

ORIGINAL ARTICLE

The relative effect of monotherapy with 5-alpha reductase inhibitors and minoxidil for female pattern hair loss: A network meta-analysis study

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Abstract

Background: Minoxidil and the 5-alpha reductase inhibitors (5-ARIs), specifically, dutasteride and finasteride, are usually used to treat pattern hair loss (PHL), but evidence on the relative effectiveness of these drugs is far less for women than men.

Aims: We performed an age-adjusted network meta-analysis (NMA) to determine the comparative efficacy of monotherapy with the three agents—in any dosage and administrative route—on PHL in adult women.

Methods: The peer-reviewed literature was systematically reviewed to obtain data for our NMA. The outcome measure for our NMA was “change in total hair density.” We referred to “regimen” as an “agent and its dosage;” our Bayesian NMA estimated regimens' surface under the cumulative ranking curve (SUCRA) values and pairwise relative effects.

Results: Our NMA used data from 13 trials—across which the following 10 regimens were identified (in decreasing order of SUCRA): 5mg/day finasteride for 24 weeks (SUCRA=95.7%), 5% topical minoxidil solution twice daily for 24 weeks (SUCRA=89.5%), 1mg/day minoxidil for 24 weeks (SUCRA=78.1%), 5% topical minoxidil foam 1 half capful/day for 24 weeks (SUCRA=66.5%), 3% topical minoxidil solution 1 mL twice daily for 24 weeks (SUCRA=45.1%), 2% topical minoxidil solution 1 mL twice daily for 24 weeks (SUCRA=44.6%), 5% topical minoxidil solution 1 mL/day for 24 weeks (SUCRA=41.7%), 0.25 mg/day minoxidil for 24 weeks (SUCRA=35.5%), 1.25 mg/day finasteride for 24 weeks (SUCRA=24.8%) and 1 mg/day finasteride for 24 weeks (SUCRA=4.3%).

Conclusion: Our findings can improve clinical guidelines and help dermatologists manage female PHL more optimally with the available options.

KEYWORDS

androgenetic alopecia, dutasteride, female pattern hair loss, minoxidil

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1 | INTRODUCTION

Androgenetic alopecia (AGA)—which is also called “pattern baldness” or “pattern hair loss” (PHL)—is the most common type of alopecia in women and men. Though dihydrotestosterone (DHT) is implicated in the condition's pathophysiology for both sexes, PHL manifests differently between men and women.¹

Minoxidil and the 5-alpha reductase inhibitors (5-ARIs) (i.e., dutasteride and finasteride) are long-standing therapeutic agents for PHL. In the dermatological literature, there is relatively more evidence on these three agents' comparative effectiveness for men² than for women.

We performed a network meta-analysis (NMA) to estimate the relative efficacy of monotherapy with minoxidil and the 5-ARIs—of any dosage and administrative route—for adult women with PHL.

2 | METHODOLOGY

Our NMA was conducted using a Bayesian model with uniform priors; in light of the patient-intervention-comparator-outcome (PICO) framework, our NMA analyzed data from trials that were reported in the English language and that: (1) investigated adult (i.e., aged ≥ 18 years) women with PHL, (2) had an arm where monotherapy with minoxidil or a 5-ARI—of any dosage/administrative route (i.e., any regimen)—was investigated and (3) used change in total hair density at 24 weeks as an outcome measure. Our NMA was age-adjusted; we performed this adjustment as assumed that age could be “proxy” for menopausal status (which can modify a regimen's therapeutic effect in women). For all our quantitative analyses, alpha (i.e., cut-off for statistical significance) was set to 5%.

The trials whose data were eligible for our analyses were identified through systematic search of the literature: we systematically searched the PubMed and Scopus databases on February 16, 2023. The Systematic Review Accelerator (SRA)-Deduplication Module aided our removal of duplicate searches³—while the *Rayyan* software⁴ assisted our screenings. Two stages of screening title and/or abstract, and full-text, were performed by two authors (MAB and TW); Any differences in opinion or interpretation were resolved through deliberation involving a third author (AKG). Three authors managed data collation with aid of spreadsheets (AKG, MAB, and MT). Our quantitative analyses were conducted with *RStudio*⁵; we used the *multinma*⁶ package for our NMA. Using the updated Cochrane risk-of-bias tool, RoB 2 tool, we evaluated the evidence quality of studies whose data were included in our quantitative analyses.⁷ The reason behind the choice for our outcome measure is the fact that it is a commonly used measure of efficacy across numerous clinical trials and meta-analyses studies on AGA.²

