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ORIGINAL PAPER

Efficacy and safety of Finasteride (5 alpha-reductase inhibitor) monotherapy in patients with benign prostatic hyperplasia: A critical review of the literature

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Summary ***Background: Combination therapy with 5 alpha-reductase inhibitor (5-ARI) and alpha-blocker can be considered as a gold standard intervention for medical management of lower urinary tract symptoms related to benign prostatic hyperplasia (LUTS/BPH). On the other hand, 5-ARI monotherapy and in particular Finasteride alone is currently getting focus of attention especially due to lack of systematic reviews investigating efficacy outcomes and/or adverse events associated.***

Objectives: Aim of the present critical review was to analyze current knowledge of clinical efficacy and incidence of adverse events associated with 5-ARI treatment for LUTS/BPH.

Materials and methods: A systematic review of clinical trials of the literature of the past 20 years was performed using database from PubMed, Cochrane Collaboration and Embase. A total of 8821 patients were included in this study and inclusion criteria for studies selection were: data from randomized clinical trials (RCTs) focusing their attention on the clinical role of Finasteride monotherapy for symptomatic BPH. Parameters of research included prostate specific antigen (PSA), prostate volume (PV), International Prostate Symptom Score (IPPS), post-void residual urine (PVR), voiding symptoms of IPSS (voiding IPSS), maximum urinary flow rate (Q_{max}), and adverse events (AEs).

Results: Overall 12 original articles were included and critically evaluated. Sample sizes of patient actively treated with finasteride varied from 13 to 1524 cases analyzed in a single study. Follow-up after treatments ranged from 3 to 54 months. The effect of finasteride in reducing prostate volume (PV) was moderate (standardized mean difference (SMD) effect between 0.5 to 0.8 for all trials evaluable) while the effect on IPSS score and Qmax was considered significant (SMD in the 0.2 to 0.5 variation range). No severe AEs and/or psychiatric disorders were retrieved among the studies. Sexual health dysfunctions were significantly influenced by finasteride therapy when compared with placebo treated patients.

Conclusions: Although significant clinical benefits of finasteride monotherapy were demonstrated, the effective size of the available reports included in the analysis is limited. Additional head-to-head studies would be needed to re-evaluate clinical efficacy and safety of 5-ARI in combination or not with alpha blockers.

KEY WORDS: *Benign prostatic hyperplasia; 5 alpha-reductase inhibitor; Finasteride; Side effects.*

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INTRODUCTION

Benign prostatic hyperplasia (BPH) with *lower urinary tract symptoms* (LUTS) is one of the most common diseases prevalent in elderly men. Prevalence of BPH among men in their 50s and 60s is 50% rising to 90% by the age of 80s with significant consequent impact on *Quality of Live* (QoL) outcomes (1, 2). *Five Alpha-Reductase Inhibitors* (5-ARI) block the conversion of testosterone to dihydrotestosterone, which accounts for the efficacy of its use in the treatment of BPH/LUTS, by reducing prostate volume (3, 4). To date, there are two types of 5-ARIs: finasteride and dutasteride. While finasteride inhibits only type 2 5-ARI, dutasteride inhibits both type 1 and 2, but both medications have shown similar efficacy (5). Primary medical management of men with BPH/LUTS include alpha-blockers and 5-ARI as standard therapy and Serenoa repens with more limited efficacy (6-8). Combination treatment with alpha blockers have been demonstrated to be able to significantly decrease *prostate volume* (PV), improve *International Prostate Symptom Score* (IPSS), improve Q_{max}, decrease risk of *acute urinary retention* (AUR) and operative procedures related with BPH/LUTS better than finasteride alone. Even studies on 5-ARI monotherapy resulted, especially for finasteride,

No conflict of interest declared.

in a significant improvement in all BPH related symptoms by long-term treatment (9, 10). However, decision of implementing a 5-ARI monotherapy regimen of treatment should be cautiously evaluated by urologists due to recent warning data suggesting adverse clinical implications of such drugs including the events of erectile dysfunction, decreased libido, clinically significant prostate cancer increase of incidence, gynecomastia, and anxiety (11-15). Moreover, in their recent systematic review and metanalysis *Kim et al.* (16) clearly raised the correlation on 5-ARI administration and possible risk for suicidal attempts and depression, showing also a considerable number of men reporting intolerable adverse effects after initiating finasteride therapy, and continuing to experience these effects after treatment withdrawal (10, 11). These peripheral or secondary effects have undesirable consequences that are collectively becoming known as post-finasteride syndrome (17-19).

