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## How to treat androgenetic alopecia – the most common form of hair loss. A review

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## **Abstract:**

### **Introduction and purpose**

Androgenetic alopecia (AGA) is one of the most common causes of baldness worldwide. It affects up to 80% of men by the age of 70 and up to 40% of postmenopausal women. In AGA etiology and pathogenesis, the three essential components play a key role - genetic inheritance, patient age and hormonal effects of androgens. In the following review, we have described the available FDA-approved and off-label treatments for AGA, along with their efficacy and potential side effects that should always be considered to prevent treatment discontinuation by the patients.

### **The state of knowledge**

The pathogenesis of AGA is based on inherited dihydrotestosterone (DHT) sensitivity in the scalp skin, which leads to progressive hair loss. The literature documents the effectiveness of several treatments with different mechanisms of action in AGA therapy, but only topical minoxidil and oral finasteride gained FDA approval so far. Minoxidil acts by the blood vessels dilatation that increases the flow of oxygenated and growth factor-enriched blood to

the hair follicles in the skin. 5-alpha reductase inhibitors, such as finasteride and dutasteride are another therapeutic option. They act by the inhibition of 5-alpha reductase, the enzyme which converts testosterone to DHT - the main causative agent of androgenetic alopecia. Recently, topical applications of minoxidil and finasterid, along with completely new emerging treatments for androgenetic alopecia are gaining popularity among doctors and patients.

### **Summary**

This review describes current treatments for AGA, considering their efficacy, optimal doses, and the most common side effects. An important fact to emphasise is that androgenetic alopecia is based on a genetic predisposition, and treatment requires long-term use. For this reason, when choosing a medication, it is essential to cooperate with the patient and combine different therapeutic methods to achieve the desirable outcome while avoiding adverse reactions.

**Keywords:** Androgenetic alopecia, male pattern hair loss, female pattern hair loss, androgens, health, hair

### **Introduction and purpose**

One of the most common causes of progressive hair loss worldwide is androgenetic alopecia (AGA), also known as male pattern hair loss (MPHL) or female pattern hair loss (FPHL) (1). Based on the limited prevalence data available, it is known that up to 30% of white men will experience AGA by the age of 30, up to 50% by the age of 50, and up to 80% by the age of 70 (2,3). However, in women, the progressive loss of terminal hair of the scalp is more common after menopause, and it can affect up to 40% of women by 60 to 69 years of age (4). AGA manifests in a distinct pattern for each sex. MPHL typically involves progressive thinning of hair in the crown and frontal regions of the scalp, often accompanied by a receding hairline (5). In contrast, FPHL is marked by diffuse hair loss and thinning across the frontal and vertex areas of the scalp while generally preserving the frontal hairline (6). In both cases, androgens play a central role, and the pattern of hair loss is determined by the different characteristic distribution of androgen receptors within the scalp (3).

The androgenetic alopecia pathogenesis is based on inherited dihydrotestosterone (DHT) sensitivity in the scalp skin. DHT is an androgen hormone that affects the hair follicles,

causing their miniaturization and preventing them from completely penetrating the epidermis; therefore, hair shedding occurs in susceptible patients. The effect especially regards the male population (7). The crucial role of DHT is confirmed by the absence of this condition in men with steroid 5 $\alpha$ -reductase (5AR) type II deficiency – the enzyme responsible for testosterone conversion to dihydrotestosterone (7,8). Another argument is that baldness does not develop in men who have not reached sexual maturity. There is a strong genetic predisposition behind the development of AGA. Twin studies demonstrate high concordance rates, between 80% and 90%, for monozygotic twins. Moreover, the risk significantly increases if there is a family history of AGA, not only on the father's side but also on the mother's side (9). In androgenetic alopecia, genetic inheritance, endocrine factors and patient age are three important determinants, all influenced by each other. The incidence of AGA increases with the patient's age, and despite the genetic predisposition to baldness, the alopecia will not occur if endocrine factors - androgens are absent (10). These factors mean that the treatment of androgenetic alopecia is not straightforward and often requires a comprehensive view. In this review, we focus on the various treatments available for AGA. We describe the effectiveness of these methods and the potential risks that are associated with each of these procedures.

## **The state of knowledge**

### **1. Treatment**

In order to successfully treat androgenetic alopecia, we do not have a wide range of well-established, scientifically proven options to choose from. We can choose between oral and topical minoxidil and 5- $\alpha$  5-reductase inhibitors—finasteride and dutasteride. Among those, only topical minoxidil in concentrations of 2% and 5% and oral finasteride at the dose of 1 mg have gained FDA approval in men and only topical minoxidil in women (3).

