Oral minoxidil treatment for hair loss: A review of efficacy and safety

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Background: Although topical minoxidil is an effective treatment option for hair loss, many patients are poorly compliant because of the necessity to apply the medication twice a day, undesirable hair texture, and scalp irritation.

Objective: In recent years, oral minoxidil at low dose has been proposed as a safe alternative. This study reviewed articles in which oral minoxidil was used to treat hair loss to determine its efficacy and safety as an alternative to topical minoxidil.

Methods: PubMed searches were performed to identify articles discussing oral minoxidil as the primary form of treatment for hair loss published up to April 2020.

Results: A total of 17 studies with 634 patients were found discussing the use of oral minoxidil as the primary treatment modality for hair loss. Androgenetic alopecia was the most studied condition, but other conditions included telogen effluvium, lichen planopilaris, loose anagen hair syndrome, monilethrix, alopecia areata, and permanent chemotherapy-induced alopecia.

Limitations: Larger randomized studies comparing the efficacy/safety of different doses with standardized objective measurements will be needed to clarify the best treatment protocol.

Conclusion: Oral minoxidil was found to be an effective and well-tolerated treatment alternative for healthy patients having difficulty with topical formulations. (J Am Acad Dermatol 2021;84:737-46.)

Key words: alopecia; alopecia treatment; androgenetic alopecia; efficacy; hair loss; minoxidil; oral minoxidil; safety; systemic minoxidil.

Minoxidil was first introduced in the 1970s as a treatment for severe refractory hypertension because of its potent vasodilatory qualities. Minoxidil has a relaxant effect on vascular smooth muscle through the opening of adenosine triphosphate–sensitive potassium channels.[1] During this time, hypertrichosis and regrowth of hair was found to be a common adverse effect among users, and a topical preparation was first marketed in 1986.[2-7] For several decades, minoxidil has been used as 2% and 5% topical solutions and, later, 5% foam for the treatment of a variety of alopecia conditions in both men and women, although it was approved only for androgenetic alopecia (AGA). The exact mechanism of action remains unknown, although the conversion of minoxidil to its active derivative, minoxidil sulphate, by follicular sulfotransferase activity is a key step in the medication's effectiveness.[8,9] Minoxidil causes a shortening of the telogen phase and lengthening of the anagen phase with a progressive growth in hair follicle diameter and length.[10,11] The topical formulation must continue to be applied, or beneficial effects will regress.[12] The adverse effects are largely cutaneous,

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with the most common complaints being scalp pruritus, scalp scaling, and hypertrichosis. Contact dermatitis can also develop over time.[13-15]

Although topical minoxidil is an effective treatment option for hair loss, many patients are poorly compliant because of the necessity to apply the medication twice a day, undesirable hair texture, and scalp irritation. Patients must also be made aware of a temporary shedding period that occurs after the initiation of topical application. If unaware of this adverse effect, patients may discontinue use prematurely.

Until recently, oral minoxidil (OM) has not been used for treatment of hair loss because of the potential adverse effects of the medication when used at doses between 10 and 40 mg daily. Sodium and fluid retention have been shown to be a significant adverse effect, especially in patients with renal conditions. This adverse effect will commonly present as edema or weight gain, although it may infrequently cause pulmonary congestion. Coadministration with beta blockers was common to reduce sodium/fluid retention and control heart rate.[16] Acute pulmonary edema and pulmonary hypertension have also been reported as possible adverse effects, although a direct causal relationship has yet to be proven.[17] Cardiac conditions associated with the medication include, most commonly, reflex tachycardia and, less commonly, electrocardiogram (ECG) changes, pericardial effusion, and congestive heart failure in patients with advanced renal disease.[18] The dose-related adverse effects were studied for the use of minoxidil as an antihypertensive agent, with a typical maintenance dose between 10 and 40 mg daily.[19]

Use of low-dose OM overcomes many of these therapeutic limitations and has recently become more popular, with several studies and reports published on its efficacy and safety.This review will analyze the available studies to determine the effectiveness and safety of OM as a treatment option for hair loss.

