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Minoxidil in Hair Disorders: Pharmacological Mechanisms, Clinical Efficacy, Formulation Advances, and Safety Profile –A Comprehensive Review

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Abstract : Minoxidil has gained considerable importance in dermatological practice because of its ability to stimulate hair growth. Although it was originally introduced as a vasodilator for managing hypertension, its hair-growth-promoting properties were identified following reports of excessive hair growth in treated patients. This observation led to the development of topical preparations, which are now widely used for androgenetic alopecia in both men and women. Oral minoxidil at lower doses has also emerged as an alternative therapeutic approach, particularly in patients experiencing difficulties with topical treatment.The therapeutic activity of minoxidil is closely associated with its conversion into an active metabolite, minoxidil sulfate, through sulfotransferase enzymes located in hair follicles. Variations in the activity of these enzymes may influence how effectively an individual responds to treatment. Its influence on several cellular signaling pathways has also been suggested, although the complete mechanism responsible for these effects remains unclear. This review discusses the pharmacological characteristics of minoxidil, its biological activity in hair follicles, therapeutic applications, available formulations, clinical findings and associated safety concerns. It also considers recent developments in drug delivery and their potential role in improving treatment outcomes. Overall, minoxidil continues to hold an important place in hair-loss management, although treatment success depends on patient-specific factors, appropriate administration and sustained therapy. Continued research will be important in clarifying its mechanisms, optimizing treatment strategies and establishing the long-term benefits and risks of newer formulations.

Keywords: *Minoxidil; androgenetic alopecia; hair follicle; sulfotransferase; topical formulation; low-dose oral minoxidil; nanocarriers; adverse effects*

I. INTRODUCTION

Hair loss is a common dermatological concern with physical, emotional and social impact. Alopecia is not a disease but a term used to describe a number of disorders. Etiology, clinical course and treatment of pattern hair loss, telogen effluvium, alopecia areata and cicatricial alopecias are different. Minoxidil is particularly important in androgenetic alopecia (AGA), also known as male- or female-pattern hair loss, as it can increase the visible density of hair without directly blocking the production of androgens.

Minoxidil was originally developed as an oral blood pressure drug. During treatment, increased hair growth (hypertrichosis) led to the development of topical formulations. Topical 2 % and 5 % preparations then became established treatments for pattern hair loss. Low-dose oral minoxidil (LDOM), usually given in doses much lower than those used in antihypertensive therapy, is now being used off label in selected [1,2].

Minoxidil was developed initially as an oral antihypertensive agent. During treatment, increased hair growth (hypertrichosis) led to the development of topical formulations. Topical 2% and 5% preparations were then accepted as treatments for pattern hair loss. Low-dose oral minoxidil (LDOM) is now used off label in selected patients typically at doses well below antihypertensive doses. Observational studies and expert opinion support its increasing use; however, the evidence base is not comparable with that of approved topical products. [3-6].

II. OVERVIEW AND CLASSIFICATION OF ALOPECIA RELEVANT TO MINOXIDIL

Alopecia can be classified into non-scarring and scarring. In non-scarring disorders, the follicles are still present and regrowth may be possible. In scarring alopecia, follicles are progressively destroyed and replaced by fibrosis. The aim of treatment is mainly to control the underlying inflammatory disease, not to stimulate a follicle that is permanently lost.

Common hair-loss disorders and the clinical role of minoxidil:

• **Androgenetic alopecia (AGA):** genetically influenced follicular miniaturization; topical minoxidil is an established treatment and oral use is off label.

• **Female pattern hair loss (FPHL):** progressive reduction in terminal hair density, usually over the central scalp; topical minoxidil is an established pharmacological option.

• **Telogen effluvium (TE):** excess follicles enter telogen after illness, stress, childbirth, nutritional deficiency or medicines; minoxidil may be considered in selected persistent cases, but evidence is less robust than in AGA.

• **Alopecia areata (AA):** autoimmune attack on anagen follicles; minoxidil is an adjunct and does not suppress the autoimmune process.

• **Scarring alopecia:** inflammatory destruction and fibrosis of follicular units; minoxidil is not a treatment for established follicular destruction.

