

Androgenetic Alopecia: An Evidence-Based Treatment Update

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Abstract

Background Androgenetic alopecia (AGA) is one of the most common chronic problems seen by dermatologists worldwide. It is characterized by progressive hair loss, especially of scalp hair, and has distinctive patterns of loss in women versus men, but in both genders the central scalp is most severely affected. It often begins around puberty and is known to effect self-esteem and the individual's quality of life. In contrast to the high prevalence of AGA, approved therapeutic options are limited. In addition to the scarce pharmacologic treatments, there are numerous nonprescription products claimed to be effective in restoring hair in androgenetic alopecia.

Objectives The purpose of this paper is to review published medical and non-medical treatments for male and female AGA using the American College of Physicians evidence assessment methods. MEDLINE, EMBASE and Cochrane Library were searched for systematic reviews, randomized controlled trials, open studies, case reports and relevant studies of the treatment of male and female AGA. The relevant articles were classified according to grade and level of evidence.

Results The medical treatments with the best level of evidence classification for efficacy and safety for male AGA are oral finasteride and topical minoxidil solution. For female AGA, topical minoxidil solution appears to be the most effective and safe treatment. The medical treatments corresponding to the next level of evidence quality are some commonly used therapeutic non-FDA-approved options including oral and topical anti-hormonal treatments. Surgical treatment of follicular unit hair transplantation is an option in cases that have failed medical treatment although there is high variation in outcomes.

Limitations Some articles, especially those concerning traditional herbs claimed to promote hair regrowth, were published in non-English, local journals.

Conclusions An assessment of the evidence quality of current publications indicates that oral finasteride (for men only) and topical minoxidil (for men and women) are the best treatments of AGA.

1 Introduction

Androgenetic alopecia (AGA), also known as male or female pattern hair loss, is one of the most common chronic problems seen in dermatologic outpatient units. It is an age-dependent disorder affecting more than 80 and 42 % of Caucasian men and women at the age of 70 years, respectively [1, 2]. It is characterized by progressive hair loss, predominantly of the central scalp, with some variation of patterned loss. Although the prevalence is high in elderly patients, AGA may also start at puberty. Patients who have prominent thinning of hair are perceived as older, which affects self-esteem and leads to psychosocial morbidity [3]. In contrast to the high prevalence of AGA, approved therapeutic options are limited. Moreover,

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besides the limited pharmacologic treatments, there are also numerous nonprescription, over-the-counter products claimed to be effective in restoring hair in AGA.

The purpose of this paper is to provide an updated review of therapeutic approaches, both medical and non-medical, for male androgenetic alopecia (MAGA) and female androgenetic alopecia (FAGA).

2 Literature Search Methods

MEDLINE, SCOPUS and Cochrane Library were searched up to December 2013 for the key terms of *androgenetic alopecia, male androgenetic alopecia, female androgenetic alopecia, pattern hair loss, male pattern hair loss, female pattern hair loss AND treatment*. Overall, 711 articles were found. Our inclusion criteria represented systematic reviews, randomized controlled trials (RCTs), open studies, and case reports of available treatments of FAGA and MAGA reported in the English language. For therapeutic agents that were claimed to have efficacy but for which there was a lack of clinical studies, in vitro studies of such agents were included. We excluded studies on FAGA secondary to underlying hormonal causes; i.e., androgen-producing adrenal or ovarian tumor. After checking for duplications and relevance, 111 articles fulfilled the inclusion criteria and were included in our review.

Study details and data of all clinical studies were extracted and classified for the grade and level of evidence according to the American College of Physicians (ACP), as described previously [4].

2.1 Grading of Quality of Evidence

Grade 1 = High-quality evidence Evidence is considered high quality when it is obtained from one or more well designed and well executed RCTs that yield consistent and directly applicable results. This also means that further research is very unlikely to change our confidence in the estimate of effect.

Grade 2 = Moderate-quality evidence Evidence is considered moderate quality when it is obtained from RCTs with important limitations, for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well designed controlled trials without randomization, well designed cohort or case-control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect

on our confidence in the estimate of effect and may change the estimate.

Grade 3 = Low-quality evidence Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on our confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose-response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

I = Insufficient evidence to determine net benefits or risks When the evidence is insufficient to determine for or against routinely providing a service, we grade the recommendation as 'insufficient evidence to determine net benefits or risks'. Evidence may be conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect is very uncertain as evidence is either unavailable or does not permit a conclusion.

