

Low-Level Light Therapy and Minoxidil Combination Treatment in Androgenetic Alopecia: A Review of the Literature

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Keywords

Alopecia · Minoxidil · Low-level light therapy · Androgenetic alopecia

Abstract

Introduction: We analyzed randomized clinical trials (RCTs) evaluating the efficacy of combined therapy with low-level light therapy (LLLT) and topical minoxidil for treatment of androgenetic alopecia (AGA). **Methods:** A literature search within PubMed identified RCTs evaluating hair regrowth following LLLT and minoxidil. Selection criteria were 600–1,100 nm wavelengths, treatment time ≥ 16 weeks, and objective evaluation for hair regrowth. **Results:** Five RCTs compared LLLT with minoxidil (2% or 5%) to 5% minoxidil treatment or LLLT treatment. One study showed combination therapy of LLLT, and 5% minoxidil improved hair density more than monotherapy. Another found combination LLLT with 2% minoxidil induced hair regrowth equivalent to 5% minoxidil. Similarly, another study described LLLT with 5% minoxidil versus minoxidil monotherapy to increase the number of hairs with no statistical difference between groups. One trial found that combination group increased hair regrowth in the first 2 months. The last study found a statistically signifi-

cant increase in hair density with combined therapy compared to monotherapy. **Conclusion:** The studies describe either superiority or equivalence of combination therapy to minoxidil monotherapy for AGA. Early outcomes appear to support the superiority of combination therapy, but this advantage wanes at the end of the study periods.

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Introduction

Traditional treatments for androgenetic alopecia (AGA) have been based on finasteride and minoxidil, which are the only two FDA-approved medications. Finasteride inhibits the type II 5 α -reductase, and daily oral intake of 1 mg finasteride has been shown to reduce systemic levels of DHT and increase hair counts in AGA [1]. Dutasteride, which inhibits both types I and II 5 α -reductase, is also effective but has not yet undergone FDA approval [2]. Minoxidil is a topical and oral treatment for AGA, and its exact mechanism is postulated to be centered around its ability to open ATP-gated potassium channels in cell membranes leading to vasodilation, progression to the G1 stage of the cell cycle, cellular prolif-

eration, and ultimately hair growth [3–5]. Minoxidil is converted to its active component minoxidil sulfate through a sulfotransferase located within hair follicles. Topical minoxidil has been shown to reduce the length of the anagen phase and extend the length of the telogen phase [6]. Evidence of hair growth following topical minoxidil therapy has been shown to occur within six to 8 weeks, and has been hypothesized to be from minoxidil facilitating the conversion of follicles in the latent telogen phase to enter into anagen phase [6]. Studies have shown that minoxidil prolongs the anagen phase in the dermal papilla through upregulating β -catenin and stimulating follicular proliferation and differentiation [7]. Topical minoxidil has been associated with adverse effects including allergic contact dermatitis, hypertrichosis, and irritation [8]. Both interventions require long-term therapy but yield diminishing improvement in hair growth and are associated with long-term side effects. A 5-year follow-up study examining minoxidil treatment in men with AGA found that hair growth peaked at 1 year followed by a slow decline in hair growth [9]. Given the limited efficacy of long-term minoxidil use as well as adverse effects that render long-term compliance difficulty, alternative therapies that offer a more favorable side effect profile are the subject of ongoing clinical research. Potential therapies that offer synergistic results with existing therapies such as minoxidil could also prove useful.

Low-level light therapy (LLLT) is a relatively recent development for the treatment of AGA. LLLT, defined by a wavelength range of 600–1,100 nm, is a simple way of treating hair loss which can be done from home and has a better side effect profile. It is hypothesized that LLLT improves hair growth by stimulating anagen phase reentry in telogen hair follicles, prolonging the duration of anagen phase, and preventing premature entry of anagen hairs to catagen phase [4, 10, 11]. Additionally, it has been shown that LLLT plays an important role in reducing inflammatory cytokines while promoting favorable growth factors for hair growth [12].

While the individual effects of topical minoxidil and LLLT have been examined in previous studies, the focus of this review will be to discuss some of the newest results with combined topical minoxidil and LLLT compared to monotherapy alone. Given that both minoxidil and LLLT act through different mechanisms, evaluating the two treatments together to assess for possible synergy or improved efficacy in patients with AGA could be valuable.

