REVIEW ARTICLE

Oral Minoxidil in the Management of Androgenetic Alopecia

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Abstract

Androgenetic alopecia (AGA) is one of the most common types of hair loss. It is estimated that 85% of men and 40% of women experience it at some point in their lifetime. Other therapies approved by the Food and Drug Administration for hair loss treatment are minoxidil (topically) and finasteride (orally). However, adherence to topical therapy with minoxidil is poor; however, with the use of finasteride, there is a potential for sexual side effects. There is an unapproved treatment called low-dose oral minoxidil (LDOM), which has shown promise in the treatment of AGA. An established literature search was performed through PubMed/MEDLINE, Embase, Cochrane Library and Scopus for the period from inception of each database through March 2026. All studies of LDOM in patients with AGA that were either randomized controlled trials (RCTs), prospective cohort studies, retrospective analyses or meta-analyses were included. The three primary outcome variables utilized in this review included: Change in hair density, terminal hair count and global photographic improvement. Other outcome variables collected from the studies included: Adverse event profiles, adherence and patient-reported outcomes. The quality of studies was evaluated utilizing the Cochrane Risk of Bias assessment tool for RCTs. Four RCTs in patients with AGA demonstrated no statistically significant difference in hair density (pooled standard mean difference [SMD] 0.02; 95% confidence interval [CI] −0.25–0.29; P = 0.88; I2 = 0%) or hair diameter (SMD −0.25; P = 0.34) for oral and topical minoxidil. One double-blinded RCT performed photographic analyses that demonstrated superior results at the vertex for oral minoxidil (P = 0.04). There were also significantly more cases of hypertrichosis (risk ratio 2.01; 95% CI 1.18–3.41; P = 0.01) in patients receiving oral minoxidil. In a multi-center safety study that included 1404 patients, there were no life-threatening adverse events reported at doses of 0.25–5 mg/day. Clinical response rates of 70–100% have been reported in cohort studies. At doses of 0.25–5 mg/day, LDOM demonstrates comparable efficacy to topical minoxidil for the treatment of both male AGA and female pattern hair loss and a manageable and dose-dependent adverse effect profile. Advantages of LDOM therapy include: Improved adherence, ease of administration, lower cost and use in patients who cannot tolerate topical therapy. The most clinically relevant adverse effect for LDOM therapy continues to be hypertrichosis, especially in women. LDOM should be considered a viable therapeutic option in patients who do not respond to or adhere to topical therapies. Larger, longer-duration standard RCTs are required to establish the recommendations for dosing and evaluate the long-term cardiovascular safety of LDOM.

Key words: Androgenetic alopecia, female pattern hair loss, hair density, hair loss treatment, low-dose oral minoxidil, male pattern hair loss, oral minoxidil, trichology

INTRODUCTION

Androgenetic alopecia (AGA), also termed male pattern hair loss (MPHL) and female pattern hair loss (FPHL), is the most prevalent form of progressive, non-scarring alopecia worldwide. According to estimates, 85% of men and nearly 40% of women will develop some form of male pattern baldness at or before age 70 and 80, respectively.[1]

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Received: 16-05-2026
Revised: 20-06-2026
Accepted: 27-06-2026

Male pattern baldness results from a combination of genetic predisposition, androgen sensitivity of scalp hair follicles, and the process of ageing. The effects of dihydrotestosterone (DHT), which is produced from testosterone through the action of the enzyme 5α-reductase Type II, result in the progressive miniaturization of susceptible hair follicles due to the binding of DHT to androgen receptors within the frontal and vertex areas of the scalp.[2]

The clinical consequences of AGA extend beyond cosmetics. Patients with AGA commonly report impaired self-image, heightened anxiety, depression, and diminished quality of life, underscoring the importance of effective management.[3] Despite its high prevalence, therapeutic options remain limited. At present, topical minoxidil (2% and 5%) and oral finasteride (1 mg/day) are the only Food and Drug Administration (FDA)-approved treatments for AGA. Finasteride is restricted to men owing to the risk of teratogenicity, and its use is complicated by reports of sexual dysfunction and post-finasteride syndrome in a subset of users.[2] Topical minoxidil, while effective and available for both sexes, suffers from poor adherence – one retrospective study of 400 patients found that 86.3% discontinued treatment, with the occurrence of side effects independently associated with a 3-fold increase in discontinuation odds.[3]

Oral minoxidil was originally developed in the 1960s and 1970s as a potent antihypertensive agent, used at doses of 10–40 mg daily for resistant hypertension. During these early trials, hypertrichosis was noted as a consistent side effect – an inadvertent observation that eventually prompted exploration of minoxidil as a hair growth agent.[4] The topical formulation was subsequently approved for AGA in 1988 (2% for men), later extended to 5% formulations and foam. In recent years, there has been renewed and growing interest in low-dose oral minoxidil (LDOM), typically prescribed at doses of 0.25–5 mg/day, far below antihypertensive dosing, for the treatment of various forms of alopecia, including AGA. LDOM circumvents the pharmacokinetic limitations of topical application, overcomes the problem of scalp irritation and altered hair texture that contribute to topical non-adherence, and does not affect androgen pathways – making it suitable for female patients and for those intolerant of 5α-reductase inhibitors.[5]

Despite an expanding body of clinical literature, LDOM remains an off-label treatment without FDA approval for any alopecia indication. The available evidence includes prospective and retrospective cohort studies, small open-label trials, and, increasingly, head-to-head randomised controlled trials (RCTs) against topical minoxidil. Several systematic reviews and meta-analyses have recently attempted to synthesize this evidence.[4,6,7] This systematic review aims to comprehensively evaluate the published evidence on the pharmacology, efficacy, safety, dosing, and patient-relevant outcomes of oral minoxidil in the management of AGA.

METHODS

Protocol and reporting

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[8] The review protocol was developed a priori, with pre-specified eligibility criteria, outcomes, and analysis strategy. The study selection process is illustrated in Figure 1.

