SPECIAL REPORT

Adverse Sexual Effects of Treatment with Finasteride or Dutasteride for Male Androgenetic Alopecia: A Systematic Review and Meta-analysis

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Treatment of male androgenetic alopecia with 5α-reductase inhibitors is efficacious. However, the risk of adverse sexual effects remains controversial. This systematic review and meta-analysis investigated the risk of adverse sexual effects due to treatment of androgenetic alopecia in male patients with finasteride, 1 mg/day, or dutasteride, 0.5 mg/day. Fifteen randomized double-blinded placebo-controlled trials (4,495 subjects) were meta-analysed. Use of 5α-reductase inhibitors carried a 1.57-fold risk of sexual dysfunction (95% confidence interval (95% CI) 1.19–2.08). The relative risk was 1.66 (95% CI 1.20–2.30) for finasteride and 1.37 (95% CI 0.81–2.32) for dutasteride. Both drugs were associated with an increased risk, although the increase was not statistically significant for dutasteride. As studies into dutasteride were limited, further trials are required. It is important that physicians are aware of, and assess, the possibility of sexual dysfunction in patients treated with 5α-reductase inhibitors.

Key words: finasteride; dutasteride; 5α-reductase inhibitor; androgenetic alopecia; sexual dysfunction; erectile dysfunction.

Accepted Sep 11, 2018; Epub ahead of print Sep 12, 2018

Acta Derm Venereol 2019; 99: 12–17.

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SIGNIFICANCE

Oral 5α-reductase inhibitors, including finasteride and dutasteride, are the preferred and most efficacious treatment modalities for male androgenetic alopecia (male pattern baldness). Despite their promising efficacy on hair regrowth, there is debate about their adverse effect of these drugs on sexual function. In this systematic review and meta-analysis of randomized double-blinded placebo-controlled trials, the use of oral 5α-reductase inhibitors had an overall 1.55-fold risk of sexual dysfunction, including erectile dysfunction, decreased libido and ejaculatory dysfunction. Therefore, potential sexual adverse events should be assessed in patients treated with oral finasteride or dutasteride.

Androgenetic alopecia (AGA) is the most common form of hair loss (1). AGA affects over 58% of males aged 50 years or older, and its prevalence increases with age (2). Patients with AGA experience loss of self-esteem and socioemotional deprivation due to their elderly appearance (3, 4). Various therapeutic options for AGA have been introduced, including oral or topical 5α-reductase inhibitors (5-ARIs), 3% or 5% minoxidil, and low-level laser (light) therapy, and their effectiveness for AGA has been discussed in a recent systematic review and meta-analysis (5).

Among these agents, 5-ARIs represent one of the main therapeutic options for male AGA. 5-ARIs decrease the dihydrotestosterone concentration in the serum and scalp by 60–70% through inhibition of 5α-reductase (6). Two 5-ARIs, finasteride and dutasteride, are currently used in clinical practice. Despite their promising efficacy, there is much debate regarding possible adverse sexual effects due to treatment with 5-ARIs. Some meta-analyses have evaluated their association; however, the results are conflicting (7–9). Mella et al. (9) reported that treatment with oral finasteride, 1 mg/day or 5 mg/day, increased the risk of sexual dysfunction. Conversely, Gupta et al. (7) and Liu et al. (8) reported that treatment with 5-ARIs did not increase the risk when these agents were indicated for male AGA. To date, their association with sexual dysfunction remains controversial. Moreover, there has been an increase in the number of reports describing the risks of sexual dysfunction associated with the use of 5-ARIs (10, 11).

The preferred treatment regimens for AGA are currently 1 mg/day finasteride or 0.5 mg/day dutasteride. However, in previous meta-analyses (8, 9), heterogeneous 5-ARI regimens consisting of 1 mg/day or 5 mg/day finasteride or 0.5 mg/day dutasteride were not separately analysed. As a result, their individual risk has not been well demonstrated. In this context, summarizing the risk of adverse sexual effects in male patients with AGA treated with finasteride 1 mg/day or dutasteride 0.5 mg/day was required.