Inferences regarding regimens' comparative effectiveness were based on their surface under the cumulative ranking curve (SUCRA) values, and pairwise relative effects. A regimen's SUCRA—whose value is between 0% and 100% (inclusive)—can be described as an overall ranking metric for its efficacy—the higher the SUCRA value, the more efficacious the regimen is. Pairwise relative effects

corresponded to the mean difference between the changes (in total hair density) brought about two regimens. Our criteria for eligible studies did not preclude inclusion of outcome data from nonrandomized controlled trials and single-arm trials—and use of such observational evidence in accordance with supporting literature.²

We also tested (i.e., conducted a node-splitting analysis) for whether there was statistical inconsistency between indirect and direct evidence. Between the random and fixed effect model, we based on results on the model whose fit was better.

3 | RESULTS

After our systematic search, we identified 13 trials whose data were used for our analysis.^{8–20} The schematic for our search strategy is illustrated in Figure 1; Table 1 presents details from 13 studies eligible for quantitative analysis; the qualitative evaluation of each trial's RoB are presented in Figure 2. Figure 3 depicts the network plot for our outcome of interest (i.e., change in total hair density). The Bayesian model for fixed effect was better than that of the random (data not shown); our node-splitting analyses of inconsistency, for our fixed effects model, showed no evidence of statistical inconsistency (data not shown). We posit that our network was transitive as (1) there was no evidence for statistical inconsistency and (2) our NMA was age-adjusted (i.e., adjusted for a plausible effect modifier).

Across the 13 trials, we identified the following 10 regimens (in decreasing order of SUCRA, Table 2): (1) 5 mg finasteride once a day for 24 weeks (SUCRA=95.7%), (2) 5% topical minoxidil solution twice a day for 24 weeks (SUCRA=89.5%), (3) 1 mg minoxidil once a day for 24 weeks (SUCRA=78.1%), (4) 5% topical minoxidil foam 1 half capful once a day for 24 weeks (SUCRA=66.5%), (5) 3% topical minoxidil solution 1 mL twice a day for 24 weeks (SUCRA=45.1%), (6) 2% topical minoxidil solution 1 mL twice a day for 24 weeks (44.6%), (7) 5% topical minoxidil solution 1 mL once a day for 24 weeks (SUCRA=41.7%), (8) 0.25 mg minoxidil once a day for 24 weeks (SUCRA=35.5%), (9) 1.25 mg finasteride once a day for 24 weeks (SUCRA=24.8%) and (10) 1 mg finasteride once a day for 24 weeks (SUCRA=4.3%).

Given that 11 interventions were identified (i.e., 10 regimens and placebo/vehicle), the total number of pairwise comparisons is 55. The relative effects of the 55 pairwise comparisons are presented in the league table in Figure 4. The outcome for data for the most effective regimen (i.e., 5 mg/day finasteride for 24 weeks) is based on empirical evidence from Yeon et al.²⁰ We imputed the outcome data for the half-year timepoint by reporting that of the full-year, and our grounds for doing so is the fact that a couple of studies showed that the rate of change (ROC) from 6 months onwards to 12 months was far less than the ROC from baseline to 6 months.^{21,22} Moreover, imputation of intermediate values (including the last observation carried backward [LOCB] approach) is used in longitudinal studies.

For a given agent, we found a dosage effect within the respective administrative routes. For example, 5% topical minoxidil solution 1 mL twice a day for 24 weeks was significantly ($p < 0.05$) more efficacious than 5% topical minoxidil solution 1 mL once a day for

