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Finasteride for hair loss: A review

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Abstract

Background and Objectives: Finasteride 1 mg/day is indicated for androgen-dependent conditions such as male androgenetic alopecia (AGA).

Methods: The literature is comprehensively summarized on the pharmacodynamics, pharmacokinetics, mechanism of action, and metabolism of finasteride. Pairwise and network meta-analyses were performed to assess the efficacy of finasteride reported in clinical trials. The adverse events profile is described along with the post-marketing reports.

Results and Conclusion: Finasteride 1 mg/day significantly increased total hair count compared to placebo after 24 weeks (mean difference = 12.4 hairs/cm^2, $p<0.05$), and 48 weeks (mean difference = 16.4 hairs/cm^2, $p<0.05$). The efficacy of the two doses of finasteride (5 mg/day and 1 mg/day) and topical finasteride (1% solution) were not significantly different. The most commonly reported sexual events include erectile dysfunction and decreased libido. Increasing patient complaints and analysis of the FAERS database led to the inclusion of depression in the FDA label in 2011, as men were found to be at a risk of suicide due to the persistent sexual side effects, commonly termed as post-finasteride syndrome. Finasteride is shown to be reasonably tolerated in both men and women; however, patients need to be educated about the possible short- and long-term side-effects.

1. Introduction

Androgenetic alopecia (AGA) is the most common non-scarring hair loss in men. It can usually be classified according to the Norwood Hamilton scale, but there are exceptions (1,2). Hair loss may significantly impair quality of life resulting in passive psychological effects (3). In genetically predisposed men, androgens have an effect on hair follicles where they may transform terminal hair into vellus-like miniaturized hair, leading to gradual hair loss (4–6). The conversion of testosterone to dihydrotestosterone (DHT) is mediated by the enzyme 5α-reductase (5AR) (4) (**Figures 1 and 2**).

Finasteride is an oral pharmacologic therapy developed for the treatment of AGA, designed to inhibit the 5AR enzyme (7). Three multi center (the USA and 16 countries), phase III trials established the efficacy of finasteride in improving hair growth in men with pattern baldness (4,7–9). We review the role of androgens and the enzyme 5AR in hair loss, the 5AR inhibitor therapy (finasteride), its mechanism of action, pharmacokinetics, efficacy, and safety in treating pattern hair loss, along with post marketing experience.

2. Androgens and 5α reductase (5AR)

The enzyme 5AR family (types I, II, and III) participates in bile, androgen, and estrogen metabolism (10). Three distinct 5AR isoenzymes, type I, II, and III are found across mammalian species and influence progesterone, corticosteroid, and androgen metabolism (11,12). The physiological distribution of 5AR isoenzymes is listed in **Table 1**. The Type I isoform is found predominantly in the liver, sebaceous glands in skin, including scalp, and to a lesser extent in the male reproductive organs such as the prostate; type II is abundantly expressed in the prostate and hair follicles, and to a lesser extent in liver (13–15); while the data on the localization of the type III enzyme is limited, it is expressed in prostate basal epithelial cells (12). Genes for 5AR type I

and II were expressed in cultured dermal papilla cells from beard and scalp hair follicles (16). The type I isoenzyme is responsible for about 1/3rd of circulating DTH and the type II is responsible for 2/3^{rds} of circulating DTH (7).

It was shown that men who had a genetic deficiency of the type II isoenzyme did not develop AGA (4). Additionally, men with pattern baldness had elevated type II 5AR activity and increased DHT levels in the scalp (4). Taken together, these findings provide a rationale for the role of the type II isoenzyme and the androgen DHT in AGA.

3. Finasteride – 5 AR inhibitor

Finasteride originated as a chemopreventive for prostate cancer in the 1930s and 1940s by Charles B Huggins, leading to the discovery of the link between the physiological role of testosterone and prostate growth (17,18). It was later developed as MK-906 (now finasteride), which was approved by the FDA in 1992 for the treatment of benign prostatic hyperplasia (BPH) as 'Proscar' (19). Merck obtained FDA approval under the name 'Propecia' for the treatment of pattern hair loss or AGA in 1997 (20,21). Finasteride, a synthetic 4-aza-3-oxosteroid compound is the active ingredient in 'Propecia' with a molecular weight of 372.55 (7,22). The optimum oral dosage suggested for the treatment of male pattern hair loss is 1 mg/day (7).

4. Mechanism of action

Finasteride inhibits the type II 5AR isoenzyme 100-fold more selectively over type I isoenzyme (7). The NAPDH-mediated irreversible inhibition leads to finasteride being reduced to dihydrofinasteride, thereby blocking the peripheral conversion of testosterone to DHT at the dermal papillae level (7,23) (**Figure 2**). Therefore, this leads to a significant reduction in scalp and serum DHT levels (7).

Finasteride reduces serum DHT levels by about 70% after administration of a single oral dose (24). Preliminary studies showed that finasteride 5 mg/day suppressed scalp DHT concentrations significantly compared to placebo (25). Thereafter, in a scalp DHT dose-ranging study (5, 1, 0.2 mg/day finasteride) demonstrated a reduction in scalp DHT levels by about 65% at doses ≥ 0.5 mg/day after 6 weeks of treatment (25,26). DHT levels are not reduced completely due to the residual conversion of testosterone through type I 5AR (4,7). DHT levels are shown to return to normal within 2 weeks of treatment discontinuation (27).

5. Metabolism

Finasteride is metabolised extensively in the liver, primarily by the cytochrome P450 3A4 (CYP 3A4) enzyme subfamily of hepatic drug metabolizing enzymes (7,20). The biotransformation of finasteride occurs in two pathways: phase I and phase II metabolism (28) (**Figure 3**). During phase I, finasteride is metabolized to ω-hydroxyfinasteride (major metabolite) through hydroxylation of the t-butyril group (29).

The phase I metabolites are further reduced to hydroxyfinasteride glucuronide and carboxylic acid metabolites through glucuronidation, known as phase II metabolism (30). The end products being finasteride carboxylic acid glucuronide and hydroxyfinasteride glucuronide (18). The final metabolites are highly hydrophilic and possess ≤20% of the 5AR inhibitory activity of finasteride (7). The documentation of the two phases of finasteride metabolism and identification of several minor metabolites *in vitro* suggest that there may be alternative pathways of finasteride metabolism yet to be discovered.

