Dermatology

Dermatology , DOI: 10.1159/000541395

Received: March 25, 2024

Accepted: September 8, 2024

Published online: September 13, 2024

Dutasteride for the Treatment of Androgenetic Alopecia: An Updated Review

Ding Y, Wang C, Bi L, Du Y, Lu C, Zhao M, Fan W

ISSN: 1018-8665 (Print), eISSN: 1421-9832 (Online)

https://www.karger.com/DRM

Dermatology

Dutasteride for the Treatment of Androgenetic Alopecia: An Updated Review

Yunbu Ding[a], Chaofan Wang[b], Linbo Bi[c], Yimei Du[d], Changpei Lu[e], Min Zhao[f], and Weixin Fan[g]

[a] Department of Dermatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; dingyunbu@163.com

[b] Department of Dermatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; wangcflily@163.com

[c] Department of Dermatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; b1359028021@163.com

[d] Department of Dermatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; littleyemay@163.com

[e] Department of Dermatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; cplu@stu.njmu.edu.cn

[f] Department of Dermatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; zhaomin20201122@sina.com

[g] Department of Dermatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; hairmanfwx@163.com

Short Title: Dutasteride in androgenetic alopecia

Corresponding Author: Weixin Fan

E-mail address: hairmanfwx@163.com

Keywords: Androgenetic alopecia; Dutasteride; Finasteride; 5α-reductase inhibitors; Mesotherapy; Microneedling.

Abstract

Background: Androgenetic alopecia (AGA) is a common skin disease characterized by gradually miniaturized hair follicles, which manifests as progressive hair thinning and produces a bald appearance. Currently, finasteride is approved by the Food and Drug Administration (FDA) for the treatment of AGA, but its efficacy remains poor in some patients.

Summary: Compared to finasteride, oral dutasteride has better efficacy and similar tolerability, and most adverse events are mild and reversible, making it an effective option for AGA, but its sexual adverse events and potential psychiatric risks still need to be concerned. Mesotherapy with dutasteride and microneedling combined with dutasteride solution can reduce adverse events caused by oral medication and exhibit certain efficacy, but standardized treatment protocols and large-scale clinical trials are still needed in the future. Liposomes or nanoparticles of dutasteride are under development and may become an efficient topical formulation.

Key Messages: We have summarized the efficacy and adverse events of dutasteride in treating AGA under different administration methods and the promise of novel topical drug carriers.

Introduction

Androgenetic alopecia (AGA) is a common disease of multifactorial inheritance characterized by progressive hair loss. In male patients, AGA manifests itself as a receding frontal hairline and (or) progressive reduction and thinning of hair on the scalp, also known as male pattern baldness[1]. In female patients, AGA is characterized by progressive reduction and thinning of hair without receding of the frontal hairline, also known as female pattern hair loss[2]. The prevalence of AGA was reported to be 50% in Caucasian men and 19% in Caucasian women[3, 4]. In China, the prevalence of male AGA was 21.3%, while for females, it was 6.0%[5]. The prevalence of AGA was 14.6% in African men and 3.5% in African women[6]. Asian and African populations had a lower prevalence than Caucasians. The results above indicate that there are racial differences and regional differences in the prevalence of AGA.

The primary pathogenesis of AGA is that 5α-reductase converts testosterone into dihydrotestosterone (DHT), which binds to the androgen receptor, thus inhibiting the Wnt/β-cyclin signaling pathway, and reducing the role of papilla cells in inducing and sustaining hair growth[7]. Eventually, genetically susceptible hair follicles are gradually miniaturized and terminal hairs grown from them are replaced by vellus hairs[8]. At the same time, the dynamics of the hair cycle change: the duration of the anagen phase gradually decreases, while the telogen phase increases. The duration of the anagen phase determines the length of the hair, so the new anagen hairs become shorter, gradually producing a bald appearance[9].

There are three isozymes of 5α-reductase: type I, type II, and type III. Type I and type II have been isolated from the scalp of AGA patients[10]. Type III mRNA expression has also been detected in anagen hairs[11]. Dutasteride and finasteride are both 5α-reductase inhibitors (5ARIs). Currently, only two drugs, topical minoxidil and oral finasteride, have been approved by the FDA for the treatment of AGA. The FDA has approved a dose of 0.5 mg/d of dutasteride for the treatment of benign prostatic hyperplasia (BPH) [12], but for male patients with AGA, only South Korea and Japan have approved the use of dutasteride[13][14]. Finasteride selectively inhibits type II 5α-reductase, while dutasteride inhibits type I and type II 5α-reductase. Finasteride (5 mg/d) can reduce scalp DHT by approximately 41%, while dutasteride (0.5 mg/d) can reduce scalp DHT by approximately 51%[15]. Another study measured the concentration of medication and DHT in the hair and found that finasteride and dutasteride reduced hair DHT levels by approximately 64% and 92%, respectively[16]. Therefore, for patients with AGA who do not respond well to finasteride, dutasteride may be a better option.

Methods

We performed a Medical Subject Heading (MeSH) search in the PubMed database using the terms "androgenetic alopecia" and "dutasteride". Since dutasteride was approved by the FDA for medical use in 2001, the publication year range for the literature search was from 2000 to February 2024. We searched for 183 articles and finally included 40 articles, and the selection process is shown in Figure 1.

Results

Pharmacology of dutasteride

Dutasteride can form a stable enzyme complex with 5α-reductase isozymes, thus inhibiting the conversion of testosterone to DHT. Dutasteride at a dose of 0.5 mg/d can reduce serum DHT levels by approximately 92%, while finasteride at 5 mg/d can reduce serum DHT levels by approximately 73%[15]. Due to the participation of 5α-reductase in the synthesis of neurosteroids such as 3α,5α-tetrahydroprogesterone (3α,5α-THP) and tetrahydrodeoxycorticosterone (THDOC), dutasteride can also have inhibitory effects on their production[17].

Absorption: After taking a 0.5 mg soft capsule, the maximum blood concentration (Cmax) of dutasteride is averaged at 1.27 ng/ml, occurring between 1-3 hours. Absolute bioavailability in healthy individuals is approximately 60% (range: 40%-94%)[18]. Distribution: Dutasteride is widely distributed in the human circulation and has a high binding affinity to plasma albumin (99%) and α-1 acid glycoprotein (96.6%)[18]. Metabolism and Excretion: Dutasteride is extensively metabolized in the liver by the cytochrome P450 (CYP) isoenzymes CYP3A4 and CYP3A5. There are 5 metabolites in human serum: 3 main metabolites (4'-hydroxydutasteride, 1,2-dihydroxydutasteride, 6-hydroxydutasteride) and 2 minor metabolites (6,4'-dihydroxydutasteride, 15-hydroxydutasteride). Due to its long half-life, dutasteride remains detectable in serum (>0.1 ng/mL) for 4-6 weeks after discontinuation of therapy. The terminal elimination half-life of dutasteride in steady state is approximately five weeks[18]. Men treated with dutasteride should not donate blood until at least six months after discontinuation of the drug to prevent the use of dutasteride in pregnant women receiving blood transfusions[15]. Feces is the main mode of excretion of dutasteride and its metabolites[18].