METHODS

A systematic review and meta-analysis was performed following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12).

doi: 10.2340/00015555-3035
Acta Derm Venereol 2019; 99: 12–17

Aims of study

The purpose of this review was defined using Patient-Intervention-Comparison-Outcome (PICO) statements. The aim was to examine whether in male patients with AGA or in the healthy population (P), treatment with oral finasteride, 1 mg/day, or oral dutasteride, 0.5 mg/day (I), compared with placebo (C), increases the risk of adverse sexual effects (O).

Search strategy

A comprehensive search was conducted to identify all randomized double-blinded placebo-controlled trials (RDBPCTs) regardless of language, publication status, or year of publication. Two main reviewers (SL and YBL) searched the MEDLINE, Embase, and Cochrane Library databases for studies published from 1 January 1946, to 20 September 2017 (see **Fig. 1** for the search terms used for each database). The reference list of publications retrieved was manually screened to obtain any available additional sources. ClinicalTrials.gov was also screened for potential unpublished studies on oral finasteride or dutasteride, but none were eligible for this analysis (accessed on 15 November 2017).

Study selection

Studies were selected using the inclusion and exclusion criteria defined prior to initiation of the literature search. Two main reviewers independently evaluated the titles and abstracts of the retrieved studies. In case of discrepancy between the 2 main reviewers, a final decision was made by consensus discussion with the other 2 reviewers (SJC and WSL). Included trials were: RDBPCTs that investigated the use of oral finasteride, 1 mg/day, or oral dutasteride, 0.5 mg/day, in male patients with AGA or healthy volunteers, and that reported the incidence of any adverse sexual effects during the trial. Exclusion criteria were: (*i*) any study design other than RDBPCTs; (*ii*) trials that investigated the use of oral 5-ARIs at other dosages (e.g. finasteride 5 mg/day) or topical 5-ARIs; (*iii*) studies that included subjects with diseases other than AGA, especially endocrine or urological diseases; (*iv*) female studies; and (*v*) studies that did not report the incidence of adverse sexual effects. If the abstract did not provide enough 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 reported first was analysed. Moreover, for crossover or multiphasic trials, only data from the first period were included, to avoid potential confounding that may have occurred during the crossover or extension of the study with the same subjects.

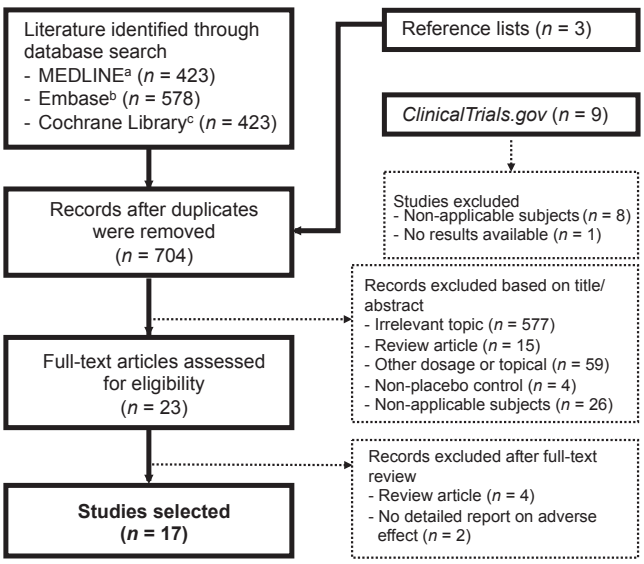

Fig. 1. Flow diagram of literature search. A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. [a](finasteride [All Fields]) OR (dutasteride [All Fields]) AND (randomized controlled trial [ptyp]). [b](finasteride OR dutasteride) AND [randomized controlled trial]/lim. [c](finasteride OR dutasteride) and (#2: "randomized controlled trial":pt).

Data extraction and quality assessment

Two main reviewers compiled the data in a predefined spreadsheet and performed data extraction and quality assessment of the included studies. Likewise, in the event of disagreement, a final decision was reached through discussion with the other 2 reviewers. The data extracted from each study were: study year, study setting, study design, study population, and trial duration. Data on the number and mean age of subjects were also collected. The main outcome for ascertainment was the incidence of any adverse sexual effects of finasteride, 1 mg/day, dutasteride, 0.5 mg/day, or placebo during the trial. If available, data on individual risk of erectile dysfunction, decreased libido, and difficulty in ejaculation were also collected. The Cochrane Collaboration risk of bias tool (13) was utilized for quality assessment to evaluate the potential risk of bias of the included RDBPCTs.

