Skin Appendage Disorders

Guidelines

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Low-Dose Oral Minoxidil for Alopecia: A Comprehensive Review

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Keywords
Oral administration · Minoxidil · Hair disorders · Androgenetic alopecia · Female-pattern hair loss

Abstract
Low-dose oral minoxidil (LDOM) has demonstrated a promising safety and efficacy profile in the treatment of various hair disorders, including male androgenetic alopecia (AGA) and female-pattern hair loss (FPHL); however, it lacks FDA approval. The usual LDOM starting dose for male AGA is 1–5 mg/day, depending on physician preference and the patient's condition. For FPHL, it is 0.5–1 mg/day. The maximum dose is generally 5 mg/day. If patients respond well without major side effects, the dose may be gradually increased since the LDOM's efficacy appears to be dose-dependent. Patients may use LDOM long term if the treatment outcome is satisfactory. The common side effects of LDOM are hypertrichosis and cardiovascular symptoms. Females are more prone to hypertrichosis than males. The side effects of LDOM can be categorized as (a) dose-dependent type A side effects (hypertrichosis and cardiovascular symptoms) and (b) idiosyncratic type B side effects (pericardial effusion). Minoxidil acts via multiple pathways. Although minoxidil has a relatively short half-life of around 4 h, its hypotensive effect may last approximately 72 h. Effective treatments for alopecia are limited. Therefore, LDOM could be an important addition to the available therapies for managing some hair disorders, including AGA.

Introduction

Treating alopecia poses a formidable challenge [1]. While topical minoxidil has FDA approval for treating both male androgenetic alopecia (AGA) and female-pattern hair loss (FPHL), the use of oral minoxidil is off-label [1]. However, several studies report that low-dose oral minoxidil (LDOM), with a daily dose ranging from 0.25 to 5 mg, has a favorable safety and efficacy profile for treating both male AGA and FPHL [2–7]. Moreover, oral minoxidil has shown some efficacy in other types of alopecia, including chronic telogen effluvium, alopecia areata, anagen effluvium, loose anagen syndrome, monilethrix, lichen planopilaris, etc. [8–14]. This article reviews the pharmacodynamics, pharmacokinetics, effectiveness, and safety of oral minoxidil in the treatment of alopecia, along with expert-recommended dosage regimens for managing male AGA and FPHL.

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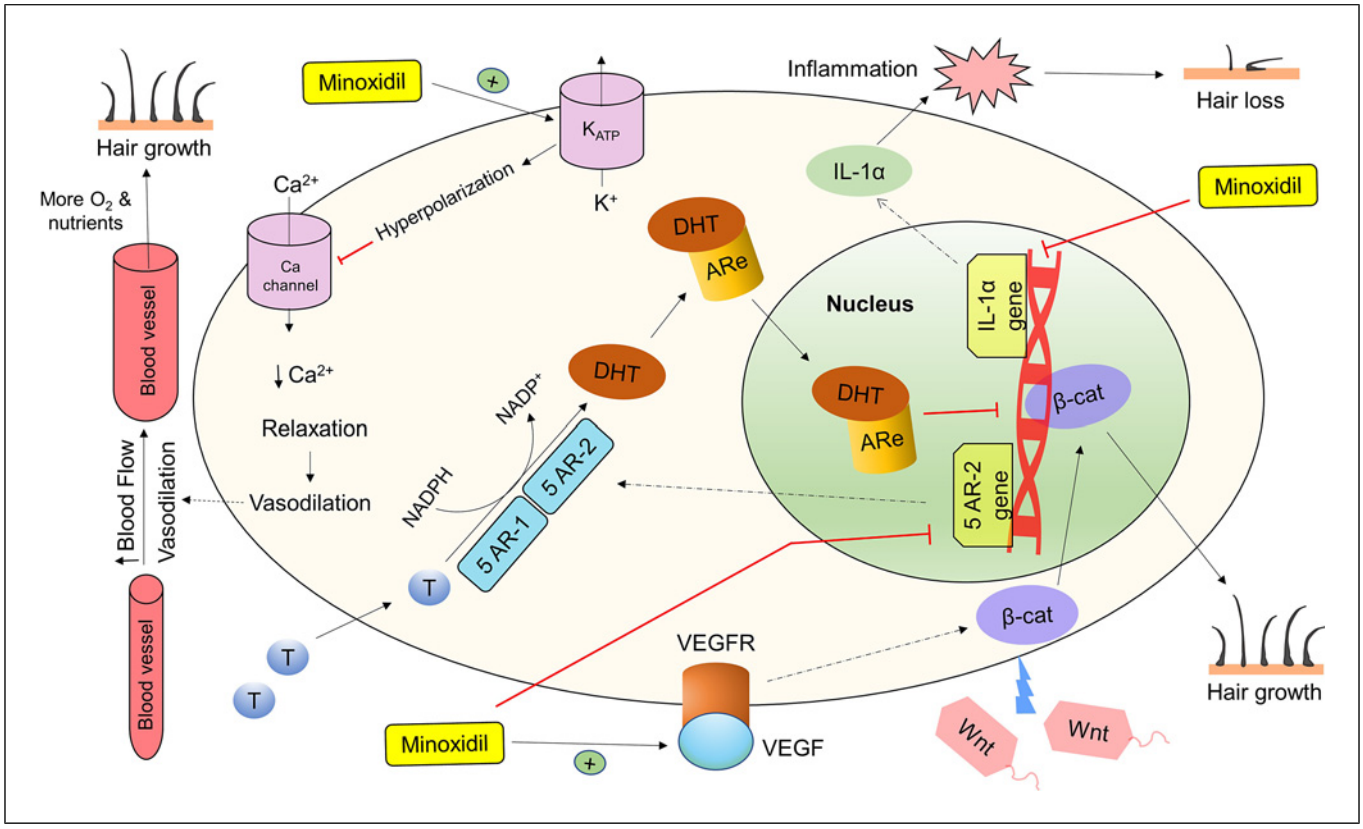

Fig. 1. The proposed mechanism of action of minoxidil. Minoxidil stimulates the ATP-sensitive potassium channel, which eventually leads to vasodilation. Dilated blood vessels can carry more oxygen and nutrients to the hair follicles and thus promote hair growth. Minoxidil may also downregulate the expression of the interleukin-1 alpha gene, and thus may reduce perifollicular microinflammation by inhibiting inflammatory mediators such as interleukin-1 alpha, which facilitates hair growth. Minoxidil may inhibit the expression of 5 alpha-reductase type II gene and thus may act as an antiandrogen and promote hair growth. Minoxidil may also induce Wnt/b-catenin signaling pathway by stimulating the release of VEGF in the dermal papilla cell, leading to hair follicle regeneration. 5 AR-1, 5 alpha-reductase type I; 5 AR-2, 5 alpha-reductase type II; ARe, androgen receptor; β-cat, beta-catenin; Ca, calcium; DHT, dihydrotestosterone, IL-1α, interleukin-1 alpha; IL-1α gene, interleukin-1 alpha gene; K, potassium; NADP+, nicotinamide adenine dinucleotide phosphate; NADPH, reduced form of NADP+; O_2, oxygen; T, testosterone; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; Wnt, wingless-related integration site.