Efficacy and adverse events of oral dutasteride

1. Efficacy

There are four double-blind, randomized, placebo-controlled trials[15, 19-21] and one prospective, evaluator-blinded, open-label, randomized controlled trial[22] using average changes in target area hair count as the efficacy endpoint. To compare the efficacy of different trials, we standardized the units for average changes in target area hair count before and after 24 weeks of treatment to " number of hairs/cm^2" (shown in Table 1). At week 24, the increase in hair count in the 0.5 mg dutasteride group was superior to the finasteride group[15, 19, 22], while the 0.1 mg dutasteride group was similar to the finasteride group[15, 19], and the treatment groups were significantly better than the placebo group[15, 19-21]. For the increase in the placebo group in Table 1, the researchers believed that it may be related to the season; Many of the subjects in that trial were enrolled in early spring, and the percentage of scalp anagen hair peaked at more than 90% in March and then gradually declined[20]. In terms of global photographic assessment, the panel of experts (composed of dermatologists) evaluated scalp vertex and frontal photographs before and after 24 weeks, and concluded that the 0.5 mg dutasteride group was superior to the finasteride group[15, 19, 22] and that all treatment groups were superior to placebo group[15, 19-21]. In terms of subjects' self-assessments, the researchers scored using the Hair Growth Index and Hair Growth Satisfaction Scale or similar questionnaires. In the 24th week, several studies suggested that the 0.5 mg dutasteride group was superior to the finasteride group[19, 22], and only one study found it not superior to the finasteride group[15], in which the finasteride group received a dose of 5 mg/d. The other studies used a dose of 1 mg/d. Each treatment group was superior to the placebo group[15, 19-21].

In a prospective open-label study of 120 AGA patients treated with 0.5 mg dutasteride for 52 weeks, the average hair count, hair width and global photographic assessment (vertex and frontal of the scalp) improved from baseline at weeks 26 and 52, and the proportion of patients with improvement ranged from 76% to 85%. The improvements in hair width and terminal hair count at week 52 continued compared with week 26[23]. In a retrospective study of 26 male patients with AGA who took 0.5 mg dutasteride orally for more than 52 weeks, 84.62% of the patients self-reported improvement or maintenance[24]. Another retrospective study included 42 patients with AGA who only took dutasteride 2-7 times a week for at least 12 months, and researchers found that efficacy was associated with a higher frequency of medication through a comparison of overall hair appearance[25].

A 6-month retrospective study included 246 patients with AGA who received 1 mg finasteride and 249 patients who received 0.5 mg dutasteride orally. By evaluating photos before and after treatment, the researchers concluded that dutasteride was superior to finasteride in improving the

overall appearance of hair[26]. In another retrospective study with an observation period of more than three years, researchers concluded that the 0.5 mg dutasteride group (n=250) was superior to 1 mg finasteride group (n=285) in improving the clinical grade of AGA in men (Basic and specific classification)[27]. Furthermore, a retrospective study included 99 male AGA patients who used dutasteride for more than five years. The researchers scored clinical photos of the frontal and vertex of the scalp, concluding that using 0.5 mg of dutasteride for at least 5 years is a safe and effective treatment that can provide good results for male AGA patients[28].

A study included 35 patients with AGA who did not show a significant clinical improvement after six months of finasteride treatment (1 mg/d). They received treatment with dutasteride at a dose of 0.5 mg/d for six months. Compared to finasteride treatment, hair density and thickness increased by 10.3% (9 /cm^2) and 18.9% (10μm), respectively. However, the study did not include a control group that continued to take finasteride[29].

2. Adverse events

2.1. Sexual adverse events

Since DHT plays a key role in erectile physiology, including activation of nitric oxide synthase and increased blood flow to penile tissue, inhibition of 5α-reductase by finasteride or dutasteride leads to erectile dysfunction. Furthermore, deficiency or reduced levels of DHT can cause the death of smooth muscle cells in the penile trabeculae, accompanied by increased deposition of connective tissue, resulting in structural changes in the penile tissue and hindering its compliance, ultimately leading to erectile dysfunction[30].

Four randomized, double-blind, placebo-controlled trials[15, 19, 20, 31] were conducted to compare the incidence of sexual adverse events (AEs) between treatment groups and placebo groups, one of which was unblinded after 24 weeks and changed to open-label dutasteride[31] (shown in Table 2). Sexual AEs included altered libido, impotence, ejaculation disorders, breast enlargement and breast tenderness[19]. The incidence of sexual AEs in the dutasteride group appeared to be similar to the finasteride group[15, 19], while the incidence of sexual AEs in the placebo group was similar to or lower than that in the treatment group[15, 19, 20, 31].

An open-label prospective 52-week study enrolling 120 patients with AGA taking 0.5 mg of oral dutasteride showed an overall incidence of 17% of drug-related AEs. Sexual AEs (15.8%) were the most common drug-related AEs, particularly erectile dysfunction and decreased libido. The incidence of most sexual AEs was high in the first six months and decreased in the subsequent six months. Of the 19 patients (15.8%) who reported AEs of sexual dysfunction, 6 patients (5%) were relieved during the 52-week treatment period; 13 patients (10.8%) achieved a recovery during the 6-month follow-up period after discontinuation of treatment[23]. A single-center retrospective study lasting more than 12 months found that among 307 patients with AGA aged 18 to 79 years who were treated with dutasteride, sexual AEs occurred in 20 cases (6.5%) when the dose ranged from 1 to 7 tablets per week. Among the 12 patients who took 0.5 mg of finasteride 2-3 times a week, no sexual AEs were reported. Researchers suggest that this dose regimen can be used for patients with AGA who were concerned about sexual AEs[25].

In a 48-week study, the first 24 weeks were a randomized, double-blind, placebo-controlled study, and the last 24 weeks were open-label 0.5 mg dutasteride treatment. During the double-blind period, the incidence of sexual AEs in the dutasteride group (16%) was approximately twice that of the placebo group (8%); during the open-label period, the overall incidence of sexual AEs was lower (5%)[31]. All AEs were mild to moderate in severity and were considered related to treatment. Most sexual AEs occurred within the first three months of dutasteride treatment and resolved during or after study treatment. The mean International Index of Erectile Function (IIEF) Questionnaire-

Erectile Function domain scores remained stable in the placebo group during the first 24 weeks, while the dutasteride group showed a trend toward worse erectile function from baseline to double-blind weeks 12 and 24[31].

In a 1-year randomized, double-blind, placebo-controlled trial, 99 healthy men were randomized to dutasteride (0.5 mg), finasteride (5 mg) or placebo orally once daily. At 26 weeks, total sperm counts in the dutasteride and finasteride groups decreased by 28.6% and 34.3%, respectively, compared to baseline. At 52 weeks, the total sperm count decreased by 24.9% and 16.2%, the semen volume decreased by 29.7% and 14.5%, and the sperm concentration decreased by 3.2% and 7.4%, respectively. Sperm motility was significantly reduced by 6% to 12% during both treatment and follow-up. Neither treatment had any effect on sperm morphology. The decrease in semen parameters was reversible after discontinuation of the drug[32].

2.2. Mental adverse events

5α-reductase is involved in the production of neurosteroids[17]. Animal studies have shown that in the brain, 5α-reductase catalyzes progesterone into 5α-dihydroprogesterone (5α-DHP), which is further catalyzed by 3α-hydroxysteroid dehydrogenase (3α-HSD) into the potent neurosteroid 3α, 5α-tetrahydroprogesterone (3α, 5α-THP). Neurosteroids have been shown to promote sexual maturation, antidepressant, and anxiolytic effects in animal studies[33]. 5ARIs can reduce neurosteroid production[34, 35].