Data synthesis and outcome

Meta-analyses were performed to calculate the overall relative risk (RR) of any adverse sexual effects of 5-ARIs. The individual RRs of erectile dysfunction, decreased libido, and difficulty in ejaculation were also calculated using the eligible studies. The meta-analysed RRs were calculated by combining the data-sets using an inverse variance method. Heterogeneity among included studies was calculated using χ^2 test for heterogeneity (with $p<0.1$ indicating significant heterogeneity) and I^2 statistic for inconsistency. A random-effects model was used for data synthesis because of the heterogeneous study population, study setting, and trial duration of the included studies. Results were expressed using a forest plot. Publication bias was evaluated with Egger's test (14) for studies on 1 mg/day finasteride or 0.5 mg/day dutasteride. Sensitivity analysis was performed by omitting studies with the most heterogeneous study population from the synthesis. Statistical analysis was performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). A p-value less than 0.05 was considered statistically significant.

RESULTS

Study selection, characteristics, and quality assessment

The PRISMA flow diagram of study selection is shown in Fig. 1. Of 17 studies, 2 (15, 16) were found to be continuation trials of previous studies (17, 18) and thus were excluded from the meta-analysis. The characteristics of the remaining 15 studies are summarized in Table SI[1]. All were RDBPCTs reporting the incidence of any adverse sexual effects during the trial in both 5-ARI and placebo groups. Of these studies, 10 investigated finasteride 1 mg/day (6, 17–25); 4 investigated dutasteride 0.5 mg/

[1]https://doi.org/10.2340/00015555-3035

day (26–29); and 1 investigated both finasteride 1 mg/day and dutasteride 0.5 mg/day (30). Except for 2 studies (21, 24), the individual incidence of erectile dysfunction, decreased libido, and difficulty in ejaculation could be obtained. The mean age of the 5-ARI and placebo groups was comparable in each study. They had moderate quality on the risk of bias assessment (Fig. S1[1]) and were included in the data synthesis. A total of 4,495 subjects treated with finasteride 1 mg/day, dutasteride 0.5 mg/day, or placebo were included in the analysis.

Data extraction and synthesis

The incidence of adverse sexual effects in groups treated with finasteride 1 mg/day, dutasteride 0.5 mg/day, or placebo is summarized in Table SII[1]. Nine of 11 studies on finasteride 1 mg/day, and all of 5 studies on dutasteride 0.5 mg/day, provided individual incidence of erectile dysfunction, decreased libido, and difficulty in ejaculation. In our pooled data, 132 of 2,257 subjects treated with 5-ARIs (5.85%) (vs. placebo: 80 of 2,122 (3.77%)) had at least one adverse sexual effect. For each regimen, 100 of 1,882 subjects treated with finasteride 1 mg/day (5.31%) (vs. placebo: 57 of 1,869 (3.05%)) had adverse sexual effects, whereas 32 of 375 subjects treated with dutasteride 0.5 mg/day (8.27%) (vs. placebo: 23 of 369 (6.23%)) had adverse sexual effects.

Overall use of 5α-reductase inhibitors

In the random-effects model, the overall use of 5-ARIs (either finasteride 1 mg/day or dutasteride 0.5 mg/day) had a 1.57-fold risk of any adverse sexual effects during the trial (95% confidence interval (95% CI) 1.19–2.08) (**Fig. 2**). Heterogeneity among included studies was minimal (I^2=0%). For specific adverse effects, the use of 5-ARIs had a 1.53-fold risk of decreased libido (95% CI 1.01–2.32) and was associated with an increased risk of erectile dysfunction (RR 1.56, 95% CI 0.97–2.51) and difficulty in ejaculation (RR 1.38, 95% CI 0.77–2.46), albeit without statistical significance (**Fig. 3**).