CAPSULE SUMMARY

- This review discusses the limitations of topical minoxidil for hair loss treatment and assesses oral minoxidil as an emerging treatment alternative.
- Low-dose oral minoxidil is an effective and safe treatment alternative for a variety of hair loss disorders in healthy patients having difficulties with topical minoxidil preparations.

METHODS

Key word searches of PubMed were performed to identify all articles discussing OM treatment of hair loss until April 2020. Search terms included "oral minoxidil," "hair loss," "systemic minoxidil," and "alopecia." No language or time restrictions were used. Articles found were read and reviewed; they were judged appropriate for inclusion if they described treatment of hair loss primarily with OM. The references of these articles were reviewed to identify additional resources.

RESULTS

Efficacy

A total of 17 studies with 634 patients were found discussing the use of OM as the primary treatment modality for hair loss (Table I). AGA was the most studied condition. In general, OM was found to be an effective treatment for AGA. In the largest study, Rodrigues-Barata et al[20] determined a mean dose of 1 mg of OM in 148 women to be an effective form of treatment for female pattern hair loss (FPHL). Response to therapy was more significant in patients with more advanced stages of FPHL. Although a large portion of patients in this study were taking concomitant treatments, little difference in effectiveness was reported between patients receiving OM monotherapy and patients receiving OM plus additional treatment. Sinclair[21] used 0.25 mg minoxidil daily in women with FPHL and showed improvement in the Sinclair hair loss severity score and hair shedding score through 1 year of treatment. OM was associated with spironolactone 25 mg daily to reduce the risk of fluid retention. Additionally, 50 mg of sodium chloride was added to the capsule for women with low blood pressure.

At a dosage of 1.25 mg daily, Beach et al[22] studied OM for treatment of AGA and traction alopecia in 18 patients, 17 of whom were female, for an average duration of 6 months. At follow-up, 33% of patients reported decreased hair shedding, and 28% reported increased scalp hair. Similar improvements were noted by Jha et al[23] in men taking 1.25 mg; however, a higher dosage may be necessary if no response is noticed within 6 months. Ramos et al[24] compared the efficacy of 1 mg daily OM to topical 5% solution daily and found OM to be as effective as the topical solution. Parietal hair density measured through a blinded analysis of trichoscopic images was the primary endpoint in this study. Ramos et al[25] also indicated that a lower follicular sulfotransferase activity threshold is needed for bioactivation of OM

Abbreviations used:

AGA: androgenetic alopecia
ECG: electrocardiography
FPHL: female pattern hair loss
OM: oral minoxidil

compared to topical minoxidil. Additionally, in this study, OM produced better improvement of hair shedding score, indicating favorable results for treatment of telogen effluvium.[24] The improved hair shedding score supported findings by Sinclair and Perera[26] in which OM effectively treated chronic telogen effluvium in women. In this study, most women (29 of 36) were taking 1 mg or less daily.

In male AGA, Lueangarun et al[27] studied the use of a 5-mg daily dose. Measured over 24 weeks, photographs showed 100% improvement, with 43% of men having remarkable improvement. With a longer duration of treatment, more patients showed remarkable improvement. Additionally, they found OM to be effective both in the vertex and frontal area, although the vertex showed greater progress.[27] Similarly, Jimenez-Cuahe et al[28] studied male AGA treated with a 5-mg or 2.5-mg daily dose. In a subgroup of patients treated with OM monotherapy, mostly at 5 mg, all showed clinical improvement, with 37.5% showing marked improvement. When using a lower dose of 0.25 mg, which was found to be effective in FPHL, Pirmez and Salas-Callo[29] found improvement or stabilization in 40% to 60% of male patients treated for AGA. However, it was not considered statistically significant when hair thickness and density were evaluated. Current data indicate that 2.5- to 5-mg daily doses are more effective in treating males with AGA. However, larger prospective studies with standardized objective measurements are needed to truly elucidate the optimum dosing protocol for both male and female patients. Interestingly, Sinclair et al[30] examined the use of sublingual administration of minoxidil because it bypasses hepatic metabolism for greater bioavailability. At a dosage of 0.45 mg daily, both male and female patients had improvements in multiple measurements including Sinclair stage, Sinclair hair shedding score, and International Global Assessment.