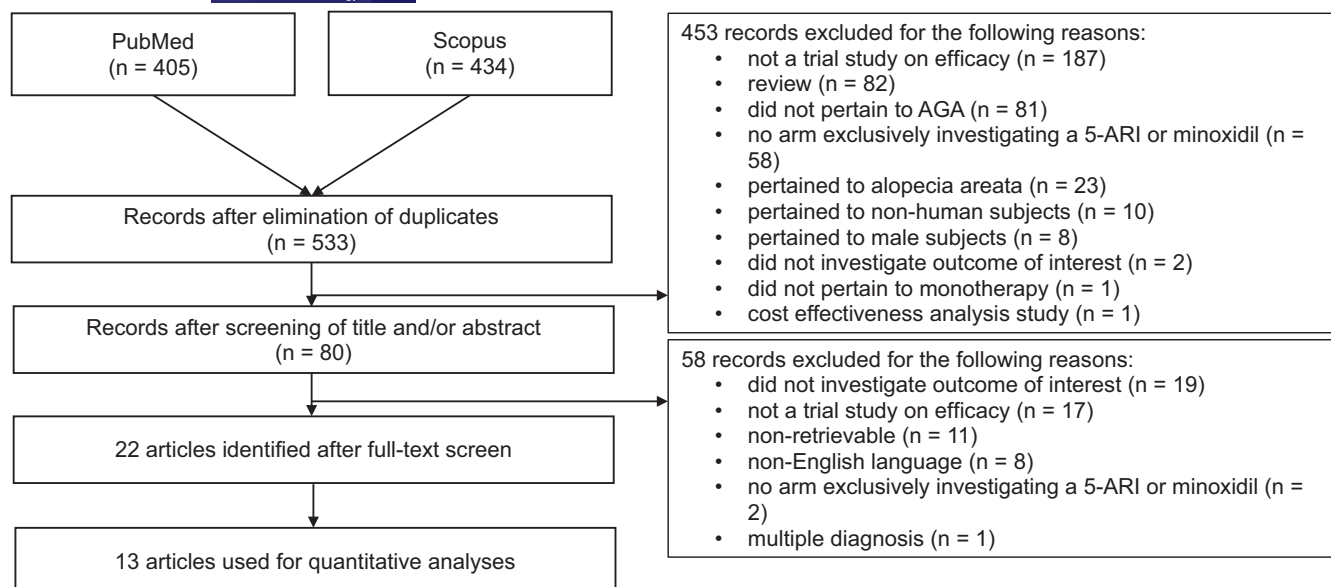


FIGURE 1 Schematic for the identification of studies for quantitative analyses.

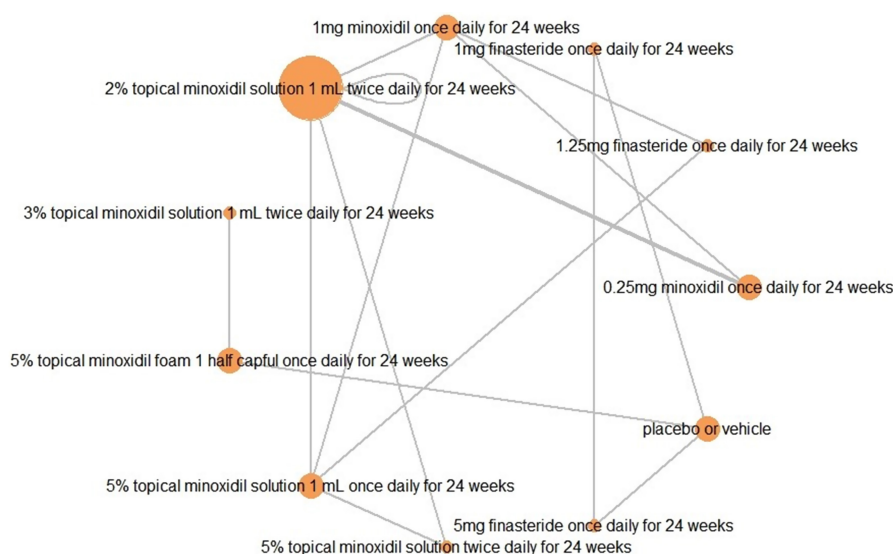
TABLE 1 Details of 13 studies eligible for quantitative analysis.