The difference is important because increased hair growth doesn't always treat the cause of hair loss. In AGA minoxidil can improve density while the androgen related process continues. It may help with regrowth once the inflammation is under control, in AA. The key in TE is to fix the trigger. The early diagnosis by a specialist and anti-inflammatory treatment are essential in the case of scarring alopecia.

III. ETIOLOGY AND RISK FACTORS IN PATTERN HAIR LOSS

AGA is a polygenic disorder in which susceptible follicles undergo progressive miniaturization. Androgen signaling, especially of dihydrotestosterone (DHT) via androgen receptors, shortens the effective phase of growth and converts terminal hairs to progressively finer hairs in genetically predisposed areas of the scalp. A family history is a risk factor. The clinical pattern and severity are influenced by age, the sex-related hormonal environment and genetic variation [1,2].

Female pattern hair loss has a more heterogeneous endocrine background than male androgenetic alopecia. Many affected women do not have a demonstrable excess of androgens. Therefore, patterned thinning should not be immediately interpreted as a sign of a hormonal disorder. If there is sudden shedding, virilization, menstrual irregularities, systemic symptoms, or rapid progression, then a targeted workup for an underlying cause may be warranted.

TE is often associated with physiological stressors like febrile illness, surgery, childbirth, rapid weight loss, iron deficiency, thyroid disease, or medication changes. These factors should be differentiated from AGA as treatment priorities are different . Minoxidil is not a substitute for correcting iron deficiency, thyroid problems, poor nutrition or a causative medication.

IV. PATHOPHYSIOLOGY AND PHARMACOLOGICAL MECHANISM

- **Hair Follicle Cycle:** Hair growth occurs through four distinct phases: anagen (active growth), catagen (regression), telogen (resting) and exogen (hair shedding). In androgenetic alopecia (AGA), the normal hair cycle becomes disturbed, resulting in a shorter growth phase and gradual reduction in follicle size, ultimately producing thinner and shorter hairs. Minoxidil helps regulate this process by encouraging hair follicles to enter the anagen phase and potentially maintaining them in the growth phase for a longer duration. This may contribute to an increase in hair density and the development of thicker terminal or intermediate hairs. Some individuals may experience temporary hair shedding during the initial weeks of treatment as older hairs are replaced by new growth. Patients should therefore be informed about this possibility to avoid unnecessary concern and premature discontinuation of treatment [1,7].

- **Chemical and Pharmacological Profile:** Minoxidil, chemically known as 6-(1-piperidinyl)-2,4-pyrimidinediamine 3-oxide, acts as a prodrug, meaning that its hair-growth-promoting effect largely depends on its conversion into minoxidil sulfate. This active metabolite is produced by sulfotransferase enzymes, particularly SULT1A1, which are present in the outer root sheath of hair follicles. The activity of these enzymes differs among individuals and may be one of the factors responsible for variations in response to topical minoxidil treatment [1,8,9].

- **Proposed Mechanisms:** Minoxidil sulfate acts by opening ATP-sensitive potassium channels in vascular smooth muscle cells, leading to membrane hyperpolarization and relaxation of blood vessels. This potassium-channel-opening activity is a well-established part of minoxidil's role in the treatment of hypertension. However, its direct involvement in promoting hair growth is still not fully understood. Messenger and Rundegren pointed out that direct evidence demonstrating the presence

of KATP channels in human hair follicles was lacking [7]. Therefore, increased blood circulation in the scalp alone cannot fully explain the hair-growth effects of minoxidil.

- **Follicular Effects:** Experimental studies have indicated that minoxidil may influence hair growth through several mechanisms. These include reducing the resting phase of the hair cycle, extending the anagen phase, increasing the size of miniaturized hair follicles and stimulating the activity of dermal papilla cells. It may also influence growth-related mediators, including vascular endothelial growth factor (VEGF), prostaglandins and Wnt/β-catenin signalling pathways. Although these findings help explain the possible biological actions of minoxidil, the available evidence varies across experimental models, and not all proposed mechanisms have been established as essential for hair growth in human scalp follicles [1,7].

