$) corresponding to a mean reduction of 6.8% (Fig. 6e). When the two studies with complete data were analysed, the decrease in prostate volume was −3.32 mL ($P = 0.18$).

Change in PSA was measured in two of the three studies [40,51] and no clinically significant change was observed when analysing data that showed no heterogeneity ($I^2 = 0\%$, $P = 0.51$).

ADRs

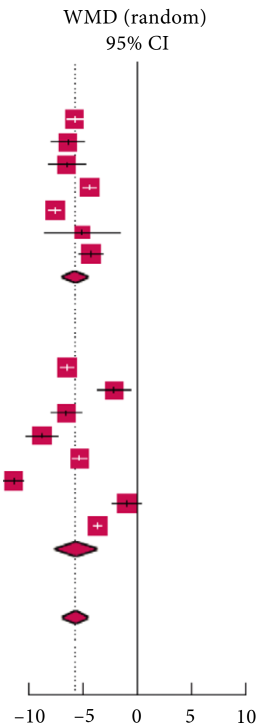
The incidence of ADRs associated with the HESr was low. Only four ADRs had a mean incidence of >1% (Table 3). Gastrointestinal disorders were reported by 3.8% of patients and nausea and vomiting each had a mean incidence of 2.6%.

Long-term treatment with the HESr was safe and well-tolerated. In the studies with 2 [51] and 5 [50] years of treatment, tolerability was reported to be good and none of the ADRs registered were considered by investigators to be associated with the HESr treatment. The third long-term treatment study [40] reported AEs and showed a marked

Figure 5 Forest plots of outcomes in all studies reporting Permixon efficacy data for (**a**) IPSS, (**b**) Q_{max}, (**c**) nocturia, (**d**) QOL (IPSS item 8), and (**e**) prostate volume.

a IPSS

Study	N	Mean	SD	Weights %	WMD (random)	95% CI
RCT						
Carraro 1996[37]	467	−5.80	8.00	7.06	−5.80	[−6.53; −5.07]
Stepanov 1999[38]	48	−6.40	5.40	6.47	−6.40	[−7.93; −4.87]
Stepanov 1999[38]	48	−6.50	5.90	6.34	−6.50	[−8.17; −4.83]
Debruyne 2002[40]	269	−4.40	5.50	7.10	−4.40	[−5.06; −3.74]
Giannakopoulos 2002[39]	50	−7.60	1.94	7.15	−7.60	[−8.14; −7.06]
Vela Navarrete 2003[41]	16	−5.10	7.04	4.48	−5.10	[−8.55; −1.65]
Latil 2015[42]	102	−4.28	5.55	6.84	−4.28	[−5.36; −3.20]
Subtotal (95% CI); Test for effect; z = −9.14, *P* < 0.001	N = 1000				−5.76	[−7.00; −4.52]
Test for heterogeneity: I-Squared = 91.1%, Q =67.69, df = 6, *P* < 0.001						
Observational						
Foroutan 1997[47]	592	−6.48	8.02	7.10	−6.48	[−7.13; −5.83]
AI-Shukri 2000[48]	57	−2.20	5.90	6.47	−2.20	[−3.73; −0.67]
Praun 2000[48]	130	−6.54	8.03	6.60	−6.54	[−7.92; −5.16]
Aliaev 2002[50]	26	−8.80	3.66	6.58	−8.80	[−10.21; −7.39]
Pytel 2002[51]	154	−5.33	4.53	7.07	−5.33	[−6.05; −4.61]
EI-Demiry 2004[52]	190	−11.40	6.68	6.93	−11.40	[−12.35; −10.45]
Djavan 2005[53]	88	−1.00	6.68	6.59	−1.00	[−2.40; −0.40]
AIcaraz 2013[18]	678	−3.70	4.40	7.22	−3.70	[−4.03; −3.37]
Subtotal (95% CI); Test for effect; z = −5.65, *P* < 0.001	N = 1915				−5.70	[−7.67; −3.72]
Test for heterogeneity: I-Squared = 97.9%, Q = 331.38, df = 7, P < 0.001						
Total (95% CI)	N = 2915				−5.73	[−6.91; −4.54]
Test for heterogeneity: I-squared = 96.7%, Q = 426.54, df = 14, P < 0.001						
Test for overall effect: P < 0.001						
Test for subgroup differences: Q = 0.00, df = 1, P = 0.958						