Considering the social burden of BPH significant symptoms on the worldwide QoL scenario in men, together with the wide prescription/assumption of these medications, more evidence is needed in order to develop better information for both clinicians and patients, which could have benefits regarding shared decision making about 5-ARI use.

Aim of our analysis was to critically update current knowledge specifically for the efficacy and safety profile of finasteride 5-ARI monotherapy in men with BPH/LUTS through a critical review of available RCTs which have systematically implemented the use of finasteride as per standard of reference. In particular we analyzed the impact of finasteride monotherapy on urodynamics variables (PV; Q_{max}), questionnaire score (IPSS) and secondary outcomes (comparison with Placebo). At the same time, we carried out a review of the drug tolerability and sides effects profile.

Materials and methods

Evidence acquisition

We performed a systematic search in *PubMed*, *Embase*, and *Cochrane Central Register of Controlled Trials* (CENTRAL) up to Dec 2018, without language restriction, to identify clinical trials implementing the use of Finasteride as the only treatment for male with BPH/LUTS and reporting side effects related to drug assumption compared to placebo. The feature of related articles in PubMed was used to identify further papers. The reference lists of the studies included were also screened. Only original articles were included and critically evaluated. We excluded case reports as well as abstracts and reports from meetings. An expert librarian was involved in the design of the search strategy and in the conduct of the literature search. Accordingly, we searched publications using the following primary and secondary fields: "*benign prostatic hyperplasia*" and "*low tract urinary symptoms*" and "*5 alpha-reductase inhibitor*" and "*finasteride*" and "*5-ARI monotherapy*" and "*side effects*" (primary fields); "*PSA reduction*" and "*placebo controlled*" and "*randomized clinical trials*" (secondary fields). For all studies, we evaluated the *level of evidence* (LE) according to the *European Association of Urology* (EAU) guidelines (Table 1) (20).

Selection of the studies, criteria of inclusion, analysis of the outcomes

Entry into the analysis was restricted to data collected from original studies, including data from BPH symptomatic men trials implementing finasteride as per standard of treatment compared with a placebo arm. Two authors (FDG and GMB) independently screened the titles and abstracts of all articles using predefined inclusion criteria. The full-text articles were examined independently by three authors (AP, FDG, and EDB) to determine whether or not they met the inclusion criteria. Then, two authors (FDG and BIC) extracted data from the selected articles. Final inclusion was determined by consensus of all investigators. Study inclusion criteria were: 1) *randomized controlled clinical trials* (RCTs) with 5-ARI and placebo administration; 2) daily 5-ARI treatment; 3) disease indication of BPH/LUTS; 4) types of functional outcomes measures including at least one of these: *prostate specific antigen* (PSA), *prostate volume* (PV), *International Prostate Symptom Score* (IPPS), *post-void residual urine* (PVR), *voiding symptoms of IPSS* (Voiding IPSS), *maximum urinary flow rate* (Q_{max}), and *adverse events* (AEs).

To evaluate the effect of the different continuous variables analyzed, *standardized mean difference* (SMD) was identified from the studies included as was recently reported by the systematic review and metanalysis of *Kim et al.* on 5-ARI monotherapy in patients with BPH (21). In their analysis, SMDs were calculated as the difference between the mean change in the treatment and placebo groups divided by the pooled *standard deviation* (SD).

