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REVIEW ARTICLE

Androgenetic Alopecia: Therapy Update

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Abstract
Androgenetic alopecia (AGA), also known as male pattern hair loss (MPHL) or female pattern hair loss (FPHL), is the most common form of alopecia worldwide, and arises from an excessive response to androgens. AGA presents itself in a characteristic distribution unique to both sexes. Despite its prevalence, AGA can be quite challenging to treat. The condition is chronic in nature and stems from an interplay of genetic and environmental factors. There are only two US Food and Drug Administration (FDA)-approved drugs for the condition: topical minoxidil and oral finasteride. However, numerous non-FDA-approved treatments have been shown to be effective in treating AGA in various studies. Some of these treatments are relatively new and still to be explored, thus emphasizing the need for an updated review of the literature. In this comprehensive review, we discuss the evaluation of AGA and the mechanisms of action, costs, efficacies, and safety profiles of existing, alternative, and upcoming therapeutics for this widespread condition.

1 Introduction

Androgenetic alopecia (AGA), also known as male pattern hair loss (MPHL) or female pattern hair loss (FPHL), is the most common form of alopecia worldwide, and is characterized by progressive terminal hair loss after puberty. Affecting at least 80% of men and 50% of women by age 70 years, the disease increases in incidence with age and is most commonly seen in Caucasians, followed by Asians and African Americans, and finally Native Americans and Eskimos [1].

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AGA presents itself in a characteristic distribution unique to both sexes. MPHL is characterized by gradual hair thinning that affects the crown and frontal areas of the scalp. In addition, hairline recession is common. FPHL is characterized by diffuse hair loss and thinning that affects the frontal and vertex scalp; however, the frontal hairline is usually spared. As the name suggests, the mechanism of disease stems from an excessive response to androgens. The characteristic pattern of hair loss in both men and women results from the distribution of androgen receptors within the scalp [2, 3].

The normal hair growth cycle consists of four phases: anagen, or growth; catagen, or involution; telogen, or resting; and exogen, or shedding. Approximately 80–90% of follicles are in the anagen phase at any time, and each day about 100 follicles are in the exogen phase. This physiological process leads to the development of large, terminal hair fibers. In AGA, hair follicles spend less time in anagen and are "miniaturized," leading to abnormally short and thin vellus hair shafts. Androgens lead to the gradual conversion of terminal hairs into intermediate and vellus hairs, resulting in the gradual hair thinning and hair loss seen in patients with AGA. Consistent with this pathophysiological mechanism, higher levels of dihydrotestosterone (DHT), a hormone that stimulates the development of male characteristics, and 5-alpha-reductase type II, an important enzyme in the conversion of testosterone to DHT in the outer root sheath of hair follicles, are common in individuals with AGA. Although levels of testosterone are similar in individuals

Key Points

There are only two US FDA-approved drugs for androgenetic alopecia, but numerous non-FDA-approved treatments have been shown to be effective in treating it in clinical trials and observational studies.

The plethora of therapeutic options, alongside the chronic and intricate nature of androgenetic alopecia, add a layer of complexity in understanding and choosing the best treatment option.

with and without AGA, levels of unbound testosterone, or active testosterone, are higher in those with AGA. Moreover, individuals castrated before puberty, with complete androgen insensitivity syndrome (CAIS), or with 5-alpha-reductase type II deficiency have a lower prevalence of AGA [4]. This provides further evidence that androgens are the basis for the development of AGA.

AGA was previously thought to be inherited in an autosomal dominant pattern, with reduced penetrance in women [5]. However, a combination of genetic and environmental factors may be involved given the extremely high prevalence of the condition and the increased risk in relatives of women with severe AGA. While the condition is familial and heritable in nature, the inheritance pattern of AGA remains unclear and is likely both polygenic and multifactorial. Multiple genetic susceptibility loci have been identified for AGA, including *HDAC9* gene on chromosome *7p21.1*, chromosome *3q26*, *PAX1/FOXA2* locus on chromosome 20p11, and androgen receptor (AR)/*EDAR2* locus on the X chromosome [6]. Moreover, AGA was found to be associated with body mass index (BMI), metabolic syndrome, and severe cases of COVID-19 [1].

Despite its high prevalence, AGA can be somewhat challenging to treat due to its chronic nature and the interplay of genetic and environmental factors. Currently, there are only two US Food and Drug Administration (FDA)-approved drugs for AGA: topical minoxidil and oral finasteride. However, numerous non-FDA-approved treatments have shown to be effective in treating AGA. In this comprehensive review, we discuss the mechanisms of action, costs, efficacies, and safety profiles of existing, alternative, and upcoming therapeutics for AGA. Treatments are summarized in Table 1.

2 Diagnosis and Evaluation

The diagnosis of AGA is usually based on the history and on clinical findings. The duration and location of hair loss are important factors to consider, as well as whether shedding or thinning has occurred. In patients with increased shedding or thinning, a thorough evaluation of potential triggers for telogen effluvium (TE) should be done (e.g., new medications, systemic illness, weight loss, general anesthesia). The provider should review the patient's medical and family history, medications, basic labs [e.g., thyroid stimulating hormone (TSH), complete blood count (CBC), iron, ferritin, vitamin D], and gynecologic history (for women) to rule out other causes of hair loss [7].

