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Review Article

Impact of 5-Alpha Reductase Inhibitors Treatment for Benign Prostatic Hyperplasia on Erectile Dysfunction: A Meta-Analysis

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Abstract: Objective To provide a meta-analysis of the available randomized clinical trials (RCTs) reporting the impact of 5-alpha reductase inhibitors treatment for BPH on erectile function. Methods According to the requirements of meta-analysis, a literature search about 5-alpha reductase inhibitors therapy in BPH was performed among PubMed, EMBASE, Science Direct and The Cochrane Library from the establishment of the database till June 2016. Rresults A total of 391 articles were included, 11 RCTs were enrolled for meta-analysis. All articles used randomized, double blind and placebo control. Within 1 year, erectile dysfunction was more common with 5-alpha reductase inhibitors than with placebo (OR=2.18, P<0.00001). In particular, considering Finasteride (OR=2.28, P<0.00001) or Dutasteride (OR=2.06, P<0.00001). Finasteride had no significantly difference with Dutasteride. In more than 1 year, erectile dysfunction was more common with 5-alpha reductase inhibitors than with placebo (OR=1.45, P<0.0001). In particular, considering Finasteride (OR=1.46, P<0.0001); conversely, Dutasteride was associated with a risk similar to placebo. Conclusion Within 1 year, 5-Alpha reductase inhibitors may increase the risk of erectile dysfunction. In more than 1 year, Finasteride was more likely to lead to erectile dysfunction. These data can be relevant both for drug selection and patients counseling.

Keywords: 5-Alpha Reductase Inhibitors, Benign Prostatic Hyperplasia, Erectile Dysfunction, Meta-Analysis

1. Introduction

Benign prostatic hyperplasia (BPH) is a common and frequently-occurring disease of the urinary system in aged men. It can cause urinary tract obstruction, urinary retention, urinary tract infection and persistent renal failure [1]. With the increasing aging population, the incidence of this disease is increasing year by year, and it has become one of the main diseases threatening the health of the aged men [2]. Drugs can not only treat BPH, but also one of the ways to avoid the operation [3]. At present, 5α-reductase inhibitors are commonly used alone or in combination with α-blockers, anticholinergic drugs for BPH. These drugs can not only reduce the concentration of serum dihydrotestosterone, but also can reduce the concentration of DHT in the prostate, thereby reducing the volume of prostate, relieve urinary tract obstruction and improve the symptoms of BPH; however, these drugs have a certain impact on patient sexual function, the most common is erectile dysfunction [4]. Age is one of the factors that decrease the erectile function, with the increase of age, male erectile function gradually decreased and it is also related to the underlying disease or long-term use of certain drugs [5]. Since 1992, a number of randomized, placebo-controlled clinical trials were published, which evaluated the clinical efficacy and side effects of 5α-reductase inhibitors. The aim of this meta-analysis study was to systematically identify, evaluate, and summarize the finding of all relevant studies updated June 2016 regarding erectile dysfunction of 5α-reductase inhibitors on BPH. The results of this study will be used for informed decisions about the role of

5α-reductase inhibitors in clinical practice and also the need for further research.

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2. Materials and Methods

2.1. Inclusion Criteria

The randomized controlled trials that met the following criteria were included: (1) the study referred to the effect of 5α-reductase inhibitors on BPH; (2) the study for provided sufficient data for analysis, including the mean values and the standard deviations of the continuous outcomes; and (3) the full text of the study could be accessed. If these inclusion criteria were not met, the studies were excluded from the analysis.

2.2. Search Strategy

We performed a literature search among PubMed, EMBASE, Science Direct and The Cochrane Library through September 2016 to identify randomized, double-blinded, placebo-controlled, parallel-group trials of 5α-reductase inhibitors in the treatment of BPH. Free text search terms used included '5-alpha reductase inhibitors', 'finasteride', 'dutasteride', 'epristeride', 'benign prostatic hyperplasia', 'sexual dysfunction', 'erectile dysfunction'. Unpublished studies and Abstracts were not sought.

2.3. Quality Assessment

Literature quality assessment and data extraction were done by two reviewers independently, and cross checked, when the opinion was not consistent through discussion or by the third party. Each report which could possibly be described as a randomized controlled trial was scored using a commonly-used scale [6-7]. The maximum score of an included study was 5 and the minimum score was 2.

