EFFICACY AND SAFETY OF MONOTHERAPY AND COMBINATION THERAPY OF ORAL MINOXIDIL FOR ANDROGENETIC ALOPECIA: A STRUCTURED REVIEW

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "Efficacy and safety of monotherapy and combination therapy of oral minoxidil for androgenetic alopecia: A structured review" submitted by Safrin Jahan (18346058) of Summer 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 30th January 2023.

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Ethics Statement

This project is a review article and it does not involve any animal trials or clinical trials on humans.

Abstract

In both men and women, AGA is a condition where dihydrotestosterone resulting from testosterone attacks hair follicles. OM is an FDA approved antihypertensive vasodilator. OM is an antihypertensive vasodilator authorized by FDA but not authorized for hair loss therapy. Despite this, low-dose oral minoxidil (LDOM) 0.25 to 5 milligram has displayed a favorable safety and effectiveness profile in numerous research studies (Jimenez-Cauhe, Saceda-Corralo et al. 2019, Vano-Galvan,, Pirmez et al., 2021). Oral minoxidil generates hypertrichosis and cardiovascular system (CVS) symptoms according to numerous clinical studies and the FAERS database. On the other hand, several clinical studies show that oral minoxidil in combination with spironolactone or dutasteride intralesional injections has less side effects than monotherapy of OM. As combination therapy data obtained are based on prospective, uncontrolled and open-label observational studies with and short follow-up. Thus, further studies are warranted for the safety and efficacy of combination therapies.

Keywords: Androgenetic alopecia; male pattern hair loss; Oral minoxidil; Spironolactone; Dutasteride intralesional microinjection

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List of Acronyms

OM Oral Minoxidil

SUR Sulfonylurea receptor

DIM Dutasteride intralesional microinjections

FPHL Female pattern hair loss

AGA Androgenetic alopecia

MPHL Male-pattern hair loss

ATP Adenosine triphosphate

VEGF Vascular endothelial growth factor

Glossary

Oral Minoxidil:	Oral Minoxidil is a vasodilator.
Sulfonylurea receptor:	Atypical ABC protein that regulates activity of the ATP channel.
Female pattern hair loss:	Pattern of hair loss caused by hormones, aging and genetics.
Male-pattern hair loss:	Pattern of receding hairline and hair thinning on the crown.
Dihydrotestosterone:	A hormone made from testosterone.
5a-reductase:	Converts testosterone to dihydrotestosterone.

Chapter 1

Introduction

Androgenetic alopecia, hair loss disorder that influences both male and female. It is an illness in which testosterone-derived dihydrotestosterone (DHT) attacks hair follicles, causing hair to fall out and cease growing. It tends to affect the top and front of the scalp hair. It can trigger a variety of mental health problems, notably reduction of self-confidence, increased self-consciousness, poor self-respect, despair, and anxiousness. Only two therapies are currently authorized through the USFDA for the medication of androgenetic alopecia. All of those are finasteride and topical minoxidil. OM is an antihypertensive vasodilator authorized by the FDA. However, off-label usage of low-dose OM for the medication of MPHL is getting more priority than other medications used in the treatment of AGA. The FDA has not yet authorized it for hair loss therapy. Despite this, low-dose oral minoxidil (LDOM) 0.25 to 5 mg has displayed a favorable safety and effectiveness profile in numerous research studies. (Jimenez-Cauhe, Saceda-Corralo et al. 2019, Vano-Galvan,, Pirmez et al., 2021). The overall plasma half-life is roughly 4 hours, and it boosts hair growth via a variety of mechanisms. Spironolactone is also frequently used in conjunction with other medications to treat hypertension and heart failure. Instead, when taken in conjunction with oral minoxidil for androgenetic alopecia, it prevents adverse effects. There were no incidents of hyperkalemia or other blood test anomalies. Similarly, oral route dutasteride (OD) is an effective and FDA-approved medicine for benign prostatic hyperplasia (BPH) as well as off-label for androgenetic alopecia (AGA). Only Japan and South Korea have authorized the 0.5 mg per day dosage for male AGA. Along with a plasma half-life of around 5 weeks and suppresses 5a-reductase (5AR), I as well as II class isoenzyme, reduction of DHT. Given the risk of negative