Mechanisms of Action

The precise mechanism by which minoxidil promotes hair growth has yet to be fully understood [1, 15]. However, minoxidil may act as a vasodilator, a Wnt/β-catenin signaling pathway inducer, an anti-inflammatory agent, and possibly an antiandrogen; perhaps, minoxidil enhances hair growth via multiple pathways (Fig. 1) [16–25].

Minoxidil as a Vasodilator

Minoxidil stimulates the ATP-sensitive potassium channel (K_{ATP}), which triggers membrane hyperpolarization, resulting in the inhibition of calcium ion entry through the voltage-gated calcium channel (Fig. 1) [16, 17]. Decreased level of calcium ions inside the cell facilitates vasorelaxation and vasodilation. Dilated blood vessels carry more oxygen and nutrients to the hair follicles, eventually promoting hair growth.

Minoxidil as a Wnt/β-Catenin Signaling Pathway Inducer

β-catenin, an important transcription factor, plays a significant role in hair follicle regeneration [18–21]. In dermal papilla cells, minoxidil may activate the vascular endothelial growth factor-related β-catenin signaling pathway by stimulating vascular endothelial growth factor release (Fig. 1) [18–21].

Minoxidil as an Anti-Inflammatory Agent

Minoxidil may reduce perifollicular microinflammation by inhibiting various inflammatory mediators such as interleukin-1α [25] and prostacyclin (Fig. 1) [22].

Minoxidil as an Antiandrogen

In an in vitro experiment, minoxidil reduced the expression of 5α-reductase type 2 gene in human keratinocyte cells [26, 27]. The enzyme 5α-reductase type 2 converts testosterone into dihydrotestosterone, a compound believed to contribute to hair loss. Thus, by reducing 5α-reductase type 2 gene expression, minoxidil may function as an antiandrogen and promote hair growth. However, other experiments conducted on human dermal papilla cells and golden Syrian hamsters have disputed minoxidil's action as an antiandrogen (Fig. 1) [23, 24].

Other Proposed Mechanisms

Minoxidil may promote hair growth by playing an important role in the anagen phase. The drug may cause the early onset of the anagen phase by enhancing the synthesis of DNA in the anagen bulb [28]. Furthermore, minoxidil may have the potential to lengthen the anagen phase, shorten the telogen phase, or influence both of these hair growth phases [15, 28]. An experiment on a rat model showed that topical minoxidil preparation did not extend the anagen phase but reduced the telogen phase duration [28]. Another study conducted on stump-tailed macaques demonstrated that the application of topical minoxidil solution contributed to the regulation of both the telogen and anagen phases, ultimately leading to an increase in hair follicle size [29].

Pharmacokinetics

Absorption

A patient can take oral minoxidil in a fed or fasted state. Food does not impact the bioavailability of oral minoxidil [1, 15]. The majority of oral minoxidil (~90%) is absorbed in the gastrointestinal tract [1]. A Latin square cross-over study found the area under the curve to be 25.3 ± 7.02 ng × h/mL and the maximum plasma concentration (C_{max}) to be 16.8 ± 7.83 ng/mL when 29 healthy, non-obese, young participants took 2.5 mg minoxidil tablets [30]. The time to reach peak drug concentration (T_{max}) was 1 h (Fig. 2) [1, 15, 30, 31].

Distribution

Orally administered minoxidil exhibits a volume of distribution exceeding 200 L [32]. Importantly, minoxidil does not penetrate the blood-brain barrier and does not bind to plasma proteins (Fig. 2) [33].

Metabolism

Minoxidil O-glucuronide appears to be the predominant metabolite of minoxidil in humans [33]. Being a prodrug, minoxidil's metabolism regulates its pharmacologic action [15]. The liver is mainly involved in the metabolism of minoxidil, where it undergoes glucuronidation, hydroxylation, and sulfation (Fig. 2) [1]. The sulfated metabolite of minoxidil, minoxidil sulfate, enhances hair growth [15].

Excretion

In men, the mean plasma half-life of orally administered minoxidil is ~4 h, but its pharmacologic action (hypotensive effect) lasts approximately 72 h (Fig. 2) [33]. The elimination of minoxidil and its metabolites primary occurs through urinary excretion [33]. A study in 29 young, healthy volunteers receiving 2.5 mg/day oral minoxidil found minoxidil's renal clearance to be 351.67 ± 86.5 mL/min [30].

Oral Minoxidil for Different Forms of Alopecia

Female-Pattern Hair Loss

The safety and efficacy of oral minoxidil for treating FPHL have been evaluated in several studies [34, 35]. These studies used minoxidil doses from 0.25 to 1.25 mg for duration of 6–12 months (Table 1) [2–7].

A randomized, double-blind study randomly divided 30 FPHL patients into two groups. Group 1 (N = 14) had 0.25 mg oral minoxidil daily for 24 weeks, while group 2 (N = 14) had 1 mg minoxidil daily for the same duration [7]. The study found that minoxidil 1 mg/day was safe and effective in treating FPHL, and its efficacy was significantly higher than that of minoxidil 0.25 mg/day. Only 2 patients in group 2 (of 12) had hypertrichosis, indicating that minoxidil 1 mg/day was generally well tolerated in FPHL patients [7].

In a three-blinded, randomized pilot study, 6 female patients (per protocol analysis) received minoxidil 0.25 mg/day for 6 months [2]. Total hair density and hair diameter increased from 102 hair/cm^2 to 112.2 hair/cm^2 and 0.043–0.045 μm, respectively (Table 1). The common side effects were hirsutism, GI intolerance, hypotension, and weight gain. The study found no statistically significant disparity in efficacy between a daily oral dose of 0.25 mg minoxidil and the application of 1 mL of 2% topical minoxidil, indicating oral minoxidil is effective even at a minimal dose.

