Role of low dose oral minoxidil in the treatment of hair loss: A review

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ABSTRACT

Low-dose oral minoxidil (OM) has increasingly been used by many doctors around the world as a treatment option for hair loss. Sufficient data regarding its effect and side effect profile are lacking. An online search was done on PUBMED and GOOGLE SCHOLAR for articles that used OM as a treatment option for hair loss. Doses ranging from 0.25 to 5 mg have been used for treatment in various studies. Good compliance and tolerability have been noticed with low-dose OM therapy. Adverse effects are few and are mild with hypertrichosis being the most common adverse effect in a majority of the studies, the risk of which increases with an increase in dosage of the drug.

Keywords: Oral minoxidil, Low dose oral minoxidil, Alopecia, Androgenetic alopecia, Hair loss

INTRODUCTION

A common treatment advised by dermatologists all around the world, topical minoxidil (TM) is an FDA approved medication for patterned hair loss.[¹] However, in cases of non-responders and in patients developing irritant or allergic contact dermatitis to the topical formulation, oral minoxidil (OM) can be an option of choice.[²]

Originally developed to treat hypertension, it was found to produce hypertrichosis in more than half of the cases treated.[³] Hair growth was noticed over the face, chest, arms, back, and much to the pleasure of many bald patients, over the scalp as well.[⁴]

Even though FDA approved for resistant hypertension,[⁵,⁶] OM is not approved for hair loss but has been used by many for the same.[²]

METHODOLOGY

A literature search for published articles was done using PUBMED and GOOGLE SCHOLAR using the keywords, “OM AND alopecia,” “OM AND androgenetic alopecia (AGA),” “OM AND AGA,” “OM AND hair loss,” “Low dose OM AND hair loss,” “Low dose minoxidil AND alopecia,” “OM AND adverse effects.”

The search resulted in 27 studies related to OM, of which fourteen studies were concerning patterned hair loss and eight studies related to its use in alopecia other than AGA. Articles which
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contained only a fleeting mention of OM were removed from our study due to insufficient data.

PHARMACOKINETICS

The chemical name of Minoxidil is piperidino-pyrimidine derivative. The chemical structure is 2, 4-primidinediamine, 6-(1-piperidinyl)-, 3-oxide (C₉H₁₅N₅O) [7]

Once taken orally, 95% of the drug is absorbed from the GIT and appears in the plasma within 15–30 min with a peak concentration seen in 30–60 min. Within the body, nearly 90% of the drug is metabolized in the liver by conjugation with glucuronic acid at the N-oxide position in the pyrimidine ring and conversion to other polar metabolites.

There is no adaptive increase in drug metabolism with repetitive/chronic dosage noticed with the whole body clearance rate of the drug being 7–10 days after chronic drug administration. [8]

The kidney is the major excretory organ for minoxidil and its metabolites with ≥90% of the administered drug [8] excreted in urine as unchanged and as a metabolite (glucuronide conjugate) within 4 days. It does not cross the blood-brain barrier. [7]

MECHANISM OF ACTION

Knowledge of how OM affects human hair growth is little as the majority of the studies are limited to the response of TM in treating AGA. [9] The main step is the sulfation of minoxidil to its active form of minoxidil sulfate by the enzyme sulfotransferases (phenol sulfotransferase) through hepatic sulfonation. [10] In non-responders to TM, with outer root sheath (ORS) sulfotransferase enzyme level of <0.4 Optical density (OD)₄₀₅, OM can be used as an alternative. [11] Having said that, recently it has been shown that ORS sulfotransferase enzyme can also be used as an enzymatic assay to detect non-responders even to OM (ORS sulfotransferase level - <0.254 OD₄₀₅). [12]

Oral administration induces relaxation of vascular smooth muscle through the opening of sarcolemmal ATP2-dependent potassium channels and thus reduces blood pressure (BP). [13]

Minoxidil has several effects which may promote hair growth:

1. Prolongation of the kenagen phase (latent period of the hair cycle-the time between the shedding of telogen hair and the onset of the next anagen). It has been suggested that minoxidil has a key role in cell proliferation as potassium channel activity is required for moving to the G1 phase of the cell cycle from the latent post telogen phase.

2. Action on smooth muscles of the peripheral artery - It opens the potassium channels leading to hyperpolarization of the cell membrane and inhibits calcium entry thus leading to hair growth.