A recent retrospective analysis by Vano-Galvan et al[31] showed that OM (0.5 mg daily for women and 2.5 mg daily for men) improved or maintained hair thickness in a majority of patients with classical lichen planopilaris and was especially beneficial for patients with diffuse lichen planopilaris. In addition to AGA, telogen effluvium, and lichen planopilaris, the review found case reports of OM therapy proving to be useful in the treatment of loose anagen hair syndrome, monilethrix, alopecia areata, and permanent chemotherapy-induced alopecia.[32-36]

Safety

This review found OM to be well tolerated with only minor adverse effects described in the literature (Table II). The most reported adverse effect was hypertrichosis, which was reported in approximately one fifth of patients. Interestingly, hypertrichosis was almost never a cause for discontinuation of the medication, because many patients considered it only a mild adverse effect and easily manageable. Overall, hypertrichosis was more common among patients who used 5 mg daily and was seen in slightly more than half of these patients.[27,28,32] A dose of 0.25 mg had the lowest incidence of hypertrichosis (less than 10% of patients).[21,29] Although hypertrichosis seems to be dose related, larger studies are needed to accurately determine the true incidence. Areas of hypertrichosis described in the studies included the face and body. Therianou et al[33] showed 0.25 mg twice daily OM to be a satisfactory and safe alternative to topical solutions in women who develop acute contact dermatitis to propylene glycol in topical minoxidil solutions. As with topical minoxidil, OM is associated with a temporary period of increased hair shedding that can last 3 to 6 weeks. Patients should be warned of this possible adverse effect to avoid premature discontinuation of treatment. Most studies did not report this adverse effect, but Sinclair[21] reported that 22 out of 100 women found this increase in shedding to be of significant concern. No women discontinued treatment due to this adverse effect, and shedding ceased for most of these women within 4 weeks.

Cardiovascular adverse effects were overall rare and relatively minor. Blood pressure was monitored in some of the studies, with only minor changes.[21,22,26,30] Ramos et al[24] found no difference in mean blood pressure when comparing groups who used topical minoxidil as opposed to oral administration; however, OM did increase heart rate by 6.5%. Postural hypotension/dizziness was reported in approximately 2% of patients. Sinclair[21] described the use of 50 mg of sodium chloride daily for treatment of patients reporting postural hypotension. Lower limb edema was seen in only approximately 3% of patients, the majority of which were taking the 5-mg dose. Of these patients, only 1 discontinued due to the edema.[28] ECG changes were reported in approximately 1% of cases; however, it is unclear if patients were regularly examined with ECG because this was reported in only 1 study.