b Qmax

Study	N	Mean	SD	Weights %	WMD (random)	95% CI
RCT						
Emili 1983[29]	15	3.37	4.94	5.59	3.37	[0.87; 5.87]
Pannunzio 1986[33]	30	5.10	1.12	8.75	5.10	[4.70; 5.50]
Descotes 1995[36]	82	3.40	14.00	4.76	3.40	[0.37; 6.43]
Carraro 1996[37]	467	2.68	6.36	8.61	2.68	[2.10; 3.26]
Stepanov 1999[38]	48	1.80	20.09	2.19	1.80	[−3.88; 7.48]
Stepanov 1999[38]	46	1.40	18.99	2.31	1.40	[−4.09; 6.89]
Debruyne 2002[40]	267	1.90	4.80	8.61	1.90	[1.32; 2.48]
Giannakopoulos 2002[39]	50	2.80	1.95	8.65	2.80	[2.26; 3.34]
Latil 2015[42]	102	1.77	4.65	8.25	1.77	[0.87; 2.67]
Subtotal (95% CI); Test for effect; z = 4.84, *P* < 0.001	N = 1107				2.87	[1.71; 4.03]
Test for heterogeneity: I^2 = 93.3%, Q =119.51, df = 8, P < 0.001						
Observational						
Martorana 1986[43]	10	11.00	5.20	4.48	11.00	[7.78; 14.22]
Foroutan 1997[47]	592	2.93	18.21	7.38	2.93	[1.46; 4.40]
AI-Shukri 2000[48]	57	0.70	4.83	7.73	0.70	[−0.55; 1.95]
Aliaev 2002[50]	26	4.13	4.47	6.95	4.13	[2.41; 5.85]
Pytel 2002[51]	154	1.13	10.30	7.11	1.13	[−0.50; 2.76]
AIcaraz 2013[18]	335	1.20	5.31	8.62	1.20	[0.63; 1.77]
Subtotal (95% CI); Test for effect; z = 3.46, *P* = 0.001	N = 1174				3.03	[1.31; 4.75]
Test for heterogeneity: I^2 = 89.6%, Q = 48.23, df = 5, *P* < 0.001						
Total (95% CI)	N = 2281				2.89	[1.92; 3.85]
Test for heterogeneity: I^2 = 93.4%, Q = 211.21, df =14, P < 0.001						
Test for overall effect: P < 0.001						
Test for subgroup differences: Q = 0.02, df = 1, P = 0.879						

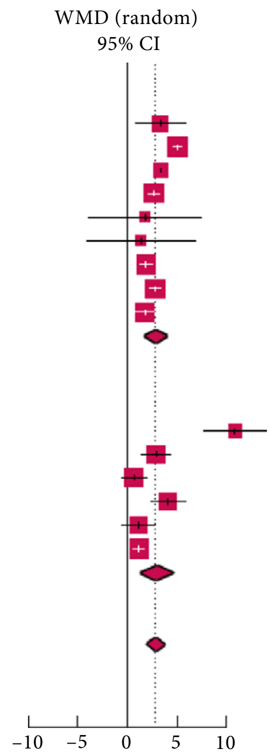
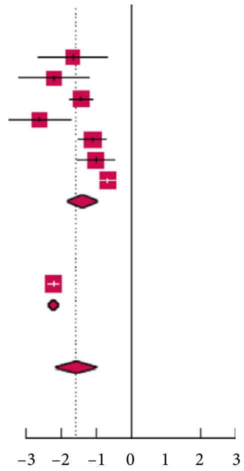


