Role of Oral Minoxidil in Patterned Hair Loss

Abstract
Recent studies have shown that low-dose oral minoxidil (OM) can be a safe and effective treatment of numerous hair disorders including male-patterned hair loss (MPHL) and female-patterned hair loss (FPHL). There are several practical advantages of OM over its topical formulation: enhanced cosmesis, cost-savings, and the possibility of co-therapy with other topical formulations or topicals used for camouflage. This treatment may be particularly helpful for patients who are unable to tolerate topical minoxidil or other systemic treatments. Doses ranging from 0.25 to 1.25 mg daily are usually used for FPHL and doses ranging from 2.5 to 5 mg/day for MPHL. The low side-effect profile of low-dose OM allows for long-term adherence to the medication and favorable clinical response, resulting in stabilization and improvement of hair loss. More studies are needed to test the efficacy of OM in other types of alopecia as well as additional comparative studies assessing OM to other commonly used medications.

Keywords: Alopecia, alopecia treatment, androgenetic alopecia, hair loss, minoxidil, oral minoxidil, systemic minoxidil

Introduction
Patterned hair loss is the most common cause of alopecia, typically presenting with progressive thinning, miniaturization, and loss of hair at classical topography depending on the sex of the patient.[1-3] Male-patterned hair loss (MPHL) and female-patterned hair loss (FPHL) affects up to 50% of males over 50 and postmenopausal women, respectively.[2] Since described, little has changed regarding its treatment. Newer treatment options such as platelet-rich plasma, low-level laser light, and microneedling have become available; nevertheless, their cost and efficacy that still needs to be confirmed have restrained its use for most patients.[2]

Minoxidil started to be implemented in the 1970s to treat severe refractory hypertension due to its vasodilatory properties.[4] Hypertrichosis was found to be a common side effect among users, which led to the development of a topical preparation that was marketed in 1986.[4] Although topical minoxidil is an effective treatment option for hair loss, many patients are poorly compliant due to undesirable hair texture, scalp irritation, the formulation’s odor, the development of allergy to minoxidil or excipients, and the need to apply the medication twice a day.[4]

Although no clinical trials have been conducted on the efficacy of the oral administration of minoxidil for patterned hair loss treatment,[5] an epidemiological study in Spain showed oral minoxidil (OM), among the most used treatments for this condition, being prescribed in male-patterned hair loss (MPHL) by 50.6% of dermatologists, and in premenopausal and postmenopausal FPHL by 67.9% and 63% of dermatologists, respectively.[6]

In recent years, OM at low doses has been proposed as a safe, effective, and well-tolerated option for patients with patterned hair loss with a good safety profile.[4,7]

Minoxidil Chemistry and Basic Pharmacology
Minoxidil shortens the telogen phase and prolongs the anagen phase with a progressive growth in hair diameter and length.[4]

The conversion of minoxidil to its active derivative, minoxidil sulfate, by follicular sulfotransferase activity is a key step in the
medication’s effectiveness, as pharmacologic action comes from its sulfated metabolite.[9]

A recent study suggests that when given orally, instead of topically, minoxidil would be converted by platelet sulfotransferase and might reach a higher follicular accumulation.[7]

Minoxidil works as a vasodilator, an inducer of the Wnt/β-catenin signaling pathway, and has anti-androgenic and anti-inflammatory properties.[9] Minoxidil relaxes blood vessels which leads to an increased supply of nutrients and oxygen to the hair follicles.[8]

Minoxidil reduces perifollicular microinflammation and it has been shown to suppress T-lymphocytes.[9] This anti-inflammatory effect is also enhanced through the inhibition of the effects of prostacyclin and interleukin-1α.[8]

Minoxidil may stimulate the release of vascular endothelial growth factors and activate the β-catenin signaling pathway. β-Catenin acts as a transcriptional factor and plays a role in hair follicle regeneration.[9]

Finally, the use of OM in scarring alopecias can be justified by the fact that it has anti-fibrotic properties by inhibiting lysyl hydroxylase, an enzyme necessary for collagen cross-linking.[9]

Advantages of Oral Minoxidil Over Topical Minoxidil

Ramos et al.,[10] compared the efficacy of 1 mg daily OM to topical 5% solution daily and found OM to be as effective as the topical solution. This author also indicated that a lower follicular sulfotransferase activity threshold is needed for bio-activation of OM compared to topical minoxidil.[10]

Common barriers for the use of topical minoxidil in male and female-patterned hair loss (FPHL) include the development of pruritus, contact dermatitis, change in hair texture, and localized hypertrichosis,[2,3]