#### **1.1. Minoxidil**

Minoxidil is a drug that foremost has vasodilatory properties, and its first administration was for severe recurrent hypertension in the 1970s. When it was discovered that 20% of patients using the drug develop excessive hair growth as a complication, the idea of using minoxidil to treat non-scarring alopecia was born (11,12). In 1988, topical use of minoxidil was approved for alopecia treatment (11). The mechanism of action is still not completely understood. Minoxidil causes the upregulation of vascular endothelial growth factor (VEGF)

that dilates the vessels and allows a more significant inflow of oxygenated and growth factor-rich blood to the hair follicles in the skin, which promotes hair growth. Minoxidil also activates potassium channels of the smooth muscle of peripheral arteries, prolonging the anagen and shortening the telogen phase of the hair. Apart from androgenetic alopecia, minoxidil can also be used in autoimmune alopecia due to the immunomodulatory properties of the suppression of the T-lymphocytes activation process (12).

Topical use of minoxidil is based on the use of 2% and 5% topical solutions and 5% foam (13). Despite being an effective and well-documented treatment option (12), minoxidil therapy is often associated with poor compliance because of the necessity to apply the product on the scalp, the product consistency that causes a change in hair texture, the scalp irritation, and the temporary period of hair loss that occurs at the beginning of the application period - the last factor especially can cause premature termination of the drug (14).

Regarding the side effects of minoxidil therapy, there is a risk of hypertrichosis in 4% of patients (0,5% according to post-marketing data) (15). There were also reports of irritant or allergic contact dermatitis or seborrheic dermatitis exacerbation after the medication. Patients complain of itchiness and scaling. In case of irritant contact dermatitis or seborrheic dermatitis exacerbation, the therapy can be continued while anti-inflammatory agents like tar shampoo or topical corticosteroids are administered. In-contact, allergic dermatitis patch tests should be conducted to confirm the allergen causing the reaction because the chances are that propylene glycol sensitivity occurs, which can be easily managed with alternative solvent use. Unfortunately, with a confirmed allergy to minoxidil, patients can no longer be treated with the substance, even in topical formulations (16). Unfortunately, the effects of minoxidil therapy are not lifelong, and the treatment should be continuous. According to the study by Price et al. (17), right after treatment cessation, patients presented rapid hair shedding and decreased hair counts, and by 24 weeks after treatment, the hair weight and hair count almost equalled the placebo and untreated group. This observation shows that minoxidil is only a symptomatic treatment and does not cure the genetic predisposition for androgenetic alopecia.

Recently, there have been reports in the literature about the effectiveness and safety of oral minoxidil therapy in androgenetic alopecia (14). Presently, oral minoxidil can be used only off-label in this indication (18). Because of the high price, limited absorption, the need for reapplication and problems with consistency and cosmetic outcome of topical minoxidil

solution, there is hope for achieving better bioavailability and treatment efficacy with the oral formulation (11). Gupta et al. (19) proposed to start the therapy with a dose of 1.25 mg/day in both men and women. The dose can subsequently be raised to 2.5 mg/day within 2-3 months, and further dose increase is possible only in male patients to 5 mg/day after an additional 2-3 months. Overall, during minoxidil therapy, women require lower doses than men to achieve maximal efficacy – 0.25-5 mg and 1.25-5.0 mg, respectively or 0.25-1.25 mg and 2.5-5 mg, respectively, according to other sources (11,14). More extensive studies comparing the effectiveness of different doses are needed to determine the best treatment protocol and dose levels. In a Jimenez-Cauhe et al. (13) retrospective study, 10 men were given 2.5 mg of oral minoxidil per day, and 31 men were given 5 mg/day for 12 months. In the results, clinical improvement was seen in 90.2% of patients, and 26.8% of them presented a marked improvement interpreted as a score of 1 point or more on the Norwood-Hamilton scale; 9.8% of patients had alopecia stabilization, and no patient deteriorated. Vastarella et al. (20) evaluated the effects of oral minoxidil at a dose of 0.5 mg/day and then 1.5 mg and 2 mg/day in 12 women with Ludwig scale I-3-III and failure to the prior treatment. After a 24-week therapy, a statistically significant improvement in the total average hair density and the total number of hairs per unit was observed in the frontal area.