Study	Study design	Study arms
Price et al., 2000 ¹⁷	Placebo-controlled, double-blind, randomized, multicenter study	Finasteride 1 mg/day versus placebo (oral)
Blume-Peytavi et al., 2007 ¹⁰	Open, comparative, randomized, multicenter phase IV study	1 mL of 2% minoxidil topical solution bid versus 3 mL of 0.025% alfatradiol topical solution once daily
Yeon et al., 2011 ²⁰	Open-labeled, nonrandomized, interventional study	5 mg/day finasteride (oral)
Kim et al., 2012 ¹⁴	Open-labeled, prospective study	1.25 mg/day finasteride (oral)
Bergfeld et al., 2016 ⁹	Phase III, double-blind, randomized, parallel-group, vehicle-controlled, multicenter trial	5% minoxidil topical foam once daily versus vehicle foam
Blume-Peytavi et al., 2016 ¹¹	Phase III, single-blind, randomized, multicenter trial	A half capful of 5% minoxidil topical foam once daily versus 1 mL of 2% minoxidil solution bid
Suchonwanit et al., 2019 ¹⁸	Prospective, pilot, double-blind, randomized, controlled trial	1 mL of 0.25% finasteride topical solution plus 3% minoxidil topical solution bid versus 1 mL of 3% minoxidil topical solution bid
Barat et al., 2020 ⁸	Double-blind, randomized, controlled trial	1 mL of 2% minoxidil topical solution bid versus 1 mL of cow placenta lotion bid
Khattab et al., 2020 ¹³	Randomized, half-split study	Poly-L-lactic acid threads therapy (once) plus 1 mL of 2% minoxidil topical solution bid on the right side of the alopecic scalp versus 1 mL of 2% minoxidil solution bid on the right side of the scalp
Liu et al., 2021 ¹⁶	Randomized, controlled trial	Laser helmet treatment for half an hour at home every other day versus 5% minoxidil topical solution bid versus 5% minoxidil topical solution bid plus laser helmet treatment for half an hour at home every other day
Vahabi-Amlashi et al., 2021 ¹⁹	Randomized, triple-blind, clinical trial	Oral minoxidil 0.25 mg/day plus 1 mL of topical placebo bid versus 1 mL of 2% minoxidil topical solution bid plus placebo tablet
Nascimento e Silva et al., 2022 ¹²	Randomized, double-blind, clinical trial	Oral minoxidil 0.25 mg/day versus oral minoxidil 1 mg/day
Liang et al., 2022 ¹⁵	Single-center, prospective, parallel-group, evaluator blinded, randomized trial	1 mL of 5% minoxidil topical solution once daily versus 1 mL of 5% minoxidil topical solution once daily plus 80–100 mg spironolactone daily versus 1 mL of 5% minoxidil topical solution once daily plus microneedling every 2 weeks for 12 sessions

Study ID	D1	D2	D3	D4	D5	Overall	
Price et al, 2000	+	+	+	+	+	+	Low risk
Blume-Peytavi et al, 2007	-	+	+	-	+	-	Some concerns
Yeon et al, 2011	-	+	+	!	+	-	High risk
Kim et al, 2012	-	+	+	-	!	-	
Bergfeld et al, 2016	+	+	+	+	+	+	D1 Randomisation process
Blume-Peytavi et al, 2016	+	+	+	!	+	!	D2 Deviations from the intended interventions
Suchonwanit et al, 2019	+	+	+	+	+	+	D3 Missing outcome data
Barat et al, 2020	+	+	+	+	+	+	D4 Measurement of the outcome
Khattab et al, 2020	+	!	+	+	+	!	D5 Selection of the reported result
Liu et al, 2021	+	!	+	+	+	!	
Vahabi-Amlashi et al, 2021	+	+	+	+	+	+	
Nascimento e Silva et al, 2022	+	+	+	+	+	+	
Liang et al, 2022	+	+	+	+	+	+	

FIGURE 2 Risk of bias was assessed for the 13 studies that were eligible for quantitative analysis across five domains. The overall risk of bias for each study is also presented. For each domain, the studies received one of three ratings: namely, low risk of bias (denoted by the plus sign in green circle), some concerns (denoted by the question mark in yellow circle), or high risk of bias (denoted by the minus sign in red circle).

FIGURE 3 Network plot for outcome of interest.



24 weeks (mean difference [MD]=13.85 hairs/cm², 95% credible interval [CI]=9.1–18.7 hairs/cm²). Likewise, 5% topical minoxidil solution twice a day for 24 weeks was significantly ($p<0.05$) more efficacious than 2% topical minoxidil solution 1 mL twice a day for 24 weeks (MD=13.3 hairs/cm², 95% CI=7.4–19.5 hairs/cm²).

We found higher doses of finasteride to be more efficacious; 5 mg finasteride once a day for 24 weeks was far more effective than 1 mg finasteride once a day for 24 weeks (MD=28.2 hairs/cm², 95% CI=19.1–37.3 hairs/cm²).

Despite identifying significant dosage effect among some regimens, some pairwise comparisons showed no significant difference. For instance, 3% topical minoxidil solution 1 mL twice a day for 24 weeks (SUCRA=45.1%) was not significantly different from 2% topical minoxidil solution 1 mL twice a day for 24 weeks (SUCRA=44.6%).