In an open-label prospective study lasting 52 weeks, 120 patients with AGA received oral 0.5 mg dutasteride. The researchers used the Columbia Suicide Severity Rating Scale to assess suicidal tendencies. At week 52, a patient had suicidal ideation and two patients had depressive symptoms, which were considered as possibly AEs related to suicide[23]. A single-center retrospective study lasting 12 months found that among 307 patients with AGA aged 18 to 79 who received oral dutasteride treatment, three patients experienced mood disorders[25].

A meta-analysis has found that 5ARIs can increase the risk of developing depression, especially in patients with risk factors or a history of depression. Clinicians should consider this information carefully[36]. Another cohort study has shown that male patients aged 50 to 90 who undergo 5ARIs treatment may have an increased risk of developing depression, with no difference in risk between finasteride and dutasteride. Furthermore, neither of these medications has been associated with suicide[37].

2.3. Other adverse events

In a case report, a 25-year-old man had taken 0.5 mg of dutasteride every other day to treat hair loss. After nine months, the patient developed cerebral venous thrombosis. The patient had no other prothrombotic conditions and was not taking any medications that could cause thrombosis. It is speculated that elevated estrogen levels caused by dutasteride may have led to the formation of the thrombus[38]. Two reviews proposed that DHT plays an essential role in liver physiology, pancreatic β-cell function and survival, eye function, prevention of dry eye, and kidney physiology. Therefore, inhibition of 5α-reductase with dutasteride or finasteride to reduce DHT biosynthesis may lead to non-alcoholic fatty liver disease, insulin resistance, type 2 diabetes mellitus, dry eye, potential renal dysfunction, and other metabolic dysfunctions[39, 40].

Efficacy and adverse events of mesotherapy with dutasteride

Mesotherapy is a technique of intradermal injection of low doses of therapeutic agents and bioactive substances into the skin. Mesotherapy treatments increase the residence time of the drug in the affected area, allowing the use of lower doses and longer intervals, which could improve treatment outcomes and patient adherence[41].

Three randomized, placebo-controlled trials[42-44] assessed the efficacy of mesotherapy with dutasteride by comparing photographs before and after treatment (shown in Table 3). Mesotherapy with dutasteride preparations is significantly superior to placebo[42-44]. However, all dutasteride preparations used in these three trials contained D-panthenol and biotin, which are thought to contribute to hair growth[45, 46]. A trial compared the efficacy of dutasteride preparations, dutasteride, and saline. The researchers found that the efficacy of the dutasteride preparation group was the best, while the dutasteride group was slightly better than the saline group[42].

Common AEs of dutasteride mesotherapy include pain during injection, headache, scalp tightness after injection[43, 44]. A randomized controlled trial involving 126 patients with female pattern hair loss showed that the incidence of pain in the treatment group and the control group was 82.6% and 80%, respectively, and the incidence of headache was 22.1% and 30%, respectively. Scalp itching occurred only in the treatment group (3.5%)[43]. Uncommon AEs include frontal edema[47], angioedema-like contact dermatitis[48], and non-scarring alopecia[49]. A randomized controlled trial included 90 male patients who did not complain of sexual AEs, but the examination of semen in the treatment group showed a decrease in semen volume, sperm concentration, and sperm viability, but the change was not statistically significant. Systemic absorption of dutasteride after mesotherapy and the effect of absorption on spermatozoa is possible[42].

Microneedle combined with dutasteride solution

Microneedling is a minimally invasive dermatologic procedure in which fine needles are rolled over the skin to puncture the stratum corneum. This treatment induces collagen formation, neovascularization, and growth factor production in the treated area[50]. A 20-week randomized, double-blind, placebo-controlled study included 34 male patients with AGA, comparing the efficacy of microneedling with topical 0.01% dutasteride solution with microneedling combined with topical saline solution in treating male AGA. Through overall photographic assessment, it was found that 52.9% of men in the microneedling combined with the topical dutasteride solution group and 17.6% of men in the microneedling combined with the topical saline solution group showed a significant improvement. AEs such as erythema and scalp sensitivity, lasting ≤36 h, affected 88.2% of the microneedling combined with the saline solution group and 84.2% of the microneedling combined with the topical dutasteride solution group[51].

Dutasteride in patients with female pattern hair loss

There is a case report of a 46-year-old woman with hair loss who showed no response to minoxidil and only limited improvement after finasteride treatment. Hair loss improved significantly after switching to 0.5 mg/d of dutasteride for six months, and no AEs were observed[52]. Another case report involved a 70-year-old woman with breast cancer who experienced diffuse hair loss after receiving estrogen suppression therapy. The patient showed improvement after taking 0.5 mg/d of dutasteride orally and using 5% minoxidil topically for three months. At month 18, the patient showed a significant improvement and no side effects were reported[53]. A retrospective study assessed the effectiveness of daily oral administration of 0.15 mg of dutasteride in 60 female patients with hair loss over three years. The results showed that 83.3% of the female patients experienced an increase in hair thickness and 65.6% improved overall hair appearance based on photography assessment[54].

Transdermal drug delivery system of dutasteride

Liposomes and nanoparticles are novel drug carriers. Liposomes are formulations that utilize vesicles formed by phospholipid bilayer membranes to encapsulate drug molecules, which have good biocompatibility, targeting, and long-lasting effects, improving drug stability while reducing drug toxicity[55]. Dutasteride is a highly lipophilic substance with poor water solubility. These

characteristics make it difficult to use dutasteride in conventional topical drug delivery systems for the scalp. However, nanoscale drug delivery systems would be ideal, as they can incorporate drugs within them while still being administered in an aqueous formulation. Furthermore, the nanoparticle system exhibits a natural tendency to adapt to the cavity of the hair follicle, and modulation of characteristics such as shape, surface charge, and aggregation state of nanoparticles can improve this targeting tendency[56, 57]. Considering that the site of action of 5ARIs for the treatment of hair loss is in the region of the hair follicle, as well as the natural tendency of nanoparticles to aggregate in structures of the skin appendage, the topical application of the nanoparticle system can improve the therapeutic outcome[56, 58]. There are studies on liposomes on mouse skin and lipid nanoparticles on pig ear skin that deliver dutasteride to the hair follicle, and both showed good targeting and drug stability[55, 59, 60].

Discussion

Hair is an integral part of our identity and body image, and healthy hair has positive connotations for them. AGA can reduce the patient's satisfaction with their body image and their attractiveness to others[61]. A study conducted in several European countries found that among male participants aware of their hair loss, 43% were concerned about a decline in personal charm, 42% feared becoming bald, 37% worried about aging, 22% believed it had a negative impact on their social life, and 21% experienced depressive moods[62]. Another study assessed the quality of life of 400 AGA patients and 100 control subjects through the quality of life questionnaire. They found that patients with AGA had lower quality of life, overall satisfaction in the psychological, social, environmental and physical assessment domains compared to controls[63].

Only two drugs, minoxidil solution and finasteride, have been approved by the FDA for the treatment of AGA. A double-blind, randomized, placebo-controlled trial of finasteride included 1,879 patients aged 18 to 41 years with mild to moderate AGA. Overall clinical photographs showed that the proportions of improvement with 1 mg/d finasteride in the first and the second year were 48% and 66%, respectively, compared to 7% in the placebo group[64]. Despite the significant efficacy of finasteride, 52% and 34% of patients with AGA did not improve after 1 and 2 years of treatment, respectively. A 5-year follow-up study divided AGA patients taking finasteride into groups with sufficient and insufficient efficacy based on scalp photography assessment scores. The study found that independent risk factors of insufficient efficacy were age at the start of treatment of 40 years or more and advanced classification of AGA[65].