6. Bioavailability

Propecia may be orally administered with or without meals as the bioavailability is not affected by food (7). The mean bioavailability of finasteride 1mg tablets is 65% (range: 26-170%) in a study conducted in 15 healthy young male volunteers (7). Multiple studies have calculated the percentage bioavailability of finasteride between 63% to 80% (29,31). Finasteride reaches a steady state in plasma within 2 hours of administration, with a peak concentration of 9.2 ng/mL (range: 4.9-13.7 ng/mL) (7). Finasteride is absorbed completely in 6-8 hours post administration (32). The circulating finasteride is bound to the plasma proteins (89.8-91.3%) and slowly accumulates after multiple doses (7,33).

The mean terminal half-life of finasteride is 5-6 hours in men 18-60 years age and approximately 8 hours in mean aged 70 years and above (7). Following oral administration of finasteride, it was reported that approximately 39% of the metabolites were excreted through urine and 57% excreted through feces (7).

7. Effect of Finasteride on Pregnancy

Propecia is a pregnancy category X drug and is not recommended for pregnant women to handle broken or crushed tablets as there may be possible absorption of finasteride which could pose a potential risk to the male fetus causing abnormalities of the external genitalia (7,32). Thus, finasteride was initially investigated in postmenopausal women to avoid teratogenic effects, with some beneficial results (34,35). Nonetheless, finasteride is used off-label to treat female pattern hair loss and frontal fibrosing alopecia (34,36).

The use of finasteride by male patients during pregnancy has been a major concern due to the involvement of androgens in fertility and more men in the reproductive age using this drug.

In randomized, controlled trials conducted by Merck in healthy individuals using finasteride 5 mg/day for 6-24 weeks, the maximum concentration of finasteride in semen ranged from 10.54 – 21 ng/mL (37,38). However, the semen parameters such as total sperm count, semen volume, sperm concentration, and sperm motility may be mildly affected with finasteride 5 mg/day which seems to be reversible within few weeks post treatment (39), The risk of this quantity of finasteride in semen and pregnancy needs to be investigated further.

On the contrary, in men taking finasteride 1 mg/day, the concentration in semen was undetectable with a maximum concentration of 1.52 ng/mL (39). Assuming 100% vaginal absorption of a 5-mL ejaculate volume, it was deducted that women would be exposed up to 7.6 ng/day (39). This concentration was found to be negligible as this was 750 times lower than levels required for the development of fetal abnormalities (39). Thus, it appears that healthy men taking 1 mg/day finasteride need not stop therapy when they are trying to conceive or in patients whose partners are pregnant as finasteride 1 mg/day does not seem to have any significant effect on spermatogenesis (37). However, men with fertility issues may need to discontinue finasteride as the sperm parameters may not reach normal levels even after cessation of therapy (40). Nonetheless, clinical judgement and caution should be exercised in men who want to continue finasteride therapy when they are planning for pregnancy, with approval from their health care providers.

9. Formulations – Oral vs Topical

Currently, only topical minoxidil and oral finasteride (1 mg/day) are approved by the FDA and the European Medicines Agency (EMA) for the treatment of AGA (27). Although finasteride has proven efficacious for hair regrowth, its systemic use is associated with side effects and upon

discontinuation of treatment, reversal of hair regrowth is observed within 12 months (7). Therefore, topical finasteride is being investigated as an alternative treatment regimen (27).

Animal studies have shown that topical finasteride may have promising effects against AGA (27). Mazzarella et al. first documented the use of topical finasteride (0.005% solution) for the treatment of AGA in humans (41), where there was significant reduction in hair loss in the treatment group at 6 months, compared to the placebo group (41). Pharmacokinetic studies comparing topical finasteride and oral finasteride for AGA therapy showed decreased systemic absorption (up to 15 times) of topical finasteride compared to oral (42,43). For topical finasteride further research is warranted to identify an optimal drug-delivery vehicle, ideal dose, frequency of application, and an adverse event profile.

10. Efficacy

The efficacy of finasteride in AGA has been investigated in several studies, while the efficacy of dutasteride (type I and II 5ARI approved for BPH; used off-label for the treatment of hair loss) has been evaluated in fewer studies (44); The effect of the two 5ARIs on total hair count was compared.

The literature was systematically searched in PubMed and Google Scholar. Pairwise and network meta-analyses were conducted on the data obtained from relevant studies. Eight eligible studies (8,9,45–50) across which five interventions were identified, namely, dutasteride 0.5mg/day, finasteride 5mg/day, finasteride 1mg/day, finasteride (topical) 1%, and vehicle. All analyses were conducted using the RStudio software (51); alpha was set to 5%. Vehicle and placebo arms were amalgamated, and were therefore treated as the same intervention.

Pairwise meta-analyses, for both the random and fixed effects models, were conducted for change in total hair count after 24 weeks as per the following three comparisons: finasteride 1mg daily vs placebo, dutasteride 0.5mg daily vs. placebo, and dutasteride 0.5mg daily vs. finasteride 1mg daily. Furthermore, the data for change in total hair count after 48 weeks for finasteride 1mg daily vs. placebo was analyzed.

Results of the head-to-head meta-analyses are presented in forest plots (**Figures 4 and 5**). Finasteride 1mg daily increased total hair count significantly more than placebo after 24 weeks (mean difference = 12.4 hairs cm^{-2}, $p<0.05$), and 48 weeks (mean difference = 16.4 hairs cm^{-2}, $p<0.05$) (**Figures 4**). Dutasteride increased total hair count significantly more than finasteride 1mg/day (mean difference = 6.1, $p<0.05$) and placebo (mean difference = 18.4, $p<0.05$) after 24 weeks (**Figures 5**). For all pairwise meta-analyses, results from the fixed effect model were reported herein as it produced 95% confidence intervals that were much narrower than the random effect model.

League tables and surface under the cumulative ranking curve (SUCRA) values were used to present results from the network meta-analyses (NMAs). League tables present every possible combination of pairwise comparisons. An intervention's SUCRA is an overall metric that ranks its efficacy; a limitation of the SUCRA is that it does not incorporate statistical evidence, nor quality assessment. The two endpoints were change in total hair count after 24 and 48 weeks of therapy. In decreasing order of SUCRA (%), the first network simultaneously compared the efficacy of dutasteride 0.5mg daily (93%), finasteride 5 mg daily (80%), finasteride 1 mg daily (44%), finasteride (topical) 1% (33%) and placebo (0%) (**Table 2**). Placebo (SUCRA = 0%), finasteride 1mg/day (SUCRA = 53%) and finasteride 5 mg/day (SUCRA = 97%) were compared in the second network (**Table 3**); the efficacy of these two

doses of finasteride were not significantly different from each other (**Figures 6 and 7**) but each was significantly more efficacious than placebo (**Figures 6 and 7**).