Table I. Summary of studies

Authors and year	Disease	Dosage/regimen	Number of participants	Results	Adverse effects
Vano-Galvan et al,[31] 2020	LPP	Median daily dose: 0.5 mg daily for women and 2.5 mg daily for men Average duration: 21 months There were no changes to concomitant therapies within the last 6 months.	N = 51 (36 F, 15 M) Mean age: 55 y	20 patients (39%) had improved hair thickness 27 patients (53%) remained stable 4 patients (8%) had worsening hair thickness Improvement was more likely with higher doses in male patients. Diffuse LPP was associated with a better response than patchy LPP	27% (n = 14) hypertrichosis 6% (n = 3) postural hypotension 4% (n = 2) tachycardia 2% (n = 1) weight gain
Therianou et al,[33] 2020	FPHL with contact dermatitis to propylene glycol in 2% and 5% solutions of TM.	0.25 mg twice per day Average duration: 17 months	N = 9 (9 F, 0 M)	All patients were satisfied with treatment.	22% (n = 2) facial hypertrichosis
Beach et al,[22] 2018	AGA Traction alopecia	1.25 mg nightly Average duration of prescription: 6 months All patients previously using TM	N = 18 (17 F, 1 M) AGA: n = 14 (13 F, 1 M) Traction alopecia: n = 4 (4 F, 0 M) Average age: 41 y	33% had decreased hair shedding 28% had increased scalp hair	6% (n = 1) hypotension and urticaria 39% (n = 7) hypertrichosis of face In all but 1 patient, blood pressure remained normal or improved in those with hypertension. No heart rate changes were found.
Cranwell and Sinclair,[34] 2018	Loose anagen hair syndrome	0.5 mg daily Previously using 5% topical solution for 5 years	N = 1 (1 F) Age: 11 y	Shedding and hair density improved in first 3 months. Discontinued after 12 months with no recurrence	Hair color change from reddish-brown to light brown
Sinclair and Perera,[26] 2017	Chronic telogen effluvium	Varied between 0.25 mg and 2.5 mg daily (29 patients used 1 mg or less daily) n = 5 at 0.25 mg n = 4 at 0.5 mg n = 19 at 1 mg n = 8 at 2.5 mg	N = 36 (36 F, 0 M) Average age: 46.9 y	Baseline HSS: 5.64 6-month HSS: 3.9 12-month HSS: 3.05	n = 2 with transient postural hypotension that resolved n = 1 with ankle edema n = 14 with hypertrichosis Average blood pressure change: S: -0.5 mm Hg D: +2.1 mm Hg

Jimenez-Cauhé et al,[28] 2019	AGA	5 mg daily (10 patients received 2.5 mg daily, 31 patients received 5 mg daily)	N = 41 (41 M, 0 F) OM monotherapy: n = 16 Average age: 33.3 y	n = 37 (90.2%) had clinical improvement. n = 11 (26.8%) had marked improvement. n = 4 (9.8%) showed stabilization. Of OM monotherapy subgroup: All had clinical improvement, with 6 (37.5%) showing marked improvement. OM at a dose of 5 mg daily was effective and presented an acceptable safety profile	n = 10 (24.3%) hypertrichosis n = 2 (4.8%) lower limb edema; 1 patient discontinued
Pirmez and Salas-Callo,[29] 2019	AGA	0.25 mg daily Measured • total hair density • density of terminal hair • new hairs • new terminal hairs	N = 25 (25 M, 0 F), all receiving monotherapy Average age: 36.7 y n = 10 mild AGA n = 15 severe AGA	Improvement or stabilization was seen in a percentage of patients but was not found to be statistically significant. Higher doses such as 2.5 mg or 5 mg might be necessary for significant effects in men	n = 5 (20%) body hypertrichosis n = 4 (16%) hair shedding n = 1 (4%) pedal edema n = 13 (52%) increased beard density
Lueangarun et al,[27] 2015	AGA	5 mg daily for 24 weeks	N = 30 (30 M,0 F) Average age: 38 y	Vertex area showed 100% improvement. Remarkable improvement was seen in 43% of patients. Significantly increased total hair count at the vertex. Significant response at the frontal area but less than at the vertex area.	93% with hypertrichosis 10% with pedal edema 10% with ECG changes
Ramos et al,[24] 2019	FPHL	1 mg daily for 24 weeks vs 5% topical solution daily	N = 52 (52 F, 0 M) TM 5%: n = 26 Average age: 47.3 y OM: n = 26 Average age: 40.6 y	Total hair density increased by 12% in OM and 7.2% in TM No significant difference between them (P = .10) OM provides improvement of FPHL that does not differ from TM, with a safe profile and well-tolerated adverse effects.	Hypertrichosis: • OM: 27% • TM: 4% Edema: • OM: 4% • TM: 0% Scalp pruritus: • OM: 0% • TM: 19% Mean heart rate: • OM: increase by 6.5% • TM: no change No difference in mean blood pressure between groups