The clinical evaluation for patients with suspected AGA involves establishing where the hair loss is occurring, the extent of shedding, and if there are signs of inflammation (perifollicular erythema and/or scale). The severity of hair shedding can be determined by the pull test. This is done by grasping 40–60 strands of hair between the thumb and the forefinger and applying gentle traction away from the scalp [8]. Extraction of three or fewer hair strands from a single area is considered a negative or normal pull test and extraction of six or more is considered a positive pull test. Trichoscopy is helpful in determining the specific type of hair loss and whether perifollicular erythema and/or scale are present. The earliest and diagnostic feature of AGA is a hair shaft diameter variation of more than 20% of the hair shafts [9, 10]. In addition, there is an increased proportion of vellus hairs. Yellow dots may also be present in severe AGA representing hypertrophied sebaceous glands.

3 Topical Therapies

3.1 Topical Minoxidil

First introduced as an antihypertensive medication in the 1970s, minoxidil is now used worldwide for various hair loss conditions. It is the first FDA-approved drug for AGA and is used off-label for many other hair loss conditions, such as central centrifugal cicatricial alopecia, alopecia areata (AA), and TE, among others. Minoxidil is converted to its active metabolite, minoxidil sulfate, and functions as a potent arteriolar vasodilator that activates potassium channels on the smooth muscles of the peripheral artery, inducing cell proliferation. Furthermore, minoxidil was found to increase vascular endothelial growth factor (VEGF) in dermal papilla cells in a dose-dependent fashion, as well as stimulate prostaglandin E2 production, leading to an increase in the duration of the anagen phase [11].

Table 1 Summary of treatments for androgenetic alopecia

Therapy	Mechanism	Dosage	Adverse effects	Price	M/F/B
Topical					
Minoxidil	Arteriolar vasodilation, inducing cell proliferation; increase vascular endothelial growth factor	2–10%; QD, BID	Headaches, hypertrichosis, irritation, contact dermatitis	$	B
Finasteride	5-alpha-reductase inhibitor—blocks formation of DHT	0.25% spray, 1% gel; QD, BID	Irritation, erythema, contact dermatitis	$	M
Latanoprost	Prostaglandin analog—prolong anagen (growth) phase	0.1% QD	Irritation, hypertrichosis	$	B
Oral					
Finasteride	Type II 5-alpha-reductase inhibitor—blocks formation of DHT	1 mg, 5 mg; QD	Sexual dysfunction, altered libido, gynecomastia, mood changes	$$	M
Dutasteride	Type I and II 5-alpha-reductase inhibitor—blocks formation of DHT	0.5 mg, 1 mg, QD	Sexual dysfunction, altered libido, gynecomastia, mood changes	$$	M
Minoxidil	Arteriolar vasodilation, inducing cell proliferation; increase vascular endothelial growth factor	0.625–10 mg	Dizziness, hypertrichosis, lower leg swelling	$	B
Hormonal					
Oral spironolactone	Antiandrogen—effectively decreases testosterone	12–200 mg QD	Postural hypotension, electrolyte imbalances	$	F
Oral flutamide	Antiandrogen—effectively blocks testosterone	62.5–250 mg QD	Elevated liver enzymes, bloating, headache, breast tenderness	$	F
Oral bicalutamide	Antiandrogen—effectively blocks testosterone	12.5–50 mg 3–5 times weekly	Elevated liver enzymes, bloating, headache, breast tenderness	$$	F
Oral cyproterone acetate	Antiandrogen—blocks gonadotropin-releasing hormone and androgen receptors	2 mg QD (often combined with ethinyl estradiol)	Weight gain, breast tenderness, decreased libido		F
Topical clascoterone	Topical androgen receptor inhibitor	5% solution QD, BID	Mild dryness, erythema, hypertrichosis	$$$	F
Injectables					
Botulinum toxin A	Interferes with the suppressive effect of DHT on the hair follicle		Mild discomfort, temporary drooping of nearby muscles, transient headache, nausea	$$$	B
Dutasteride	Type I and II 5-alpha-reductase inhibitor—blocks formation of DHT on the hair follicle (local)	Injection every 3 months	Pain	$$$	M
Nonsurgical nondrug					
Platelet-rich plasma	Contains concentrated platelets, growth factors, and cytokines that aid in hair regrowth	Every 1–6 months	Scalp pain, pinpoint bleeding, headache, and burning sensation	$$$$	B
Low-level light therapy	Upregulation of endogenous growth factors and nitric oxide leading to cellular proliferation and vasodilation	Three times a week/daily	Scalp tenderness, paresthesia, and mild urticaria	$$$	B
Exosomes	Contain cytokines and growth factors that aid in hair regrowth		Pain, bruising, or swelling at the injection site	$$$$	B
Microneedling	Releases growth factors that promote angiogenesis		Pain, bruising, discomfort at site	$$	B
Supplementation					
Vitamins/minerals	Certain micronutrients are necessary for hair growth (vitamins C and D, iron, folate, selenium)	Daily as needed		$	B
Nutrafol	Contains 21 phytocompounds and other ingredients that support hair growth	Daily as needed		$$	B

Table 1 (continued)

