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Androgenetic alopecia - a literature review

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Abstract

Introduction and Purpose: Androgenetic alopecia (AGA) is the most common form of hair loss, affecting both men and women worldwide. It is characterized by progressive miniaturization of hair follicles due to the influence of dihydrotestosterone (DHT) and genetic predisposition. AGA has significant cosmetic and psychological implications and is associated with systemic health issues, including cardiovascular and metabolic disorders. Despite the availability of FDA-approved treatments such as finasteride and minoxidil, alternative therapies are being explored to enhance efficacy and reduce side effects. This review aims to provide an updated overview of AGA pathogenesis and emerging treatment strategies.

Material and Methods: A comprehensive review of the literature was conducted, analyzing recent studies on AGA pathophysiology, genetic factors, and treatment approaches. Research findings on FDA-approved drugs, alternative pharmacological interventions, mesotherapy, and low-level light therapy (LLLT) were included to assess their effectiveness and safety profiles.

Description of the State of Knowledge: The pathogenesis of AGA involves hormonal, genetic, and environmental factors. DHT binds to androgen receptors in susceptible hair follicles, leading to progressive follicular miniaturization and hair loss. Genetic predisposition plays a crucial role, with loci such as AR/EDA2R implicated in AGA susceptibility. While finasteride and minoxidil remain the primary treatments, newer approaches such as dutasteride, androgen receptor antagonists (spironolactone, clascoterone, pyrilutamide), mesotherapy, and low-dose oral minoxidil show promising results. Additionally, LLLT, particularly red LED therapy (630–660 nm), has emerged as a non-invasive method to stimulate hair growth, improving follicular density and reducing inflammation. Clinical studies suggest that combination therapy yields superior outcomes compared to monotherapy.

Conclusions: AGA treatment remains challenging due to its multifactorial nature and the need for long-term management. While finasteride and minoxidil are effective, alternative

treatments such as dutasteride, mesotherapy, androgen receptor antagonists, and LED therapy offer promising results. Red LED therapy has demonstrated efficacy in enhancing hair growth and reducing shedding, making it a valuable non-invasive option. Combination therapies appear to be the most effective approach, but further research is needed to establish standardized protocols and confirm long-term safety and efficacy.

Keywords: "androgenetic alopecia", "dihydrotestosterone", "finasteride", "minoxidil", "mesotherapy", "low-level light therapy", "red LED therapy", "androgen receptor antagonists".

Introduction

Androgenetic alopecia (AGA), commonly referred to as pattern baldness, is the most prevalent form of hair loss affecting both men and women worldwide. Characterized by progressive miniaturization of hair follicles, it leads to a distinctive pattern of hair thinning, primarily mediated by the androgen hormone dihydrotestosterone (DHT) and its interaction with androgen receptors (ARs) in genetically predisposed individuals .

In men, AGA manifests as a receding hairline and vertex balding, commonly referred to as male pattern baldness. In women, the condition is known as female androgenetic alopecia (FAGA), characterized by diffuse thinning on the vertex with preservation of the frontal hairline . This condition not only has significant cosmetic and psychological impacts but is also linked to various systemic health issues, including cardiovascular and metabolic disorders .

Recent advancements in understanding the molecular mechanisms of AGA have highlighted the critical roles of genetic, hormonal, and environmental factors. Research emphasizes that androgens, particularly dihydrotestosterone (DHT), play a central role in the pathogenesis of AGA. Genetic predisposition also contributes significantly, with specific loci, such as the AR/EDA2R region on the X chromosome, implicated in susceptibility to AGA .

Currently, there are two Food and Drug Administration (FDA)–approved medications for androgenetic alopecia: finasteride and minoxidil . This introduction aims to provide a comprehensive overview of the epidemiology, pathophysiology, and emerging perspectives on AGA, serving as a foundation for exploring its clinical management and future research directions. (1)(2)(3)(4)

Pathognesis

Androgenetic alopecia (AGA) is a multifactorial condition influenced by genetic, hormonal, and environmental factors. At its core, the pathology involves the progressive miniaturization of terminal hair follicles and alterations in the hair growth cycle. This leads to a shorter anagen phase (growth phase), prolonged telogen phase (resting phase), and ultimately, the transformation of terminal hairs into vellus hairs, characteristic of balding areas . (4)(5)

The Role of Androgens

Androgens, particularly dihydrotestosterone (DHT), play a pivotal role in AGA. DHT, formed from testosterone via the enzyme 5-α reductase, binds to androgen receptors (ARs) in susceptible hair follicles, primarily in the frontal and vertex regions. This interaction triggers a cascade of molecular events that contribute to the miniaturization of hair follicles and the progressive loss of hair .

