Low-Level Laser Therapy as a Treatment for Androgenetic Alopecia

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Background and Objectives: Androgenetic alopecia (AGA) affects 50% of males by age 50 and 50% of females by age 80. Recently, the use of low-level laser therapy (LLLT) has been proposed as a treatment for hair loss and to stimulate hair regrowth in AGA. This paper aims to review the existing research studies to determine whether LLLT is an effective therapy for AGA based on objective measurements and patient satisfaction.

Study Design: A systematic literature review was done to identify articles on Medline, Google Scholar, and Embase that were published between January 1960 and November 2015. All search hits were screened by two reviewers and examined for relevant abstracts and titles. Articles were divided based on study design and assessed for risk of bias.

Results: Eleven studies were evaluated, which investigated a total of 680 patients, consisting of 444 males and 236 females. Nine out of 11 studies assessing hair count/hair density found statistically significant improvements in both males and females following LLLT treatment. Additionally, hair thickness and tensile strength significantly improved in two out of four studies. Patient satisfaction was investigated in five studies, and was overall positive, though not as profound as the objective outcomes.

Conclusion: The majority of studies covered in this review found an overall improvement in hair regrowth, thickness, and patient satisfaction following LLLT therapy. Although we should be cautious when interpreting these findings, LLLT therapy seems to be a promising monotherapy for AGA and may serve as an effective alternative for individuals unwilling to use medical therapy or undergo surgical options. Lasers Surg. Med. 49:27–39, 2017. © 2016 Wiley Periodicals, Inc.

Key words: alopecia; androgenetic alopecia; HairMax LaserComb; low-level laser therapy (LLLT); TOPHAT 655

INTRODUCTION

Androgenetic alopecia (AGA), also known as male pattern hair loss (MPHL) and female pattern hair loss (FPHL), affects 50% of males by age 50 and 50% of females by age 80 [1]. AGA is commonly recognized to have a strong psychological impact on the patient, and as a result, has negative effects on their quality of life [2]. Women affected by AGA reported dissatisfaction with their appearance, concern about hair loss continuing, and concern about others noticing their hair loss [3]. Additionally, these women ranked emotional aspects high, including self-consciousness, jealousy, embarrassment, and a feeling of powerlessness to stop hair loss. Current treatment includes medication, the most popular being the 5 alpha-reductase inhibitor finasteride and the antihypertensive medication minoxidil, and surgical options such as hair transplantation. However, these treatments have either shown limited effectiveness, unwanted side effects, and/or high cost.

Recently, the use of low-level laser therapy (LLLT) has been proposed as an alternative treatment for the prevention of hair loss and to stimulate hair regrowth in both MPHL and FPHL, with possibly better outcomes and minimal risk. A previous review concluded that LLLT appears to be a safe and effective therapy for multiple forms of alopecia [4]. Due to their minimal risk, there are now two commercially available LLLT devices that are FDA-approved: the HairMax LaserComb (Lexington Int. LLT, Boca Raton, FL) and TOPHAT 655 (Apira Science Inc., Boca Raton, FL). Several studies have investigated their safety and effectiveness for AGA; however, most are limited by sample size, and therefore findings of single studies should be interpreted with care. Moreover, additional studies have investigated possible alternatives, such as the 5x Hairlaser (Spencer Forrest Inc., Los Angeles, CA), and found promising results. It is, therefore, challenging for both patients and clinicians to keep oversight and to determine which commercially available device would be most effective in their individual case. This systematic review aims to evaluate the existing literature

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on AGA and LLLT specifically and determine whether (i) LLLT is indeed an effective therapy for AGA and to (ii) determine what expectations patients should anticipate when using these devices.

METHODS

Literature Search

Studies published up to November 2015 were obtained from Medline, Google Scholar, and Embase that report on LLLT as a treatment for AGA. Additionally, reference lists of original articles and review articles were searched. Table 1 details the search strategy.

Inclusion and Exclusion Criteria

All search hits were screened by two reviewers and examined for relevant abstracts and titles. Potentially relevant studies were then read full text to determine eligibility for final inclusion. Articles were recognized as eligible when they (i) included adults with AGA; (ii) investigated at least one type of LLLT; and (iii) were written in English.

