Safety of low-dose oral minoxidil for hair loss: A multicenter study of 1404 patients

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Background: The major concern regarding the use of low-dose oral minoxidil (LDOM) for the treatment of hair loss is the potential risk of systemic adverse effects.

Objective: To describe the safety of LDOM for the treatment of hair loss in a large cohort of patients.

Methods: Retrospective multicenter study of patients treated with LDOM for at least 3 months for any type of alopecia.

Results: A total of 1404 patients (943 women [67.2%] and 461 men [32.8%]) with a mean age of 43 years (range 8-86) were included. The dose of LDOM was titrated in 1065 patients, allowing the analysis of 2469 different cases. The most frequent adverse effect was hypertrichosis (15.1%), which led to treatment withdrawal in 14 patients (0.5%). Systemic adverse effects included lightheadedness (1.7%), fluid retention (1.3%), tachycardia (0.9%), headache (0.4%), periorbital edema (0.3%), and insomnia (0.2%), leading to drug discontinuation in 29 patients (1.2%). No life-threatening adverse effects were observed.

Limitations: Retrospective design and lack of a control group.

Conclusion: LDOM has a good safety profile as a treatment for hair loss. Systemic adverse effects were infrequent and only 1.7% of patients discontinued treatment owing to adverse effects. (J Am Acad Dermatol 2021;84:1644-51.)

Key words: alopecia; androgenetic alopecia; arterial hypotension; dizziness; edema; effluvium; fluid retention; frontal fibrosing alopecia; hair loss; hypertrichosis; lichen planopilaris; lightheadedness; new treatments; periorbital edema; safety; tachycardia.

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INTRODUCTION

Minoxidil is a potent arteriolar vasodilator that was approved by the US Food and Drug Administration for the treatment of severe refractory hypertension in 1979.[1,2] For patients aged >12 years, the dosage range is usually between 10-40 mg/day, with a maximum recommended dose of 100 mg.[2,3] Minoxidil has a duration of action of approximately 24 hours despite having a plasma half-life of 4.2 hours,[2,3] suggesting extravascular accumulation.[4] Minoxidil sulfate, the biologically active metabolite of minoxidil, lowers blood pressure by opening sarcolemmal adenosine triphosphate-sensitive potassium channels in vascular smooth muscle cells.[5]

Oral minoxidil has dose-dependent predictable side effects at doses of 10-40 mg, including postural hypotension, fluid retention, tachycardia, pericarditis, and nausea.[2] However, the most common adverse effect is hypertrichosis, which occurs in approximately 80% of patients.[2] Based on this serendipitous adverse effect, topical minoxidil was developed in 1987 for male and female pattern hair loss.[6,7] The precise mechanism through which minoxidil promotes hair growth is unclear. Minoxidil shortens the telogen phase of the hair growth cycle, thus causing premature transition to anagen.[1] It also prolongs anagen, resulting in increased hair length and diameter. The initial hair growth-promoting effects of minoxidil occur after approximately 2 months, with maximal effects observed at 4 months.[1]

Low-dose oral minoxidil (LDOM) (0.25-5 mg/day) has been used off label to treat various forms of alopecia.[8-21] The use of LDOM for the treatment of hair loss has significantly increased in the last few years for several reasons: (1) many patients find oral administration more convenient than the topical application of a lotion or foam; (2) topical application is operator-dependent, ie, some parts of the scalp may be missed in those with widespread alopecia; and (3) LDOM circumvents the local side effects associated with topical minoxidil such as irritation and allergic contact dermatitis.[22] Nevertheless, the major concern of oral administration is the potential risk of systemic adverse effects. Although published studies of LDOM for hair loss have demonstrated a favorable safety profile,[8,9,13,14] the number of patients evaluated in these studies is generally low, and therefore, infrequent adverse effects may not have been detected. The objective of this study was to investigate the safety of LDOM for hair loss in a large cohort of patients.

CAPSULE SUMMARY

- Low-dose oral minoxidil for hair loss has a good safety profile. Only 1.7% of patients discontinued the drug owing to adverse effects.
- Although infrequent, dermatologists should be aware of the potential systemic adverse effects of low-dose oral minoxidil, which include lightheadedness, fluid retention, tachycardia, headache, periorbital edema, and insomnia.