Aside from tolerability, there are several practical advantages of OM over its topical formulation: It’s more convenient to swallow minoxidil than to apply it topically.[11] With OM, patients note better cosmesis, because prescription oral therapy doesn’t distort gray hair color or generate product residue. OM is cheaper than the topical over-the-counter formulations.[11] Application of keratin fibers to visually enhance scalp fullness is simpler without the use of topical minoxidil.[11]

OM in monotherapy may show an initial clinical response after approximately 3 months of treatment.[12]

Indications

Up to this day, OM is only approved for the treatment of hypertension.[7] OM has promising results as an effective and safe option for a variety of hair loss conditions other than patterned hair loss including chronic telogen effluvium, traction alopecia, loose anagen syndrome, alopecia areata, monilethrix, chemotherapy-induced hair loss, and even scarring alopecia.[4] FPHL is the most studied condition; however, several authors have reported successful use of low-dose OM in men with MPHL.[13]

Nevertheless, OM is still an off-label therapy and its use for patterned hair loss should be individualized.[12] Patients who can benefit from OM are young adult patients with moderate patterned hair loss, or those with low compliance, local intolerance, or no response to topical minoxidil.[12]

Dosages

OM for the treatment of hypertension is usually given with standard doses ranging between 10 and 40 mg daily (up to 100 mg/day).[7] Much lower doses are needed to treat alopecia, avoiding systemic adverse effects.

Female-patterned hair loss

OM, 0.25–1.25 mg daily, has been used for the treatment of FPHL, traction alopecia, and telogen effluvium, showing improvement in 61–86% of patients with a good safety profile.[4,12]

Therianou et al.[14] showed 0.25 mg twice daily OM to be a satisfactory and safe alternative to topical solutions in women.

Sinclair has reported positive outcomes with 0.25 mg of OM in women combined with spironolactone 25 mg.[13] This very low dose of OM limits side effects while spironolactone aids in reducing fluid/sodium retention properties of minoxidil.[4]

Male-patterned hair loss

Effective treatment in males is generally seen with doses ranging from 2.5 to 5 mg/day.[4,13] Overall, OM 5 mg/day is a very effective therapy for mild–moderate MPHL.[12] It can be used in monotherapy or combined with other topical or oral therapies, such as 5-alpha reductase inhibitors.[12,15]

The combination of OM 5 mg/day with oral dutasteride 0.5 mg/day is one of the most effective therapies for MPHL.[12]

Therapy starting with 1.25 mg/day has been evaluated in male androgenetic alopecia, although a higher dose (2.5–5 mg/day) may be required if, despite 6 months of treatment, the response is suboptimal.[16]

Very low dose of OM (0.25 mg/day) as monotherapy in the treatment of male subjects with MPHL has been evaluated with controversial results.[4,13] When using a lower dose of 0.25 mg, which is found to be effective in FPHL, Pirmez and Salas-Calvo found improvement or stabilization in 40–60% of male patients treated for patterned hair loss.[13]

However, it was not considered statistically significant when
hair thickness and density were evaluated with a Tricholab system.[13]

Sinclair et al.,[17] examined the use of sublingual administration of minoxidil as 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.[17]

**Contraindications and Precautions**

Minoxidil is indicated for refractory hypertension carrying a black box warning for the risk of pericardial effusion that may progress to cardiac tamponade and angina pectoris exacerbation.[18] The use of OM in people who have severe hypertension and risk of cardiovascular events should be carefully planned.[15]

Interestingly, the drug has a minimal hypotensive effect in normotensive patients.[18] OM is contraindicated in patients with pheochromocytoma or previous hypersensitivity reactions.[21] Baseline investigations for this reason should include urinary catecholamines, electrocardiogram, and monitorization of blood pressure. Relative contraindications include hypotension, cardiac comorbidities (in BID dose of oral low-dose minoxidil >5 mg/day), and pregnancy.[5] OM is not safe during pregnancy due to the increased risk of neonatal hypertrichosis (pregnancy category C)[8] and may be secreted in human milk, thus contraindicated in nursing mothers.[8]

OM should not be prescribed to elderly patients with an increased risk for myocardial infarction, heart failure, chronic renal failure, or severe hypertension.[15]

