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REVIEW ARTICLE

Treatment options for androgenetic alopecia: Efficacy, side effects, compliance, financial considerations, and ethics

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Abstract

Background: Androgenetic alopecia (AGA) is the most common form of hair loss consisting of a characteristic receding frontal hairline in men and diffuse hair thinning in women, with frontal hairline retention, and can impact an individual's quality of life. The condition is primarily mediated by 5-alpha-reductase and dihydrotestosterone (DHT) which causes hair follicles to undergo miniaturization and shortening of successive anagen cycles. Although a variety of medical, surgical, light-based and nutraceutical treatment options are available to slow or reverse the progression of AGA, it can be challenging to select appropriate therapies for this chronic condition.

Aims: To highlight treatment options for androgenetic alopecia taking into consideration the efficacy, side effect profiles, practicality of treatment (compliance), and costs to help clinicians offer ethically appropriate treatment regimens to their patients.

Materials and Methods: A literature search was conducted using electronic databases (Medline, PubMed, Embase, CINAHL, EBSCO) and textbooks, in addition to the authors' and other practitioners' clinical experiences in treating androgenetic alopecia, and the findings are presented here.

Results: Although topical minoxidil, oral finasteride, and low-level light therapy are the only FDA-approved therapies to treat AGA, they are just a fraction of the treatment options available, including other oral and topical modalities, hormonal therapies, nutraceuticals, PRP and exosome treatments, and hair transplantation.

Discussion: Androgenetic alopecia therapy remains challenging as treatment selection involves ethical, evidence-based decision-making and consideration of each individual patient's needs, compliance, budget, extent of hair loss, and aesthetic goals, independent of potential financial benefits to the practitioners.

KEYWORDS
androgenetic alopecia, ethics, review, therapies, treatments

1 | INTRODUCTION

Androgenetic alopecia, also known as male or female pattern baldness, is the most common type of hair loss and affects at least 80% of men and half of women by age 70, with the incidence increasing with age.[1–3] Although commonly encountered by practicing dermatologists and hair specialists, it can be one of the most challenging conditions to address as treatment selection often involves a complex consideration of multiple factors and ethical decision-making. Effectiveness, side effect profiles, practicality leading to compliance, and cost of treatment are among the most important factors to be considered especially given the chronic nature of AGA. Physician knowledge base, familiarity with specific treatment modalities, and financial compensation can also limit and obscure, respectively, a clinician's ability to select the most appropriate treatment option for each patient.[4]

The large variety of treatment options available and lack of standardization among existing studies complicates treatment selection even further. This makes it difficult to determine which treatment options are best in part because standardized grading techniques have not been consistently implemented. In meta-studies of current data available, change in anagen hair count appears to be the most consistent endpoint in determining treatment success.[5–7] This review is intended to help guide practitioners in their decision-making processes with regard to treating AGA by deconstructing the medical literature, presenting the breadth of treatment options available, and identifying the ethical consequences involved in selecting each treatment. Before deciding on the most optimal treatment for AGA, practitioners must have an understanding of its etiology and molecular mechanisms.

Androgenetic alopecia is an autosomal dominant condition composed of the gradual conversion of terminal hairs into intermediate and vellus hairs. Alterations in the hair cycle include reduced duration of anagen phase and increased duration of telogen phase, resulting in shorter hairs and eventual balding.[8] Early-onset AGA has a strong association with severe coronary artery disease and metabolic syndrome and individuals with a high body mass index have been found to have increased incidences of severe AGA.[9] Recent evidence has also demonstrated that AGA, occurring in both genders, has been linked to a number of severe cases of COVID-19 which has been termed the "Gabrin sign."[10–13]

In men, AGA begins as a bitemporal thinning of the frontal scalp which spreads to the vertex. In women, AGA presents as diffuse hair thinning between the frontal scalp and vertex, typically sparing the frontal hairline, which creates a more visible scalp. The condition is particularly more common among those undergoing menopause.[14] The diagnosis is usually clinical, but follicular miniaturization is the histological footprint of AGA.[15] Hair loss negatively impacts self-esteem and overall quality of life. Multiple studies have shown that men who experience premature loss of hair often exhibit emotional distress and express significant concern to their peers and family.[16,17] Studies have also shown that the psychological impact in women is more devastating than in male counterparts.[18]

Current FDA-approved therapies include topical minoxidil, oral finasteride, and low-level light therapy. However, there is a multitude of other primary and complementary treatment options commonly utilized among practitioners. The efficacy and mechanisms of existing, alternative, and upcoming therapeutics for AGA, as well as ethical and financial factors to consider when selecting a treatment option, will be covered in the following sections.

1.1 | COMPARING AGA THERAPEUTIC OPTIONS

In order to appropriately compare various therapeutic options for AGA and attempt to create a choice matrix for each therapeutic class, we will evaluate efficacy, side effect profiles, ease of use (compliance factors), and cost. It is also important to recognize that AGA is a chronic, lifelong condition, which makes comparing ease of use and cost more challenging. We therefore will look at ease of use and cost during monthly and over a 5 year period*. Additionally, we separate the medical options into topical and oral formulations.

2 | TOPICAL THERAPIES

For patients that have early or mild-to-moderate hair loss, and want to avoid oral medications due to the potential systemic side effects, topical therapies may serve as a viable first-line option or adjuvant for the treatment of AGA.

2.1 | Topical minoxidil

2.1.1 | Background and efficacy

Topical minoxidil is one of the only three FDA-approved treatments for male and female pattern hair loss. It was approved specifically for AGA in 1988 as a first-line treatment for men with mild-to-moderate AGA.[19,20] The oral formulation was originally used in the 1960s as a vasodilator for the treatment of hypertension.[21] Hypertrichosis was discovered as a side effect with chronic use of oral minoxidil, which prompted the development of a topical formulation for hair growth stimulation.[22] Minoxidil is readily available in both 2% and 5% foam and liquid solutions with varying efficacies.[23,24] Compounding pharmacies may also provide higher concentrations, such as 6–7% liquid solutions, at the clinician's discretion.

Minoxidil elicits its greatest effect at the vertex and frontal regions of the scalp where it is known to slow the rate of hair loss by prolonging the anagen phase and promote hair regrowth by increasing both hair diameter and density. The active metabolite, minoxidil sulfate, is proposed to bind adenosine triphosphate (ATP) sensitive potassium channels and relax the surrounding smooth muscle.[25] Topical application has been shown to stimulate cutaneous blood flow within 10–15 min.[26] Minoxidil's effect is specific to

the hair follicle as the conversion to its active metabolite is higher in hair follicles than in surrounding skin.[25]

Although efficacy of topical minoxidil is patient-dependent, multiple studies have demonstrated its effectiveness in promoting hair growth.[27] In a 1 year study of 904 males with AGA, 62% of the patients exhibited a significant decrease in the affected region of the scalp when treated with 5% topical minoxidil twice daily and 84.3% of patients reported hair regrowth of varying degrees.[28] The 2% and 5% solutions have elicited a 70% greater improvement in mean hair density compared with placebo after 16 and 26 week treatment periods.[29–31] In a randomized control trial (RCT) of 278 patients treated with minoxidil, 45% demonstrated more hair regrowth when treated with 5% solution vs. 2% by 48 weeks of treatment.[29]

*Dollar range: $ =< $100; $$ = $100–$1000; $$$ = $1000–$5000; $$$$ = $5000–$15 000; $$$$$ => $15 000;? = Unknown number of treatments (final cost).

2.1.2 | Side effects

Patients may exhibit side effects with topical minoxidil use which include irritant and allergic contact dermatitis, pruritus, scalp irritation, and facial hypertrichosis, which are more often seen with use of 5% solutions rather than 2%.[32] Overall, the incidence of side effects with minoxidil use is fairly low and non-serious.[33] More often, patients may report discomfort and inconvenience of topical application rather than actual side effects. One advantage of the 5% foam is that it is free of propylene glycol, the irritant component present in solution forms, and it is associated with a lower incidence of skin irritation.[29] Resistance to minoxidil with consistent use does not seem to be an issue.[34]

2.1.3 | Ease of use

Due to the necessity for frequent treatment application, compliance is a critical factor to consider when recommending minoxidil to a patient.[35] Minoxidil must be applied once or twice daily for full effect. If used properly, patients can expect to see hair growth within 4–8 months which stabilizes after 12–18 months.[36] If a patient terminates treatment, progressive hair loss can be expected within 12–24 weeks.[37]

Minoxidil is available in both 2% and 5% solutions and in foam preparation, so clinicians and patients have flexibility to select their preferred strength and formulation. The 5% solution has demonstrated greater efficacy than the 2% solution, and the 5% foam has shown equivalency to the 2% and 5% solutions depending on frequency of use.[23,30,38] The foam is often more convenient to use, as it dries quicker and has less tendency to spread to the peripheral areas. Some patients report an unpleasant residue after applying the foam, in which case a solution formulation may be preferred.