Dutasteride 0.5 mg/day increased total hair count at 24 weeks significantly more than finasteride 1 mg/day and finasteride (topical) 1% (**Figure 6**). There was no significant difference in efficacy between dutasteride 0.5 mg/day and finasteride 5 mg/day. The two doses of finasteride (5 mg/day and 1 mg/day) and topical finasteride (1% concentration) were not significantly different in terms efficacy (**Figure 6**).

The meta-analyses verify causal findings from randomized trials: the results confirm the superior efficacy of dutasteride 0.5 mg/day (off-label use) over finasteride 1 mg/day (FDA-approved). Furthermore, our findings serve as some evidence on the relative efficacy of AGA therapies that are yet to be compared in head-to-head studies; for example, while the efficacy of finasteride 1 mg/day has been compared with dutasteride 0.5 mg/day in randomized trials (46,50), it has not been compared with finasteride 5 mg/day. Though inferences from the meta-analyses are not causal, finasteride 5mg/day is shown to be just as effective as dutasteride 0.5 mg/day, nonetheless, contributes to the efficacy literature for pattern baldness.

These findings also support the need for continued research in the development of a topical finasteride formulation that may be as effective as the oral formulation but with localized side-effects or reduced systemic effects.

11. Safety and Adverse events

11.1 Prostate Cancer

The 5AR inhibition prevents the conversion of androgens in prostate and lowers prostate volume and serum prostate specific antigen (PSA) levels. Thus, it was hypothesized that finasteride

could reduce the risk of prostate cancer development and some studies also established this relation (52). However, finasteride was not labeled for prostate cancer. The Prostate Cancer Prevention Trial (PCPT) showed that finasteride dosages used to treat BPH increased the risk of high-grade cancer (Gleason score of 7-10) in prostate cancer patients (53–56). The exact reason(s) has not yet been elucidated (53,55,56). Several studies investigated the effect of finasteride in prostate cancer, but with inconsistent results. Larger trials are required to establish the correlation between finasteride and prostate cancer.

11.2 Sexual dysfunction

Based on the clinical trials since 1990s, finasteride therapy is considered relatively safe and well tolerated among patients. Moreover, a higher frequency of side effects is being documented for finasteride 5 mg/day intended to treat conditions such as BPH, compared to finasteride 1 mg/day or other lower doses (off-label or pilot studies) intended for hair loss (19,57).

DHT plays a significant role in erectile physiology and inhibition through 5ARIs may impact penile histoarchitecture in men (57). Accordingly, sexual dysfunction is the most commonly observed adverse events in clinical trials investigating finasteride for male pattern hair loss where ≥ 1% of patients reported decreased libido, erectile dysfunction, a reduction in the ejaculated semen volume, and impotence (**Table 4**) (8,9,46–49,58–65).

Clinical trials investigating finasteride for female pattern hair loss used higher dosages (2.5-5 mg/day) in both pre- and post-menopausal women (35,66–68). The most commonly reported adverse events by women include decreased libido, menstrual irregularity, headache, hypertrichosis, and very rarely mastalgia and cutaneous issues (dry skin and acne) (**Table 4**).

However, these effects were mild and most of them were reversible, even with the continuation of therapy.

However, these trials have been criticized recently for inadequate safety reporting, systemic bias, and poor-quality evidence (69).

Nonetheless, there are studies that report no sexual dysfunction or that the sexual risks in the treatment group did not differ significantly from placebo or vehicle (70–72). For example, a survey based observational study using Arizona Sexual Experience Scale, reported that sexual function did not differ between finasteride users and non-user controls (73). Due to the conflicting reports, the International Society of Hair Restoration Surgery (ISHRS) established a Task Force on Finasteride Adverse Event Controversies to evaluate published data and thereby make recommendations (74).

12. Post-marketing reports

The introduction of finasteride in the clinical practice was followed by a post-market surveillance period due to the increasing patient complaints and rising concerns about sexual side effects being persistent and sometimes irreversible (57). Initially, depression was rarely reported as an adverse reaction with Propecia and Proscar (7,38). With increasing small studies and anecdotal evidence, a number of insomnia-, depression-related, and suicide-related cases were identified (7,75). Men in the age group of 18-64 years who used finasteride were found to be at a risk of suicide due to the persistent sexual side effects which continued for at least 3 months after cessation of therapy (76,77). Subsequently in 2011, depression was added to the list of adverse events to the Propecia FDA product label and in at least 13 countries including Canada, UK, and

South Korea (7,76). Additionally, the adverse reactions section of the labeling was also updated with breast tenderness and enlargement (7,78).

12.1 Finasteride and FAERS

Reports from the United States Food and Drug Administration Adverse Event Reporting System (FAERS) found about 11.8% reported sexual dysfunction; 1814 depression and 39 suicidal cases were identified in young men with AGA who used finasteride 1 mg/day (76,79).

Gupta et al. studied the association of obstructive sleep apnea (OSA) and finasteride as the drug can cross blood-brain barrier and lower androgen activity leading to low sleep efficiency (80). Finasteride causing higher odds of insomnia was previously reported, however, Gupta et al. reported the correlation of finasteride causing higher odds of OSA, a finding that had not been reported previously (80).

Possibly relating to the FDA labeling changes from 2011, there was a significant increase in the reporting of sexual dysfunction and mental domains due to the 1 mg/day dosing, especially in the age group of 31-45 years, despite a low percentage reported in clinical trials (81). FAERS data suggests that adverse events are dose-independent with higher occurrence in younger patients, and majority of these events reported was serious, possibly contributing to the hospitalization, disability, or a patient's death (76,79,82). There could be a complex relation between sexual adverse events and depression which needs to be further investigated.

12.2 Post finasteride syndrome (PFS)

Several groups around the world have coined the term "Post finasteride syndrome (PFS)" in a subset of men who used finasteride, who experienced persistent sexual dysfunction (decreased libido and ejaculation disorder) and psychological effects (increased depression, anxiety, and

suicidal ideas) after cessation of therapy, irrespective of age, drug, or duration of treatment (81,83). Men using finasteride for more than 205 days had a higher risk for persistent erectile dysfunction (76,84).