The androgen-AR interaction induces the transcription of specific genes responsible for shortening the anagen (growth) phase of the hair cycle and prolonging the telogen (resting) phase. This process leads to the conversion of terminal hair follicles into smaller, vellus-like follicles, resulting in the characteristic thinning observed in AGA .
Interestingly, DHT and AR expression are significantly higher in balding areas such as the frontal and vertex scalp regions compared to the occipital scalp, which is typically spared in AGA. This regional variation underscores the importance of androgen sensitivity in the pathogenesis of the condition . (1)(2)(4)

The role of genetic
Current genome-wide association studies (GWAS) have primarily focused on MAGA susceptibility loci and genes linked to sex steroid hormone pathways. Detailed genome-wide linkage or association studies specifically addressing FAGA have yet to be comprehensively evaluated, leaving significant gaps in understanding the genetic architecture of FAGA. However a study by MP Birch et al., involving 572 men, revealed that those with bald fathers had a fivefold increased likelihood of developing MAGA compared to others. Another case–control study conducted by Jungyoon Ohn et al. in 2022 identified a significantly higher prevalence of a positive family history in individuals with early-onset female pattern hair loss (FPHL) compared to controls (71.4% vs. 51.0%, $p = 0.004$). (6)(7)

Treatment
Despite the widespread occurrence of androgenetic alopecia (AGA), managing and treating the condition remains challenging, driving many individuals to seek medical assistance. Current treatment options include lifestyle adjustments, specialized hair care practices, and medications. However, only two drugs—oral finasteride (approved for men) and topical minoxidil (approved for both men and women)—have received FDA approval for AGA treatment. While other approaches, such as off-label use of topical formulations, are being explored, further research is needed to establish their safety and efficacy. (8)

Finasteryd
Finasteride is a competitive and specific inhibitor of type II 5α-reductase (SRD5A2), effectively blocking the conversion of testosterone to dihydrotestosterone (DHT). This mechanism reduces androgen-mediated follicular miniaturization, a hallmark of androgenetic alopecia (AGA). It is approved for use in adult men with mild to moderate AGA at an oral dosage of 1 mg/day. Notably, finasteride is contraindicated in women, particularly during pregnancy, as it is classified as a category X drug due to its potential to cause ambiguous genitalia in male fetuses.
Evidence supports the efficacy of finasteride in managing AGA, with long-term use—up to 10 years—demonstrating significant hair regrowth and stabilization of hair loss. The drug exhibits higher effectiveness in treating vertex balding compared to frontal scalp thinning, and its sustained use is recommended, as efficacy does not diminish over time.
A randomized controlled trial (RCT) involving 65 male patients with mild to severe AGA showed superior outcomes with 1 mg/day oral finasteride compared to 5% topical minoxidil foam. Finasteride is generally well tolerated, with adverse effects including orthostatic hypotension, dizziness, and sexual dysfunction (e.g., decreased libido, erectile dysfunction, ejaculatory dysfunction, and gynecomastia). Persistent sexual side effects have been reported in some patients, lasting at least three months post-discontinuation, potentially contributing to increased rates of depression and suicidal ideation. (8)(9)(10)(11)
Topical formulations of finasteride, though not FDA-approved, have been explored as an alternative for female patients to mitigate systemic hormonal side effects. It was first

introduced by Mazzarella et al., who conducted a placebo-controlled study. The results of this study demonstrated that using a 0.005% finasteride solution twice daily for 16 months led to hair regrowth as early as four months and reduced hair loss compared to the placebo group. (12)(13)

Minoxidil

Topical minoxidil is the primary therapeutic agent for androgenetic alopecia (AGA) and is frequently used off-label for other types of alopecia. Originally developed as an oral antihypertensive, minoxidil was repurposed for hair loss management following the observation of increased hair growth as a side effect in hypertensive patients. Its mechanism of action is postulated to involve vasodilation of scalp blood vessels, enhancing nutrient and oxygen delivery to hair follicles and promoting their activity.