2.1.4 | Patient cost

$ monthly, $$ 5 year.

2.2 | Topical finasteride

2.2.1 | Background and efficacy

Finasteride as a topical formulation is available from compounding pharmacies and at least some formulations have been shown to reduce plasma and scalp DHT levels significantly well.[39,40] It was first evaluated by Mazzarella et al. in 1997 with a placebo-controlled trial involving 52 participants with promising results with regard to hair regrowth and reduction of balding without any side effects reported.[41] Compared to the oral form, topical finasteride gel has demonstrated similar efficacy in one study.[42] Studies comparing the two forms, however, did not progress beyond a 6-month period.[42] It must be noted that there is no standard formulation with different compounding pharmacies so it is impossible to determine the efficacy of a given formulation.[43]

2.2.2 | Side effects

In further studies, however, potential side effects included skin erythema and contact dermatitis, as well as increased liver enzymes, nocturnal enuresis, testicular pain, headaches, presyncope, and oropharyngeal pain.[40]

2.2.3 | Ease of use

Topical finasteride usually has a once daily regimen but must be used chronically. Also, there is no data available on patient compliance.

2.2.4 | Patient cost

$ monthly, $$ 5 year.

3 | ORAL THERAPIES

Oral therapies are often the easiest treatment options for patients with progressing and moderate AGA, but certainly have more potential side effects than topical agents. Since oral medications are convenient options it is common for many medically based physicians to default to this treatment option while dismissing other complementary, invasive, or alternative therapies that may very well be more effective and better-suited to particular subsets of patients.

3.1 | Oral finasteride

3.1.1 | Background and efficacy

As a well-studied and widely used medication, finasteride has been approved for the treatment of male pattern baldness since 1997. The drug functions by inhibiting Type II 5-alpha-reductase enzyme thereby blocking the conversion of testosterone to DHT.[44] It is available in 1 mg and 5 mg tablets, of which the lower dose is indicated for male pattern baldness. It is not approved for use in women and is assigned to pregnancy category X due to risk of causing ambiguous genitalia in a male fetus. This drug can be purchased over the counter which has made it much more cost-effective for patients.

The literature has shown finasteride to be effective in treating patients with AGA and long-term use of up to 5 years has shown significant hair growth and permanent stabilization of hair loss.[45,46] The drug is more effective in treating balding at the vertex, rather than at the frontal scalp, and it is recommended that finasteride be continued indefinitely in order to preserve the hair salvaged by initial treatment.[47] Finasteride's efficacy also seems to improve with time and in a few cases improved with consistent use.[48] A well-known large Japanese study of over 3000 males with AGA demonstrated that 11.1% of subjects exhibited significant hair regrowth with finasteride use, 36.5% exhibited moderate growth, and 39.5% had only a slight increase in hair growth over a period of 3 years.[49]

3.1.2 | Side effects

Side effects from finasteride use include orthostatic hypotension in about 9% of patients, dizziness in 7%, erectile dysfunction in 5–19%, ejaculatory dysfunction in 1–7%, and decreased libido in 2–10%, all of which may or may not decrease with time.[50] A retrospective study of 71 men with AGA experiencing sexual side effects with daily finasteride use was performed 15 years after initial FDA approval of finasteride.[51] The subjects exhibited persistence of these side effects 3 months after discontinuing the drug.[51] About 89% of these subjects re-interviewed at 14 months continued to report sexual side effects.[52] Another study of 79 men demonstrated sexual symptoms persisting close to 4 years after discontinuation of treatment.[53] Other research presents data in contrast with the above findings. One large double-blinded, placebo-controlled clinical trial demonstrated greater persistence of sexual dysfunction symptoms in the placebo group compared to those that received a daily dose of 5 mg of finasteride.[54,55] In another retrospective study of over 400 men taking 1 mg of finasteride daily, 0.8% developed persistent erectile dysfunction (PED) after a median of 4 years following discontinuation of treatment.[56] The main predictor of development of PED was use of the drug for at least 7 months.[56]

Due to the risk of sexual side effects, clinicians should exercise caution when treating AGA patients with finasteride. In addition, there is a recognized conglomerate of sexual side effects accompanied by neuropsychiatric effects including depression that have been grouped into a term known as post-finasteride syndrome (PFS).[55] In the majority of patients, this "syndrome" is reversible; however, there is a subset of patients that develop irreversible sexual dysfunction and depression.[51,52,57] In a 2012 study by Irwig et al., rates of depression and suicidal thoughts were noted to be significantly higher among former finasteride users compared with controls.[58] Therefore, it is important to screen all patients on finasteride therapy for symptoms of erectile dysfunction, decreased libido, and ejaculation disorders regardless of their dose. If any of these findings are positive, it warrants consideration of discontinuation of the drug or a switch to topical formulation. The International Post-Finasteride Syndrome Foundation was established to provide public education and support for those patients living with PFS.[59]

Finally, there is mixed evidence regarding the development of fertility issues with finasteride use and patients seeking finasteride treatment will often express concerns regarding the risk of infertility with treatment. Some research has demonstrated decreases in sperm count and spermatogenesis in both rats and humans while others have shown no alteration in sperm with daily finasteride at 1 mg daily.[60–62] Studies that demonstrated decreased concentrations of sperm with finasteride use typically showed reversal or improvement 3–4 months after treatment termination.[62,63] A multicenter, randomized, double-blinded study demonstrated a mean reduction in sperm count and motility after 6 months of treatment. However, after 1 year of continued use, sperm count improved to non-statistically significant levels.[64] While the causation of infertility with finasteride use is not conclusive, it is important to make patients aware of the developing literature.

3.1.3 | Ease of use

Once daily oral regimen and high likelihood of patients' compliance.

3.1.4 | Patient cost

$ monthly, $$ 5 year.

3.2 | Oral dutasteride

3.2.1 | Background and efficacy

Dutasteride is the successor to finasteride acting as a second-generation 5-alpha-reductase inhibitor and functioning as a selective competitive inhibitor of type 1 and type 2 isoenzymes of 5-alpha-reductase.[65] Dutasteride is reported to be three times more potent at inhibiting the Type I enzyme and 100 times more potent at inhibiting the type II enzyme than finasteride.[66] The drug comes in 2.5 and 5 mg doses, both of which have shown superior efficacy to finasteride 5 mg.[67] Due to dutasteride's large molecular size, it is difficult to formulate and deliver as a topical agent. However, its

large size and lipophilic nature contribute to it remaining on the scalp and preventing systemic absorption. If requested by clinicians, compounding pharmacies may formulate dutasteride topical solutions, although literature is sparse regarding its utility in treating androgenetic alopecia.

Olszewska and Rudnicka reported a case of a female patient with androgenetic alopecia who did not respond to minoxidil and initially benefited from finasteride. Given her persistent AGA, the patient was started on oral dutasteride. After 6 months of treatment, clinical and trichogram assessments revealed significant improvement in hair density.[68] Several randomized, double-blind, placebo-controlled clinical studies have demonstrated dutasteride's efficacy for treating androgenetic alopecia.[65,69] Intralesional dutasteride was also reported in order to decrease the systemic side effects. Saceda-Corralo et al. administered 1 mL intradermal dutasteride 0.01% injections every 3 months for a total of three sessions to six subjects. Trichoscopy assessments revealed increased hair diameter and density, in addition to clinical improvement in AGA. There were no statistically significant differences in serum levels of total and free testosterone, 3 alpha androstanediol glucuronide, and dihydrotestosterone before and after treatment.[70] Similar studies injecting dutasteride mesotherapy yielded promising results.[71–73] Overall, oral dutasteride appears to be superior to the intralesional route. However, more studies are warranted.[69]

Overall, dutasteride has shown superior efficacy both in blocking DHT and promoting hair growth compared to finasteride. In a study of 399 patients, dutasteride was found to block 98.4% of DHT, while finasteride blocked about 70%.[66] In another study of 416 men between 21 and 45 years of age, dutasteride was found to produce better hair count results than finasteride over a period of 12–24 weeks.[67] Despite the greater efficacy demonstrated by dutasteride, finasteride is still likely to be prescribed more often as a first-line agent in treating AGA due to FDA approval and insurance coverage.

3.2.2 | Side effects

Similar to finasteride, the side effects of oral dutasteride include decreased libido, erectile dysfunction, and ejaculatory dysfunction.[69]

3.2.3 | Ease of use

Dutasteride is used as a once daily oral regimen and has a high likelihood of patient compliance.

3.2.4 | Patient cost

$ monthly, $$ 5 year.