sexual anomalies from Dutasteride monotherapy, many male are unwilling to cure it with reductase inhibitors (DIM). As an outcome, when paired with oral minoxidil therapy, DIM may serve as a powerful antiandrogen substitute therapy for AGA. There is no oedema, infection, or just about any intralesional adverse effect with this multimodal treatment. All of these combinations might be a consideration, notably for individuals who have poor compliance with oral minoxidil therapy and want to boost their terminal hair count, hair diameter, and overall hair count. Oral minoxidil generates hypertrichosis and cardiovascular system (CVS) symptoms, according to numerous clinical studies and the FAERS database, whereas dutasteride monotherapy causes sexual dysfunction and neuropsychiatric negative impacts. Several clinical investigations, on the other hand, imply that coupling oral minoxidil with spironolactone or dutasteride intralesional injections had less side effects than OM monotherapy. Data from the SALT, Norwood Hamilton, and Sinclair scales are utilized to evaluate the effectiveness of adjunctive therapy. The SALT score is generated by dividing the percentage of hair loss from each of the four quadrants of the scalp by the surface area of the quadrant, then merging the four results to generate a summary measure. A SALT score of 100 implies full scalp hair loss, whereas a score of 0 denotes no hair loss. The Norwood Hamilton taxonomy, on the other hand, divides scalp into two primary categories: "not bald" and "bald." The "not bald" group incorporates varieties I-III, whereas the "bald" division covers varieties IV-VIII (Wirya, Wu et al. 2017). Furthermore, the Sinclair scale comprises five categories. The findings obtained for combination treatment are based on a prospective, uncontrolled, open-label observational trial with a short follow-up period(Kaneko and Kaneko 2018). As a result, further research on the safety and efficacy of concomitant medicines is required. This article examines the pharmacokinetics, effectiveness, pharmacodynamics and safety of OM monotherapy and concomitant therapy for the medication of AGA.

Table 1. PICO Table

Parameter	Inclusion	Exclusion
Patients	Patients of any age treated for androgenetic alopecia	Any other type of alopecia
Intervention	Oral minoxidil as alone or combination therapy	Other drugs as individual therapy except oral minoxidil
Comparator	The effectiveness of OM mono and combination therapy for treating hair loss	
Outcomes	End point measurements of hair parameters, terminal hair count, hair diameter and total hair count	Any study not designed to adequately test for standalone or combination effect of oral minoxidil

Chapter 2

Sources and search strategy

On July 10 2022, They conducted an investigation in a structured way on pubmed, openathens and google scholar using keywords and medical subject heading terms for the safety and efficacy of OM mono and co- treatment of MPHL and FPHL varieties of AGA mechanism of action, pharmacokinetics and pharmacodynamics the search turns up 212 results the number was dropped to 142 after deduplication as well as the first screening the clinical studies exploring the safety and effectiveness of om mono and co-treatment for AGA were included in the paper. As a matter of fact, studies on all other sorts of alopecia such as alopecia universalis and alopecia areata were excluded Figure 1 depicts the inclusion and exclusion norms.