3. Minoxidil also causes a delay in the hydrolysis of cAMP through inhibition of phosphodiesterase, thus resulting in vasodilatory action [6,14] [Figure 1].

EFFICACY

OM is a U.S. FDA-approved medication for hypertension but not approved for hair loss [2] and has been given a grade D recommendation by the Japanese Dermatological Association due to its side effect profile and lack of clinical trials. [5,15] Nevertheless, several studies have been conducted all over the world with various doses for treatment of alopecia and an increasing number of data show that OM can be considered as a possible therapeutic option for AGA. [2,16–20]

Due to its side effect profile, recently many authors have propounded a low dose OM regimen for treating AGA. In patients not responding to or are resistant to conventional therapy the search for other treatment avenues has been discouraging. As a result, many are revisiting the use of OM as a plausible option in the management of alopecia.

Our search revealed 14 studies in relation to OM therapy in patterned hair loss and 8 studies concerning its use in alopecia due to other causes. Three studies combined OM with other drugs to increase efficacy and compliance. The

Figure 1: Mechanism of action of Oral Minoxidil in Hair growth.
various studies and features of these studies have been explained in [Tables 1 and 2]. The dosage used in these studies ranged from 0.25 mg to 5 mg with a majority of them using doses <2.5 mg to avert any untold side effects. Most of these have been conducted over of 6 months with daily dosing the rule and lower doses being offered to women compared to

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage (mg)</th>
<th>Duration (months)</th>
<th>n*</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinclair et al.[16]</td>
<td>0.25 mg + Tab. Spironolactone 25 mg</td>
<td>12</td>
<td>100</td>
<td>Mean reduction in hair loss severity score was 1.3 from baseline value of Sinclair 2.79 (range 2–5), Mean reduction in hair shedding score was 2.6 from baseline value 4.82 (range 1–6)</td>
</tr>
<tr>
<td>Jimenez-Cauhe et al.[17]</td>
<td>2.5 mg</td>
<td>&gt;6</td>
<td>16</td>
<td>37.5% - Marked improvement 62.5% - Good improvement</td>
</tr>
<tr>
<td>Beach et al.[18]</td>
<td>1.25 mg</td>
<td>6</td>
<td>16</td>
<td>Decreased hair shedding - 37.5% Increased scalp hair growth - 28%</td>
</tr>
<tr>
<td>Lueangarun et al.[19]</td>
<td>5 mg</td>
<td>6</td>
<td>30</td>
<td>Improvement seen in all patients, Remarkable improvement 43%, Significant improvement in total hair count (Vertex &gt; Frontal)</td>
</tr>
<tr>
<td>Pirmez and Salas-Callo[21]</td>
<td>0.25 mg</td>
<td>6</td>
<td>25</td>
<td>Improvement noticed in Frontal scalp: New hair growth-52% Total hair density-60% Improvement noticed in occipital scalp: New hair growth - 40% Total hair density - 40%</td>
</tr>
<tr>
<td>Therianou et al.[25]</td>
<td>1 mg</td>
<td>17</td>
<td>9</td>
<td>Good improvement</td>
</tr>
<tr>
<td>Ramos et al.[23]</td>
<td>1 mg</td>
<td>6</td>
<td>52</td>
<td>Total hair density - 12% increase OM superior to TM therapy</td>
</tr>
<tr>
<td>Lueangarun et al.[19]</td>
<td>5 mg</td>
<td>6</td>
<td>30</td>
<td>5 patients demonstrated a 1-grade improvement and 1 patient maintained the same grade but clinically was slightly improved</td>
</tr>
<tr>
<td>Panchaprateep and Lueangarun [30]</td>
<td>5 mg</td>
<td>6</td>
<td>30</td>
<td>Significant increase in total hair counts from baseline notice  Assessment of the vertex area revealed 100% improvement with 43% of patients showing excellent improvement 58% had marked improvement while 42% had mild improvement</td>
</tr>
<tr>
<td>Vastarella et al.[40]</td>
<td>1.25 mg</td>
<td>6</td>
<td>12</td>
<td>8% had marked improvement while 42% had mild improvement</td>
</tr>
<tr>
<td>Jha et al.[41]</td>
<td>1.25 mg</td>
<td>6</td>
<td>32</td>
<td>Marked improvement - 43.3% Mid improvement - 40.6%</td>
</tr>
<tr>
<td>Rodrigues-Barata et al.[42]</td>
<td>0.25–2 mg</td>
<td>9</td>
<td>148</td>
<td>Stabilization of alopecia noticed in 20.3% while 79.7% had clinical improvement. Of these, 64.2% presented with mild improvement and 15.5% with marked improvement. The clinical improvement was higher in more advanced stages of alopecia.</td>
</tr>
<tr>
<td>Jha et al.[43]</td>
<td>Group A: 1.25 mg +PRP Group B: 2.5 mg +PRP therapy</td>
<td>6</td>
<td>A=47</td>
<td>Marked improvement on GCP seen in 40.4% and 58.3% patients in Group A and B respectively. Patient satisfaction score between both groups were statistically significant with Group B patients having a better satisfaction score.</td>
</tr>
</tbody>
</table>