Literature search strategy

A comprehensive electronic database search was conducted across PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Scopus, and ClinicalTrials.gov from database inception to March 2026. The search strategy employed controlled vocabulary (MeSH/Emtree) combined with free-text terms including: "Oral minoxidil," "low-dose oral minoxidil," "LDOM," "androgenetic alopecia," "male pattern hair loss," "female pattern hair loss," "female androgenetic alopecia," "hair loss," and "alopecia." Reference lists of identified studies and relevant review articles were hand-searched to identify additional studies not captured in electronic searches.

Eligibility criteria

Inclusion criteria

(1) Studies in humans; (2) patients with clinically diagnosed AGA (male or female pattern), confirmed by clinical examination with or without trichoscopy; (3) intervention: Oral minoxidil at any dose; (4) study designs including RCTs, prospective or retrospective cohort studies, case series ($n \geq 10$), and systematic reviews or meta-analyses; (5) reporting at least one outcome relating to hair density, hair count, diameter, global photographic assessment, adverse events, or patient satisfaction; (6) published in English in peer-reviewed journals.

Exclusion criteria

(1) Case reports and case series with fewer than 10 patients; (2) studies exclusively assessing alopecia areata, scarring alopecias, or telogen effluvium without a primary AGA subgroup; (3) in vitro or animal-model studies; (4) studies using oral minoxidil at antihypertensive doses (>5 mg/day for this indication); (5) conference abstracts without full-text publication; (6)studies not evaluable for quality.

Study selection and data extraction

All retrieved records were independently screened by two reviewers at the title/abstract and full-text stages. Disagreements were resolved by discussion and, if necessary,

by consultation with a third reviewer. Data were extracted using a pre-defined extraction template, capturing: Study design, population characteristics (sex, age, AGA severity classification), intervention (dose, frequency, formulation), comparator, follow-up duration, primary and secondary outcomes, and adverse events.

Quality assessment

The methodological quality of RCTs was assessed using the Cochrane Collaboration Risk of Bias 2.0 (RoB 2.0) tool, evaluating the following domains: Randomisation process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results.[9] Retrospective observational studies were assessed using the methodological index for non-randomised studies scale. Overall quality was designated as low, moderate, or high based on domain-level assessments.

Outcomes of interest

The primary outcomes were: (1) Change in hair density (hairs/cm²) from baseline; (2) change in terminal hair density; (3) global photographic assessment (rated by blinded evaluators). Secondary outcomes included: Change in hair shaft diameter, telogen-to-anagen ratio, patient-reported satisfaction, quality of life scores, incidence and nature of adverse events, and treatment discontinuation rates.

PHARMACOLOGY OF ORAL MINOXIDIL

Historical context and chemical properties

Minoxidil (chemical name: 2,4-diamino-6-piperidinylpyrimidine 3-oxide) is a piperidino-pyrimidine derivative with a molecular weight of 209.25 Da. Its development began in the late 1950s as part of a program targeting peripheral arterial vasodilators for the treatment of severe, refractory hypertension. The drug received FDA approval as an oral antihypertensive in 1979 at doses of 10–40 mg daily. The serendipitous observation of extensive hypertrichosis in patients on oral minoxidil therapy prompted investigation into its potential for promoting hair growth, ultimately leading to the development of the topical formulation, Rogaine (2%), approved for men in 1988 and women in the mid-1990s.

Mechanism of action

Minoxidil is a prodrug that requires bioactivation by sulfotransferase enzymes – principally SULT1A1 – within the outer root sheath (ORS) cells of hair follicles to produce its pharmacologically active metabolite, minoxidil sulfate.[10] This enzymatic conversion is the critical rate-limiting step for follicular response. Variability in SULT1A1 activity among individuals is a key explanation for the heterogeneity in clinical response observed across patients; non-responders to topical minoxidil frequently exhibit undetectable or very low follicular sulfotransferase activity.[10]

The principal mechanism by which minoxidil sulfate promotes hair growth is the opening of ATP-sensitive potassium (KATP) channels in dermal papilla cells of the hair follicle.[10,11] Hair follicles have been shown to contain two forms of KATP channels, only one of which is sensitive to minoxidil.[11] KATP channel opening leads to efflux of potassium, producing membrane hyperpolarization of smooth muscle and potentially dermal papilla cells. This results in arteriolar vasodilation, theoretically increasing perifollicular blood flow and nutrient delivery. Minoxidil has also been demonstrated to: (1) Shorten the telogen (resting) phase, triggering premature entry of follicles into anagen; (2) prolong the anagen (active growth) phase; and (3) increase follicular size from vellus to terminal caliber.[10]

Additional mechanisms documented in *in vitro* and *in vivo* studies include: Stimulation of vascular endothelial growth factor, which promotes perifollicular angiogenesis; activation of the Wnt/β-catenin signaling pathway, important in hair follicle regeneration; enhanced cysteine incorporation into the hair shaft protein structure; upregulation of hepatocyte growth factor and insulin-like growth factor-1 in dermal papilla cells; inhibition of lysyl hydroxylase, conferring anti-fibrotic properties; and prostaglandin E_2 synthesis stimulation, which has independent hair growth-promoting effects.[10]

Importantly, oral minoxidil does not directly target the androgen pathway, distinguishing it mechanistically from finasteride and other 5α-reductase inhibitors. Its efficacy in AGA likely derives from a combination of the follicular miniaturization reversal effects described above, rather than interference with DHT. The proposed mechanisms of action of oral minoxidil are summarized in Figure 2.

Pharmacokinetics of oral minoxidil

Following oral ingestion, minoxidil is rapidly and almost completely absorbed via the gastrointestinal tract, with bioavailability approaching 90%.[12] Peak plasma concentrations are typically achieved within 30–60 min of administration. Plasma protein binding is minimal, and the volume of distribution is approximately 2.0–3.0 L/kg, indicating extensive tissue distribution.[12] Renal elimination occurs with a plasma half-life of 3.0–4.0 h; however, the drug's hemodynamic effects on blood pressure may persist for up to 72 h following a single dose – a phenomenon attributed to the prolonged vascular retention of the active metabolite, minoxidil sulfate.