METHODS

A retrospective, multicenter, and descriptive study including 10 centers from 6 different countries was designed. Patients treated with LDOM for ≥3 months for hair loss of any cause were included. Epidemiological and safety data were collected. In patients who developed adverse effects, the type and time to development of the adverse effect, in addition to the need to withdraw or adjust the dose of LDOM, were also recorded. We analyzed the above parameters for each dose in patients who received >1 dose of LDOM.

Logistic regression was used to identify the variables associated with an increased risk of adverse effects in a multivariate model adjusted for age, weight, and sex.

RESULTS

A total of 1404 patients (943 women [67.2%] and 461 men [32.8%]) with a mean age of 43 years (range 8-86) were included. The most common indication for LDOM was androgenetic alopecia (82.4%), followed by telogen effluvium (4.8%), alopecia areata (3.8%), frontal fibrosing alopecia (2.8%), lichen planopilaris (2.5%), and fibrosing alopecia in a pattern distribution (1.8%). LDOM was the only systemic therapy in 20.8% of patients. Three hundred and thirty-nine patients received a fixed dose regimen of LDOM with no increments. The remaining 1065 patients received LDOM at various incremental doses as tolerated, resulting in a total of 2469 doses administered to 1404 patients (Table I). The mean dose used was 1.63 mg (range 0.03-15) and the mean duration of treatment was 7.9 months (range 3-79). Adverse effects were detected in 509 cases (20.6%), leading to treatment withdrawal in 43 patients (1.7%). The most common adverse effect was hypertrichosis (374 patients, 15.1%), which resulted in discontinuation in 14 cases (0.5%).

Abbreviations used:

EOD: every other day
LDOM: low-dose oral minoxidil

Systemic adverse effects (Table II) were observed in 135 patients (5.5%), of whom 29 (1.2%) discontinued treatment, and these adverse effects included lightheadedness (n = 43), fluid retention/leg edema (n = 32), tachycardia (n = 21), headache (n = 9), periorbital edema (n = 7), and insomnia (n = 6). Fourteen patients (0.9%) had >1 adverse effect. Of those, 6 (5 female and 1 male; median dose 1 mg; range 0.25-5 mg) developed hypertrichosis as well as lower limb edema (n = 3), lightheadedness (n = 2), or periorbital edema (n = 1). The overall frequency of adverse effects and the proportion of patients requiring discontinuation did not significantly differ in patients with androgenetic alopecia from those with other types of alopecia.

Less common adverse effects included increased hair shedding (n = 5), nausea (n = 2), mild increase in liver enzymes (n = 2), menorrhagia (n = 2), self-limiting chest pain (n = 1), and acne (n = 1).

All systemic adverse effects improved with dose adjustment or withdrawal of LDOM, and no life-threatening adverse effects were reported. The most common adverse effects that resulted in discontinuation (n = 43, 1.7%; 39 female and 4 male) were hypertrichosis (n = 14, 0.5%), fluid retention (n = 8, 0.3%), tachycardia (n = 7, 0.2%), lightheadedness (n = 5, 0.2%), and headaches (n = 4, 0.1%) (Fig 1).

Weight was recorded in 342 patients (24.3%; mean 67.2 kg; range 42-124). No statistically significant association was found between weight and any of the adverse effects. Topical minoxidil was used in 26.1% of patients in combination with LDOM and was not associated with a higher risk of hypertrichosis or other adverse effects. LDOM was administered daily in 95% of patients and every other day (EOD) in 5% of patients. Bivariate analysis showed that EOD administration was associated with a lower risk of hypertrichosis (15.8% vs 9.8%, $P = .04$). The compounded medication was associated with a higher risk of hypertrichosis, but no other adverse effects, compared with the commercially marketed drug (Loniten) (18.7% vs 14.5%, $P = .014$).

Multivariate analysis showed that the most important risk factor for hypertrichosis was the dose of LDOM (odds ratio 1.26 [95% confidence interval: 1.17-1.35], $P < .001$), when adjusted for age, weight, sex, and duration of treatment. EOD administration showed a trend toward a protective affect against hypertrichosis [odds ratio 0.55, $P = .062$]. However, neither the dose of LDOM nor the other variables were associated with a higher risk of systemic adverse effects.