Therapy	Mechanism	Dosage	Adverse effects	Price	M/F/B
Viviscal	Marine complex supplement that consists of several vitamins/minerals that support hair growth	Daily as needed		$	B
Caffeine	Increases cyclic adenosine monophosphate and cell metabolism leading to cellular proliferation	Daily as needed		$	B
Rosemary oil	Contains caffeic acid, rosmarinic acid, camphor, and 12-methoxycarnosic acid that work together to reduce inflammation and infection	Daily as needed		$	B
Pumpkin seed oil	Contains various saturated and unsaturated fatty acids has been hypothesized to inhibit 5-alpha-reductase and thus reduce levels of DHT	Daily as needed		$	B
Saw palmetto	Competitively inhibits both types of 5-alpha-reductase at multiple sites and thus reduces binding of DHT to the androgen receptor	Daily as needed	Cold feeling, burning sensation	$	B
Surgical treatments					
Hair transplant	FUT and FUE. FUT uses individual hair follicles that are transplanted on the alopecic areas. FUT involves a single-strip method of donor hair using an elliptical incision followed by suturing.		Pain, bleeding, edema, pruritis	$$$$	B

QD daily, *BID* twice daily, *FUT* follicular unit transplantation, *FUE* follicular unit extraction, *M* male, *F* female, *B* both

Minoxidil is typically dosed at 2% and 5% minoxidil solution, with 1 mL applied twice daily for patients over the age of 18 years. The 5% solution is preferred in men. Patients should be assessed after 6 months. Studies have found that both the 2% and 5% formulations have shown a significant difference in hair growth versus placebo at 6 months and 1 and 5 years, described below. In men, the 5% formulation is significantly more effective than the 2% solution, whereas in women, both 2% and 5% showed promising improvements in FPHL [12, 13]. Concentrations higher than 5% have shown improvement in efficacy but have also been found to increase propensity for local irritation [14]. Side effects include contact dermatitis, headaches, and hypertrichosis. Local cutaneous side effects are more common with higher percent formulations of minoxidil solution, likely due to higher propylene glycol content. Short-term telogen shedding can be seen in the first 8 weeks of therapy [15]. Overall, topical minoxidil is relatively inexpensive in the USA, costing patients around $12 USD for a 60 mL bottle [16].

3.2 Topical Finasteride

Finasteride is a member of a class of drugs known as 5-alpha-reductase inhibitors. These drugs block the enzyme 5-alpha-reductase, thus blocking the conversion of testosterone to its active form dihydrotestosterone (DHT). Finasteride is a type II 5-alpha-reductase inhibitor and dutasteride blocks both type I and type II. Given that higher levels of DHT are associated with AGA, it follows that blocking DHT would improve the condition. The promising effects of topical finasteride as treatment for hair regrowth were first published by Mazzarella et al. in 1997 in a placebo-controlled trial [17].

Topical finasteride is typically given as 0.25% finasteride spray, or 1% topical finasteride gel applied twice daily to the scalp. A recent phase III, randomized, controlled clinical trial of 458 patients found that topical 0.25% finasteride significantly improves hair count compared with placebo in patients with MPHL despite maintaining relatively stable serum DHT concentrations. Furthermore, it was found to be well tolerated, particularly in comparison with its oral formulation [18]. Although the use of topical 0.5% finasteride combined with 2% minoxidil solution was found to be effective in FPHL, the use of topical finasteride alone is not very effective and thus is not used [19]. Scalp pruritus, burning, irritation, contact dermatitis, and erythema may occur. These side effects are rare and localized to the application site. Overall, topical finasteride costs slightly more than minoxidil, costing patients < $30 USD per month [16].

3.3 Latanoprost

The use of prostaglandin analogs for alopecia came about when eyebrow and eyelash hair growth were observed in glaucoma patients. Prostaglandin F2 (PGF2) and PGE2 cause hair growth and prolong the anagen phase, whereas PGD2 inhibits hair growth [20, 21]. Blume-Peytaavi et al. conducted a randomized control trial using 0.1% latanoprost, a PGF2 analog, in 16 patients with MPHL [22]. After 24 weeks, there was significantly increased hair density compared with baseline and placebo-treated areas. A limitation of this study was that only young men with AGA were included in this study; therefore, the results may not be applicable to patients with differing demographics. Further studies would be helpful to evaluate the efficacy of latanoprost in treating AGA.

4 Oral Therapies

4.1 Oral Finasteride

Finasteride has been FDA-approved for MPHL since 1997. The drug works similarly to topical finasteride by inhibiting 5-alpha-reductase type 2, which blocks the conversion of testosterone to DHT and reduces androgen-mediated follicular miniaturization [23]. Finasteride is available in 1 and 5 mg tablets. In patients with MPHL, it is usually prescribed as 1 mg once daily. This drug is contraindicated in premenopausal women and is classified as pregnancy category X due to the feminization of male fetuses in several animal studies. It is used off-label to treat FPHL in postmenopausal women at doses of 2.5–5 mg once daily [24].

The efficacy of finasteride for AGA has been investigated in several studies. The drug improves hair growth within 1 year of treatment, and further improvement up to 10 years of treatment [25]. It is more effective at regrowing hair at the vertex scalp compared with the frontal/centroparietal scalp, and its efficacy does not reduce over time. Several studies have shown that patients older than 30 years seem to have better hair growth than patients younger than 30 years [26, 27]. A randomized control trial (RCT) showed better results with 1 mg finasteride than 5% minoxidil foam in 65 male patients with mild to severe AGA [28].

Finasteride 1 mg once daily is generally well tolerated and side effects resolve with cessation of the drug [29]. Reported side effects include sexual dysfunction, altered libido, erectile dysfunction, ejaculatory dysfunction, and gynecomastia. Some patients may have persistent sexual side effects for at least 3 months despite cessation of the drug, which may lead to increased rates of depression and suicidal thoughts [30]. In regards to concerns about prostate cancer as a side effect of 5-alpha-reductase inhibitors, a recent meta-analysis showed that finasteride does not increase the risk of developing high-grade prostate cancer [31]. For a 30 day supply of finasteride 1 mg tablets, the average retail price is $78 USD [16].