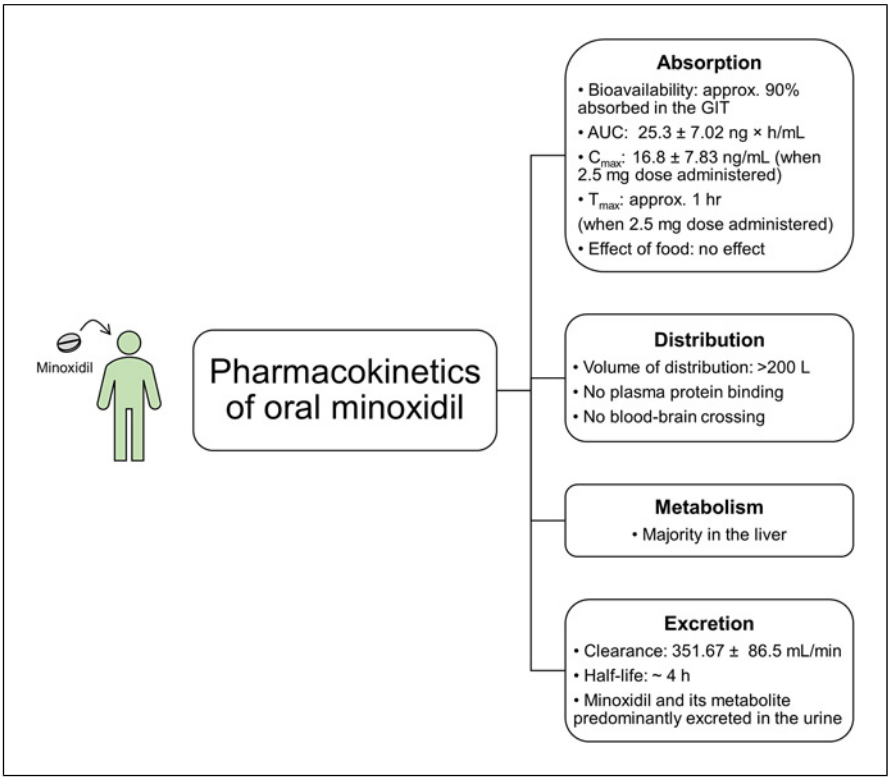

Fig. 2. Pharmacokinetics of oral minoxidil.

In a randomized, open-label, comparative study, 25 patients with FPHL received 1 mg/day of oral minoxidil for 24 weeks [3]. The results indicated a stronger trend toward improvement with oral minoxidil compared to the daily topical application of 1 mL of 5% minoxidil. Although the oral form showed promise, it did not demonstrate a statistically significant advantage over the topical preparation. After 24 weeks of treatment, both total hair count and terminal hair count showed an increase, from 164.6 and 106.5 hair/cm^2 to 184.7 and 112.6 hair/cm^2, respectively, in the group receiving oral minoxidil. Hypertrichosis was commonly reported side effect in the study, with 1 patient experiencing pedal edema (Table 1).

In a retrospective analysis conducted by Vasteralla and colleagues, 12 patients with FPHL were treated with 1.25 mg of minoxidil for 24 weeks [4]. The results showed an improvement in hair density by 38% in the frontal area and 23% in the vertex area after treatment (Table 1). Common side effects observed included hypertrichosis and pedal edema, with no instances of scalp pruritus. Apart from minoxidil as a standalone treatment, an observational pilot study conducted on 100 patients with FPHL revealed that once daily intake of capsules containing a combination of 0.25 mg of minoxidil and 25 mg of spironolactone proved to be both safe and effective for 12 months [36].

Male-Pattern Hair Loss

Various clinical trials have evaluated minoxidil doses ranging from 0.25 to 5 mg (Table 1). A retrospective trial of 25 male AGA patients who ingested 0.25 mg/day of minoxidil for 24 weeks revealed no substantial enhancement in total hair count and terminal hair count (Table 1) [5]. The authors speculated that a higher minoxidil dose might be necessary to generate noticeable outcomes in male patients. The frequently reported side effects in the study were the perception of increased beard density, hypertrichosis, hair shedding, and pedal edema. Patients did not experience any change in mean arterial pressure, fainting, or dizziness.

In a prospective, open-label, single-arm study, 30 patients with male AGA took 5 mg minoxidil once daily [6]. The results indicated a significant increase in total hair count in patients after 12 weeks and 24 weeks of treatment. The improvement in hair growth was more pronounced in the vertex region compared to the frontal region. The predominant side effect was

Table 1. Clinical trials indicating LDOM use for treating FPHL and male AGA

Study	Study design	Daily dose	Outcomes			Adverse effects	Comments
			total hair density, hair/cm^2	terminal hair density, hair/cm^2	hair diameter, μm		
FPHL Nascimento et al. [7], 2022	• Randomized, double-blind • 24 weeks • 26 patients randomized into two groups; group 1 (N = 14), group 2 (N = 12)	• 0.25 mg (group 1) • 1 mg (group 2)	**For group 1** **Baseline** 292.0±63.1¶¶ **At 24 weeks** 299.8±70.7¶¶ **For group 2** **Baseline** 272.2±46.6¶¶ **At 24 weeks** 304.0±39.0¶¶			Group 2 (1 mg/day): Hypertrichosis (2/12, 16.67%	LDOM 1 mg/day was safe and effective, and its efficacy was higher than LDOM 0.25 mg/day in a 24 weeks study
FPHL Vahabi-Amlashi et al. [2], 2021	• Pilot study, three-blinded, randomized • 6 months • N = 6 (PP analysis); 26 (ITT analysis)	0.25 mg	**Baseline** 102.0±50.76¶¶ **At 6 months** 112.2±68.4¶¶	NR	**Baseline** 0.043±0.001¶¶ **At 6 months** 0.045±0.001¶¶	Hypotension (1/26, 3.85%)[a] Hirsutism 2/26, 7.69%)[a] Weight gain (1/26, 3.85%)[a] GI intolerance (2/26, 7.69%)[a]	The efficacies of oral 0.25 mg/day and 1 mL of 2% topical minoxidil BID were statistically indifferent
FPHL Ramos, Sinclair et al. [3], 2020	• Randomized open-label, comparative study • 24 weeks • N = 25	1 mg	**Baseline** 164.6±48.1¶¶ **At 24 weeks** 184.7±57.1¶¶	**Baseline** 106.5±34.2¶¶ **At 24 weeks** 112.6±36.4¶¶	NR	Edema of limbs (1/25, 4.0%)[a] Hypertrichosis (7/25; 28.0%)[a]	Oral minoxidil showed a greater improvement trend compared to 1 mL of 5% topical minoxidil QD. However, oral minoxidil was not significantly superior to topical minoxidil
FPHL Vastarella et al. [4], 2020	• Retrospective analysis • 24 weeks • N = 12	1.25 mg	**Baseline (vertex)** 136.61±51.30¶¶ **At 24 weeks (vertex)** 168.92±58.59¶¶ **Baseline (frontal)** 131.47±36.11¶¶ **At 24 weeks (frontal)** 181.40±57.38¶¶	**Baseline (vertex)** 68.66±32.56¶¶ **At 24 weeks** 97.75±45.08¶¶ **Baseline (frontal)** 72.68±22.12¶¶ **At 24 weeks (frontal)** 108.53±43.17¶¶	**Baseline (vertex)** 0.04±0.01¶¶ **At 24 weeks (vertex)** 0.05±0.01¶¶ **Baseline (frontal)** 0.04±0.01¶¶ **At 24 weeks (frontal)** 0.05±0.01¶	Edema of limbs (3/12, 25.0%)[a] Hypertrichosis (3/12; 25.0%)[a] Scalp pruritus (0/12; 0.0%)[a]	Hair density in the frontal and vertex area improved by 38% and 23%, respectively