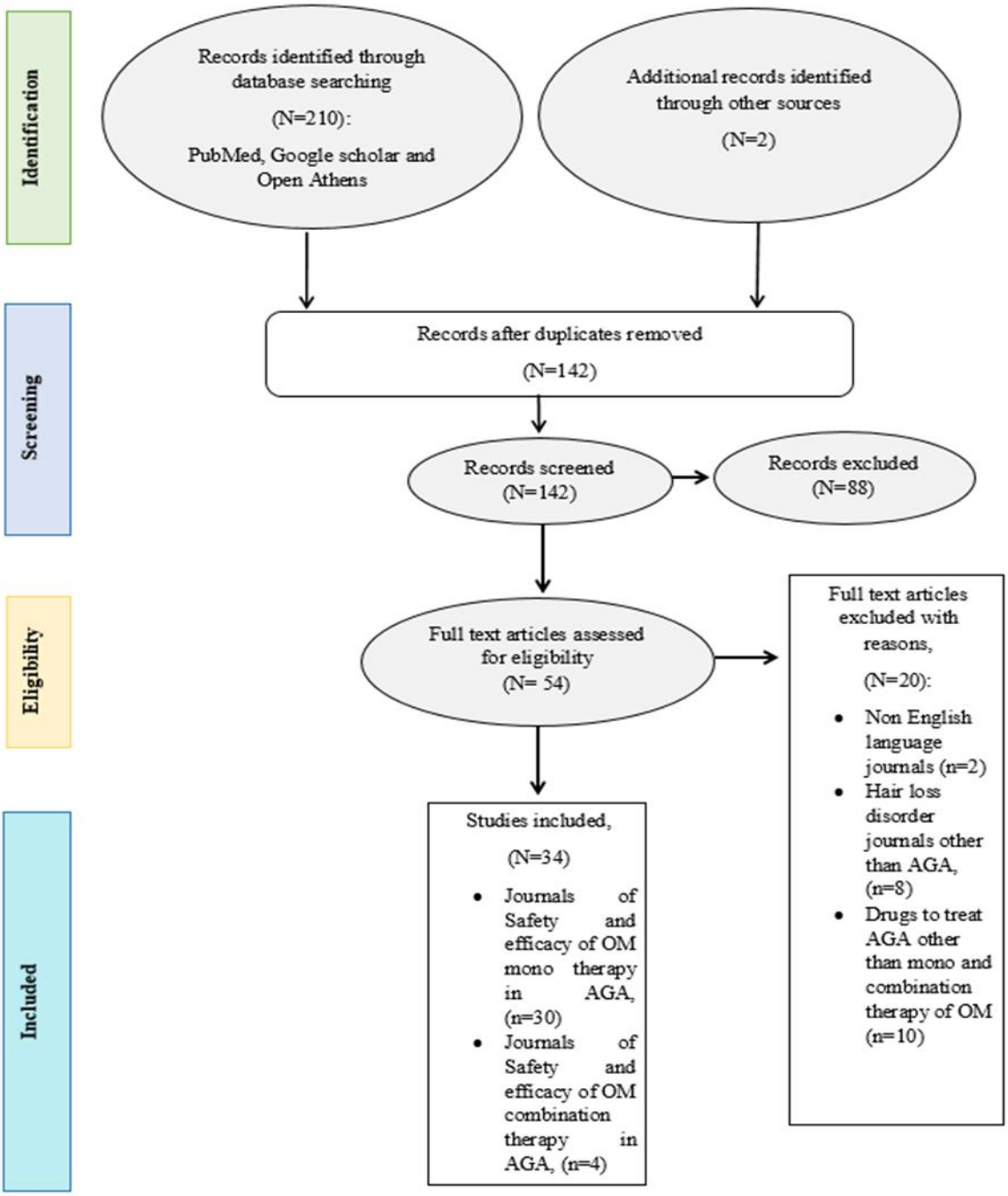

Figure 1. Search approach with inclusion and exclusion standards for the articles

Chapter 3

Pharmacokinetics

3.1. Absorption

Most of the projected 90 percent of total OM is taken by the GIT. (Gupta et al., 2022). Furthermore, in a research 29 healthy non-obese individuals were given a 2.5 mg pill of OM where the ideal plasma max concentration as well as AUC of OM were calculated to be 16.8± 7.83 mg/mL and 25.3± 7.02 mg h/mL, respectively (Table 2) (Lowenthal and Affrime 1980, Fleishaker, Andreadis et al. 1989). Cmax was attained around 1 hour (Tmax) after medication delivery. Food has no consequence on the bioavailability of minoxidil, which may be taken before or after a meal.