Study Quality Assessment

Studies were divided using the Cochrane Evidence-Based Medicine Pyramid, where study designs that have greater quality of evidence are ranked higher [5]. Assessment of the risk of bias involved evaluation of the following study design characteristics: (i) randomization of group assignment; (ii) investigator and subject blinding of group assignment; (iii) blinding of outcome assessment or use of computer software for outcome assessment; and (iv) standardization of outcome assessments (same lighting, head positioning, hair style used when assessing hair count, etc.).

Data Extraction

Data regarding study design, type of intervention, and outcome were independently extracted by the two reviewers. Study design characteristics were extracted based on the Agency for Healthcare and Research Quality's manuscript that outlines essential study elements that are critical to incorporate when designing a study assessment tool for randomized controlled trials (RCTs) and observational studies [6]. The following study characteristics were recorded: Study design (case report, case series, prospective cohort study, retrospective cohort study, and randomized controlled trial), blinding, and number of study participants.

In terms of intervention, the following information was gathered; (i) the type of laser used; (ii) irradiation parameters; (iii) irradiation time; (iv) session frequency (days/week); and (v) treatment duration (weeks). In terms of outcome, the type of measurement was described (unit area trichogram, phototrichogram, global photography, direct hair count, software hair analysis, blinded or non–blinded investigator hair analysis), as well as the primary endpoints (hair count/density, hair thickness/shaft diameter, vellus hair count/density, terminal hair count/density, anagen percentage, telogen percentage, tensile strength, and investigator global assessment) and secondary endpoints (patient satisfaction and subject global assessment). A sub-analysis was performed for the HairMax LaserComb and TOPHAT 655 because of their FDA approval and consumer availability. Study results and adverse events were also extracted. A complete oversight of study characteristics can be found in Table 2.

RESULTS

Study Selection

The search yielded a total of 162 studies, of which 15 were potentially relevant based off their titles or abstracts. Among them two were animal studies and two did not investigate AGA. Eleven were eventually evaluated including one case report, one case series, four cohort studies, and five RCTs [7–17].

Study Characteristics

Ten studies evaluated a total of 444 males, compared to six studies with a total of 236 females. The efficacy of the

TABLE 1. Summary of Search Terms

Search strategy component and step No	Query
Patient	
1	MeSH descriptor alopecia explode all trees
2	Androgenetic or male pattern or female pattern and alopecia or baldness
Intervention	
3	MeSH descriptor laser therapy, low-level explode all trees
4	(Low) and (level or power) and (laser or light or irradiation) and (therapy)
5	"HairMax LaserComb"
6	"TOPHAT 655"
Merge	
7	1 or 2
8	3 or 4 or 5 or 6
9	7 and 8

TABLE 2. Summary of Methods and Endpoints

Author, year	Study score	Study type	Subject group	Device type	Treatment regimen	Efficacy evaluation	Assessed parameters
Rushton et al. (2012) [17]	2	Case report	2 M	HairMax LaserComb	**Irradiation parameters**: 655 nm laser (<5 mW) **Irradiance time**: 7.5 min **Session frequency**: 3 days per week **Treatment duration**: 26 weeks	Unit area trichogram and contrast-enhanced phototrichogram assessed by a blinded reviewer	• Hair count • Hair thickness • Vellus hair count • Anagen hair count • Telogen hair count • Villous hair count
Avram et al. (2009) [16]	1	Case series	7 1 M 6 F	Laser Hood	**Irradiation parameters**: 650 nm laser (5 mW) **Irradiance time**: 20 min **Session frequency**: 2 days per week **Treatment duration**: 12–24 weeks	Global clinical photographs assessed by three blinded reviewers	• Vellus hair count • Terminal hair counts • Shaft diameter
Satino et al. 2003 [7]	1	Prospective cohort study	35 28 M 7 F	Hair-Max LaserComb	**Irradiation parameters**: 655 nm laser (<5 mW) **Irradiance time**: 5–10 min **Session frequency**: Every other day **Treatment duration**: 24 weeks	Hair count assessed by two non-blinded reviewers Tensile strength assessed with VIP HairOScope	• Hair count • Tensile strength
Munck et al. (2014) [10]	1	Retrospective cohort study	32 11 M 21 F	HairMax LaserComb	**Irradiation parameters 1**: Seven-beam laser 655 nm (<5 mW) **Dose**: 15 min **Irradiation parameters 2**: Nine-beam laser 655 nm (<5 mW) **Irradiance time**: 11 min **Irradiation parameters 3**: 12-beam laser; six beams at 635 nm and six beams at 655 nm (<5 mW) **Irradiance time**: 8 min **Session frequency**: Three times per week **Treatment duration**: 8–48 weeks	Global Photography evaluated by two non-blinded reviewers	• Hair growth