Methods and Materials

Literature Search

A systematic review of the literature from 2015 to 2022 was performed in January 2022 using the PubMed, Embase, and Medline databases (Fig. 1). Double-blinded randomized controlled studies that assess the use of LLLT and topical minoxidil in combination to treat AGA were included. The databases were searched using different combinations of the following keywords: low level laser therapy, androgenetic alopecia, minoxidil, hair loss, hair regrowth, low level light therapy, and combined therapy.

Inclusion and Exclusion Criteria

All search results from both databases were reviewed for relevant studies. Full text of relevant studies was reviewed to determine appropriateness according to established inclusion criteria. Case reports and case series were excluded. Articles were recognized as appropriate when they (a) included human subjects, (b) used a wavelength between 600 and 1,100 nm, (c) had a control group, (d) used an objective measure for hair regrowth, and (e) involved a 16-week or greater randomized double-blinded control trial. Studies that were published but violated any of these criteria, particularly the wavelength parameters previously set forth, were not evaluated in this review.

Results

In total, 5 randomized control trials met our inclusion criteria comparing LLLT with topical 5% or 2% minoxidil to either a control group with no treatment, 5% minoxidil only treatment group, or LLLT only group (Table 1). Study populations varied with two studies using only men, two studies using only women, and one study using both men and women.

Esmat et al. [13] conducted a randomized, double-blind, control trial examining 45 adult female patients with confirmed diagnosis of FPHL. Patients were divided randomly into 3 treatment groups receiving the iGrow helmet (wavelength of 650–675 nm), a combination of both 5% minoxidil daily and LLLT for 3 days weekly, or topical minoxidil 5% for 4 months. At 2 months, statistically significant increase in the number of hair follicles was only seen in the combined group, while the other two groups showed nonsignificant findings. At 4 months, the combined group and the LLLT treatment groups both showed a statistically significant increase in the number of follicles, with the combined group showing the greatest increase. According to self-reported patient satisfaction scoring, the combined LLLT and minoxidil treatment group reported the highest personal satisfaction with the results ($p = 0.027$).