In that case, does the oral form have better therapeutic effects than the topical one? Pehna et al. (21), on 68 male participants, compared the effectiveness, tolerance, and safety of 5 mg oral minoxidil to 5% topical minoxidil twice daily in the period of 24 weeks. Both treatment methods improved the patient's outcome. Oral minoxidil had better results on the vertex, but such correlation was not observed on the scalp. Overall, the advantage of oral minoxidil compared to topical therapy was not proven. In the study by Ramos et al. (22), similar conclusions were made comparing 1 mg oral minoxidil to 5% topical minoxidil in 52 women. However, the researchers state the advantage of choosing minoxidil in a group of patients with poor compliance or who have experienced adverse effects with topical minoxidil.

Oral minoxidil's side effects reported in the literature are minor, and the main concern is hypertrichosis in the face and body areas. Cardiovascular changes might include lowered blood pressure, postural hypotension, dizziness, increased heart rate, lower limb oedema, and small EKG changes (14). The adverse events are more likely to occur at the higher therapeutic dose - 5 mg rather than 2.5 mg (13,14). It is essential to remember the hypotensive properties of minoxidil and to control the patient's blood pressure before prescribing it, especially in

combination with another blood pressure-lowering drug. Fortunately, with doses like 0.25–5 mg daily, the impact on systemic pressure was minor (11). Postural hypotension can be treated with 50 mg of sodium chloride daily (23). Similar to topical solutions, oral minoxidil is also associated with temporary hair loss at the beginning of the therapy, which can last approximately 3-6 weeks. It requires informing the patients to prevent treatment discontinuation (14). Serious systemic reactions are rarely reported. However, cases of Steven Johnson syndrome or toxic necrolysis syndrome after hypertension treatment with minoxidil were described in the literature (24,25). To summarize, the side effects profile is, in fact, minimal and taking into consideration the problem that androgenetic alopecia is to the patients and the fact that there is a small choice of therapeutic substances possible to prescribe to all patients (oral finasteride or spironolactone are contraindicated in childbearing age), therapy with small doses of oral minoxidil has the potential for wider clinical use (11).

### **1.2. 5-alpha reductase inhibitors**

5-alpha reductase (5AR) inhibitors, finasteride and dutasteride, are commonly used in androgenetic alopecia treatment. Their gripping point in therapy is blockage of the 5-alpha reductase, the enzyme responsible for the conversion of testosterone to dihydrotestosterone that acts at the hair follicles level, causing a clinical picture of androgenetic alopecia (26,27). Three isoenzymes of 5AR receptors exist, with only I and II types participating in hair loss pathogenesis. Type I isoenzyme is present in the skin and its derivatives- sebaceous glands and hair follicles, whereas, above other locations of type II isoenzyme, the most significant to alopecia one is in the inner root sheath of hair follicles in the scalp, beard, and chest. Dutasteride inhibits type I 5AR isoenzyme three times stronger than finasteride and is also 100 times more potent in isoenzyme II inhibition (26).

According to Frankel et al. (28) study, a dose of 0.05 mg finasteride can reduce DHT levels in the scalp skin, remaining at the same point up to the highest tested dose of 5 mg. In Kaufman et al. (7) study on 1553 men, the first visible results of 1 mg finasteride therapy were noticed after three months of use, and they increased with the treatment continuation. The medication significantly increased hair count at time points of 1 and 2 years of treatment compared to placebo, which caused progressive hair shedding. The improved hair appearance was not only assessed by the investigators but also noticed by the patients. The positive impact of finasteride therapy on hair loss was also confirmed in Mella et al. (29) systematic

review of 10 papers. Some studies state that the biggest hair regrowth due to finasteride is observed after one year (30). Rossi et al. (31) showed that after ten years of continuous treatment with finasteride 1 mg per day, 21% of 113 men continued to improve, and 65% maintained positive treatment results. Only 14% of men experienced deterioration. Observing the results of treatment in the first year allows assumptions to be made about the results of long-term therapy, as some patients may not respond to treatment at all. However, a large proportion of those surveyed with no change after one year improved after that, keeping the positive trend. In female patients with androgenetic alopecia, off-label finasteride use in doses of 2.5 to 5 mg per day turned out to be effective. In comparison, the lower dose of 1 mg was connected with very little change (32).

