

ORIGINAL ARTICLE

Sexual, physical, and overall adverse effects in patients treated with 5α -reductase inhibitors: a systematic review and meta-analysis

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Postfinasteride syndrome (PFS) is a term coined to characterize a constellation of reported undesirable sexual, physical, and neuropsychiatric side effects. In the present study, we conducted the meta-analysis to demonstrate whether the use of 5α -reductase inhibitors (5ARIs) increases the risk of PFS-like adverse effects. A search of studies published until May 10, 2020, was performed using PubMed, EMBASE, and the Cochrane Library. We included randomized controlled trials with at least one comparison between male patients receiving 5ARIs versus placebo for the treatment of benign prostatic hyperplasia (BPH) or androgenetic alopecia (AGA), and identified 34 studies from 28 articles that met our eligibility criteria. In the random-effects model, the overall use of 5ARIs exhibited a 1.87-fold risk of PFS-like adverse effects during the trial (95% confidence interval [CI]: 1.64–2.14). Regarding specific types of adverse effects, the use of 5ARIs had a 1.89-fold risk of sexual adverse effects (95% CI: 1.74–2.05) and was associated with an increased risk of physical adverse effects (relative risk [RR]: 1.31, 95% CI: 0.80–2.15), albeit without statistical significance. This meta-analysis helped to better define the adverse effects caused by 5ARIs. We concluded that the overall use of 5ARIs significantly increased the risk of PFS-like adverse effects in men with AGA or BPH during treatment. Enhanced awareness of and education on the PFS-like adverse effects are necessary for clinicians.

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Keywords: 5α-reductase inhibitors; adverse effects; androgenetic alopecia; benign prostatic hyperplasia; postfinasteride syndrome

INTRODUCTION

Postfinasteride syndrome (PFS) is an ill-defined and controversial syndrome associated with a constellation of sexual, physical, and neuropsychiatric symptoms that develop during or after 5α-reductase inhibitor (5ARI) exposure and persist after discontinuation.¹ Sexual symptoms include loss of libido, erectile dysfunction (ED), ejaculatory disorders, sexual anhedonia, decreased semen volume and force, reduction in penis size and scrotal shrinkage, and numbness. Physical symptoms include skin rash, gynecomastia, fatigue, muscle weakness and elevated creatine kinase levels, lipoatrophy, hearing defects and tinnitus, and metabolic anomalies. Neuropsychiatric symptoms associated with PFS include memory impairment, slow cognition, depression, suicidal ideation, anxiety, emotional flatness and anhedonia, insomnia, and obstructive sleep apnea.¹⁻⁴

The hallmark of PFS is persistent adverse events after discontinuing 5ARIs. However, researchers rarely focus on this special point in clinical trials. By searching the PubMed, Embase, and Cochrane Library databases, information regarding PFS mostly originate from case reports, observational studies, and uncontrolled surveys, making a systematic review and meta-analysis difficult.¹

Given the abovementioned reasons, we conducted a systematic review and meta-analysis to focus on the PFS-like (sexual, physical, and neuropsychiatric) adverse effects during treatment. To our knowledge, this is the first attempt to pool current evidence from placebo-controlled randomized clinical trials (RCTs) to evaluate PFS-like adverse effects. This study may provide new insights and inspiration for future research on PFS and help us better define the adverse effects of 5ARIs.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.⁵ This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42020191731).

Study aim

The purpose of this systemic review and meta-analysis was defined using Patient-Intervention-Comparison-Outcome (PICO) statements. The aim was to examine male patients with androgenetic alopecia (AGA) or benign prostatic hyperplasia (BPH; P) to determine whether treatment with oral 5ARIS (I)

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Search strategy

A comprehensive search of studies published before May 10, 2020, was performed in the following electronic databases: PubMed, EMBASE, and Cochrane Library. The combined search terms ("finasteride" OR "dutasteride") AND "placebo" AND "adverse effects" were used. The reference list of retrieved publications was manually screened to identify any additional sources.

Study selection

Studies were selected using the inclusion and exclusion criteria defined prior to initiation of the literature search. Two main reviewers (JJZ and XS) independently evaluated the titles and abstracts of the retrieved studies, and discrepancies were discussed with the research group. The included trials were RCTs that investigated the use of oral 5ARIs in male patients with BPH or AGA and that reported the incidence of any sexual, physical, and neuropsychiatric adverse effects during the trial. The exclusion criteria were as follows: (1) trials that investigated the use of topical 5ARIs; (2) studies that included subjects with diseases other than BPH or AGA, such as prostate cancer; (3) studies including female studies; (4) studies that did not report the incidence of adverse effects; or (5) open-label extension studies. If the abstract did not provide sufficient information for study inclusion or exclusion, a full-text review was performed to determine eligibility. When at least 2 studies were reported by the same institution and/or investigators in an overlapping or continuing period, only the study that was reported first was included. Moreover, for crossover trials, only data from the first period were included to avoid potential confounding events that may have occurred during the crossover of the study with the same subjects.

Data extraction and quality assessment

Two main reviewers (JJZ and TW) compiled the data in a predefined spreadsheet and performed data extraction and quality assessment of the included studies. In the event of disagreement, a final decision was reached through consensus discussion. The data extracted from each study included year, setting, design, trial duration, study population, specific 5ARI and dose, and data on the number, mean age, and age range of subjects. If data measurements among different studies were not the same, data were converted (*e.g.*, from month to week). The main outcome for ascertainment was the incidence of PFS-like adverse effects of 5ARIs or placebo during the trial. If available, data on individual risk of sexual, physical, and neuropsychiatric adverse effects were also collected. The Cochrane Collaboration risk of bias tool was utilized for quality assessment to evaluate the potential risk of bias of the included RCTs.⁶

Data synthesis and outcome

Meta-analyses were performed to calculate the overall relative risk (RR) of PFS-like adverse effects of 5ARIs. The individual RRs of sexual, physical, and neuropsychiatric adverse effects were also calculated using the eligible studies. The meta-analyzed RRs were calculated by combining the datasets using an inverse variance method. Heterogeneity among the included studies was calculated using the χ^2 test for heterogeneity (with P < 0.1 indicating significant heterogeneity) and the I^2 statistic for inconsistency. A random-effects model was used for data synthesis given the heterogeneous study population, study setting, and trial duration of the included studies. The results were expressed using a forest plot. If an adequate number of related studies were available to assess the same outcome, publication bias was assessed using Egger's

test.⁷ Sensitivity analysis was undertaken to demonstrate the overall influence of an individual study where l^2 >50%. Statistical analysis was performed using RevMan 5.2 (the Cochrane Collaboration) and STATA 16.0 (StataCorp., College Station, TX, USA). All *P* values reported were two-sided with *P* < 0.05 considered statistically significant.

RESULTS

Study selection, characteristics, and quality assessment

The PRISMA flow diagram of study selection is shown in **Figure 1**. Of 621 retrieved articles, 28 were included in the study. The characteristics of the 34 studies from 28 articles are summarized in **Table 1**. All studies involved RCTs reporting the incidence of any sexual, physical, and neuropsychiatric adverse effects during the trial in both the 5ARIs and placebo groups. Of these articles, 9 investigated 5 mg day⁻¹ finasteride;⁸⁻¹⁶ 7 investigated 1 mg day⁻¹ finasteride;¹⁷⁻²³ 6 investigated 0.5 mg day⁻¹ dutasteride;²⁴⁻²⁹ 4 investigated both 5 mg day⁻¹ finasteride and 1 mg day⁻¹ finasteride;³⁰⁻³³ 1 investigated both 5 mg day⁻¹ finasteride and 0.5 mg day⁻¹ dutasteride;³⁴ and 1 investigated both 1 mg day⁻¹ finasteride and 0.5 mg day⁻¹ dutasteride.³⁵ The mean age of the 5ARI and placebo groups was comparable in each study. These studies had a moderate risk of bias assessment (**Supplementary Figure 1**) and were included in the data synthesis. A total of 25 696 subjects treated with 5ARIs or placebo were included in the analysis.

