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

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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.

Article type: Review

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

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Abstract

Background: Although topical minoxidil is an effective treatment option for hair loss, many patients are poorly compliant due to 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 utilized 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 16 studies with 622 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.

Introduction:

Minoxidil was first introduced in the 1970s as a treatment for severe refractory hypertension due to its potent vasodilatory qualities. Minoxidil has a relaxant effect on vascular smooth muscle through the opening of ATP sensitive potassium channels (1). During this time, hypertrichosis and regrowth of hair was found to be a common side effect among users and a topical preparation was first marketed in 1986 (2–7). For several decades, minoxidil has been utilized as 2% and 5% topical solutions, and later, 5% foam for the treatment of a variety of alopecia in both men and women although only approved for androgenetic alopecia (AGA). The exact mechanism of action remains unknown, though 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 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 due to 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 following the initiation of topical application. If unaware of this side effect, patients may discontinue use prematurely.

Until recently, oral minoxidil (OM) has not been used for treatment of hair loss due to the potential side effects of the medication when used at doses between 10-40 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. Co-administration with beta blockers was common to reduce

sodium/fluid retention and controlling heart rate (16). Acute pulmonary edema and pulmonary hypertension have also been reported as possible side 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, EKG changes, pericardial effusion, and congestive heart failure in patients with advanced renal disease (18). The dose related side effects were studied for the use of minoxidil as an antihypertensive agent, with a typical maintenance dose between 10-40 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.

Methods:

Keyword searches of PubMed were performed to identify all articles discussing oral minoxidil treatment of hair loss until April 2020. Search terms included “oral minoxidil,” “hair loss,” “systemic minoxidil,” “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 16 studies with 622 patients were found discussing the use of oral minoxidil as the primary treatment modality for hair loss. 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. determined a mean dose of 1mg of OM in 148 women to be an effective form of treatment for FPH (20)L. 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 on OM monotherapy and patients on OM plus additional treatment (20). Sinclair R.

utilized 0.25mg minoxidil daily in women with female pattern hair loss and showed improvement in the Sinclair hair loss severity score and hair shedding score through 1 year of treatment (21). 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. studied OM for treatment of AGA and traction alopecia in 18 patients, 17 of which 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 (22). Similar improvements were noted by Jha et al. in males on 1.25 mg, however, a higher dosage may be necessary if no response is noticed within 6 months (23). Ramos et al., compared 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 (24). Ramos et al. also indicated that a lower follicular sulfotransferase activity threshold is needed for bio-activation of OM compared to topical minoxidil (25). 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 Perera and Sinclair in which OM effectively treated chronic telogen effluvium in females. In this study, most women (29 of 36) were on 1 mg or less daily (26).

In male AGA, Lueangarun et al., 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., studied male AGA treated with 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 (28). When using a lower dose of 0.25 mg, which was found

to be effective in Female Pattern Hair Loss (FPHL), Pirmez and Salas-Callo found improvement or stabilization in 40-60% of male patients treated for AGA. However, it was not considered statistically significant when hair thickness and density were evaluated with the Tricholab system (29). Current data indicate that 2.5 mg- 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. examined the use of sublingual administration of minoxidil as it bypasses hepatic metabolism for greater bioavailability (30). 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 (IGA) (30).

A recent retrospective analysis by Vano-Galvan et al. showed 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 (31). 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 as described in table 1.

-Safety

This review found OM to be well tolerated with only minor adverse effects described in the literature. The most reported side effect was hypertrichosis, which was reported in approximately one fifth of patients. Interestingly, hypertrichosis was almost never a cause for discontinuation of the medication as many patients considered it only a mild side effect and easily manageable. Overall, hypertrichosis was more common among patients who used 5 mg daily and was seen in a little over 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. 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 (33). As with topical minoxidil, OM is associated with a temporary period of increased hair shedding that can last 3-6 weeks. Patients should be warned of this possible side effect to avoid premature discontinuation of treatment. Most studies did not report this side effect, but Sinclair et al. reported 22 out of 100 women found this increase in shedding to be of significant concern. No women discontinued treatment due to this side effect, and shedding ceased for most of these women within 4 weeks (21).