2.2 Grading of Guideline Recommendations

++ = Strong recommendation A strong recommendation means that benefits clearly outweigh risks and burden.

+ = Weak recommendation When benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks, a recommendation is classified as weak. Patient preferences may strongly influence the appropriate therapy.

- = Not recommended When risks and burden clearly outweigh benefits.

3 Medical Treatment

The medical treatment for AGA can be generally divided into *androgen-dependent* and *androgen-independent*. Androgen-dependent agonists act against androgen, for example, reduce testosterone levels, serve as androgen-receptor blockers, or 5-alpha-reductase inhibitors (5-ARIs). Androgen-independent drugs work through different mechanisms other than hormones.

3.1 Androgen-Dependent Agents

3.1.1 5-Alpha-Reductase Inhibitors (Table 1)

Finasteride is, so far, the only US FDA-approved oral medication for the treatment of MAGA; it was approved in

Table 1 Summary of evidence for the use of 5-alpha-reductase inhibitors for the treatment of androgenetic alopecia (AGA)

Male			Female						
Agents	Grading of evidence ^a	Recommendation ^b	Safety	Notes	Agents	Grading of evidence ^a	Recommendation ^b	Safety	Notes
<i>Oral</i>									
Finasteride 1 mg OD	1	++	Erectile dysfunction PSA screening (pretreatment + annually)	FDA approved	Finasteride 1 mg OD	2	-	Pregnancy category X	Study in postmenopausal subjects
Dutasteride 0.5 mg OD	2	++	Erectile dysfunction PSA screening (pretreatment + annually)	Phase III study	Dutasteride 0.5 mg OD	3	+	Pregnancy category X	Case report
<i>Topical</i>									
Finasteride 0.05 % gel	2	+	No sexual side effects		Finasteride	I			
0.1 % lotion (in combination with 5 % minoxidil solution)									

Summary

Oral finasteride 1 mg OD is the first-line treatment of male AGA due to the highest level of evidence and the only oral treatment with FDA approval. Dutasteride is a possible effective alternative but is still an off-label therapy and has a higher rate of potential side effects

OD once daily, PSA prostate-specific antigen

^a Grading of evidence: 1 = meta-analysis or consistent results of high-quality randomized controlled trials (RCTs); 2 = moderate quality RCTs, high quality comparative studies; 3 = observational studies; I = insufficient evidence to determine net benefits or risks

^b Recommendation: ++ strong recommend; + weak recommend; - not recommended

1997. It is a type 2, 5-ARI that blocks the conversion of testosterone to dihydrotestosterone (DHT). A recent systematic review by Mella et al. examining the efficacy and safety of finasteride therapy for patients with MAGA showed that there is moderate quality evidence suggesting approximately 30 % hair improvement in patients with long-term use of finasteride 1 mg daily [5]. The response to treatment was significantly detected at 6 months' duration. In MAGA, the response in the vertex area was more prominent than in the frontal/centroparietal region [6]. Among the commonly mentioned sexually adverse effects, including erectile dysfunction, decreased libido, and ejaculation dysfunction, the only adverse effect that was significantly more frequent with finasteride therapy in comparison with placebo treatment was erectile dysfunction, and there is moderate-quality evidence suggesting an absolute increase in the risk of erectile dysfunction of approximately 1.5 % [5, 7]. In 2011, the patient information leaflet for Propecia[®] (finasteride 1 mg) in the USA was updated to include a statement that it may cause "difficulty in achieving an erection that continues after stopping the medication". These persistent sexual side effects, defined as sexual side effects associated with finasteride use which persisted for at least 3 months despite cessation of the medication, were found from the post-marketing surveillance in a subset of patients who were treated for AGA [8, 9]. The exact prevalence of this condition is still unknown but it has a great impact on a patient's quality of life because the affected patients continue to have a high prevalence of sexual dysfunction for years [10]. Moreover, many of the patients have consequently developed anxiety and depression [11]. Reduced levels of several neuroactive steroids linked to sexual function and mood due to finasteride was proposed to be the pathogenesis of this persistent sexual side effect.

As benefits require indefinite use, long-term side effects of the drugs should be monitored. Regarding concerns for increased risk of high-grade prostate cancer in men taking 5-ARIs, a recent meta-analysis concluded that finasteride does not increase the risk of developing high-grade prostatic cancer [12]. However, finasteride 1 mg/day reduces prostate-specific antigen (PSA) levels and thus could mask the early symptoms of prostate cancers. Therefore, it has been suggested that the levels of PSA should be checked prior to treatment and then annually, especially in patients with a positive family history for prostate adenocarcinoma [12, 13]. Gynecomastia has been reported in rare cases [14].