2.4. Statistical Analysis

The meta-analysis of comparable data was carried out using Review Manager 5.3.5 (The Nordic Cochrane Center, The Cochrane Collaboration, 2016). For continuous outcomes, the results were expressed as the mean difference with 95% confidence intervals (95%CI), with $P<0.05$ indicating the difference was statistically significant. The degree of heterogeneity among the results of different studies was quantitatively assessed by I^2, where $I^2>50\%$ indicated a substantial heterogeneity. In the case of no conspicuous heterogeneity, a "fixed-effects" statistical model was used, and if heterogeneity was detected, a "random-effects" model was used. The publication bias was assessed by funnel plot (Figure 1), which did not show any evidence of a publication bias.

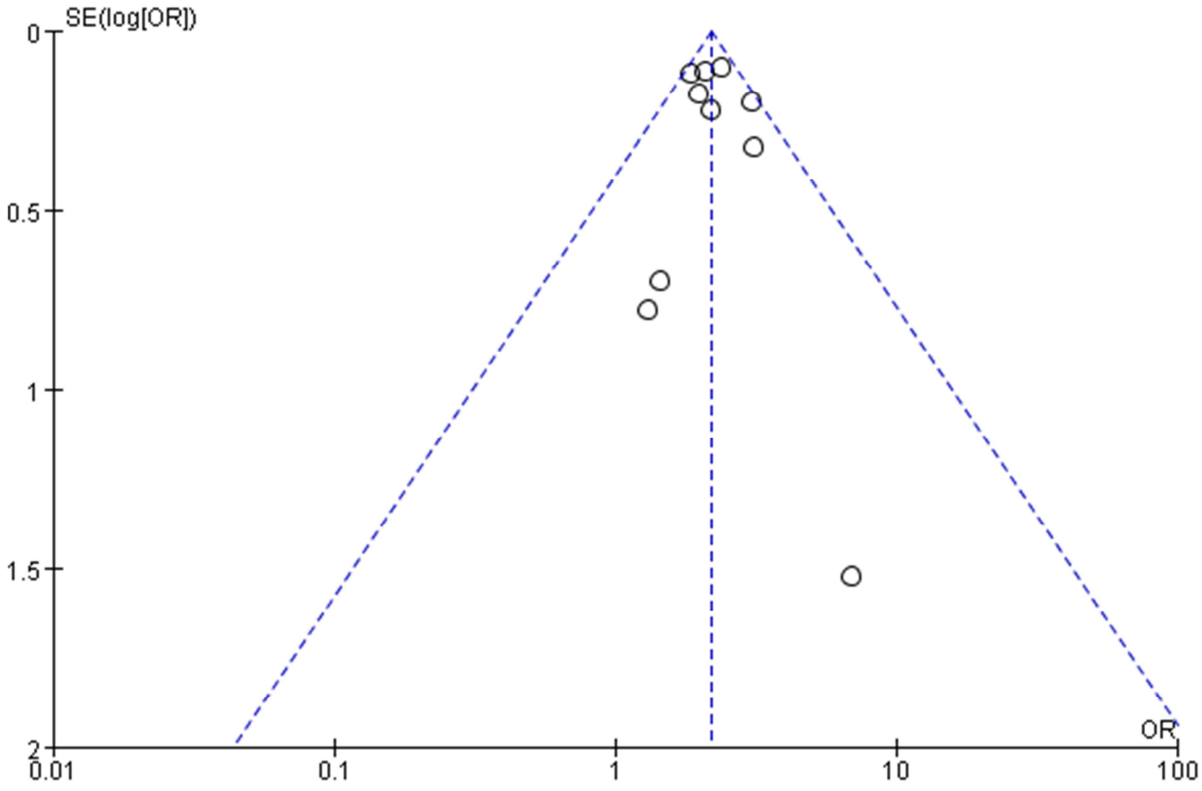

Figure 1. *The funnel plots of referenced articles. The plot is for qualitative estimation of publication bias of the studies. No bias was found.*