Data extraction and synthesis

The number of PFS-like adverse effects in groups treated with 5ARIs or placebo is summarized in **Table 2**. All studies provided the individual number of sexual adverse effects. Ten studies from 8 articles provided the exact number (not zero) of physical adverse effects.^{10,11,14,15,25,26,31,35} Only 1 study provided the exact number (not zero) of neuropsychiatric adverse effects.³¹ Thirty studies were included in our pooled data, and 4 were excluded due to the lack of exact total data.^{10,12,14,17} Of these subjects, 1804 of 11 886 treated with 5ARIs and 800 of 9524 treated with placebo experienced at least one PFS-like adverse effect. Regarding the dose/5ARI subgroup, 1275 of 7473 subjects treated with 5 mg day⁻¹ finasteride and 545 of 5127 subjects treated with placebo experienced at

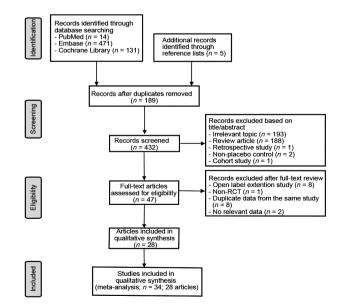


Figure 1: Flow diagram of literature search. A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines. RCT: randomized clinical trial.



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Table 1: Characteristics of the included studies

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Study	Setting	Design	Trial duration	~	Dose/5ARIs	Age (yea	Age (yea	ar), range	
			(week)	population		5ARIs	Placebo	5ARIs	Placebo
Gormley et al. ^{31,a} 1992	USA and Canada	RCT	48	Men with BPH	5 mg day ⁻¹ F	64	64	40-80	45-82
Gormley et al. ^{31,b} 1992	USA and Canada	RCT	48	Men with BPH	1 mg day ⁻¹ F	64	64	41–83	45–82
The Finasteride Study Group ^{33,a} 1993	World wide	RCT	48	Men with BPH	5 mg day-1 F	66	66	46-83	40-81
The Finasteride Study Group ^{33,b} 1993	World wide	RCT	48	Men with BPH	1 mg day ⁻¹ F	65	66	46-81	46-81
Kirby <i>et al.</i> ⁸ 1993	UK	RCT	12	Men with BPH	5 mg day ⁻¹ F	64.4	64.4	48–87	48–87
Byrnes <i>et al.</i> ⁹ 1995	USA	RCT	48	Men with BPH	5 mg day-1 F	65	65.1	42–91	45–91
Lepor <i>et al.</i> ¹⁰ 1996	USA	RCT	52	Men with BPH	5 mg day ⁻¹ F	65	65	45–80	45-80
Nickel et al.12 1996	Canada	RCT	96	Men with BPH	5 mg day ⁻¹ F	63	63.5	46–79	47–80
Tenover <i>et al.</i> ¹³ 1997	USA	RCT	48	Men with BPH	5 mg day-1 F	NA	NA	Over 45	Over 45
Kaufman <i>et al.</i> ¹⁷ 1998	World wide	RCT	48	Men with AGA	1 mg day ⁻¹ F	USA: 33 Non-USA: 31	USA: 34 Non-USA: 31	18–41	18–41
Marberger ¹¹ 1998	World wide	RCT	96	Men with BPH	5 mg day ⁻¹ F	NA	NA	50–75	50–75
Mcconnell et al.15 1998	USA	RCT	192	Men with BPH	5 mg day ⁻¹ F	64	64	NA	NA
Drake <i>et al</i> . ^{30,a} 1999	USA and Canada	RCT	6	Men with AGA	5 mg day ⁻¹ F	37	38	22–46	19–49
Drake <i>et al</i> . ^{30,b} 1999	USA and Canada	RCT	6	Men with AGA	1 mg day ⁻¹ F	36	38	21–50	19–49
Leyden <i>et al</i> . ¹⁸ 1999	USA	RCT	48	Men with AGA	1 mg day ⁻¹ F	33	32	18–40	18–40
Roberts et al.32,a 1999	USA	RCT	48	Men with AGA	5 mg day ⁻¹ F	30	30	18–36	18–36
Roberts et al.32,b 1999	USA	RCT	24	Men with AGA	1 mg day ⁻¹ F	30	30	18–36	18–36
Van Neste et al.19 2000	World wide	RCT	48	Men with AGA	1 mg day ⁻¹ F	30.2	29.3	18–40	18–40
Price et al.21 2002	USA	RCT	48	Men with AGA	1 mg day ⁻¹ F	32.9	30.9	22–40	22–40
Roehrborn et al.26 2002	World wide	RCT	96	Men with BPH	0.5 mg day ⁻¹ D	66.5	66.1	Over 50	Over 50
Leavitt et al.20 2005	USA	RCT	48	Men with AGA	1 mg day ⁻¹ F	40	41	20–45	20–45
Olsen <i>et al.</i> ^{34,a} 2006	USA	RCT	24	Men with AGA	5 mg day ⁻¹ F	38.5	35.8	21–45	21–45
Olsen <i>et al.</i> ^{34,b} 2006	USA	RCT	24	Men with AGA	0.5 mg day ⁻¹ D	36.1	35.8	21–45	21–45
Stough ²⁷ 2007	USA	RCT	48	Men with AGA	0.5 mg day ⁻¹ D	NA	NA	18–50	18–50
Tsukamoto <i>et al.</i> ²⁸ 2009	Japan	RCT	52	Men with BPH	0.5 mg day ⁻¹ D	67.7	64.4	Over 50	Over 50
Eun <i>et al.</i> ²⁴ 2010	Korea	RCT	24	Men with AGA	0.5 mg day ⁻¹ D	37.8	38.4	18–49	18–49
Na <i>et al.</i> ²⁵ 2012	China	RCT	24	Men with BPH	0.5 mg day ⁻¹ D	65.8	66.9	Over 50	Over 50
Gubelin Harcha et al.35,a 2014	World wide	RCT	24	Men with AGA	1 mg day ⁻¹ F	38	38.7	21-50	20–50
Gubelin Harcha et al.35,b 2014	World wide	RCT	24	Men with AGA	0.5 mg day ⁻¹ D	38.6	38.7	20–50	20–50
Kaplan <i>et al.</i> ¹⁴ 2016	USA	RCT	48	Men with BPH	5 mg day ⁻¹ F	NA	NA	Over 50	Over 50
Tsai <i>et al.</i> ²⁹ 2018	World wide	RCT	24	Men with AGA	0.5 mg day ⁻¹ D	39.1	39	18–50	18–50
Yu <i>et al.</i> ¹⁶ 1995	China	RCT	24	Men with BPH	5 mg day ⁻¹ F	66.4	65.1	50-82	50-82
Whiting et al.23 2003	USA	RCT	96	Men with AGA	1 mg day ⁻¹ F	49.9	49.8	41–60	41–60
Kawashima <i>et al.</i> ²² 2004	Japan	RCT	48	Men with AGA	1 mg day ^{_1} F	40	40	20–50	20–50

^{ah}One article includes 2 studies. 5ARIs: 5α-reductase inhibitors; RCT: randomized controlled trials; BPH: benign prostatic hyperplasia; AGA: androgenetic alopecia; F: finasteride D: dutasteride; NA: not available

least one PFS-like adverse effect. In total, 134 of 1650 subjects treated with 1 mg day⁻¹ finasteride and 60 of 1650 subjects treated with placebo experienced at least one PFS-like adverse effect. In total, 395 of 2763 subjects treated with 0.5 mg day⁻¹ dutasteride and 195 of 2747 subjects treated with placebo experienced at least one PFS-like adverse effect (**Figure 2**). For the disease subgroup, 1677 of 10 164 subjects treated with 5ARIs and 718 of 7786 subjects treated with placebo in the BPH subgroup had at least one PFS-like adverse effect; 127 of 1722 subjects treated with 5ARIs and 82 of 1738 subjects treated with placebo in the AGA subgroup had at least one PFS-like adverse effect (**Figure 3**).