3.2. Distribution

OM seems to have a VD upwards of 200 liters. Incapable of interacting to blood proteins and incapable of passing the BBB (blood-brain barrier) (Lowenthal and Affrime 1980).

3.3. Metabolism

A pro-drug called OM is activated inside the liver through the steps of glucuronidation, sulfation and hydroxylation (Table 2) (Fleishaker, Andreadis et al. 1989, Gupta, Talukder et al. 2022). Furthermore, OM is processed by follicular sulfotransferase generating minoxidil sulfate metabolites (active form) (Gupta et al., 2022). Patients who have more sulfotransferase expression are far more inclined to respond rapidly versus those who have lower sulfotransferase activity.

Minoxidil O-glucuronide represents the most abundant OM metabolite in humans ("LONITEN® | Pfizer", 2022).

3.4. Excretion

During a research 29 young normal volunteers were given OM 2.5 mg per day, the renal clearance of OM was estimated to be approximately 351.67 86.5 mL/min (Fleishaker, Andreadis et al. 1989). OM and its metabolites are almost always eliminated in the urine and, to a slightly lesser degree in the feces ("LONITEN® | Pfizer", 2022). It has a plasma half-life of nearly 4 hours on average and can last for consecutive days up to 72 hours ("LONITEN® | Pfizer", 2022).

Table 2. Pharmacokinetics of OM.

Parameters		**OM**
Absorption	Bioavailability	90 percentage of total
	Cmax	16.8 ± 7.83 ng/mL
	Tmax	30 min to 1hour
	Area under curve	25.3 ± 7.02 ng hour per mL
	Food ramification on Bioavailability	Unaffected by food
	Drugs interacting to decrease efficacy	Acetylsalicylic acid
Distribution	Vss or VD	<200 L
	Plasma protein binding	Does not bind
	BBB	Does not cross
	Presence in semen	NR

Metabolism		• Liver • Major metabolite is glucuronide conjugate • By glucuronidation, hydroxylation, and sulfation process
Excretion	Total clearance	351.67 ± 86.5 mL/min
	Half-life	4.2 hours
	Via	Majorly in urine and minorly in feces

Chapter 4

Pharmacodynamic

The effects of OM on cell and channel function are diverse. It boosts the formation of epithelial and fibroblast cellular processes, while also encouraging the extension of keratinocyte lifespan (Messenger and Rundegren 2004). PGE2 synthesis is also boosted, however prostacyclin formation is repressed (Messenger and Rundegren 2004). Sarcolemma potassium channel openers potentially aid hair development. Following OM sulphation, minoxidil sulphate operates on the SUR to liberate ATP from cells. The liberated ATP is therefore metabolized into adenosine by ATPase, which then interacts on adenosine receptors in DP cells to cause them to generate VEGF (Gupta, Talukder et al. 2022). Both lysyl hydroxylase and collagen manufacture are suppressed (Messenger and Rundegren 2004). Dermal papilla (DP) cells boost VEGF generation via adenosine (Gupta, Talukder et al. 2022).