Finasteride 1 mg/day

In the subgroup analysis of 11 studies, finasteride 1 mg/day had a 1.66-fold risk of adverse sexual effects (95% CI 1.20–2.30) compared with placebo (Fig. 2). Heterogeneity among included studies was minimal (I^2=0%). The risk of publication bias was low in Egger's test (p=0.39). The report by Whiting et al. (23) was omitted from the sensitivity analysis owing to its older study population (men aged 40–60 years). As a result, the adjusted RR was 1.65 (95% CI 1.15–2.26), which was the same as in the original analysis. For specific adverse effects, there was a 1.99-fold risk of erectile dysfunction (95% CI 1.10–3.60), and the incidence of decreased libido (RR 1.40, 95% CI 0.87–2.27) and difficulty in ejaculation (RR 1.59, 95% CI 0.76–3.29) also tended to be higher than that for placebo, albeit without statistical significance (Fig. 3).

Dutasteride 0.5 mg/day

In the subgroup analysis of 5 studies, dutasteride 0.5 mg/day was associated with an increased risk of any adverse sexual effects, albeit without statistical significance (RR 1.37, 95% CI 0.81–2.32) (Fig. 2). Heterogeneity among included studies was minimal (I^2=0%). However, publication bias could not be evaluated owing to the small number of relevant studies (n=5). In the sensitivity analysis, the report by Amory et al. (28) was omitted because of its heterogeneous study population (healthy control without AGA). As a result, the adjusted RR was 1.25 (95% CI 0.63–2.46), which was still not statistically significant. For specific discomforts, dutasteride 0.5 mg/day tended to decrease the subjects' libido (RR 1.99,

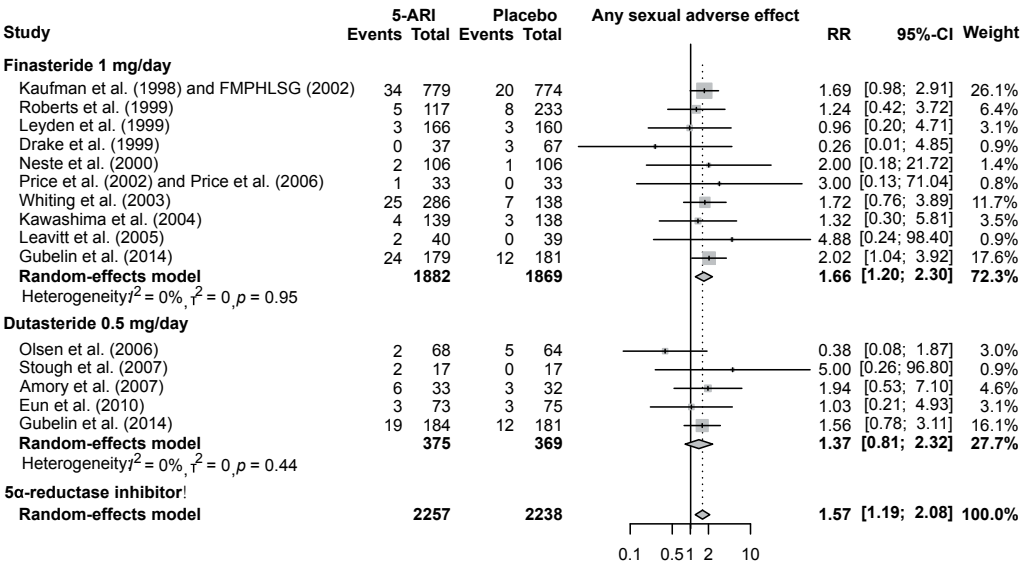

Fig. 2. Increased risk of adverse sexual outcomes with the use of 5α-reductase inhibitors (5-ARIs) for male androgenetic alopecia (AGA). The use of 5-ARIs had a 1.57-fold risk of any adverse sexual effects. In the subgroup analysis, finasteride 1 mg/day had a 1.66-fold risk. In addition, dutasteride 0.5 mg/day was associated with an increased risk of any adverse sexual effects, albeit without statistical significance. RR: relative risk; CI: confidence interval.