DISCUSSION

To our knowledge, this research represents the largest study on the safety of LDOM for the treatment of patients with hair loss disorders. Since the first report of its use in 2 women with monilethrix in 2016,[19,21] LDOM has been widely used for various types of alopecia,[22] especially male[10,16] and female pattern hair loss.[13,14]

LDOM was found to be well-tolerated in 2 recent systematic reviews investigating its effectiveness and safety in patients with hair loss.[15,16] The most frequent adverse effect was hypertrichosis (20%-24%), which rarely led to treatment discontinuation.[23] Cardiovascular adverse effects, which are relatively common with antihypertensive doses, were rare and typically minor. Symptoms of postural hypotension, tachycardia, and lower limb edema were reported by 1%-3% of patients, while pedal edema was associated with higher doses (5 mg). No serious or life-threatening adverse effects were reported, supporting the good safety profile of LDOM for the treatment of hair loss.

The overall frequency of adverse effects in our study was 20.6%. Hypertrichosis was by far the most common and was associated with a mean dose of LDOM of 1.4 mg in females and 4.1 mg in males. Interestingly, only 3.7% of patients who grew unwanted hair on the face/body discontinued treatment. Our findings reflect those of Jimenez-Cauhe et al[23] who found that only 4% of patients who developed hypertrichosis discontinued LDOM treatment for their hair loss. In our experience, patients prefer to manage hypertrichosis with hair removal methods while continuing therapy, provided that they can appreciate the benefits of LDOM (decreased hair shedding and increased scalp hair density). We found that EOD administration may be associated with a lower risk of hypertrichosis. The reason for this observation is unclear and more studies are required to corroborate this finding and to define whether EOD administration is better tolerated than daily intake. Both scalp hair growth and hypertrichosis in patients on LDOM therapy are dose-dependent. In our experience, the correlation between the increase in scalp hair growth and hypertrichosis is not linear. In fact, the mean dose of LDOM that resulted in hypertrichosis was 1.77 mg. However, improvements in hair density can be achieved with doses as low as 0.25-1 mg.[11,13,14,18] Due to the absence of marketed tablets of oral

Table I. Description of the cohort of women and men treated with low-dose oral minoxidil (LDOM) and frequency of adverse effects (N = 2469, different doses of LDOM)

	Women (n = 1612)	Men (n = 857)	Total (N = 2469)
Mean age in years (range)	47 (8-86)	37 (14-78)	43 (8-86)
Country of origin	Australia (n = 528), Brazil (n = 173), Italy (n = 135), Poland (n = 51), Spain (n = 574), and United States (n = 151)	Australia (n = 323), Brazil (n = 129), Italy (n = 71), Poland (n = 0), Spain (n = 260), and United States (n = 74)	Australia (n = 851), Brazil (n = 302), Italy (n = 206), Poland (n = 51), Spain (n = 834), and United States (n = 225)
Median dose in mg (range)	1.11 (0.03-12.5)	2.60 (0.15-15)	1.63 (0.03-15)
Median treatment duration in months (range)	8 (3-79)	7.8 (3-63)	7.9 (3-79)
Marketed drug	1402 (87%)	542 (63%)	1943 (78.7%)
Concomitant use of topical minoxidil	442 (27.4%)	184 (21.5%)	626 (25.4%)
Adverse effects (any)	422 (26.1%)	87 (10.1%)	509 (20.6%)
Required discontinuation	39 (2.5%)	4 (0.5%)	43 (1.7%)
Hypertrichosis	324 (20.1%)	50 (5.8%)	374 (15.1%)
Median latency period (in days) until hypertrichosis (range)	60 (14-450)	60 (21-120)	60 (14-450)
Mean dose in mg (range) that produced hypertrichosis	1.42 (0.25-5)	4.10 (0.5-12.5)	1.77 (0.25-12.5)
Required dose adjustment	84 (5.2%)	9 (1.1%)	93 (3.8%)
Required discontinuation	14 (0.9%)	0	14 (0.5%)
Mean time (in days) receiving LDOM until discontinuation (range)	73 (45-100)	-	73 (45-100)
Systemic side effects	98 (6.1%)	37 (4.3%)	135 (5.5%)
Required discontinuation	25 (1.6%)	4 (0.5%)	29 (1.2%)
Mean time (in days) receiving LDOM until discontinuation (range)	34 (1-120)	45 (1-60)	36 (1-120)