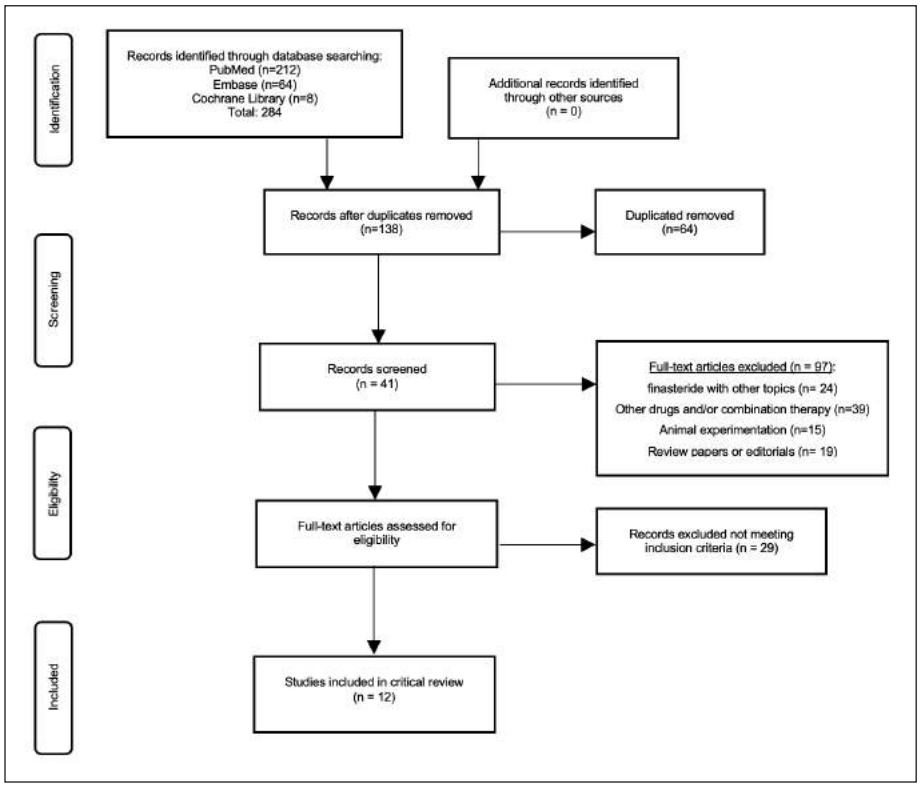
Table 1.
Characteristics of the studies included in the analysis.

	Publication		No. of patients		Mean age (year)				
Author	**Year**	**Country**	**Tx**	**Placebo**	**Tx.**	**Placebo**	**Finasteride dose (mg)**	**F/U duration (months)**	**LE**
Feneley	2000	UK, Netherland	18	9	67.5	67.5	NA	6	1b
Isotalo	2001	Finland	29	19	71	71	5	18	1b
Espana	2002	Spain	30	10	66.7	69.5	NA	9	1b
Haggstrom	2002	Sweden	13	15	NA	NA	5	3	1b
Kirby	2003	Europe	239	253	63	64	5	13	1b
McConnell	2003	NA	89	128	62.6	62.5	5	54	1b
Roehrborn	2004	USA	1524	1516	64	63.9	5	48	1b
Crawford	2006	NA	NA	737	-	62.5	5	54	1b
Kaplan	2006	USA	232	250	61	60.5	5	54	1b
			281	274	61.8	62.4			1b
			252	213	65.1	64.8			1b
Kaplan	2008	USA	768	737	62.6	62.5	5	54	1b
Kaplan	2011	USA	281	276	60.7	60.3	5	54	1b
			295	288	63.9	64.1			1b
Qian	2015	China	45	42	70.1	72.3	5	6	1b

To identify the effect of placebo on the continuous outcomes, the *ratio of means* (ROM), which was a measure of relative change compared with the baseline, was reported as previously calculated by *Kim et al.* (21).

To assess the *risk of bias* (RoB), all included reports were reviewed using the *Quality Assessment of Diagnostic Accuracy Studies* (QUADAS-2) tool for diagnostic accuracy studies (22). The two reviewing authors independently assessed the methodological quality based on sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and additional sources of bias.

Figure 1.
PRISMA flow diagram.



Results

Search results

The database searches initially yielded 284 articles (*PubMed: 212; Cochrane: 8 and Embase: 64*) from the past 20 years until Dec 2018. One-hundred-forty-six were excluded because they contained overlapping data or appeared in more than one database. Of these, 64 were subsequently removed due to duplication. On more detailed review, additional 97 papers were excluded for the following reasons: finasteride with other topics (24), other drugs and/or combination therapy (39), animal experiment (15), and review paper or editorials (19).

Full-text articles were then reevaluated and critically analyzed for the remaining 41 journal references. Of these, 29 did not meet the inclusion criteria. The remaining 12 studies were considered for our critical review (Figure 1 and Table 1). RoB assessment according to QUADAS-2 tool for each of the individual studies is illustrated in Figure 2.

Study locations and types

Of the 12 studies included in our review, 5 were conducted in Europe, 4 in USA, 1 in China, 1 was globally dis-

Figure 2.
PRISMA flow diagram.