Overall use of 5ARIs

In the random-effects model, the overall use of 5ARIs had a 1.87fold risk of PFS-like adverse effects during the trial (95% confidence interval [CI]: 1.64–2.14). Heterogeneity among the included studies was acceptable ($I^2 = 26\%$), and heterogeneity among studies in the dose/5ARI subgroup was minimal ($I^2 = 0$), as shown in **Figure 2**. However, the heterogeneity among studies in the disease subgroups was significant ($I^2 = 72\%$; **Figure 3**). Regarding specific types of adverse effects, the use of 5ARIs exhibited a 1.89-fold risk of sexual adverse effects (95% CI: 1.74–2.05) and was associated with an increased risk of physical adverse effects (RR: 1.31, 95% CI: 0.80–2.15), albeit without statistical significance (**Supplementary Figure 2** and **3**). Only 1 study reported the exact number of neuropsychiatric adverse effects.³¹ Thus, we did not calculate the RR.

Different 5ARI subgroups

<u>5 mg day⁻¹ finasteride</u>

In the subgroup analysis of 11 studies, 5 mg day⁻¹ finasteride had a 1.85-fold risk of PFS-like adverse effects (95% CI: 1.49–2.29) compared with placebo.^{8,9,11,13,15,16,30–34} Heterogeneity among the included studies was moderate ($I^2 = 53\%$; **Figure 2**). The risk of publication bias was low based on Egger's test results (P = 0.518). To explore the sources of heterogeneity, sensitivity analysis was performed by excluding studies sequentially. The results showed that after omitting the study by Marberger,¹¹ the I^2 value decreased from 53% to 20%, and the RR increased to 2.01 (95% CI: 1.67–2.42). These findings suggested the main source of the heterogeneity. Regarding specific types of adverse

Table 2: Outcomes of the included studies

Study	Number o	of subjects	Number of sexual adverse effects		Number of physical adverse effects			europsychiatric e effects	Number of total PFS-like adverse effects	
	5ARIs	Placebo	5ARIs	Placebo	5ARIs	Placebo	5ARIs	Placebo	5ARIs	Placebo
Gormley <i>et al.</i> ^{31,a} 1992	297	300	39	15	5	4	0	0	44	19
Gormley et al. ^{31,b} 1992	298	300	47	15	3	4	1	0	51	19
The Finasteride Study Group ^{31,a} 1993	246	255	12	1	0	0	0	0	12	1
The Finasteride Study Group ^{31,b} 1993	249	255	10	1	0	0	0	0	10	1
Kirby <i>et al.</i> ⁸ 1993	29	21	1	0	0	0	0	0	1	0
Byrnes et al. ⁹ 1995	1821	596	222	29	0	0	0	0	222	29
Lepor <i>et al.</i> ¹⁰ 1996	310	305	49	22	23	21	NA	NA	NA	NA
Nickel <i>et al.</i> ¹² 1996	310	303	104	43	NA	NA	NA	NA	NA	NA
Tenover et al.13 1997	1736	579	271	41	0	0	0	0	271	41
Kaufman <i>et al.</i> ¹⁷ 1998	779	774	34	20	NA	NA	0	0	NA	NA
Marberger ¹¹ 1998	1577	1591	200	127	28	45	0	0	228	172
McConnell et al.15 1998	1524	1516	433	247	50	23	0	0	483	270
Drake <i>et al.</i> ^{30,a} 1999	38	67	1	3	0	0	0	0	1	3
Drake <i>et al.</i> ^{30,b} 1999	37	67	0	3	0	0	0	0	0	3
Leyden <i>et al</i> . ¹⁸ 1999	166	160	3	3	0	0	0	0	3	3
Roberts <i>et al</i> . ^{32,a} 1999	111	116	5	5	0	0	0	0	5	5
Roberts et al. ^{32,b} 1999	117	233	5	7	0	0	0	0	5	7
Van Neste et al.19 2000	106	106	2	1	0	0	0	0	2	1
Price <i>et al.</i> ²¹ 2002	33	33	1	0	0	0	0	0	1	0
Roehrborn et al.26 2002	2167	2158	297	149	50	16	0	0	347	165
Leavitt <i>et al.</i> ²⁰ 2005	40	39	2	0	0	0	0	0	2	0
Olsen <i>et al.</i> ^{34,a} 2006	70	64	6	5	0	0	0	0	6	5
Olsen <i>et al.</i> ^{34,b} 2006	68	64	2	5	0	0	0	0	2	5
Stough ²⁷ 2007	17	17	2	0	0	0	0	0	2	0
Tsukamoto <i>et al.</i> ²⁸ 2009	70	66	3	0	0	0	0	0	3	0
Eun <i>et al</i> . ²⁴ 2010	73	75	3	3	0	0	0	0	3	3
Na <i>et al.</i> ²⁵ 2012	126	127	2	1	1	0	0	0	3	1
Gubelin Harcha <i>et al.</i> ^{35,a} 2014	179	181	30	16	1	0	0	0	31	16
Gubelin Harcha <i>et al.</i> ^{35,b} 2014	184	181	25	16	1	0	0	0	26	16
Kaplan <i>et al</i> . ¹⁴ 2016	768	737	185	99	9	12	NA	NA	NA	NA
Tsai <i>et al.</i> ²⁹ 2018	58	59	9	5	0	0	0	0	9	5
Yu <i>et al</i> . ¹⁶ 1995	24	22	2	0	0	0	0	0	2	0
Whiting et al.23 2003	286	138	25	7	0	0	0	0	25	7
Kawashima <i>et al.</i> ²² 2004	139	138	4	3	0	0	0	0	4	3

abOne article includes 2 studies. PFS: postfinasteride syndrome; 5ARIs: 5α-reductase inhibitors; NA: not available

effects, there was a 1.93-fold risk of sexual adverse effects (95% CI: 1.70–2.18), and the incidence of physical adverse effects (RR: 1.06, 95% CI: 0.62–1.82) also tended to be greater than that for placebo, albeit without statistical significance (**Supplementary Figures 2** and **3**).

<u>1 mg day⁻¹ finasteride</u>

In the subgroup analysis of 11 studies, 1 mg day⁻¹ finasteride had a 2.08-fold risk of PFS-like adverse effects (95% CI: 1.54–2.82) compared with placebo.^{18–23,30–33,35} Heterogeneity among the included studies was minimal ($I^2 = 0$; **Figure 2**). The risk of publication bias was low based on the Egger's test results (P = 0.568). Regarding specific types of adverse effects, a 1.85-fold risk of sexual adverse effects (95% CI: 1.50–2.28) was observed. However, the incidence of physical adverse effects (RR: 0.97, 95% CI: 0.25–3.73) tended to be lower than that for placebo, albeit without statistical significance (**Supplementary Figure 2** and **3**).

0.5 mg day⁻¹ dutasteride

In the subgroup analysis of 8 studies, 0.5 mg day⁻¹ dutasteride was significantly associated with an increased risk of PFS-like adverse effects

(RR: 2.01, 95% CI: 1.71–2.37; **Figure 2**).^{24-29,34,35} Heterogeneity among the included studies was minimal ($I^2 = 0$). The risk of publication bias was low based on the Egger's test results (P = 0.506). Regarding specific types of adverse effects, 0.5 mg day⁻¹ dutasteride tended to increase the sexual adverse effects (RR: 1.85, 95% CI: 1.50–2.28). The incidence of physical adverse effects (RR: 3.10, 95% CI: 1.80–5.35) also tended to be significantly higher than that for placebo (P < 0.001), as shown in **Supplementary Figure 2** and **3**.