3.3 | Oral minoxidil

3.3.1 | Background and efficacy

Although not FDA-approved and not nearly as popular as finasteride, multiple studies were conducted to evaluate oral minoxidil for treating both male and female patients with AGA. The drug is available as a 2.5 mg tablet, and it can be cut in halves or quarters to achieve optimal safe dosing for the treatment of AGA. Sinclair first reported the combination of oral minoxidil 0.25 mg and spironolactone 25 mg to be a safe and effective option in managing female pattern hair loss.[74]

Several retrospective case series reported oral minoxidil to be an effective treatment for female AGA with favorable side effects.[75,76] Studies suggested that optimal safe doses range between 0.625 mg and 1.25 mg daily.[77] Oral minoxidil has also shown equivalent efficacy in women compared to the 5% topical formulation.[78] Jimenez-Cauhe et al. conducted a retrospective review of 41 men diagnosed with AGA undergoing oral minoxidil 5 mg daily treatment. Adverse effects were detected in about 30% of the participants, but they were all tolerable.[79] Another prospective study using a 5 mg once daily regimen showed 100% improvement at week 12 and 24 with 43% patients achieving excellent improvement.[22] Pirmez et al. suggested that very low dose oral minoxidil (0.25 mg once daily) may be less effective in treating moderate AGA and higher dosage might be needed. However, the sample size was small.[80]

3.3.2 | Side effects

Although it may be more convenient for patients to take the oral form of minoxidil, its systemic side effects such as increased heart rate, weight gain, hirsutism, hypertrichosis, and lower extremity edema make it unfavorable compared to topical minoxidil as a first-line treatment.[22] In a recent study of 1404 subjects, the most common side effect was noted to be hypertrichosis in about 15% of patients and the incidence of systemic adverse effects was noted in 1.7% of patients.[81] Oral minoxidil's side effects, however, are typically dose-dependent and reversible with discontinuation of the drug. Rare side effects include pericardial effusion, congestive heart failure, and allergic reactions.[22]

3.3.3 | Ease of use

Once daily oral regimen and high likelihood of patients' compliance.

3.3.4 | Patient cost

$ monthly, $$ 5 year.

4 | HORMONAL THERAPIES

4.1 | Spironolactone

4.1.1 | Background and efficacy

Although labeled for the treatment of cardiovascular diseases, spironolactone has been widely used as a treatment for female pattern hair loss due to its antiandrogenic properties. It works by decreasing testosterone production in the adrenal gland by affecting the 17a-hydroxylase and desmolase, as well as the competitive inhibitor of the androgen receptor.[82] Spironolactone is the most commonly used antiandrogen for female pattern hair loss (FPHL), and the standard dose is 100–200 mg daily.[83] A clinical trial conducted by Sinclair et al. studied 80 female patients with either cyproterone acetate or spironolactone 200 mg daily and found that 44% subjects experienced hair regrowth, 44% had no change in their hair density, and 12% had reduced hair density. There was no significant difference between both treatment groups.[84] There were also case reports demonstrating the efficacy of spironolactone alone or when combined with topical minoxidil.[85,86] In a retrospective survey of 166 patients with FPHL being managed with spironolactone, over 70% of patients noted stabilization or improvement of their disease.[87]

4.1.2 | Side effects

Although well-tolerated and has been on the market for decades, the side effects of spironolactone include electrolyte imbalance, worsening of renal function, and hypotension.

4.1.3 | Ease of use

Once daily oral regimen with high likelihood of patients' compliance.

4.1.4 | Patient cost

$$ monthly, $$ 5 year.

4.2 | Flutamide and bicalutamide

4.2.1 | Background and efficacy

Flutamide is an oral antiandrogen medication rarely used in practice. Oral flutamide first reported to be an appropriate option for managing hyperandrogenic alopecia.[88] Oral flutamide 250 mg daily was noted to be effective in managing FPHL refractory to topical minoxidil and oral spironolactone in a 55-year-old female.[89] A large population study evaluated yearly reduction of oral flutamide in managing AGA. A significant decrease in alopecia score was seen and 4% of the patients dropped out the study in the initial phase due to liver toxicity.[90] No patients abandoned the study in the following year when they were treated with a lower dose. Other common side effects of flutamide include hot flashes and potentially increasing the effect of warfarin.[91]

Bicalutamide is a nonsteroidal, antiandrogen medication. It has a more favorable safety profile than flutamide when treating prostate cancer. Recent retrospective review study of 17 women given oral bicalutamide (OB) with or without adjuvant therapies showed OB as a useful option in treatment of female pattern hair loss, especially patients with other comorbidities such as polycystic ovarian syndrome or hirsutism.[92]

4.2.2 | Side effects

Flutamide carries a risk of hepatic injury and has a Black box warning of hepatic failure. The most common side effect of bicalutamide is mild and transient elevation of liver enzymes.[92] Two retrospective reviews also suggested bicalutamide as a safe and effective option for female pattern hair loss with 95% adherence.[93,94] The most common side effects of OB were mild hepatic injury, peripheral edema, and gastrointestinal complaints. A retrospective review of OB reported three and four out of 316 patients dropped out of the study due to elevated liver enzymes and GI discomfort, respectively.[94]

4.2.3 | Ease of use

Oral medication with high likelihood of compliance.

4.2.4 | Patient cost

$ monthly, $$ 5 year.

4.3 | Cyproterone acetate

Cyproterone acetate (CA) inhibits gonadotrophin secretion and cutaneous 5-alpha-reductase activity and inhibits the androgen receptor.[95] CA is not available in the United States, but has been used in other countries. It has shown efficacy in treating AGA and acne vulgaris in female patients.[96] Although cyproterone acetate and topical minoxidil are both safe and effective options, CA may be a superior choice when patients have other signs of hyperandrogenism and elevated BMI.[95,97]

4.3.1 | Side effects

Cyproterone acetate is associated with weight gain, breast tenderness, and decreased libido.

4.3.2 | Ease of use

Oral antiandrogen medication; high likelihood of compliance. Not available in the United States.

4.3.3 | Patient cost

$$ monthly, $$$ 5 year (US?).

5 | LIGHT THERAPIES

5.1 | Low-level laser therapy

5.1.1 | Background and efficacy

Low-level laser therapy (LLLT) was discovered serendipitously in the 1960s when mice irradiated with a low fluence red laser were found to grow hair. After several decades of research, LLLT has emerged as a more commercially available therapeutic method for treating AGA. LLLT is typically administered through home-use devices that are available in the forms of combs, helmets, and caps. The Capillus® laser cap and Hairmax® Lasercomb/Laserband are two such devices that are FDA-cleared for the management of AGA.[5] The mechanism of action is not completely elucidated; however, it is believed that red light absorption by cytochrome c oxidase (CCO) in mitochondria leads to photodissociation of inhibitory nitric oxide (NO), which causes increased ATP production, reactive oxygen species modulation, and transcription factor induction.[98] These transcription factors induce protein synthesis and lead to downstream effects of NO-related vasodilation. Other proposed theories include a mechanism of action similar to that of minoxidil with blood flow promotion in the scalp via NO production and reduced follicular inflammation.[99,100]

In a randomized, double-blind, placebo-controlled trial comprising 42 female subjects with androgenetic alopecia, 24 active group subjects were treated with 655 nm LLLT vs. 18 placebo group subjects were treated with incandescent red lights (sham).[101] Subjects were treated on alternate days for 16 weeks, and photography and hair count assessments revealed a 37% increase in terminal hair counts in the active treatment group as compared to the control group. In a review of 11 trials, 10 demonstrated significant improvement in AGA compared to baseline or controls when treated with LLLT.[102] Two of the trials demonstrated efficacy for LLLT in combination with topical minoxidil, and one trial showed efficacy in combination with finasteride.

5.1.2 | Side effects

Minimal side effects were reported. Small number of participants reported adverse events of acne, mild paresthesia such as burning sensation, dry skin, headache, and pruritus.[102]

5.1.3 | Ease of use

Treatment frequency was not standardized across the literature, ranging from daily to several times per week. However, patients can use the device at home or at the clinical office.

5.1.4 | Patient cost

$$ one time, $$$ 5 year.

5.2 | Light-emitting diode devices

5.2.1 | Background and efficacy

In contrast with LLLT that delivers a single, collimated wavelength of light, light-emitting diode (LED) devices may emit a small band of wavelengths. In particular, an all-LED device that delivers dual dark orange (620 nm) and red light (660 nm) (Revian Red) to promote blood flow, reduce inflammation, and inhibit DHT via 5-AR downregulation.[103,104] In a prospective, randomized, double-blind, controlled study, 18 male AGA subjects were treated with Revian Red cap vs. 18 male AGA subjects were treated with a sham light device for 10 min daily for 16 weeks total.[105] Preliminary photographic assessments revealed increased mean hair count in the active group as compared to placebo group. Specifically, active group participants demonstrated approximately 26.3 more hairs per cm^2 compared to the placebo group.