(*Continued*)

TABLE 2. (*Continued*)

Author, year	Study score	Study type	Subject group	Device type	Treatment regimen	Efficacy evaluation	Assessed parameters
Blum et al. (2014) [15]	1	Prospective cohort study	70 M	5X HairLaser	**Irradiation parameters**: 15 laser diodes (30–34 mW) **Irradiance time**: 10–15 min **Session frequency**: Three times per week '**Treatment duration**: 26 weeks	Hair count analyzed by Canfield technology	• Hair count
Kim et al. (2007) [14]	1	Prospective cohort study	24 M	Portable light source	**Irradiation parameters**: 655 nm red light and 780 nm infrared portable light source **Irradiance time**: 10 min **Session frequency**: Daily **Treatment duration**: 14 weeks	Global photography and phototrichogram assessed by image analyzer program	• Hair density • Anogen/telogen ratio • Patient satisfaction
Leavitt et al. (2009) [8]	4	Double-blind, sham device-controlled, multicenter RCT	110 M	HairMax Laser Comb	**Irradiation parameters**: 655 nm laser (<5 mW) **Irradiance time**: 15 min **Session frequency**: 3 days per week **Treatment duration**: 26 weeks	Global photography assessed by image analysis software	• Hair count • Subjective satisfaction by the patient • Subjective assessment by investigator
Kim et al. (2013) [13]	3	Double-blind, sham device-controlled, RCT	40 26 M 14 F	Helmet-type device	**Irradiation parameters**: 630 (3.5 mW) LED, 660 (2.5 mW) LED, and 650 nm (4 mW) LD **Total energy**: 92.15 mW/cm^2 **Irradiance time**: 18 min **Session frequency**: Daily **Treatment duration**: 24 weeks	Phototrichogram assessed by image analyzer and global assessment evaluated by blinded reviewer	• Hair density and thickness • Investigator global assessment • Subject global assessment
Lanzafame et al. (2013) [12]	4	Double-blind, sham device-controlled, RCT	44 M	TOPHAT655	**Irradiation parameters**: 5 mW LD 655 ± 5 nm, and 30 LEDS 655 ± 20 nm (2.9 J per treatment session: 60 tx = 67 J/cm^2) **Irradiance time**: 25 min **Session frequency**: Every other day **Treatment duration**: 16 weeks	Global photography assessed by blinded reviewer	• Hair count

(*Continued*)

TABLE 2. (*Continued*)

Author, year	Study score	Study type	Subject group	Device type	Treatment regimen	Efficacy evaluation	Assessed parameters
Lanzafame et al. (2014) [11]	4	Double-blind, sham device-controlled, RCT	47 F	TOPHAT655	**Irradiation parameters**: 5 mW LD 655 ± 5 nm, and 30 LEDS 655 ± 20 nm (2.9 J per treatment session: 60 tx = 67 J/cm^2) **Irradiance time**: 25 min **Session frequency**: Every other day **Treatment duration**: 16 weeks	Global photography assessed by blinded reviewer	• Hair count
Jimenez et al. (2014) [9]	4	Double-blind, sham device-controlled, multicenter RCT	269 128 M 141 F	HairMax Laser Comb	**Irradiation parameters 1**: Seven-beam laser 655 nm (<5 mW) **Irradiance time**: 15 min **Irradiation parameters 2**: Nine-beam laser 655 nm (<5 mW) **Irradiance time**: 11 min **Irradiation parameters 3**: 12-beam laser; six beams at 635 nm and six beams at 655 nm (<5 mW) **Irradiance time**: 8 min **Session frequency**: Three times per week **Treatment duration**: 16 weeks	Global photography assessed by blinded reviewer using computer-assisted hair count software	• Hair density and hair count • Patient self-assessment

LED, light-emitting diodes; LD, laser diodes.