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Table 1 (continued)

Study	Study design	Daily dose	Outcomes			Adverse effects	Comments
			total hair density, hair/cm^2	terminal hair density, hair/cm^2	hair diameter, μm		
MPHL Pirmez and Salas-Callo [5], 2020	• Retrospective review • 24 weeks • *N* = 25	0.25 mg	**Baseline (vertex)** 184 (Median) **At 24 weeks (vertex)** 176 (Median) **Baseline (frontal)** 200 (Median) **At 24 weeks (frontal)** 194, median	**Baseline (vertex)** 114 (Median) **At 24 weeks (vertex)** 100 (Median) **Baseline (frontal)** 130 (Median) **At 24 weeks (frontal)** 115, median	NR	Hypertrichosis (5/25, 20.0%)[a] Perception of increased beard density (13/25, 52.0%)[a] Hair shedding (4/25,16%)[a] Pedal edema (1/25, 4.0%)[a] No reports of mean arterial pressure change, fainting or dizziness	At the 0.25 mg/day dose, no significant increase was observed in total and terminal hair counts
MPHL Panchaprateep and Lueangarun [6], 2020	• Prospective, open-label, single-arm study • 24 weeks • *N* = 30	5 mg	**Baseline** 182.5±43.3[¶¶] **At 12 weeks** 208.5±42.8[¶¶] **At 24 weeks** 217.6±44.9[¶¶]	**Baseline** 153±33[¶¶] **At 12 weeks** 178±38[¶¶] **At 24 weeks** 188.1±37[¶¶]	**Baseline** 58.5±11.8[¶¶] **At 12 weeks** 64.7±15.2[¶¶] **At 24 weeks** 67.4±4.5[¶¶]	Pedal edema (3/30, 10%) PVC (2/30, 6.67%) Fatigue (2/30, 6.67%) Tachycardial palpitation (1/30, 3.33%) Abnormal EKG findings (6/30, 20%) Hypertrichosis (28/30, 93.33%) Urticaria (1/30, 3.33%) Itchy rash (1/30, 3.33%)	• Total hair count from the baseline significantly increased after 12 weeks (mean change from baseline +26; $p = 0.007$) and 24 weeks (mean change from baseline +35.1; $p = 0.007$) • Hair growth improvement was more prominent in the vertex area compared to the frontal area

BID, twice daily; EKG, electrocardiogram; FPHL, female-pattern hair loss; GI, gastrointestinal; ITT, intention-to-treat; LDOM, low-dose oral minoxidil; MPHL, male-pattern hair loss; NR, not reported; N, number of patients; PP, per protocol; PVC, premature ventricular contraction; QD, once daily. [¶¶]Standard deviation. [a]The numerator indicates the number of participants who experienced the adverse effect, and the denominator represents the total number of participants. The data are also presented as percentages.

Table 2. Clinical trials indicating LDOM use for treating alopecia other than FPHL and male AGA

Study	Study design	Daily minoxidil dose	Outcomes	Adverse effects	Comments
Alopecia areata Wambier et al. [8], 2021	• Prospective • At least 6 months • *N* = 12 (5 males and 7 females) • Male: tofacitinib 5 mg BID plus oral minoxidil 2.5 mg BID • Female: tofacitinib 5 mg BID plus oral minoxidil 2.5 mg QD	Male: 5 mg (2.5 mg BID) Female: 2.5 mg (2.5 mg QD)	• 67% (8/12) achieved ≥75% scalp hair regrowth • 33% (4/12) achieved 11–74% scalp hair regrowth	Hypertrichosis (6/12, 50.0%)[a] Acne (2/12, 16.67%)[a]	Tofacitinib plus oral minoxidil could be more efficacious than tofacitinib monotherapy
Alopecia areata Fiedler-Weiss et al. [9], 1987	• Prospective • Mean duration, 53 weeks (range, 10–115) • *N* = 65 (27 males and 38 females) • Mean age: 31 years (range, 13–55)	5 mg oral minoxidil BID	• 80% (52/65) of patients showed a positive response • 18% (12/65) of patients experienced a cosmetically effective response	Facial hypertrichosis (11/65, 17%)[a]	
Chronic telogen effluvium Perera et al. [10], 2017	• Retrospective • 12 months • *N* = 36 females • Mean age: 46.9 years (range, 20–83)	0.25–2.5 mg (majority of patients took 1 mg)	• At 6 months, mean HSS improved by 1.7 ($p < 0.001$) • At 12 months, mean HSS improved by 2.58 ($p < 0.001$)	Facial hypertrichosis (14/36, 38.9%)[a] Postural dizziness (2/36, 5.6%)[a] Ankle edema (1/36, 2.7%)[a]	
LAHS Cranwell and Sinclair [11], 2018	• Case report • 12 months • *N* = 1 female • Age: 11 years	0.5 mg	• Patient experienced improved shedding and hair density within 3 months • Hair color changed from reddish-brown to light brown		No recurrence of LAHS after minoxidil discontinuation
LAHS Jerjen et al. [37], 2020	• Retrospective review of patient records • 7–26 months • *N* = 8 females • Age: 2–10 years	0.10–0.50 mg	• Hair length increased in all patients • Global hair density improved in 7 of 8 patients • Hair color changed from reddish/dark brown to light brown	Hypertrichosis (1/8, 12.5%)[a]	