Male breast cancer, which is generally much rarer in men than in women, is one of the recent concerns in long-term finasteride use. In 2011, the UK Medicines and Healthcare products Regulatory Agency (MHRA) reported cases of male breast cancer associated with finasteride use

[15]. The proposed mechanism by which finasteride could cause male breast cancer is the increased proportion of estrogen to testosterone ratio secondary to DHT conversion blockage [16]. Among 50 worldwide cases, the majority of cases received 5 mg of finasteride for the treatment of benign prostatic hyperplasia (BPH) while only three cases have been reported with the use of finasteride 1 mg for AGA. From the relatively short times to onset in all three cases, it is unlikely that finasteride is the causal agent for male breast cancer [15]. Moreover, a recent study investigated the association between 5-ARIs (finasteride and dutasteride) and male breast cancer and revealed the lack of a positive association [16]. Dermatologists should be aware of abnormal breast symptoms, especially a breast mass, in male patients treated with long-term finasteride [5]. Since finasteride is metabolized in the liver, it should be avoided in patients with liver diseases [17].

The use of finasteride in women is limited due to its teratogenicity. However, existing studies were in postmenopausal subjects. Two large, controlled trials in postmenopausal women with AGA showed that finasteride 1 mg daily failed to improve hair loss over placebo [18, 19]. However, an open study in premenopausal women revealed that 2.5 mg daily of finasteride in combination with the oral contraceptive pill improved hair loss in 62 % of subjects; whether this was due to the higher dosage of finasteride or the anti-androgenic effect of the oral contraceptive pill is unclear [20]. It was also shown in case reports that finasteride might be of benefit in premenopausal FAGA patients with associated hyperandrogenism [21]. The cautious use of finasteride in women with childbearing potential should be accompanied by strict birth control methods since it can cause ambiguous genitalia in the male fetus [22].

Dutasteride is a potential alternative to finasteride with proposed increased efficacy. It blocks both type I and type II of the 5-alpha reductase enzyme. Dutasteride is approved for the treatment of BPH at the dose of 0.5 mg daily. There are controlled trials comparing the efficacy of dutasteride with finasteride in the treatment of AGA. In phase II studies, daily ingestion of dutasteride 2.5 mg has shown superior efficacy to finasteride 5 mg [23, 24]. From a recent meta-analysis by Gupta and Charrette [25], dutasteride 0.5 mg daily was not significantly different than finasteride 1 and 5 mg in terms of efficacy and safety. Impotence, decreased libido, breast tenderness and breast enlargement, and ejaculation disorders are more common with dutasteride than with finasteride [14].

In females, a case report showed that dutasteride 0.5 mg daily for 6 months was effective in a patient with limited response to topical minoxidil and oral finasteride [26]. Similar to finasteride, dutasteride should not be used in women of reproductive age without contraception, and

liver function should be monitored while taking this drug [22].

There have been attempts to use topical 5-ARIs as a treatment for AGA. Two small RCTs introduced the potential efficacy of topical finasteride in the formulation of 0.05 % gel and 0.1 % lotion, respectively, in MAGA without sexual side effects [26, 27]. A study of mesotherapy with dutasteride in FAGA also concluded that this treatment was effective and safe [28].

3.1.2 Estrogen and Other Anti-Androgen Treatments (Table 2)

Hormonal treatment for AGA can be divided into two broad groups, anti-androgens and estrogenic (or anti-estrogenic) drugs. This group of therapies has particular utility in FAGA patients, especially in those with androgen excess or hormonal dysregulation [6, 17, 29]. However, according to a current systematic review in FAGA treatment, there is still limited evidence to support the efficacy of hormonal therapy in FAGA [30].

Spirolactone is the most commonly used off-label anti-androgen for the treatment of FAGA. It is a potassium-sparing diuretic, and a structural antagonist of aldosterone. In the treatment of AGA, it acts by decreasing the production and competitively blocking the androgen receptor in the target tissue [30]. It has been used to treat FAGA at the dose of 50–200 mg daily for at least 6 months. Side effects include postural hypotension and electrolyte imbalance [17]. Although there is no RCT to confirm the efficacy of spironolactone in FAGA, an open, before–after study in 40 FAGA patients receiving 200 mg of spironolactone daily for 12 months showed improvement in hair regrowth in up to 44 % of patients [31].