LDOM, Low-dose oral minoxidil.

minoxidil at low doses, the administration of non-marketed compounds is necessary in some countries. The use of compounded LDOM capsules was associated with a higher risk of hypertrichosis. This finding may suggest unintended dose variations in compounded capsules. At least 3 patients in the current study developed hypertrichosis as a result of errors in the dosage of the medication by the compounding pharmacy, resulting in a higher dose of LDOM than that prescribed by their dermatologist. This highlights the importance of a carefully controlled compounding pharmacy environment, which should include handling only by a licensed compounding pharmacist.

Systemic adverse effects of LDOM occurred in 5.5% of patients (Fig 1). In all cases, these were mild and resolved with dose reduction or treatment discontinuation. Twenty-nine patients (1.2%) stopped LDOM therapy owing to systemic adverse effects, mostly edema (n = 8), tachycardia (n = 7), lightheadedness (n = 5), and headache (n = 4). In concordance with previous studies,[15,16] there were no serious or life-threatening side effects associated with LDOM therapy. The risk of systemic adverse effects associated with LDOM was unrelated to dose, age or sex. Despite the relatively high incidence of systemic side effects with antihypertensive doses of minoxidil (10-40 mg),[2,3] we found that systemic side effects associated with low doses of oral minoxidil (≤5 mg) were uncommon and not dose-dependent. We hypothesize that the systemic adverse effects of LDOM may be influenced by idiosyncratic patient characteristics and individual genetic variations in the activity of the minoxidil sulfotransferase enzyme (SULT1A1).[24,25]

Pericardial effusions occur in approximately 3% of patients treated with high-dose oral minoxidil and are most common among patients with advanced nephropathy or on dialysis.[26] In a study of 1869 patients with severe hypertension treated with minoxidil, approximately 5% developed pericardial disorders, including pericarditis, pericardial effusion,

Table II. Description of the systemic side effects associated with the use of low-dose oral minoxidil in men and women

	Women (n = 1612)	Men (n = 857)	Total (N = 2469)
Systemic side effects	98 (6.1%)	37 (4.3%)	135 (5.5%)
Lightheadedness	33 (2.0%)	10 (1.1%)	43 (1.7%)
Median latency period (in days) until lightheadedness (range)	5 (1-20)	5 (1-20)	5 (1-20)
Mean dose in mg that produced lightheadedness	0.93	3.90	1.62
Required discontinuation	4/33 (12%)	1/10 (10%)	5/44 (11.3%)
Fluid retention (leg edema)	18 (1.1%)	14 (1.6%)	32 (1.3%)
Median latency period (in days) until fluid retention (range)	90 (15-360)	57 (30-90)	60 (15-360)
Mean dose in mg that produced fluid retention	0.97	3.25	1.97
Required discontinuation	6/18 (33%)	2/14 (14%)	8/32 (25%)
Tachycardia	15 (0.9%)	6 (0.7%)	21 (0.9%)
Median latency period (in days) until tachycardia (range)	2 (0-7)	1 (0-2)	1 (0-7)
Mean dose in mg that produced tachycardia	0.73	2.52	1.24
Required discontinuation	7/15 (46%)	0/6	7/21 (33.3%)
Headache	8 (0.5%)	1 (0.1%)	9 (0.4%)
Median latency period (in days) until headache (range)	19 (5-20)	25 (25-25)	20 (5-25)
Mean dose in mg that produced headache	1.28	1.25	1.27
Required discontinuation	4/8 (50%)	0/1	4/9 (44.4%)
Periorbital edema	4 (0.2%)	3 (0.3%)	7 (0.3%)
Median latency period (in days) until periorbital edema (range)	105 (30-210)	60 (30-60)	60 (30-210)
Mean dose in mg that produced periorbital edema	0.75	5.80	2.92
Required discontinuation	0/4	0/3	0/7
Insomnia	5 (0.3%)	1 (0.1%)	6 (0.2%)
Median latency period (in days) until insomnia (range)	120 (7-180)	7 (7-7)	90 (7-180)
Mean dose in mg that produced insomnia	1	1	1
Required discontinuation	3/5 (60%)	0/1	3/6 (50%)
Others	15 (0.9%)	2 (0.2%)	17 (0.7%)
Required discontinuation	1/15 (7%)	1/2 (50%)	2/17 (11.7%) (both: intense hair shedding)