Author	Year	RoB Patient Selection	RoB Index test	RoB Reference standard	RoB Flow and timing
Feneley et al.	2000	+	?	?	?
Isotalo et al.	2001	?	-	?	?
Espana et al.	2002	-	+	?	?
Haggstrom et al.	2002	+	+	+	-
Kirby et al.	2003	+	+	+	+
McConnell et al.	2003	?	?	+	+
Roehrborn et al.	2004	+	+	+	+
Crawford et al.	2006	?	+	+	-
Kaplan et al.	2006	?	?	+	+
Kaplan et al.	2008	+	+	+	+
Kaplan et al.	2011	+	+	+	?
Qian et al.	2015	-	+	?	-

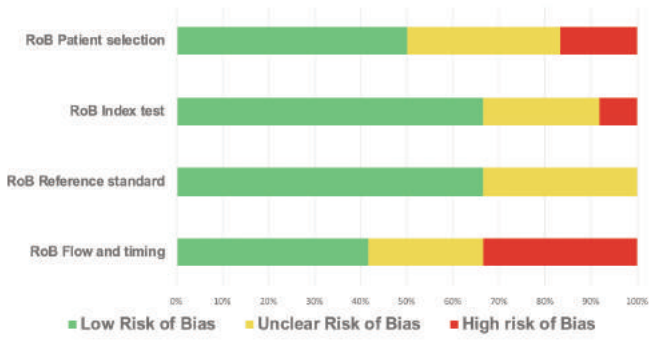


Table 2.
Standardized mean difference (SMD) effect for Prostate Volume (PV) change over treatment with finasteride.

		N. Pts. treated		Measure of effect	
Author	**Year**	**Tx**	**Placebo**	**SMD**	**CI%95**
Feneley et al.	2000	18	9	-0.62	-0.80 to -0.44
Isotalo et al.	2001	29	19	-0.63	-0.80 to -0.45
Kaplan et al.	2006	232	250	-0.61	-0.77 to -0.44
		281	274	-0.60	-0.75 to -0.46
		252	213	-0.60	-0.74 to -0.46
Kaplan et al.	2008	768	737	-0.63	-0.76 to -0.49
Kaplan et al.	2011	281	276	-0.63	-0.75 to -0.51
		295	288	-0.64	-0.76 to -0.52
Qian et al.	2015	45	42	-0.63	-0.74 to -0.52

Table 3.
Standardized mean difference (SMD) effect for International Prostate Symptom Score (IPSS) change over treatment with finasteride.

		N. Pts. treated		Measure of effect	
Author	**Year**	**Tx**	**Placebo**	**SMD**	**CI%95**
Kirby et al.	2003	239	253	-0.25	-0.33 to -0.18
McConnell et al.	2003	89	128	-0.24	-0.31 to 0.17
Roehrborn et al.	2004	1524	1516	-0.21	-0.31 to -0.11
Kaplan et al.	2011	281	276	-0.20	-0.29 to -0.11
		295	288	-0.19	-0.28 to -0.11

Table 4.
Standardized mean difference (SMD) effect for Maximum flow (Q_{max}) change over treatment with finasteride.

		N. Pts. treated		Measure of effect	
Author	**Year**	**Tx**	**Placebo**	**SMD**	**CI%95**
Feneley et al.	2000	18	9	0.36	0.23 to 0.50
Isotalo et al.	2001	29	19	0.36	0.23 to 0.50
Kirby et al.	2003	239	253	0.33	0.23 to 0.42
McConnell et al.	2003	89	128	0.32	0.24 to 0.40
Crawford et al.	2006	NA	737	0.32	0.24 to 0.40
Kaplan et al.	2011	281	276	0.30	0.22 to 0.38
		295	288	0.30	0.23 to 0.37
Qian et al.	2015	45	42	0.29	0.22 to 0.36

played while for one study was not available information regarding location. All of the studies were prospective RCTs placebo-controlled implementing finasteride as reference of standard.

Study sample sizes, participant ages, and follow-up

The sample sizes of patient actively treated with finasteride varied from 13 to 1524 cases analyzed in a single study. The total sample size of the twelve studies was 8821 patients. The total sample size of each individual treatment was 4096 for finasteride 4725 for placebo. Two studies did not report participant's age. The range of mean age across the remaining ten studies varied from 61 to 71 years for patients undergone finasteride monotherapy while varied from 60 to 72 for placebo group. In the studies, the follow-up after treatments ranged from 3 to 54 months.