Continued

Table I. Cont'd

Authors and year	Disease	Dosage/regimen	Number of participants	Results	Adverse effects
Sinclair,[35] 2016	Monilethrix	0.25 mg to 0.5 mg n = 1 at 0.25 mg	N = 2 (2 F, 0 M) 35 y and 40 y	Patient 1: Hair growth with reduced breakage and increased hair volume/length; maintained through 2 years of follow-up. Patient 2: Decreased shedding with 0.25 mg; improved hair density when dosage increased to 0.5 mg Maintained through 18 months of follow-up	No reported adverse effects
Sinclair,[21] 2017	FPHL	Once-daily capsule containing 0.25 mg minoxidil and 25 mg spironolactone	N = 100 (100 F, 0 M) Average age: 48.44 y	Baseline Sinclair hair loss severity score: 2.79 Baseline HSS: 4.82 Reduction in hair loss severity score: 0.1 at 3 months 0.85 at 6 months 1.1 at 9 months 1.3 at 12 months Reduction in HSS: 1.1 at 3 months 2.3 at 6 months 2.7 at 9 months 2.6 at 12 months Low-dose OM is well tolerated and a reasonable alternative to TM.	n = 4 facial hypertrichosis n = 2 postural hypotension n = 2 urticaria (likely due to spironolactone) Average decrease of 4.52 mm Hg in systolic and 6.48 mm Hg in diastolic blood pressure
Wambier et al,[32] 2019	Alopecia areata	Tofacitinib 5 mg 2 times daily or 10 mg 2 times daily OM: 2.5 mg daily for women OM: 2.5 mg twice daily for men	N = 12 (7 F, 5 M)	n = 8 (67%) achieved >75% scalp regrowth. n = 4 (33%) achieved 11% to 75% scalp regrowth. Median baseline SALT score: 99.5% Median final SALT score: 6.5% Combination tofacitinib and OM may be more efficacious than tofacitinib monotherapy.	n = 6 (50%) hypertrichosis n = 2 (17%) acne No reported blood pressure changes, peripheral edema, or symptoms of hypotension
Yang and Thai,[36] 2015	Permanent chemotherapy-induced alopecia	OM 1 mg daily	N = 1 F Age: 39 y	Subjective increase in hair growth was seen at 6 weeks. After 1 year, the patient regrew significant amounts of hair. Significant decreases in telogen follicles and a reversal of follicle miniaturization were seen.	None

Rodrigues-Barata et al,[20] 2020	FPHL	0.25 to 2 mg daily	N = 148 (148 F, 0 M) 125 patients received concomitant therapies, including • Dutasteride • Mesotherapy dutasteride • TM 5% • PRP • Finasteride • Flutamide • Bicalutamide • Cyproterone acetate • LLLT • Latanoprost	30 patients (20.3%) had stabilization of hair loss. 118 patients (79.7%) had clinical improvement (95 had slight improvement, 23 had marked improvement) OM may be an effective and safe therapy for FPHL	n = 25 hypertrichosis n = 2 tachycardia n = 1 peripheral edema
Jha et al,[23] 2020	AGA	1.25 mg	N = 32 (0 F, 32 M) Age range: 18-45 y	14/32 patients experienced marked improvement. 13/32 experienced mild improvement on global assessment. 25/32 patients experienced statistically significant improvement in average total hair density per unit area and hair shaft diameter. 1.25 mg/d can be used in male AGA, although 2.5-5 mg/d may be necessary if response is suboptimal after 6 months of treatment.	n = 1 peripheral edema n = 1 hypertrichosis
Sinclair et al,[30] 2020	AGA	0.45 mg daily (sublingual)	N = 64 (31 F, 33 M) Mean age: 50.92 y	Male and female patients had mean reduction of Sinclair stage and Sinclair HSS. Male patients had mean improvement of Investigator Global Assessment. Sublingual minoxidil at a dose of 0.45 mg daily was effective and had an acceptable safety profile.	n = 8 hypertrichosis n = 5 postural dizziness n = 2 peripheral edema Average blood pressure at start of study: 126.27/76.69 mm Hg Average blood pressure after 12 months of OM use: 121.85/77.46 mm Hg