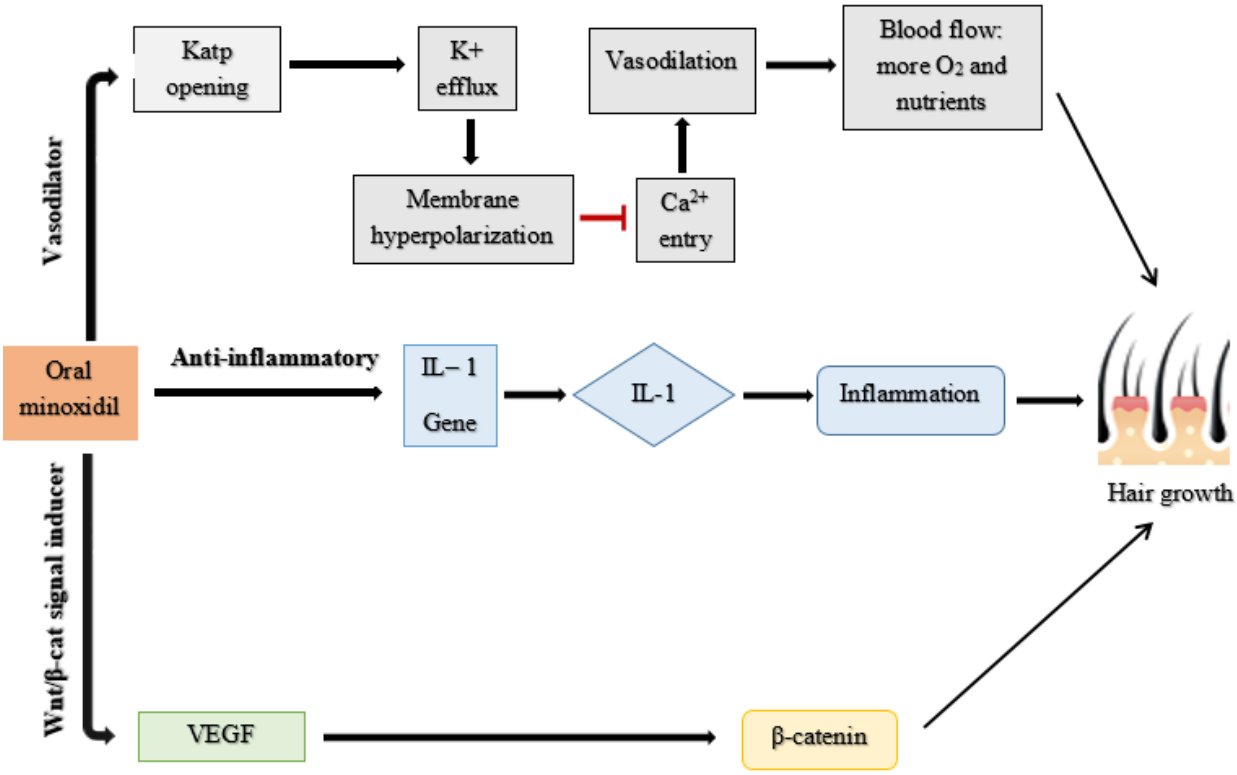

Figure 2. OM mechanisms to stimulate hair growth.

Chapter 5

Efficacy

5.1. OM monotherapy

Several clinical investigations used oral minoxidil at various dosages extending from 0.25 to 5 mg/d (Table 3) (Gupta, Talukder et al. 2022). As an outcome, daily intake of LDOM (0.25-5 mg daily) is less effective than minoxidil at 5 mg daily.