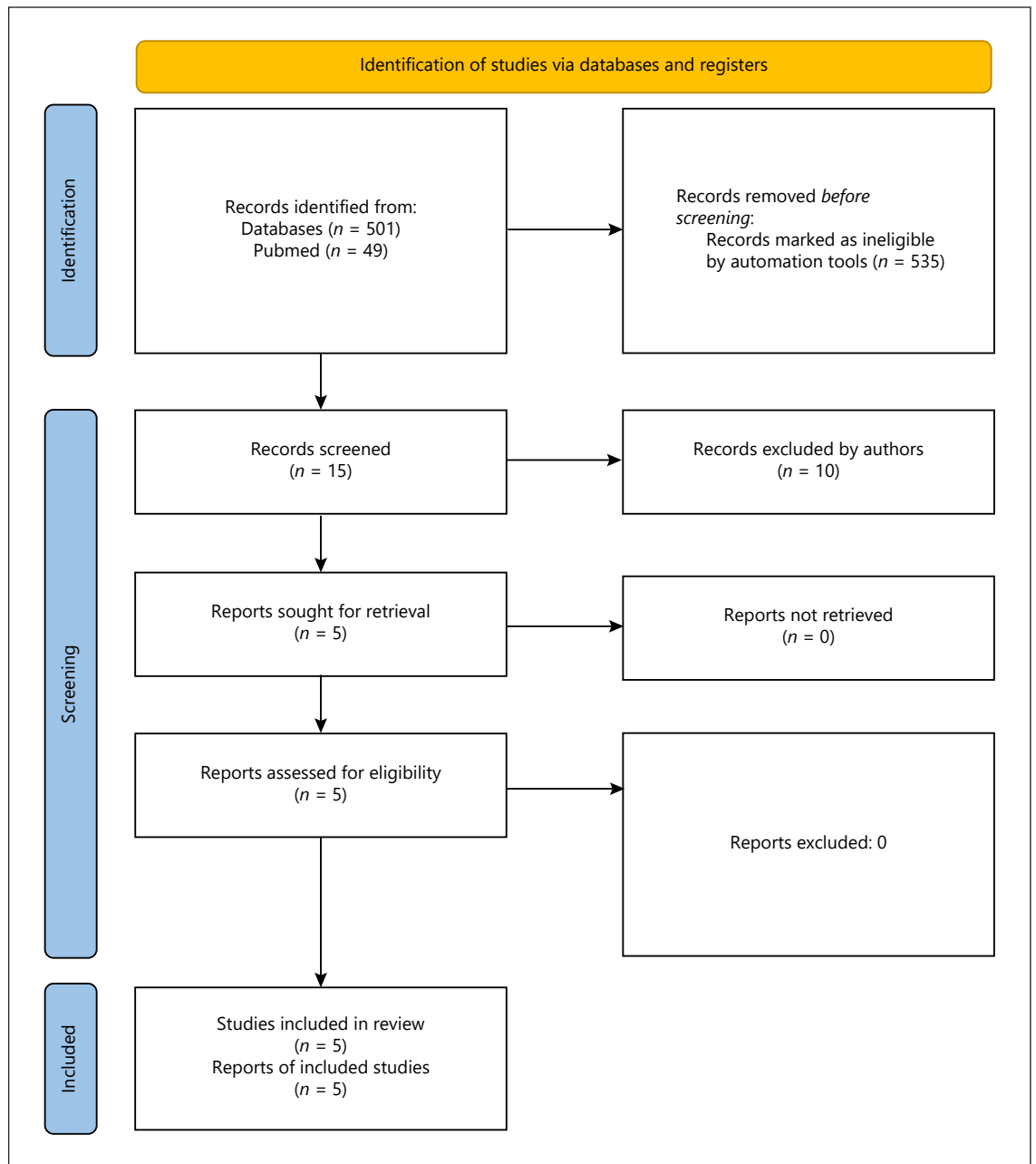


Fig. 1. Identification of appropriate studies for analysis. Flowchart depicting the exclusion processes for the identification of studies that are included in this review.

Liu et al. [14] conducted a randomized, double-blind, controlled trial examining 90 women with FPHL. Patients were randomly divided into three groups: one group received LLLT using the iHelmet device (650 nm), one group used topical 5% minoxidil daily, and the final group received both topical 5% minoxidil and LLLT. Hair density and hair thickness were evaluated using standard-

ized phototrichograms recorded at baseline, 3 months, and 6 months. Hair density was found to be significantly increased in the combination group compared to the minoxidil only group ($p = 0.036$) and the LLLT only group ($p = 0.012$). Hair diameter was also found to be increased in the combined group compared to the minoxidil group ($p = 0.036$) and LLLT group ($p = 0.048$). There was no

Table 1. Summary of studies examining the efficacy of combined therapy versus monotherapy