4.2 Oral Dutasteride

Dutasteride is a dual inhibitor of type 1 and type 2 5-alpha-reductase and is a potential alternative to finasteride with reported improved efficacy in treating AGA. It is 100 times more potent at inhibiting type 1 5-alpha-reductase compared with finasteride and three times more potent at inhibiting type 2 [32]. Dutasteride is available in 0.5 mg tablets as treatment for AGA.

In two large, randomized control trials, dutasteride was found to improve hair growth within 12–24 weeks and 6 months, respectively, compared with finasteride [33, 34]. In addition, a recent meta-analysis showed that 0.5 mg dutasteride once daily was significantly more efficacious at increasing hair count at 24 weeks compared with 1 mg finasteride once daily and 0.25/5 mg minoxidil once daily [35]. Despite studies showing that dutasteride is more efficacious, finasteride is still the first-line treatment for AGA due to its FDA approval and therefore greater likelihood of being covered by insurance.

Like finasteride, side effects of dutasteride include sexual dysfunction, altered libido, erectile dysfunction, ejaculatory dysfunction, and gynecomastia [36]. For a 30 day supply of dutasteride 0.5 mg tablets, the average retail price is $150 USD [16].

4.3 Oral Minoxidil

Although not FDA approved, low-dose oral minoxidil has recently received more attention for the treatment of AGA. Oral minoxidil is available as a 2.5 mg tablet that can be split in half or quarters to achieve the ideal dose based on patient and provider preferences.

A combination of 0.25 mg oral minoxidil and 25 mg spironolactone has been shown to decrease hair shedding and improve hair density in patients with FPHL [37]. An open-label prospective clinical trial showed that 5 mg oral minoxidil once daily significantly improved hair growth in 30 men aged 24–59 years [38]. In a retrospective study of 12 women with AGA, hair density improved by 38% and 23% in the frontal and vertex scalp, respectively, after 24 weeks of treatment with 0.50 mg minoxidil that was increased to 2 mg daily at 3 months [39]. Ramos et al. compared the efficacy of 1 mg oral minoxidil daily with 5% topical minoxidil solution daily and found that oral minoxidil was as effective as the topical form. In addition, oral minoxidil showed better improvement of hair shedding scores [40].

The most common reported adverse effect of oral minoxidil is hypertrichosis. It is more common among patients on higher doses of minoxidil (5 mg daily) whereas those on 2.5 mg daily had a lower incidence of hypertrichosis [41]. Cardiovascular effects such as hypotension, tachycardia, pericardial effusion, lower limb edema, and electrocardiogram (ECG) changes (tachycardia, preventricular contractions, t-wave changes) are feared complications that make topical minoxidil more favorable. In general, the side effects of oral minoxidil are typically dose dependent and reversible with cessation of the drug [39]. For a 30 day supply of minoxidil 2.5 mg tablets, the average retail price is $17 USD [14].

4.4 Janus-Kinase (JAK) inhibitors

JAK inhibitors have shown promise as an effective treatment for AA, especially with the FDA approval of baricitinib in June 2022. The pathogenesis of AA is mediated by interleukin-15 production by hair follicles in response to interferon-gamma secretion. JAK 1/2 and JAK 1/3 signaling in T-cells release more interferon-gamma in response to interleukin-15, creating a positive feedback loop [42]. JAK inhibitors halt this positive feedback loop, leading to hair regrowth. Unfortunately, JAK inhibitors may not be an effective treatment for AGA. Yale et al. reported a case series of four men diagnosed with AA and treated with an oral JAK 1/2 inhibitor for 24–40 weeks [43]. They found that these patients experienced notable hair regrowth, except regrowth occurred in an AGA pattern (bitemporal recession). Further studies need to be done to characterize the role of JAK inhibitors in treating AGA.

5 Hormonal Therapies

5.1 Oral Spironolactone

Spironolactone is a potassium-sparing diuretic and antiandrogen. It decreases testosterone production by inhibiting 17-alpha hydroxylase and 17, 20 lyase [44]. Its antiandrogen properties make it a great treatment for FPHL but contraindicated in male AGA. The standard dose for FPHL is 12.5–200 mg daily.

Sinclair et al. performed a single center before–after open interventional study including 80 women with FPHL between the ages of 12 and 79 years receiving 200 mg of spironolactone daily for 12 months. They found that 44% of these subjects showed improvement in hair regrowth [45]. Furthermore, significant hair regrowth was noted after 6 months in a 9-year-old patient with FPHL receiving 100 mg of spironolactone daily [46]. In a retrospective study of 79 patients receiving an average dose of 100 mg of spironolactone daily, all patients noted stable or improved hair growth [47]. However, patients with a Sinclair Score of 2.5 or higher noted greater improvement. Side effects include postural hypotension, electrolyte imbalances, breast tenderness, and irregular menses [48]. For a 30 day supply of spironolactone 25 mg tablets, the average retail price is $16 USD [16].