Cyproterone acetate is the other commonly used oral anti-androgen for FAGA in Europe, but is unavailable in the USA. It directly blocks the androgen receptor and decreases testosterone levels by suppressing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release. Treatment with cyproterone acetate, alone or in combination with ethinylestradiol, can improve hair growth in FAGA. An RCT confirmed the efficacy of Diane® (50 µg ethinylestradiol + 2 mg cyproterone acetate) on days 1–14 each month for a year; there was a statistically significant improvement in the anagen percentage over that in the control subjects [32]. Subgroup analysis of a meta-analysis showed that cyproterone acetate has a tendency (not statistically significant) to improve hair count in women with signs of hyperandrogenism at 12 months of treatment compared with women without hyperandrogenism [6]. Side effects of cyproterone acetate include depressed mood changes and liver toxicity.

Flutamide is a potent anti-androgen that competitively blocks the androgen receptor. Flutamide can improve hair growth after only 6 months of treatment, and offers long-term stability in FAGA [33]. One randomized study reported that flutamide at a dose of 250 mg daily provided a modest improvement in FAGA after 1 year, while cyproterone acetate and finasteride were not considered to be effective [34]. A case report showed that flutamide improved hair growth in a patient with FAGA who did not respond to topical minoxidil and oral spironolactone [35]. Flutamide use is limited by its risk of causing severe hepatic toxicity, which is dose-dependent. A report reveals that a low dose of 62.5 mg/day is effective and well tolerated [33].

There are no clinical trials to support the use of oral estrogens or anti-androgens to improve or prevent progression of MAGA [6]. However, a case report in a male-to-female transsexual candidate showed the effectiveness of systemic and topical estrogen in combination with aldosterone and minoxidil in partially reversing severe MAGA [36].

There are multiple clinical trials showing the efficacy of the following novel non-FDA-approved *topical hormonal agents* in AGA.

Alfatradiol (17 α -estradiol) is a topical anti-androgen that works by blocking the enzyme 5-ARI. The recommended application is 0.025 % alfatradiol lotion twice daily. In females, an open, randomized, comparative study showed that subjects treated with 0.025 % alfatradiol lotion had decreased total hair counts at 6 months while 2 % minoxidil solution promoted increased hair counts [37]. In contrast, another open study showed that alfatradiol statistically significantly increased the proportion of frontal anagen/telogen hair after 7.5 months of treatment in both genders [6, 38].

Fluridil is a topical anti-androgen available for the treatment of AGA in the Czech and Slovak Republics but is not approved by the US FDA. It dissolves in the sebum and blocks the androgen receptor in hair follicles but is not systemically absorbed. A small, double-blinded, RCT in MAGA showed that increased anagen hair percentage can be detected at 3 months of 2 % topical fluridil daily application, whereas the average anagen percentage did not change in the placebo group [39]. In FAGA, there was only one open study showing that 2 % fluridil solution did not change the anagen/telogen ratio after 9 months of treatment. Of note, there was no progression of FAGA observed in the patients using 2 % fluridil solution [40].

Fulvestrant is a pure estrogen receptor antagonist that is used as an anti-estrogen therapy in patients with hormone receptor-positive metastatic breast cancer. Studies in mice showed that fulvestrant can increase hair growth [41]. In a human study, topical fulvestrant 70 mg/mL twice daily did

Table 3 Summary of evidence for the use of topical minoxidil for the treatment of androgenetic alopecia (AGA)

Male			Female			Notes	Safety	Recommendation	Grading of evidence	Notes
Agents	Grading of evidence	Recommendation	Agents	Notes	Agents					
<2 % minoxidil solution	1	-	Hypertrichosis, contact dermatitis		1 % minoxidil solution	1	Hypertrichosis, contact dermatitis, contraindicated during pregnancy and lactation	+	1	FDA approved
2 % minoxidil solution BID	1	+		FDA approved	2 % minoxidil solution BID	1		++	1	FDA approved
5 % minoxidil solution BID	1	++		FDA approved	5 % minoxidil solution BID	1	More irritation than 2 %	++	1	FDA approved
5 % minoxidil foam BID	2	++	No propylene glycol	FDA approved	5 % minoxidil foam OD	2	No propylene glycol	++	2	FDA approved