On the basis of dutasteride's stronger inhibition of 5-alpha reductase alone, its more potent therapeutic effect in androgenetic alopecia may be presumed. Shanshanwal et al. (33) compared the activity of oral finasteride 1 mg with dutasteride 0.5 mg during 24-week therapy in 90 men with androgenetic alopecia. Their observations confirmed the validity of the assumption of higher activity of dutasteride - after 24 weeks, significantly greater hair regrowth was observed in the finasteride group, and moreover, significantly greater reversal of follicular miniaturization as measured by a reduction in the number of fine hairs per cm<sup>2</sup>. A similar conclusion of the superiority of 0.5 mg/day of dutasteride over 1 mg finasteride after 12 and 24 weeks was stated by Harcha et al. (34). The increase in the number and width of hairs after dutasteride was dose-dependent with a minimum therapeutic dose of 0.1 mg/d to observe effects. Regarding the long-term use of 0.5 mg dutasteride, the results of the 5-year treatment of men had comparable efficacy and adverse effect profile to the long-term use of 1 mg finasteride described in the literature (35). A conducted meta-analysis by Zhou et al. (36) agreed with the finding that dutasteride provided better efficacy than finasteride in the treatment of androgenetic alopecia, while the incidence of side effects, especially regarding sexual functions, was not statistically different between patients taking it. Oral dutasteride (0.5 mg/d) was approved for male AGA in Japan and South Korea (37). To summarize, dutasteride might be considered an effective treatment method in case of finasteride inefficiency (30).

5ARIs side effects are connected to their antiandrogenic activity. Those concerning sexual functions are the most frequently addressed. In men, the most frequently erectile dysfunction occurs, followed by ejaculatory dysfunction and loss of libido. Gynecomastia and



muscle atrophy can also occur. Some studies report that the symptoms tend to decrease over time. What is more, although there is no increase in prostate cancer incidence, a relationship between higher-grade neoplasms and taking 5ARIS was noted - fortunately, without any difference in overall survival after 18 years (26,30). In women, the matter of adverse effects is not well investigated enough in the long-term studies. However, among the reported ones, we can distinguish the risk of congenital disabilities in male fetuses, decreased libido, acne, skin dryness, headaches, gastrointestinal symptoms and menstrual abnormalities. There were also some reports of the connection between 5ARIs and depression, but currently, such a direct connotation is not proved and might concern only a particular group of individuals (26). It is worth noting that the use of these medications, similar to minoxidil treatment, should be continuous to maintain hair growth (26,30).

Due to side effects, the trials of topical finasteride application emerged, which can locally reduce DHT production in the hair follicle with diminished systemic activity (38). The topical 1% solutions are found to have a similar therapeutic activity to oral 1 mg/day tablets with no significant differences between the treated patients in terms of hair thickness, hair counts and the size of the bald area (39). What is more, the combination topical therapy of 5% minoxidil and 0.25% finasteride solutions was compared to the monotherapies with these medications by Rossi et al. (40) on 42 male participants with androgenetic alopecia. After three and six months, the study group presented a more considerable change in hair density with a statistical difference compared to the group treated with finasteride and a significantly higher global photographic assessment score than both monotherapies.

Adverse reactions after topical finasteride are mainly localized to the treatment area – patients can develop scalp itchiness, burning sensation, erythema and contact dermatitis. The risk of sexual dysfunction is reduced compared to systemic use (41).

In a meta-analysis of 23 trials by Gupta et al. (42), the efficiency of monotherapy in different doses and administration routes with 5-ARIs and minoxidil was investigated. The endpoints were changes in total and terminal hair count after the time of 24 and 48 weeks. Fifteen different treatment regimens were found in the studies considered and compared with each other. Total hair count at 24 weeks increased the most with the treatment with 0.5 mg/d of oral dutasteride, but the terminal hair count presented a greater increase while administering 5 mg/d of minoxidil. After 48 weeks, the corresponding result for total hair

count was 5 mg/d of finasteride, and for terminal hair count, it was 1 mg/d of finasteride. Overall, according to the researchers, 0.5 mg/d of oral dutasteride is probably the most effective alopecia treatment (the results of dutasteride's relative effectiveness after 48 weeks were unavailable) and further medications rank of decreasing efficacy goes as follows: 5 mg/d of oral finasteride, 5 mg/d of oral minoxidil, 1 mg/d of oral finasteride, 5% topical minoxidil, 2% topical minoxidil, and 0.25 mg/d of oral minoxidil.