5.2 Oral Flutamide and Bicalutamide

Flutamide is a potent antiandrogen that inhibits androgen receptors. It is shown to be effective in hyperandrogenic women with FPHL at a dose of 250 mg daily [49]. A case report showed that flutamide reversed hair loss in a patient with FPHL who was nonresponsive to spironolactone and topical minoxidil [50]. In a large prospective study including 101 women with FPHL receiving varying doses of flutamide for 4 years, there was a significant reduction in alopecia scores compared with baseline. The maximum drug effect occurred after 2 years and was maintained for 2 years thereafter [51]. Flutamide has a well-known risk of causing elevated liver enzymes, especially at high doses [51], something not seen commonly with another drug in its class, bicalutamide.

Bicalutamide is a novel nonsteroidal, pure antiandrogen medication that has a better safety and tolerability profile than flutamide [52, 53]. In a retrospective study including 17 FPHL patients treated with 50 mg bicalutamide daily or every other day for 24 weeks, 57% of patients had significant regrowth and 12.5% of patients had a mild elevation of liver enzymes [54].

A retrospective review of 316 women on oral bicalutamide showed that the drug is well tolerated [55]. The most common side effect was a mild elevation in liver enzymes in nine patients that resolved without a dose change in four out of nine of these patients. Two patients previously discontinued flutamide due to the development of colitis but tolerated bicalutamide without issue [55].

For a 30 day supply of bicalutamide 50 mg tablets, the average retail price is $126 USD [16]. For a 30 day supply of flutamide 125 mg tablets, the average retail price is $31 USD [16].

5.3 Oral Cyproterone Acetate

Cyproterone is an antiandrogen that blocks gonadotropin-releasing hormones and androgen receptors. It is commonly used for FPHL in Europe, but it is not available in the USA. An RCT of 20 patients receiving 50 mcg ethinyl-estradiol and 2 mg cyproterone acetate on days 1–14 and an additional 20 mg cyproterone acetate on days 5–20 of their menstrual cycle found a significant increase in the number of anagen hairs on the frontal scalp [56]. A 12 month randomized

control trial comparing 2% topical minoxidil and cyproterone for treatment of FPHL found that cyproterone was more effective in treating women with additional signs of hyperandrogenism, while topical minoxidil was more effective in women without hyperandrogenism [57]. Cyproterone is associated with weight gain, breast tenderness, and decreased libido [58].

5.4 Topical Clascoterone

Clascoterone is a novel topical androgen receptor inhibitor. It has shown promising results for use in patients with acne vulgaris [59]. It is thought that the antiandrogenic properties of clascoterone may be helpful in treating AGA.

In a phase I single-center, open label clinical trial, 18 patients with AGA applied topical clascoterone solution 5% twice a day to the affected areas [60]. They found that clascoterone levels in the bloodstream cumulatively increased 4 h after application. However, day 28 pre-dose clascoterone concentrations were similar to 12 h post-dose concentrations, indicating a steady state. In a phase II exploratory study, clascoterone was more effective than cyproterone acetate or 17-alpha estradiol in increasing hair shaft diameter and hair follicle density [60]. Furthermore, hair growth was higher in patients using clascoterone compared with topical minoxidil.

Clascoterone is generally well tolerated. In a phase II and III acne clinical trial, adverse effects included mild dryness, erythema, and hypertrichosis at the application site [59]. For one tube (60 g) of 1% clascoterone, the average retail price is $656 USD [16].

5.5 Topical Pyrilutamide

Pyrilutamide is another novel topical androgen receptor inhibitor. In a phase II clinical trial by Kintor Pharma, the drug was effective and showed good safety profile in patients with MPHL [61]. Currently, there are phase II and phase III clinical trials in China for FPHL and MPHL patients, respectively. In the USA, there is a phase II trial for MPHL patients.

6 Injectable Medications

6.1 Intradermal Botulinum Toxin

The use of injectable botulinum A toxin has gained popularity as a treatment for AGA in recent years because of its ability to interfere with the suppressive effect of DHT on the hair follicle. A prospective 24 week study of 18 male patients with AGA showed significant improvement at week 24 ($p = 0.031$) [62]. Another RCT found combination therapy of botulinum toxin A injections and oral finasteride and minoxidil to be more effective than treatment with oral finasteride and minoxidil alone [63]. More research has yet to be performed to understand the role of botulinum as treatment for AGA. The average cost per treatment was $466 USD per unit of injection in 2020 [16].

6.2 Dutasteride Mesotherapy

Injectable dutasteride has gained popularity over the last several years due to limited systemic absorption, and therefore, reduced side effects. A multicenter retrospective study assessed 541 patients that were treated with dutasteride mesotherapy every 3 months with at least 6 months of follow-up. Response to the therapy was assessed in 16% of patients after 1 year, and most reported improvement, with pain being the most frequent side effect (45.5%). This side effect was considered mild by most patients and self-limited [64]. One session costs between $250 and $500 USD.

7 Nonsurgical Nondrug Treatments

7.1 Platelet-Rich Plasma (PRP)

Platelet-rich plasma (PRP) is a more recent treatment modality for AGA that has risen in popularity due to its effectiveness, autologous nature, minimal side effect profile, and nominal responsibility placed on the patient. PRP consists of a preparation of plasma with concentrated platelets, growth factors, and cytokines that aid the body's inherent capacity to regrow and regenerate. To prepare PRP, 10–30 mL of blood are drawn from the patient via venipuncture and centrifuged under a "soft" speed for approximately 10 min to separate the blood into various components of red blood cells (RBCs), platelets, and white blood cells (WBCs). Through this process, the normal 94:6 ratio of RBCs to platelets is reversed to achieve a 94:6 ratio of platelets to RBCs [65]. After separation, 4–8 mL of the platelet-rich plasma component of the sample are injected into the patient. In some cases, an activator such as calcium, thrombin, and collagen may be added to enhance growth factor secretion [66].