*n=Sample size. TM: Topical minoxidil, PRP: Platelet rich plasma, GCP: Global clinical photography
males. One such study utilized 0.25 mg OM for the treatment of patterned hair loss in 100 females. OM was combined with 25 mg spironolactone in this study to avoid fluid retention that may arise due to the former. The study demonstrated significant improvement with a very low side effect profile (8%) after 12 months of therapy. The same cannot be said about patterned hair loss in males where similar dosage as above only resulted in mild improvement suggesting the need for higher doses in men. The above statement was reaffirmed in another study where higher doses led to better response in men.

Higher doses of 5 mg given as a single dose or divided over a day for treatment of patterned hair loss revealed dramatic clinical improvement but the associated side effects were far more frequent than those seen in lower doses. However, these side effects were mild, tolerable, and reversible.

In another study, 1.25 mg/day of OM was given for 3 months resulting in increased scalp hair growth and decreased hair shedding in 28% and 33%, respectively. The interesting aspect of this study was that except for two all other subjects were females and while hypertrichosis was noticed in 39% of patients, none deferred from continuing the therapy revealing good compliance and tolerability by patients. About 78% of patients continued therapy even 6 months post-study period.

Ramos et al. reported that 1 mg OM was superior to the TM 5% and that it could be used as an alternative to TM. The above conclusion supports the findings of Fiedler-Weiss et al. who compared OM and TM in the treatment of alopecia areata. Reasons for this are:

- **Better convenience** as swallowing a tablet is easy compared to applying lotions
- **Increased cosmesis** as OM didn’t produce any residue unlike after TM application
- **Low cost** of purchase for the same period
- **Co-therapy** was made possible for people with visible bald patches where commercial fibers could be used to enhance the fullness of hair without any hassle.
- **Increased compliance** and
- **Better tolerability**

Apart from AGA, low-dose OM has also been used in the treatment of other conditions associated with hair loss. We found eight such studies that used OM as a treatment option for indications other than AGA. Doses as low as 0.25–10 mg have been used in these studies. The different studies, indications, dosage, and outcomes are enumerated in Table 2. As noticed in Table 2, OM has been used in both non-cicatricial and cicatricial alopecia. Clinically evident improvement has been noticed in the form of hair regrowth and decreased hair shedding and has been noticed in all studies with good patient satisfaction in many of the studies. An improvement of 80% and 93% have been noticed by Fiedler-Weiss et al. and Wambier CG et al. in their respective studies when used for alopecia areata while an improvement of 92% in Telogen effluvium was noticed by Perera and Sinclair in his study on 36 subjects. Granted that these studies have had many flaws such as small sample size and lack of control; however, the results, as well as the patient satisfaction scores, are significantly high enough to demand attention. Furthermore, the adverse effects noticed with doses ranging from 0.25 mg to 5 mg in these studies were very minuscule.

Regarding adverse effects, a dose-dependent relation has been noticed with adverse effects more common in the higher dosage of 5 mg and least in lesser dosages.

Hypertrichosis is the most common effect with 4% risk at 0.25 mg, 37.5% at 1.25 mg, and 93% at 5 mg. First noticed on the temples, glabella, forehead, or along with the sideburns, it is reversible on discontinuation.

Hypotension has been noticed to occur in few studies as well. Fleshaker et al. in his study concluded that doses ranging from 2.5 mg to 10 mg had little effect on BP in normotensive subjects. Nevertheless, measurement of baseline BP of all patients planning to be started on OM is recommended and in patients with values <90/60 mmHg, the addition of 50 mg of sodium chloride to the dose can be considered.