HairMax LaserComb and TOPHAT 655 were investigated in five [7–10,17] and two [11,12] studies, respectively. Other lasers studied include an LLLT hood device [16], application of 655 nm red light and 780 nm of infrared light [14], a Helmet type LLLT [13], and the X5 Hair-Laser [15]. Nine studies out of the 11 exclusively utilized a wavelength between 630 nm and 660 nm, with the most popular being 655 nm [7–13,16,17], while one study used a mix of 655 nm and 780 nm [14] and another study did not specify the wavelength of the laser device [15]. Nine out of 11 studies utilized a power setting of 5 mW or less [7–13,16,17], while one study utilized a power setting of 30–34 mW [15], and one did not report a power setting [14]. An irradiance setting of the laser device was reported in only one study with a value of 92.15 mW/cm^2, while another studied provided the energy value of 2.9 J per session. Six of the 11 studies utilized a LLLT treatment length of either 24 or 26 weeks; however, the length of treatment varied between 8 weeks and 24 months. There were minor differences in the frequency per week and the length of time per session. Individual study details of laser settings, doses and irradiation parameters can be found in Table 2.

Hair changes were assessed using a variety of methods including unit area trichogram (UAT), phototrichogram, global photography, investigator global assessment, VIP HairOScope, and direct scalp hair count. Hair analysis was either done by the authors, an outside investigator, or by computer software. A variety of outcomes were assessed; however, specifically of importance to this review were hair count/hair density and hair thickness/shaft diameter/tensile strength. Additionally, a subset of studies included secondary outcomes determining patient satisfaction and subject global assessment.

Study Quality Assessment

All RCTs randomized and blinded their group assignment. Several observational studies also blinded their outcome assessors by blinding them to either which side of the patient's head received treatment or by blinding reviewers to the chronological order of the photographs taken of the scalp. This ensured that the reviewers were unaware of which photographs were pre- and post-treatment. Two observational studies did not blind their outcome assessors, which can introduce an ascertainment bias where results of the study are influenced by knowledge of the assessor [7,10]. One study did not standardize their measurement procedure[16], while three did not specify how they standardized their measurements [13–15]. Standardizations of the outcomes are important to ensure measurements are comparable. Changes in hairstyles, hair color, lighting, or head positioning during each follow-up visit can result in hair count and hair strength changes not attributable to the intervention. Additionally, lack of standardization results in differences in technique among multiple outcome assessors, which potentially may lead to a measurement bias if a disproportionate amount of participants from one group were evaluated by one of the outcome assessors. There is no gold standard for irradiation parameters and dose in terms of minutes per session, frequency of sessions, and treatment length; therefore, it was difficult to assess studies based on the treatment regimen. Similarly, there is no gold standard for hair analysis making it difficult to score studies based on the type of measurement tools implemented.

Primary Outcomes

Hair count/hair density. Eleven studies assessed hair count/hair density as an endpoint, and nine found statistically significant improvements in both males and females following LLLT treatment. Three prospective studies had positive results and collectively showed an increase in hair density on the vertex and occiput regions [14], an increase in overall hair count [15], and an increase in hair counts by 93.5% in the vertex and temporal regions [7]. One retrospective cohort study found significant or moderate improvement in 28 out of the 32 subjects [10].

Additionally, five randomized controlled trials found improvements in hair density/hair count in LLLT-treated subjects compared to the sham-treated subjects. In a multi-centered RCT consisting of four trials, the authors found an increase in terminal hair density in both males and females who were treated with LLLT, with a mean relative increase of 15.27 hairs/cm^2 compared to controls [9]. Another study found an increase in terminal hair density where the LLLT-treated group experienced a mean increase of 19.8 hairs/cm^2 compared to the sham-treated group, which experienced a mean decrease of 7.6 hairs/cm^2 from baseline [8]. Similarly, a third study found an increase of 17.2 hairs/cm2 in the LLLT-treated patients versus a decrease of 2.1 hair/cm2 in the sham-treated patients [13]. Two separate studies in males and females conducted by the same research group found that LLLT increased the hair count by 35% in males and by 37% in females compared to controls [11,12]. Details of the results for each study can be found in Table 3.