The association of sexual and nonsexual side effects in former finasteride users may be due to the fact that finasteride irreversibly inhibits 5AR with a slow rate of dissociation, probably leading to a long-lasting effect on the body, regardless of the time and dose of administration (83). Additionally, an alteration in the brain neurosteroids such as progesterone and dihydroprogesterone, could possibly contribute to the persistent psychological effects, as the inhibition of 5AR is a rate-limiting step in the production of neurosteroids (76,85). Preclinical animal studies showed that finasteride lowered plasma and hippocampal neurosteroids and increased depression (86,87).

With increasing reports worldwide, in 2012, a health advocacy group called the 'Post-Finasteride Syndrome Foundation' was formed in the Unites States, with the purpose of helping fund research on the characterization, underlying biologic mechanisms, and treatments of PFS, while improving public awareness of the condition (88,89). However, it remains to be established whether PFS is caused by finasteride or if the symptoms are incidentally associated with therapy, but not caused by finasteride. Additionally, the extent of the risk remains unknown.

13. Conclusion

Finasteride was the first selective type II 5ARI introduced for BPH, which was later FDA-approved for male AGA. It has been used off-label to treat female pattern baldness, especially in post-menopausal women due to the potential risk to the male fetus in pregnant and nursing women. Physicians should educate patients, especially men and women in the reproductive age,

about potential adverse events of finasteride such as sexual dysfunction and psychological effects. Clinical trials have proven the efficacy of oral finasteride significantly improves the progression of hair loss in men with a reversal of the miniaturization process. There may be a significant increase in the total and terminal anagen hairs; and improved anagen/telogen ratio, compared to placebo, after 12 months of finasteride therapy. The topical formulations of finasteride have to be examined in more detail for efficacy and safety.

References

1. Hamilton JB. Patterned loss of hair in man; types and incidence. Ann N Y Acad Sci. 1951 Mar;53(3):708–28.

2. Norwood OT. Male pattern baldness: classification and incidence. South Med J. 1975 Nov;68(11):1359–65.

3. Cash TF. The psychological effects of androgenetic alopecia in men. J Am Acad Dermatol. 1992 Jun;26(6):926–31.

4. Kaufman KD, Dawber RP. Finasteride, a Type 2 5α-reductase inhibitor, in the treatment of men with androgenetic alopecia. Expert Opin Investig Drugs. 1999;8(4):403–15.

5. Marshall WA, Tanner JM. Variations in the Pattern of Pubertal Changes in Boys. Arch Dis Child. 1970 Feb;45(239):13–23.

6. Nyholt DR, Gillespie NA, Heath AC, Martin NG. Genetic basis of male pattern baldness. J Invest Dermatol. 2003 Dec;121(6):1561–4.

7. PROPECIA® (finasteride) tablets for oral use [Internet]. FDA U.S. Food and Drug Administration. 2016 [cited 2018 Sep 18]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020788s024lbl.pdf

8. Kaufman KD, Olsen EA, Whiting D, Savin R, DeVillez R, Bergfeld W, et al. Finasteride in the treatment of men with androgenetic alopecia. Finasteride Male Pattern Hair Loss Study Group. J Am Acad Dermatol. 1998;39(4 Pt 1):578–89.

9. Leyden J, Dunlap F, Miller B, Winters P, Lebwohl M, Hecker D, et al. Finasteride in the treatment of men with frontal male pattern hair loss. J Am Acad Dermatol. 1999 Jun;40(6 Pt 1):930–7.

10. Dhurat R, Sharma A, Rudnicka L, Kroumpouzos G, Kassir M, Galadari H, et al. 5-Alpha reductase inhibitors in androgenetic alopecia: Shifting paradigms, current concepts, comparative efficacy, and safety. Dermatol Ther. 2020 May;33(3):e13379.

11. Finn DA, Beadles-Bohling AS, Beckley EH, Ford MM, Gililland KR, Gorin-Meyer RE, et al. A new look at the 5α-reductase inhibitor finasteride. CNS Drug Rev. 2006;12(1):53–76.

12. Godoy A, Kawinski E, Li Y, Oka D, Alexiev B, Azzouni F, et al. 5α-reductase type 3 expression in human benign and malignant tissues: a comparative analysis during prostate cancer progression. The Prostate. 2011 Jul;71(10):1033–46.

13. Nickel JC. Comparison of clinical trials with finasteride and dutasteride. Rev Urol. 2004;6 Suppl 9:S31-39.

14. Unger WP, Shapiro R, Unger R, Unger M, editors. Hair Transplantation. 5th ed. Informa Healthcare; 2011. 538 p.

15. Rogers NE, Gupta AK. Medical Treatment of Male and Female Pattern Hair Loss. In: Hair Transplantation. 5th ed. Thieme; In press. p. 554.

16. Liu S, Yamauchi H. Different patterns of 5alpha-reductase expression, cellular distribution, and testosterone metabolism in human follicular dermal papilla cells. Biochem Biophys Res Commun. 2008 Apr 18;368(4):858–64.

17. HUGGINS C, STEVENS RE Jr, HODGES CV. STUDIES ON PROSTATIC CANCER: II. THE EFFECTS OF CASTRATION ON ADVANCED CARCINOMA OF THE PROSTATE GLAND. Arch Surg. 1941 Aug 1;43(2):209–23.

18. Hulin-Curtis SL, Petit D, Figg WD, Hsing AW, Reichardt JKV. Finasteride metabolism and pharmacogenetics: new approaches to personalized prevention of prostate cancer. Future Oncol Lond Engl. 2010 Dec;6(12):1897–913.

19. Gormley GJ, Stoner E, Bruskewitz RC, Imperato-McGinley J, Walsh PC, McConnell JD, et al. The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. N Engl J Med. 1992 Oct 22;327(17):1185–91.

20. Alwaleedi SA. The involvement of androgens in human hair growth. Am J Biomed Sci. 2015 Apr;105–24.

21. Andy G, John M, Mirna S, Rachita D, Michael K, Maja K, et al. Controversies in the treatment of androgenetic alopecia: The history of finasteride. Dermatol Ther. 2019 Mar;32(2):e12647.

22. Rossi A, Anzalone A, Fortuna MC, Caro G, Garelli V, Pranteda G, et al. Multi-therapies in androgenetic alopecia: review and clinical experiences. Dermatol Ther. 2016;29(6):424–32.

23. Price TM, Allen S, Pegram GV. Lack of effect of topical finasteride suggests an endocrine role for dihydrotestosterone. Fertil Steril. 2000 Aug;74(2):414–5.

24. Gormley GJ, Stoner E, Rittmaster RS, Gregg H, Thompson DL, Lasseter KC, et al. Effects of finasteride (MK-906), a 5 alpha-reductase inhibitor, on circulating androgens in male volunteers. J Clin Endocrinol Metab. 1990 Apr;70(4):1136–41.