5.2.2 | Side effects

Overall, literature has suggested light therapy to be a safe treatment modality for AGA in both male and female patients when used independently or in combination with topical/oral therapies.[102,106] Light therapy has an excellent side effect profile, and there are no contraindications for use, although caution may be taken when administering in patients with dysplastic lesions on the scalp.[107]

5.2.3 | Ease of use

Light therapy is ideal for patients who prefer non-invasive options, or for those who lack a flexible schedule to come into the office for regular treatments. These devices can be self-administered at home and controlled by a mobile application to also record daily compliance. Treatment is generally performed for 10 min daily for 6 months, which is easy to incorporate into a patient's schedule.[108]

5.2.4 | Patient cost

$$ one time, $$ 5 year.

6 | INJECTABLES

6.1 | Platelet-rich plasma

6.1.1 | Background and efficacy

Platelet-rich plasma (PRP) is another alternative treatment for AGA with the benefit that it is performed without any patient responsibilities. PRP is generally indicated for patients with early-stage AGA, as intact hair follicles are present and a more significant hair restorative effect can be achieved. During the procedure, approximately 10–30 mL of blood are drawn from the patient's vein and centrifuged for 10 min in order to separate the plasma from red blood cells. The platelet-rich plasma, containing numerous growth factors, is then injected into the deep dermis or subcutaneous tissue at a volume of 4–8 mL per session. Mild side effects include scalp pain, headache, and burning sensation, but these effects usually subside in 10–15 min post-injection and do not warrant use of topical anesthesia or pain medications.[109] Vibration or cool air is typically sufficient to alleviate any significant pain that a patient may feel from the treatment. Patients can resume regular activities immediately after treatment but should avoid strenuous physical activity 24 h post-treatment to allow for optimal absorption of PRP into tissue.

Hausauer and Jones conducted a single center, blinded, randomized controlled trial investigating the efficacy of two PRP regimens in 40 AGA subjects.[110] Participants received either subdermal PRP injections with 3 monthly sessions and booster 3 months later (group 1) or 2 sessions every 3 months (group 2). Folliscope hair count and shaft caliber, global photography, and patient satisfaction questionnaires were completed at baseline, 3-month, and 6-month visits. The authors reported statistically significant increases in hair count and shaft caliber in both groups at 6 months. Importantly, improvements occurred more rapidly and profoundly in group 1, indicating that PRP injections should be administered first monthly.[110] Alves and Grimalt demonstrated significant differences in mean anagen hair and telogen hair count as well as telogen and overall hair density when compared to baseline. In a review of 16 studies comprising a total of 389 patients with AGA, the majority demonstrated efficacy in promoting successful hair growth after 3–4 sessions on a monthly basis, followed by quarterly maintenance sessions.[111] PRP is not curative for hair loss and must be continued long term for hair sustenance. However, patient satisfaction is typically very high and 60–70% of patients continue to undergo maintenance treatments. Due to the relatively recent introduction of PRP injections for AGA, there are no long-term studies evaluating its effectiveness. Additionally, it is difficult to compare the efficacy with other remedies due to the lack of standardization in regard to PRP kits, treatment fractions, and regimens, including the use of newer multi-needle injectors.

6.1.2 | Side effects

While PRP injections are considered safe when performed by a trained medical provider, these treatments are not suitable for everyone. PRP may not be appropriate for those with a history of bleeding disorders, autoimmune disease, or active infection, or those currently taking an anticoagulant medication. Although the majority of patients seem to tolerate the pain associated with scalp injections, some patients may prefer to avoid it.

6.1.3 | Ease of use

Platelet-rich plasma injections are performed as an in-office procedure and ongoing therapy is required for hair restoration.

6.1.4 | Patient cost

$$ monthly, $$$$ 5 year.

6.2 | Exosomes

6.2.1 | Background and efficacy

Mesenchymal stem cell-derived exosomes (MSC-Exosomes) represent a new frontier in regenerative medicine.[112] These nanometer-sized, membrane-bound vesicles are secreted from cells to mediate cell-to-cell communication. Due to their acellular nature, they represent a novel therapeutic paradigm with low risk of immunogenicity and tumor formation. Exosomes are currently being used to treat a variety of medical conditions spanning pulmonary, cardiac, neurologic, and other organ systems. MSC exosomes have also shown promise in hair restoration as they contain potent cytokines and growth factors that promote hair growth.[113,114] Initial studies have demonstrated that MSC exosomes induce proliferation and migration of human dermal papilla cells and secretion of VEGF and IGF-1 *in vitro*.[115] Moreover, mice intradermally injected with MSC exosomes underwent telogen to anagen conversion, suggesting hair growth stimulation *in vivo*. In a study by Zhou et al., injection of dermal papilla cell-derived exosomes in mice was shown to accelerate the onset of hair follicle anagen phase and delay catagen phase, while simultaneously stimulating the expression of beta-catenin and sonic hedgehog growth factors.[116] Chang-Hun Huh et al. demonstrated increased mean hair density and thickness among 20 patients after 12 weeks of exosome treatment. The study found that exosomes stimulate hair follicle proliferation, accelerate their transition from telogen to anagen phase, and protect hair follicle cells against reactive oxygen species. ExoFlo and ExoCel are exciting and novel therapies which harness the power of exosomes. Similar to PRP, exosomal aliquots are injected into the scalp and treatments may be spaced apart depending on extent of hair loss. Further research is necessary

to optimize MSC-exosomal therapies for routine use in treating androgenetic alopecia.

6.2.2 | Side effects

Side effects include minor pain at the scalp injection site, which subsides 24–48 h post-treatment.

6.2.3 | Ease of use

Exosomal injections are an in-office procedure; there is no responsibility on the part of the patient. Monthly sessions are required for maximal hair restoration.

6.2.4 | Patient cost

$$$ monthly,? 5 year.

7 | ADJUVANT THERAPY

7.1 | Microneedling

7.1.1 | Background and efficacy

Microneedling appears to work by releasing growth factors and dermal papilla-associated stem cells, activating wound regeneration mechanisms with collagen formation secondary to physical minor wounding from the needles, and creating channels to enhance topical penetration. Studies revealed that microneedling appears to be a safe and effective adjuvant therapy and can enhance penetration of topical therapies. It was first noted in 100 male patients with mild-to-moderate AGA who were randomized into 5% minoxidil lotion twice daily group or 5% minoxidil lotion twice daily plus microneedling once weekly group. Significant improvements were noted in the combined treatments group per investigator's and subjects' ratings, as well as hair counts.[117] Similar studies were also conducted and yielded equivalent results of increased hair density and thickness.[118–121] Dhurat and Parajuli reported a case series of patients who were poor responders to conventional therapies and gained significant improvement after the addition of microneedling.[122,123] Jha et al. also reported superior clinical outcomes seen in the PRP, microneedling, and topical minoxidil patients vs. monotherapy patients.[124] There is evidence that microneedling preceding PRP enhances the efficacy of PRP as the pinpoint bleeding provoked by microneedling allows more uniform absorption of PRP[125]; there is lack of standardization in this method of treatment. The only study investigating optimal needle depth was conducted by Faghihi et al. who suggested 0.6 mm is a better choice than 1.2 mm.[119]

7.1.2 | Side effects

Common side effects of microneedling include pain, bruising, and folliculitis.[121] Patient compliance is an important factor to consider as the procedure is typically costly and often painful.

7.1.3 | Ease of use

Microneedling is an in-office procedure.

7.1.4 | Patient cost

$$ monthly, $$$ 5 year.

8 | SUPPLEMENTS & OTC TREATMENTS

Phytomedicine was previously introduced as a monotherapy or adjuvant therapy for several dermatologic conditions, such as photoprotection, vitiligo, and melasma.[126–128] A variety of nutraceuticals have appeared in the market over the past few years.[129] The oral regimens are convenient for many patients, but clinical evidence supporting its efficacy is still minimal. Nutraceuticals are tolerated in clinical trials and can be used as monotherapy or adjuvant therapy.