Summarization statements: *Male* topical 5 % minoxidil solution twice daily shows the best evidence and is FDA approved. 5 % minoxidil foam twice daily was proved to be effective and is also FDA approved in the treatment of AGA. *Female* topical 2 % minoxidil solution twice daily is the only topical agent with FDA approval and has the highest evidence for both efficacy and safety. However, topical 5 % minoxidil foam once daily is comparable to 2 % minoxidil solution twice daily. Minoxidil 5 % foam once daily application was FDA approved February, 2014

Grading of evidence: 1 = meta-analysis or consistent results of high-quality randomized controlled trials (RCTs); 2 = moderate quality RCTs, high quality comparative studies; 3 = observational studies; I = insufficient evidence to determine net benefits or risks. Recommendation: ++ strong recommend; + weak recommend; - not recommended

OD once daily; BID twice daily

not show superiority over control vehicle in the treatment of AGA in both sexes [42].

3.2 Androgen-Independent Agents

3.2.1 Minoxidil

Minoxidil was originally developed as an oral medication for hypertension. The common side effect, hypertrichosis, was found in 24–100 % of patients treated with oral minoxidil, which led to the treatment of AGA with topical minoxidil [43]. The exact mechanism of action of minoxidil on hair growth is still unclear but is probably mediated via potassium channel opening, which leads to increased cutaneous blood flow, stimulated vascular endothelial growth factor and hair growth promoters in dermal papilla [44]. Recent studies suggest that it also enhances hair growth by increasing the production of prostaglandin E2 (PGE2) through stimulation of prostaglandin endoperoxide synthase-1 [45].

Minoxidil was the first and, so far, the only topical product that has been FDA approved for the treatment of AGA.

Minoxidil solutions of 2 and 5 % were approved for the treatment of MAGA in 1988 and 1991, respectively. In FAGA, 2 % minoxidil was FDA approved in 1991.

Recent meta-analytic studies in AGA treatment confirm the best level of evidence supports the efficacy of minoxidil in both sexes (Table 3) [6, 30, 46]. Most studies revealed that minoxidil statistically significantly increases non-velus and total hair count at 24 weeks of treatment. Regarding concentration, in MAGA, 5 % solution is superior to 2 % [47]. Concentrations under 2 % have no

benefit and there is no difference in the ability to increase hair count between 2 and 3 % solutions applied twice daily.

In FAGA, both 1 and 2 % minoxidil solutions increase hair count at 6 months in comparison with placebo, with better efficacy for the 2 % solution. However, the ability to enhance hair growth was not significantly different between the 2 and 5 % solutions with twice daily application, while more side effects were reported with the 5 % solution. To the best of our knowledge, there has been no study comparing the effectiveness of 2 % minoxidil solution twice daily and 5 % minoxidil solution once daily.

There were also many studies looking at the efficacy of combination treatment of topical minoxidil and other medications, including oral finasteride, oral contraceptive pill, topical tretinoin, topical azelaic acid, topical steroids, ketoconazole shampoo, and zinc pyrithione shampoo (Table 4) [48–53].

The recommended dosage for minoxidil solution is 1 ml twice daily on dry scalp, which should be left in place for at least 4 hours. Patient should be treated for at least 6 months prior to efficacy assessment. Although the standard formulation of minoxidil is a solution, an RCT confirmed that 5 % minoxidil foam could induce significant hair growth after 16 weeks of treatment, thus the FDA approved 5 % minoxidil foam for the standard treatment of MAGA in 2006 [54]. The recommended dosage for the foam formulation is half a cap twice a day. Interestingly, a randomized trial also revealed that 5 % minoxidil foam once daily was similar in effectiveness to 2 % minoxidil solution twice a day for the treatment of FAGA [55]. Recently, 5 % minoxidil foam once daily application was approved by FDA as a treatment for FAGA. Patients should be advised to continue minoxidil as long as they

Table 4 Summary of evidence for the use of combination treatment of topical minoxidil in androgenetic alopecia (male and female)

Combination	Grading of evidence ^a	Recommendation ^b	Notes
2–5 % minoxidil solution + finasteride 1 mg/day + 2 % ketoconazole shampoo [47]	2	++	
5 % minoxidil solution + 1 % zinc pyrithione shampoo [48]	2	++	Minox ≫ minox + ZnPT > ZnPT
0.5 % minoxidil solution + 0.025 % tretinoin solution [49]	2	+	Minox + tret > tret > minox
5 % minoxidil solution + 0.01 % tretinoin solution [50]	2	+	Minox + tret = minox
2 % minoxidil solution + OC vs CPA + ethinylestradiol [51]	2	++	Minox + OC > CPA + ethinylestradiol
12.5 % minoxidil + 5 % azelaic acid + 0.025 % betamethasone-17-valerate (MHEC) [52]	2	++	MHEC > 5 % minox in decreasing hair shedding MHEC = 5 % minox in hair growth