25. Dallob A.L., Sadick N.S., Unger W., Lipert S., Geissler L.A., Gregoire S.L., et al. The effect of finasteride, a 5alpha-reductase inhibitor, on scalp skin testosterone and dihydrotestosterone concentrations in patients with male pattern baldness. J Clin Endocrinol Metab. 1994;79(3):703–6.

26. Waldstreicher J, Fiedler V, Hordinsky M, Swinehart JM, Thiboutot D, Unger W. Effects of finasteride on dihydrotestosterone content of scalp skin in men with male pattern baldness. J Invest Dermatol. 1994;615.

27. Lee SW, Juhasz M, Mobasher P, Ekelem C, Mesinkovska NA. A Systematic Review of Topical Finasteride in the Treatment of Androgenetic Alopecia in Men and Women. J Drugs Dermatol JDD. 2018 Apr 1;17(4):457–63.

28. Wrighton SA, Stevens JC. The human hepatic cytochromes P450 involved in drug metabolism. Crit Rev Toxicol. 1992;22(1):1–21.

29. Huskey SW, Dean DC, Miller RR, Rasmusson GH, Chiu SH. Identification of human cytochrome P450 isozymes responsible for the in vitro oxidative metabolism of finasteride. Drug Metab Dispos Biol Fate Chem. 1995 Oct;23(10):1126–35.

30. Smith RL, Williams RT. Implication of the conjugation of drugs and other exogenous compounds. In: Glucuronic acid: free and combined: chemistry, biochmeistry, pharmacology and medicine. NY, USA: Dutton GJ (Ed.). Academic Press; 1966. p. 58–69.

31. Lundahl A, Hedeland M, Bondesson U, Knutson L, Lennernäs H. The effect of St. John's wort on the pharmacokinetics, metabolism and biliary excretion of finasteride and its metabolites in healthy men. Eur J Pharm Sci Off J Eur Fed Pharm Sci. 2009 Mar 2;36(4–5):433–43.

32. Carlin JR, Höglund P, Eriksson LO, Christofalo P, Gregoire SL, Taylor AM, et al. Disposition and pharmacokinetics of [14C]finasteride after oral administration in humans. Drug Metab Dispos Biol Fate Chem. 1992 Apr;20(2):148–55.

33. PROSCAR [Internet]. Merck.com. [cited 2021 Jun 21]. Available from: https://www.merck.com/research-and-products/proscar/

34. Iamsumang W, Leerunyakul K, Suchonwanit P. Finasteride and Its Potential for the Treatment of Female Pattern Hair Loss: Evidence to Date. Drug Des Devel Ther. 2020 Mar 2;14:951–9.

35. Price VH, Roberts JL, Hordinsky M, Olsen EA, Savin R, Bergfeld W, et al. Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. J Am Acad Dermatol. 2000 Nov;43(5 Pt 1):768–76.

36. Seale LR, Eglini AN, McMichael AJ. Side Effects Related to 5 α-Reductase Inhibitor Treatment of Hair Loss in Women: A Review. J Drugs Dermatol JDD. 2016 Apr;15(4):414–9.

37. Laborde E, Brannigan RE. Effect of 1-mg dose of finasteride on spermatogenesis and pregnancy. J Androl. 2010 Apr;31(2):e1-2.

38. PROSCAR [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2013.

39. Amory JK, Wang C, Swerdloff RS, Anawalt BD, Matsumoto AM, Bremner WJ, et al. The effect of 5alpha-reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men. J Clin Endocrinol Metab. 2007 May;92(5):1659–65.

40. Using Finasteride when trying to conceive [Internet]. Mens Pharmacy Blog. 2018 [cited 2021 Jun 21]. Available from: https://www.menspharmacy.co.uk/blog/finasteride/using-finasteride-when-trying-to-conceive/

41. Mazzarella G, Loconsole G, Cammisa G, Mastrolonardo G, Vena G. Topical finasteride in the treatment of androgenic alopecia. Preliminary evaluations after a 16-month therapy course. J Dermatol Treat. 1997 Jan;8(3):189–92.

42. Caserini M, Radicioni M, Leuratti C, Annoni O, Palmieri R. A novel finasteride 0.25% topical solution for androgenetic alopecia: Pharmacokinetics and effects on plasma androgen levels in healthy male volunteers. Int J Clin Pharmacol Ther. 2014;52(10):842–9.

43. Caserini M., Mailland F., Radicioni M., Annoni O., Palmieri R. Single and repeated dose of finasteride topical solution in subjects with androgenetic alopecia: A pharmacokinetic and pharmacodynamic study. J Am Acad Dermatol. 2013;68(4 SUPPL. 1):AB108.

44. Gupta AK, Bamimore MA, Foley KA. Efficacy of non-surgical treatments for androgenetic alopecia in men and women: a systematic review with network meta-analyses, and an assessment of evidence quality. J Dermatol Treat. 2020 Apr;1–34.

45. Eun HC, Kwon OS, Yeon JH, Shin HS, Kim BY, Ro BI, et al. Efficacy, safety, and tolerability of dutasteride 0.5 mg once daily in male patients with male pattern hair loss: a randomized, double-blind, placebo-controlled, phase III study. J Am Acad Dermatol. 2010 Aug;63(2):252–8.

46. Gubelin Harcha W, Barboza Martínez J, Tsai T-F, Katsuoka K, Kawashima M, Tsuboi R, et al. A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with androgenetic alopecia. J Am Acad Dermatol. 2014;70(3):489-498.e3.

47. Hajheydari Z, Akbari J, Saeedi M, Shokoohi L. Comparing the therapeutic effects of finasteride gel and tablet in treatment of the androgenetic alopecia. Indian J Dermatol Venereol Leprol. 2009;75(1):47–51.

48. Van Neste D, Fuh V, Sanchez-Pedreno P, Lopez-Bran E, Wolff H, Whiting D, et al. Finasteride increases anagen hair in men with androgenetic alopecia. Br J Dermatol. 2000;143(4):804–10.

49. Roberts JL, Fiedler V, Imperato-McGinley J, Whiting D, Olsen E, Shupack J, et al. Clinical dose ranging studies with finasteride, a type 2 5α-reductase inhibitor, in men with male pattern hair loss. J Am Acad Dermatol. 1999;41(4):555–63.