FDA-approved formulations for men include 2% and 5% solutions, as well as a 5% foam, while for women, a 2% solution and 5% foam are available. Clinical evidence indicates that the 5% topical solution is more efficacious than the 2% formulation in men when applied twice daily. Similarly, in women, the 5% solution has demonstrated either superior or comparable efficacy to the 2% solution. Hair growth typically begins to improve within 6–8 weeks of treatment initiation, with maximal effects observed by 12–16 weeks. A transient increase in hair shedding may occur within the first two weeks of treatment, likely due to the rapid transition of hair follicles from the telogen to the anagen phase. If shedding persists beyond this period, medical evaluation is advised.

Recent studies have investigated low-dose oral minoxidil (OM) as a potential alternative for AGA, with doses ranging from 2.5–5 mg/day for men and 0.25–1.25 mg/day for women. Results suggest that OM is generally safe and effective, with hypertrichosis being the most frequently reported adverse effect, occurring in approximately 20% of patients. Hypertrichosis, often considered mild and manageable, rarely leads to treatment discontinuation. Similar to topical formulations, OM can cause an initial increase in hair shedding lasting 3–6 weeks. Cardiovascular side effects are infrequent and typically mild, with postural hypotension or dizziness reported in approximately 2% of cases.

Adverse effects of OM are dose-dependent. At doses ≤2.5 mg/day, hypertrichosis occurred in 27% of patients compared to 72% at doses of 2.5–5 mg/day. Cardiovascular symptoms were reported in 4% of patients receiving ≤2.5 mg/day and in 9% of those receiving higher doses. Notably, the incidence of hypertrichosis is higher in females compared to males. Blood pressure monitoring during treatment has revealed only minor fluctuations. (8)(14)(15)(16)(17)(18)

Combined therapy

The combination of topical minoxidil and oral finasteride has shown enhanced therapeutic efficacy compared to monotherapy in treating androgenetic alopecia. This approach is a promising option for individuals with AGA, though further studies are needed to identify optimal dosages and formulations.

In a 12-month, randomized, open-label, comparative trial, 428 Chinese patients were included, divided into three treatment groups: finasteride, minoxidil and combined therapy. The results shown that hair growth increased significantly over time for all three groups ($p < 0.01$), however combination therapy led to significantly better outcomes in global photographic evaluation and patient-reported improvements. Patients treated with both minoxidil and finasteride had higher rates of marked improvement and fewer cases of no change or deterioration compared to either treatment alone. Notably, hair density showed greater improvement in the combination group, indicating enhanced hair regrowth .

The incidence of adverse events, including contact dermatitis and mild sexual side effects, was comparable between combination therapy and monotherapy groups. This suggests that the combined use of these treatments does not significantly increase the risk of side effects . (19) (20)

Dutasteride

Dutasteride is a 5-alpha reductase inhibitor that inhibits the production of dihydrotestosterone (DHT), which is involved in the pathogenesis of androgenetic alopecia (AGA). Dutasteride at a dose of 0.5 mg once daily for 24 weeks is ranked as the most effective regimen in improving total hair density and terminal hair density. A clinical study by Olsen et al. (2006) compared the effectiveness of dutasteride and finasteride, both of which are 5-alpha reductase inhibitors, in reducing dihydrotestosterone (DHT) levels and promoting hair growth in men with AGA. Dutasteride was found to be more effective than finasteride in inhibiting both types of 5-alpha reductase enzymes (Type 1 and Type 2). This broader suppression of DHT production resulted in better clinical outcomes for dutasteride. The study demonstrated that dutasteride produced greater improvements in hair density compared to finasteride, particularly at the dose of 0.5 mg daily. Dutasteride's effects were dose-dependent, with higher doses leading to more significant hair density increases. Several other clinical trials, including double-blind, placebo-controlled studies, show that dutasteride (0.5 mg daily) significantly increases hair density and hair width compared to finasteride and placebo over 24 weeks. Notably, it has demonstrated better results in terms of hair growth. The reported side effects include sexual dysfunction, including decreased libido, erectile dysfunction, and ejaculation disorders, (reported in 10–16% of cases). However, these effects are generally mild, reversible, and decline over time with continued treatment. Other risks such as potential psychiatric effects, including depression, are mentioned, though rare. Cases of metabolic or systemic effects due to DHT inhibition, such as nonalcoholic fatty liver disease and changes in androgen levels, are also discussed. (21) (22)