Different disease subgroups

BPH group

In the subgroup analysis of 16 studies from 14 articles, patients treated with 5ARIs had a 2.05-fold risk of PFS-like adverse effects (95% CI: 1.71–2.46) compared with placebo.^{8–16,25,26,28,31,33} Heterogeneity among the included studies was moderate ($I^2 = 58\%$; **Figure 3**). The risk of publication bias was significant based on Egger's test results (P = 0.034). To explore the sources of heterogeneity, sensitivity analysis was performed by excluding studies sequentially. The results showed that after omitting the study by Marberger,¹¹ the I^2 value decreased

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Experimental

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M-H random

M-H random

Control

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Study or subgroup	Events	Iotal	Events	Iotal	Weight	Risk ratio (95% CI)	Risk ratio (95% CI)
5 mg day 1 finasteride							
Byrnes et al.º 1995	222	1821	29	596	8.0%	2.51 [1.72, 3.65]	
Drake <i>et al.</i> ^{30,a} 1999	1	38	3	67	0.4%	0.59 [0.06, 5.45]	
The Finasteride Study Group ^{33,a} 1993		246	1	255	0.4%	12.44 [1.63, 94.95]	
Gormely et al. ^{31,a} 1992	44	297	19	300	5.2%	2.34 [1.40, 3.91]	——
Kirby et al. ⁸ 1993	1	29	0	21	0.2%	2.20 [0.09, 51.49]	
Marberger ¹¹ 1998	228	1577	172	1591	15.4%	1.34 [1.11, 1.61]	+
Mcconnell et al. ¹⁵ 1998	483	1524	270	1516	18.1%	1.78 [1.56, 2.03]	-
Olsen et al.34,a 2006	6	70	5	64	1.3%	1.10 [0.35, 3.42]	
Roberts et al.32,a 1999	5	111	5	116	1.1%	1.05 [0.31, 3.51]	
Tenover et al.13 1997	271	1736	41	579	9.9%	2.20 [1.61, 3.02]	
Yu <i>et al.</i> ¹⁶ 1995	2	24	0	22	0.2%	4.60 [0.23, 90.84]	
Subtotal (95% CI)	-	7473	Ū	5127	60.0%	1.85 [1.49, 2.29]	
Total events	1275	1410	545	0121	00.070	1.00 [1.40, 2.20]	
Heterogeneity: Tau ² = 0.04; Chi ² = 21.		10 (P =)	0.02); <i>l</i> ² =	53%			
Test for overall effect: Z = 5.67 (P < 0.	.00001)						
1 mg day 1 finasteride							
Drake et al.30,6 1999	0	37	3	67	0.2%	0.26 [0.01, 4.82] -	
The Finasteride Study Group ^{33,b} 1993	10	249	1	255	0.4%	10.24 [1.32, 79.41]	
Gormely et al.31,b 1992	51	298	19	300	5.3%	2.70 [1.64, 4.46]	
Gubelin Harcha et al.35,a 2014	31	179	16	181	4.4%	1.96 [1.11, 3.45]	
Kawashima <i>et al.</i> ²² 2004	4	139	3	138	0.8%	1.32 [0.30, 5.81]	
Leavitt et al.20 2005	2	40	0	39	0.2%	4.88 [0.24, 98.47]	
Leyden <i>et al.</i> ¹⁸ 1999	3	166	3	160	0.7%	0.96 [0.20, 4.71]	
Van Neste et al. ¹⁹ 2000	2	106	1	106	0.3%	2.00 [0.18, 21.72]	
Price et al. ²¹ 2002	1	33	0	33	0.2%	3.00 [0.13, 71.07]	
Roberts et al.32,b 1999	5	117	7	233	1.3%	1.42 [0.46, 4.39]	
Whiting et al.23 2003	25	286	7	138	2.4%	1.72 [0.76, 3.89]	
Subtotal (95% CI)		1650		1650	16.3%	2.08 [1.54, 2.82]	
Total events	134		60		10.070	2.00 [1.0 1, 2.02]	•
Heterogeneity: Tau ² = 0; Chi ² = 7.66,	df = 10 (P = 0.66); <i>I</i> ² = 0				
Test for overall effect: Z = 4.77 (P < 0.	.00001)						
0.5 mg day-1 dutasteride							
Eun <i>et al.</i> ²⁴ 2010	3	73	3	75	0.7%	1.03 [0.21, 4.93]	
Gubelin Harcha <i>et al.</i> 35,6 2014	26	184	16	181	4.2%	1.60 [0.89, 2.88]	<u> </u>
Na et al.25 2012	3	126	1	127	0.3%	3.02 [0.32, 28.68]	
Olsen et al. ^{34,b} 2006	2	68	5	64	0.7%	0.38 [0.08, 1.87]	
Roehrborn et al.26 2002	347	2167	165	2158	15.9%	2.09 [1.76, 2.50]	-
Stough ²⁷ 2007	2	17	0	17	0.2%	5.00 [0.26, 97.00]	
Tsai et al. ²⁹ 2018	9	58	5	59	1.6%	1.83 [0.65, 5.14]	
Tsukamoto et al.28 2009	3	70	Ő	66	0.2%	6.61 [0.35, 125.49]	
Subtotal (95% CI)	0	2763	0	2747	23.7%	2.01 [1.71, 2.37]	
Total events	395	2100	195	2141	20.170	2.01[1.11, 2.01]	▼
Total events	555		100				
Heterogeneity: Tau ² = 0; Chi ² = 6.84, o	df = 7 (F	P = 0.45);	<i>I</i> ² = 0				
Test for overall effect: $Z = 8.38$ ($P < 0.2$.00001)						
Total (95% CI)		11886		9524	100.0%	1.87 [1.64, 2.14]	•
Total events	1804		800				,
						—	
Heterogeneity: Tau ² = 0.02; Chi ² = 39.		29 (P =	u.10); /² =	26%		0.01	0.1 1 10 100
Test for overall effect: $Z = 9.20$ ($P < 0$.		0 (D					Favours [experimental] Favours [control]
Test for subgroup differences: Chi ² = 0	u.53, df	= 2 (P =)	U.((); f ² =	0%			

Figure 2: Increased risk of PFS-like adverse effects with the use of 5α-reductase inhibitors (dose subgroup). ^{a/b}One article includes 2 studies. PFS: postfinasteride syndrome; df: degree of freedom; CI: confidence interval; M–H: Metropolis-Hastings.

from 58% to 20%, and the RR increased to 2.12 (95% CI: 1.85–2.43). These findings suggested the main source of the heterogeneity. Regarding specific types of adverse effects, a 2.02-fold risk of sexual adverse effects (95% CI: 1.80–2.26) was observed, and the incidence of physical adverse effects (RR: 1.26, 95% CI: 0.75–2.13) also tended to be greater than that for placebo, albeit without statistical significance (**Supplementary Figure 4** and **5**).

AGA group

In the subgroup analysis of 17 studies from 14 articles, patients treated with 5ARIs had a 1.49-fold risk of PFS-like adverse effects (95% CI: 1.13–1.97) compared with placebo.^{17–24,27,29,30,32,34,35} Heterogeneity among the included studies was minimal ($I^2 = 0$; **Figure 3**). The risk of publication bias was low based on the Egger's test results (P = 0.210). Regarding specific types of adverse effects, a 1.50-fold risk of sexual adverse effects (95% CI: 1.17–1.91) was observed. The incidence of physical adverse effects (RR: 2.99, 95% CI: 0.31–28.63) tended to be greater than that for placebo, albeit without statistical significance (**Supplementary Figure 4** and **5**).