50. Shanshanwal SJS, Dhurat RS. Superiority of dutasteride over finasteride in hair regrowth and reversal of miniaturization in men with androgenetic alopecia: A randomized controlled open-label, evaluator-blinded study. Indian J Dermatol Venereol Leprol. 2017;83(1):47–54.

51. RStudio Team. RStudio: Integrated Development Environment for R. Boston, MA; 2021.

52. Wang L, Lei Y, Gao Y, Cui D, Tang Q, Li R, et al. Association of finasteride with prostate cancer. Medicine (Baltimore). 2020 Apr 10;99(15):e19486.

53. Miyamoto H, Messing EM, Chang C. Androgen deprivation therapy for prostate cancer: current status and future prospects. The Prostate. 2004 Dec 1;61(4):332–53.

54. Goodman PJ, Tangen CM, Darke AK, Lucia MS, Ford LG, Minasian LM, et al. Long-Term Effects of Finasteride on Prostate Cancer Mortality. N Engl J Med. 2019 Jan 24;380(4):393–4.

55. Traish AM, Zitzmann M. The complex and multifactorial relationship between testosterone deficiency (TD), obesity and vascular disease. Rev Endocr Metab Disord. 2015 Sep;16(3):249–68.

56. Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. Nat Rev Cancer. 2001 Oct;1(1):34–45.

57. Said MA, Mehta A. The Impact of 5alpha-Reductase Inhibitor Use for Male Pattern Hair Loss on Men's Health. Curr Urol Rep. 2018 Jun 16;19(8):65.

58. Arca E, Acikgoz G, Tastan HB, Kose O, Kurumlu Z. An open, randomized, comparative study of oral finasteride and 5% topical minoxidil in male androgenetic alopecia. Dermatol Basel Switz. 2004;209(2):117–25.

59. Olsen EA, Hordinsky M, Whiting D, Stough D, Hobbs S, Ellis ML, et al. The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride. J Am Acad Dermatol. 2006 Dec;55(6):1014–23.

60. Khandpur S, Suman M, Reddy BS. Comparative efficacy of various treatment regimens for androgenetic alopecia in men. J Dermatol. 2002 Aug;29(8):489–98.

61. Overstreet JW, Fuh VL, Gould J, Howards SS, Lieber MM, Hellstrom W, et al. Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men. J Urol. 1999 Oct;162(4):1295–300.

62. Price VH, Menefee E, Sanchez M, Kaufman KD. Changes in hair weight in men with androgenetic alopecia after treatment with finasteride (1 mg daily): three- and 4-year results. J Am Acad Dermatol. 2006 Jul;55(1):71–4.

63. Rossi A., Cantisani C., Scarno M., Trucchia A., Fortuna M.C., Calvieri S. Finasteride, 1 mg daily administration on male androgenetic alopecia in different age groups: 10-year follow-up. Dermatol Ther. 2011;24(4):455–61.

64. Sato A, Takeda A. Evaluation of efficacy and safety of finasteride 1 mg in 3177 Japanese men with androgenetic alopecia. J Dermatol. 2012 Jan;39(1):27–32.

65. Yanagisawa M, Fujimaki H, Takeda A, Nemoto M, Sugimoto T, Sato A. Long-term (10-year) efficacy of finasteride in 523 Japanese men with androgenetic alopecia. Clin Res Trials [Internet]. 2019 [cited 2021 Jun 21];5(5). Available from: https://www.oatext.com/Long-term-(10-year)-efficacy-of-finasteride-in-523-Japanese-men-with-androgenetic-alopecia.php

66. Yeon JH, Jung JY, Choi JW, Kim BJ, Youn SW, Park KC, et al. 5 mg/day finasteride treatment for normoandrogenic Asian women with female pattern hair loss. J Eur Acad Dermatol Venereol JEADV. 2011 Feb;25(2):211–4.

67. Oliveira-Soares R, E Silva J, Correia M, André M. Finasteride 5 mg/day treatment of patterned hair loss in normo-androgenetic postmenopausal women. Int J Trichology. 2013;5(1):22–5.

68. Oliveira-Soares R, André MC, Peres-Correia M. Adverse Effects with Finasteride 5 mg/day for Patterned Hair Loss in Premenopausal Women. Int J Trichology. 2018 Feb;10(1):48–50.

69. Belknap SM, Aslam I, Kiguradze T, Temps WH, Yarnold PR, Cashy J, et al. Adverse event reporting in clinical trials of finasteride for androgenic alopecia ameta-analysis. JAMA Dermatol. 2015;151(6):600–6.

70. Stough D.B., Rao N.A., Kaufman K.D., Mitchell C. Finasteride improves male pattern hair loss in a randomized study in identical twins. Eur J Dermatol. 2002;12(1):32–7.

71. Rossi A., Mari E., Scarno M., Garelli V., Maxia C., Scali E., et al. Comparitive effectiveness and finasteride vs Serenoa repens in male androgenetic alopecia: A two-year study. Int J Immunopathol Pharmacol. 2012;25(4):1167–73.

72. Lin J-H, Chen W-C. Finasteride in the treatment of Taiwanese men with androgenetic alopecia: a 12-month open-label study. Kaohsiung J Med Sci. 2002 Aug;18(8):379–85.

73. Haber RS, Gupta AK, Epstein E, Carviel JL, Foley KA. Finasteride for androgenetic alopecia is not associated with sexual dysfunction: a survey-based, single-centre, controlled study. J Eur Acad Dermatol Venereol JEADV. 2019 Jul;33(7):1393–7.

74. Mysore V. Finasteride and sexual side effects. Indian Dermatol Online J. 2012;3(1):62–5.

75. Hirshburg JM, Kelsey PA, Therrien CA, Gavino AC, Reichenberg JS. Adverse Effects and Safety of 5-alpha Reductase Inhibitors (Finasteride, Dutasteride): A Systematic Review. J Clin Aesthetic Dermatol. 2016 Jul;9(7):56–62.

76. Irwig MS. Finasteride and Suicide: A Postmarketing Case Series. Dermatol Basel Switz. 2020;236(6):540–5.

77. Irwig MS. Depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects. J Clin Psychiatry. 2012 Sep;73(9):1220–3.

78. Research C for DE and. October – December 2009 | Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS). FDA [Internet]. 2021 Feb 3 [cited 2021 Jun 21]; Available from: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/october-december-2009-potential-signals-serious-risksnew-safety-information-identified-adverse-event

79. Ali AK, Heran BS, Etminan M. Persistent Sexual Dysfunction and Suicidal Ideation in Young Men Treated with Low-Dose Finasteride: A Pharmacovigilance Study. Pharmacotherapy. 2015 Jul;35(7):687–95.