Finasteride inhibits type II 5α-reductase, while dutasteride inhibits type I and type II 5α-reductase and has a stronger inhibitory effect. Changes in target area hair count, overall scalp photographic assessment, and subjects' self-assessments show that the overall clinical efficacy of 0.5 mg/d dutasteride is superior to finasteride. In other words, dutasteride is superior to finasteride in promoting hair growth and increasing hair count and width. Two meta-analyses also support this conclusion[66, 67]. Currently, randomized controlled trials of oral dutasteride for the treatment of AGA are limited to 24 weeks. Larger and longer randomized controlled trials could be conducted in the future.

AEs for dutasteride were predominantly sexual, with an incidence rate ranging from 2% to 16%, compared to 8% to 13.4% for finasteride (shown in Table 2). The most common sexual AEs are altered libido (primarily decreased libido), followed by impotence, ejaculation disorders, breast enlargement, and breast tenderness. Most sexual AEs occur in the early stages of treatment, with a decrease in incidence in the later stages. These sexual AEs are usually mild to moderate and may resolve during treatment or after discontinuation of the drug [31]. In a 4-year Phase III clinical trial of 0.5 mg oral dutasteride daily for BPH, there was an overall decreasing trend in the incidence of the most common sexual AEs, such as decreased libido of 3.7% in the first year, 0.6% in the second year 0.4% in the third year, and 0.1% in the fourth year[68]. Therefore, 0.5 mg/d dutasteride is well

tolerated in the long term. In addition, there was a similar downward trend in the rate of sexual AEs for finasteride treatment of AGA, which was 4.4% in the first year compared with 0.6% in the fifth year[69]. A meta-analysis showed that the number of available randomized, double-blind, placebo-controlled trials and the total sample size in dutasteride studies for the treatment of AGA in men were limited and did not adequately determine the risk of AEs of dutasteride 0.5 mg/d for the treatment of AGA in men. Physicians should be aware and assess the potential for sexual dysfunction in patients treated with 5ARIs [70]. Some studies have also questioned the incidence and duration of sexual AEs, arguing that some studies derived sexual AEs only from interviews between researchers and patients without providing adequate objective safety evaluations or reports, such as not using the IIEF questionnaire to assess sexual function[30]. A study of 120 patients with BPH taking oral finasteride divided the subjects into groups informed about drug side effects and uninformed groups. The researchers found that the rate of sexual AEs in the informed group was approximately three times that of the uninformed group (43.6% vs 15.3%)[71]. Researchers who ask questions about sexual function and patients who inquire about sexual AEs may be factors that lead to the increase in the rate of sexual AEs. To reduce bias in physician interviews and subjective patient thoughts, future clinical trials can adopt standardized scales such as the IIEF questionnaire to assess the incidence and severity of sexual AEs related to dutasteride.

In addition to common sexual AEs, some studies have shown that 5ARIs may increase the risk of developing depression, with no difference between finasteride and dutasteride[36, 37]. The mechanism by which 5ARIs play a role in the development of depression can include changes in neurosteroid levels (especially THP), dopaminergic dysfunction, decreased hippocampal neurogenesis, increased neuroinflammation, alterations in the hypothalamic-pituitary-adrenal axis alterations and epigenetic modifications[72]. However, the safety and tolerability of many clinical trials for AGA have not involved the assessment of psychological AEs, and the few studies reporting depressive symptoms did not use standardized tools such as the Beck Depression Inventory (BDI) or the Hospital Anxiety and Depression Scale (HADS) for evaluation. Considering the potential negative impact of 5ARIs on patients' psychological status, we recommend that in subsequent related clinical trials, researchers should not only focus on the most common sexual AEs but also comprehensively assess patients' psychological conditions. We suggest using standardized tools such as the BDI and the HADS to determine whether patients exhibit depressive moods, suicidal ideation, or other psychological AEs before and during treatment.

5ARIs reduce serum prostate-specific antigen (PSA) concentrations by 50%, and prostate diseases such as prostate cancer cause elevated PSA. The use of 5ARIs before diagnosis is associated with delayed prostate cancer diagnosis and worsened prostate cancer outcomes among men in a PSA-screened population[73]. Men taking dutasteride had a 23% lower overall risk of prostate cancer detected by biopsy compared to men taking placebo, and the overall risk reduction was limited to prostate cancer with a Gleason score of 6 or less, while the dutasteride group had a higher incidence of prostate cancer with a Gleason score of 8 to 10 than the placebo group[74]. The mean age of the participants in these studies was greater than 60 years, whereas the mean age of the participants in the AGA clinical trials was no more than 50 years, and there are no reports of prostate cancer after dutasteride use in patients with AGA.

Mesotherapy is a technique that involves injecting small amounts of drugs into the middle layer of the skin, bypassing the obstacles faced by topical medications, and achieving targeted treatment[41]. It is an effective choice for the treatment of AGA, as it can reduce the systemic side effects caused by dutasteride. However, only a few small randomized clinical trials have tested intradermal injection of dutasteride, and all of them have used dutasteride preparations containing ingredients that promote hair growth. The duration and frequency of treatment also varied. AEs of mesotherapy mainly include pain during injection and post-injection headache, with the former occurring in over 80% and the latter in over 22%. The pain during injection typically subsided quickly, though it may persist for

several hours to two days in some patients, while post-injection headaches did not last more than a day[43]. Less common AEs include scalp tightness, scalp itching, forehead edema[47], scarring alopecia[49], and angioedema-like contact dermatitis[48]. Due to the abundance of blood vessels in the scalp, systemic absorption of dutasteride after mesotherapy treatment and the effect of absorption on spermatozoa are possible[42].

Microneedling induces collagen formation, neovascularization, and growth factor production in the treated area and has a favorable safety and tolerability profile[50]. Only one randomized controlled trial has examined the efficacy and safety of microneedling in combination with dutasteride solution, in which 52.9% of men showed improvement, while scalp erythema and pain occurred in 84.2% of men, lasting ≤36 h[51]. One review suggested that most AEs of microneedling are transient and mild, including scalp erythema, pinpoint bleeding, seborrheic dermatitis, irritation, itching, granulomatous reactions, or lymph node enlargement[75].

Although topical administration may reduce systemic exposure, given the abundance of blood vessels in the scalp, clinical trials are needed to compare whether the degree of systemic absorption of mesotherapy or microneedling in combination with dutasteride solution is less than that following oral dutasteride administration. In addition to focusing on efficacy, researchers should also monitor androgen levels and psychological status in these trials. We look forward to large-scale clinical trials and standardized treatment protocols in the future.

Liposomes or nanoparticles of dutasteride remain in the phase of animal experimentation and have yet to undergo clinical trials. They can reduce the adverse effects associated with systemic exposure to dutasteride and avoid the drawbacks of poor water solubility of dutasteride, while reducing skin irritation, with good hair follicle targeting, drug stability, and long-lasting effects. Future researches still need to fully evaluate the pharmacokinetics, pharmacodynamics and toxicology of dutasteride liposomes or nanoparticles in animal experimentation, and optimize their preparation process to ensure the stability of drug quality. The data from animal experimentation will then be summarized, comprehensively analyzed, and evaluated for safety in clinical trials. After that, the researchers can then submit a clinical trial application to the drug regulatory agency and, after receiving approval, recruit healthy volunteers to evaluate its safety and pharmacokinetic properties in humans. Finally, AGA patients will be selected for randomized, double-blind, placebo-controlled trials to assess the efficacy and safety of the drug.

Limitation

We selected only the PubMed database as the source of our literature. Due to economic and technical constraints, a very small number of citations were not available in full text for deeper analysis.