DISCUSSION

In this meta-analysis, available data regarding the neuropsychiatric adverse effects were limited. The low prevalence and incidence of

neuropsychiatric adverse effects are inconsistent with the literature data. In a cohort study, 19 of 23 patients developed a mood disturbance (moderate to severe depression) during treatment; depression significantly impaired social relations and increased anxiety.³³ Several other studies also reported that neuropsychiatric adverse effects were significantly more prevalent in finasteride users compared with nonusers.^{36,37} Potential biases, including sample size, targeted population, cultural and psychological differences between genders, and lack of rigorous prospective investigations, may account for this difference. Additionally, compared with the other two adverse effects, the neuropsychiatric adverse effects may be more complicated and hidden, and the investigators typically conducting such RCTs may not necessarily be well trained to spot mental symptoms. Thus, further studies are needed to confirm the risk of neuropsychiatric adverse effects with the use of 5ARIs.

Regarding sexual adverse effects, surprisingly, we found a higher RR in patients treated with 1 mg day⁻¹ finasteride compared with patients treated with 5 mg day⁻¹ finasteride, albeit without statistical significance. This finding may be partly due to the nondose-dependent effect of finasteride on dihydrotestosterone (DHT) pharmacokinetics.³⁸ All daily finasteride doses between 0.4 mg and 100 mg lead to steady-state DHT plasma levels between 0.1 ng ml⁻¹ and 0.15 ng ml^{-1.38}

Study or subgroup	Experim Events	ental Total	Cont Events		Weight	M–H, random Risk ratio (95% Cl)	M–H, random Risk ratio (95% CI)
	LYCINS	Jotai	Lycins	, Jtai		Mar 1400 (8570 CI)	
8PH group Byrnes <i>et al.</i> º 1995	222	1821	29	596	8.0%	2.51 [1.72, 3.65]	
The Finasteride Study Group ^{33,a} 1993	12	246	29	255	0.4%	12.44 [1.63, 94.95]	
The Finasteride Study Group ^{33,b} 1993	12	240	1	255	0.4%	10.24 [1.32, 79.41]	
Gormely <i>et al.</i> ^{a31} 1992	44	249 297	19	200	0.4% 5.2%	2.34 [1.40, 3.91]	
Gormely et al. ^{b31} 1992	44 51	297	19	300	5.3%	2.70 [1.64, 4.46]	
Kirby et al. ⁸ 1993	1	298	0	21	0.2%	2.20 [0.09, 51.49]	
Marberger ¹¹ 1998	228	29 1577	172		0.2% 15.4%		
Mcconnell et al. ¹⁵ 1998	483	1577	270	1516	15.4%	1.34 [1.11, 1.61]	
Na et al. ²⁵ 2012	403	126	270	127	0.3%	1.78 [1.56, 2.03]	
Roehrborn <i>et al.</i> ²⁶ 2002	3 347	2167	165	2158	0.5%	3.02 [0.32, 28.68]	
Tenover et al. ¹³ 1997						2.09 [1.76, 2.50]	
	271	1736	41	579	9.9%	2.20 [1.61, 3.02]	
Tsukamoto <i>et al.</i> ²⁸ 2009	3	70	0	66	0.2%	6.61 [0.35, 125.49]	
Yu et al. ¹⁶ 1995	2	24	0	22 7786	0.2%	4.60 [0.23, 90.84]	
Subtotal (95% CI) Total events	1677	10164	718	1180	79.4%	2.05 [1.71, 2.46]	◆
Heterogeneity: Tau ² = 0; Chi ² = 28.39, Test for overall effect: $Z = 7.74$ ($P < 0.0$		0.00	5), 7 = 50	, ,0			
GA group		20	0	07	0.40/	0.50.00.00.5.451	
Drake et al. ^{a30} 1999	1 0	38 37	3	67 67	0.4%	0.59 [0.06, 5.45]	
Drake et al. b30 1999	3	37 73	3 3	75	0.2%	0.26 [0.01, 4.82]	
Eun <i>et al.</i> ²⁴ 2010	-	73 179	-		0.7%	1.03 [0.21, 4.93]	
Gubelin Harcha et al. ^{35,a} 2014	31 26	179	16	181	4.4% 4.2%	1.96 [1.11, 3.45]	
Gubelin Harcha et al. ^{35,b} 2014			16	181		1.60 [0.89, 2.88]	
Kawashima et al.22 2004	4 2	139	3 0	138	0.8%	1.32 [0.30, 5.81]	
Leavitt et al. ²⁰ 2005		40		39	0.2%	4.88 [0.24, 98.47]	
Leyden <i>et al.</i> ¹⁸ 1999	3	166	3	160	0.7%	0.96 [0.20, 4.71]	
Van Neste et al. ¹⁹ 2000	2 6	106	1 5	106	0.3%	2.00 [0.18, 21.72]	
Olsen et al. ^{34,a} 2006		70 68		64	1.3%	1.10 [0.35, 3.42]	
Olsen et al. ^{34,b} 2006	2 1	33	5 0	64	0.7% 0.2%	0.38 [0.08, 1.87]	
Price et al.21 2002	5		5	33		3.00 [0.13, 71.07]	
Roberts et al. ^{32,a} 1999	5	111 117	7	116 233	1.1% 1.3%	1.05 [0.31, 3.51] 1.42 [0.46, 4.39]	
Roberts et al. ^{32,b} 1999	2	17	0		0.2%		
Stough ²⁷ 2007	2 9	58	5	17 59	0.2% 1.6%	5.00 [0.26, 97.00]	
Tsai et al. ²⁹ 2018	9 25	58 286	5	59 138	2.4%	1.83 [0.65, 5.14] 1.72 [0.76, 3.89]	
Whiting et al.23 2003	20		'				
Subtotal (95% CI)		1722		1738	20.6%	1.49 [1.13, 1.97]	▼
Total events Heterogeneity: $Tau^2 = 0$: $Chi^2 = 8.74$, d	127 f = 16 /D	- 0 02)-	82 <i>R</i> = 0				
Test for overall effect: $Z = 2.86$ ($P = 0.0$,,	, = 0				
Total (95% CI)		11886		9524	100.0%	1.87 [1.64, 2.14]	♦
Total events	1804		800				
11 T 3 0.00 01 3 00 1	12 df - 2	0 / 0 - 0	10) 8 -	26%			
Heterogeneity: Tau ² = 0.02; Chi ² = 39.1						0.01	0.1 1 10

Figure 3: Increased risk of PFS-like adverse effects with the use of 5α-reductase inhibitors (disease subgroup). ^{a/b}One article includes 2 studies. BPH: benign prostatic hyperplasia; AGA: androgenetic alopecia; PFS: postfinasteride syndrome; df: degree of freedom; CI: confidence interval; M–H: Metropolis-Hastings.

Additionally, the discontinuation of finasteride treatment results in a normalization of DHT levels within 2 weeks, irrespective of the finasteride dose. In this regard, more underlying mechanisms are worth of further exploration.

In our study, patients treated with 5ARIs in the BPH subgroup were associated with a 2.02-fold risk of sexual adverse effects. However, the risk of sexual adverse effects was only 1.5-fold for men with AGA. This finding is consistent with previously reported results.³⁹ BPH is a common medical condition in men over 50 years old, and sexual dysfunction in men increases with age. The different risks of sexual dysfunction between these two groups may be partly due to advancing age.