Given that intact hair follicles are needed for treatment success, PRP is more often used on early stage AGA patients. It is not curative and must be continued long term to sustain growth. In a 2018 review of the literature on patients with FPHL and MPHL, PRP demonstrated therapeutic efficacy in 10 out of 12 studies, most of which used a control group as a comparison [66]. A recent 2022 review article found a significant increase in hair density and hair diameter in numerous studies in FPHL and MPHL patients, respectively [67]. A randomized controlled trial in 2020 reported a noted increased hair density in participants treated with PRP,

although this difference was not significant when compared with patients treated with saline across 3 months [68].

The standardization of PRP preparation is still debated in the literature. While some studies have conducted sessions every 2 weeks, others wait a month between sessions or gradually increase the interval between sessions as they progress [69]. Potential side effects include scalp pain, pinpoint bleeding, headache, and burning sensation that typically subside 10–15 min after injections. Most patients do not need any topical or oral pain medications to combat these effects and can resume their normal activities. Strenuous activity should be avoided 24 h after treatment. Some patients with a history of bleeding disorders, active infection, or autoimmune disease should refrain from using PRP due to increased risks [66]. PRP is relatively expensive, ranging from $500 to $2500 USD per treatment, and is not covered by insurance for hair loss [16].

7.2 Low-Level Light Therapy (LLLT)

LLLT was first reported in the 1960s when hair regrowth was observed in mice exposed to low-energy lasers (694 nm) [68, 69]. Since then, LLLT has been used to treat several types of alopecia. The proposed mechanism is that photons emitted from the LLLT oxidize cytochrome C oxidase, thus activating the electron transport chain and increasing ATP production [70]. Endogenous growth factors and nitric oxide are upregulated, leading to cellular proliferation and vasodilation, respectively [71]. LLLT at 650–900 nm at 5 mW is generally used for the treatment of AGA [72].

The HairMax LaserComb is a hand-held low-level laser containing one laser module (655 nm). Leavitt et al. conducted a RCT involving 110 male patients with AGA. Patients in the treatment group used the HairMax LaserComb three times a week for 15 min for a total of 6 months. They found that patients in the treatment group showed significant improvement in hair regrowth with no serious adverse effects [73]. In another RCT, 40 subjects with AGA received treatment with a helmet LLLT (630, 650, and 660 nm) daily or a sham device for 18 min daily. After 24 weeks, patients using the LLLT device showed greater hair density and mean hair diameter compared with those on the sham device [74]. LLLT in combination with minoxidil and finasteride showed efficacy in hair regrowth as well [75, 76]. Moreover, a systematic review found that phototherapies containing red and infrared light may be more effective at treating AGA [77].

LLLT is generally well tolerated. Reported side effects include scalp tenderness, paresthesia, and mild urticaria [78]. HairMax LaserComb costs range from $200 to $1900 USD [16].

7.3 Exosomes

Mesenchymal stem cells (MSCs) are stromal cells that can self-renew and differentiate into various types of specialized cells. The concept of MSC-derived exosomes, or extracellular vesicles (EV), is relatively new and has been increasing in practice as a means of combining the regenerative capacity of MSCs with the cell–cell communication mediated by exosomes. MSC–exosomes are currently being used to treat a variety of medical conditions including cardiac and neurologic deficits, along with types of malignancy [79]. MSC–exosomes have shown promise in hair regrowth, as they contain cytokines and growth factors that play a role in hair restoration. A laboratory study that tested the efficacy of MSC–EV treatment on hair growth in an animal model demonstrated increased dermal papilla cell proliferation and increased levels of various growth factors. Injection of MSC–EVs intradermally into C57BL/6-strain mice promoted hair follicle conversion from telogen to anagen [80].

Hair follicle-derived MSCs have also been shown to reduce inflammation and decrease hair loss in vitro in mice with AA, an autoimmune type of hair loss [81]. However, specific guidelines on their use have not been generated. Furthermore, the use of exosomes in AGA is not well supported, as data showing clear efficacy and safety of exosomes for alopecia is lacking [82]. Additional research is necessary to justify the routine use of MSC–exosomes in treatment of AGA. Currently, the US Food and Drug Administration does not allow use of exosomes for the treatment of FPHL or MPHL.

7.4 Microneedling

Microneedling is a minimally invasive procedure whereby small percutaneous wounds are induced with small needles, resulting in the release of platelet-derived growth factor and VEGF. These factors promote angiogenesis and wound healing and reverse fibrosis. It was first described in 1996 by Orentreich for the use of wrinkles and atrophic scars but was found to have a beneficial effect as an adjunct treatment for hair loss through its effect on dermal papilla stem cell proliferation. Furthermore, the induced wounds form channels to improve absorption of topical treatments, such as 2–5% minoxidil or finasteride [83].

A review article by English Jr et al. published in 2021 found that among 17 clinical studies featuring 911 subjects with AGA, microneedling improved hair parameters when used with growth factor solutions, 5% minoxidil and/or PRP [84]. Another study from 2015 showed the benefits of using microneedling treatment in men with AGA who failed to

respond to conventional oral finasteride and 5% minoxidil solution therapy for 2–5 years [85].