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. 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% (24). Postural hypotension/dizziness was reported in about 2% of patients. Sinclair described use of 50mg of sodium chloride daily for treatment of patients reporting postural hypotension (21). Lower limb edema was only seen in approximately 3% of patients, a majority of which were on 5 mg. Of these patients, only 1 discontinued due to the edema (28). EKG changes were reported in approximately 1% of cases, however, it is unclear if patients were regularly examined with EKG as this was only reported in one study. The EKG changes were mild and consisted of tachycardia, PVC, 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 treatment of severe refractory hypertension. Hypertrichosis was quickly noted as a frequent side effect and topical option was created to provide the hair growth benefits of minoxidil while circumventing the unwanted, and occasionally severe, side effects of OM. However, the topical preparation is not without limitation as 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 dosages between 0.25 mg to 1.25 mg proving to be effective and safe. The combination of 0.25 mg minoxidil and 25 mg of spironolactone may prove to be the best option as the low dose of OM limits side effects while spironolactone aids in reducing 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 males was seen with 2.5 mg or 5 mg minoxidil daily. Larger studies comparing 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 10-40 mg daily maintenance doses. At this amount, minoxidil was associated with several severe cardiopulmonary side effects. However, this review has found OM at lower doses (< 5 mg) to be tolerable with few and mild side effects. By far, the most common side effect was hypertrichosis, which was reported as mild and easily manageable. Other less common side effects include postural hypotension/dizziness, lower limb edema, mild blood pressure changes, and EKG changes. No severe cardiopulmonary side 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.

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Table 1: Summary of adverse effects with varying oral minoxidil dosages.

*=Sublingual administration

ᵗ=Includes data from Rodrigues-Barata R., et al. Patients took a range of dosages, however mean dose was 1mg and multivariate analysis revealed no significant statistical differences between dosages.

Minoxidil Dosage	Males	Female	Hypertrichosis	Lower Limb Edema	Hypotension	EKG changes
0.25mg	25	106	9 (6.8%)	1 (0.7%)	3 (2.3%)	0
*0.45mg**	33	31	8 (12%)	2 (3.1%)	5 (7.8%)	0
0.5mg	0	15	4 (27%)	0	0	0
1 mgᵗ	0	220	46 (21%)	3 (1.4%)	1 (1.4%)	2 (0.9%)
1.25 mg	33	17	8 (16%)	1 (2%)	1 (5.5%)	0
2.5 mg	10	15	13 (52%)	1 (4%)	0	0
5 mg	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%)**

Table 2: Summary of studies

AGA= Androgenetic Alopecia **F**= Female, **M**= Male, **y/o**= years old,
OM= Oral minoxidil, **FPHL**= Female Pattern Hair Loss, **TM**= Topical Minoxidil,
SALT= Severity of Alopecia Tool **LLLT**= Low Level Light Therapy **PRP**= Platelet Rich Plasma

Author	Disease	Dosage/ Regimen	Number of participants	Results	Adverse Effects

Vano-Galvan et al. 2020 (31)	Lichen planopilaris	Median daily dose= 0.5 mg daily for female 2.5 mg daily for male Average duration= 21 months There were no changes to concomitant therapies within the last 6 months.	Total n=51 (36 F, 15 M) Mean age= 55 y/o	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. 2020 (33)	FPHL with contact dermatitis to propylene glycol in 2% and 5% solutions of TM.	0.25 mg twice per day Average duration of 17 months	Total n=9 (9F, 0M)	All patients satisfied with treatment.	22% (n=2) Facial hypertrichosis

Beach et al. 2018 (22)	AGA Traction alopecia	1.25 mg nightly Average duration of prescription = 6 months All patients previously on topical minoxidil	Total n=18 (17 F, 1 M) AGA n= 14 (13 F, 1M) Traction Alopecia n= 4 (4F, 0M) Average age= 41 y/o	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 hypertensive patients. No heart rate changes were found.
Cranwell W., Sinclair S. 2018 (34)	Loose anagen hair syndrome	0.5 mg daily Previously on 5% topical solution for 5 years.	n=1 (1 F) 11 y/o	Shedding and hair density improved in first 3 months. Discontinued after 12 months, no recurrence.	Hair color change from reddish-brown to light brown.
Perera E., Sinclair R. 2017 (26)	Chronic telogen effluvium	Varied between 0.25mg to 2.5mg daily (29 patients used 1 mg or less daily) 5 at 0.25 mg 4 at 0.5 mg 19 at 1 mg 8 at 2.5 mg	n=36 (36F, 0M) Average age=46.9 y/o	Baseline Hair Shedding Score (HSS)= 5.64 6-month HSS=3.9 12-month HSS=3.05	n=2 experienced transient postural hypotension that resolved. n=1 ankle edema n=14 hypertrichosis Average blood pressure change: S: -0.5mmHg D: +2.1mmHg