8.1 | Oral nutraceutical supplement containing Synergen Complex®

8.1.1 | Efficacy and background

A novel nutraceutical supplement containing a proprietary Synergen Complex® (Nutrafol® Capsules; Nutraceutical Wellness, Inc.) composed of phytoactive extracts, vitamins, minerals, and botanicals was developed to improve hair growth and hair quality. The active ingredients include saw palmetto, ashwagandha, curcumin, hydrolyzed marine collagen type I & III, palm extract (tocotrienol/tocopherol complex), horsetail, amino acids, black pepper fruit extract (piperine), Japanese knotweed, hyaluronic acid, and biotin. These ingredients inhibit 5-alpha-reductase, lower cortisol levels, reduce inflammation, promote homeostasis, and maintain collagen stores. Farries et al. presented four patients who used this oral nutraceutical supplement as a monotherapy with excellent results and high patient satisfaction.[130] Ablon and colleagues reported a 6 month, placebo-controlled trial with 40 participants to evaluate the effects of an oral nutraceutical supplement in managing female AGA. Daily intake of the oral supplement resulted in a significant increase in terminal and vellus hairs, and hair quality in the treatment group. Almost 85% of the patients noted feasibility of adding an oral regimen to their daily routine and preferred oral intake over topical applications. Most importantly, no adverse events or side effects were reported.[131]

Ablon and Kogan recently reported the 6-month interim results of a double-blind, placebo-controlled trial assessing the safety and efficacy of an oral nutraceutical supplement (Nutrafol® Women's Balance Capsules; Nutraceutical Wellness, Inc.), which contained patented Synergen Complex Plus®, maca, astaxanthin, and additional saw palmetto.[132] Women aged 40–65 with self-perceived hair thinning were randomly placed in the active treatment group ($N = 40$) or placebo group ($N = 30$). Subjects took four capsules of this nutraceutical supplement or placebo daily with 90- and 180-day follow-up visits. Hair shedding was measured by subjects washing their hair in a cheesecloth-covered sink, and fallen hairs were counted. The investigators also took 2-D global photographs and scored hair growth and quality on a 7-point scale. There was a statistically significant increase in the number of terminal and vellus hairs from phototrichogram analysis, and the active treatment group had a significant increase in terminal and total hair counts at 90 and 180 day visits. Moreover, the active treatment group experienced a 32.41% decrease in hair shedding by day 180. These results encourage the use of an oral nutraceutical supplement for reduction of hair shedding and promotion of hair growth in women experiencing the menopausal transition.[132]

8.1.2 | Side effects

None noted. As with any supplement, it is important to be aware of allergies to any active ingredients.

8.1.3 | Ease of use

Oral nutraceutical supplement with four capsules daily.

8.1.4 | Patient cost

$ monthly, $$$ 5 year.

8.2 | Marine complex supplement

8.2.1 | Background and efficacy

An oral marine complex supplement (Viviscal®; Lifes2good, Inc.) has demonstrated hair growth promotion in patients with AGA. The supplement is formulated with a proprietary blend of extracellular matrix components of shark and mollusks, vitamin C, horsetail extract, and flax seed extract.[133] This marine complex supplement has become increasingly popular over the past two decades for hair rejuvenation and comes in multiple formulations such as tablets, shampoos, conditioners, and creams for both men and women. Products can be purchased individually or as a subscription kit, and they are useful alone or as adjuvants for patients with AGA.[134]

Initial studies with this marine complex supplement for the treatment of androgenetic alopecia were performed in the 1990s. Lassus and Eskelinen conducted a 6-month, controlled, randomized, double-blind, parallel-group study of 20 male subjects with hereditary androgenic alopecia receiving once daily marine complex supplement vs. 20 male subjects receiving once daily fish extract.[135] The marine complex supplement group showed a mean increase in non-vellus hair of 38% compared with a 2% increase in the fish extract group. Moreover, 19 subjects in the marine complex supplement group showed both clinical and histological improvement, while subjects in the fish extract group did not. More recently, in a 6-month, double-blind clinical trial, adult male subjects with thinning hair were randomized to marine complex supplement or placebo administration twice daily.[136] Subjects taking the marine complex supplement experienced decreased shedding and increased hair growth (total hair count, total hair density, and terminal hair density) at 180 days. Digital photography, trichoanalysis, and investigator assessments demonstrated significant improvements in terminal and vellus hair count. Hair pull test results were also lower in the marine complex supplement group. Similar research conducted in female patients also has shown promising results.[137,138] These studies revealed that a marine complex supplement has efficacy in treating AGA.

8.2.2 | Side effects

Based on known side effects from its active ingredients, the supplement may have the potential to cause arthralgias, bloating, constipation, diarrhea, nausea, and allergic reaction but none of these have been seen in clinical trials.[139]

8.2.3 | Ease of use

Due to the availability of this product in multiple formulations, there is a lot of versatility in its use. Like any oral therapeutic, the product requires a high rate of daily compliance since results take months to elicit full effect. Oral tablets are taken twice daily.

8.2.4 | Patient cost

$ monthly, $$$ 5 year.

8.3 | Serenoa repens

8.3.1 | Background and efficacy

The active ingredient of Serenoa repens (SR) is saw palmetto, which is a palm tree berry extract that inhibits the 5-alpha-reductase and was advertised as a regimen for benign prostatic hyperplasia and AGA.[140–142] In a study with 10 male subjects with AGA, improvement

was noted in 60% of the participants.[143] Another study applying topical SR extract in lotion and shampoo for 3 months led to 35% increase in hair density.[140] Rossi et al. conducted an open-label study enrolling 100 male patients to study the efficacy of Serenoa repens 320 mg daily vs. finasteride 1 mg daily for 24 months. 38% of patients treated with Serenoa repens noted hair growth, whereas 68% of patients treated with finasteride noted hair growth. The investigators also noted that finasteride affected the vertex and frontal scalp, while SR primarily affected the vertex scalp.[144]

8.3.2 | Side effects

Side effects of SR are minimal. The most common side effect is gastric discomfort. SR may reduce PSA levels by 50% after 6–12 months of treatment, thus possibly missing early detection of prostate cancer in patients self-medicating with Serenoa repens.[140]

8.3.3 | Ease of use

Serenoa repens is an oral, once daily regimen.

8.3.4 | Patient cost

$ monthly, $$$ 5 year.

8.4 | Plant-based oils: rosemary oil, tea tree oil, pumpkin seed oil, coconut oil, castor oil, amla oil

8.4.1 | Background and efficacy

Hair oiling has deep cultural roots in Ayurvedic medicine dating back thousands of years. Plant-based oils are affordable and holistic hair growth options that have remained popular over time and are largely backed by anecdotal evidence. In many regions of the world, it is common practice for families to routinely massage oil into their scalps before bedtime. Rosemary oil (*Rosmarinus officinalis*) is a medicinal plant with diverse actions, including enhancing microcapillary perfusion, increasing prostaglandin E2 production, and decreasing leukotriene B4 production.[145] A randomized clinical trial compared the efficacy of topical rosemary oil vs. minoxidil 2% for the treatment of androgenetic alopecia.[146] 50 subjects were assigned to each treatment group, and they were observed for a 6-month period with microphotographic assessments. Both groups experienced a significant increase in hair count at the 6-month endpoint compared to the baseline and 3-month endpoint. Moreover, scalp itching was less frequent in the rosemary oil group. Pumpkin seed oil has also been shown to promote hair growth via 5-AR antagonism. In a randomized, double-blind trial, 76 male patients with AGA received 400 mg of pumpkin seed oil or a placebo daily for 24 weeks. Mean hair count among the treatment group increased by 40% while mean hair count among the placebo group increased by 10%.[147] Tea tree oil has been shown to have anti-inflammatory and antimicrobial effects, which are beneficial in treating dermatological conditions. In a double-blind, randomized, placebo-controlled study, subjects receiving a microemulsion of minoxidil, diclofenac, and tea tree oil, vs. minoxidil alone or placebo, demonstrated an earlier response in AGA treatment.[148] Overall, hair oils are typically affordable and may be purchased over-the-counter. While they are readily available, there are no FDA regulations on hair oil ingredients and further robust clinical studies are needed to better characterize their efficacy. Therefore, these products may serve best as complementary supplements to prescription or conventional treatments.

8.4.2 | Side effects

Side effects are minimal and most commonly include scalp irritation.

8.4.3 | Ease of use

Topical application of hair oils can be performed at home, but may interfere with hair styling due to greasy texture.

8.4.4 | Patient cost

$$ monthly, $$$ 5 year.

8.5 | Ketoconazole

8.5.1 | Background and efficacy

Long-term use of topical ketoconazole has shown efficacy in androgenetic alopecia. In addition to its antifungal and anti-inflammatory properties against Malassezia for the treatment of seborrheic dermatitis, ketoconazole has antiandrogenic properties with DHT inhibition. A systematic review of ketoconazole for the treatment of AGA revealed increased hair shaft diameter and increase in pilary index (percent anagen phase ×diameter) following treatment. Studies also demonstrated clinical improvement of AGA based on photographic evaluation.[149] Shampoos containing 2% ketoconazole may be applied to the scalp as a promising adjuvant or alternative therapy in the treatment of AGA. Robust studies, including randomized controlled trials, are needed to better characterize its mechanism of action and effectiveness.

8.5.2 | Side effects

Topical ketoconazole has no significant side effects.[149]

8.5.3 | Ease of use

Treatment regimen varies. Current literature reported once daily, twice daily, and 2–3 times/week regimen.

8.5.4 | Patient cost

$ monthly, $$ 5 year.