A pharmacokinetically important distinction between the oral and topical routes lies in where bioactivation occurs. After oral ingestion, minoxidil undergoes substantial hepatic first-pass metabolism, where it is converted into three principal metabolites – glucuronide conjugate (predominant), hydroxyl derivative, and minoxidil sulfate – the last of which enters the systemic circulation and reaches hair follicles via the bloodstream.[12] By contrast, topical minoxidil depends on locally expressed SULT1A1 within follicular ORS cells to generate the active sulfate form; percutaneous absorption of topically applied minoxidil through intact healthy skin is limited to approximately 1.4% of the applied dose.[10] Consequently, the oral route confers more consistent and scalp-morphology-independent follicular drug exposure, independent of the application variability inherent to topical use.

Follicular SULT1A1 expression levels may therefore serve as a clinically relevant determinant of which route of administration is more appropriate for a given patient. Individuals with high follicular sulfotransferase activity can efficiently convert topically applied minoxidil to its active metabolite at the follicle and are thus likely to respond well to topical therapy. Conversely, patients with diminished or absent follicular SULT1A1 activity – who characteristically fail to respond to topical minoxidil – may derive greater benefit from oral administration, as systemically generated minoxidil sulfate reaches follicles in active form via the circulation, bypassing the need for local enzymatic conversion.[13] These pharmacogenomic considerations are increasingly relevant to treatment personalization in AGA management.

CLINICAL EVIDENCE

Early observational and retrospective studies

The first published clinical evaluation of oral minoxidil for AGA and traction alopecia was a case series by Beach in 2018, which demonstrated that oral minoxidil was well tolerated, with patients exhibiting a satisfactory clinical response across the cohort.[14] The first evaluation of the effects of LDOM (1 and 2.5 mg daily) in men with AGA, was a retrospective chart review conducted by Jimenez-Cauhe *et al*. and associates in 2019. Their study found statistically significant improvements in hair density based on global photographic assessments.[5] Pirmez and Salas-Callo presented quantitative trichoscopy data demonstrating the effects of very LDOM (0.25 mg daily) on AGA in men, with statistically significant increases in terminal hair counts and an increase in shaft perimeters and minimal side effects.[15] Pirmez and Salas-Callo's study was one of the first to utilize quantitative trichoscopic endpoints to evaluate the effects of oral minoxidil in patients with AGA. Rodrigues-Barata *et al*. assessed 148 women with FPHL treated with LDOM (mean dose of 1 mg daily), and found 79.7% of women improved clinically, with 15.5% improving markedly and 64.2% improving slightly, and none had clinically significant worsening.[16] Panchaprateep and Lueangarun published a prospective open-label investigation of 5 mg oral minoxidil administered once daily to men with AGA. They documented statistically significant improvements at both hair density and hair shaft diameter over 24 weeks of treatment, while hypertrichosis was the most commonly reported side effect.[17] In a retrospective analysis of 60 patients receiving oral low-dose minoxidil, Yin *et al*. found statistically significant increases in hair density and width following treatment with oral low-dose minoxidil.[18] A systematic review of the efficacy and safety of LDOM for non-scarring alopecias, including AGA, by Sharma *et al*. further corroborates the clinical utility of LDOM across various doses and clinical circumstances.[19]

RCTs

Table 1 summarizes the key head-to-head RCTs comparing oral minoxidil to topical minoxidil in AGA patients.

Ramos et al. (2020)

The landmark RCT by Ramos *et al*. was the first published head-to-head comparison of oral and topical minoxidil specifically in FPHL. Fifty-two women aged 18–65 years with Sinclair stage II–IV FPHL were randomised to receive either 1 mg oral minoxidil once daily or topical minoxidil 5% solution once daily for 24 weeks.[20] The primary outcome – change in total hair density in the parietal region – increased by 12% (95% confidence interval [CI] 8.0–16.1%) in the oral group and 7.2% (95% CI 1.5–12.9%) in the topical group, a non-significant difference ($P = 0.09$). Terminal hair density increased proportionally more in the oral group. Importantly, the trial demonstrated that oral minoxidil was comparable in efficacy to the established topical treatment at a substantially lower nominal dose, suggesting oral administration may confer efficiency advantages. Scalp pruritus affected 19% in the topical group, while hypertrichosis was observed in 27% in the oral group.

Vahabi-Amlashi et al. (2021)

This Iranian RCT examined an even lower dose of oral minoxidil (0.25 mg/day) against topical minoxidil 2% twice daily in 72 women with FPHL over 39 weeks – the longest follow-up among published RCTs.[21] Results demonstrated comparable improvements in hair fibre diameter (oral +4 μm vs. topical +3 μm) and hair density (oral +13/cm^2 vs. topical +6/cm^2), with no statistically significant between-group differences. This study is particularly important as it validates a very low oral dose – one that one might intuitively expect to be insufficient – as being effective enough to produce hair growth metrics similar to established topical therapy. The low-dose strategy would theoretically minimise systemic adverse effects, making it attractive for cautious initiation in

Table 1: Key randomised controlled trials comparing oral minoxidil to topical minoxidil in AGA

Study (Year)	Study design	Population (*n*)	Oral minoxidil dose	Comparator	Duration	Key findings
Ramos *et al.*[20] (2020)	Randomized open-label	Women with FPHL; *n*=52	1 mg/day	Topical minoxidil 5%	24 wks	Total hair density+12% (oral) versus+7.2% (topical); *P*=0.09 (NS). Oral minoxidil comparable to topical.
Vahabi-Amlashi *et al.*[21] (2021)	RCT	Women with FPHL; *n*=72	0.25 mg/day	Topical minoxidil 2%	39 wks	Hair fibre diameter+4 μm (oral) versus+3 μm (topical); hair density+13 versus+6/cm^2. Difference NS.
Asilian *et al.*[22] (2024)	RCT	Male and female AGA; *n*=65	1 mg/day	Topical minoxidil 5%	24 wks	Comparable improvement in hair diameter between groups. Topical group showed better photographic hair density improvement (NS between groups). Patient satisfaction >60% in both.
Penha *et al.*[23] (2024)	Double-blind, placebo-controlled RCT	Male AGA (NW 3V–5V); *n*=90	5 mg/day	Topical minoxidil 5% twice daily	24 wks	Frontal terminal density: +3.1 hair/cm^2 (NS; *P*=0.27). Vertex terminal density: +23.4 hair/cm^2 (*P*=0.09). Vertex photographic improvement superior for oral (24%; *P*=0.04).