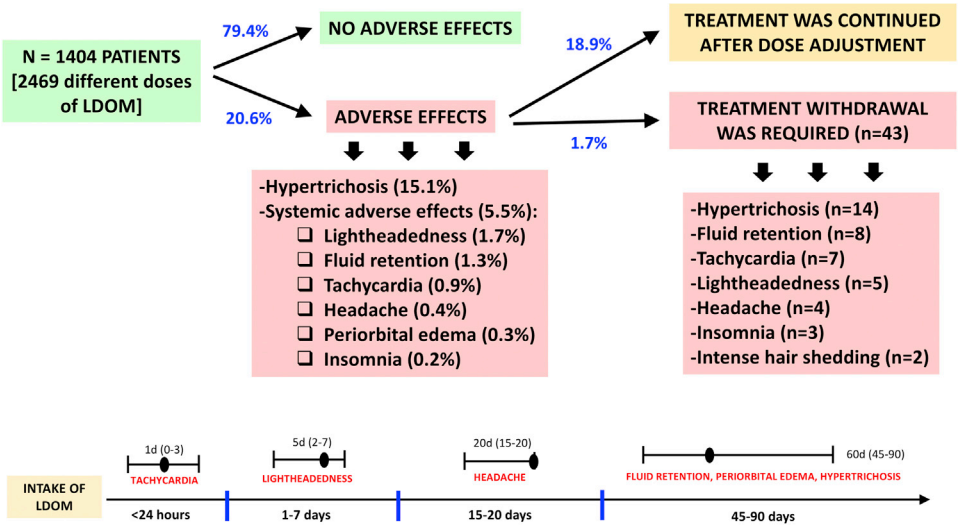

Fig 1. Schematic of total number of patients treated with low-dose oral minoxidil (N = 1404), percentage of patients who developed adverse effects and number of patients requiring discontinuation owing to adverse effects. The time from starting low-dose oral minoxidil therapy to the development of adverse effects (median and range, days) is shown at the bottom. *LDOM,* Low-dose oral minoxidil.

Table III. Common adverse effects of low-dose oral minoxidil, mean time to development of adverse effects, and suggested management strategies

Adverse effect of LDOM	Mean time for adverse effect to develop (days)	Management*
Hypertrichosis	60	Hair removal methods (laser, shaving, plucking, bleaching, waxing)
Lightheadedness	5	Taking LDOM at bedtime, getting up slowly from a lying/sitting position, increasing fluid intake, adjusting doses of antihypertensives (by general practitioner)
Fluid retention	60	Limiting salt intake; diuretics, eg, furosemide (in males and females) and spironolactone (in females)
Periorbital edema	60	
Tachycardia	1	Beta-blockers; if persistent, refer to cardiologist
Headache	20	Simple analgesics, eg, paracetamol, nonsteroidal anti-inflammatory drugs
Insomnia	90	Sleep strategies/relaxation, pharmacotherapy (by general practitioner)

LDOM, Low-dose oral minoxidil.
*If adverse effects are severe or persist in spite of the above management strategies, consider dose reduction or discontinuation.