Conclusion

The efficacy of oral dutasteride is better than finasteride, and their tolerability is similar. Most adverse events are mild and reversible. It is an effective option for the treatment of AGA. Mesotherapy with dutasteride can be effective in patients with AGA, but standardized treatment protocols and large-scale clinical trials are needed to further validate its efficacy and safety. Microneedling combined with dutasteride solution also has its own unique efficacy for treating AGA. Liposomes or lipid nanoparticles of dutasteride are still under development and may become a more optimized topical agent in the future.

Statements

Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Sources

This study was supported by a grant from the National Natural Science Foundation of China (No. 81972954).

Author Contributions

Y.B.D. and C.F.W. contributed to the conception and design of the work, acquisition, analysis, and interpretation of data for the work, and drafting and revising of the submitted work. L.B.B. and Y.M.D. contributed to the analysis and interpretation of data for this work and critically revising this work. C.P.L. and M.Z. contributed to the acquisition of data for this work as well as critically revising this work. W.X.F. contributed to the conception and design of the work and critically revised it. All authors gave final approval for this work.

References

1. Lolli F, Pallotti F, Rossi A, Fortuna MC, Caro G, Lenzi A, et al. Androgenetic alopecia: a review. Endocrine. 2017;57(1):9-17. Epub 20170328. doi: 10.1007/s12020-017-1280-y. PubMed PMID: 28349362.

2. Bertoli MJ, Sadoughifar R, Schwartz RA, Lotti TM, Janniger CK. Female pattern hair loss: A comprehensive review. Dermatol Ther. 2020;33(6):e14055. Epub 20200831. doi: 10.1111/dth.14055. PubMed PMID: 32700775.

3. Hamilton JB. Patterned loss of hair in man; types and incidence. Ann N Y Acad Sci. 1951;53(3):708-28. doi: 10.1111/j.1749-6632.1951.tb31971.x. PubMed PMID: 14819896.

4. Norwood OT. Incidence of female androgenetic alopecia (female pattern alopecia). Dermatol Surg. 2001;27(1):53-4. PubMed PMID: 11231244.

5. Wang TL, Zhou C, Shen YW, Wang XY, Ding XL, Tian S, et al. Prevalence of androgenetic alopecia in China: a community-based study in six cities. Br J Dermatol. 2010;162(4):843-7. Epub 20090122. doi: 10.1111/j.1365-2133.2010.09640.x. PubMed PMID: 20105167.

6. Khumalo NP, Jessop S, Gumedze F, Ehrlich R. Hairdressing and the prevalence of scalp disease in African adults. Br J Dermatol. 2007;157(5):981-8. Epub 20070824. doi: 10.1111/j.1365-2133.2007.08146.x. PubMed PMID: 17725667.

7. Ceruti JM, Leirós GJ, Balañá ME. Androgens and androgen receptor action in skin and hair follicles. Mol Cell Endocrinol. 2018;465:122-33. Epub 20170912. doi: 10.1016/j.mce.2017.09.009. PubMed PMID: 28912032.

8. Randall VA. Androgens and hair growth. Dermatol Ther. 2008;21(5):314-28. doi: 10.1111/j.1529-8019.2008.00214.x. PubMed PMID: 18844710.

9. Piérard-Franchimont C, Piérard GE. Teloptosis, a turning point in hair shedding biorhythms. Dermatology. 2001;203(2):115-7. doi: 10.1159/000051723. PubMed PMID: 11586007.

10. Asada Y, Sonoda T, Ojiro M, Kurata S, Sato T, Ezaki T, Takayasu S. 5 alpha-reductase type 2 is constitutively expressed in the dermal papilla and connective tissue sheath of the hair follicle in vivo but not during culture in vitro. J Clin Endocrinol Metab. 2001;86(6):2875-80. doi: 10.1210/jcem.86.6.7545. PubMed PMID: 11397903.

11. Sánchez P, Serrano-Falcón C, Torres JM, Serrano S, Ortega E. 5α-Reductase isozymes and aromatase mRNA levels in plucked hair from young women with female pattern hair loss. Arch Dermatol Res. 2018;310(1):77-83. Epub 20171128. doi: 10.1007/s00403-017-1798-0. PubMed PMID: 29185104.

12. U.S. Food and Drug Administration. Avodart[Internet]. [cited 2024 March 1]Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

13. Ministry of Food and Drug Safety[Internet]. [cited 2024 March 1]. Available from: https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCache?cacheSeq=200409982aupdateTs2024-02-10%2019:57:48.0b

14. Pharmaceuticals and Medical Devices Agency[Internet]. [cited 2024 March 1]. Available from: https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/480235_249900AM1031_1_06

15. 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;55(6):1014-23. doi: 10.1016/j.jaad.2006.05.007. PubMed PMID: 17110217.

16. Hobo Y, Nishikawa J, Taniguchi Asai N, Yoneyama K, Watanabe Y, Miyashiro Y, Fujikata A. Evaluation of the therapeutic effects of AGA drugs by measuring finasteride, dutasteride, and dihydrotestosterone in hair. Clin Chim Acta. 2023;547:117456. Epub 20230628. doi: 10.1016/j.cca.2023.117456. PubMed PMID: 37385468.

17. Traish AM. 5α-reductases in human physiology: an unfolding story. Endocr Pract. 2012;18(6):965-75. doi: 10.4158/ep12108.Ra. PubMed PMID: 23246684.

18. Keam SJ, Scott LJ. Dutasteride: a review of its use in the management of prostate disorders. Drugs. 2008;68(4):463-85. doi: 10.2165/00003495-200868040-00008. PubMed PMID: 18318566.

19. Gubelin Harcha W, Barboza Martínez J, Tsai TF, 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):489-98.e3. Epub 20140109. doi: 10.1016/j.jaad.2013.10.049. PubMed PMID: 24411083.

20. 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;63(2):252-8. Epub 20100603. doi: 10.1016/j.jaad.2009.09.018. PubMed PMID: 20605255.

21. Stough D. Dutasteride improves male pattern hair loss in a randomized study in identical twins. J Cosmet Dermatol. 2007;6(1):9-13. doi: 10.1111/j.1473-2165.2007.00297.x. PubMed PMID: 17348989.

22. Shanshanwal SJ, 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. doi: 10.4103/0378-6323.188652. PubMed PMID: 27549867.

23. Tsunemi Y, Irisawa R, Yoshiie H, Brotherton B, Ito H, Tsuboi R, et al. Long-term safety and efficacy of dutasteride in the treatment of male patients with androgenetic alopecia. J Dermatol. 2016;43(9):1051-8. Epub 20160219. doi: 10.1111/1346-8138.13310. PubMed PMID: 26893187.

24. Chung HC, Lee S, Lee WS. Long-term efficacy and safety of the dual 5-alpha reductase blocker dutasteride on male androgenetic alopecia patients. J Dermatol. 2017;44(12):1408-9. Epub 20161218. doi: 10.1111/1346-8138.13710. PubMed PMID: 27988928.

25. Vañó-Galván S, Saceda-Corralo D, Moreno-Arrones OM, Rodrigues-Barata R, Morales C, Gil-Redondo R, et al. Effectiveness and safety of oral dutasteride for male androgenetic alopecia in real clinical practice: A descriptive monocentric study. Dermatol Ther. 2020;33(1):e13182. Epub 20191218. doi: 10.1111/dth.13182. PubMed PMID: 31820540.