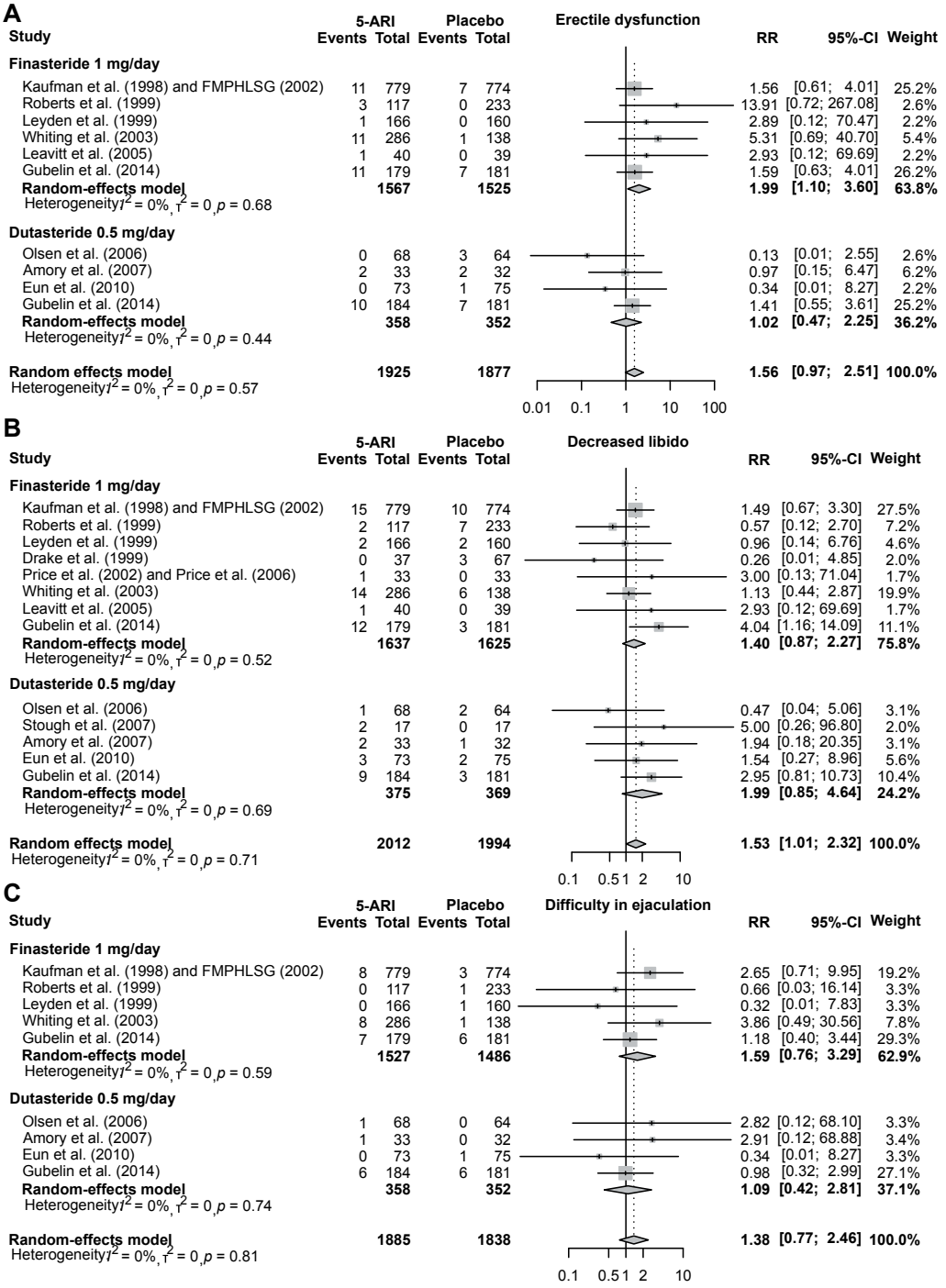

Fig. 3. Individual risk of erectile dysfunction, decreased libido, and difficulty in ejaculation with the use of 5α-reductase inhibitors (5-ARIs) for male androgenetic alopecia (AGA). Use of 5-ARIs was associated in particular with an increased risk of decreased libido and erectile dysfunction. (A) Erectile dysfunction. (B) Decreased libido. (C) Difficulty in ejaculation. RR: relative risk; CI: confidence interval.