Summary

Efficacy of minoxidil could be increased using combined therapy. However, supportive studies are not available

CPA cyproterone acetate, MHEC minoxidil high extra combination therapy, Minox minoxidil, OC oral contraceptive pill, tret tretinoin, ZnPT zinc pyrithione, ≫ much better than, > better than, = similar to

^a Grading of evidence: 1 = meta-analysis or consistent results of high-quality randomized controlled trials (RCTs); 2 = moderate quality RCTs, high quality comparative studies; 3 = observational studies; I = insufficient evidence to determine net benefits or risks

^b Recommendation: ++ strong recommend; + weak recommend; – not recommended

want to maintain the efficacy. Discontinuation of minoxidil induces telogen effluvium in the minoxidil-dependent hair within 4–6 months [56].

Adverse effects of minoxidil include contact dermatitis, facial hypertrichosis, and transient increasing hair shedding. Constituents of the vehicle, especially propylene glycol, can cause skin irritation while true allergic reactions to minoxidil are rare. To reduce the irritation, a foam alcohol-based formulation is an option since it does not contain propylene glycol. Transient hair shedding is common during the first month of treatment due to the synchronization of the hair cycle, which is caused by stimulation of telogen follicles to re-enter anagen. The cycle normalizes within a few weeks to months with continuation of minoxidil use. Although there is no evidence of teratogenicity in animals, data in humans is still lacking. For this reason, minoxidil is not advised for females who are pregnant. Since minoxidil is excreted into breast milk in very low levels and no adverse effects were reported in the infants, the American Academy of Pediatrics considers minoxidil to be compatible with breast feeding [57].

3.2.2 Prostaglandin Analogs

The potential role of prostaglandin analogs in the treatment of alopecia was noted after the lengthening of eyelashes and eyebrows was observed when they were used topically for glaucoma. Recent studies reveal that an increased prostaglandin D2 (PGD2) level is correlated with miniaturization of hair follicles and, moreover, topical application of PGD2 also inhibited hair growth [58]. In contrast, PGF2 and PGE2 are synergistic, the result of which induces hair growth and prolongs anagen [45]. A small placebo-controlled trial in men with mild AGA has shown that 0.1 % latanoprost, a PGF2 analog, significantly increased hair density and pigmentation at 24 weeks compared with baseline and the placebo-treated site [59]. Bimatoprost, another PGF2 analog, in 0.03 % ophthalmic solution, is FDA approved for eyelash hypotrichosis. It has been shown to enhance and prolong anagen in mice. However, a case report of postmenopausal FAGA has failed to demonstrate the efficacy of locally injected 0.03 % bimatoprost for 16 weeks [60]. Viprostol, a synthetic PGE2 analog, is not an effective hair growth promoter in MAGA [61].

3.2.3 Ketoconazole

Ketoconazole is an imidazole antifungal. The use of ketoconazole shampoo results in increased hair growth in FAGA. The mechanism of action is unclear. Evidence supports the hypothesis that ketoconazole 2 % shampoo causes a local disruption of the DHT pathway, but the effect may also be related to its anti-inflammatory and

antifungal effect. Ketoconazole shampoo, especially in combination with oral finasteride, has been clinically shown to be effective in the treatment of MAGA [62, 63]. In FAGA with hyperandrogenism, 2 % ketoconazole shampoo has shown benefit in treatment [64].

3.2.4 Melatonin

Melatonin, the secretory product of the pineal gland, has been known to modulate hair growth, pigmentation, and molting in many species including humans [65]. Topical application of melatonin 0.1 % solution was shown to significantly increase anagen hair in MAGA and FAGA in two controlled studies, with good tolerability [66, 67].

3.2.5 Platelet-Rich Plasma

Platelet-rich plasma (PRP) is an autologous preparation of plasma with >1,000,000/ μ l platelets that are capable of secreting growth factors and cytokines, which stimulate stem cells [45]. PRP is frequently used in cosmetic surgery and related aspects of wound healing. The stimulatory factors in PRP, including fibrin, fibronectin, and vitronectin, may be involved in hair follicle growth and development. Some hair transplant surgeons have used PRP in hair transplantation procedures, either by storing the grafts in PRP until they are placed on the scalp, or by injecting PRP into the scalp prior to placement of grafts [68]. A recent study in mice confirmed that PRP can shorten the time of hair follicle formation and enhance the number of newly formed hair follicles [69]. However, the results of studies on the use of PRP as an adjunctive modality in hair transplantation remain controversial [70–72]. A comparative study in AGA patients has shown that injected PRP, in dalteparin and protamine microparticles, significantly increased hair cross-sectional diameter although it did not increase hair density after 12 weeks [73].