Figure 5 Continued

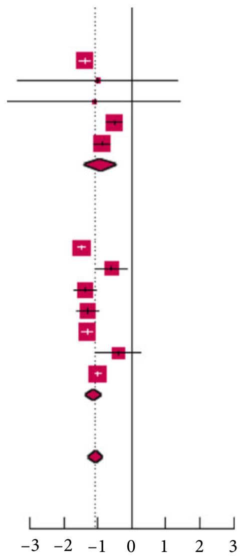
c Nocturia

Study	N	Mean	SD	Weights %	WMD (random)	95% CI
RCT						
Emili 1983[29]	15	−1.66	1.94	10.3	−1.66	[−2.64; −0.68]
Boccafoschi 1983[28]	11	−2.20	1.69	10.2	−2.20	[−3.20; −1.20]
Champault 1984[30]	47	−1.43	1.17	13.8	−1.43	[−1.77; −1.09]
Tasca 1985[32]	14	−2.60	1.69	10.9	−2.60	[−3.48; −1.72]
Cukier 1985[31]	70	−1.10	1.69	13.5	−1.10	[−1.49; −0.71]
Reece-Smith 1986[34]	33	−1.00	1.57	12.9	−1.00	[−1.54; −0.46]
Descotes 1995[38]	82	−0.67	1.05	14.1	−0.67	[−0.90; −0.44]
Subtotal (95% CI); Test for effect; z = −6.21, *P* < 0.001	N = 272				−1.39	[−1.83; −0.95]
Test for heterogeneity: I^2 = 82.4%, Q = 34.18, df = 6, P < 0.001						
Observational						
Authié 1987[44]	500	−2.21	1.69	14.3	−2.21	[−2.36; −2.06]
Subtotal (95% CI); Test for effect; z = −29.31, *P* < 0.001	N = 500				−2.21	[−2.36; −2.06]
Test for heterogeneity: not applicable for a single study						
Total (95% CI)	N = 772				−1.56	[−2.16; −0.97]
Test for heterogeneity: I^2 = 95.2%, Q = 146.94, df = 7, P < 0.001						
Test for overall effect: P < 0.001						
Test for subgroup differences: Q = 12.01, df = 1, P = 0.0005						



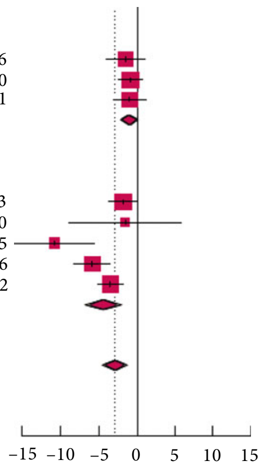
d QOL

Study	N	Mean	SD	Weights %	WMD (random)	95% CI
RCT						
Carraro 1996[37]	467	−1.38	1.82	11.3	−1.38	[−1.54; −1.22]
Stepanov 1999[38]	48	−1.00	8.31	0.71	−1.00	[−3.35; 1.35]
Stepanov 1999[38]	48	−1.10	9.01	0.61	−1.10	[−3.65; 1.45]
Giannakopoulos 2000[39]	50	−0.52	0.86	10.4	−0.52	[−0.76; −0.28]
Latil 2015[42]	102	−0.87	1.21	10.5	−0.87	[−1.11; −0.63]
Subtotal (95% CI); Test for effect: Z = −3.78, *P* < 0.001	N = 715				−0.94	[−1.42; −0.45]
Test for heterogeneity: I^2 = 89%, Q = 36.42, df = 4, P < 0.001						
Observational						
Foroutan 1997[47]	592	−1.49	1.44	11.7	−1.49	[−1.61; −1.37]
AI-Shukri 2000[48]	57	−0.60	1.69	7.80	−0.60	[−1.04; −0.16]
Praun 2000[49]	130	−1.37	1.97	9.12	−1.37	[−1.71; −1.03]
Aliaev 2002[50]	26	−1.31	0.84	9.31	−1.31	[−1.63; −0.99]
Pytel 2002[51]	154	−1.31	1.05	11.3	−1.31	[−1.48; −1.14]
Djavan 2005[53]	88	−0.40	3.10	5.48	−0.40	[−0.05; −1.25]
Alcaraz 2013[18]	678	−1.00	1.20	11.9	−1.00	[−1.09; −0.91]
Subtotal (95% CI); Test for effect: Z = −9.37, *P* < 0.001	N = 725				−1.14	[−1.38; −0.90]
Test for heterogeneity: I^2 = 89.9%, Q = 59.12, df = 6, P < 0.001						
Total (95% CI)	N = 2440				−1.07	[−1.28; −0.87]
Test for heterogeneity: I^2 = 89%, Q = 100.4, df = 11, P < 0.001						
Test for overall effect: P < 0.001						
Test for subgroup differences: Q = 0.54, df = 1, P = 0.461						