- **Follicular Bioactivation and Response Variability:** The response to topical minoxidil may depend partly on the ability of hair follicles to convert the drug into its active form. Studies have associated lower follicular sulfotransferase activity with a reduced response to treatment. Goren and colleagues introduced an enzyme-based assay to help predict an individual's response to minoxidil [9]. In a subsequent study, topical tretinoin was found to influence follicular sulfotransferase activity, with some individuals initially identified as non-responders showing a response after treatment [10]. However, these findings represent preliminary evidence and are not sufficient to support the routine use of tretinoin alongside minoxidil. Similarly, a small randomized study evaluating an adjunct intended to support sulfotransferase activity reported potential improvement in hair regrowth. Nevertheless, the limited sample size and short study duration highlight the need for further independent research to confirm these findings [11].

V. PHARMACOKINETICS AND ROUTES OF ADMINISTRATION

Topical minoxidil is directly applied to the scalp, allowing the drug to act locally while limiting its entry into the systemic circulation when used correctly on healthy, intact skin. However, systemic absorption may increase if the medication is applied in excessive amounts, used over large skin areas, or applied to damaged or inflamed skin, particularly under occlusive conditions. The composition of the formulation also plays an important role in determining drug solubility, skin penetration and overall tolerability. Despite its local application, topical treatment requires regular and consistent use, and some formulations may leave residue on the scalp or affect hair styling.

Following oral administration, minoxidil is readily absorbed through the gastrointestinal tract and undergoes metabolism mainly in the liver, including through glucuronidation. Formation of its sulfate metabolite is also important for its pharmacological activity. Unlike topical treatment, oral minoxidil produces systemic vasodilatory effects and was initially prescribed at considerably higher doses for patients with severe hypertension. Low-dose oral minoxidil (LDOM) is now used for hair loss, but its systemic exposure and potential risks must be considered rather than regarding it as merely a more convenient alternative to topical application [3–6].

It is sometimes suggested that oral minoxidil completely avoids the involvement of follicular SULT1A1 because the drug is fully activated in the liver before reaching the hair follicles. However, this explanation is an oversimplification of its metabolism. The relative contribution of hepatic and follicular metabolism to hair growth has not yet been clearly established, and current evidence does not support the conclusion that the response to oral minoxidil is entirely independent of follicular biological activity.

VI. TOPICAL FORMULATIONS: SOLUTION, FOAM AND NOVEL VEHICLES

Conventional topical minoxidil formulations are commonly available in 2% and 5% concentrations. Liquid solutions generally contain alcohol and propylene glycol, which help dissolve the drug and improve its delivery through the skin. However, propylene glycol may cause irritation or allergic contact dermatitis in some individuals, leading to itching, scaling and redness. Foam formulations generally do not contain propylene glycol and may be better tolerated by individuals who experience irritation with liquid solutions. They may also be more convenient to apply, as they are less likely to leave the scalp feeling wet or greasy.

In a randomized study involving 113 women, once-daily application of 5% foam showed similar effectiveness to twice-daily 2% solution in terms of target-area hair count at 24 weeks. The foam formulation also provided better acceptance during hair styling and fewer local tolerability issues; however, complete blinding of participants was not possible because the formulations were different [12]. A larger phase III study involving 404 women reported an increase in target-area hair count with 5% foam compared with the vehicle at 12 and 24 weeks [13]. Another phase III comparative study showed similar numerical improvements in hair count with 5% foam and 2% solution, although the predefined noninferiority criteria were not achieved [14]. Overall, these findings support the effectiveness of foam formulations but do not establish their superiority over liquid preparations in all patients.

Newer formulations, including liposomal, nano emulsion, ethosomal, niosomal and cetosomal systems, are being explored to improve follicular drug deposition, enhance drug retention or minimize irritation. These delivery systems may help improve minoxidil delivery to the pilosebaceous unit. However, improved drug penetration observed in laboratory studies does not necessarily indicate greater hair density or better long-term tolerability in patients.

VII. LOW-DOSE ORAL MINOXIDIL

Low-dose oral minoxidil (LDOM) is increasingly used off-label in dermatological practice, particularly when topical treatment is inconvenient, poorly tolerated, difficult to apply over larger areas or does not provide satisfactory results. Treatment regimens may differ depending on individual patient characteristics, including sex, age, existing medical conditions and clinical requirements. The

selected dose should not be considered suitable for every patient, as oral minoxidil is a prescription medicine with cardiovascular effects and requires proper clinical evaluation before use [3–6].