Many systematic reviews and meta-analyses concerning the adverse effects of 5ARIs have been conducted and are reported in the literature.^{39–41} Lee *et al.*⁴¹ investigated the risk of adverse sexual effects caused by 5ARIs in male patients with AGA. The use of 5ARIs carried a 1.57-fold risk of sexual dysfunction (95% CI: 1.19–2.08). In the subgroup analysis, the RR was 1.66 (95% CI: 1.20–2.30) for 1 mg day⁻¹ finasteride and 1.37 (95% CI: 0.81–2.32) for 0.5 mg day⁻¹ dutasteride, respectively.⁴¹ In our study, there was a 1.89-fold risk of sexual adverse effects (95% CI: 1.74–2.05) in patients treated with 5ARIs. In the subgroup analysis, the RR was 2.01 (95% CI: 1.53–2.63) for 1 mg day⁻¹ finasteride and 1.85 (95% CI: 1.50–2.28) for 0.5 mg day⁻¹ dutasteride, respectively. This difference may be attributed to different inclusion criteria between the two studies. In addition to patients with AGA, we also included BPH patients. Patients with BPH more easily develop sexual dysfunction.

In the case of PFS, there are strong selection biases and the nocebo factors. A significant placebo/nocebo effect has been documented among patients informed about possible side effects, which may explain the high prevalence of reported sexual dysfunction and psychiatric side effects in subjects participating in internet groups and blogs.⁴² Mondaini *et al.*⁴³ also reported that the nocebo effect was relatively significant when patients were informed about possible sexual dysfunction caused by the therapy. Sexual side effects increased from 29.3% to 43.6% when information was given at the beginning of the treatment. Thus, this finding may inspire us to balance the information bias in the design of future studies and inform the participants about the potential adverse effects in both groups before the start of the experiment.

Several potential solutions have been proposed to protect patients from the immediate and persistent adverse effects of finasteride.⁴⁴ For BPH patients, administration of finasteride concomitantly with a phosphodiesterase type 5 inhibitor may provide an improvement in sexual function with no reduction of effectiveness in prostate treatment. In addition, tamsulosin and surgery may be an alternative treatment options for BPH patients. For AGA patients, the use of topical finasteride (0.25% solution) seems to be less harmful than an oral formulation with a similar effectiveness. Other auxiliary treatments, such as topical minoxidil, platelet-rich plasma, low-level laser therapy, and surgery, may also represent good treatment choices.

To date, there are no predictive factors for the risk of developing PFS. Nevertheless, it would seem appropriate to evaluate the history of preexisting mental health issues and the possibility of potential

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sexual dysfunction.⁴⁵ Additionally, a stricter selection of patients is needed before the initiation of 5ARI treatment, such as patients with repeated inquiries on safety issues of the drug or holding on to their belief system tenaciously despite any rational argumentation against it.⁴⁵ Administration of 5ARIs may more easily put these patients at an increased risk of developing sexual or emotional disorders.

The greatest limitation of our study is that we focused on sexual, physical, and overall adverse effects rather than real PFS. The persistent effect is the hallmark of PFS, and this phenomenon is particularly prominent in the subset of young AGA patients. Both AGA (<40 years old) and BPH (> 40 years old) patients were included in the present study. Data obtained in different situations might cause some confusion and bias. Although we employed subgroup analysis to reduce this deviation, it is not sufficient. In the future, we may solve this problem by improving the acquisition, analysis, and interpretation of data on PFS. Additionally, to examine the persistence of symptoms, placebo-controlled RCTs using validated questionnaires and long-term follow-up after the discontinuation of 5ARIs are needed.

CONCLUSION

Our study demonstrated that 5ARIs were associated with a significantly increased risk of sexual, physical, and overall adverse effects than placebo for men with AGA or BPH during treatment. Clinicians should assess the risk of preexisting mental health issues and the possibility of potential sexual dysfunction before 5ARI treatment. Alternative treatments may be used to protect patients from the immediate and persistent adverse effects of 5ARIs.

AUTHOR CONTRIBUTIONS

JJZ and LW contribute to conception and design. JJZ and XS contribute to acquisition of data. JJZ and TW contribute to analysis of data. JJZ contributes to drafting the article. MDZ, JT, GMY, ZL, LYH, and LQ contribute to revising it critically for important intellectual content. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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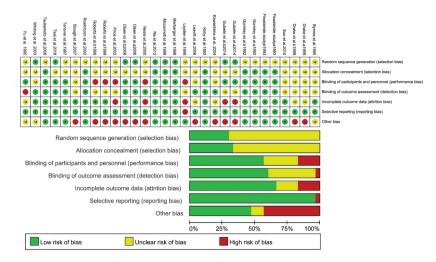
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Supplementary Figure 1: Quality assessment and risk of bias summary.

Chudu an Cubanaun	Experim		Conti		Mainht	Risk Ratio	Risk Ratio
<u>Study or Subgroup</u> I.3.1 Finasteride 5mg/d	Events	Iotal	Events	Iotal	weight	M-H, Random, 95% C	I M-H, Random, 95% Cl
-	222	4004	29	596	4 40/	0 54 [4 70 0 65]	
Byrnes et al. 1995		1821 38	29	596 67	4.4%	2.51 [1.72, 3.65]	
Drake et al.a1999	1	246		255	0.1%	0.59 [0.06, 5.45]	
Finasteride studya1993 Gormley et al.a1992	12 39	246 297	1 15	255	0.2% 1.9%	12.44 [1.63, 94.95]	
Kaplan et al.2016	185	768	99	737	11.7%	2.63 [1.48, 4.66] 1.79 [1.44, 2.24]	-
Cirby et al. 1993	105	29	99 0	21	0.1%	2.20 [0.09, 51.49]	
epor et al. 1995	49	310	22	305	2.8%	2.20 [0.09, 51.49]	
larberger et al.1998	200	1577	127	1591	12.8%	1.59 [1.29, 1.96]	+
Acconnell et al. 1998	433	1524	247	1516	25.2%	1.74 [1.52, 2.00]	-
lickel et al.1996	104	310	43	303	6.1%	2.36 [1.72, 3.25]	
Disen et al.a2006	6	70	-5	64	0.5%	1.10 [0.35, 3.42]	
oberts et al.a1999	5	111	5	116	0.4%	1.05 [0.31, 3.51]	
enover et al.1997	271	1736	41	579	6.2%	2.20 [1.61, 3.02]	
'u et al. 1995	2/1	24	0	22	0.1%	4.60 [0.23, 90.84]	
ubtotal (95% CI)	2	8861	0	6472	72.4%	1.93 [1.70, 2.18]	•
otal events	1530		637				
leterogeneity: Tau ² = 0.0		7 23 df		0 19) 1	² = 25%		
est for overall effect: Z =				5.10),1	2070		
		5.0000	• /				
.3.2 Finasteride 1mg/d							
Drake et al.b1999	0	37	3	67	0.1%	0.26 [0.01, 4.82]	
inasteride studyb1993	10	249	1	255	0.2%	10.24 [1.32, 79.41]	
Gormley et al.b1992	47	298	15	300	2.0%	3.15 [1.80, 5.52]	
Subelin et al.a2014	30	179	16	181	2.0%	1.90 [1.07, 3.35]	
Caufman et al.1998	34	779	20	774	2.2%	1.69 [0.98, 2.91]	
awashima 2004	4	139	3	138	0.3%	1.32 [0.30, 5.81]	
eavitt et al.2006	2	40	0	39	0.1%	4.88 [0.24, 98.47]	
eyden et al.1999	3	166	3	160	0.3%	0.96 [0.20, 4.71]	
leste et al.2000	2	106	1	106	0.1%	2.00 [0.18, 21.72]	
Price et al.2002	1	33	0	33	0.1%	3.00 [0.13, 71.07]	
Roberts et al.b1999	5	117	7	233	0.5%	1.42 [0.46, 4.39]	
Whiting et al. 2003	25	286	7	138	1.0%	1.72 [0.76, 3.89]	
Subtotal (95% CI)		2429		2424	8.7%	2.01 [1.53, 2.63]	•
Total events	163		76				
Heterogeneity: Tau ² = 0.0		.32, df =	11 (P = ().59); l²	= 0%		
est for overall effect: Z =				,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			
	(,				
.3.3 Dutasteride 0.5mg/	/d						
Eun et al.2010	3	73	4	75	0.3%	0.77 [0.18, 3.32]	
Subelin et al.b2014	25	184	16	181	1.8%	1.54 [0.85, 2.78]	
la et al.2012	2	126	1	127	0.1%	2.02 [0.19, 21.95]	
Disen et al.b2006	2	68	5	64	0.3%	0.38 [0.08, 1.87]	
Roehrborn et al.2002	297	2167	149	2158	15.7%	1.99 [1.65, 2.39]	
Stough et al.2007	2	17	0	17	0.1%	5.00 [0.26, 97.00]	
sai et al.2018	9	58	5	59	0.6%	1.83 [0.65, 5.14]	
Sukamoto et al.2009	3	70	0	66	0.1%	6.61 [0.35, 125.49]	
Subtotal (95% CI)		2763		2747	18.9%	1.85 [1.50, 2.28]	•
Total events	343		180				
Heterogeneity: Tau ² = 0.0	1; Chi ² = 7	.18, df =	7 (P = 0.	41); l² =	2%		
Test for overall effect: Z =				,.			
	`						
Total (95% CI)		14053		11643	100.0%	1.89 [1.74, 2.05]	♦
Fotal events	2036		893				
Heterogeneity: Tau ² = 0.0	0; Chi ² = 3	3.99, df	= 33 (P =	0.42); I	² = 3%		
est for overall effect: Z =				,, .			0.01 0.1 1 10 1
Fest for subaroup differen	ices: Chi² =	= 0.22. d	f=2(P=	0.90). I	² = 0%		Favours [experimental] Favours [control]
Test for subaroup differen	ices: Chi² =	= 0.22. d	t = 2 (P =	0.90). I	² = 0%		