Androgen Receptor Antagonists

One of the emerging treatment strategies involves androgen receptor antagonists, which block the action of androgens at the follicular level, potentially preventing hair follicle miniaturization and promoting hair regrowth. While androgen receptor antagonists offer promising alternatives for AGA treatment, further research is required to establish their long-term efficacy and safety. Currently, topical formulations such as clascoterone and pyrilutamide show the most potential for clinical application. (23)

Spironolactone

Spironolactone is a synthetic aldosterone receptor antagonist that also inhibits androgen receptors. It is primarily used to treat female AGA but has shown effectiveness in men as well. However, its systemic effects, including gynecomastia and feminization, limit its widespread use in male patients. A randomized controlled trial included 60 participants (39 males and 21 females) divided into three groups: one group received a 1% topical spironolactone gel twice daily, the second group used a combination of topical minoxidil gel and 1% spironolactone gel, and the third group applied a 5% topical minoxidil gel twice daily over a 12-month period. The results showed that topical spironolactone combined with minoxidil led to significant improvements in hair regrowth . (23) (24)

Bicalutamide

Bicalutamide, an androgen receptor antagonist primarily used for prostate cancer, has been explored as an off-label treatment for female AGA. It can be combined with therapies such as minoxidil, spironolactone, or mesotherapy to enhance efficacy. A study investigated the safety and efficacy of oral bicalutamide (OB) in 44 women with female pattern hair loss (FPHL).

Patients received OB at doses of 25-50 mg daily, with safety as the primary objective and treatment response assessed using the Sinclair scale. Mild and transient increases in liver transaminases were observed in 11.4% of patients, but no one discontinued treatment. Other side effects included hair shedding, transient amenorrhea, endometrial hyperplasia, and headaches. Among 32 patients treated for over six months, the average Sinclair scale reduction was 27.5%. The study suggests that OB is a promising and well-tolerated treatment for FPHL, particularly at higher doses, but further research is needed to confirm its efficacy. However, its use in male AGA remains limited due to potential side effects and a lack of extensive clinical studies . (23) (25)

Clascoterone

Clascoterone (CB-03-01) is a topical androgen receptor inhibitor that has demonstrated efficacy in reducing hair loss and increasing hair density. It competitively binds to androgen receptors, blocking dihydrotestosterone (DHT) and preventing its effects on hair follicles. In a phase II clinical trial, subjects who applied clascoterone showed a higher hair count compared to those using topical minoxidil. The treatment was well-tolerated, with a favorable safety profile . Unlike systemic 5α-reductase inhibitors such as finasteride and dutasteride, which lower DHT levels and can cause side effects like sexual dysfunction, clascoterone acts locally. Preliminary studies suggest it has comparable efficacy to finasteride in vitro, with no evidence of systemic effects. Its unique mechanism of action makes it a promising therapeutic option for androgenetic alopecia. (23) (26)

Pyrilutamide (KX-826)

Pyrilutamide is another topical androgen receptor antagonist currently undergoing clinical trials. A phase II study indicated that a 0.5% pyrilutamide solution, applied twice daily, led to an increase in non-vellus hairs, suggesting a potential role in treating AGA. Pyrilutamide has advanced to phase III trials in China and is the first androgen receptor inhibitor that successfully completed phase II clinical trial. (23)

Mesotherapy

Mesotherapy, a technique involving intradermal microinjections of therapeutic agents, has gained attention as a promising treatment option. It involves injecting medications, growth factors, and vitamins directly into the scalp, increasing local bioavailability while minimizing systemic exposure. The reviewed studies highlight several key findings: dutasteride-based mesotherapy has shown significant improvements in hair density and follicle health, with concentrations ranging from 0.005% to 0.05% administered weekly or monthly. Mesotherapy with minoxidil was tested against topical 5% minoxidil, with some studies reporting similar efficacy, while others showed superior hair follicle count increases in the mesotherapy group. Combination therapies, such as dutasteride with biotin, pyridoxine, and panthenol, resulted in better outcomes compared to monotherapy. Botulinum toxin A injections have been explored for their potential to increase scalp vasodilation and improve hair growth. Overall, over 95% of patients in the analysed studies reported satisfactory results, indicating mesotherapy's potential as an alternative or adjunct to existing treatments.