Two out of the 11 studies did not find a statistically significant increase in hair count or hair density in their subjects following LLLT Therapy. One reported no difference between areas irradiated for 6 months with the HairMax LaserComb compared to non-irradiated regions in their case report of two males with AGA [17]. A second study followed six females and one male using a 650 nm laser hood for 3–6 months and found an overall increase of 7.57 terminal hairs, but this value was not statistically significant [16].

Hair thickness/shaft diameter/tensile strength. Four studies examined hair thickness, shaft diameter, and tensile strength as an endpoint following LLLT therapy. Of these, two studies found statistically significant improvements in tensile strength and hair thickness, while the other two found no difference. In one prospective cohort study consisting of 28 males and seven females, the authors found an overall increase in tensile strength of

TABLE 3. Summary of Results

Author, year	Quantitative results	Subject assessment/satisfaction	Adverse effects
Rushton et al. (2012) [17]	• No SS increase in hair count CE-PTG hair count (all hair/cm^2) • Treated half of head: at baseline 230 ± 3 and 243 ± 5 at 26 weeks • Untreated half of head: at baseline 235 ± 2 and 257 ± 3 at 26 weeks UAT (all hair/cm^2) • Treated half of head: at baseline 257 and 244 at 26 weeks • Untreated half of head: at baseline 216 and 222 at 26 weeks • No SS increase in hair thickness CE-PTG All hair greater than 40 μm diameter/cm^2 • Treated half of head: at baseline 206 ± 3 and 220 ± 1 at 26 weeks • Untreated half of head: at baseline 209 ± 3 and 220 ± 3 at 26 weeks UAT greater than 30 mm diameter/cm^2 • Treated half of head: at baseline 108 and 131 at 26 weeks • Untreated half of head: at baseline 136 and 150 at 26 weeks	Not assessed	Not Available
Avram et al. (2009) [16]	No statistically significant increase in terminal hairs • On average patients had increase in terminal hairs 7.57 at 3 months (not SS) No statistically significant change in hair thickness • On average patients had an increase of 1 μm diameter at 3 months (not SS)	• Two found LLLT helpful • Two did not find LLLT helpful • Three were unsure	• One patient reported occasional slight itching of the scalp • One patient reported two basal cell carcinomas on the scalp at the end of study
Satino et al. 2003 [7]	• Hair counts increased in temporal region by 55.2% in women, 74.1% in men, and 69.1% for all patients • Hair counts increased in vertex region by 64.9% in women, 120.1% in men, and 111.9% for all patients • Total hair count increase of 93.5% for both temporal and vertex regions in all patients • Tensile strength increased in temporal region by 82.6% in women, 64.4% in men, and 69.3% for all patients • Tensile strength increased in vertex region by 71.1% in women, 89.3% in men, and 86.4% for all patients	Not assessed	One-third of the patients did report temporary slightly increased hair shedding during the first 1 or 2 months of treatment

(*Continued*)

TABLE 3. (*Continued*)

Author, year	Quantitative results	Subject assessment/satisfaction	Adverse effects
	• Total tensile strength increase of 78.9% for both temporal and vertex regions in all patients		
Munck et al. (2014) [10]	• Eight showed significant improvement • 20 showed moderate improvement • Four showed no improvement • Improvement seen in both monotherapy with LLLT and concomitant therapy with minoxidil and/or finasteride	Not assessed	No adverse events were reported by subjects
Blum et al. (2014) [15]	• Statistically increase in mean hair count from baseline to 26 weeks in all age groups: 159 hair/cm^2 at baseline versus 174.80 hair/cm^2 at 26 weeks • Older population experienced more consistent and stronger linear trend of the hair growth over time than younger population • Fitzpatrick skin type IV demonstrated greater response than Fitpatrick I, II, and III.	Not assessed	No side effects or adverse effects reported by subjects
Kim et al. (2013) [13]	• Increase in hair density on vertex and occiput • The mean hair counts of baseline were 137.3 hair/cm^2 on the vertex and 153.3 hair/cm^2 on the occiput, versus mean hair counts after 14 weeks were 145.1 hair/cm^2 on the vertex and 163.3 hair/cm^2 on the occiput. ($P < 0.005$)	83% of patients were satisfied with LLLT therapy	Not available
Leavitt et al. (2009) [8]	• Increase in terminal hair density in LLLT group of 19.8 hairs/cm^2 versus sham-treated 7.6 hairs/cm^2	Patients reported increase in overall hair growth, slower hair loss, better scalp health, thicker feeling, more shine to hair, and overall hair improvement than control group • Did not report faster growing or more manageable hair than sham-treated control group	• Four cases of paraesthesia • Four cases of mild urticaria
Kim et al. (2013) [13]	• Increase in hair count: 17.2 hair/cm^2 in LLLT group compared to a decrease of 2.1 hair/cm^2 in sham-treated • LLLT-treated males had greater hair thickness ($12.6 \pm 19.4\ \mu m$) versus sham-treated ($3.9 \pm 7.3\ \mu m$)	• No significant difference in subject global assessment and subject satisfaction between the LLLT treatment group and sham-treated control group	• Nine subjects in LLLT group and seven subjects in sham-treated group reported headache • Five patient in LLLT and four patient in sham-treated group reported skin pain, pruritus, erythema, and/or acne • No significant difference