26. Kang MJ, Choi JY, Sim WY, Lew BL. 5α-Reductase inhibitors in men aged 50 years or older with androgenetic alopecia: A retrospective study. J Am Acad Dermatol. 2021;84(1):172-3. Epub 20200419. doi: 10.1016/j.jaad.2020.04.051. PubMed PMID: 32320771.

27. Choi GS, Sim WY, Kang H, Huh CH, Lee YW, Shantakumar S, et al. Long-Term Effectiveness and Safety of Dutasteride versus Finasteride in Patients with Male Androgenic Alopecia in South Korea: A Multicentre Chart Review Study. Ann Dermatol. 2022;34(5):349-59. doi: 10.5021/ad.22.027. PubMed PMID: 36198626; PubMed Central PMCID: PMC9561294.

28. Choi S, Kwon SH, Sim WY, Lew BL. Long-term efficacy and safety of dutasteride 0.5 mg in Korean men with androgenetic alopecia: 5-year data demonstrating clinical improvement with sustained efficacy. J Dermatol. 2024. Epub 20240206. doi: 10.1111/1346-8138.17138. PubMed PMID: 38321615.

29. Jung JY, Yeon JH, Choi JW, Kwon SH, Kim BJ, Youn SW, et al. Effect of dutasteride 0.5 mg/d in men with androgenetic alopecia recalcitrant to finasteride. Int J Dermatol. 2014;53(11):1351-7. Epub 20140605. doi: 10.1111/ijd.12060. PubMed PMID: 24898559.

30. Traish AM. Post-finasteride syndrome: a surmountable challenge for clinicians. Fertil Steril. 2020;113(1):21-50. doi: 10.1016/j.fertnstert.2019.11.030. PubMed PMID: 32033719.

31. Tsai TF, Choi GS, Kim BJ, Kim MB, Ng CF, Kochhar P, et al. Prospective randomized study of sexual function in men taking dutasteride for the treatment of androgenetic alopecia. J Dermatol. 2018;45(7):799-804. Epub 20180418. doi: 10.1111/1346-8138.14329. PubMed PMID: 29667763; PubMed Central PMCID: PMC6055634.

32. 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;92(5):1659-65. Epub 20070213. doi: 10.1210/jc.2006-2203. PubMed PMID: 17299062.

33. Stoffel-Wagner B. Neurosteroid biosynthesis in the human brain and its clinical implications. Ann N Y Acad Sci. 2003;1007:64-78. doi: 10.1196/annals.1286.007. PubMed PMID: 14993041.

34. Melcangi RC, Santi D, Spezzano R, Grimoldi M, Tabacchi T, Fusco ML, et al. Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients. J Steroid Biochem Mol Biol. 2017;171:229-35. Epub 20170410. doi: 10.1016/j.jsbmb.2017.04.003. PubMed PMID: 28408350.

35. Caruso D, Abbiati F, Giatti S, Romano S, Fusco L, Cavaletti G, Melcangi RC. Patients treated for male pattern hair with finasteride show, after discontinuation of the drug, altered levels of neuroactive steroids in cerebrospinal fluid and plasma. J Steroid Biochem Mol Biol. 2015;146:74-9. Epub 20140406. doi: 10.1016/j.jsbmb.2014.03.012. PubMed PMID: 24717976.

36. Deng T, Duan X, He Z, Zhao Z, Zeng G. Association Between 5-Alpha Reductase Inhibitor Use and The Risk of Depression: A Meta-Analysis. Urol J. 2020;18(2):144-50. Epub 20200823. doi: 10.22037/uj.v16i7.5866. PubMed PMID: 32869255.

37. Garcia-Argibay M, Hiyoshi A, Fall K, Montgomery S. Association of 5α-Reductase Inhibitors With Dementia, Depression, and Suicide. JAMA Netw Open. 2022;5(12):e2248135. Epub 20221201. doi: 10.1001/jamanetworkopen.2022.48135. PubMed PMID: 36547981; PubMed Central PMCID: PMC9857015.

38. Choi BK, Cheon K, Cho BH, Jung JW, Lee KY. Cerebral Venous Sinus Thrombosis Associated with Dutasteride Use. Yonsei Med J. 2020;61(6):553-5. doi: 10.3349/ymj.2020.61.6.553. PubMed PMID: 32469180; PubMed Central PMCID: PMC7255996.

39. Traish AM. Negative Impact of Testosterone Deficiency and 5α-Reductase Inhibitors Therapy on Metabolic and Sexual Function in Men. Adv Exp Med Biol. 2017;1043:473-526. doi: 10.1007/978-3-319-70178-3_22. PubMed PMID: 29224108.

40. Traish AM. Health Risks Associated with Long-Term Finasteride and Dutasteride Use: It's Time to Sound the Alarm. World J Mens Health. 2020;38(3):323-37. Epub 20200320. doi: 10.5534/wjmh.200012. PubMed PMID: 32202088; PubMed Central PMCID: PMC7308241.

41. Gupta AK, Polla Ravi S, Wang T, Talukder M, Starace M, Piraccini BM. Systematic review of mesotherapy: a novel avenue for the treatment of hair loss. J Dermatolog Treat. 2023;34(1):2245084. doi: 10.1080/09546634.2023.2245084. PubMed PMID: 37558233.

42. Sobhy N, Aly H, A E, M E. Evaluation of the effect of injection of dutasteride as mesotherapeutic tool in treatment of androgenetic alopecia in males. Our Dermatology Online. 2013;4:40-5. doi: 10.7241/ourd.20131.08.

43. Moftah N, Moftah N, Abd-Elaziz G, Ahmed N, Hamed Y, Ghannam B, Ibrahim M. Mesotherapy using dutasteride-containing preparation in treatment of female pattern hair loss: photographic, morphometric and ultrustructural evaluation. J Eur Acad Dermatol Venereol. 2013;27(6):686-93. Epub 20120406. doi: 10.1111/j.1468-3083.2012.04535.x. PubMed PMID: 22486925.

44. Abdallah M, el-zawahry K, Besar H. Mesotherapy using Dutasteride-Containing Solution in Male Pattern Hair Loss: a Controlled Pilot Study. Journal of Pan-Arab League of Dermatologists. 2009;20.

45. Shin JY, Kim J, Choi YH, Kang NG, Lee S. Dexpanthenol Promotes Cell Growth by Preventing Cell Senescence and Apoptosis in Cultured Human Hair Follicle Cells. Curr Issues Mol Biol. 2021;43(3):1361-73. Epub 20210928. doi: 10.3390/cimb43030097. PubMed PMID: 34698060; PubMed Central PMCID: PMC8929036.

46. Samadi A, Ketabi Y, Firooz R, Firooz A. Efficacy of intramuscular injections of biotin and dexpanthenol in the treatment of diffuse hair loss: A randomized, double-blind controlled study comparing two brands. Dermatol Ther. 2022;35(9):e15695. Epub 20220715. doi: 10.1111/dth.15695. PubMed PMID: 35791704.

47. Melo DF, Saceda-Corralo D, Tosti A, Weffort F, Carla Jorge M, de Barros CC, et al. Frontal edema due to mesotherapy for androgenetic alopecia: A case series. Dermatol Ther. 2022;35(2):e15247. Epub 20211213. doi: 10.1111/dth.15247. PubMed PMID: 34877759.

48. Magdaleno-Tapial J, Valenzuela-Oñate C, García-Legaz-Martínez M, Martínez-Domenech Á, Alonso-Carpio M, Talamantes CS, et al. Angioedema-like contact dermatitis caused by mesotherapy with dutasteride. Contact Dermatitis. 2020;83(3):246-7. Epub 20200701. doi: 10.1111/cod.13585. PubMed PMID: 32356373.