**Side Effects**

At the high doses used for hypertension, adverse effects include fluid retention, acute pulmonary edema, pulmonary hypertension, electrocardiogram (EKG) alterations, and pleural effusion.[7] Cardiac conditions associated with the medication include, most commonly, reflex tachycardia and, less commonly, pericardial effusion, and congestive heart failure in patients with advanced renal disease.[4] Use of low-dose OM overcomes many of these therapeutic limitations.[4]

Hypertrichosis is more common among patients who use 5 mg daily and is seen in a little over half of these patients.[12,19] A dose of 0.25 mg has the lowest incidence of hypertrichosis (less than 10% of patients).[11,20] Areas of hypertrichosis described in the literature include face and body. In a multicentric study that involved 1404 patients,[21] only 3.7% of patients who grew unwanted hair on the face/body discontinued treatment. Patients prefer to manage hypertrichosis with hair removal methods while continuing therapy, provided that they can appreciate the benefits of low-dose OM.[21]

OM is less commonly associated with a temporary period of increased hair shedding as compared with topical minoxidil. Most studies did not report this side effect, but Sinclair et al.,[20] reported 22 out of 100 women. However, no women discontinued treatment due to this side effect, and shedding ceased for most of these women within 4 weeks.[22]

Other less common side effects of OM used at low doses for alopecia include postural hypotension/dizziness, lower limb edema, headaches, mild blood pressure changes, and EKG changes. In a study, lower limb edema was only seen in approximately 3% of patients, a majority of which were on 5 mg. Of these patients, only one discontinued due to the edema.[12] The EKG changes that have been reported are mild and consist of tachycardia, premature ventricular contractions, and T-wave changes in lead one.[23] No severe cardiopulmonary events have been reported.

Some measures can be taken to avoid these side effects: For lightheadedness, taking the OM at bedtime has been proven to be useful, also getting up slowly from a lying/sitting position, increasing fluid intake, and adjusting doses of antihypertensives in case the patient is using them.[21] Sinclair described the use of 50 mg of sodium chloride daily for treatment of patients reporting postural hypotension.[20]

For fluid retention/edema, limiting salt intake, and the use of diuretics, for example, furosemide (in males and females) and spironolactone (in females), is helpful.[21] Coadministration with β-blockers can reduce sodium and fluid retention and help control the heart rate.[4] If the patient presents with a persistent tachycardia, it is imperative to refer the patient to a cardiologist. Headaches can be managed with simple analgesics: paracetamol and nonsteroidal anti-inflammatory drugs. For insomnia, the patient can be educated in sleep strategies/relaxation, and pharmacotherapy can be implemented.[21]

If adverse effects are severe or persist despite the above management strategies, the dermatologist should consider dose reduction, using every other day dose, or discontinuation. A multicentric study showed that <2% of patients require treatment discontinuation after all the measures to control side effects.[21]

**Special Considerations: Pediatric Patients**

Recently, small descriptive case series have evaluated low-dose OM for loose anagen hair syndrome,[24] androgenetic alopecia, and telogen effluvium in pediatric patients with promising results; nevertheless, bigger studies are needed to better understand safety and efficacy among this age group.[25] Knowledge about the effects and safety of low-dose OM in pediatric patients is limited; a 2-year-old boy who accidentally ingested 100 mg of OM in a single dose recovered fully after developing a transient reflex tachycardia.[26]
A study where 20 patients aged between 2 months and 13 years were accidentally exposed to high doses of OM (mean dose 0.90 mg/kg/day) showed that systemic side effects developed only in 15% of patients,[27] with no severe disorders, the most common side effects were diarrhea, anxiety, headache, facial edema, and severe asthenia; these manifestations appeared during treatment, and were transient, resolving within 3 days.[27] Sixty-five percent of them presented hypertrichosis, with a wide range of latency from treatment onset. Initial zone of appearance was the face, back, and limbs. Resolution happened for 61.5% of patients within 6 months; after this time, 38.5% of the patients had persistent hypertrichosis.[27] The tachycardia, pedal edema, and postural hypotension reported in adults are rarely seen at the doses used in children.[24]

**Conclusion**

In conclusion, OM can be a safe and effective treatment in hair loss from different causes. This treatment may be particularly helpful for patients who are unable to tolerate topical minoxidil or have failed previous therapeutic options. OM dosages implemented for patterned hair loss are lower in female than in male patients. OM seems to improve long-term adherence to therapy when compared with topical formulations. More studies are needed to look for the efficacy of OM in other types of alopea as well as to compare its use as monotherapy or as adjunctive treatment to other commonly used medications in these conditions.

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**Conflicts of interest**

There are no conflicts of interest.

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