Table 3. Effectiveness of OM therapy in clinical studies

Type of Dose		**OM 2.5 – 5 mg per day**	**OM 1 mg per day**	**OM<2.5 mg once daily**		
Study		Jha Sonthalia et al., 2020	Ramos et al., (2020)	Vahabi- Amlashi et al., (2021)	Vastarella et al., (2020)	Jha, Sonthalia et al., 2020
Study type		Open-label	Randomized	Randomized	Retrospective	Open-label
Disease		Male AGA	FPHL	FPHL	FPHL	AGA
Dosage regimen		5 mg daily (24 weeks)	1 mg daily (24 weeks)	0.25 mg daily(6 months)	1.5 to 2 mg daily	1.25 mg daily(6 months)
N		30	26	6	12	32
Result	Total hair density (hairs/cm^2)	**Before Treatment Baseline ,**182.5 ± 43.3**,** 208.5 ± 42 (12 week).,217.6 ± 44.9 (24 week)	**Before Treatment Baseline** 164.6 ± 48.1, 184.7 (24-week)	**Before Treatment Baseline** 102.0 ± 50.76,112.2 ± 68.4 (6 month)	**Before Treatment Baseline** (on vertex arena):136. ±51.30, (vertex):168.92± 58.59 (24 week), Baseline (frontal): 131.47 ± 36.11, (frontal):181.40 (24 week)	**Before Treatment Baseline** 48.4%
	Terminal hair density (hairs/cm^2)	**Before Treatment Baseline,** 153 ± 33**,** 178 ± 38 (12 week), 188.1 ± 37 (24 week),	**Before Treatment Baseline** 106.5 ± 34.2 112.62 (4 week)	Not Reported	**Before Treatment Baseline** (vertex): 68.66 ± 32.56,97.75 ± 45.08 (24 week), **Before Treatment Baseline** (frontal): 72.68 ± 22.12, (frontal):108.53 (24 week)	Not Reported
	Hair diameter (µm)	**Before Treatment Baseline ,**58.5 ± 11.8**,**64.7 ± 15.2 (12 week)**,** 67.4 ± 4.5 (24 week)	Not Reported	**Before Treatment Baseline** 0.043 ± 0.001,0.045 (6-month)	**Before Treatment Baseline** (vertex):0.04 ± 0.01, (vertex):0.05 ± 0.01 (24-week), **Before Treatment Baseline** (frontal):0.04 ± 0.01, (frontal):0.05(At 24 week)	**Before Treatment Baseline** 46**,** 50 ± 11.7 (12 week)**,** 68.1± 11.6 (6 month)
Comment		• For unmanageable hypertension.	• Low-dose oral minoxidil provides efficacy in FPHL	• OM 0.25 mg/day Shows insignificant difference	• Overall 38 % and 23% improvement in hair density	• Efficacies were not statistically different.

5.2. OM combination therapy

5.2.1. OM 0.25 mg and spironolactone 25 mg

One study claims that 100 women who have been detected with a range of 2 to 5 FPHL (Sinclair stage) were medicated for a year with a regular dosage of 25 mg of spironolactone in conjunction with OM 0.25 mg (Sinclair 2018). When the average age was 48.44 years, the baseline hair losing score was 4.82. At the start, the extremity of hair fall was 2.79. Minor adverse events in 8 women included face hypertrichosis (4), postural hypotension (2), and urticaria (2) (Sinclair 2018). On a clinical examination, nobody suffered from hyperkalemia or faced other anomalies. Six of the eight individuals who had adverse effects resumed their medication, whereas two patients with urticaria stopped it. At rest, the average systolic and diastolic blood pressures were 122.92 mmHg and 79.17 mmHg, correspondingly. Employing follow-up assessments, systolic and diastolic blood pressure was estimated toward being 118.40 and 72.69 following three months, with an average turnaround blood pressure of 4.52 mmHg (systolic) and blood pressure of 6.48 mmHg(diastolic)(Sinclair 2018). 22 participants projected a brief shoot up in hair fall 3 to 6 weeks after the very first stage of the therapy. Despite this, the majority of women saw very little hair falling out at three months and far more hair density at six months(Sinclair 2018) . Likewise, in a 6-patient open-label, prospective, single-arm research employing OM with spironolactone more than a span of 5 to 13 months, 5 participants exhibited a 1-grade improvement, whereas 1 patient retained the same grade with a modest clinical improvement even without side effects (Olamiju and Craiglow 2021).

5.2.2. Dutasteride intralesional microinjection and oral minoxidil 5 mg

According to one survey, 58 subjects (55.5%) who underwent OM monotherapy as well as 47 (44.5%) whom received OM in association with DIM out of 105 male patients with an average age of 34.5 years were analyzed (Villarreal-Villarreal, Boland-Rodriguez et al. 2022). As per self - regulation, there was a substantial improvement in both groups: 34 (72.3%) in the OM+ DIM group vs. 37 (63.8%) in the OM monotherapy group (P = 0.589). Clinical assessment demonstrated statistically insignificant distinction amongst OM monotherapy and OM + DIM in the frontal area (P = 0.587), meanwhile a statistically considerable difference was found between the OM plus DIM and OM monotherapy groupings in the vertex area (P 0.001) (Villarreal-Villarreal, Boland-Rodriguez et al., 2022).