49. Reguero Del Cura L, De Quintana Sancho A, Rubio Lombraña M, López Sundh AE, González López MA. Two Cases of Paradoxical Nonscarring Alopecia after Mesotherapy with Dutasteride. Skin Appendage Disord. 2022;8(1):46-8. Epub 20210818. doi: 10.1159/000518043. PubMed PMID: 35118130; PubMed Central PMCID: PMC8787501.

50. Fertig RM, Gamret AC, Cervantes J, Tosti A. Microneedling for the treatment of hair loss? J Eur Acad Dermatol Venereol. 2018;32(4):564-9. Epub 20171221. doi: 10.1111/jdv.14722. PubMed PMID: 29194786.

51. Sánchez-Meza E, Ocampo-Candiani J, Gómez-Flores M, Herz-Ruelas ME, Ocampo-Garza J, Orizaga YQTL, et al. Microneedling plus topical dutasteride solution for androgenetic alopecia: a randomized placebo-controlled study. J Eur Acad Dermatol Venereol. 2022;36(10):e806-e8. Epub 20220616. doi: 10.1111/jdv.18285. PubMed PMID: 35648446.

52. Olszewska M, Rudnicka L. Effective treatment of female androgenic alopecia with dutasteride. J Drugs Dermatol. 2005;4(5):637-40. PubMed PMID: 16167423.

53. Dubin C, Lamb A. Hair regrowth in endocrine therapy alopecia with dutasteride treatment in woman with estrogen positive breast cancer. JAAD Case Rep. 2023;35:5-7. Epub 20230309. doi: 10.1016/j.jdcr.2023.02.021. PubMed PMID: 37034026; PubMed Central PMCID: PMC10073935.

54. Boersma IH, Oranje AP, Grimalt R, Iorizzo M, Piraccini BM, Verdonschot EH. The effectiveness of finasteride and dutasteride used for 3 years in women with androgenetic alopecia. Indian J Dermatol Venereol Leprol. 2014;80(6):521-5. doi: 10.4103/0378-6323.144162. PubMed PMID: 25382509.

55. Sharma P, Jain D, Maithani M, Mishra SK, Khare P, Jain V, Singh R. Development and characterization of dutasteride bearing liposomal systems for topical use. Curr Drug Discov Technol. 2011;8(2):136-45. doi: 10.2174/157016311795563901. PubMed PMID: 21513483.

56. Radtke M, Patzelt A, Knorr F, Lademann J, Netz RR. Ratchet effect for nanoparticle transport in hair follicles. Eur J Pharm Biopharm. 2017;116:125-30. Epub 20161031. doi: 10.1016/j.ejpb.2016.10.005. PubMed PMID: 27810473.

57. Matos BN, Reis TA, Gratieri T, Gelfuso GM. Chitosan nanoparticles for targeting and sustaining minoxidil sulphate delivery to hair follicles. Int J Biol Macromol. 2015;75:225-9. Epub 20150131. doi: 10.1016/j.ijbiomac.2015.01.036. PubMed PMID: 25647618.

58. Angelo T, El-Sayed N, Jurisic M, Koenneke A, Gelfuso GM, Cunha-Filho M, et al. Effect of physical stimuli on hair follicle deposition of clobetasol-loaded Lipid Nanocarriers. Sci Rep. 2020;10(1):176. Epub 20200113. doi: 10.1038/s41598-019-56760-w. PubMed PMID: 31932640; PubMed Central PMCID: PMC6957495.

59. Noor NM, Umar S, Abdul-Aziz A, Sheikh K, Somavarapu S. Engineered Dutasteride-Lipid Based Nanoparticle (DST-LNP) System Using Oleic and Stearic Acid for Topical Delivery. Bioengineering (Basel).

2022;9(1). Epub 20220101. doi: 10.3390/bioengineering9010011. PubMed PMID: 35049720; PubMed Central PMCID: PMC8773293.

60. Ushirobira CY, Afiune LAF, Pereira MN, Cunha-Filho M, Gelfuso GM, Gratieri T. Dutasteride nanocapsules for hair follicle targeting: Effect of chitosan-coating and physical stimulus. Int J Biol Macromol. 2020;151:56-61. Epub 20200214. doi: 10.1016/j.ijbiomac.2020.02.143. PubMed PMID: 32068053.

61. Cash TF. The psychology of hair loss and its implications for patient care. Clin Dermatol. 2001;19(2):161-6. doi: 10.1016/s0738-081x(00)00127-9. PubMed PMID: 11397595.

62. Alfonso M, Richter-Appelt H, Tosti A, Viera MS, García M. The psychosocial impact of hair loss among men: a multinational European study. Curr Med Res Opin. 2005;21(11):1829-36. doi: 10.1185/030079905x61820. PubMed PMID: 16307704.

63. Elsaie LT, Elshahid AR, Hasan HM, Soultan F, Jafferany M, Elsaie ML. Cross sectional quality of life assessment in patients with androgenetic alopecia. Dermatol Ther. 2020;33(4):e13799. Epub 20200709. doi: 10.1111/dth.13799. PubMed PMID: 32520416.

64. 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. doi: 10.1016/s0190-9622(98)70007-6. PubMed PMID: 9777765.

65. Yoshitake T, Takeda A, Ohki K, Inoue Y, Yamawaki T, Otsuka S, et al. Five-year efficacy of finasteride in 801 Japanese men with androgenetic alopecia. J Dermatol. 2015;42(7):735-8. Epub 20150422. doi: 10.1111/1346-8138.12890. PubMed PMID: 25903108.

66. Zhou Z, Song S, Gao Z, Wu J, Ma J, Cui Y. The efficacy and safety of dutasteride compared with finasteride in treating men with androgenetic alopecia: a systematic review and meta-analysis. Clin Interv Aging. 2019;14:399-406. Epub 20190220. doi: 10.2147/cia.S192435. PubMed PMID: 30863034; PubMed Central PMCID: PMC6388756.

67. Gupta AK, Venkataraman M, Talukder M, Bamimore MA. Relative Efficacy of Minoxidil and the 5-α Reductase Inhibitors in Androgenetic Alopecia Treatment of Male Patients: A Network Meta-analysis. JAMA Dermatol. 2022;158(3):266-74. doi: 10.1001/jamadermatol.2021.5743. PubMed PMID: 35107565; PubMed Central PMCID: PMC8811710.

68. Debruyne F, Barkin J, van Erps P, Reis M, Tammela TL, Roehrborn C. Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. Eur Urol. 2004;46(4):488-94; discussion 95. doi: 10.1016/j.eururo.2004.05.008. PubMed PMID: 15363566.

69. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. Eur J Dermatol. 2002;12(1):38-49. PubMed PMID: 11809594.

70. Lee S, Lee YB, Choe SJ, Lee WS. Adverse Sexual Effects of Treatment with Finasteride or Dutasteride for Male Androgenetic Alopecia: A Systematic Review and Meta-analysis. Acta Derm Venereol. 2019;99(1):12-7. doi: 10.2340/00015555-3035. PubMed PMID: 30206635.

71. Mondaini N, Gontero P, Giubilei G, Lombardi G, Cai T, Gavazzi A, Bartoletti R. Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon? J Sex Med. 2007;4(6):1708-12. Epub 20070726. doi: 10.1111/j.1743-6109.2007.00563.x. PubMed PMID: 17655657.