e Prostate volume

Study	N	Mean	SD	Weights %	WMD (random)	95% CI
RCT						
Carraro 1996[37]	467	−1.50	28.36	13.1	−1.50	[−4.07; 1.07]
Debruynet 2002[40]	269	−0.90	13.40	16.3	−0.90	[−2.50; 0.70]
Latil 2015[42]	102	−0.99	10.91	14.6	−0.99	[−3.11; 1.13]
Subtotal (95% CI); Test for effect: z = −1.79, *P* = 0.073	N = 838				−1.04	[−2.19; 0.10]
Test for heterogeneity: I^2 = 0%, Q = 0.15, df = 2, P = 0.926						
Observational						
Foroutan 1997[47]	592	−1.84	23.33	15.4	−1.84	[−3.72; 0.04]
AI-Shukri 2000[48]	57	−1.60	28.30	4.01	−1.60	[−8.95; 5.75]
Aliaev 2002[50]	26	−10.81	13.45	6.68	−10.81	[−15.98; −5.64]
Pytel 2002[51]	154	−5.89	14.96	13.8	−5.89	[−8.25; −3.53]
Alcaraz 2013[18]	582	−3.50	21.12	16.0	−3.50	[−5.22; −1.78]
Subtotal (95% CI); Test for effect: z = −3.61, *P* < 0.001	N = 1411				−4.43	[−6.84; −2.02]
Test for heterogeneity: I^2 = 72.8%, Q = 14.69, df = 4, P = 0.005						
Total (95% CI)	N = 2249				−2.93	[−4.58; −1.28]
Test for heterogeneity: I^2 = 73.1%, Q = 26.03, df = 7, P = 0.0005						
Test for overall effect: P = 0.0005						
Test for subgroup differences: Q = 6.20, df = 1, P = 0.013						