An international modified Delphi consensus involving 43 hair-loss specialists from 12 countries established agreement on 76 recommendations related to treatment indications, precautions, initial assessment, monitoring and the use of minoxidil in adults and adolescents. However, the experts did not reach agreement on certain aspects, particularly some paediatric considerations and dose-adjustment practices [4]. These consensus recommendations offer useful clinical guidance in areas where clinical trial evidence remains limited, although they cannot replace findings from large randomized controlled trials.

An Indian evidence- and experience-based consensus statement also provides recommendations relevant to the use of oral minoxidil in local clinical practice. However, these recommendations should be considered expert guidance rather than evidence of regulatory approval [5]. In 2025, Olsen and colleagues reviewed recommendations for the safe and effective use of topical and oral minoxidil, highlighting the importance of appropriate patient selection, counselling and regular monitoring during treatment [6].

VIII. CLINCAL EFFICACY IN ANDROGENETIC ALOPECIA

The most established clinical evidence for minoxidil is related to its topical use in androgenetic alopecia (AGA). In a 48-week randomized, double-blind clinical trial involving 393 men, 5% minoxidil solution demonstrated better results than both 2% solution and placebo in terms of non-vellus hair count and scalp coverage assessed by investigators and patients. Participants receiving the 5% formulation also experienced an earlier treatment response, although itching and local irritation were reported more frequently than with the 2% formulation [15]. Similarly, a systematic review and meta-analysis reported that topical minoxidil was more effective than placebo in improving total and non-vellus hair growth, while also highlighting certain limitations in the available clinical studies [16].

A network meta-analysis evaluating minoxidil and 5-alpha-reductase inhibitors in men with AGA showed that treatment effectiveness rankings varied depending on the outcome measured and the dose used. Although such comparisons help understand the relative position of different treatments, they should not be considered equivalent to direct clinical comparisons between every treatment regimen [17]. Unlike 5-alpha-reductase inhibitors, minoxidil does not block the activity of this enzyme and therefore does not directly address the androgen-related cause of AGA. Combining treatments with different mechanisms of action may be beneficial in selected patients, provided that their individual benefits and potential risks are carefully considered.

In recent years, randomized clinical trials have also examined the differences between oral and topical minoxidil treatment. Penha and colleagues conducted a 24-week study involving 90 men who received either oral minoxidil at 5 mg daily or topical 5% minoxidil twice daily. Oral treatment did not demonstrate superiority for the primary outcome of hair density at the vertex, although some secondary findings indicated a possible benefit in this area. The study was limited by its single-centre design and relatively short duration [18]. Similarly, Asilian and colleagues conducted a randomized study involving 65 patients and observed improvement with both treatment approaches. However, no statistically significant difference in hair diameter was found between the two groups. The small sample size and six-month follow-up were important limitations of this study [19]. Overall, these findings do not provide sufficient evidence to recommend oral minoxidil as a replacement for topical treatment as the first-line option.

Minoxidil does not produce immediate results, and noticeable improvement generally requires several months of regular treatment. An initial assessment of hair growth is commonly made after approximately 4–6 months, although further improvement may occur with continued use. Maintaining the achieved results usually requires ongoing treatment, as the newly grown hair may gradually be lost over the following months after discontinuation. Treatment response differs from person to person and may depend on factors such as the duration of hair loss, degree of follicular miniaturization, treatment adherence, formulation, dosage and the individual's ability to convert minoxidil into its active form.

IX. EVIDENCE IN OTHER HAIR DISORDERS

1. Alopecia Areata: Alopecia areata is an autoimmune condition in which immune-mediated reactions damage hair follicles during the anagen phase. Minoxidil does not act on the underlying autoimmune mechanism and therefore should not be considered an independent treatment capable of controlling or modifying the disease. According to the British Association of Dermatologists guideline, topical or oral minoxidil may be considered alongside other treatments, as it may help improve hair density and potentially reduce the risk of relapse [20]. However, its role in alopecia areata is mainly supportive, and the available evidence is not as strong as that established for androgenetic alopecia (AGA).