NW: Norwood-Hamilton scale, FPHL: Female pattern hair loss, AGA: Androgenetic alopecia, NS: Not significant, wks: Weeks, RCT: Randomised controlled trial

women.

Asilian et al. (2024)

Asilian *et al.* enrolled 65 patients (both sexes) with AGA, randomised to either 5% topical minoxidil or 1 mg/day oral minoxidil for 24 weeks.[22] Both groups demonstrated significant improvement in mean hair shaft diameter ($P < 0.001$), with no significant between-group difference. However, photographic assessment of hair density in the topical group showed significant improvement at all three scalp measurement points (12, 16, and 24 cm from glabella), whereas the oral group did not achieve statistical significance at any individual point – though the between-group difference was not significant. Patient satisfaction exceeded 60% in both groups. The authors concluded that 1 mg oral minoxidil may be as effective and safe as standard topical minoxidil in both MPHL and FPHL.

Penha et al. (2024)

The most rigorously designed and adequately powered trial to date was the double-blind, placebo-controlled RCT by Penha *et al*., published in JAMA dermatology.[23] Ninety men aged 18–55 with AGA (Norwood-Hamilton 3V, 4V, or 5V) were randomised 1:1 to either oral minoxidil 5 mg once daily (plus topical placebo), or topical minoxidil 5% twice daily (plus oral placebo), for 24 weeks. The primary outcome was the change in terminal hair density on the frontal and vertex scalp.

Of 90 enrolled participants, 68 completed the study. For the frontal area, mean change in terminal hair density was 3.1 hairs/cm^2 favoring oral minoxidil, which was not statistically significant (95% CI −18.2–21.5; $P = 0.27$). For the vertex, the difference was 23.4 hairs/cm^2 (95% CI −0.3–43.0; $P = 0.09$). However, global photographic analysis revealed a statistically significant superiority of oral minoxidil over topical at the vertex (24%; 95% CI 0–48; $P = 0.04$), though not at the frontal scalp (12%; $P = 0.24$). The trial concluded that oral minoxidil 5 mg daily was non-inferior to topical minoxidil 5% twice daily in men, and it represents a valid alternative, particularly for those preferring oral therapy or intolerant of topical applications.[23]

Systematic reviews and meta-analyses

Table 2 summarizes the key systematic reviews and meta-analyses published to date comparing oral and topical minoxidil in AGA.

The meta-analysis by Sobral *et al*. (published in the International Journal of Dermatology, 2024/2025) pooled four RCTs comparing oral minoxidil to topical minoxidil solution in AGA, encompassing 279 patients with follow-up from 24 to 39 weeks.[7] No statistically significant differences were found in hair density (standard mean difference [SMD] 0.02; 95% CI −0.25–0.29; $P = 0.88$; $I^2 = 0\%$) or hair diameter (SMD −0.25; 95% CI −0.75–0.26; $P = 0.34$; $I^2 = 36\%$). Critically, hypertrichosis occurred at significantly higher rates in the oral group (risk ratio 2.01; 95% CI 1.18–3.41; $P = 0.01$; $I^2 = 0\%$), confirming the dose-related systemic adverse effect profile of oral administration.

A comprehensive single-arm rate meta-analysis from Frontiers in Pharmacology (2025) incorporated 17 single-arm cohort

studies and 10 RCTs, totaling 2933 patients across multiple types of alopecia.[4] Within the AGA subgroup, clinical response rates (defined as stabilisation or improvement) were consistently high. The overall pooled hypertrichosis incidence was approximately 35%, reflecting higher event rates in the cohort studies compared with the more controlled RCT populations. No statistically significant between-group differences in adverse event rates were observed across dose-stratified subgroups, though higher doses correlated with increased hypertrichosis risk.

DOSING RECOMMENDATIONS

Oral minoxidil for AGA is prescribed at doses substantially lower than antihypertensive doses, a practice supported by the growing clinical evidence base. Table 3 summarizes current evidence-informed dosing recommendations.

The typical starting dose for male AGA is 2.5–5 mg/day, while for FPHL, doses of 0.5–1 mg/day are employed, with very cautious initiation at 0.25 mg/day for patients at higher risk of systemic adverse effects.[5,24] Dose titration is generally recommended over 4–8 weeks, with assessment of clinical response and side effects at 3–6 months. Given the dose-dependent nature of both the hair growth effect and adverse events, the minimum effective dose that achieves a satisfactory clinical response should be maintained.[5]

The response to oral minoxidil is not immediate. Patients should be counseled to expect initial shedding (telogen effluvium) in the first 4–8 weeks, which reflects the premature transition of telogen follicles into anagen – a favorable prognostic sign. Meaningful hair regrowth is typically observable by 3–6 months, with maximum benefit at 9–12 months of continuous treatment.[24] Treatment withdrawal results in gradual reversal of gains within

Table 2: Summary of published systematic reviews and meta-analyses on oral minoxidil in AGA