and cardiac tamponade.[27] Most of the patients who developed pericarditis had an underlying systemic disorder such as systemic lupus erythematosus, whereas most of those who developed pericardial effusion and cardiac tamponade had chronic renal failure or chronic congestive cardiac failure. It is unclear whether minoxidil was responsible for these pericardial disorders as other risk factors were present and no baseline echocardiogram was performed. Most of the effusions resolved despite continued treatment with minoxidil. Moreover, there are no reports of pericardial disorders among patients treated with minoxidil for hair loss. Fortunately, there were no cases of pericardial disorders or ischemic heart disease in our large cohort. Theoretically, myocardial ischemia can be aggravated by oral minoxidil-induced reflex tachycardia. In fact, minoxidil therapy for hypertension was sometimes administered with a diuretic and a beta-blocker to reduce sympathetic tone and sodium retention.[26] The absence of severe cardiovascular side effects in our cohort may be related to the favorable risk profile of our population, most of whom were relatively young and healthy, in addition to the low doses required for the treatment of hair loss. We suggest that a baseline electrocardiogram is unnecessary when doses of minoxidil ≤5 mg are administered, which most of our patients were on. However, this should be assessed on a case-by-case basis, and we recommend a low threshold for performing an electrocardiogram in patients with cardiovascular risk factors such as angina, pericarditis, chronic heart failure, and renal impairment.

The management of adverse effects of LDOM raises an interesting issue for dermatologists. We suggest strategies that we have found helpful in managing common side effects (Table III). Given that lightheadedness can occur with LDOM therapy, special caution should be exercised in patients with a history of orthostatic hypotension and syncope and in patients taking calcium channel antagonists (which are peripheral vasodilators). Lower extremity edema is related to sodium and water retention secondary to renal hemodynamic and/or neurohumoral changes as well as direct tubular effects of oral minoxidil.[28] Spironolactone, a potassium-sparing diuretic with antiandrogenic properties, may be used to manage LDOM-induced fluid retention in women, especially those with female pattern hair loss. Tachycardia is the result of reflex sympathetic activation in response to the vasodilatory effect of oral minoxidil. In most of our 21 cases, the reflex tachycardia was transient, but in persistent cases, it led to treatment discontinuation. Although tachycardia can theoretically be managed with beta-blockers, we argue that a persistently elevated heart rate may warrant LDOM withdrawal or consultation with a cardiologist. Interestingly, there were no reports of nausea or vomiting in our study, even though nausea is cited as a common side effect of high-dose oral minoxidil.[2]

We found that LDOM-induced adverse effects developed in a time-dependent fashion (Fig 1). While reflex tachycardia and orthostatic hypotension manifested early (median latency periods of 1 and 5 days, respectively), fluid retention, periorbital edema, and hypertrichosis had a delayed onset (median latency period of 60 days). These data will help dermatologists counsel their alopecia patients on when to anticipate various adverse effects. As hypertrichosis usually develops within 3 months of initiation or dose escalation, we suggest that the dose of LDOM can be uptitrated after 3 months in the absence of undesirable hair growth.[23]

We cannot exclude that other drugs used for hair loss were responsible for some of the side effects. For

example, 13 of 43 patients who complained of lightheadedness were also taking oral spironolactone. However, there was no association between the development of orthostatic hypotension and concomitant use of specific antihypertensive drugs. Further research is required to equip dermatologists with data on the use of LDOM in patients with preexisting cardiovascular diseases or arterial hypertension, including those on antihypertensives.

Based on our safety data, we propose the following starting doses and titration regimens for females: starting dose of 0.5 mg/day followed by 0.25 mg increments every 3 months depending on response and tolerability up to a maximum dose of 2.5 mg; and males: starting dose of 2.5 mg/day followed by 1.25 mg increments every 3 months depending on response and tolerability up to a maximum dose of 5 mg/day. We recommend this protocol for patients aged ≥12 years, although lower starting doses should be considered in those aged 12-17 years. Experience with oral minoxidil in children under 12 is still limited. In patients with chronic hair loss conditions, LDOM may be used indefinitely, otherwise any improvement in hair density may be lost within a few months of treatment discontinuation. We should emphasize that this is strictly an off-label indication and detailed informed consent should be obtained. Furthermore, the dose and titration regimen should be adjusted depending on comorbidities.

The limitations of our study were the retrospective design, lack of a control group, and lack of recording of patient comorbidities.

In conclusion, LDOM had a favorable safety profile in this large cohort of patients with various types of alopecia. Hypertrichosis was the most frequent adverse effect, and the frequency of systemic side effects was low, with <2% of patients requiring treatment discontinuation.

Conflicts of interest

None disclosed.

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