72. Saengmearnuparp T, Lojanapiwat B, Chattipakorn N, Chattipakorn S. The connection of 5-alpha reductase inhibitors to the development of depression. Biomed Pharmacother. 2021;143:112100. Epub 20210831. doi: 10.1016/j.biopha.2021.112100. PubMed PMID: 34479019.

73. Sarkar RR, Parsons JK, Bryant AK, Ryan ST, Kader AK, McKay RR, et al. Association of Treatment With 5α-Reductase Inhibitors With Time to Diagnosis and Mortality in Prostate Cancer. JAMA Intern Med.

2019;179(6):812-9. doi: 10.1001/jamainternmed.2019.0280. PubMed PMID: 31058923; PubMed Central PMCID: PMC6503564.

74. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med. 2010;362(13):1192-202. doi: 10.1056/NEJMoa0908127. PubMed PMID: 20357281.

75. Gupta AK, Quinlan EM, Venkataraman M, Bamimore MA. Microneedling for Hair Loss. J Cosmet Dermatol. 2022;21(1):108-17. Epub 20211029. doi: 10.1111/jocd.14525. PubMed PMID: 34714971.

Figure Legends

Fig. 1. Flowchart describing the selection process of the included literature.

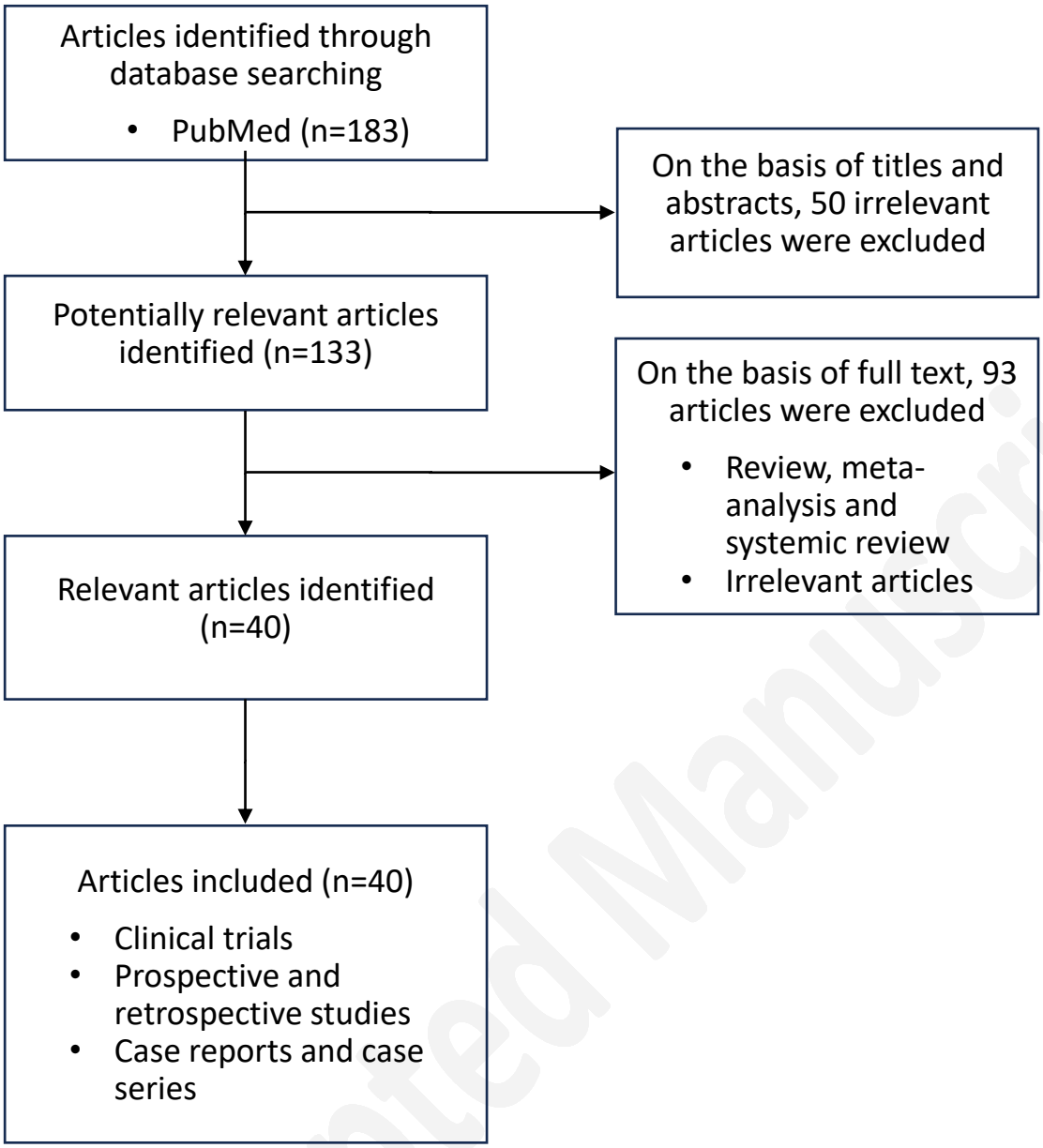

Table 1: Mean change from baseline to 24 weeks in target area hair density (unit: number of hairs/cm^2).

Different groups	Gubelin *et al.* n=732	Olsen *et al.* n=274	Eun *et al.* n=148	Stough *et al.* n=27	Shanshanwal *et al.* n=72
0.1mg Dutasteride	12.43	15.49	/	/	/
0.5mg Dutasteride	17.68	18.67	12.20	6.8	23.14
Finasteride[1]	11.15	14.92	/	/	4.30
Placebo	-0.97	-6.37	4.70	-11.0	/

Finasteride[1]: Olsen et al.: 5 mg; Gubelin et al. and Shanshanwal et al.: 1 mg; "/" means "not studied".

Table 2: Proportion of subjects experiencing sexual adverse events from baseline to 24 weeks (unit: %).

	Gubelin *et al.*				**Olsen *et al.*[4]**				**Eun *et al.***		**Tsai *et al.***	
	Placebo	0.1mg Dut[2]	0.5mg Dut	1.0mg Fin[3]	Placebo	0.1mg Dut	0.5mg Dut	5.0mg Fin	Placebo	0.5mg Dut	Placebo	0.5mg Dut
	n=181	n=188	n=184	n=179	n=64	n=72	n=68	n=70	n=75	n=73	N=59	N=58
Sexual AEs[1]	6.6	12.8	10.3	13.4	8	7	2	8	4.0	4.1	8	16
Altered libido	1.7	6.9	4.9	6.7	3	3	1	4	2.7	4.1	3	2
Impotence	3.9	3.7	5.4	6.1	5	0	0	1	1.3	0	5	12
Ejaculation disorders	3.3	4.8	3.3	3.9	0	4	1	3	1.3	0	0	2
Breast enlargement	0	0.5	0.5	0.6			/			/		/
Breast tenderness	0	0.5	0	0			/			/		/

AEs[1]: adverse events. Dut[2]: dutasteride; Fin[3]: finasteride; "/" means "not studied". Olsen et al.[4]: the study didn't provide the proportion of sexual AEs, and the results are obtained by summing the rates of partial sexual AEs. Altered libido includes decreased libido, sexual dysfunction, loss of libido and libido disorder. Impotence includes erectile dysfunction and organic erectile dysfunction

Table 3: Proportion of subjects with photographic improvement at the end of treatment (unit: %).

Different groups	Sobhy *et al.* n=90	Moftah *et al.* n=126	Abdallah *et al.* n=28
Dutasteride preparations	80	62.8	92.9
Dutasteride	30	/	/
Saline	30	17.5	28.6

"/" means "not studied".