80. Gupta M.A., Vujcic B., Sheridan A.D., Gupta A.K. Finasteride is associated with a higher odds of obstructive sleep apnea (OSA): Results from the us FDA adverse events reporting system (FAERS). Sleep. 2018;41(Supplement 1):A340–1.

81. Gupta AK, Carviel J, MacLeod MA, Shear N. Assessing finasteride-associated sexual dysfunction using the FAERS database. J Eur Acad Dermatol Venereol JEADV. 2017 Jun;31(6):1069–75.

82. Baas WR, Butcher MJ, Lwin A, Holland B, Herberts M, Clemons J, et al. A Review of the FAERS Data on 5-Alpha Reductase Inhibitors: Implications for Postfinasteride Syndrome. Urology. 2018 Oct;120:143–9.

83. Traish AM. Post-finasteride syndrome: a surmountable challenge for clinicians. Fertil Steril. 2020 Jan;113(1):21–50.

84. Great Britain, Medicines and Healthcare products Regulatory Agency, Breckenridge A, Woods K. Medicines and Healthcare products Regulatory Agency annual report and accounts 2010/11. London: The Stationery Office; 2011.

85. Traish AM, Mulgaonkar A, Giordano N. The dark side of 5α-reductase inhibitors' therapy: sexual dysfunction, high Gleason grade prostate cancer and depression. Korean J Urol. 2014 Jun;55(6):367–79.

86. Frye CA, Walf AA. Changes in progesterone metabolites in the hippocampus can modulate open field and forced swim test behavior of proestrous rats. Horm Behav. 2002 May;41(3):306–15.

87. Frye CA, Edinger KL. Testosterone's metabolism in the hippocampus may mediate its anti-anxiety effects in male rats. Pharmacol Biochem Behav. 2004 Jul;78(3):473–81.

88. Trüeb RM, Régnier A, Dutra Rezende H, Gavazzoni Dias MFR. Post-Finasteride Syndrome: An Induced Delusional Disorder with the Potential of a Mass Psychogenic Illness? Skin Appendage Disord. 2019 Aug;5(5):320–6.

89. Tacklind J, Fink HA, Macdonald R, Rutks I, Wilt TJ. Finasteride for benign prostatic hyperplasia. Cochrane Database Syst Rev. 2010 Oct 6;(10):CD006015.

Figure legends

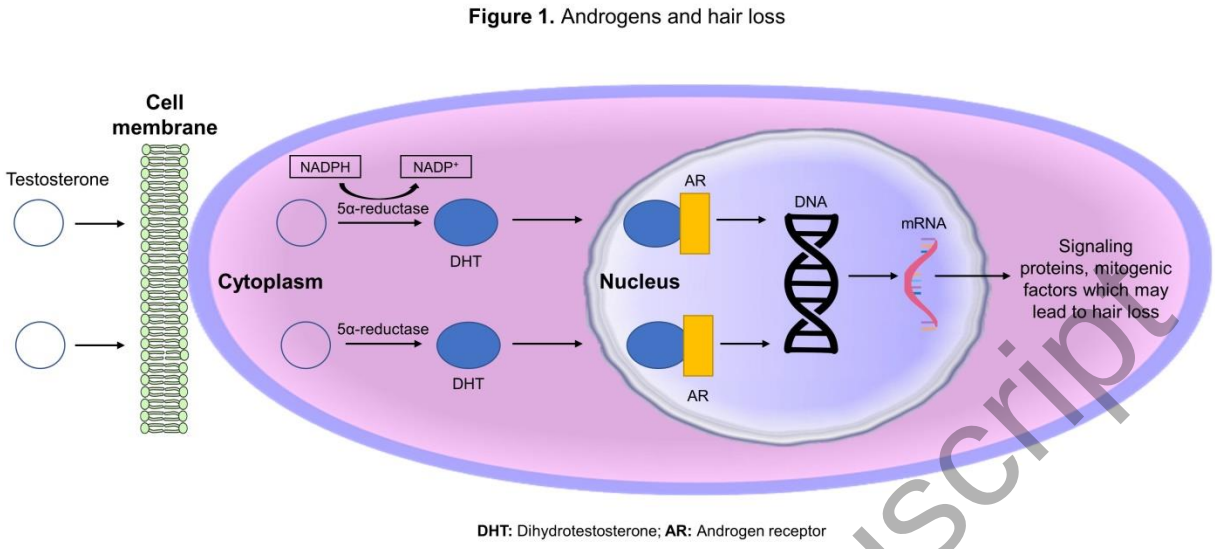

Figure 1: Androgens and hair loss

Figure 2. Mechanism of action of finasteride

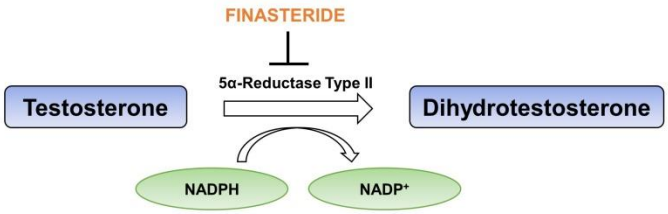

Figure 2: Mechanism of action of finasteride

Figure 3. Metabolism of Finasteride

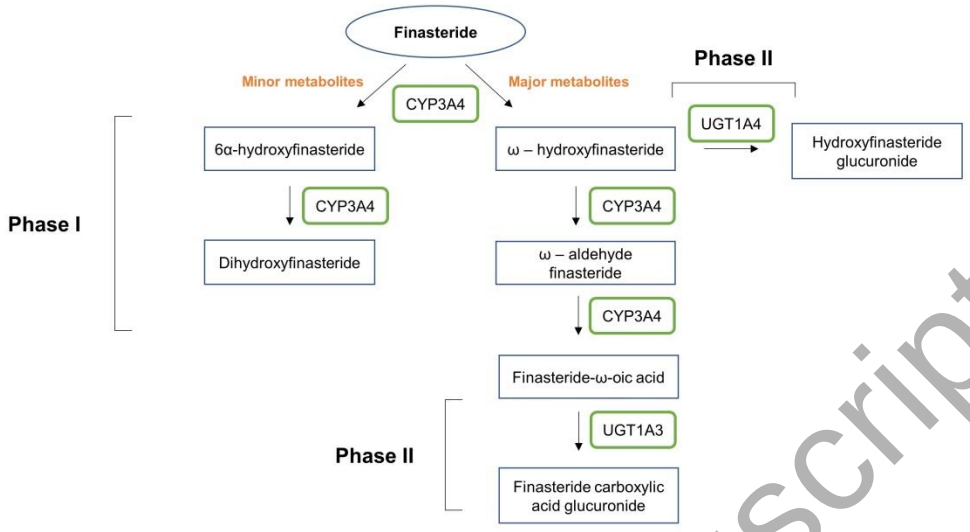

Figure 3: Metabolism of finasteride

Figure 4. Forest plots for efficacy of finasteride 1mg/day vs. placebo. The endpoint is change in total hair count, after 24 weeks (top) and 48 weeks (bottom). Abbreviations: CI: confidence interval, MD: mean difference, SD: standard deviation, τ^2: between study variance.