Table 2 (continued)

Study	Study design	Daily minoxidil dose	Outcomes	Adverse effects	Comments
Monilethrix Sinclair [12], 2016	• Case series • *N* = 2 females • Patient 1: 24 months; patient 2: 18 months • Age: patient 1 (40 years); patient 2 (35 years)	Patient 1: 0.25 mg Patient 2: 0.25 mg for first 3 months, followed by 0.5 mg	• Patient 1: experienced significant hair regrowth at 6 months. Hair volume and length also increased with reduced breakage • Patient 2: hair shedding decreased after 3 months. Hair density increased significantly after increasing the dose to 0.5 mg at 6 months	None	
Lichen planopilaris Vano-Galvan et al. [13], 2021	• Retrospective • Mean treatment duration: 21 months • *N* = 51 (15 males and 36 females)	Median daily dose 1 mg (male: 2.5 mg; female: 0.5 mg)	Out of 51 patients, 20 patients (39%) experienced improved hair thickness; it remained unchanged in 27 patients (53%), and deteriorated in the remaining 4 patients (8%)	Hyperttichosis (14/51, 27.5%)[a] Postural hypotension (3/51, 5.9%)[a] Tachycardia (2/51, 3.9%)[a] Weight gain (1/51, 2.0%)[a]	• Patients who took higher minoxidil dose were more likely to have improvement • Patients with diffuse LLP exhibited better response compared to patchy LPP
Permanent Chemotherapy-induced alopecia Yang and Thai [14], 2016	• Case report • 1 year • *N* = 1 female	1 mg	Patient experienced cosmetically significant hair regrowth	None	

BID, twice daily; EKG, electrocardiogram; FPHL, female-pattern hair loss; GI, gastrointestinal; HSS, hair shedding score; IQR, interquartile range (quartile 1 – quartile 3); ITT, intention-to-treat; LDOM, low-dose oral minoxidil; Max, maximum; Min, minimum; MPHL, male-pattern hair loss; N, number of patients; NR, not reported; PP, per protocol; PVC, premature ventricular contraction; QD, once daily; LAHS, loose anagen hair syndrome. [a]The numerator indicates the number of participants who experienced the adverse effect, and the denominator represents the total number of participants. The data are also presented as percentages.

hypertrichosis, followed by abnormal electrocardiogram findings, pedal edema, premature ventricular contraction, fatigue, tachycardial palpitation, urticaria, and an itchy rash.

Alopecia Areata

In a prospective study, 65 patients with severe alopecia areata (27 males and 38 females) took 5 mg minoxidil twice daily for a mean duration of 53 weeks, ranging from 20 to 115 weeks (Table 2) [8–14]. Of 65 patients, 52 (80%) showed some level of response to the therapy, ranging from slight to fair or cosmetically effective, with only 12 (18.5%) exhibiting a cosmetically effective response [9]. A cosmetically effective response meant the patient no longer required a wig or cap to cover any residual alopecia. Of the 12 patients who had a cosmetically effective response, 8 had less than 75% hair loss at baseline, and 4 had ≥75% hair loss at baseline.

A prospective study identified 12 patients (5 males and 7 females) with severe alopecia areata who received treatment with a combination of tofacitinib and oral minoxidil for a minimum of 6 months (Table 2) [8]. The male patients took tofacitinib 5 mg twice daily, with 2.5 mg of oral minoxidil twice a day. The females, on the other hand,

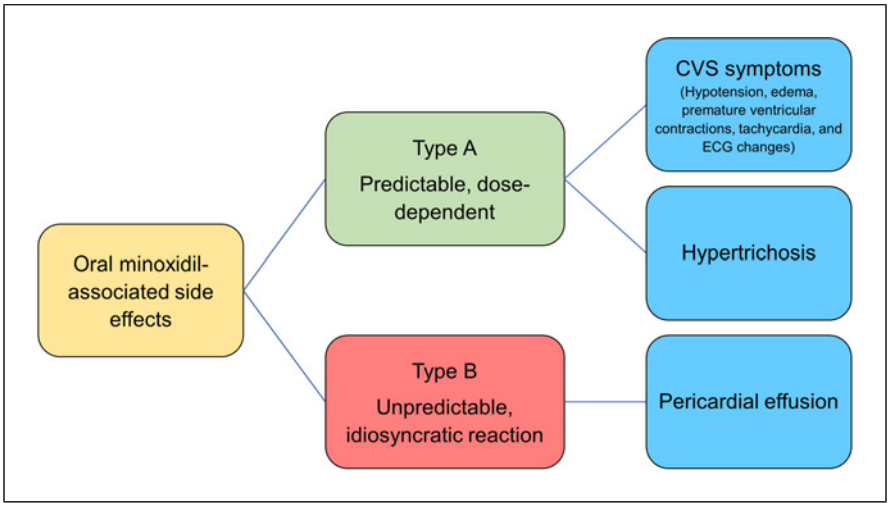

Fig. 3. Classification of side effects of LDOM.

took tofacitinib 5 mg twice daily plus oral minoxidil 2.5 mg once a day. Of the 12 patients, 8 experienced at least 75% regrowth of scalp hair, while the remaining 4 showed 11%–74% regrowth. The common side effects were hypertrichosis (6 of 12, 50.0%) and acne (2 of 12, 16.67%). Oral and sublingual dosage forms of minoxidil have also been shown to be safe and effective maintenance treatments in patients with alopecia areata [38].

Chronic Telogen Effluvium

In a retrospective study, 36 females with chronic telogen effluvium took oral minoxidil ranging from 0.25 to 2.5 mg daily for 6 months (Table 2) [10]. The majority (19 of 36 subjects) took 1 mg daily, 5 took 0.25 mg daily, four took 0.5 mg daily, and eight took 2.5 mg daily. The age of female participants in the retrospective study ranged from 20 to 83 years, with a mean age of 46.9 years.

After the treatment, the mean hair-shedding score (HSS) improved significantly in 31 subjects. The mean improvement in HSS was 1.7 at 6 months and 2.58 at 12 months from the baseline [10]. Fourteen subjects experienced facial hypertrichosis – six did not need any treatment, four performed waxing, and three opted for laser treatment. Additionally, two subjects experienced self-resolving transient postural dizziness, and one had ankle edema.