(*Continued*)

TABLE 3. (*Continued*)

Author, year	Quantitative results	Subject assessment/satisfaction	Adverse effects
			between the two groups in terms of incidence and adverse reaction
Lanzafame et al. (2013) [12]	• 37% increase in hair count in LLLT-treated males versus sham-treated controls	Not assessed	No side effects or adverse effects reported by subjects
Lanzafame et al. (2014) [11]	• 35% increase in hair count in LLLT-treated females versus sham-treated controls	Not assessed	No side effects or adverse effects reported by subjects
Jimenez et al. (2014) [9]	• Combined analysis of all four trials showed increase of terminal hair density: 15.27 hairs/cm^2 versus sham-treated group at 26 weeks • Trial 1 with females using nine-beam laser showed increase in terminal hair density: increase of 20.2 hair/cm^2 in LLLT group versus 2.8 hair/cm^2 in sham group (strongly SS) at 26 weeks • Trial 2 with females using 12-beam laser showed increase in terminal hair density: increase of 20.6 hair/cm^2 in LLLT group versus 3.0 hair/cm^2 in sham group (strongly SS) at 26 weeks • Trial 3 with males using seven-beam laser showed increase in terminal hair density: increase of 18.4 hair/cm^2 in LLLT group versus 1.6 hair/cm^2 in sham group (strongly SS) at 26 weeks • Trial 4 with males using 9- and 12-beam showed increase in hair density: increase of 25.7 hair/cm^2 in 12-beam LLLT group and 20.9 hair/cm^2 in nine-beam laser group versus 9.4 hair/cm^2 in sham group (strongly SS) at 26 weeks	• Trial 1: female patients with LLLT therapy reported overall improvement of hair loss and condition and increases in fullness and thickness • Trial 2: female patients with LLLT patient satisfaction did not reach statistical significance • Trials 3 and 4 conjoined analysis: increases in perceived thickness and fullness; overall improvement and hair loss did not reach statistical significance	Reported: dry skin (5.1%), pruritus (2.5%), scalp tenderness (1.3%), irritation (1.3%), and warm sensation at the site (1.3%)

CE-PTG, contrast enhanced-phototrichogram; UAT, unit area trichogram; SS, statistically significant.

78.9% when compared to baseline [7]. In an RCT study, LLLT-treated males were found to have a greater mean hair thickness ($12.6 \pm 9.4\,\mu m$) compared to the sham-treated males ($3.9 \pm 7.3\,\mu m$) [13]. Alternatively, one study found no change in their case report of two male patients with AGA while a second study did not reach statistical significance when comparing hair thickness in their study involving six females and one male with AGA [16,17].

Hairmax lasercomb and TOPHAT 655. Out of the five studies (total of 404 participants, 254 males and 150 females) using the HairMax LaserComb, two cohort studies and two RCTs found positive results (increase in hair counts, increase in tensile strength, increase in terminal hair density, and decrease in hair loss) following the use of all models of HairMax LaserComb [7–10,17]. One study consisting of two male subjects did not find the HairMax LaserComb to be an effective treatment method for MPHL [17]. Two RCT studies using the TOPHAT 655 (total of 91 patients, 44 males and 47 females) found this device to increase hair counts [11,12].