Mesotherapy is generally well tolerated, with minor side effects such as mild pain, redness, and temporary swelling at the injection site. While rare, some studies reported more severe reactions, including frontal edema and allergic responses, particularly with dutasteride formulations. However, mesotherapy reduces systemic risks associated with oral medications like finasteride.

Despite these concerns, mesotherapy reduces the risk of systemic side effects associated with oral medications, such as finasteride-related sexual dysfunction. However, standardized

treatment protocols are lacking, contributing to variability in outcomes and safety profiles. (27)(28)(29)

LED therapy

LED therapy, particularly red light therapy, has emerged as a promising treatment for androgenetic alopecia (AGA) by stimulating hair growth and improving follicular density. Unlike traditional treatments such as minoxidil and finasteride, LED therapy offers a non-invasive alternative with minimal side effects. Red LED light, typically in the 630–660 nm range, penetrates deeply into the scalp, enhancing mitochondrial activity, increasing ATP production, and promoting oxygenation, which supports hair follicle regeneration. It also reduces inflammation by lowering cytokine levels such as IL-6 and TNF-alpha, while activating the Wnt/β-catenin signaling pathway, prolonging the anagen (growth) phase. Studies have shown that red LED therapy significantly increases hair thickness, accelerates hair regrowth, and decreases hair shedding, with better results compared to green LED light. Research on post-COVID hair loss further supports its effectiveness in stopping excessive shedding and restoring hair density. Given its safety and positive outcomes, red LED therapy represents a valuable option for AGA treatment, either as a standalone approach or in combination with other hair loss therapies.

However, further studies are needed to optimize treatment protocols and confirm long-term efficacy. (30)(31)

Treatment Method	Mechanism of Action	Efficacy	**Side Effects**
Finasteride (1 mg/day, oral)	Type II 5α-reductase inhibitor – reduces conversion of testosterone to DHT	Effective in slowing hair loss and promoting regrowth, especially at the crown	Sexual dysfunction (decreased libido, erectile dysfunction), depression, gynecomastia
Dutasteride (0.5 mg/day, oral)	Inhibits both Type I and Type II 5α-reductase – stronger DHT suppression than finasteride	More effective than finasteride in increasing hair density	Hormonal disturbances, sexual dysfunction, possible metabolic effects
Minoxidil (2% and 5%, topical)	Vasodilates scalp blood vessels, stimulates hair follicles	Effective, results visible after 12–16 weeks	Scalp irritation, initial shedding phase
Oral Minoxidil (2.5–5 mg/day for men, 0.25–1.25 mg/day for women)	Enhances scalp blood supply and stimulates hair growth	Alternative to topical treatment	Hypertrichosis (excess hair growth), dizziness, low blood pressure
Spironolactone (topical and oral, primarily for women)	Androgen receptor antagonist – blocks DHT activity	Mainly used in women, potentially effective for FAGA	Gynecomastia, electrolyte imbalances, low blood pressure
Bicalutamide (25–50 mg/day, oral)	Androgen receptor antagonist, blocks	Used off-label for female AGA	Potential hormonal effects, elevated

	DHT action		liver enzymes
Clascoterone (topical)	Blocks DHT binding to androgen receptors	Promising results in clinical trials No reported	No reported systemic side effects
Pyrilutamide (topical)	Androgen receptor inhibitor, prevents follicle miniaturization	In clinical trials	No known side effects
Mesotherapy (scalp injections)	Delivers active ingredients (e.g., minoxidil, dutasteride, biotin) directly to hair follicles	Improves hair density, alternative to oral treatments Possible irritation and allergic	Possible irritation and allergic reactions
LED Therapy (red light 630–660 nm)	Stimulates mitochondria in hair follicle cells, increases proliferation, and reduces inflammation	Increases hair density and reduces shedding	No major side effects, non-invasive method
Combination Therapy (Finasteride + Minoxidil)	Combines mechanisms of both drugs	Most effective available treatment	Possible side effects of both drugs

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