9 | COMBINATION THERAPY

The literature on combination therapies is still sparse and none are FDA-approved; however, some patients may exhibit significant benefit keeping in mind the cost and risks of utilizing more than one therapy. Topical minoxidil with oral finasteride is one of the most common combinations used to treat AGA. Compared with oral finasteride, topical minoxidil has demonstrated inferior results.[150,151] However, when used in combination with oral finasteride, superior clinical response has been demonstrated when compared with monotherapy.[152] A recent meta-analysis of 809 patients among 8 studies by Zhou et. al. (2020) indicated superior efficacy of topical minoxidil with oral finasteride.[153] Another study showed an 84.44% success rate in maintaining good hair density with topical minoxidil and finasteride combination 1–12 months after discontinuation of oral finasteride.[154]

Other combination therapies have yielded promising results as well. An open-label study using a combination of topical finasteride, dutasteride, and minoxidil observed significant hair regrowth in all of the 15 subjects.[155] One study investigated a combination of 0.1% finasteride and 3% minoxidil solution which yielded better results in global photographic assessments than 3% minoxidil solution used alone, albeit no difference in hair counts.[156] The combination of topical retinoid, minoxidil, and oral finasteride was also reported to be effective in a refractory patient.[157] It is thought that retinoid acid increases the follicular sulfotransferase enzymes.[158]

Superiority of combination topical minoxidil and spironolactone gel has also been demonstrated compared with monotherapy.[159] Oral medications have been combined for greater effect in other studies. Low-dose oral minoxidil (0.25 mg) and spironolactone (25 mg) were shown to decrease the severity of hair loss and shedding in a study of 100 women.[74] An open-labeled study on Japanese male patients who were treated with 1 mg oral finasteride daily, 2.5 mg oral minoxidil twice daily, and 5% topical minoxidil solution twice daily, as well as 4 mL injections (lidocaine, minoxidil, caffeine, and other components) once a month yielded promising clinical results.[160]

Combinations with LLLT have also undergone investigation. In a meta-analysis of 133 subjects across 3 studies treated with LLLT and topical minoxidil, combination therapy proved superior to monotherapy in global assessment ratings.[153] Two of these studies demonstrated a significant increase in hair count as well.[106,161] Finasteride has also been suggested to yield better results with LLLT.[102] A study of 32 patients, however, demonstrated no differences between LLLT alone and in combination with minoxidil or finasteride.[162]

Hair transplantation and PRP are often supplemented by medical therapy and microneedling. In a study of 79 men with AGA who received hair transplants, 94% of those treated in conjunction with finasteride from a period of 4 weeks prior to transplant to 48 weeks post-transplant exhibited visible increases in superior/frontal scalp hair compared to 67% of the placebo-treated group.[163] In a trial in which PRP was administered to 12 patients in combination with 5% topical minoxidil and 13 patients in combination with 1 mg oral finasteride improvements in mean hair count, hair density, anagen and telogen percentages, and mean anagen/telogen ratio were noted in both groups. The effect was even greater in the group treated with PRP and minoxidil combination compared to the PRP and finasteride combination group.[164] Microneedling in combination with topical minoxidil has also demonstrated superiority to monotherapy in 192 patients across 3 studies with regard to increase in hair count and as mentioned previously, microneedling in combination with PRP.[125,165,166] Lee et al. reported a split scalp study of topical growth factors plus microneedling vs. placebo in treating 11 Korean patients with FPHL. The treatment side showed a significant increase in hair shaft counts and no reports of adverse events.[167]

10 | HAIR TRANSPLANTATION

10.1 | Efficacy and background

Patients that opt for hair transplantation have either failed medical therapy or have lost a significantly large and non-recoverable surface area of scalp hair that can only be treated by implanting new hairs into the area. The procedure, if done successfully, induces a natural-appearing look in both men and women and essentially lasts permanently with graft survival among AGA patients being greater than 90%.[168] Transplantation can be done in the office with topical anesthesia in a matter of hours. Lidocaine 0.5–1.0% with epinephrine as field block or local infiltration is typically sufficient. Anesthesia may need to be reinjected at regular intervals due to the length of the procedure.

When conducting a consultation for hair transplantation, there are a number of key factors to consider. Caliber of the hair follicles helps to determine the perceived density of the transplanted hair rather than the number of hair follicles transplanted. Norwood/Ludwig stage of hair loss is also an important consideration when evaluating a patient for transplant. Chouhan et al. conducted a retrospective study and reported that hair transplant was effective in treating advanced (Norwood/Hamilton stage V-VII) AGA.[169] Ongoing hair loss will affect the density and cosmetic appearance of a hair transplant procedure so it is often useful to combine transplantation with medical therapy.

Donor harvesting options include ellipse and robotic follicular unit extraction (FUE), both of which demonstrate similar efficacy. Ellipses are removed through the depth of the dermis and retracted perpendicular to the length of the incision which allows for better visibility of the hair follicles and minimizes their transection and bleeding.[170] Longer ellipses with widths of 1 cm or less yield a larger and desired number of follicles. The follicles are usually separated into follicular unit grafts by highly trained surgical assistants. The downside of donor harvesting is that it leaves a linear scar which may be of less practical importance to patients that wear their hair long. For men who wear their hair short, follicular unit extraction may be more appropriate.

Women typically opt for ellipse procedures while men opt for either ellipse or FUE equally. This procedure involves removing up to four hair follicle groupings from a donor region using small caliber punches manually or robotically and circumvents the development of a linear visible scar as in ellipse procedures although there is the possibility of scattered 1mm pin point white scars left over from punches.[171] The challenges of performing the procedure manually are that transection of follicles is more likely due to human error and determination of the angle of hair growth is difficult as this varies throughout a patient's scalp. Robotic FUE helps to minimize these challenges as it continuously adjusts punch angles per unit of hair, can harvest a large number of follicular groupings while avoiding follicle transection, and eliminates operator fatigue. Robotic FUE is an automated process that can create 80–120 grafts per 3 × 3 cm grid and can extract 500–800 grafts per hour.[172] Although the process is monitored by the operator, it rarely requires override or correction. In a study of 38 consecutive robotic FUE procedures, the transection rate was comparable to the ellipse procedure when performed by an experienced transplant team, both around 5–7%.[173] Robotics also has the capability to create recipient sites and replace hairs. Disadvantages of robotic FUE include high cost, maintenance, office space, and need to trim a wider donor region in order to harvest follicular groupings.[172]

10.2 | Side effects

Since hair transplant is an in-office procedure. Side effects include adverse reaction to anesthesia, bleeding, pain, edema, intraoperative or postoperative pain, and patient dissatisfaction. For FUE, problems with wound healing may occur, such as keloid or hypertrophic scar formation.

10.3 | Ease of use

Hair transplantation is an in-office procedure that takes several hours. Hair restoration results are permanent.

10.4 | Patient cost

$$$$ single treatment,? Five year.

11 | NEW AND UPCOMING TREATMENT OPTIONS

11.1 | Clascoterone

Clascoterone gained FDA approval in August 2020 as the first topical antiandrogen agent to treat hormonal acne. The molecule resembles DHT and spironolactone in molecular structure and works by antagonizing androgen receptors on dermal papillae and inhibiting DHT's effect on hair miniaturization and dermal inflammation.[174] Due to its mechanism of action, it has potential in treating AGA. In a 6-month dose-ranging study, patients with AGA who received clascoterone 7.5% twice a day showed a significant improvement in hair loss from baseline and compared to those who received placebo.[175]

11.2 | Oral JAK inhibitors

Recently, JAK inhibitors have been considered to be effective therapies for alopecia areata (AA).[176] The underlying mechanism of AA involves an autoimmune attack on hair follicles with IL-15 production in response to interferon-γ secretion. This phenomenon is mediated by JAK 1/2 and JAK 1/3 signaling in T cells via a positive feedback loop. JAK inhibitors disrupt this cycle and cause reentry of hair follicles into the anagen phase, leading to hair growth. Despite their therapeutic success in alopecia areata, JAK inhibitors may not be useful for targeting androgenetic alopecia. Yale et al. reported 4 male patients with AA who were treated with oral JAK inhibitors, and subsequently developed hair growth in an androgenetic alopecia pattern. Future studies will be necessary to better characterize the role of JAK inhibitors in AGA.