Reference	Patient population	Experimental groups	Assessment	Results
Ferrara 2021 [16]	21 men with AGA	12 min of LLLT followed by topical minoxidil application (1 mL of 5% solution), to the affected scalp two times per day for 6 months. LLLT devices were modified such that the left half emitted light, and the right half did not	Efficacy assessed by blinded analyses of clinical photos and automated phototrichograms (TrichoScan) taken before treatment and after 3 and 6 months of treatment	In combined treatment group, the number of total hairs was significantly increased after 3 ($p < 0.001$) and 6 months ($p = 0.001$) An increase was observed on the minoxidil-only side, at both 3 ($p < 0.001$) and 6 months ($p < 0.001$) No statistically significant differences were detected between sides ($p > 0.05$)
Mahe 2021 [17]	135 volunteers with alopecia	Group A: 45 patients received full-head exposure of 0.1 J/cm ² once per day for 70 s and used minoxidil 2% twice daily for 5 straight days per week for 6 months Group B: 45 used minoxidil 5% twice daily for 5 consecutive days per week for 6 months Group C: 22 patients who received no treatment	Change in hair density measured by Tiff counting method Tiff counting method: phototrichogram photograph from pre-shaved area of the scalp of 1 cm ² New photographs are taken of the same precisely delineated area after 1.5, 3, 4, and 6 months of treatment	Similar increase in hair density in the combined treatment group and the 5% minoxidil treatment group compared to control At 6 months, the rate of increase in hair growth began to decrease in the 5% minoxidil group but was sustained in the combination group
Liu 2021 [14]	Ninety women (age between 18 and 60 years old) with FPHL	Group A: 30 patients received a 30-min laser helmet treatment with iHelmet device (650 nm) at home every other day for 6 months Group B: 30 patients used 5% minoxidil twice daily for 6 months Group C: 30 patients received a combination of both 5% minoxidil twice daily and iHelmet device (650 nm) 30 min every other day for 6 months	Hair density (n/cm ²) and hair thickness evaluated by standardized phototrichograms recorded at baseline, 3 and 6 months The levels of scalp oil secretion assessed by TrichoScan digital image analysis conducted at baseline and 6 months Global macroscopic photographs taken at baseline and 6 months were assessed by 3 blinded experts	Hair microscopy and global photographs showed hair density and hair diameter of the three groups were significantly improved ($p < 0.05$) Sebum secretion significantly decreased in group A (LLLT) and group C (minoxidil and LLLT combination groups), but not in group B (minoxidil) Hair density: improvement of hair density in the combined group was higher than that in minoxidil group ($p = 0.036$) and LLLT group ($p = 0.012$) Minoxidil group improved hair density to a higher degree than the LLLT group; difference was not statistically significant (0.409)
Esmat 2017 [13]	45 female patients with FPHL randomly divided into three equal groups	Group A: 15 patients applied topical minoxidil 5% twice daily Group B: 15 patients received LLLT using the iGrow helmet device for 25 min 3 days weekly Group C: 15 patients received a combination of both topical minoxidil 5% twice daily and LLLT for 25 min 3 days weekly for 4 months	Evaluation was done according to clinical, dermoscopic, and UBM parameters	The combination (group C) was best regarding Ludwig classification and patient satisfaction UBM and dermoscopic findings showed significant increase in the number of hair follicles at 4 months in all groups UBM showed such significant increase at 2 months in the combination group (C) only UBM at 4 months showed significant increase in the number of hair follicles detected in both groups B and C A nonsignificant increase in the hair diameter was also documented in the three groups
Faghghi 2018 [15]	50 patients with AGP The patients were randomly divided into a control and a treatment group	Group A received topical minoxidil 5% solution plus LLLT twice per day Group B Topical 5% minoxidil and a laser comb system that was turned off to act as a placebo	Changes in patients' hair density and diameter and overall regrowth as well as their satisfaction with the treatment were assessed at months 0, 3, 6, 9, and 12	Group A showed a significant increase in recovery percentage at 6, 9, and 12 months after the intervention ($p < 0.001$) compared to group B Mean hair count was higher in group A compared to group B at 9 and 12 months ($p < 0.001$) Group A showed an increase in hair diameter at 12 months compared to group B ($p = 0.045$) Mean increase in hair count was higher in group A compared to group B (78.3% versus 51.3%; $p < 0.001$) Mean increase in hair diameter was higher in group A compared to group B (45.4% vs. 32.3%; $p = 0.002$)

UBM, ultrasound biomicroscopic.

Table 2. Summary of clinical treatment response in each study

Reference	Minoxidil treatment	LLLT treatment	Combination treatment
Ferrara 2021 [16]	+	NA	+
Mahe 2021 [17]	+	NA	+
Liu 2021 [14]	+	+	++
Esmat 2017 [13]	+	+	++
Faghihi 2018 [15]	+	NA	++

+, improvement in hair growth; ++, greater improvement compared to other treatment groups; NA, not assessed.

significant difference in self-reported patient satisfaction between the treatment groups.

Faghihi et al. [15] performed a randomized double-blind clinical trial examining 50 male and female patients with AGA randomly divided into a treatment group that received topical 5% minoxidil solution for 6 months plus LLLT (wavelength 785 nm) for 24 weeks. This was compared against a control group receiving only topical 5% minoxidil with a sham device as placebo. At 3 months, no significant difference in hair growth between the treatment and control groups was noted. Importantly, at 6, 9, and 12 months a statistically significant increase in percentage of hair recovery was seen in the treatment group (5% minoxidil + LLLT ($p < 0.001$)). The treatment group was found to have an increased hair count compared to control (5% minoxidil + sham placebo) at months 9 and 12 ($p < 0.001$). There was a significant increase in hair diameter at 12 months in the treatment group compared to control ($p = 0.045$). Lastly, the authors found a statistically significant mean increase in hair count in the treatment group (78%) compared to control (51.3%) ($p < 0.001$).