Jimenez-Cauh et al. 2019 (28)	AGA	5 mg daily (10 patients received 2.5 mg daily, 31 patients received 5 mg daily)	n=41 (41M, 0F) Oral minoxidil (OM) monotherapy n= 16 Average age= 33.3 y/o	37 (90.2%) had clinical improvement. 11 (26.8%) had marked improvement. 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, one patient discontinued
Pirmez R., Salas-Callo C.I. 2019 (29)	AGA	0.25mg daily Measured: -total hair density -density of terminal hair -new hairs -new terminal hairs.	n=25 (25M, 0F) all on monotherapy Average age= 36.7 y/o n=10 mild AGA n=15 severe AGA	Improvement or stabilization was seen in a percentage of patients, but not found to be statistically significant. Higher doses such as 2.5mg or 5mg 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 S., et al. 2015 (27)	AGA	5 mg daily for 24 weeks	n=30 (30M,0F) Average age=38 y/o	vertex area revealed 100% improvement. remarkable improvement in 43% of patients. Significantly increased total hair count at the vertex. Significant response at the frontal area, but less than the vertex area.	93%-hypertrichosis 10%-Pedal edema 10%-EKG changes

Muller Ramos P., et al. 2019 (24)	FPHL	1mg daily for 24 weeks vs. 5% topical solution daily	n=52 (52F, 0M) 5% TM n=26 Avg Age=47.3 OM n=26 Avg Age=40.6	Total hair density increased by 12% in OM and 7.2% in TM No significant difference between them (p=0.10). 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 hear rate: -OM= increase by 6.5% -TM= no change No difference in mean blood pressure between groups
Sinclair R. 2016 (35)	Monilethrix	0.25mg to 0.5mg 1 at 0.25mg	n=2 (2F, 0M) 35 y/o and 40 y/o	Patient 1: Hair growth with reduced breakage and increased hair volume/length. Maintained through 2 years of follow up. Patient 2: Decreased shedding with 0.25mg, improved hair density when dosage increased to 0.5mg. Maintained through 18 months of follow up.	No reported adverse effects

Sinclair R. 2017 (21)	FPHL	Once daily capsule containing 0.25mg minoxidil and 25mg spironolactone.	n=100 (100F, 0M) Average age= 48.44 y/o	Baseline Sinclair hair loss severity score=2.79 Baseline hair shedding score=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 hair shedding score: 1.1 at 3 months 2.3 at 6 months 2.7 at 9 months 2.6 at 12 months Low-dose oral minoxidil is well tolerated and a reasonable alternative to topical minoxidil.	n=4 facial hypertrichosis n=2 postural hypotension n=2 urticaria (likely due to spironolactone) Avg decrease of 4.52mmHg in systolic blood pressure and 6.48mmHg in diastolic.
Wambier C., et al. 2019 (32)	Alopecia areata	Tofacitinib 5mg 2x daily Or 10mg 2x daily OM 2.5mg daily for women OM 2.5mg twice daily for men	n=12 (7F, 5M)	n=8 (67%) achieved >75% scalp regrowth n=4 (33%) achieved 11%-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 BP changes, peripheral edema, or symptoms of hypotension.

Yang X., Thai K. 2015 (36)	Permanent chemotherapy induced alopecia	OM 1mg daily	n=1F Age=39 y/o	Subjective increase in hair growth at 6 weeks. After 1 year the patient regrew significant amounts of hair. Significant decreases in telogen follicles and a reversal of follicle miniaturization	None
Rodrigues-Barata R., et al. 2020 (20)	FPHL	0.25mg-2mg daily	n=148 (148F, 0M) *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 A., et al. 2020 (23)	AGA	1.25mg	n=32 (0F, 32M) 18-45 years	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/day can be used in male AGA, although 2.5-5 mg/day may be necessary if response is suboptimal after 6 months of treatment.	n=1 peripheral edema n=1 hypertrichosis
Sinclair R., et al. 2020 (30)	AGA	0.45mg daily (sublingual)	n=64 (31F, 33M) Mean age of 50.92 years	Male and Female patients had mean reduction of Sinclair Stage, and Sinclair hair shedding score. Male patients had mean improvement of Investigator Global Assessment. Sublingual minoxidil at a dose of 0.45mg daily was effective and had an acceptable safety profile	n=8 hypertrichosis n=5 postural dizziness n=2 peripheral edema Avg BP at start of study: 126.27/76.69 Avg BP after 12 months of OM use: 121.85/77.46