Salt and water retention in the form of swelling of the feet, lower legs, hands or face, and rapid weight gain can occur. This risk varies from 4% at doses of 0.25 mg to 10% at doses of 5 mg. The addition of 25 mg of spironolactone has been shown to mitigate this risk while potentiating the effect of minoxidil; however, caution is advised as it can, in theory, worsen postural hypotension.

ECG changes noticed include T-wave flattening or inversion, other T-wave alterations and other ST wave changes which are improved within 24 h of withdrawal of the drug. These changes have been reported in only two studies where low-dose OM was used.

Cardiac manifestations have rarely been reported in the literature and are unseen with low dose OM (tachycardia, congestive cardiac failure, pericardial effusion, and pulmonary hypertension).

Other adverse effects noted but uncommonly seen include headache, rash, nausea, gynecomastia, bullous eruptions, drowsiness, fatigue, polynorrenia, and itchy eyes.

Three cases of Stevens-Johnson syndrome due to OM have been reported in the literature. Two of these three cases transformed into toxic epidermal necrolysis and eventually culminated in death while one of the patients subsequently improved on cessation of the drug. These patients were on OM to manage hypertension and all three had a history of underlying chronic
renal impairment before the initiation of minoxidil therapy.\footnote{31} Since the kidney is the main route of excretion of minoxidil, the hypothesis is that there is defective detoxification of minoxidil sulfate which triggers an immune response and an inability to clear these metabolites leading to an accentuation of the immune response.\footnote{2,32-35} Having said that the adverse effects associated with the use of low-dose OM for the treatment of alopecia were considered mild and insignificant in six studies while there were no adverse effects noticed in five studies. These studies used doses ranging from 0.25 mg to 2.5 mg while studies with higher doses were associated with more frequent side effects [Table 3].\footnote{22,27,28,29,38-41,43,47}

Contraindications to OM include pheochromocytoma or previous hypersensitivity reactions to ingredients, hypotension, cardiac comorbidities, and pregnancy or breast feeding.\footnote{26}

Considered as Pregnancy Category-C drug, rare reports of fetal malformations have been reported.\footnote{36} Use of OM has also been studied in pediatric patients in a review article by Lemes et al. where they concluded that data for use in hair growth was insufficient and that adverse effects were a cause of concern in this age group. However, they also commented that although TM was the preferred choice, in special circumstances such as hair shaft disorders, cicatricial alopecia, precocious, and severe AGA, or in extensive AA, OM may be considered in very low doses.\footnote{37}

With regards to combination therapy, we found three studies where OM was combined with other medications such as oral tofacitinib and spironolactone. Oral spironolactone was used in two studies, 25 mg combined with 0.25 mg of OM in one study for the treatment of AGA while 50 mg of spironolactone was combined with 2.5 mg of OM in another. The purpose of combining the former drug with OM in both these studies was to allay fluid retention that may arise as a result of the use of OM. None of the above two

<table>
<thead>
<tr>
<th>Table 2: Other indications for low dose oral minoxidil in hair loss.</th>
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<td><strong>Indication</strong></td>
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<tr>
<td>AA</td>
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<td></td>
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<tr>
<td>TE</td>
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<tr>
<td>Permanent CIA</td>
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<tr>
<td>Loose anagen hair syndrome</td>
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<tr>
<td>LPP</td>
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<tr>
<td>Lichen planopilaris</td>
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<tr>
<td>FFA</td>
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<tr>
<td>Traction alopecia</td>
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<tr>
<td>Central centrifugal cicatricial alopecia</td>
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<tr>
<td>Chemotherapy Induced alopecia</td>
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</tbody>
</table>

*\(n\)-Sample size. AA: Alopecia areata, TE: Telogen effluvium, CIA: Chemotherapy induced alopecia, LPP: Lichen planopilaris, FFA: Frontal fibrosing alopecia, HSS: Hair shedding score
studies developed any symptoms or signs suggestive of fluid retention in their respective studies.[16,36]

One study combined OM with oral tofacitinib 10 mg in the treatment of alopecia areata where they noticed a median percentage improvement of 93% in hair regrowth.

CONCLUSION

Low dose OM appears to be a tolerable[42,43] and effective alternative to TM in patients not responding to the latter. However, it has to be stressed at this time that evidence for OM is low and concerns over systemic side effects remain and larger studies involving greater sample size should be done in the future for a better understanding of its role in hair loss.

Declaration of patient consent

Patient’s consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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