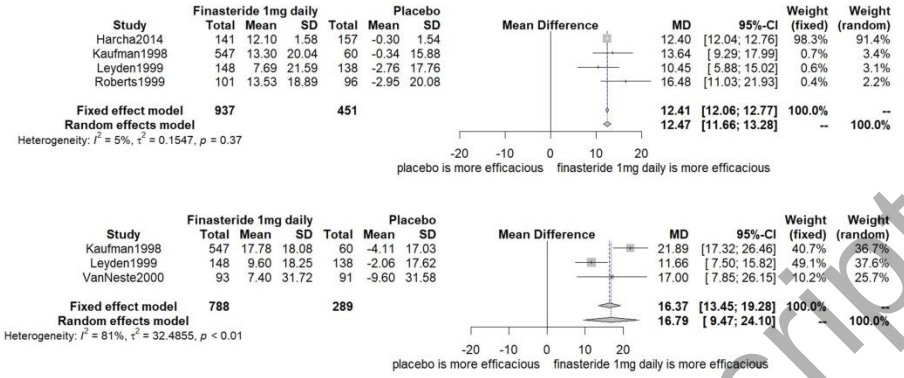

Figure 4: Forest plots for efficacy of finasteride 1mg/day vs. placebo. The endpoint is change in total hair count, after 24 weeks (top) and 48 weeks (bottom)

Figure 5. Forest plots for efficacy of dutasteride 1mg/day vs. placebo, and vs. finasteride 1mg/day. Meta-analyses of change in total hair count, after 24 weeks, for dutasteride 0.5mg daily vs. placebo (top) and dutasteride 0.5mg daily vs. finasteride 1mg daily (bottom). Abbreviations: CI: confidence interval, MD: mean difference, SD: standard deviation, τ^2: between study variance.

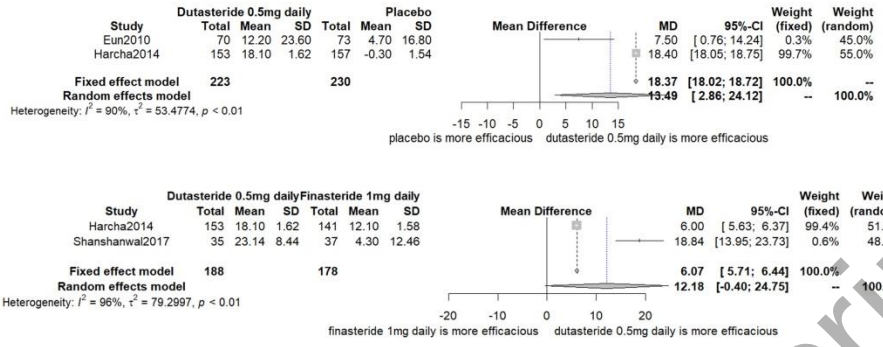

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Figure 6. League table for change in total hair count at 24 weeks; yellow-coloured cells correspond to significant associations

dutasteride 0.5mg daily	-6.998 (-9.249, -4.945)	-1.802 (-8.368, 4.795)	-7.751 (-11.38, -4.326)	-18.2 (-21.56, -14.91)
6.998 (4.945, 9.249)	**finasteride 1 mg daily**	5.225 (-1.074, 11.57)	-0.7543 (-3.559, 2.062)	-11.19 (-13.99, -8.376)
1.802 (-4.795, 8.368)	-5.225 (-11.57, 1.074)	**finasteride 5 mg daily**	-5.983 (-12.89, 0.9036)	-16.42 (-22.04, -10.81)
7.751 (4.326, 11.38)	0.7543 (-2.062, 3.559)	5.983 (-0.9036, 12.89)	**finasteride (topical) 1%**	-10.45 (-14.36, -6.435)
18.2 (14.91, 21.56)	11.19 (8.376, 13.99)	16.42 (10.81, 22.04)	10.45 (6.435, 14.36)	**vehicle or placebo**

Figure 6: League table for change in total hair count at 24 weeks; yellow-coloured cells correspond to significant associations

Figure 7. League table for change in total hair count at 48 weeks; yellow-coloured cells correspond to significant associations.

finasteride 1 mg daily	5.172 (-1.65, 12.03)	-16.38 (-19.6, -13.16)
-5.172 (-12.03, 1.65)	**finasteride 5 mg daily**	-21.54 (-27.53, -15.58)
16.38 (13.16, 19.6)	21.54 (15.58, 27.53)	**vehicle or placebo**

Figure 7: League table for change in total hair count at 48 weeks; yellow-coloured cells correspond to significant associations

Table 1. Physiological distribution of 5AR isoenzymes in humans

Type I 5AR isoenzyme	Type II 5AR isoenzyme	Type III 5AR isoenzyme
Liver	Prostate	Basal epithelium of prostate glands
Adult facial and scalp sebaceous glands	Testes	
Dermal papilla	Dermal papilla	
Prostate	Liver	

Table 2. SUCRA for change in total hair count at 24 weeks

Treatment	SUCRA (%)
dutasteride 0.5mg daily	92.6475
finasteride 5 mg daily	79.97375
finasteride 1 mg daily	43.9525
finasteride (topical) 1%	33.42625
vehicle or placebo	0

Table 3. SUCRA for change in total hair count at 48 weeks

Treatment	SUCRA (%)
finasteride 5 mg daily	96.605
finasteride 1 mg daily	53.395
vehicle or placebo	0

Table 4. Commonly reported adverse events profile by patients in clinical trials investigating finasteride 1 mg/day for male and female pattern baldness

Male	Female
Decreased libido	Decreased libido
Erectile dysfunction	Menstrual irregularity
Ejaculation disorder	Headache
Impotence	Hypertrichosis