95% CI 0.85–4.64), albeit with no statistical significance (Fig. 3).

DISCUSSION

Treatment with 5-ARIs is among the preferred strategies for male AGA. Therefore, clear information must be provided to patients on whether their use increases the risk of adverse sexual effects. Although there were sufficient RDBPCTs on finasteride 1 mg/day for male AGA, only a few studies on dutasteride 0.5 mg/day were available.

The overall use of 5-ARIs (either finasteride 1 mg/day or dutasteride 0.5 mg/day) for male AGA had increased risk of adverse sexual effects. In particular, the risk of decreased libido was significantly increased. In the subgroup analysis of the 2 regimens, finasteride 1 mg/day

increased the risk of any adverse sexual effects compared with placebo, which contradicted the results of previous meta-analyses that showed an insignificant association (7, 8). In particular, the risk of erectile dysfunction was nearly 2-fold with finasteride 1 mg/day, which was consistent with the results of the study by Mella et al. (9). The risk of decreased libido or difficulty in ejaculation also tended to be increased, but not significantly. Conversely, with the use of dutasteride 0.5 mg/day, the overall risk of any adverse sexual effects and individual risk of decreased libido showed a tendency to be higher, albeit without statistical significance. For erectile dysfunction and difficulty in ejaculation, only minimal associations were found.

Belknap et al. (31) have suggested the poor reliability of adverse effect reporting in clinical trials on finasteride 1 mg/day for AGA. This question had originated from recent meta-analyses (7, 9) that reported the negative association between the use of 5-ARIs and adverse sexual effects. Nevertheless, our analysis suggested that the use of 5-ARIs for male AGA increases the risk of adverse sexual outcomes during treatment. One unexpected finding in this study was that, unlike finasteride 1 mg/day, no statistically significant risks were associated with dutasteride 0.5 mg/day. However, it cannot be concluded from these results that the use of dutasteride 0.5 mg/day is safer than the use of finasteride 1 mg/day with respect to adverse sexual effects, because the number of available RDBPCTs and overall sample size were limited for studies on dutasteride 0.5 mg/day for male AGA. Moreover, a recent meta-analysis on the use of dutasteride 0.5 mg/day in subjects with benign prostatic hyperplasia (BPH) showed a 1.60-fold risk of erectile dysfunction and decreased libido (32). Nevertheless, a separate evaluation of dutasteride for AGA is essential, considering that BPH itself can induce sexual dysfunction, and study populations usually consist of older individuals. However, currently available studies are limited and do not sufficiently allow determination of the risks of adverse effects due to dutasteride 0.5 mg/day for male AGA.

Study limitations

This study has some limitations: first, most included studies do not describe a detailed methodology on randomization, concealment allocations, or blinding methods; therefore, a low risk of bias cannot be guaranteed. Secondly, most studies disclose various degrees of conflict of interest and relationships with pharmaceutical companies. Thirdly, evaluation of adverse sexual effects in all studies was based on patients' self-reports and was not objective assessment or the use of measurement tools. Fourthly, most studies did not specify the timing of onset of adverse effects or recovery after drug discontinuation. In order to minimize any potential biases in our analysis only RDBPCTs were included. Apart from finasteride 5 mg/day, data on finasteride 1 mg/day were also analysed independently as the most preferred dosage for AGA. Finally, the safety profile of dutasteride 0.5 mg/day for male AGA was summarized.

Conclusion

The overall use of 5-ARIs for male AGA increased the risk of adverse sexual effects, especially erectile dysfunction and decreased libido. Both regimens were associated with increased risk of adverse sexual effects, but this increase was not statistically significant for dutasteride 0.5 mg/day. However, due to the limited available data on the use of dutasteride 0.5 mg/day for male AGA, additional studies are needed to confirm its risk. As 5-ARIs can increase the probability of adverse sexual effects, physicians should assess for symptoms of sexual dysfunction and counsel patients about these throughout treatment.

The authors have no conflicts of interests to declare.

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