Hair Shaft Disorders

Loose Anagen Syndrome

Cranwell and Sinclair documented a case of an 11-year-old girl with loose anagen hair syndrome (LAHS) who was treated with daily oral minoxidil at a dose of 0.5 mg for 12 months (Table 2) [11]. Within 3 months, hair shedding improved, and the hair color transformed from reddish-brown to light brown. After 12 months of treatment, the patient's hair density and length were consistent with what would be expected for her age. Furthermore, there was no recurrence of LAHS after minoxidil therapy was discontinued.

A retrospective review of 8 young patients with LAHS (7 years of median age) found that oral minoxidil ranging from 0.10 to 0.50 mg as a daily dose could be a promising treatment [37]. Hair length increased in all patients, and 7 of 8 patients experienced improved global hair density.

Monilethrix

A case series reported 2 female patients with monilethrix who received 0.25 mg of oral minoxidil daily (Table 2) [12]. The patients were 40 and 35 years old. The first patient observed significant hair regrowth at 6 months. Hair volume and length also increased, and hair breakage was reduced. For the second patient, hair shedding improved after 3 months of treatment, but hair density did not change. When the dose was increased to 0.5 mg minoxidil daily, the patient's hair density improved. No side effects were reported in the first and second patients after 2 years and 18 months of additional follow-ups, respectively.

Lichen Planopilaris

Fifty-one patients (15 males and 36 females) with lichen planopilaris received oral minoxidil at a median dose of 1 mg (0.5 mg for females and 2.5 mg for males) (Table 2) [39]. The average treatment duration was 21 months, ranging from 6 to 87 months. Of 51 patients, 20 (39%) reported improved hair thickness, while 27 (53%) reported no change, and 4 patients (8%) observed a decrease in hair thickness after treatment. Hair counts were not reported.

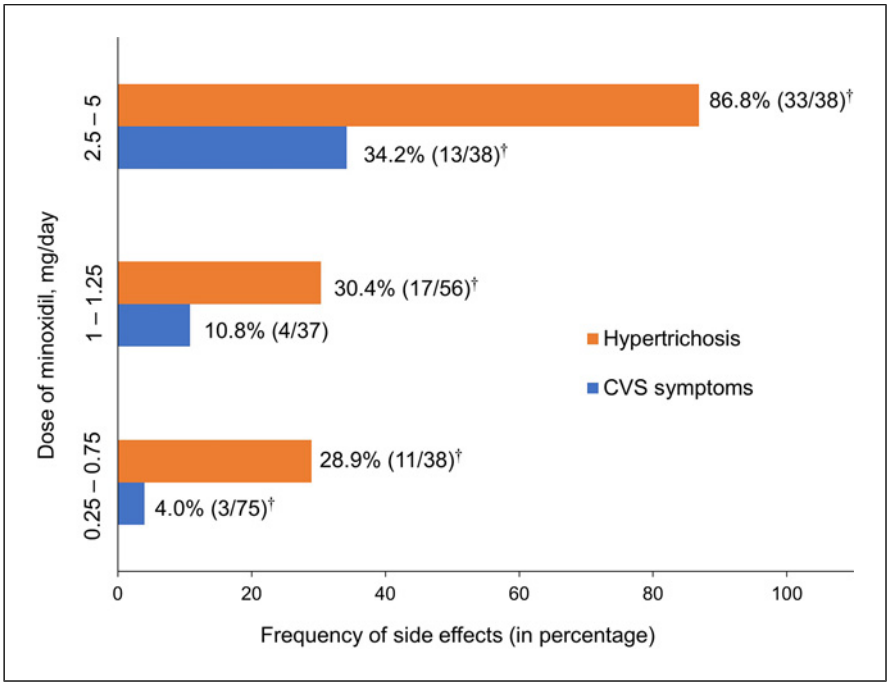

Fig. 4. Oral minoxidil-associated CVS symptoms and hypertrichosis seem to be dose-dependent. CVS symptoms included hypotension, edema, premature ventricular contractions, fatigue, tachycardia, and ECG changes. †The numerator indicates the patient number experiencing the side effect, and the denominator indicates the total number of participants in clinical studies.

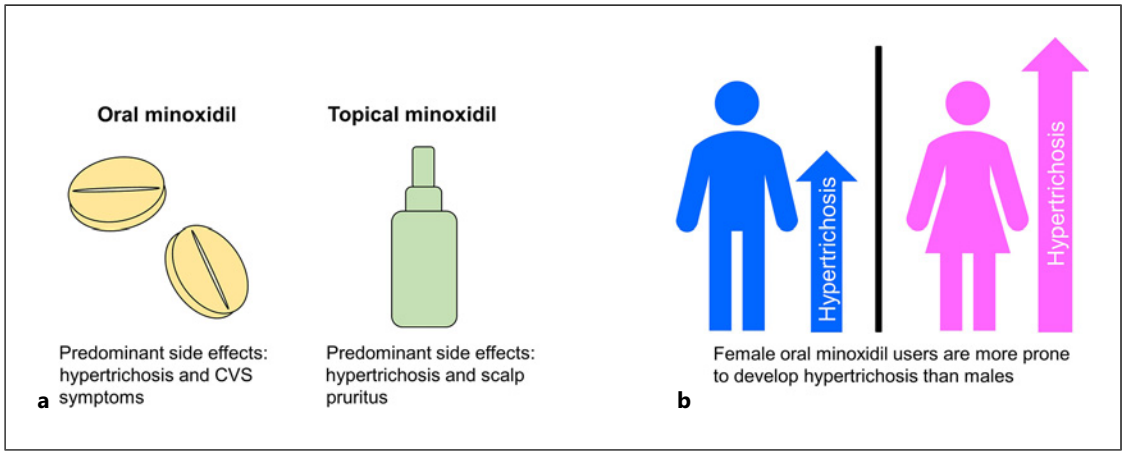

Fig. 5. a Distinction in side effects between oral and topical minoxidil. **b** Hypertrichosis is more prone in female oral minoxidil users.

Chemotherapy-Induced Alopecia (Anagen Effluvium)

Yang and co-workers reported a case of a 39-year-old female Caucasian patient with acute myeloid leukemia who experienced chemotherapy-induced hair loss (Table 2) [14]. The patient took minoxidil 1 mg/day along with other antiandrogens to treat her hair loss. After 1 year of treatment, the patient observed an improvement in hair count and an increase in hair length. The patient did not report any change in blood pressure or hypertrichosis; the therapy was well tolerated with no reported side effects.