2. Telogen Effluvium: Telogen effluvium (TE) is generally a temporary form of hair loss that may improve once the underlying triggering factor has been addressed. Treatment mainly involves identifying and managing possible causes, including illness, nutritional deficiencies, hormonal disturbances or medication-related effects. Compared with AGA, the evidence supporting minoxidil use in TE is relatively limited. A dermatologist may consider its use in persistent or chronic cases, although its routine application in acute TE is not supported by an equivalent level of controlled clinical evidence.

3. Scarring Alopecia: In scarring alopecia, hair follicles are permanently damaged and replaced by scar tissue, making regrowth from the destroyed follicles impossible. However, minoxidil may be considered in selected patients to support the growth of remaining healthy follicles once the underlying inflammatory condition has been brought under control. It does not treat the primary

inflammatory process responsible for the disease, making early diagnosis and appropriate dermatological management particularly important.

X. COMBINATION AND ADJUNCTIVE APPROACHES

Minoxidil can be used in combination with other treatments when supported by the diagnosis and clinical need. In male AGA, finasteride reduces the conversion of testosterone into DHT, whereas minoxidil mainly influences the hair-growth cycle, making their mechanisms of action complementary. However, the available evidence does not mean that every patient needs both treatments. Finasteride also has certain reproductive and sexual adverse effects and may not be suitable for all patients.

Microneedling has been studied as an additional treatment alongside topical minoxidil. Its proposed benefits include improved drug penetration and stimulation of wound-healing signals. Although small clinical trials using different protocols have reported additional hair growth, variations in needle depth, frequency, technique and patient selection make comparisons difficult. Improper microneedling may also cause infection, irritation and post-inflammatory changes.

Tretinoin may affect follicular sulfotransferase activity, although the available evidence is still preliminary [10]. Using multiple topical products together may increase irritation and make treatment adherence more difficult. Therefore, combination treatment should be based on available evidence and professional supervision rather than simply on the assumption that their mechanisms are complementary.

XI. ADVERSE EFFECTS, TOXICITY AND PRECAUTIONS

Topical Adverse Effects: The commonly reported local side effects of topical minoxidil include itching, dryness, scaling, redness and irritant or allergic contact dermatitis. Some of these reactions may be caused by propylene glycol present in the formulation. Excessive hair growth may also develop outside the scalp, especially when the product spreads to the face or comes into contact with the hands or bedding. Temporary increased hair shedding may be noticed during the initial period of treatment. Dizziness, palpitations and oedema are less common with proper topical application but should be assessed if they occur [22].

Oral Adverse Effects: As oral minoxidil acts as a systemic vasodilator, it may cause adverse effects such as excessive hair growth, fluid retention, swelling of the ankles or around the eyes, light-headedness, headache, increased heart rate and palpitations. Serious cardiovascular events are uncommon in patients receiving low doses for hair loss, although observational studies cannot completely rule out these risks. The product information for antihypertensive doses also includes warnings about pericardial effusion and worsening angina. These potential risks should not be overlooked simply because lower doses are used for hair loss.

A multicentre retrospective study involving 1,404 patients treated with low-dose oral minoxidil (LDOM) for at least three months reported hypertrichosis in 15.1% of patients, light-headedness in 1.7%, fluid retention in 1.3% and tachycardia in 0.9%. Systemic adverse effects resulted in treatment discontinuation in 1.2% of patients. No life-threatening events were reported in the study; however, its retrospective design and lack of a control group limit the conclusions regarding rare and long-term adverse effects [20]. Patient Assessment and Monitoring: Before prescribing oral minoxidil, clinicians generally assess blood pressure, pulse rate, cardiovascular history, kidney function, concurrent antihypertensive medications and any symptoms of fluid retention.

Monitoring requirements may differ between individuals, particularly in patients with low baseline blood pressure, arrhythmias, kidney impairment, heart failure or a history of pericardial disease. Pregnancy and breastfeeding require particular caution, and the use of minoxidil should be discussed with a qualified healthcare professional. Patients should not start the medication, increase its dose or discontinue it without medical advice[19].