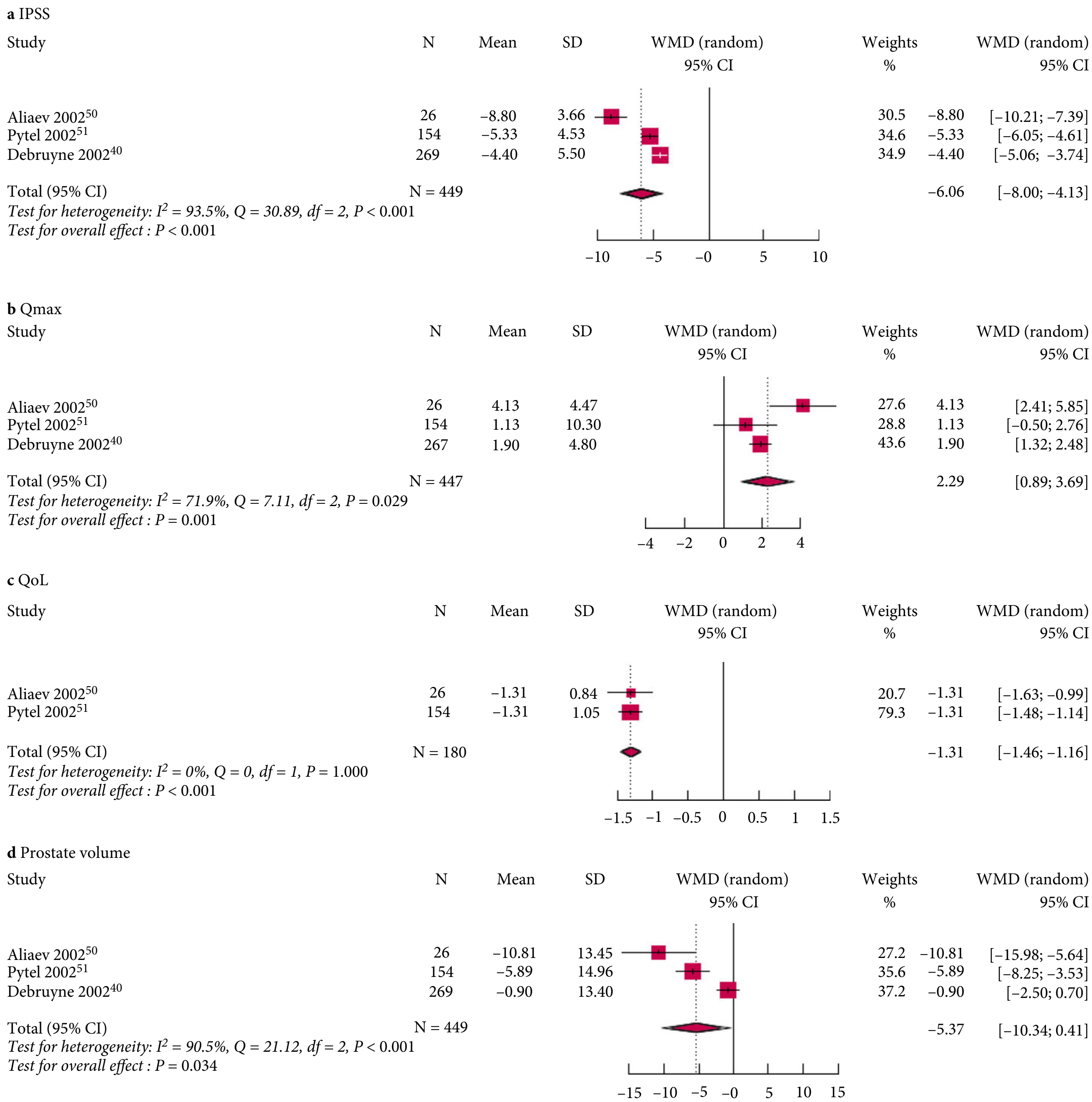


Figure 6 Forest plots of outcomes for Permixon studies of ≥1 year: efficacy data for (**a**) IPSS, (**b**) Q_{max}, (**c**) QOL (IPSS item 8), and (**d**) prostate volume.

reduction in the incidence of ejaculation disorders with the HESr in comparison with tamsulosin (P = 0.001).

Discussion

This comprehensive systematic review and meta-analysis of outcomes with Permixon, a *HESr*, confirms that the HESr has a positive effect on the endpoints most commonly used to assess treatment efficacy in patients with LUTS/BPH. Effectively, analysis of data from RCTs showed superiority for the HESr over placebo on the analysed outcomes and equivalent efficacy to α-blockers on IPSS and Q_{max} improvement. The HESr was also found to have equivalent efficacy to short-term treatment (6 months) with 5ARIs in terms of impact on the IPSS.

Table 3 Rates of ADRs associated with Permixon (only ADRs with an incidence >1% are shown).

ADR	Mean % (95% CI)
Gastrointestinal disorders	3.8 (2.2–6.5)
Nausea and vomiting	2.6 (0.8–8.6)
Hypertension	1.2 (0.2–8.0)
Tinnitus	1.2 (0.2–8.0)

When compared with baseline values, Permixon was associated with a clinically significant improvement in the IPSS, an increase in Q_{max} and an improvement in patient QOL. The HESr was also associated with a slight decrease in prostate volume. There was no evidence of a negative impact on sexual function and treatment benefits were accompanied by a very low rate of ADRs, indicating excellent tolerability.