Side Effects of LDOM

LDOM-associated side effects can be categorized into two groups: predictable, dose-dependent side effects (type A) and unpredictable, idiosyncratic reactions (type B)

Table 3. Recommended dosage regimen, monitoring guidelines, contraindication, warnings, and management of side effects LDOM in treating male and female AGA [33, 47–49]

	Expert opinion-1 (AS)	Expert opinion-2 (BMP)	Expert opinion-3 (AT)
Recommended dosage regimen	• Male AGA patients: start minoxidil at 1 mg/day for 2–3 months, then gradually increase the dose by 0.5 mg every 2–3 months until it reaches a maximum daily dose of 5 mg	• Male AGA patients: start minoxidil at 2 mg/day. Depending upon response, increase to 2.5–3 mg/day at 6 months	• Male AGA patients: start minoxidil at 1.25 mg/day for 6 months, then increase the dose to 2.5 mg/day
	• Female AGA patients: start minoxidil dose at 0.5 mg/day for 2–3 months, then gradually increase the dose by 0.5 mg every 2–3 months until it reaches a maximum daily dose of 5 mg	• Female AGA patients: start at 1 mg/day. Depending upon response, increase to 1.5–2 mg/day in post-menopausal patients at 6 months	• Female AGA patients: start minoxidil dose at 0.625 mg/day for 6 months, then increase to 1.25 mg/day
	• If the patient's BP is either borderline or unstable, continue the starting dose for 3 months, and the dose can be gradually increased at 3-month intervals	• If the patient is already on an antihypertensive, BP is borderline or unstable, monitor BP every week for 1 month	• Monitor BP in patients taking other antihypertensive drugs and adjust if necessary. In patients complaining of low blood pressure, administer at night together with licorice gum
	• Patients may continue to take oral minoxidil long term if the results are satisfactory and there are no major side effects	• During summer months: take electrolyte-containing beverages (potassium and magnesium) • Take minoxidil before bedtime to decrease the risk of orthostatic hypotension • Patients may continue to take oral minoxidil long term if the results are satisfactory and there are no major side effects	• Treatment can be continued in the long term. LDOM is usually well-tolerated
Monitoring guidelines	• Monitor BP every day for the first week, then once a week for a month, then once a month. If the patient is on other antihypertensive medications, monitor BP more often	• Monitor only if symptomatic of hypotension; otherwise, no regular monitoring	• Usually not recommended. Monitor only in case of patients taking antihypertensive medications at the start of treatment or if the patient complains of symptoms
	• CBC, LFT, and RFT at baseline, after 1 month of starting minoxidil therapy, then every 2–3 months	• CBC, LFT, and RFT are not required to perform routinely	
Contraindication			• Heart rhythm disorders • Kidney diseases • Pheochromocytoma • Pregnancy • Not recommended for women with a history of laser epilation because of hypertrichosis/hirsutism

Table 3 (continued)

	Expert opinion-1 (AS)	Expert opinion-2 (BMP)	Expert opinion-3 (AT)
Warnings and precautions	• Oral minoxidil: not recommended in alopecia patients with low BP (e.g., BP reading of 100/60 mm Hg)	• Oral minoxidil: not recommended in alopecia patients with low BP	• Consult a cardiologist before prescribing LDOM to a patient with a history of heart disorders, particularly in the elderly
Management of side effects	• Hypertrichosis: more frequent in females than males Females: gradually reduce the dose by 0.5–1 mg/day each time until the side effect disappears	• Hypertrichosis: more frequent in females than males Females (light-skinned): generally, not bothersome Females (dark-skinned): suggest topical eflornithine cream application or use of depilatory cream or may require epilation; may need to decrease dosage by 0.5 mg/day	• Hypertrichosis: dose-dependent Young men can be very bothered as many of them now remove hair in the trunk Recommend eflornithine cream when localized in the face in women, decrease dose waxing or epilation. Bicalutamide perhaps does not improve hypertrichosis due to minoxidil
		• Palpitations/tachycardia: if it occurs, it generally appears during the first 2–3 months; may need to discontinue minoxidil	• Discontinue minoxidil and see a cardiologist in case of any cardiac side effects
	• Peripheral edema: in case of peripheral edema, treatment should be stopped	• Peripheral edema: more frequent in females; first try spironolactone 25 mg/day; if there is no relief, then discontinue minoxidil	Mild ankle edema: add spironolactone 25 mg/day. Reduce the dose if it improves Severe edema: stop treatment and see a cardiologist
Minoxidil discontinuation	• Patients are expected to see results within the first 3–4 months of oral minoxidil therapy; however, if no positive outcome appears after 6–8 months, discontinue therapy	• If the outcome is not satisfactory (clinically and trichoscopy) after 1 year, discontinue therapy	• Discontinue therapy in case of side effects. Otherwise, LDOM therapy may continue

AS, Avner Shemer; AT, Antonella Tosti; BMP, Bianca Maria Piraccini; BP, blood pressure; CBC, complete blood count; LFT, liver function tests; LDOM, low-dose oral minoxidil; RFT, renal function tests. Disclaimer: Table 3 is for general information only and does not constitute professional advice. Please consult the relevant up-to-date guidelines, package inserts, and authoritative texts before making a clinical decision.

(Fig. 3). Hypertrichosis and CVS symptoms are the two predominant side effects of LDOM when used to treat alopecia. CVS symptoms refer to a group of side effects that include hypotension, edema, premature ventricular contractions, fatigue, tachycardia, and ECG changes [2–6, 9, 10]. Very few patients have been reported to develop type B idiosyncratic reactions: pericardial effusion and generalized anasarca [40–44].

Type A Side Effect: Hypertrichosis and CVS Symptoms

Clinical trial data suggest that the incidence of hypertrichosis rises with increasing dose of minoxidil. Specifically, 28.9% of patients taking 0.25–0.75 mg minoxidil/day developed hypertrichosis. This increased to 30.4% among patients taking 1–1.25 mg/day and reached 86.8% in patients taking 2.5–5 mg/day (Fig. 4) [2–6, 9, 10]. A retrospective analysis involving 35 patients with FPHL demonstrated that a daily mean dose of 14.4 mg of bicalutamide, a nonsteroidal androgen receptor inhibitor, could potentially mitigate minoxidil-induced hypertrichosis [45]. The study also suggested that clinicians could potentially raise the mean dose of minoxidil by 0.7 mg/day without encountering additional hypertrichosis.