Ferrara et al. [16] examined 21 male patients with AGA who were treated with LLLT using Capellux (wavelength 650 nm) followed by topical 5% minoxidil solution for 6 months. In this split scalp study, the LLLT device was altered such that it only emitted therapy to half the scalp region, and the other half of the device was shut off. The efficacy of treatment was assessed by clinical photos and automated trichograms taken at baseline, 3 months, and 6 months. The researchers found that both the combination therapy side of the scalp and the minoxidil monotherapy increased in total hair count, but the difference was not statistically significant ($p > 0.05$).

Mahe et al. [17] examined the effect of LLLT/Gentle-Waves devices (primary wavelength 590 nm and second-

ary 870 nm) and topical minoxidil therapy in 112 males with AGA. 45 patients received whole head exposure of LLLT combined with topical 2% minoxidil daily for 6 months. In the second treatment group, 45 patients applied topical 5% minoxidil for 6 months. The control group was 22 patients who did not receive any treatment. The researchers reported a similar increase in hair density in the combined treatment group and the 5% minoxidil treatment group compared to control. Notably, at 6 months, the rate of increase in hair growth began to decrease in the 5% minoxidil group but was sustained in the combination group.

Discussion

Minoxidil therapy has consistently demonstrated modest therapeutic effects at improving hair growth and is usually used in either 2% or 5% topical formulations (Table 2). Goren and Naccarato [18] reported that following twice daily topical application of minoxidil, less than 40% of patients regrow hair. The prolonged treatment course and delayed onset of results are barriers to long-term minoxidil use. Other barriers to long-term compliance are adverse effects of minoxidil including scalp pruritis, contact dermatitis, scaling, and hypertrichosis in undesirable areas such as the forehead. Additionally, topical therapy with minoxidil can cause a shedding period, which can temporarily worsen physical appearance [19]. Compliance is the major limiting factor in long-term success with minoxidil therapy.

LLLT has been examined as a possible alternative therapy to treating AGA. Studies have shown that LLLT has similar efficacy to traditional minoxidil therapy, with far fewer adverse effects. In several studies, LLLT was found to improve hair density more than minoxidil [20–22]. Darwin et al. [22] performed a review of clinical trials involving LLLT, and of the 13 human studies only 5 reported side effects including acne, mild paresthesia, and pruritis. Given the much milder adverse effects of LLLT compared to existing treatments, long-term compliance is greater. Drawbacks to LLLT could be the initial cost of obtaining a device, and the long-term usage required demonstrates meaningful results.

The purpose of this study was to analyze existing trials comparing combined therapy of LLLT with minoxidil to either LLLT or minoxidil monotherapy. While all these studies met the inclusion criteria, there were considerable differences in treatment length, patient population, and the method of quantifying the magnitude of effect. Most

notably, there were no reported adverse effects of combination treatment. While the studies demonstrated mixed findings, there at least appears to be an early improvement seen in combined therapy with topical application of minoxidil with LLLT. Some of this could be attributed to the transient telogen effluvium that occurs after 2–3 months after 5% minoxidil use [17]. During the later stages of treatment (after 6 months), there does not appear to be a meaningful difference between the minoxidil and LLLT treatment groups compared to combined therapy. It could be reasonably concluded that LLLT used with minoxidil has an early treatment benefit, but in the later treatment stage both therapies appear to have similar results in improving hair growth. Future studies should aim at standardizing the treatment protocols for more accurate comparison between groups. Furthermore, direct comparison between male and female populations would be useful to determine if there is greater efficacy in either population. It would also be of benefit to assess outcomes in different ethnic populations.

Statement of Ethics

Ethical approval and consent were not required as this study was based on publicly available data.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Michael A. Kaiser wrote, edited, and proofread the paper, and is the corresponding author. Stephanie M. Almeida helped write and proofread the paper. Mario Rodriguez helped write and proofread the paper. Najy Issa helped research the articles for the paper and helped write part of the paper. Naiem T. Issa helped proofread, research, and write the paper. Joaquin J. Jimenez oversaw the research and writing of the paper, helped edit the paper, and provided some of the research for the paper.

Data Availability Statement

The data are available on PubMed in the referenced articles. The corresponding author can assist in further investigation of the data used in this review.

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