XII. PSYCHOLOGICAL IMPACT AND QUALITY OF LIFE

Pattern hair loss can affect self-image, confidence and social well-being. Treatment studies often include patient-reported outcomes because objective hair counts do not fully capture perceived benefit. The 2002 male trial reported improved psychosocial perceptions among participants receiving 5% minoxidil [15]. However, quality-of-life improvement is not guaranteed and depends on baseline distress, expectations, visible response and treatment burden. Counselling should explain the slow onset of benefit, possible early shedding, need for maintenance and realistic limits of regrowth.[20]

XIII. DISCUSSION OF EXISTING RESEARCH

The strongest and most consistent evidence supports topical minoxidil for AGA. Placebo-controlled trials show improved hair counts and patient- or investigator-rated coverage, with 5% generally producing greater regrowth than 2% in men at the cost of more local irritation [15,16]. In women, 5% foam once daily has demonstrated efficacy, but active-comparator trials show that noninferiority conclusions depend on the prespecified statistical margin and formulation [12-14].

LDOM is attractive because it avoids daily scalp application and may be useful when topical treatment is poorly tolerated or impractical. Nevertheless, oral-versus-topical trials have not shown consistent superiority of oral treatment [18,19]. Observational

safety cohorts are reassuring but cannot reliably quantify rare adverse events or establish long-term cardiovascular safety [21]. International consensus statements address this evidence gap pragmatically, but consensus should not be confused with high-certainty comparative evidence [4-6].

Mechanistic explanations also require caution. Minoxidil sulfate and potassium-channel opening are established in vascular pharmacology, but the precise follicular targets and relative contributions of blood flow, growth factors, Wnt signalling and cell survival remain incompletely resolved [7]. The uploaded reference paper presents several pathways in a confident, linear manner; the broader literature supports them as proposed or partially demonstrated mechanisms rather than a fully settled causal sequence [18]. Evidence outside AGA is weaker and condition-specific.

Minoxidil may be a useful adjunct in AA or selected chronic TE, but it does not remove the underlying autoimmune, endocrine, nutritional or inflammatory cause. A general statement that minoxidil is an effective treatment for all scarring and non-scarring alopecia's would therefore be scientifically inaccurate. Diagnosis remains the first step in rational treatment selection [16].

XIV. FUTURE PERSPECTIVES AND RESEARCH GAPS

Future trials should compare topical and oral regimens using standardized hair-count methods, validated patient-reported outcomes and follow-up long enough to assess maintenance and relapse after discontinuation. Trials should stratify by sex, age, baseline severity, scalp region, prior treatment and comorbidities. Larger prospective registries are needed to assess long-term cardiovascular safety and uncommon adverse events associated with LDOM.

Biomarker research may help identify patients likely to respond to topical treatment. Follicular sulfotransferase activity is promising, but assays require external validation, reproducibility testing and proof that test-guided treatment improves outcomes. Genetic and molecular predictors should be evaluated alongside clinical factors rather than treated as stand-alone decision tools.

For advanced delivery systems, future research should report particle size, polydispersity, encapsulation efficiency, drug release, follicular deposition, skin irritation, stability and batch reproducibility. Formulation studies should progress from ex vivo skin models to well-designed clinical trials. A formulation that increases skin penetration is not necessarily safer: excessive systemic absorption could increase adverse effects.

Research is also needed in underrepresented populations, including diverse skin and hair types, adolescents, older adults and people with relevant comorbidities. Better evidence is required for chronic TE, AA adjunctive use and post-transplant protocols. Studies should measure adherence, cost, patient satisfaction and quality of life, not only hair counts.

XV. CONCLUSION

Minoxidil remains an important pharmacological option for androgenetic alopecia because topical preparations have demonstrated clinically meaningful hair-growth benefits in controlled trials. Its activity depends in part on conversion to minoxidil sulfate, while the full set of follicular mechanisms is still being investigated. Topical solution and foam differ in vehicle tolerability and convenience; low-dose oral minoxidil offers an alternative route but is off label for hair loss and carries systemic cardiovascular considerations.

Recent clinical trials have not established that oral minoxidil is consistently more effective than topical treatment. Large observational cohorts and international consensus statements have improved understanding of oral safety and practical monitoring, while nanocarrier and cetosomal formulations represent promising but still developing approaches. Overall, treatment should be based on accurate diagnosis, realistic expectations, continued assessment and individualized risk-benefit evaluation. More large, long-term, well-controlled studies are needed to define the optimal route, dose, formulation and patient selection.

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