11.3 | Prostaglandin analog

Latanoprost, a prostaglandin analog, was originally used to treat glaucoma. In 1997, the side effects of hypertrichosis at the eyelashes and surrounding hair in the region of the ipsilateral eyelids were reported.[177] It was used for scalp alopecia as latanoprost prolongs the anagen phase of the hair cycle.[178] Sixteen men with mild AGA (Hamilton II-III) enrolled in a double-blinded, placebo-controlled clinical to evaluate the effects of daily application of latanoprost 0.1%. An increase in hair density was noted in the treatment group. The limitation of this study is that only patients with mild AGA were included.[179]

12 | A DISCUSSION OF THE ETHICAL CONSIDERATIONS IN TREATING AGA

The cornerstone of medical ethics is to have a thorough discussion with patients regarding treatment efficacy, side effect profiles, ease of use (need for compliance), and costs absolutely independent of the potential benefit to the clinician.[180] While some hair loss treatments must be performed in office by a physician, contributing to their popularity as lucrative modalities, recommendations should not be based on the monetary benefit to the practitioner. Creating an algorithm for treating AGA provides clinicians with a foundation to triage available therapies based on clinical factors, and an ethical framework encourages clinicians to tailor treatment regimens according to patients' needs and expectations including preferences, budget, and aesthetic goals. A subset of male patients may even choose to decline treatment, as they do not want to adhere to lifelong therapies and balding is socially acceptable. Patients should understand the significance of treatment compliance and motivation when treating their AGA, as well as treatment practicality. Preferences are critical to compliance that is, many individuals will not apply a topical agent to their scalp once or twice daily and/or do not have the time or the budget to undergo multiple treatments in the physician's office. The clinician must recognize the risk/benefit balance of any treatment and clearly convey this to patients. AGA is a chronic condition; therefore, any treatment option (perhaps excluding hair transplantation after a series of sessions) is lifelong. Patient education is a paramount part of ensuring hair restoration results, otherwise, treatment cessation can cause loss of any benefits gained. The treatment matrix is outlined in Table 1 which will be discussed further.

12.1 | Consideration of efficacy

Horizontal comparisons among various options have rarely been reported in the literature. It is challenging to compare treatments for AGA due to lack of head-to-head clinical trials and insufficient data on therapeutic effectiveness. All the treatments discussed appear to have some efficacy, but no robust studies have concluded that one option is more effective than another. Furthermore, there is no universal consensus as to how the scientific community defines therapeutic effectiveness for AGA. While photography and trichoscopy are frequently performed to report global assessments and general hair counts in the literature, utilizing change in anagen hair count over time may be a more viable standard of comparison as anagen hair represents a hair follicle in an active growth phase. Moreover, new photography systems allow clinicians to measure hair counts without plucking hair or performing a scalp biopsy.

Cross-sectional studies and reviews have attempted to compare efficacies across different therapies for treating AGA. A recent publication comparing the hair counts among all FDA-approved treatment options ranked them from highest to lowest: finasteride 1 mg daily (18.37 hairs/cm^2), LLLT (17.66 hairs/cm^2), 5% minoxidil twice daily (14.94 hairs/cm^2), and 2% minoxidil twice daily (8.11 hairs/cm^2).[5] These results, however, were based on studies that varied in methodology for assessing outcomes and comparing mean differences in hair counts without statistical significance. Another meta-analysis ranked the efficacy of non-surgical treatment modalities in male AGA patients from most to least effective: PRP, LLLT, 0.5 mg dutasteride, 1 mg finasteride, 5% minoxidil, 2% minoxidil, and bimatoprost. In regard to female AGA patients, the ranking was as follows: PRP, 5% minoxidil, and 2% minoxidil.[181] The caveat with this analysis is that its ranking method was based on a non-universal formula developed specifically by the authors and also did not generate statistically significant differences between therapies. None of the studies evaluated in these comparative analyses measured anagen hairs as an end point but rather increase in terminal hair density, overall hair count, hair growth, and hair diameter.

It may be more useful to conduct new meta-analyses focused on studies that measure change in anagen hair counts after treatment. Dhurat et al. conducted a randomized, open-label, multicenter study to assess whether a caffeine-based 0.2% topical liquid would be non-inferior to minoxidil 5% solution in 210 males with AGA.[182] The primary endpoint was the percentage change in the proportion of anagen hairs from baseline to 6 months using a frontal and occipital trichogram. At 6 months, the 5% minoxidil solution group showed a mean improvement in anagen ratio of 11.68%, and the 0.2% caffeine solution group had an anagen improvement of 10.59%. The difference of mean values between both groups was 1.09%. Their data suggest that a caffeine-based topical liquid should be considered as non-inferior to minoxidil 5% solution in men with androgenetic alopecia.

Van Neste et al. also reported a placebo-controlled trial using a phototrichogram to measure the anagen hair and anagen:telogen hair ratio for patients taking oral finasteride vs. placebo. Their results revealed that oral finasteride was effective in both increasing anagen hair counts and anagen:telogen hair ratio.[6] Fischer et al. also published a trial evaluating the effects of topical melatonin in managing diffuse alopecia ($N = 28$) and androgenetic alopecia ($N = 12$) in female patients. This study used a trichogram and showed that topical melatonin was effective in increasing anagen hair rates in the occipital scalp.[7] Mean change in anagen hair has also been utilized as an endpoint in subjects with AGA treated with PRP.[183] Although these studies are limited in number, they may set a new standard in determining relative efficacy of treatment by focusing on change in anagen hair counts.

12.2 | Consideration of side effect profiles

Side effects need to be separated into short-term procedure related (pain, wound, etc) and treatment associated longer term. Oral treatments tend to have more long-term side effects than the topical and procedural options. Patients that begin a trial of topical agents like minoxidil may be unable to tolerate the formulation as it can cause scalp irritation, interfere with other hair products and ability to style

TABLE 1 Efficacy, side effects, clinical evidences supported in various treatment options in AGA

Treatment	Clinical evidence (weak, moderate, strong)	Side effects, short-term	Side effects, long-term	Likelihood of patient compliance (low, moderate, high, extremely high)	Monthly cost ($ ≤ $100; $$ = $100-$1000; $$$ = $1000-$5000; $$$$ = $5000-$15000; $$$$$ ≥ $15000; ? = unknown number of treatments (final cost))	5 year cost ($ ≤ $100; $$ = $100-$1000; $$$ = $1000-$5000; $$$$ = $5000-$15000; $$$$$ ≥ $15000; ? = unknown number of treatments (final cost))	Special considerations
Topical minoxidil	Strong, multiple RCTs	Unlikely, scalp irritation	Rare, dizziness, cardiac arrhythmia	Low to moderate	$	$$	Hair growth in undesired locations. May leave residue on hair which interferes with styling.
Topical finasteride	Weak	Unlikely, skin erythema, contact dermatitis	Rare	High	$	$$	May be used as a maintenance therapy
Oral finasteride	Strong, multiple RCTs	Uncommon	Post-finasteride syndrome	High	$	$$	Avoid in females of childbearing potential
Oral minoxidil	Moderate, mainly retrospective case reviews	Unlikely	Rare, unless patients with cardiovascular comorbidities. Weight gain	High	$	$$	Hair growth in undesired locations
Spironolactone	Weak, but commonly used by clinicians	Rare, possible SE include postal hypotension, electrolytic disturbance	Rare, unless patients with renal failure.	High	$$	$$	Contraindicated in males, pregnant females, and individuals with renal failure
Flutamide & bicalutamide	Weak	Hepatic injury	Flutamide has black box warning of hepatic failure	Moderate to high	$	$$	Potential interaction with other medications
Platelet-rich plasma	Strong	Unlikely, scalp pain	Rare	Moderate	$$	$$$$	Avoid in patients with bleeding disorder, lack of standardized protocol
Exosomes	Moderate	Unlikely, scalp pain	Rare	Moderate	$$$	?	Lack of standardized protocol
Microneedling	Weak to moderate	Unlikely, scalp pain	Rare	Moderate	$$	$$$	Lack of standardized protocol

(Continues)

TABLE 1 (Continued)

Treatment	Clinical evidence (weak, moderate, strong)	Side effects, short-term	Side effects, long-term	Likelihood of patient compliance (low, moderate, high, extremely high)	Monthly cost ($ ≤ $100; $$ = $100-$1000; $$$ = $1000-$5000; $$$$ = $5000-$15000; $$$$$ ≥ $15000; ? = unknown number of treatments (final cost))	5 year cost ($ ≤ $100; $$ = $100-$1000; $$$ = $1000-$5000; $$$$ = $5000-$15000; $$$$$ ≥ $15000; ? = unknown number of treatments (final cost))	Special considerations
Oral nutraceutical supplement containing Synergen Complex®	Moderate	Unlikely	Rare	PO BID, high compliance	$	$$$	Four capsules daily
Marine complex supplement	Moderate	Unlikely	Rare	PO BID, high compliance	$	$$$	Fishy taste for oral supplement
Serenoa repens	Weak	Unlikely	Rare	PO BID, high compliance	$	$$$	Possibility of missing early detection of prostatic cancer
Light devices	Strong	Unlikely	Rare	Daily, high compliance	$$	$$ or $$$	Noninvasive, convenient to use at home
Hair transplant	Strong	Infection, scarring, pain, itching, swelling, bleeding	Rare	Permanent, one-time treatment	$$$$	?	May need concurrent medical treatment

their hair in the morning, and may leave an uncomfortable residue after application. Oral finasteride is often used as the next alternative. The greatest downfall of finasteride, however, is its potential for hormonal and sexual side effects due to the downregulation of DHT. It is important to keep in mind that DHT acts on other areas of the body and has implications in anti-aging, libido, muscle and fatty tissue metabolism, and mental health.[184,185] Inhibition of its production has been linked to predisposition of nonalcoholic fatty liver disease (NAFLD), hyperglycemia, insulin resistance, elevated liver function enzymes, and worsening erectile dysfunction.[186] Post-finasteride syndrome is the most feared complication of this medication and can significantly impair one's quality of life.