Impact of finasteride monotherapy on Prostate Volume, International Prostate Symptom Score and Maximal Urinary Flow Rate

Regarding PV, a total of 6 articles out of the 12 included reported extractable outcomes (23-34). The effect of finasteride in reducing PV compared to placebo after a median follow-up of 36 (range 6-54) months, was overall moderate (SMD effect between 0.5 to 0.8 for all trials evaluable) achieving maximum outcome in the study of *Kaplan et al.* (27) (-0.64; CI%95: -0.76 to -0.52). Of note, no studies reported failure in significant decrease of PV. Each trial effect for PV reduction resulted similar independently from sample sizes treated demonstrating no significant differences among studies (*Feneley et al.* (23), n = 18; SMD: -0.62; CI%95: -0.80 to -0.44 *Vs. Kaplan et al.* (24), n = 768; SMD: -0.63; CI%95: -0.75 to -0.51; p = 0.782) (Table 2).

For IPSS, a total of 5 out of 12 studies were critically evaluated (27-31). All the studies reported a significant improvement in the IPSS score domains after a median follow up of 48 (range 6-54) months. The SMD effect of finasteride for IPSS score reduction was significant (SMD in the 0.2 to 0.5 variation range) varying from -0.19 (CI%95: -0.27 to -0.11) in the study of *Quian et al.* (28) to -0.25 (CI%95: -0.33 to -0.18) in the study of *Kirby et al.* (29) (Table 3).

At the same time effect of finasteride on Q_{max} resulted in significant improvement after a median follow-up of 18 (range 6 - 54) months. Seven out of 12 studies were considered (23, 24, 27-30, 32). Improvement was considered overall small (SMD in the 0.2 to 0.5 variation range) showing minimal increase in the study of *McConnel and Crawford* (30, 32) who presented identical SMD of 0.32 (CI%95: 0.24 to 0.40) compared to the study of *Feneley and Isotalo* (23, 24) where a SMD of 0.36 (CI%95: 0.23 to 0.50) was retrieved (Table 4).

Ratio of the means for PV, IPSS and Q_{max}, as previously calculated by the metanalysis of *Kim et al.* (21), for the efficacy of the placebo group according to our inclusion criteria were summarized in Table 5.

Table 5.
Ratio of the means for PV, IPSS and Q_{max} for the studies included in the analysis.

Author (year)	**No. of samples**	**Ratio of mean (95% CI)**		
		PV	**IPSS**	**Q_{max}**
Feneley (2000)	9	0.82 (0.52, 1.31)		1.23 (0.85, 1.77)
Isotalo (2001)	19	0.91 (0.75, 1.11)		1.09 (0.76, 1.56)
Kirby (2003)			0.69 (0.63, 0.74)	1.12 (1.06, 1.18)
McConnell (2003)			0.76 (0.73, 0.80)	1.13 (1.10, 1.16)
Roehrborn (2004)			0.97 (0.94, 1.00)	
Crawford (2006)				1.13 (1.11, 1.16)
Kaplan (2008)	249	1.34 (1.22, 1.46)		
Kaplan (2008)a	214	1.12 (1.04, 1.21)		
Kaplan (2008)b	112	1.20 (1.08, 1.32)		
Kaplan (2008)c	161	1.21 (1.16, 1.27)		
Qian (2015)	42	0.60 (0.57, 0.63)	0.36 (0.32, 0.41)	2.79 (2.36, 3.30)

Table 6.
OR of the Adverse events (AEs) among studies enrolled for finasteride treatment compared to placebo.

Complication	Effect size	
	OR (95% CI)	p-value
Decreased libido		
Kirby (2003)	1.83 (0.62-5.4)	0.271
Roehrborn (2004)	1.97 (1.39-2.79)	< 0.001
Ejaculatory disorder		
Kirby (2003)	1.53 (0.44-5.35)	0.507
Roehrbn (2004)	2.81 (1.62-4.87)	< 0.001
Impotence	1.68 (1.3-2.17)	< 0.001
Kirby (2003)	1.47 (0.64-3.38)	0.363
Roehrborn (2004)	1.83 (1.42-2.36)	< 0.001
Postural hypotension	1.18 (0.27-5.12)	0.821
Kirby (2003)	0.51 (0.09-2.76)	0.434

Analysis of significant adverse events rate for finasteride monotherapy vs. placebo

Among the twelve articles included in the analysis only the experience of *Kirby et al.* and *Roehrborn et al.* (29, 31), clearly identified relationships between finasteride vs. placebo in adverse events rate. Table 6 illustrates estimated OR (CI%95) previously identified by *Kim et al.* (23) for AEs retrieved in these studies included in our critical review. Interestingly in their large experience *Roehrborn et al.* (31) are the only that demonstrated a significant correlation between finasteride assumption and increased risk of developing sexual health dysfunctions: impotence (1.83; CI%98: 1.42-2.36; $p < 0.001$), decreased libido (1.97; CI%95: 1.39-2.79; $p < 0.001$); ejaculatory disorder (2.81; CI%95: 1.62-4.87; $p < 0.001$) and gynecomastia (3.11; CI%95: 1.78-5.45; $p < 0.001$), when compared to placebo group. Of note, none of the previous AEs was statistically found to be related in the analysis of *Kirby et al.* (29) (Table 6).