Microneedling with a depth of 0.6 mm in combination with minoxidil was found to be more effective than a depth of 1.2 mm. Sessions last about 20–25 min. Microneedling is often an adjunct treatment; therefore, the frequency of dosage varies by individual [86]. Pain, bruising, and folliculitis have been seen with microneedling, as with other procedures involving injections. The procedure costs vary widely depending on the device used but is approximately $100–500 USD per treatment [86].

8 Nutrition/supplementation

Although topical minoxidil and oral finasteride are the only two FDA-approved treatments for AGA, patient compliance for either treatment is not optimal. Decreased libido and erectile dysfunction from oral finasteride and increased pruritus from topical minoxidil present a barrier to consistent use. Natural remedies are alternative treatments with potentially fewer side effects.

8.1 Vitamins/minerals

For many years, micronutrient deficiencies have been linked to increased hair loss and shedding. In the late 1700s, James Lind linked scurvy to vitamin C deficiency, noting hair loss as a prominent feature. Children with kwashiorkor and marasmus, along with other protein–energy malnutrition disorders, also demonstrate hair loss and skin changes. In more recent years, vitamin D, iron, vitamin B12, folate, and selenium have been found to be involved in hair aging and loss [87]. As a result, the concept of nutrient supplementation as a means of treating hair loss has emerged in recent years.

A variety of studies have shown the use of vitamin D supplementation in those with deficiency and hair loss, and the role of vitamin C supplementation in iron deficiency. In 2007, a randomized control trial was conducted to examine the role of Pantogar, a complex of vitamins, amino acids, keratin, and yeast, in women with TE, a self-limiting form of hair loss due to excessive shedding of telogen hair that follows a period of stress or imbalance. Significant improvement and normalization of the mean anagen hair rate was found in the Pantogar group within 6 months of treatment, compared with no significant change in the placebo group [88, 89]. Additional large double-blind, placebo-controlled trials are needed to determine the effect of micronutrient supplementation in hair growth, particularly in AGA. No true evidence has found a space for biotin supplementation in AGA. Moreover, given that over-supplementation of vitamin A, vitamin E, and selenium has been shown to increase hair loss, vitamin and mineral supplementation should not be blindly encouraged [90].

8.2 Nutraceuticals

With the rise of Instagram, TikTok, and various other forms of social media advertising, oral and topical nutraceuticals have emerged as methods to increase hair growth and density. These supplements often contain phytochemicals or naturally derived, biologically active compounds that are thought to improve health. Although these products are regulated by the FDA, they are not as rigorously tested as pharmaceuticals [91]. Given this lack of regulation and easy accessibility, the safety and efficacy of these treatments may be compromised.

Launched in 2016, Nutrafol is a hair growth supplement made of a Synergen Complex consisting of 21 phytocompounds and other ingredients that prides itself on supporting "hair wellness from within." Some of the active ingredients include ashwagandha, saw palmetto, curcumin, palm extract, amino acids, biotin, and hydrolyzed marine collagen, among others [91]. Ashwagandha is a botanical that works to reduce cortisol levels and subjective feelings of stress. Saw palmetto extract naturally inhibits both subtypes of 5-alpha-reductase. In 2018, a 6 month randomized, double-blind, placebo-controlled trial found a statistically significant increase in hair growth and thickness in women with self-perceived thinning [92]. In 2022, a prospective, single-blind study involving a diverse group of healthy men and premenopausal women with mild-to-moderate hair thinning found that Nutrafol improved hair growth, fullness, and coverage with less noticeable hair shedding for men and women of various ethnic backgrounds. These results and various self-assessment parameters continued to improve at week 24, suggesting a time-dependent response [93]. None of these trials found significant side effects. The compound is taken orally with four pills daily. Limitations of these studies are the lack of hair counts done by trichoscopy, which is the gold standard in alopecia clinical trials, and the possibility that patients with self-resolving hair conditions such as telogen effluvium were included.

Viviscal is an oral-based marine complex supplement that consists of extracellular matrix components of shark and mollusks, millet seed extract, calcium, iron, vitamin C, horsetail extract, and flax seed extract, among others. Since its debut in 1990, it has been formulated in tablets, shampoos, creams, and conditioners, and has been used in patients with AGA [92]. In the last 30 years, various 3–6 month clinical trials have been conducted in patients with AGA and AA to evaluate the safety and efficacy of this supplement. The results have been largely positive, with reduced shedding, increased hair thickness and diameter, and increased growth. In addition to encouraging hair growth, Viviscal has shown

to improve growth and appearance of eyebrows, nails, skin, and eyelashes in both men and women [94, 95]. Notable side effects have not been found in clinical trials. It is worth noting, however, that it is unclear who the sponsors of these studies are. Oral tablets are prescribed twice daily, but the supplement exists in various forms.

8.3 Caffeine

Given its easy penetrability across the skin barrier and stimulant properties, topical caffeine has been considered as a potential treatment for AGA. It is a phosphodiesterase inhibitor, and functions to increase cyclic adenosine monophosphate (cAMP) levels and cell metabolism. As a result, it triggers cell proliferation that helps to reverse hair follicle miniaturization. In various in vitro studies, topical caffeine at various concentrations was able to halt hair follicle growth suppression and stimulate growth [96, 97]. A trial in 210 males with AGA demonstrated that caffeine-related growth was not any less than growth seen with 5% minoxidil solution [90]. There was no difference in side effects between groups. Similar efficacy was also seen with caffeine-based shampoo formulations. It is important to note that female hair follicles appeared to be less resistant to caffeine than male hair follicles [98]. Oral caffeine supplements have not yet been studied treatment of alopecia.