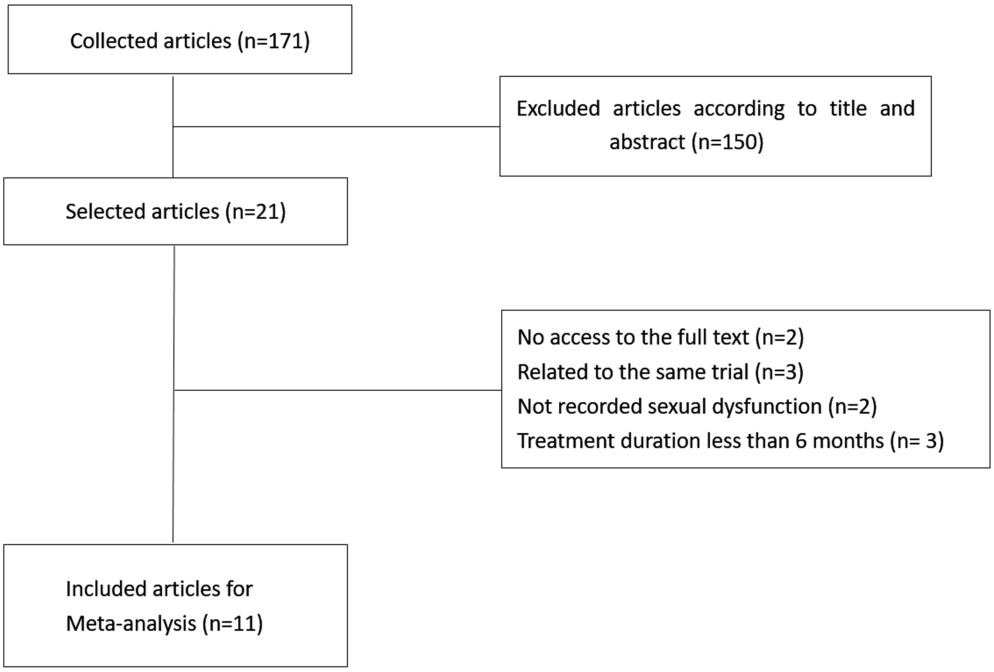

Figure 2. *Flow diagram of article selection.*

3. Results

3.1. Search Results

Initially, a total of 21 articles were identified to meet the inclusion criteria. On closer inspection, two articles had no access to the full text, three articles were found to be the same trial, two articles not recorded sexual dysfunction and three articles were found treatment duration less than six months, thus were excluded from the meta-analysis. Finally, a total of eleven articles were included for the meta-analysis [8-18] (Figure 2). A summary of the included articles, their size at randomization, quality score, duration were given in Table 1.

Table 1. *General information that involved in the research.*

Author	Duration/months	Treatments	Age	Erectile Dysfunction (%)	Quality score
Andersen 1995	24	Finasteride 5mg(n=353)	46-80	55(15.6)	3
		Placebo(n=354)	46-80	30(8.5)	
Byrnes 1995	12	Finasteride 5mg(n=1821)	42-91	124(6.8)	3
		Placebo (n=596)	42-91	19(3.2)	
Roehrborn 2003	48	0-12: Finasteride 5mg(n=1524)	45-78	123(8.1)	4
		Placebo (n=1516)	45-78	56(3.7)	
		12-48: Finasteride 5mg(n=1524)	45-78	77(5.1)	
		Placebo(n=1516)	45-78	77(5.1)	
Marberger 1998	24	Finasteride 5mg(n=1450)	50-75	104(6.6)	5
		Placebo (n=1452)	50-75	74(4.7)	
Nickel 1996	24	Finasteride 5mg(n=310)	45-80	49(15.8)	5
		Placebo (n=303)	45-80	19(6.3)	
Gormley 1992	12	Finasteride 5mg(n=297)	40-83	10(3.4)	3
		Placebo (n=300)	40-83	5(1.7)	
Roehrborn 2006	24	0-12: Dutasteride 0.5mg(n=82)	52-82	2(2.4)	4
		Placebo (n=79)	47-81	1(1.3)	
		12-24: Dutasteride 0.5mg(n=64)	52-82	1(1.6)	
		Placebo (n=67)	47-81	0	
Tsukamoto 2009	12	Dutasteride 0.5mg(n=70)	＞50	3(4.3)	3
		Placebo (n=66)	＞50	0	
Roehrborn 2002	24	0-12: Dutasteride 0.5mg(n=2167)	＞50	130(6.0)	5
		Placebo (n=2158)	＞50	65(3.0)	
		12-24: Dutasteride 0.5mg(n=1774) ＞50		29(1.7)	
		Placebo (n=1736)	＞50	21(1.2)	
Nickel 2011	12	Dutasteride 0.5mg(n=813)	＞50	69(8.5)	4
		Finasteride 5mg(n=817)	＞50	74(9.0)	
Clark 2004	6	Dutasteride 0.5mg(n=57)	＞50	2(4)	4
		Finasteride 5mg(n=55)	＞50	6(11)	
		Placebo (n=59)	＞50	2(3)	