3.3 Other Miscellaneous Treatments

Apart from the previously described anti-AGA agents, there are numerous products claimed to be efficient in AGA that have insufficient supportive evidence or are still under investigation (Table 5). These products originate from different types of modalities including pharmaceutical products, natural products, nutritional supplements, and cosmetics. The proposed mechanisms of action of these products in AGA can be generally categorized as (i) promotion of hair regrowth by activation of the dermal papillae and induction of anagen hair regrowth; (ii) improvement of perifollicular vascularization; (iii) inhibition of 5-alpha-reductase and reduction of DHT activity;

Table 5 Summary of evidence for the use of miscellaneous agents in the treatment of androgenetic alopecia

Agents	Formulation/treatment recommendation	Supportive evidences
Promotion of hair regrowth by activation of the dermal papillae and induction of anagen hair regrowth		
Adenosine	Topical 0.75 % adenosine lotion/2 times daily	RCT in 102 males [74], 30 females [75]
Aloe vera	Not stated	In vitro study [76]
Amino acids	Oral cysteine, histidine, copper and zinc/4 times daily	RCT in 24 males, 24 females [77]
	Oral cysteine, calcium pantothenate, millet seed extracts/2 times daily	RCT in 40 females [78]
Bergamot	Topical bergamot extract	Study in mice [79]
Caffeine	Topical caffeine containing lotion/once daily	Open study in 40 males [80]
Crescina® Human Follicular Stem Cells (HFSC)	Topical application 5 ml of product once a day for 5 consecutive days per week	RCT in 46 males [81]
Dabao (Chinese mixed herb extracts)	Topical hair tonic/2 times daily	RCT in 396 males [82]
<i>Ginkgo biloba</i>	Topical ethanoic extract of <i>Ginkgo biloba</i> leaf	Study in mice [83]
Ginseng	Topical methanol extract of <i>Panax ginseng</i> , topical water fraction of <i>Panax ginseng</i>	In vitro study [84] Study in mice [85]
Hibiscus	Topical 2 % extract of <i>Hibiscus rosa sinensis</i> flowers/2 times daily	In vitro study [86]
Melatonin	Topical 0.1 % solution/once daily	Open studies [67] RCT in 30 females [66]
Proanthocyanidins	Topical 1 % procyanidin B-2 tonic/2 times daily	RCT in 29 males [87]
Prostaglandin analogs	Topical 0.1 % latanoprost solution/once daily	RCT in 15 males [59]
Raspberry ketone	Topical 0.01 % raspberry ketone/once daily	Study in mice and open study in 10 males [88]
Retinoids	Topical 0.025 % tretinoin solution/2 times daily	Open study [50]
	Topical 0.01 % tretinoin solution (in combination with 5 % minoxidil solution)/once daily	RCT in 31 males [51]
<i>Sophora</i>	Topical <i>Sophora flavescens</i> extract	Study in mice [89]
Improving the perifollicular vascularization		
Aminexil® (2,4-diamino-pyrimidine-3-oxide)	Topical Aminexil solution/once daily	Open study in 180 males and females [90]
Botulinum toxin type A	150 unit intramuscular at scalp/single dose	Open study in 30 males [91]
Inhibition of 5-alpha-reductase and reducing dihydrotestosterone (DHT) activity		
<i>Cimicifuga racemosa</i>	Not stated	In vitro study [92]
<i>Citrullus colocynthis</i> (Schrad fruit)	Topical 2 and 5 % petrolatum ether extract	Study in mice [93]
<i>Curcuma aeruginosa</i>	Topical 5 % hexane extract/2 times daily	RCT in 87 males [94]
<i>Cuscuta reflexa</i> Roxb.	Topical petroleum ether extract	Study in mice [95]
Green tea	Topical 10 % epigallocatechin-3-gallate in ethanol, oral polyphenol extract	In vitro study [96] Study in mice [97]
Ketoconazole	2 % ketoconazole shampoo/2–4 times a week	RCT in 39 males [98]
Saw palmetto (<i>Serenoa repens</i>)	Oral <i>Serenoa repens</i> 320 mg/day	Open study in 100 males [99]
	Oral <i>Serenoa repens</i> 200 mg, β -sitosterol 50 mg/2 times daily	RCT in 26 males [100]
	Topical lotion containing saw palmetto/2 times daily	RCT in 24 males, 24 females [77]
Anti-inflammatory effect		
Zinc pyrithione	1 % zinc pyrithione shampoo/once daily	RCT in 200 males [49]
Improvement of hair follicle nutrition and energy		
Biotin	Oral biotin 2.5 mg daily	Open study in 93 patients [101]
Copper	11 % tripeptide-copper complex in water solution	In vitro studies [102, 103]
Niacin	Topical niacin derivatives (0.5 % octyl nicotinate and 5.0 % myristyl nicotinate)/once daily	RCT in 60 females [104]
Platelet-rich plasma	Intralesional injection every 2–3 weeks for 12 weeks	Study in mice [105] RCT in 26 males [73]