### **1.3. Spironolactone**

Spironolactone, an aldosterone antagonist that binds and inhibits androgen receptors, is commonly used as a hypertensive agent and also has applications in the treatment of hirsutism and acne in the course of PCOS (30). Its off-label use in androgenetic alopecia in women is based on the mechanism of reduction of the levels of systemic androgens and inhibition of their tissue's receptors (38). According to Alissa et al. (43), systematic review and meta-analysis, oral spironolactone can be an effective therapeutic option, especially as a combination therapy. However, treatment outcomes are variable, suggesting individual susceptibility to the medication. The adverse effects occurred in 3.69%, and scalp itchiness or increased flaking were the most often encountered, but menstrual disorders and facial hypertrichosis after spironolactone are also possible. Hyperkalemia and postural hypotension prevalence were low. Topical spironolactone use might also be considered (30). Another antiandrogen, cyproterone, which inhibits the androgen receptor, is also sometimes used orally in androgenetic alopecia but only in female patients. On the other hand, flutamide, a nonsteroidal antiandrogen usefulness, is limited because of liver toxicity (38).

## **2. Other treatment options**

Recently, new treatments for androgenetic alopecia are entering clinical use and gaining their advocates. We can distinguish low-level laser therapy (LLLT), also known as photobiomodulation, whose ability to induce hair regrowth and prevent further recurrent hair loss is reported in the literature (44). LLT therapy uses wavelengths between 600 and 1100 nm. The photobiomodulation reportedly induces hair follicles to transition from the telogen phase back to the anagen phase, extends the anagen phase duration and prevents conversion to the catagen phase. Moreover, hair follicles with pseudo-vellus hair are stimulated to grow normal terminal hairs. According to Egger et al. (45), in a review of ten randomized controlled trials, LLLT significantly increases hair diameter and density compared to the

sham device and can be a safe and effective therapeutic option for androgenic alopecia. Among other treatments, Platelet Rich Plasma (PRP) use finds inconsistency in scientific reports. In Gressenberg et al. study it was not effective in hair growth, but Verma et al. proved its better than topical minoxidil efficacy (46,47). Because of the long-term treatment of androgenic alopecia, patients may also reach for topical solutions such as 0.2% caffeine-based preparations, prostaglandins, adipose-derived stem cell constituent extract and alternatives such as botulinum toxin injections or microneedling (38,48). Hair transplantation, characterized by over 90% graft survival, might be considered (48). The ablative fractional 2940-nm Er: YAG laser has also shown beneficial effects in combination with pharmacotherapy with oral finasteride and topical minoxidil (49).

## **Conclusions**

This literature review describes currently available treatments for androgenic alopecia, the ones well investigated and commonly used, and others that require further research and confirmation of their efficacy. Topical minoxidil remains one of the first-line treatments for androgenic alopecia, although low compliance and sometimes side effects might be a problem. Withdrawing topical minoxidil too quickly without establishing the cause of side effects may be to the detriment of patients for whom there are few effective therapeutic options for treating androgenic alopecia. Patch testing is recommended to determine the potential allergen. Oral minoxidil might become an effective and safe treatment option, especially for patients with low compliance and problems using the topical solution. Among 5-alpha reductase inhibitors, oral finasteride administration is an effective, well-investigated treatment method, but its long-term use might be limited because of some adverse events. For some patients, a topical application might become an efficient alternative. Oral dutasteride administration, although not FDA approved, in some papers turned out to be superior to finasteride, and, therefore, in case of finasteride inefficacy, might be used as another therapeutic option. In addition, the opportunity for better results is provided by emerging therapeutic options such as LLLT, which is not only safe and effective but also relatively inexpensive to apply. When determining the choice of therapy with the patient, it is essential to cooperate in order to reduce the risk of choosing substances with unacceptable side effect profiles and thus reduce the risk of withdrawal. It is also important to combine different therapeutic options in order to increase treatment efficacy and patient satisfaction. Extensive group studies evaluating the efficacy and safety of novel therapies are needed to

establish new effective treatment methods and improve the quality of life for patients with androgenetic alopecia.

### **Author's contribution**

Conceptualization, MS, ŁM; methodology, MS, BR, WM, ŁM; software, MS, ŁM, WK, JO; check, MS, BR, WM, ŁM, MP, BK, WK, JO, ZC, DB; formal analysis, MS, BR, WM, ŁM, MP, BK, WK, JO, ZC, DB; investigation, MS, ŁM; resources, MS, BR, MP; data curation, MS, JO, ZC; writing - rough preparation, MS, WM, ŁM, DB; writing - review and editing, MS, BR, WM, ŁM; visualization, MS, ŁM; supervision, MS, BR, WM, ŁM, MP, BK, WK, JO, ZC, DB; project administration, MS, ŁM;

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