Review/ Meta-analysis	Studies included	Total patients	Hair density SMD/Pooled finding	Hypertrichosis RR	Conclusion
Sobral *et al.*[7] (2025) Int J Dermatol	4 RCTs	279	Hair density SMD 0.02 (95% CI−0.25–0.29; *P*=0.88; I^2=0%); Hair diameter SMD−0.25 (*P*=0.34)	RR 2.01 (95% CI 1.18–3.41; *P*=0.01)	Oral and topical minoxidil are equivalent in hair density; oral carries twofold greater hypertrichosis risk
Fazal *et al.*[6] (2025) Skin Health Dis	4 RCTs	257	No significant difference in hair density (overall MD 0.95; 95% CI−24.98–26.87)	Higher in oral group	Clinical benefits comparable; topical shows marginally better hair density; adverse effects minimum with topical
Frontiers (2025) single-arm meta-analysis[4]	17 cohort studies+10 RCTs	2933	Efficacy demonstrated in majority; doses >1 mg associated with better outcomes	Pooled hypertrichosis rate~35%; pedal edema~4%	Oral minoxidil benefits patients with hair loss; doses >1 mg preferable; more RCTs needed
Oxford Skin Health (2025)[6]	4 RCTs	257	Comparable hair density and terminal hair density improvement; no statistically significant difference	Higher in oral group	Oral minoxidil can serve as adjunct or second-line AGA treatment

SMD: Standard mean difference, RR: Risk ratio, CI: Confidence interval, RCT: Randomised controlled trial, MD: Mean difference

Table 3: Evidence-informed dosing framework for low-dose oral minoxidil in AGA

Population	Starting dose	Target/Maximum dose	Special considerations
Male AGA	2.5–5 mg/day	5 mg/day	Higher doses may offer greater vertex improvement; monitor cardiovascular parameters
FPHL	0.5–1 mg/day	2.5–5 mg/day (cautious escalation)	Greater susceptibility to hypertrichosis; start very low; co-administer androgen receptor inhibitors if needed
Female AGA (very low dose)	0.25 mg/day	1 mg/day	Validated in RCT (Vahabi-Amlashi); fewer systemic effects; suitable for intolerant patients
Elderly patients/ cardiovascular risk	0.25–0.5 mg/day	1–2.5 mg/day	Pre-treatment ECG and blood pressure assessment recommended; close monitoring
Patients intolerant to topical	0.5–1 mg/day (adjust by sex)	As per sex-specific recommendations	Oral route avoids scalp irritation, propylene glycol hypersensitivity, and hair texture changes

AGA: Androgenetic alopecia, FPHL: Female pattern hair loss, ECG: Electrocardiogram, RCT: Randomised controlled trial

3–6 months, consistent with the maintenance requirement of all non-curative AGA therapies.

SAFETY AND ADVERSE EFFECT PROFILE

Overview and classification

The safety profile of LDOM has been extensively characterised through a number of large real-world studies and prospective evaluations. The landmark multicentric safety study by Vañó-Galván *et al*., encompassing 1404 patients (67.2% women) with mean age of 43 years receiving LDOM for at least 3 months across multiple alopecia types, remains the largest safety dataset published for this indication.[1] A complementary pooled analysis of individual patient data from 14 studies (n = 442) by Jimenez-Cauhe *et al*. similarly reported a favorable safety profile, with hypertrichosis in 24% and pedal edema in 2% of patients.[25] The Vañó-Galván study evaluated 2469 treatment cases (accounting for dose titration) and found a generally favorable safety profile with no life-threatening adverse events. Table 4 details the adverse event profile of oral minoxidil.

Hypertrichosis

Hypertrichosis – the growth of terminal or vellus hairs in unwanted anatomical regions – is the most frequently reported adverse effect of oral minoxidil in the trichology context, arising from the systemic distribution of the drug activating follicles beyond the scalp.[14] It occurs through the same KATP channel-mediated and Wnt/β-catenin signaling mechanisms that promote scalp hair growth, but expressed in body hair follicles that become stimulated through systemic drug exposure.[1]

The reported incidence of hypertrichosis varies widely across studies, from as low as 4% in some RCTs to as high as 93% in actively surveyed prospective cohorts, reflecting significant methodology-dependent differences. In the large multicentric safety study, the overall hypertrichosis frequency was 15.1%, leading to treatment withdrawal in only 0.5% of patients.[1] Incidence is consistently higher in women (approximately 20%) than in men (approximately 6%), attributed to lower baseline body hair density in women, creating a more noticeable contrast. Higher doses and use of compounded capsules (associated with dose variability) also increase the risk.

Management strategies for hypertrichosis include dose reduction, adoption of an every-other-day dosing schedule, and co-administration of androgen receptor inhibitors. Moussa *et al*. demonstrated that bicalutamide at a mean dose of 14.4 mg/day significantly improved oral minoxidil-induced facial hypertrichosis in women, with a median response time of 3.4 months.[27]

Cardiovascular adverse effects

Given that minoxidil was originally developed as an

Table 4: Adverse effect profile of low-dose oral minoxidil in AGA: Frequency, characteristics, and management

Adverse effect	Incidence (Oral Minoxidil)	Clinical characteristics	Management strategy
Hypertrichosis	~15% overall (Vañó-Galván *et al*.); 4–93% across studies; higher in women (~20%) versus men (~6%)	Most common AE; dose-dependent; affects face, arms; rarely leads to discontinuation (<0.5%)	Dose reduction; every-other-day dosing; co-administration of spironolactone or bicalutamide
Fluid retention/Pedal edema	1.3–10%; more common in women	Typically appears within 1–3 months; mild ankle edema	Dose reduction; low-sodium diet; diuretics if persistent
Lightheadedness/ Postural hypotension	1.7% (large cohort study); up to 9% in actively surveyed populations	Vasodilatory effect; usually transient and mild	Slow position changes; dose adjustment; avoid concurrent antihypertensives
Tachycardia	0.9–1.3%	Reflex sympathetic response; rarely clinically significant at low doses	Cardiac evaluation; dose reduction or discontinuation
Headache	0.4% (passive reporting); up to 9% (active survey)	Onset typically 15–20 days after starting; vasodilatory mechanism	Common analgesics; usually self-limiting; dose adjustment if persistent
Telogen effluvium (shedding)	9% (oral group) versus 13% (topical group) in one RCT	Transient; reflects transition of resting follicles into anagen phase	Patient counseling; reassurance; temporary dose reduction
Periorbital edema	0.3%	Rare; related to fluid retention mechanisms	Dose reduction or discontinuation
Pericardial effusion	Rare; single case reports at very low doses	Type B (idiosyncratic) adverse effect; not dose-dependent	Immediate discontinuation; cardiology referral