Table 4. Effectiveness of OM combination therapy in clinical studies

Dose		**Oral Minoxidil and spironolactone combination in adolescent girls**	**Dutasteride intralesional microinjections (duta 1 ml + saline 1 ml) and oral minoxidil 5 mg**	**Oral minoxidil 0.25 mg and spironolactone 25 mg Once daily**
Study		(Olamiju & Craiglow, 2021)	(Villarreal-Villarreal et al., 2022)	(Sinclair,2017)
Study type		single-arm study	Retrospective analysis	Observational pilot study
Disease		AGA	AGA	FPHL
Dosage regimen		OM 2.5 mg in adjunct with spironolactone 50 mg/day for 13 months	Oral minoxidil 5 mg and DIM 1 mL/day respectively for 3 months	OM 0.25 mg in adjunct with spironolactone 25 mg/day respectively for 6 and 12
N		6	47	100
Result	Total hair density (hairs/cm^2)	**Baseline:** **After 13 months** Sinclair scale stage Onset – 2 After therapy –1	**Baseline:** **At 16-week:** **Hamilton-Norwood** **II - 2 (4.3%)** **III - 24 (51.1%)** **IV - 14 (29.8%)** **V - 5 (10.6%)** **VI - 2 (4.3%)**	**Baseline:** **Sinclair scale** Onset Hair shedding score 4.82 **At 6-month: Reduced by 0.85** **At 12-month: Reduced by 1.3**
	Terminal hair	Not Reported	Not Reported	Not Reported
	Hair diameter (µm)	Not Reported	Not Reported	Not Reported
Comments		• **<u>Limitation of study</u>** includes small sample size and retrospective nature.	• Could be an alternative, especially in men who are reluctant to use reductase inhibitors outcome unfavorable sexual anomalies.	• Could be an alternative, who show minor compliance with OM or topical minoxidil.

Chapter 6

Safety

6.1. OM

LDOM somewhere around 0.25 to 5 mg per day generates CVS anomalies, hypertrichosis, as well as scalp pruritus or skin rashes, according to numerous clinical study data (Table 5) (Gupta et al., 2022). The dosage of OM determines when hypertrichosis and CVS symptoms emerge. Based on a six-month research, the probability of acquiring hypertrichosis and CVS symptoms jumps by 17.6% and 4.8% (Gupta et al., 2022), respectively, whenever the dose of 1 mg of OM is increased. According to the FAERS database (2000–2021), CVS symptoms are disclosed by the individuals who took Loniten for AGA (Table 6) ("FDA Adverse Event Reporting System (FAERS) Public Dashboard", 2022). Furthermore, volunteers employing OM 5 mg per day continued for about 24 weeks claiming that they had no extreme cardiovascular anomaly symptoms in a prospective study which included 34 male AGA patients (21–58 years) (Sanabria, Palmegiani et al. 2022). Additionally, in an investigation was aimed including 34 males (aged between 19 to 58) who received OM 5 mg per day continuing about 24 weeks, said not to have encountered extreme cardiovascular anomaly symptoms. Consequently, OM medication for 24 weeks is safe for male participants who have never experienced first-hand cardiovascular anomalies low dose OM 0.25 to 5mg once daily (Sanabria, Palmegiani et al. 2022). Four patients throughout all withdrew out of the research for various reasons, comprising two suffering headaches, one exhibiting edema, and single person suffering from a condition independent to the OM treatment (Sanabria, Palmegiani et al. 2022). After 24 weeks of therapy, the corresponding participant numbers have been

investigated again: 19 (55.9%) suffered hypertrichosis; 7 (20.6%) having headaches; one participant experienced edema and another participant experienced vertigo. The standard heart rate turnaround on week 24 was analytically minor (1.1%;95% CI;1.0 to 3.2%: p: 14.323), whereas a patient additionally exhibited tachycardia. Hence, 24 weeks of 5 mg/d OM therapy indicated in a minor decline in standard of (3%:, 95% CI;, 0.6 to 5.4%;, p: 14.015) arterial pressure (Sanabria, Palmegiani et al. 2022).