Supplementary Figure 2: Individual risk of sexual adverse effects with the use of 5α -reductase inhibitors (dose subgroup).

	Experim		Conti			Risk Ratio	Risk Ratio
Study or Subgroup			Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
2.2.1 Finasteride 5mg	/d Subgrou	up					
Gormley et al.a1992	5	297	4	300	8.4%	1.26 [0.34, 4.66]	
Kaplan et al.2016	9	768	12	737	12.5%	0.72 [0.31, 1.70]	
Lepor et al.1996	23	310	21	305	15.8%	1.08 [0.61, 1.91]	
Marberger et al.1998	28	1577	45	1591	17.0%	0.63 [0.39, 1.00]	
Mcconnell et al.1998	50	1524	23	1516	16.8%	2.16 [1.33, 3.53]	
Subtotal (95% CI)		4476		4449	70.5%	1.06 [0.62, 1.82]	•
Total events	115		105				
Heterogeneity: Tau ² =	0.25; Chi ² =	13.87,	df = 4 (P	= 0.008	3); l² = 71%	D	
Test for overall effect:	Z = 0.21 (P	= 0.83)					
2.2.2 Finasteride 1mg	/d Subgrou	up					
Gormley et al.b1992	3	298	4	300	7.1%	0.76 [0.17, 3.34]	
Gubelin et al.a2014	1	179	0	181	2.1%	3.03 [0.12, 73.97]	
Subtotal (95% CI)		477		481	9.3%	0.97 [0.25, 3.73]	
Total events	4		4				
Heterogeneity: Tau ² =	0.00; Chi ² =	0.60, d	f = 1 (P =	0.44);	l² = 0%		
Test for overall effect:	Z = 0.05 (P	= 0.96)					
2.2.3 Dutasteride 0.5n	ng/d Subgi	roup					
Gubelin et al.b2014	1	184	0	181	2.1%	2.95 [0.12, 71.98]	
Na et al.2012	1	126	0	127	2.1%	3.02 [0.12, 73.53]	
Roehrborn et al.2002	50	2167	16	2158	16.0%	3.11 [1.78, 5.45]	
Subtotal (95% CI)		2477		2466	20.2%	3.10 [1.80, 5.35]	
Total events	52		16				
Heterogeneity: Tau ² =	0.00; Chi ² =	0.00, d	f = 2 (P =	1.00);	l² = 0%		
Test for overall effect:	Z = 4.09 (P	< 0.000	1)				
Total (95% CI)		7430		7396	100.0%	1.31 [0.80, 2.15]	◆
Total events	171		125				
Heterogeneity: Tau ² =	0.32; Chi² =	26.47,	df = 9 (P	= 0.002	2); I ² = 66%	b	0.01 0.1 1 10
Test for overall effect: 2	Z = 1.08 (P	= 0.28)					0.01 0.1 1 10 Favours [experimental] Favours [control]
Test for subaroup diffe	rences: Chi	² = 8.29	. df = 2 (F	P = 0.02	2), $ ^2 = 75.9$	9%	Favours [experimental] Favours [control]

Supplementary Figure 3: Individual risk of physical adverse effects with the use of 5a-reductase inhibitors (dose subgroup).