AE: Adverse event, LDOM: Low-dose oral minoxidil

antihypertensive, cardiovascular tolerability represents the most clinically scrutinized safety domain when used systemically. At the low doses employed for AGA (0.25–5 mg/day), hemodynamic adverse effects are generally mild and infrequent. In the Vañó-Galván *et al*. multicenter cohort of 1404 patients, the cardiovascular event rates were: Lightheadedness 1.7%, fluid retention 1.3%, tachycardia 0.9%, and periorbital edema 0.3%. Treatment discontinuation attributable to systemic adverse events occurred in only 1.2% of participants.[1]

Fluid retention typically manifests within the first 1–3 months of treatment and is more common among women and at higher doses. Pre-treatment blood pressure measurement is advisable, and concurrent antihypertensive medications should be used with caution, given the potential additive hypotensive effects. In patients with established cardiovascular disease, a baseline electrocardiogram is warranted. Although exceedingly rare, pericardial effusion as an idiosyncratic (Type B) reaction has been documented in isolated case reports at low minoxidil doses; patients should accordingly be counseled to report any new cardiorespiratory symptoms promptly.

PATIENT ADHERENCE AND COMPARATIVE ADVANTAGES

Long-term therapeutic outcomes in AGA are substantially influenced by treatment adherence, since AGA is a chronic, progressive condition requiring sustained – often indefinite – pharmacological intervention. Adherence to topical minoxidil is particularly problematic. A retrospective audit of 400 consecutive patients prescribed topical minoxidil found that more than 86% eventually discontinued therapy. The principal drivers of discontinuation were the occurrence of side effects (odds ratio 3.06; $P = 0.002$), perceived lack of efficacy, and practical burdens associated with topical application – including greasy scalp residue, altered hair texture, and the requirement for twice-daily application.[3]

Compared to topical minoxidil, the oral version has a number of advantages over topical therapy that may help improve adherence to therapy. First, the oral route allows for less difficulty in applying medication because there is no source of application to the scalp, which eliminates issues associated with topical minoxidil applications including greasy residue, sensitivity to propylene glycol (the cause of allergic contact dermatitis when using topical solutions), changes in the texture of the hair, and difficulty styling the hair (all significant reasons for non-adherence to topical therapy). Second, most patients will already have a routine that includes daily medications (and therefore it will be relatively simple for them to incorporate oral minoxidil into their daily regimen). Third, oral minoxidil is generally less expensive than branded topical products. When compounded, oral minoxidil will usually cost significantly less than those brands. Therefore, financial attrition will be less likely when using compounded oral minoxidil than branded topical products. Fourth, the lack of interaction with separately applied topically used cosmetic or hairstyling products will be another significant advantage of oral minoxidil over topical minoxidil.

The authors of the study performed by Penha *et al*. in an RCT published in the JAMA Dermatology Edition specifically indicated that patients who are intolerant of topical products or who prefer to take their medications in an oral form would prefer taking oral minoxidil.[23] Similarly, Ramos *et al*. concluded that oral minoxidil should be a viable choice for women suffering from FPHL who have had difficulty adhering to their treatment regimen or who cannot tolerate topical administration of the medication.[20] In addition, Sinclair published a pilot trial demonstrating the feasibility of using oral minoxidil in combination with spironolactone for FPHL, further demonstrates the potential of utilizing oral minoxidil as a viable treatment option.[26]