3.2. Erectile Dysfunction

Within 1 year, 5-alpha reductase inhibitors may increase the risk of erectile dysfunction. Ten studies [8-16, 18] were identified for the effect of 5-alpha Reductase Inhibitors on the erectile dysfunction of BPH with total 6074 participants involved in the 5-alpha Reductase Inhibitors group and 4833 participants involved in the placebo group. Within 1 year, erectile dysfunction was more common with 5-alpha reductase inhibitors than with placebo (OR=2.18, 95%CI[1.79, 2.65], P<0.00001). In particular, considering Finasteride (OR=2.28, 95%CI[1.76, 2.95], P<0.00001) or Dutasteride (OR=2.06, 95%CI[1.53, 2.77], P<0.00001) had no significantly difference with Placebo (Figure 3). Two studies [17, 18] compared the incidence of erectile dysfunction with Finasteride and Dutasteride with total 872 participants involved in the Finasteride group and 870 participants involved in the Dutasteride group. Finally, meta-analysis shows Finasteride had no significantly difference with Dutasteride (OR=1.14, 95%CI[0.81, 1.59], P=0.45) (Figure 4).

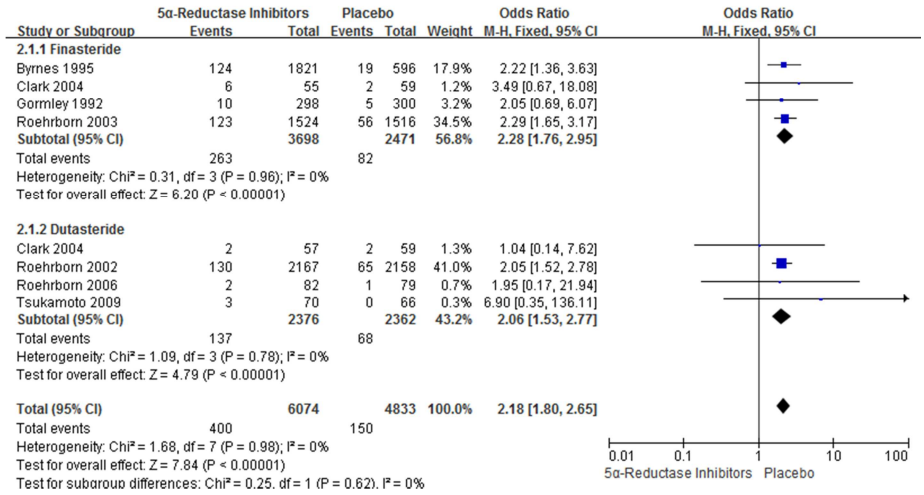

Figure 3. *The Incidence of Erectile Dysfunction within 1 year.*

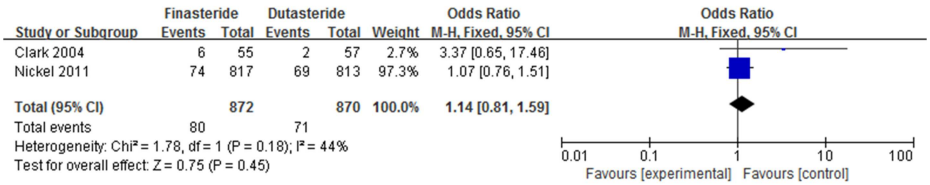

Figure 4. *Finasteride vs. Dutasteride.*

In more than 1 year, Finasteride was more likely to lead to erectile dysfunction. Six studies [8, 10, 11, 12, 14, 16] were identified for the effect of 5-Alpha Reductase Inhibitors on the erectile dysfunction of BPH with total 5748 participants involved in the 5-Alpha Reductase Inhibitors group and 5766 participants involved in the placebo group. In more than 1 year, erectile dysfunction was more common with Finasteride than with placebo (OR=1.46, 95%CI[1.21, 1.76], P<0.0001). Dutasteride (OR=1.43, 95%CI[0.82, 2.49], P=0.21) had no significantly difference with Placebo. (Fig. 5).

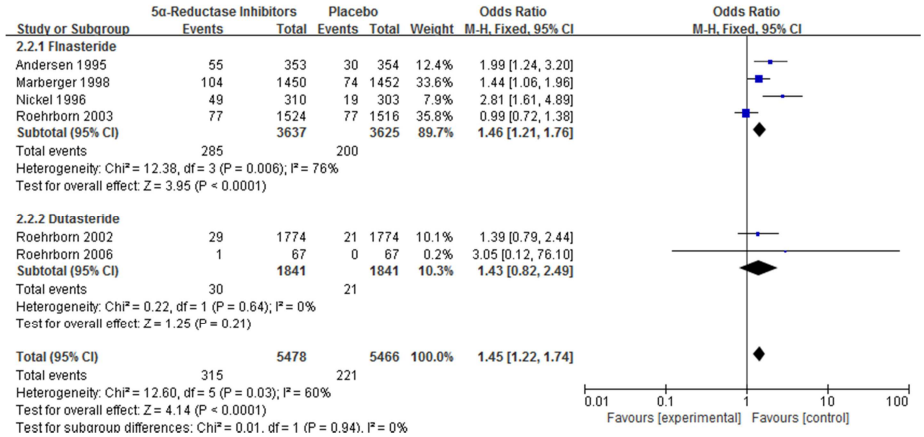

Figure 5. *The Incidence of Erectile Dysfunction in more than 1 year.*

4. Discussion