Oral dutasteride may exhibit an even greater likelihood of eliciting these side effects. Patients being considered for this medication should understand the risk of sexual side effects. Clinicians and patients should be aware that more studies are needed to evaluate the safety and effectiveness of dutasteride. Like oral dutasteride, oral minoxidil is not commonly prescribed due to the propensity of facial hypertrichosis, but it may be of benefit for patients with concomitant hypertension. Some practitioners may exercise caution in using oral minoxidil among patients with a history of cardiovascular disease or obtain clearance by a cardiologist.[22] If a trial is warranted and the patient has no underlying factors, such as orthostatic hypotension that may put them at risk for side effects, then this therapy may be appropriate. For pregnant women and patients with renal failure, spironolactone is contraindicated.

Low-level laser therapy and LED are two therapies that have shown to be safe and well-supported by many large population studies. The side effects are minimal in comparison with oral and topical therapies. Patients that have complicated medical conditions managed by multiple medications may also benefit from nutraceuticals, rather than adding more medical therapies with potential drug-drug interactions or lowering the threshold for development of side effects. Procedural therapies such as PRP and hair transplantation may be more appropriate for patients willing to tolerate the pain induced by them. HT is usually reserved for patients who have failed the medical therapies. Contraindications of HT include scalp infection, mental illness, rapidly progressive variants of AGA, and diffuse hair loss. Antiplatelet and anticoagulants should also be stopped to mitigate the risk of excessive bleeding.[187] Hair transplantation is also limited by each patient's supply of donor hair and the procedure can lead to possible scarring in donor sites. Finally, when using combination therapy, medical history and concomitant medications should always be taken into consideration to minimize the risk of drug-drug interactions.

12.3 | Consideration of ease of use (Compliance)

Compliance associated with the ease of use of treatments for AGA is highly dependent on the patient's scheduling, personal preference, motivation, and treatment goals. As treatments usually require a lifelong commitment, it is essential for patients to understand the significance of treatment compliance and practicality when treating AGA, otherwise, treatment cessation can cause loss of any benefits gained. It is important to also keep in mind that treatment is oftentimes not desired by patients. Many patients in fact decline treatment, as they do not want to adhere to lifelong therapies and are indifferent or accepting of losing their hair or even balding. Applying a topical agent to one's scalp or taking a pill once or twice daily can be an enormous commitment for a patient. The clinician must recognize the balance between risk and benefit of any treatment specific to each patient and clearly convey that in the office visit. It is important to manage a patient's expectation given the number of factors at play when selecting an optimal treatment for AGA. A 6-month trial is a useful way to gauge compliance with any treatment approach followed by subjective and objective metrics of success.

Topical agents like minoxidil cater to the compliant patient who is willing to apply a topical formulation or who are reluctant to take oral medications due to concern for systemic side effects. Topicals may also be a good option for patients already taking multiple medications that could potentially interact with additional medications to treat AGA. Oral agents like finasteride also require a lifelong daily commitment in order to sustain its effects. The same commitment to frequent and consistent administration of therapy applies for essentially all other topical and oral formulations for AGA, as well as light therapies. PRP, although not administered as frequently, will require multiple painful injections throughout one's life that many patients cannot tolerate. Before prescribing any of these therapies, clinicians must determine whether a patient is willing to make the therapeutic commitment. For some patients, the inconvenience of continuous administration and time constraints may outweigh the desire for hair preservation, and other patients may not desire treatment at all. Hair transplantation is the only therapy for AGA that is performed as a one-time procedure to offer permanent results. This procedure suits the patient that would like lifelong results without relying on daily treatment regimens.

12.4 | Consideration of cost

Due to the chronic nature of AGA, lifelong therapy is needed to maintain results and this directly influences patient-incurred costs. When advising patients on appropriate treatment options, it is important to discuss monthly and 5-year treatment expenses to estimate a real world and lifelong cost. Topical minoxidil is cheap for a short period of use, but quite expensive over time with continued use. While a light therapy device is more expensive for one-time purchase, there are no additional costs over a 5-year period as devices function for several years with warranty. Thus, topical minoxidil is much less expensive than a light therapy device for 1-month use, but will be more expensive after 5 years of use. Hair transplantation is very expensive and not covered by insurance but by rough estimation, the cost of hair transplantation is equivalent to taking oral finasteride for over 25 years which is a lifelong treatment in itself.

Nutraceuticals can be even more expensive than prescription therapies as they come with costly monthly subscriptions. These products are often added on top of conventional therapies which may drive up patient cost even more. Many clinicians also formulate and sell their own nutraceuticals in office, so it is important to keep in mind financial biases when suggesting our own products to patients over another therapy that could be more appropriate or effective for a particular patient.

Patients opting to undergo procedures, such as PRP, must be willing to pay the high cost of treatment. Just like other specialized procedures, the tremendous potential for financial compensation using PRP can cloud a clinician's judgement so it is important for physicians to be conscious of their own vested interests when deciding to select PRP as a treatment modality over more simple, less invasive, and inexpensive options.

When considering combination therapy, physicians should keep in mind whether the patient is willing to pay a higher cost for multiple modalities of treatment. Compounding topical or medical formulations into a single vehicle may help to increase the likelihood of compliance but they are not generally covered by insurance and increase the financial burden to the patient.

12.5 | Patient and physician choice of treatment options

Patients who come to a physician for evaluation of hair loss need to be properly evaluated and once the diagnosis is established, the physician needs to discuss all appropriate treatment options available. A history, including family history of hair loss, and physical examination needs to be performed (including often a hair pull test) in order to clearly establish the diagnosis. Family history and other pieces of information will also assist in not only the established diagnosis but in the prognosis for the individual. For instance, a 20-year-old male exhibiting significant AGA with a long family history of extensive baldness needs to be approached differently from a 45-year-old male with some slight recession of the frontal hairline and thinning. The approach is also very different from a post-menopausal female with diffuse thinning.

It is also important to ensure that secondary factors that may cause telogen effluvium may or may not be contributing to the situation.

Ethically, all treatment options should be considered whether or not that physician utilizes all options in their practice. Sometime the best treatment option is to refer a patient either for hair transplantation or other procedural treatments that an individual physician may not perform. One of most important points to discuss is the fact that AGA is a chronic progressive condition and most treatments will only partially improve the condition and perhaps slow its progression.

All evidence-based options should be discussed and should include efficacy, side effect profiles, ease of use (compliance), and cost. At that point, it is the patient's choice to determine what is most important to them, in consultation to the physician, when it comes to treatment options. Very often this may include combinations of treatments and may change over time.

13 | CONCLUSION

There are a variety of options in a practitioner's armamentarium for treating AGA which include oral and topical medications, hormonal therapies, nutraceuticals, PRP, exosomes, microneedling, and more invasive techniques such as hair transplantation. The treatment of AGA can be particularly challenging due to non-uniformity in patient response to conventional therapies and even the incomplete understanding of the exact pathogenesis of the condition itself. Patients must adhere to lifelong therapy as AGA continues to progress if treatment is stopped. Oral finasteride, topical minoxidil, and LLLT are currently the only FDA-approved treatments for this condition, all of which may be effective in treating particular patients with AGA. However, selecting an appropriate therapy for a patient should take into consideration the individual's age and aesthetic concerns, lifestyle and preferences, access to treatment, compliance, extent of hair loss, and financial budget.

As clinicians, we have an ethical obligation to do what is best for our patients: to provide treatments with greatest efficacy and fewest side effects and to exclude personal financial compensation as a factor in treatment selection. Practitioners should advise patients of all possible AGA treatment options, so both parties may make informed decisions. Moreover, if providers are inexperienced or unable to provide particular modality of treatment that may be more suited to a patient's needs, he or she should be willing to refer to an expert colleague that may offer that particular modality.

Although many therapies are reported to be helpful and well-tolerated, most studies are yet limited by small sample sizes and varying study methodologies. Direct comparisons among the various therapeutic options are not commonly reported. As a result, treatment efficacy is often derived from cross-study comparisons of published results. Future high-quality randomized controlled trials and head-to-head trials should be conducted to better characterize net change in hair counts vs. placebo/control groups, particularly ones that utilize change in anagen hair counts as an end point as this may provide a more accurate measure of treatment efficacy. Further research in these avenues will help to clarify efficacies of different treatments among diverse groups of patients and varying degrees of AGA so that practitioners and patients can make more informed decisions when selecting the optimal treatment.

CONFLICT OF INTEREST

Dr. Ablon is an investigator for Nutrafol and Viviscal.

AUTHOR CONTRIBUTION

M.N., G.A., H.H., A.G., and D.F. contributed to the research, wrote edited, and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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