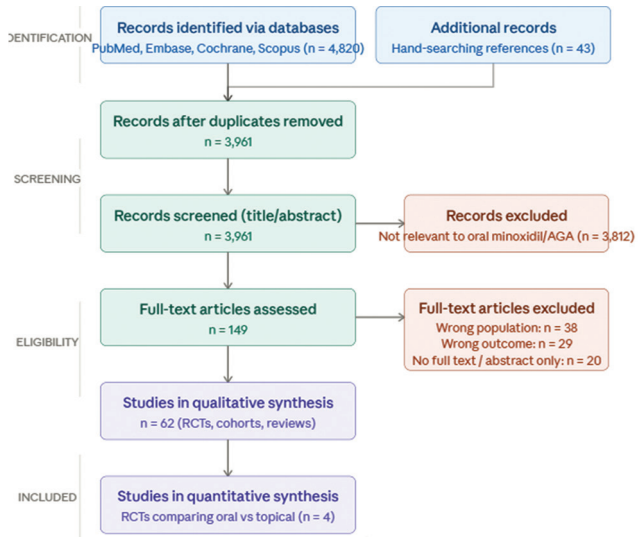

Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow diagram

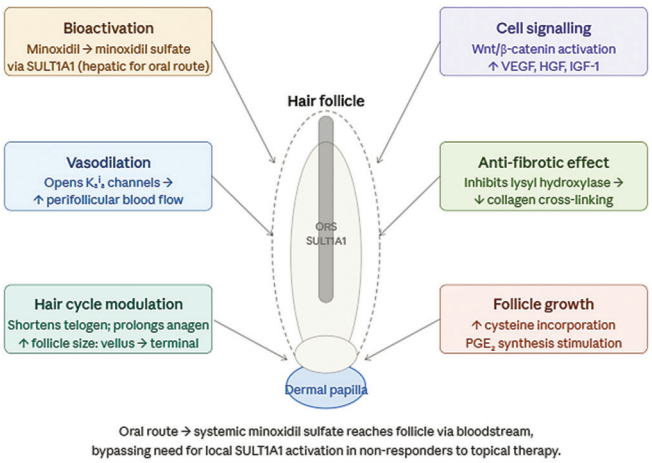

Figure 2: Mechanisms of action of oral minoxidil

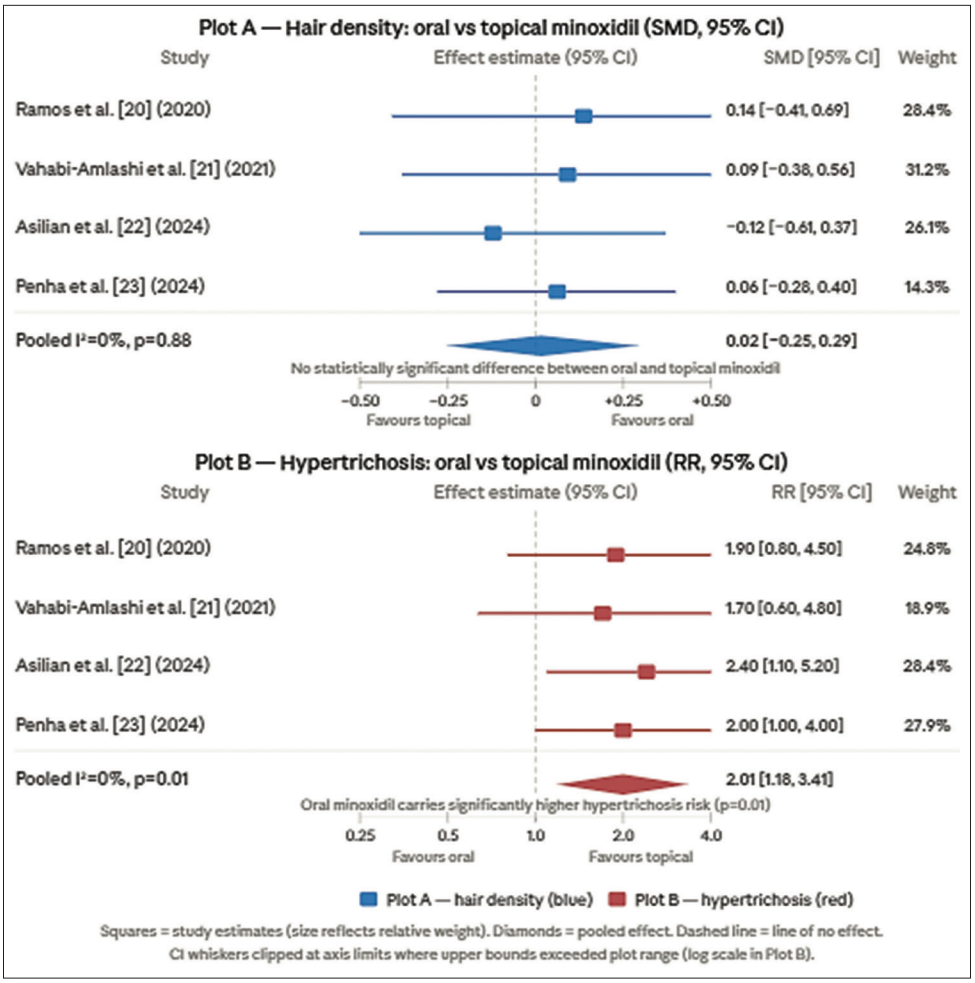

Figure 3: Forest plot

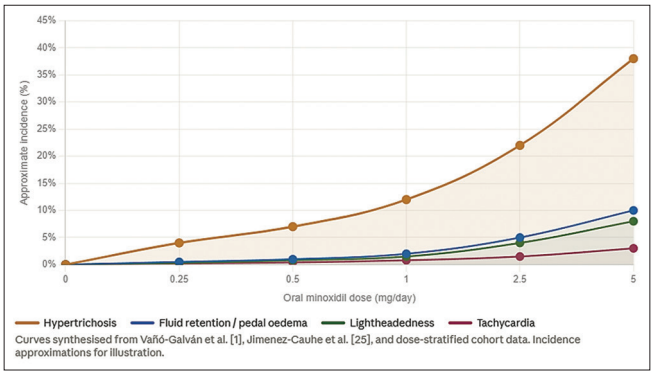

Figure 4: Dose-dependent adverse effect profile (interactive)

DISCUSSION

This review shows that (LDOM) can be used instead of topical minoxidil on an off-label basis and will work clinically for the treatment of (AGA). Using the data from all four of the head-to-head, RCTs and multiple pooled meta-analyses involving oral minoxidil, it has been shown that oral and topical formulations do not differ in terms of efficacy concerning objective endpoints for hair density and diameter of the hair shaft. Furthermore, oral (LDOM) provides advantages over topical minoxidil in terms of administration route and tolerability. As shown in Figure 3, pooled analysis of the randomized controlled trials demonstrated no statistically significant difference between oral and topical minoxidil with respect to hair density, whereas oral minoxidil was associated with a significantly higher risk of hypertrichosis.

Of note in all of the meta-analyses with respect to hair density was that there were no statistically significant differences between the oral and the topical formulations of minoxidil.[6,7] This is particularly noteworthy given that oral minoxidil is administered at much lower doses than topical minoxidil (i.e. the typical dose for oral minoxidil is about 1 mg/day whereas topical minoxidil is usually a 5% solution applied to the scalp 2 times a day), as pharmacokinetic theory dictates that because of the higher systemic bioavailability of oral minoxidil, that more drug will be available for the follicles to absorb it indiscriminately from [variations in] topical absorption. In addition, since minoxidil sulfate is produced by the liver after oral administration of minoxidil, the lack of responsiveness that occurs with (topical minoxidil) could be attributed to the inability to produce sufficient levels of (minoxidil sulfate) to support continued hair growth in a (SULT1A1) intolerant patient.