Likewise, the effect of 1 mg minoxidil once a day for 24 weeks (SUCRA=78.1%) and 0.25 mg minoxidil once daily for 24 weeks (SUCRA=35.5%) are not significantly different.

Regimen	SUCRA (%)
5 mg finasteride once daily for 24 weeks	95.7
5% topical minoxidil solution 1 mL twice daily for 24 weeks	89.5
1 mg minoxidil once daily for 24 weeks	78.1
5% topical minoxidil foam 1 half capful once daily for 24 weeks	66.5
3% topical minoxidil solution 1 mL twice daily for 24 weeks	45.1
2% topical minoxidil solution 1 mL twice daily for 24 weeks	44.6
5% topical minoxidil solution 1 mL once daily for 24 weeks	41.7
0.25 mg minoxidil once daily for 24 weeks	35.5
1.25 mg finasteride once daily for 24 weeks	24.8
Placebo or vehicle	24.5
1 mg finasteride once daily for 24 weeks	4.3

TABLE 2 Regimens' surface under the cumulative ranking curve (SUCRA) values for change in total hair density at 24 weeks in women with pattern hair loss.

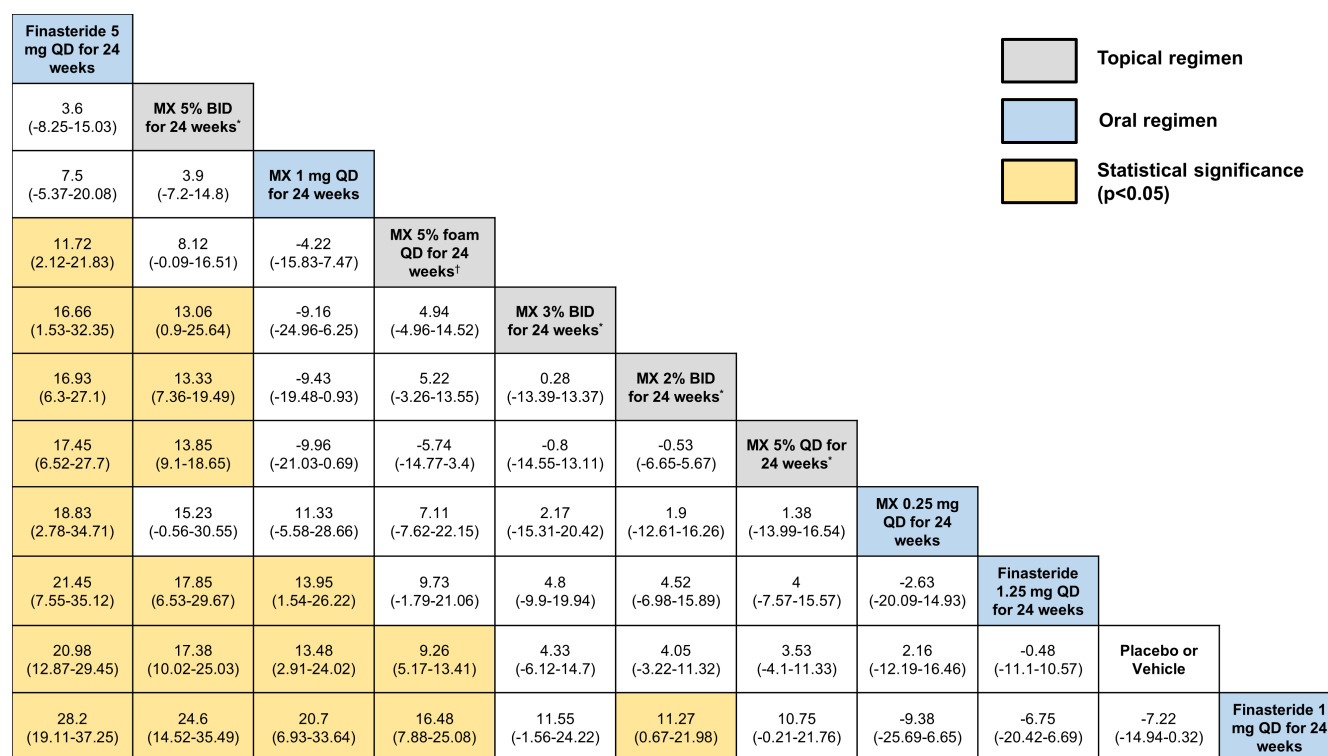


FIGURE 4 League table for the relative efficacy of eleven regimens in achieving improvements of total hair density at week 24. Regimens are sorted based on the order of decreasing SUCRA estimates (e.g., “finasteride 5 mg QD for 24 weeks” = 95.7%, “finasteride 1 mg QD for 24 weeks” = 4.3%). All possible pairwise comparisons are presented in cells below the diagonal line (log odds [95% credible interval]). Topical regimens are shaded gray. Oral regimens are shaded blue. Pairwise comparisons with a statistically significant difference ($p < 0.05$) are shaded yellow. *Topical agents were applied at a volume of 1 mL. †Topical foam agent was applied a volume of one-half capful. BID, twice daily; MX, minoxidil; QD, once daily.

4 | DISCUSSION

Female AGA is quite common with an estimated prevalence rate of 50%.²³ Female AGA can occur at any age after puberty and its prevalence increases with age. Effective treatments for female pattern AGA are limited; there is a lack of well-designed randomized controlled trials (RCTs) investigating potential therapies.

In the current NMA study, we determined the relative efficacy of minoxidil and finasteride—of various administrative routes and

dosages—on change in total hair density at 24 weeks in women with pattern hair loss. An advantage of the NMA technique is that it can determine the relative effect of regimens that are yet to be directly compared in a head-to-head trial. For example, the relative efficacy of 5 mg/day finasteride for 24 weeks versus 5% topical minoxidil solution 1 mL/day for 24 weeks has not been reported from a comparative trial.

We could not find sufficient data on the use of oral minoxidil exceeding 1 mg/day to treat female pattern AGA. It is possible that

higher daily doses might have greater efficacy and still have an acceptable safety profile. The only FDA-approved minoxidil regimens are 5% and 2% topical minoxidil.