RCT randomized controlled trial

Strong evidence is lacking to support efficacy of miscellaneous agents. None of these above agents are FDA approved for the treatment of AGA

(iv) anti-inflammatory effect; and (v) improvement of hair follicle nutrition [6].

The details of the more common products are listed in Table 5 [49–51, 66, 67, 74–105].

4 Non-Medical Treatment

4.1 Surgical Treatment

Surgical treatments play an important role in AGA patients who do not have success with medical therapies. These include *hair transplantation* and *scalp reduction*, or a combination of both. Among these, hair transplantation is the most popular because it is less invasive while scalp reduction with flap is successfully performed only by a skilled surgeon. Regarding publications, hair replacement surgery for AGA is considered to have insufficient evidence in both sexes because of variation in study results due to different techniques, characteristics of the subjects, and skills of the surgeon and team [68]. Hair replacement surgery also has the limitation of not having efficacy in preventing the progression of AGA [6]. Therefore, long-term combination therapy of hair transplantation and oral finasteride 1 mg daily in male patients has been suggested [106].

4.2 Light Therapy

The paradoxical increase in hair growth observed with the use of 810-nm pulsed laser, low light, and intense pulsed light intended for hair removal led to the initiation of using laser light therapy for AGA. The mechanism of action of low-level light therapy continues to be poorly understood. The proposed theory is that the cellular respiratory chain of mitochondria absorbs the light energy, resulting in increased electron transport and promoting cellular signaling and purportedly allowing for possible hair regrowth [107].

Low-level light therapy (LLLT) is a relatively new technique used in the treatment of AGA. Several types of product using LLLT, including comb, hood, and helmet, are available for the adjunctive treatment of AGA. A number of studies have investigated the efficacy of LLLT for alopecia with different results [108]. Among these, the Hair Max LaserComb® (Lexington International, LLC, Boca Raton, FL) is a hand-held, noninvasive device with a wavelength of 655 nm that was approved by the FDA for the safe treatment of MAGA and FAGA. Regarding its efficacy, a double-blind, sham device-controlled, company-sponsored study of HairMax LaserComb® in the treatment of MAGA showed that subjects who used it for 15 minutes, three times a week, had a statistically significant increase of terminal hair in comparison with the control group at

6.5 months [109]. A very recently published study of HairMax LaserComb® also confirmed a statistically significant difference in the increase in terminal hair density between the lasercomb- and sham (control)-treated subjects with androgenetic alopecia in both sexes at 26 weeks [110]. Expert consensus based on their experience concluded that LLLT, particularly 650–900 nm wavelength at 5 mW, may be an effective alternative treatment for AGA patients either as a stand-alone or adjunctive therapy [111].

5 Conclusion

In summary, the medical treatments with the best level of evidence in terms of efficacy and safety for MAGA are oral finasteride and topical minoxidil solution. For FAGA, topical minoxidil solution appears to be the most effective and safe treatment. There is a limited amount of high-grade evidence to conclude the efficacy of some commonly used therapeutic options, including oral and topical anti-hormonal treatments. Besides the pharmaceutical agents, there are numerous cosmeceuticals, nutritional supplements, herbal and miscellaneous agents that are claimed to have anti-AGA effects with in vitro, animal, and small human pilot studies. These offer opportunities for further efficacy studies. Regarding non-medical treatment, follicular unit hair transplantation is a good option in cases that have failed medical treatment, although there is high variation in outcome. LLLT may be an alternative treatment but there is a paucity of efficacy studies.

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