Continued

Table I. Cont'd

Authors and year	Disease	Dosage/regimen	Number of participants	Results	Adverse effects
Ramos et al,[25] 2020	FPHL	1 mg daily for 24 weeks	N = 13 (13F, 0M)	Bio-activation of OM related to TM requires a lower sulfotransferase activity threshold. This may be explained by the impact of liver and platelet sulfotransferase activity on OM, as well as greater follicular accumulation of minoxidil.	Not discussed

AGA, Androgenetic alopecia; *D*, diastolic; *F*, female; *FPHL*, female pattern hair loss; *HSS*, hair shedding score; *LLLT*, low-level light therapy; *LPP*, lichen planopilaris; *M*, male, *OM*, oral minoxidil; *PRP*, platelet-rich plasma; *S*, systolic; *SALT*, Severity of Alopecia Tool; *TM*, topical minoxidil.

The ECG changes were mild and consisted of tachycardia, premature ventricular contractions, and T-wave changes in lead 1.[20,27] No severe cardiopulmonary events were reported in any study.

DISCUSSION

Introduced in the 1970s, OM was originally intended for the treatment of severe refractory hypertension. Hypertrichosis was quickly noted as a frequent side effect, and a topical option was created to provide the hair growth benefits of minoxidil while circumventing the unwanted, and occasionally severe, adverse effects of OM. However, the topical preparation is not without limitations, because patient compliance is frequently low.

This review found that OM has promising results as an effective and safe option for a variety of hair loss conditions, including AGA, chronic telogen effluvium, traction alopecia, loose anagen syndrome, alopecia areata, monilethrix, chemotherapy-induced hair loss, and even scarring alopecia. AGA in females was the most studied condition, with doses between 0.25 mg and 1.25 mg proving to be effective and safe. The combination of 0.25 mg minoxidil and 25 mg spironolactone may prove to be the best option because the low dose of OM limits adverse effects, and spironolactone aids in reducing the fluid/sodium retention properties of minoxidil. In male AGA, low doses of OM (0.25 mg) were found to be less effective. Effective treatment in men was seen with 2.5 mg or 5 mg minoxidil daily. Larger studies comparing the efficacy of different doses with standardized objective measurements will be needed to clarify the best treatment protocol.

As an antihypertensive agent, minoxidil was typically used at 10- to 40-mg daily maintenance doses. At this amount, minoxidil was associated with several severe cardiopulmonary adverse effects. However, this review has found OM at lower doses (<5 mg) to be tolerable, with few and mild adverse effects. By far, the most common adverse effect was hypertrichosis, which was reported as mild and easily manageable. Other less common adverse effects include postural hypotension/dizziness, lower limb edema, mild blood pressure changes, and ECG changes. No severe cardiopulmonary adverse effects were noted. However, providers must remain cautious and continue to monitor patient blood pressure, heart rate, and signs of fluid retention such as weight gain and pedal edema. Additionally, physicians should recognize OM as an option for healthy young patients who are having difficulty with the topical formulation.

Table II. Summary of adverse effects with varying oral minoxidil doses

Minoxidil dosage, mg/d	Men, n	Women, n	Hypertrichosis, n (%)	Lower limb edema, n (%)	Hypotension, n (%)	ECG changes, n (%)
0.25	25	106	9 (6.8)	1 (0.7)	3 (2.3)	0
0.45*	33	31	8 (12)	2 (3.1)	5 (7.8)	0
0.5	0	15	4 (27)	0	0	0
1†	0	220	46 (21)	3 (1.4)	1 (1.4)	2 (0.9)
1.25	33	17	8 (16)	1 (2)	1 (5.5)	0
2.5	10	15	13 (52)	1 (4)	0	0
5	66	0	36 (55)	5 (7.6)	0	3 (4.5)
Total	167	404	117 (20.5)	13 (2.2)	10 (1.8)	5 (0.9)

ECG, Electrocardiography.
*Sublingual administration.
†Includes data from Rodrigues-Barata et al.[20] Patients took a range of doses; however, the mean dose was 1 mg, and multivariate analysis showed no significant statistical differences among dosages.

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