Our present findings are similar to those reported in the two other systematic reviews and meta-analysis of Permixon performed to date [9,10]. The authors of those reviews also reported that the HESr was associated with a clinically significant reduction in IPSS, a mean increase in Q_{max}, and fewer episodes of nocturia, and that it showed similar efficacy to tamsulosin and short-term finasteride in relieving LUTS [10]. Permixon's safety profile was also excellent, with a low incidence of reported ADRs. In the studies that compared AEs of the HESr and α-blockers, the most notable difference was the higher prevalence of ejaculation disorders associated with α-blockers [18,40,42]. This is important because, as well as negatively impacting patients' QOL, treatments affecting sexual function can be associated with poorer adherence [54,55]. Finally, the results of the long-term treatment analysis were similar to those obtained with the whole sample, confirming the sustained efficacy and safety of the HESr.

In an increasingly polymedicated population, such as elderly men affected by LUTS/BPH, the availability of an effective treatment with a very low rate of ADRs and very limited drug interactions is of relevance. This is highlighted in the LUTS-Fit fOR The Aged (FORTA) 2014 classification [56], which classifies α_1-blockers (tamsulosin, silodosin) as FORTA C (careful; questionable use) in older persons and suggests that alternatives should be sought if necessary. Other α-blockers (alfuzosin, doxazosin, terazosin) are considered FORTA D (avoid in older people) and the guidelines indicate that alternatives with a better safety/efficacy profile should be identified for elderly patients. As only the most widely used oral drugs were included in the LUTS-FORTA classification, the HESr and other phytotherapeutic drugs were not evaluated.

Together with the fact that the present review contained all available published data for Permixon, from both RCTs and observational studies, a further strength of the study is that it focused exclusively on one particular extract of *S. repens*. This contrasts with earlier Cochrane meta-analyses, which included different *S. repens* extracts and did not investigate results for individual brands [4,57], despite evidence of differences in composition between them [7]. It has been emphasised that different compositions lead to differences in potency, with Permixon showing considerably greater inhibition of 5α-reductase types I and II isoenzymes than other *S. repens* extracts [58,59]. In the most recent published Cochrane meta-analysis of *S. repens* extracts, it was reported that they were no better than placebo in reducing LUTS symptoms or nocturia, or in increasing Q_{max} [57]. However, the authors acknowledged that their conclusions may not be generalisable to proprietary products of *S. repens* extracts, such as Permixon or Prostagutt® forte (Dr Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany). Interestingly, in feedback to the full report of the Cochrane meta-analysis, Bilia et al. [4] noted some flaws, including non-equivalence among the different *S. repens* extracts and the fact that dose was not taken into account. When assessing plant extracts, this issue is critical; for example, the publication by Scaglione et al. [59] found that about five-times the dose of another *S. repens* extract was needed to achieve the same *in vitro* inhibitory effect on the 5ARI enzyme type II as Permixon, which was the most potent extract. One of the explanations for this difference appears to be the content in free fatty acids of the different brands. Composition analysis showed that Permixon has the highest proportion of free fatty acids (>80%), whilst the brand with the lowest amount had just 40% and there was substantial variability among brands in general [7].

Moreover, some inaccuracies have been observed in the data extraction for the Cochrane meta-analysis [4]. For example, mean urine flow data was registered instead of Q_{max} data in two studies [30,34] and the number of patients reported for Cukier et al. [31] differed from the number reported in the article. The conclusions of the Cochrane meta-analysis should therefore be treated with caution.

The current European LUTS/BPH EAU guidelines [3] propose that different brands of phytotherapy should be assessed individually because differences in potency mean that results cannot be extrapolated from one brand to another. In relation to this, a recent European Medicines Agency (EMA) report concluded that 'only the hexanic extract of the fruit of *S. repens* is considered to be supported by sufficient evidence to support the use as a well-established medicinal product with recognized efficacy and acceptable safety' [60]. The ethanolic and the supercritical CO_2 extracts of *S. repens* do not seem to have enough clinical evidence to support their use as a medicinal product [60]. In the case of Permixon, *in vitro* and *in vivo* studies have evidenced its mechanism of action, which includes an anti-inflammatory effect [41,42,61,62], 5α-reductase inhibition [58,63,64], and inhibition of growth factors in the prostatic tissue [64].