BPH is a chronic and progressive medical condition among aged men, which bothers their life qualities. Currently, 5α reductase inhibitor is one of the main drugs for the treatment of BPH which can inhibit the activity of 5α reductase, decrease the conversion of testosterone into DHT, decrease the concentration of DHT, induce prostate epithelial cell apoptosis and reduce the volume of prostate, thereby leading to significant reductions in symptom severity, improvement of urinary flow rate, reduction of prostate volume and risk of acute urinary retention, as well as a reduction of the need for surgical intervention [19]. But the attendant side effects such as sexual dysfunction, erectile dysfunction can not be ignored. In 2010, FDA warned that the 5-alpha reductase inhibitors may increase the incidence of sexual dysfunction [20]. The erectile dysfunction caused by 5-alpha reductase inhibitors is closely related to the inhibition of DHT formation. Castrated animals exhibit poor erectile response and T or DHT treatment reverses this effect on erectile physiology. Administration of the 5-alpha reductase inhibitors to castrated animals blocked the stimulatory effects of T on erection [21]. Furthermore, 5 alpha reductase inhibitors can reduce the electrical stimulation induced or acetylcholine induced relaxation of corpus cavernosum smooth muscle [22], reduce the cavernous sinus expansion and decrease the intracavernous pressure (ICP); 5-alpha reductase inhibitors can also decrease the sensitivity of cavernous nerve electrical stimulation, thus affecting the erectile function [23].

All studies included in this meta-analysis are derived from prospective, randomized, double blinded, placebo controlled, parallel-grouped trials. Meta-analysis is appropriate because of the similar study design, minimal heterogeneity of the patients included in the trials, and similarity in outcome measurements.

5. Conclusion

Within 1 year, 5-Alpha reductase inhibitors may increase the risk of erectile dysfunction. In more than 1 year, Finasteride was more likely to lead to erectile dysfunction. The results of this study will be used for informed decisions about the role of 5α-reductase inhibitors in clinical practice and also the need for further research.

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