Study or Subgroup	Experim Events		Cont Events		Waight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H. Random, 95% Cl
1.2.1 BPH Group	Events	TOLAI	Events	Total	weight	M-H, Kanuom, 95% Ci	M-H, Randolli, 95% Cl
		4004		500		0 54 44 70 0 051	
Byrnes et al. 1995	222	1821	29	596	4.4%	2.51 [1.72, 3.65]	
Finasteride studya1993	12	246	1	255	0.2%	12.44 [1.63, 94.95]	
Finasteride studyb1993	10	249	1	255	0.2%	10.24 [1.32, 79.41]	
Gormley et al.a1992	39	297	15	300	1.9%	2.63 [1.48, 4.66]	
Gormley et al.b1992	47	298	15	300	2.0%	3.15 [1.80, 5.52]	
Kaplan et al.2016	185	768	99	737	11.7%	1.79 [1.44, 2.24]	
Kirby et al.1993	1	29	0	21	0.1%	2.20 [0.09, 51.49]	·
Lepor et al.1996	49	310	22	305	2.8%	2.19 [1.36, 3.53]	+
Marberger et al.1998	200	1577	127	1591	12.8%	1.59 [1.29, 1.96]	
Mcconnell et al.1998	433	1524	247	1516	25.2%	1.74 [1.52, 2.00]	
Na et al.2012	2	126	1	127	0.1%	2.02 [0.19, 21.95]	
Nickel et al.1996	104	310	43	303	6.1%	2.36 [1.72, 3.25]	
Roehrborn et al.2002	297	2167	149	2158	15.7%	1.99 [1.65, 2.39]	-
Tenover et al.1997	271	1736	41	579	6.2%	2.20 [1.61, 3.02]	
Tsukamoto et al.2009	3	70	0	66	0.1%	6.61 [0.35, 125.49]	
Yu et al. 1995	2	24	0	22	0.1%	4.60 [0.23, 90.84]	
Subtotal (95% CI)		11552		9131	89.4%	2.02 [1.80, 2.26]	♦
Total events	1877		790				
Heterogeneity: Tau ² = 0.0)1; Chi ² = 2	21.27, df	= 15 (P =	0.13); I	² = 29%		
Test for overall effect: Z =	= 12.07 (P	< 0.0000	1)				
1.2.2 AGA Group							
Drake et al.a1999	1	38	3	67	0.1%	0.59 [0.06, 5.45]	
Drake et al.b1999	0	37	3	67	0.1%	0.26 [0.01, 4.82]	· · · · · · · · · · · · · · · · · · ·
Eun et al.2010	3	73	4	75	0.3%	0.77 [0.18, 3.32]	
Gubelin et al.a2014	30	179	16	181	2.0%	1.90 [1.07, 3.35]	
Gubelin et al.b2014	25	184	16	181	1.8%	1.54 [0.85, 2.78]	
Kaufman et al.1998	34	779	20	774	2.2%	1.69 [0.98, 2.91]	
Kawashima 2004	4	139	3	138	0.3%	1.32 [0.30, 5.81]	
Leavitt et al.2006	2	40	Ő	39	0.1%	4.88 [0.24, 98.47]	
Levden et al.1999	3	166	3	160	0.3%	0.96 [0.20, 4.71]	
Neste et al.2000	2	100	1	106	0.1%	2.00 [0.18, 21.72]	
Olsen et al.a2006	6	70	5	64	0.5%	1.10 [0.35, 3.42]	
Olsen et al.b2006	2	68	5	64	0.3%	0.38 [0.08, 1.87]	
Price et al.2002	2	33	0	33	0.3%	3.00 [0.13, 71.07]	
				116	0.1%	1.05 [0.31, 3.51]	
		114	E			1.0010.01.3.511	
Roberts et al.a1999	5	111 117	5				
Roberts et al.a1999 Roberts et al.b1999	5 5	117	7	233	0.5%	1.42 [0.46, 4.39]	
Roberts et al.a1999 Roberts et al.b1999 Stough et al.2007	5 5 2	117 17	7 0	233 17	0.5% 0.1%	1.42 [0.46, 4.39] 5.00 [0.26, 97.00]	
Roberts et al.a1999 Roberts et al.b1999 Stough et al.2007 Tsai et al.2018	5 5 2 9	117 17 58	7 0 5	233 17 59	0.5% 0.1% 0.6%	1.42 [0.46, 4.39] 5.00 [0.26, 97.00] 1.83 [0.65, 5.14]	
Roberts et al.a1999 Roberts et al.b1999 Stough et al.2007 Tsai et al.2018 Whiting et al. 2003	5 5 2	117 17 58 286	7 0	233 17 59 138	0.5% 0.1% 0.6% 1.0%	1.42 [0.46, 4.39] 5.00 [0.26, 97.00] 1.83 [0.65, 5.14] 1.72 [0.76, 3.89]	
Roberts et al.a1999 Roberts et al.b1999 Stough et al.2007 Tsai et al.2018 Whiting et al. 2003 Subtotal (95% CI)	5 5 9 25	117 17 58	7 0 5 7	233 17 59	0.5% 0.1% 0.6%	1.42 [0.46, 4.39] 5.00 [0.26, 97.00] 1.83 [0.65, 5.14]	
Roberts et al.a1999 Roberts et al.b1999 Stough et al.2007 Tsai et al.2018 Whiting et al.2003 Subtotal (95% CI) Total events	5 5 9 25 159	117 17 58 286 2501	7 0 5 7 103	233 17 59 138 2512	0.5% 0.1% 0.6% 1.0% 10.6%	1.42 [0.46, 4.39] 5.00 [0.26, 97.00] 1.83 [0.65, 5.14] 1.72 [0.76, 3.89]	•
Roberts et al.a1999 Roberts et al.b1999 Stough et al.2007 Tsai et al.2018 Whiting et al. 2003 Subtotal (95% CI)	5 5 2 9 25 159 00; Chi ² = 9	117 17 58 286 2501 9.25, df =	7 0 5 7 103	233 17 59 138 2512	0.5% 0.1% 0.6% 1.0% 10.6%	1.42 [0.46, 4.39] 5.00 [0.26, 97.00] 1.83 [0.65, 5.14] 1.72 [0.76, 3.89]	
Roberts et al.a1999 Roberts et al.b1999 Stough et al.2007 Tsal et al.2018 Whiting et al. 2003 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	5 5 2 9 25 159 00; Chi ² = 9	117 17 58 286 2501 9.25, df =	7 0 5 7 103	233 17 59 138 2512 0.93); I ²	0.5% 0.1% 0.6% 1.0% 10.6% = 0%	1.42 [0.46, 4.39] 5.00 [0.26, 97.00] 1.83 [0.65, 5.14] 1.72 [0.76, 3.89] 1.50 [1.17, 1.91]	•
Roberts et al.a1999 Roberts et al.b1999 Stough et al.2007 Tsai et al.2018 Whiting et al.2003 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = Total (95% CI)	5 5 2 9 25 159 00; Chi ² = 9 = 3.22 (P =	117 17 58 286 2501 9.25, df = 0.001)	7 0 5 7 103 17 (P =	233 17 59 138 2512 0.93); I ²	0.5% 0.1% 0.6% 1.0% 10.6%	1.42 [0.46, 4.39] 5.00 [0.26, 97.00] 1.83 [0.65, 5.14] 1.72 [0.76, 3.89]	•
Roberts et al.a1999 Roberts et al.b1999 Stough et al.2007 Tsal et al.2018 Whiting et al. 2003 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	5 5 2 9 25 159 00; Chi ² = 9 = 3.22 (P = 2036	117 17 58 286 2501 0.25, df = 0.001) 14053	7 0 5 7 103 17 (P =	233 17 59 138 2512 0.93); I ² 11643	0.5% 0.1% 0.6% 1.0% 10.6% = 0%	1.42 [0.46, 4.39] 5.00 [0.26, 97.00] 1.83 [0.65, 5.14] 1.72 [0.76, 3.89] 1.50 [1.17, 1.91]	• • •

Supplementary Figure 4: Individual risk of sexual adverse effects with the use of 5a-reductase inhibitors (disease subgroup).

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI
2.3.1 BPH Group							
Gormley et al.a1992	5	297	4	300	8.4%	1.26 [0.34, 4.66]	
Gormley et al.b1992	3	298	4	300	7.1%	0.76 [0.17, 3.34]	
Kaplan et al.2016	9	768	12	737	12.5%	0.72 [0.31, 1.70]	
Lepor et al.1996	23	310	21	305	15.8%	1.08 [0.61, 1.91]	_ _
Marberger et al.1998	28	1577	45	1591	17.0%	0.63 [0.39, 1.00]	
Mcconnell et al.1998	50	1524	23	1516	16.8%	2.16 [1.33, 3.53]	
Na et al.2012	1	126	0	127	2.1%	3.02 [0.12, 73.53]	
Roehrborn et al.2002	50	2167	16	2158	16.0%	3.11 [1.78, 5.45]	
Subtotal (95% CI)		7067		7034	95.7%	1.26 [0.75, 2.13]	•
Total events	169		125				
Heterogeneity: Tau ² =	0.35; Chi ² =	= 25.95,	df = 7 (P	= 0.000)5); l ² = 73	%	
Test for overall effect:	Z = 0.88 (P	= 0.38)					
2.3.2 AGA Group							
Gubelin et al.a2014	1	179	0	181	2.1%	3.03 [0.12, 73.97]	
Gubelin et al.b2014	1	184	0	181	2.1%	2.95 [0.12, 71.98]	
Subtotal (95% CI)		363		362	4.3%	2.99 [0.31, 28.63]	
Total events	2		0				
Heterogeneity: Tau ² =	0.00; Chi ² =	= 0.00, d	f = 1 (P =	0.99);	l² = 0%		
Test for overall effect:	Z = 0.95 (P	= 0.34)	``	,,			
		7430		7396	100.0%	1.31 [0.80, 2.15]	•
Fotal (95% CI)		7430					
, ,	171	7430	125				
Fotal events				= 0.002	2): ² = 66%	6	r
Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect;	0.32; Chi ² =	= 26.47,		= 0.002	?); I² = 66%	6	0.01 0.1 1 10 11 Favours [experimental] Favours [control]

Supplementary Figure 5: Individual risk of physical adverse effects with the use of 5α-reductase inhibitors (disease subgroup).