A similar dose-dependent trend was also observed for CVS symptoms, although cardiovascular side effects were

less prevalent than hypertrichosis. At 0.25–0.75 mg minoxidil/day, 4.0% of patients experienced CVS symptoms, which increased to 10.8% at 1–1.25 mg/day and 34.2% at 2.5–5 mg/day, respectively (Fig. 4) [2–6, 9, 10].

A separate prospective study evaluated the cardiovascular health of 34 male AGA patients who were treated with 5 mg minoxidil daily for 24 weeks [46]. During the follow-up, 20.6% of the patients (7/34) experienced headache, 2.9% (1/34) experienced vertigo, and another 2.9% (1/34) had edema [46]. Four patients discontinued the study, with 2 leaving due to headache, 1 due to swelling in the legs and face, and 1 dropping out for reasons unrelated to the therapy. The rest, 30 patients, underwent 24-h Holter monitoring and 24-h ambulatory blood pressure monitoring at baseline and 24 weeks. The results revealed a minor drop in blood pressure, but it did not reach the level for clinical diagnosis of hypotension – indicating oral 5-mg per day minoxidil did not cause clinical hypotension in participants [46]. Authors of the study also opined that tachycardia might be a rare and early side effect of LDOM, with only 1 patient reporting it [46].

While both oral and topical minoxidil can lead to hypertrichosis, CVS symptoms are rarely reported among topical minoxidil users [15]. Instead, scalp pruritus emerges as a predominant side effect in this user group (Fig. 5a) [15]. A recent article suggested that females were more prone to develop hypertrichosis (31.4%) compared to males (23.7%) when taking less than 2.5 mg minoxidil orally per day (Fig. 5b) [15]. A multicenter study conducted on 1,404 patients reported a similar finding – 20.1% of female participants experienced hypertrichosis at a median minoxidil dose of 1.11 mg/day (0.03–12.5), whereas 5.8% of male participants reported hypertrichosis at a relatively higher median dose, 2.60 mg/day (0.15–15) [13]. The study also found that systemic side effects (lightheadedness, leg edema, tachycardia, headache, insomnia) were slightly higher in females (6.1%) than in males (4.3%) [13].

Type B Side Effect: Pericardial Effusion

LDOM-associated pericardial effusion may be idiosyncratic; patients rarely experience the side effect [44]. The antihypertensive dose of oral minoxidil is 10 mg–40 mg, at which only approximately 3% of patients experience pericardial effusion [42]. While it is not possible to establish a definitive relationship, there may be a higher risk of pericardial effusion development among renally impaired patients undergoing dialysis [40, 42].

Reichgott reported 91 episodes of pericardial disease in 1,869 subjects (4.8%), including pericardial tamponade and 8 associated deaths (0.43%) [44]. Causality has been confirmed in a very small number of subjects. Reichgott indicates that the development of pericardial effusion is not dose-related or related to the duration of therapy. Two contributory facts may be impaired renal function and volume retention.

On the other hand, Martin and colleagues associated with the Upjohn Company in Kalamazoo, MI, USA, write that the data do not implicate minoxidil to be a cause of pericardial disorders [42]. Martin indicates that in minoxidil-treated patients, the pericardial fluid is not a toxic effect of minoxidil; however, the effusions may be related to the hemodynamic effects of the drug, especially positive sodium and water retention [42]. The mechanism of pericardial fluid accumulation or hydropericardium remains uncertain.

Recommendations on LDOM Use

Table 3 displays the dosage regimens of oral minoxidil recommended by some authors for treating FPHL and male AGA [33, 47–49]. Since the use of oral minoxidil for treating AGA lacks FDA approval, the recommended dosage regimens show variability.

Notably, the efficacy and side effects of LDOM for treating AGA appear to be dose-dependent [50, 51]. A meta-regression analysis of clinical trials found that increasing the daily dose of oral minoxidil by 1 mg in AGA patients led to an increase in total hair density of 47.1 hairs/cm^2 (p = 0.0071) and an increase in terminal hair density of 9.1 hairs/cm^2 (p = 0.0014), as well as a rise of 1.4 μm in hair thickness (p = 0.013), after 24 weeks [50]. However, the study also found that a minoxidil dose increase by 1 mg may lead to a higher chance of hypertrichosis and cardiovascular side effects. The risk of hypertrichosis rose by 17.6% (p = 0.0057), and the risk of cardiovascular side effects increased by 4.8% (p = 0.00382), after 24 weeks [50].

LDOM Use in Pregnancy and Breastfeeding

Minoxidil falls under pregnancy category C and may cause neonatal hypertrichosis if taken during pregnancy [1, 33]. The drug may be secreted in breast milk and potentially pose a risk to a nursing infant. Therefore, LDOM use is not recommended for pregnant women and breastfeeding mothers [1, 15, 33]. Besides, there is no

definitive safety information available on LDOM use by males whose female partners are pregnant [1]. On the other hand, topical minoxidil is generally considered to be a safer option. However, Rogers and Avram recommended a cautious approach by advising against its use during pregnancy and breastfeeding [15, 52].

LDOM Use in Pediatric Patients

Only a few trials are available that have explored LDOM use in pediatric patients. For example, a descriptive study involving 45 patients with AGA or telogen effluvium, with a mean age of 16 years (range: 10–17 years), found promising results when using LDOM [53]. The boys had a higher mean daily minoxidil dose (2.35 mg/day; range: 0.5–5 mg/day) than the girls (0.63 mg/day; range: 0.14–2.5 mg/day) [53]. Besides, a 2-year-old boy accidentally took 100 mg of oral minoxidil – after a short episode of reflex tachycardia, he completely recovered [54]. Furthermore, two other studies also confirmed the safety and efficacy of LDOM in young patients with alopecia [55, 56]. Nonetheless, further studies are required to establish the safety and efficacy of LDOM use in pediatric patients [47].

Conclusion

Oral minoxidil could be a potential alternative for the treatment of various types of alopecia, particularly for male AGA and FPHL patients who have not obtained satisfactory outcomes with topical minoxidil. Even though the FDA has not yet approved oral minoxidil, many clinics use it off-label to treat AGA [57]. Further clinical experience will confirm the safety, effectiveness, and management guidelines of oral minoxidil.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Authors Contributions

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