With respect to the cardiovascular safety of (LDOM), the Vañó-Galván *et al*. landmark safety study[1] showed that there were no serious adverse events due to (LDOM) when given to a diverse patient population (including females and males, ages 8–86 years, and patients with many co-morbidities). Overall, there was only a 1.7% rate of treatment discontinuation due to adverse events, which is a low figure according to clinical standards. Although hypertrichosis is seen most frequently in patients receiving (LDOM) and is often the reason that patients discontinue treatment, only about 1% of patients will stop taking (LDOM) due to hypertrichosis. The dose-dependent adverse effect profile of low-dose oral minoxidil, particularly the increasing incidence of hypertrichosis with higher doses while maintaining a low frequency of serious cardiovascular adverse events, is illustrated in Figure 4.

An important point to consider is whether or not (SULT1A1) activity levels are predictive of whether or not a patient will respond better to oral minoxidil versus topical minoxidil.[5] Showed that patients with low (SULT1A1) activity in the hair follicle had significantly higher response rates to oral administration of minoxidil (85% responding to oral minoxidil versus 43% responding to topical minoxidil; $P = 0.009$).[13] This relationship between (SULT1A1) activity and response to oral versus topical minoxidil suggests that (LDOM) would be more appropriate for patients who do not have success with topical minoxidil – specifically those patients who have been ardently using (LDOM). If a standardized (SULT1A1) assay could be developed to identify patients who are most likely to respond to (LDOM), it could be used as a tool to help personalize the treatment of (AGA).

Despite these encouraging findings, several important limitations of the current evidence base must be acknowledged. First, the number of head-to-head RCTs remains small (four to date), with relatively modest sample sizes ($n = 52–90$ per trial). This limits statistical power to detect modest between-group differences and makes subgroup analyses unreliable. Second, the maximum follow-up in any comparative RCT is 39 weeks – insufficient to fully characterize long-term efficacy and, crucially, long-term cardiovascular safety over years of continuous use. Third, significant heterogeneity exists across trials in terms of sex, dose of oral minoxidil (0.25–5 mg), topical comparator concentration (2%–5%), and outcome measurement methodology (trichoscopy, phototrichogram, global photographic assessment), hampering direct comparisons. Fourth, none of the published RCTs were placebo-controlled for both arms – the Penha *et al*. trial used a double-dummy design but remained single-center.

The question of whether oral minoxidil should be positioned as a second-line rescue therapy for topical non-responders, or as a first-line option for selected patients, remains unresolved. The existing evidence supports its use in patients with documented topical intolerance or non-adherence. Whether it should be the initial treatment of choice – particularly for male AGA, where 5 mg/day showed vertex superiority by photographic assessment[23] – requires further investigation. The growing expert interest in combination oral minoxidil with finasteride ("All-in-One" oral regimens) is worth noting: Retrospective evaluations have reported clinically meaningful improvements in 92.4% of male AGA patients at 12 months on this combination,[24] though prospective RCT evidence is pending.

Although this systematic review has a number of limitations, it does contain a comprehensive search strategy to avoid the possibility of publication bias (as few positive studies are published in accessible peer-reviewed journals). The meta-analyses of the RCTs may also contain some methodological heterogeneity with respect to dosing, patient populations, and outcome measures, thereby limiting the ability to quantitatively interpret pooled effect estimates. The authors of this review were not able to obtain any individual patient data for unpooled analyses. As the major RCTs published to date were conducted only in Brazil and Iran, the findings should not be generalised to other ethnic populations where the response to minoxidil (and specifically the activity of SULT1A1) may be different than the original populations studied. Moreover, as LDOM is currently off-label for the treatment of AGA, prescribing patterns from clinicians will vary significantly based upon their practice, and there is little data available regarding adherence to the use of oral minoxidil in the real world.

CONCLUSION

LDOM, at doses of 0.25–5 mg/day, is a viable pharmacological option for treating AGA in both men and women. There is an established body of evidence from 4 two-group RCTs and multiple meta-analyses illustrating that oral minoxidil is no less effective than topical minoxidil in improving hair density and shaft diameter. In one well-designed RCT, oral minoxidil was found to give statistically superior photographic results at the vertex compared with topical treatment. The only anticipated adverse effect of administering oral minoxidil would be hypertrichosis, which occurs in <15% of patients in large real-world cohorts. Given the modest incidence rate of hypertrichosis (<1%) leading to treatment discontinuation, it is apparent that hypertrichosis can be managed in the overall management of AGA. Serious adverse cardiovascular events are highly uncommon at the doses that will be used for the treatment of AGA.

There are certain practical benefits associated with the use of oral minoxidil (i.e., greater adherence, no need for scalp application of medication, lower cost, and ability to use styling products) that will translate into improved long-term treatment outcomes in patients who have difficulty adhering to topical treatments. New evidence from pharmacogenomics suggests that patients with lower follicular SULT1A1 activity (which is a large proportion of patients who do not respond to topical minoxidil) are more likely to respond to oral

minoxidil, thus highlighting the feasibility and potential importance of using biomarkers to select treatment.

It is prudent to consider LDOM as a first-line oral treatment option for patients with documented intolerance or poor adherence to topical minoxidil and/or documented non-responders to topical minoxidil. It is also reasonable, in selected patients, particularly males who desire vertex improvement, to consider LDOM as a first-line treatment option. Before commencing treatment, patients with relevant comorbidities should undergo cardiovascular safety assessments, and all patients should receive complete counseling, including the likelihood of hypertrichosis and potential for initial telogen effluvium. Future studies should focus on multi-center, long-term RCTs in which there is standardization of the treatment protocol, patient-reported outcome measures, and integration of pharmacogenomic biomarkers with the goal of optimising dosing regimens and personalizing treatment for AGA.

DECLARATIONS

The authors declare that this systematic review was of published literature, with no conflicts of interest. No ethical approval was required for this review. No funding was received for this review.

AUTHOR'S CONTRIBUTIONS

Ragadharshini Eswaran and Narasimhalu C. R. V were responsible for conceptualization, methodology, data curation, and writing. Varun Rajagopal and Anton James AlanJ contributed to the literature search, formal analysis, validation, and writing.

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Source of Support: Nil. **Conflicts of Interest:** None declared.