6.1.1. Pregnant and lactating mothers

OM is not advised for use by pregnant women or nursing mothers since it falls under pregnancy category C (hazard cannot be excluded out) (Gupta, Talukder et al. 2022). There are no reliable prenatal trials for category C medications. Neonatal hypertrichosis can be caused by OM. Additionally, OM may be passed in human milk during lactation and can be hazardous for newborns ("LONITEN® | Pfizer", 2022).

6.1.2. Impact of OM intake within males on female companions

Until now there is no documented OM secretion in semen and made the assumption that the amount excreted in semen is insignificant ("Minoxidil (Rogaine) | Parsa Mohebi", 2022). Before finalizing any recommendation, more investigation is essential, and the most recent statistics should be obtained from healthcare professionals. So far, it has not been established that using OM when their female companion is expecting is safe for men.

6.2. Topical minoxidil

According to one research, a total of 9 people may have experienced hypertrichosis. Additionally, headache was experienced by 25% of minoxidil 10% patients compared to just 11.1% of minoxidil 5% patients (Ghonemy, Alarawi et al. 2021). Especially in comparison to the 5% topical minoxidil group, only (55%) patients complained in the 10% minoxidil treatment group for all patients. There was no evidence of sexual side effects, vital sign alteration, or palpitation (Ghonemy, Alarawi et al. 2021). On table 6 it is stated that patients who used minoxidil 5% for AGA reported experiencing CVS symptoms ("FDA Adverse Event Reporting System (FAERS) Public Dashboard", 2022).

Table 5. Side effects of OM vs topical (Clinical trial statistic)

Side effects	**Oral minoxidil**				**Topical minoxidil**			
	< 2.5mg/d		2.5 – 5 mg/d		5%		10%	
	Male	Female	Male	Female	Male	Female	Male	Female
CVS anomalies	2/57 (3.51%)	6/63 (9.52%)	12/30 (40.0%)	Not reported	Not reported	Not reported	Not reported	Not reported
Muscle atrophy	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Hypertrichosis	19/57 (55.9%)	12/63 (19.04%)	Not reported	Not reported	6/27 (22.2%)	Not reported	Not reported	9/24 (37.5%)
CNS anomalies	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Scalp pruritus and skin rashes	Not reported	0/12 (0.00%)	2/30 (6.63%)	Not reported	1/19 (3.2%)	Not reported	Not reported	Not reported
Sexual dysfunction	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Table 6. Side effects of oral minoxidil vs topical (FAERS Database)

Side effects	**Oral minoxidil**		**Topical minoxidil 5%**	
	Male	Female	Male	Female
CVS symptoms	10/14 (71.43%)	Not reported	Not reported	Not reported
Skin-related adverse events	Not reported	Not reported	Not reported	Not reported
Hypertrichosis	Not reported	Not reported	Not reported	Not reported
CNS symptoms	1/14 (7.14%)	Not reported	Not reported	Not reported
Musculoskeletal side effects	Not reported	Not reported	Not reported	Not reported
Sexual dysfunction	Not reported	Not reported	1/1 (100%)	Not reported

Chapter 7

Conclusion

Some clinics are still utilizing LDOM, which ranges from 0.25 to 5 mg/d, to treat AGA patients despite the fact that it is not authorized. Overall, mono and combination OM therapy might be potential evolution to the AGA treatment, particularly for people who shows adverse reactions experienced by the application or use of topical minoxidil and all the trending and ongoing AGA therapies or to avoid or how to manage the adverse effects. Thus, the safety and effectiveness of OM monotherapy and combination therapy still require further clinical studies and post-marketing data to be fully understood.

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