The use of finasteride (oral and topical) and oral minoxidil to treat female pattern AGA is off label in the USA. Topical finasteride is not approved nor commercially available in the USA. However, there is a commercially available topical finasteride preparation approved in some European countries and south Korea.²⁴ It would be interesting to be able to compare the efficacy of topical finasteride to treat female pattern AGA against oral finasteride, and the oral and topical preparations of minoxidil.

Our systematic search did not identify studies evaluating the use of dutasteride to treat female AGA. Finasteride is known to inhibit predominantly Type II 5- α reductase isoenzyme; dutasteride inhibits both Type I and Type II 5- α reductase isoenzymes with a higher activity than finasteride in inhibiting Type I 5- α reductase isoenzyme (100:1) and type II 5- α reductase isoenzyme (3:1). In postmenopausal women, or those past child-bearing age, dutasteride might be used off label to determine its efficacy in female AGA. In male AGA, dutasteride 0.5 mg once a day demonstrated higher efficacy than finasteride 5 mg once a day.² In one study, dutasteride 0.5 mg once a day and finasteride 5 mg once a day produced dihydrotestosterone (DHT) inhibition of 94.7% and 70.8%, respectively.²⁵

In this NMA we have evaluated monotherapies to treat female AGA; in reality, treatments are often combined for maximal benefit while keeping potential adverse effects to a minimum. For example, an oral therapy such as finasteride may be combined with a topical therapy with a different mechanism of action, such as minoxidil.

As more well conducted RCTs exploring the use of 5ARIs and minoxidil in female AGA become available the use of NMAs will provide us with better guidance about the relative efficacies of the oral and topical formulations of finasteride and minoxidil.

5 | CONCLUSION

To our knowledge this is the first report of an NMA in female AGA comparing the relative efficacies of oral finasteride (5, 1.25, 1 mg/day), oral minoxidil (1, 0.25 mg/day), and topical minoxidil (5% and 2% each applied twice daily) in total hair regrowth. The efficacy demonstrated a possible dose-dependent effect for oral finasteride, and oral and topical minoxidil.

AUTHOR CONTRIBUTIONS

Conception of the manuscript was done by MT and AKG. The work was drafted by MAB, AKG, TW, MT and substantively revised by AKG and MT.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data will be made available upon reasonable request.

ETHICAL APPROVAL

Not applicable. The authors declare that human ethics approval was not required for this article.

CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

CODE AVAILABILITY

Not applicable.

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