Even a comparison with other 5-ARIs (dutasteride) demonstrated an inferior effect on male sexuality (35).

Relevantly, none of the studies included in the present analysis found or demonstrated any significant correlation between implementation of finasteride and development of anxiety and minor/major depression syndrome.

Discussion

Androgens release and modulation profoundly regulate homeostasis of both prostate growth and differentiation, as well as sexual function and are associated with general men health, including bone metabolism regulation and cardiovascular health (36). Therefore, even if guidelines on BPH suggest the administration of 5-ARI in patients with symptomatic LUTS and/or prostate size greater than 30 ml, serious implications may derive from prescription of both dutasteride and finasteride. In this field, the overall long-term adherence to the prescribed regimen (alpha blockers or 5-ARI or combination) has been demonstrated to be generally low, but it is even more limited in patients under 5-ARI, probably due to the incidence of AEs (37). Significant higher events of heart failure compared to placebo group have been indeed described in the study of Andriole et al in 2010 looking at correlation between 5-ARI and risk of prostate cancer development (38). Moreover, many observational studies and the recently published metanalysis by *Kim et al.* have shown increased incidence of possible risk for suicidal attempts and minor/major depression events (16, 39).

On the other hand, the indication of treatment with 5-ARI seems clear and confirmed from many available trials and review analysis. Goals of finasteride treatment are represented by preventing over the years the exacerbation of BPH and urinary retention and therefore its routinely use demonstrated to be a reliable tool able to impact clinical urinary outcomes and at the same time to improve perioperative results of patients candidate for endourological procedures such as TURP/simple prostatectomy and others. In 2015 *Busetto GM et al.* (40) in their observational study demonstrated how preoperative (TURP) 5-ARI treatment could have improved estimated blood loss and histopathological findings of prostate vascularity by impacting on *vascular endothelial growth factor* (VEGF) immunoreactivity and *micro-vessel density* (MVD) modulation specifically in large prostates (> 50 ml).

From all these observations, necessity arises to periodically update data regarding the worldwide impact of these medications and the real clinical benefit for men suffering from BPH. Moreover, new formulations of finasteride drug have been yearly introduced in the pharmacy market in the last few years demonstrating the continuous interest in the field of BPH medical therapy.

We on purpose decided to restrict the field of research of the present review on a smaller window (20 years) when compared to previously published reviews articles in order to photograph the current changes in literature. Finasteride is indeed for sure the 5-ARI medication which has been more prescribed and on which are present most of the available trials in literature antecedent to year 2000. The first two RCT using finasteride noteworthy are dated 1992 when *Beisland et al.* (41) and *Gormley et al.* (42) respectively published their analysis on *European Urology and New England Journal of Medicine*, demonstrating, especially the last one, a significant effect despite the short term follow-up on voiding IPSS scores (OR: 0.88; CI%95: 0.80 to 0.97).

Therefore, our review has been based on the results recently provided by the metanalysis published by *Kim et al.* (21), but with different criteria of inclusion and a shorter time frame of literature review focusing only on finasteride monotherapy. The level of evidence raised by the 12 included RCT articles was overall good (LE: ≥ 2a) with homogeneous distribution in terms of sample size, balanced treatment groups and placebo arms and both urinary and AEs outcomes investigated. Finasteride monotherapy demonstrated to be able to positively and significantly impact all the urinary variables (PV, IPSS, Q_{max}) in all the studies included, showing a SMD effect ranging between small to moderate effect on the analyzed variable. Severe AEs were not reported, and the main issue was again the impact of the drug on sexual health life. Only *Roehrborn et al.* RCT (31) reported an association between finasteride and sexuality (31). Finasteride sexual side effects profile is better when compared with dutasteride (35). Even if our results did not identify any correlation among the studies included and

the risk of psychiatric AEs, the metanalysis of *Kim et al.* (16) published in 2019, investigating the risk of depression with 5-ARI, showed a not high risk but however a relevant distribution of these events which for their clinical importance needs validation by further studies.

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