8.4 Plant-Based Oils

Rosemary oil (*Rosmarinus officinalis*) contains caffeic acid, rosmarinic acid, camphor, and 12-methoxycarnosic acid that work together to reduce inflammation and infection. In a randomized, single-blind clinical trial of 100 male AGA patients, both the experimental group, treated with 1 mL of 3.7 mg/mL rosemary oil lotion, and the control group, treated with 2% minoxidil, experienced increased hair counts after 6 months of continued treatment. Both groups experienced similar side effects of increased pruritis [99].

Pumpkin seed oil containing various saturated and unsaturated fatty acids has been hypothesized to inhibit 5-alpha-reductase and thus reduce levels of DHT. A double-blind clinical trial of 76 males with AGA demonstrated increased self-rated improvement and satisfaction along with increased mean hair count of 40% in the experimental group compared with 10% in the placebo group [100].

8.5 *Seronoa repens* (saw palmetto)

Saw palmetto, or *Serenoa repens*, is derived and extracted from the berries of the American dwarf palm tree and contains fatty acids, beta carotene, polysaccharides, and phytosterols. It is thought to competitively inhibit both types of 5-alpha-reductase at multiple sites, and thus reduce binding of DHT to the androgen receptor. It also reduces levels of DHT by converting it to a weaker metabolite. It is produced for topical use and has been incorporated in soft gels for oral use [101]. When administered to male AGA patients, saw palmetto led to significantly improved outcomes and increased hair compared with a placebo group [102]. However, when a group receiving 320 mg saw palmetto and a group receiving 1 mg oral finasteride for 24 months were compared, the finasteride group experienced significantly greater outcomes, with growth in both the front and vertex versus only the vertex from saw palmetto [103]. Across various studies, minor side effects including cold feeling and burning sensation were seen with saw palmetto administration [102, 103].

9 Combination Therapy

Although topical minoxidil and oral finasteride are the only two FDA-approved drugs for AGA, many studies and small RCTs have investigated the use of combination treatments. In particular, the efficacy of topical minoxidil combined with finasteride [104–111], LLLT combined with topical minoxidil [112–114], and microneedling combined with minoxidil have been studied [115–118]. One meta-analysis including 15 RCTs found that all combination therapies produced higher global photographic assessment scores compared with monotherapy [119]. A combination of LLLT and microneedling with minoxidil showed significant increases in hair counts compared with monotherapy. In one RCT including 60 patients with AGA, topical minoxidil gel 5% and topical spironolactone gel 1% combined showed significant increases in anagen hairs within 12 months [120]. These combined treatments are good options for patients with AGA. However, more studies should be done to further investigate their efficacy.

10 Surgical Treatments

10.1 Hair Transplant

Patients with AGA who do not have success with medical treatment may opt for a hair transplant. In fact, the most common indication for hair transplantation in both men and women is AGA [121]. There are two types of hair transplant techniques: follicular unit transplantation (FUT) and follicular unit extraction (FUE). In FUE, individual hair follicles are extracted and transplanted on the alopecic areas of the scalp. FUT involves a single-strip method of donor hair using an elliptical incision followed by suturing. FUE is more common due to its potential advantages compared with FUT such as an increased number of harvestable grafts, less

postoperative pain and healing time, and the ability to target follicular groups of a specific size and hair shaft diameter [122]. However, FUE has a longer operative time compared with FUT [122]. In general, healthy patients with enough scalp hair loss, sufficient donor hair, and no evidence of cicatricial alopecia are great candidates for hair transplantation. Contraindications to this procedure include patients with diffuse unpatterned alopecia, cicatricial alopecia, AA, unstable hair loss, insufficient hair loss, sparse donor hair, and those with psychological issues such as body dysmorphic disorder and trichotillomania [122]. Anxiety and depression are not contraindications to hair transplantation.

A retrospective study of 52 patients with AGA found that patients less than 33 years old and with Hamilton stage 4a or less showed significant improvement in hair density [123]. In another retrospective study of 1106 male AGA patients, hair transplantation significantly improved self-esteem and increased patient satisfaction regarding their appearance [124]. General complications of hair transplants are bleeding, tachycardia, pain, pruritis, scarring, and edema [125]. Hair transplant costs can range anywhere from $4000 to $20,000 USD [125].

11 Conclusions

The two most efficacious medications for AGA are topical minoxidil and oral finasteride. Oral minoxidil is increasing in use and has proven to be efficacious but is limited by its side effects compared with the topical formulation. Nonmedical treatments such as PRP and microneedling are good options for treatment but are costly and may not be helpful for patients with severe AGA. Hair transplantation is a good option for individuals that have failed pharmacological treatment. There is limited amount of evidence to conclude the efficacy of other commonly used medications for this condition, such as topical and hormonal medications, and over-the-counter supplements. Furthermore, the multifactorial origin and chronic nature of AGA make it challenging to treat. It is important to consider cost, side effects, ease of use, and patient preferences when discussing therapeutic options.

While the efficacy of these treatments has been studied in clinical trials, some studies are limited by small sample sizes, varying methodologies and endpoints, and short follow-up periods. Direct comparisons between different treatment options are often not found, further complicating the ability for clinicians to choose the appropriate treatment for their patients. Additional large, double-blinded, placebo-controlled randomized trials and studies with direct comparisons between treatments will be helpful for healthcare providers and patients in making informed decisions about AGA treatments.

Declarations

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