One of the limitations of the present study was the quality of some of the original studies included in the meta-analysis. This was addressed to some extent by analysing RCTs and observational studies separately, with no clinically relevant differences observed in the most important outcomes between the two types of study. The relatively limited follow-up duration of several of the studies might also be considered a limitation, although it was sufficient to register clinical changes in the outcomes evaluated. The sub-analysis of data from studies with a treatment period of ≥1 year, in which we found similar results to those from the analysis using complete data, also addressed this point. Moreover, the mean follow-up period of the studies included in the complete analysis was similar to that used in recent trials to study the efficacy of various treatments for LUTS/BPH [65–67]. Finally, we also observed some heterogeneity between studies. This was taken into account by carrying out sensitivity analysis which showed that, in general, the exclusion of outliers did not substantially affect the results of the different meta-analyses. The use of a random effects model approach to meta-analysis likewise takes the variability between studies into account and provides a more conservative estimate of effect.

In conclusion, this exhaustive systematic review and meta-analysis of studies assessing Permixon in the treatment of LUTS/BPH found a positive effect over and above placebo on the most relevant outcomes. The mean 5.73 points improvement from baseline in the IPSS with the HESr treatment is higher than the minimum 3.1 points that is deemed necessary to be perceived as a clinically meaningful improvement by the patient [19]. Moreover, the available studies comparing Permixon and α-blockers and short-term 5ARIs showed that the HESr led to similar levels of improvement on the IPSS, with a better tolerability profile. Permixon could therefore be a valid therapeutic option to consider for first-line treatment of LUTS/BPH. The results of the present meta-analysis suggest that the HESr should be considered as a treatment option in the next update of LUTS treatment guidelines.

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Conflict of Interests

Alfredo Rodríguez-Antolín has been a consultant for Janssen, Astellas and Bayer. Francisco J. Brenes has been a speaker and consultant for Pfizer, GSK, Almirall, Lilly, Astellas and Pierre Fabre Ibérica S.A. and an investigator in Pfizer sponsored studies. José Mª Molero García has been a speaker and/or scientific advisor for GSK and Gilead José Manasanch is a medical advisor with Pierre Fabre Ibérica S.A., a company that commercializes Permixon, a hexanic extract of *Serenoa repens*. Michael Herdman received a professional fee from Pierre Fabre Ibérica S.A., for his contribution to the current study. Vincenzo Ficarra has been a speaker for Pierre Fabre and an investigator in Pierre Fabre sponsored studies. The other authors do not declare any competing interests. Of the studies included, no information on the source of financing was provided in 23 cases. Two studies were funded by Pierre Fabre Médicament [40,42], one by Pierre Fabre Ibérica S.A. [18], and one by Germania Pharmazeutika [47].

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Abbreviations: 5ARI, 5α-reductase inhibitor; ADR, adverse drug reaction; AE, adverse event; DBQI, Downs and Black Quality Index; EAU, European Association of Urology; FORTA, Fit fOR The Aged; HESr, hexanic extract of *Serenoa repens*; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Q_{max}, maximum urinary flow rate; QOL, quality of life; RCT, randomised controlled trial; WMD, weighted mean difference.

Supporting Information

Additional Supporting Information may be found online in the supporting information section at the end of the article.

Figure S1. HESr vs placebo. Nocturia; funnel plot.
Figure S2. HESr vs placebo. Q_{max}; funnel plot.
Figure S3. Forest plots of studies comparing Permixon with α-blockers on IPSS, excluding outliers.
Figure S4. HESr end of treatment vs baseline. IPSS; funnel plot.
Figure S5. HESr end of treatment vs baseline. IPSS, excluding outliers; forest plot.
Figure S6. HESr end of treatment vs baseline. IPSS, excluding outliers; funnel plot.
Figure S7. HESr end of treatment vs baseline. Q_{max}; funnel plot.
Figure S8. HESr end of treatment vs baseline. Q_{max}, excluding outliers; forest plot.
Figure S9. HESr end of treatment vs baseline. Q_{max}, excluding outliers; funnel plot.
Figure S10. HESr end of treatment vs baseline. Change in PSA; forest plot.
Figure S11. HESr end of treatment vs baseline. Change in sexual function; forest plot.