Secondary Outcomes

Five studies included questionnaires assessing patient satisfaction and subject assessment as a secondary endpoint. One study reported two patients that found LLLT helpful, two that did not find the therapy helpful, and three that were not sure [16]. In a prospective study of 24 male patients, the authors found 83% of subjects to be satisfied with LLLT therapy results [14]. An RCT study found varying results in subject assessment in their four trials. Trial 1 with female patients demonstrated a statistical significance in subject's reporting overall improvement of hair loss and condition and increased fullness and thickness following LLLT therapy compared to controls. Trial 2 with female patients did not reach statistical significance in either category [9]. Conjoined analysis of male participants in Trials 3 and 4 found statistically significant increases in subject-perceived thickness and fullness, while overall improvement in the hair loss condition did not reach statistical significance [9]. Alternatively, another RCT found that subject global assessment and satisfaction between the two groups were not significantly different despite positive findings in their primary outcomes [13]. In one study, LLLT-treated patients reported a slower rate of hair loss and an overall increase in hair growth, scalp health, subjective feeling of thickness, shine, and hair improvement [8]. The study, however, did not find a statistical significance in the patients' perception of there being an increase in the rate of hair growth or manageability of their condition.

Costs and Safety (Adverse Events)

The majority of subjects did not report any serious adverse effects with only a few reporting minor side effects: headache, dry skin, pruritus, scalp tenderness, acne, irritation, redness, and warm sensation at the site [8,9,13,16]. Regarding costs, there are three commercially available devices, HairMax LaserComb, TOPHAT 655, and X5 Hairlaser with varying prices. The TOPHAT 655 is marketed at a higher cost (695 dollars) than the other two devices. The HairMax LaxerComb has various models with varying cost (ranges from 195 to 495 dollars), while the X5 Hairlaser is sold within that range (299 dollars).

DISCUSSION

With this systematic review, we aimed to review the existing literature and determine whether (i) LLLT is an effective therapy for AGA and (ii) determine what expectations patients should anticipate when using these devices. Overall, the results of the 11 studies investigating the safety and effectiveness of LLLT were favorable. All five RCTs and four prospective cohort studies collectively found improvements in hair regrowth and prevention of hair loss. Moreover, there is evidence of patient satisfaction with LLLT and no serious adverse events were encountered.

The great merit of this study is that it is, to our knowledge, the first to systematically review all evidence regarding LLLT for AGA. Previous reviews regarding the effectiveness of LLLT for hair loss did not incorporate all studies investigating AGA, evaluate the quality of studies, and provide a comprehensive review of subject satisfaction. Their main conclusion, however, that LLLT appears to be safe and effective, is concordant with our results.

Two studies did not find beneficial results using laser therapy [16,17]. The first found no significant difference in the areas treated with the HairMax LaserComb compared to the untreated areas; however, both areas showed improvements in the hair count and hair thickness from baseline [17]. This raises the concern if whether the energy from the laser dissipated onto areas that were designated as 'non-laser' treated areas. The second study found an increase in hair count and shaft diameter following laser therapy, but these increases were statistically insignificant [16]. The authors discussed various limitations to the study, including the small sample size, the lack of normalizing the hairstyle and camera settings before and after treatment, and the period of treatment, which may have been insufficient to observe the positive effects of LLLT. The authors also questioned the effectiveness of laser devices designed as a hood, stating that the existing hair may interfere with the hood's delivery of the laser beam to bald/balding areas.

In terms of how LLLT therapy compares with commonly prescribed pharmacological AGA treatments like minoxidil and finasteride was touched open in several studies. A systematic review found finasteride therapy in males to have approximately 30% hair improvement in patients with long term use of finasteride, which was significantly detected at 6 months [18]. In women, finasteride failed to show improvements in hair loss in postmenopausal women, but was found to be affective in premenopausal women in conjunction with oral contraceptive pills [18]. Finasteride complications include increased risk of erectile dysfunction by 1.5%, development of anxiety and depression, very rare cases of gynecomastia and breast cancer in men, and teratogenicity [18–21]. One prospective study found 19 (14 males and five females) out of the 23 patients (17 males and five females) developed moderate to severe depression within 9–19 weeks of use of 1 mg/day orally of finasteride treatment [22]. Topical minoxidil increased non-vellus hair and total hair count in both sexes [23–26]. Adverse effects of minoxidil entail contact dermatitis, facial hypertrichosis, and transient increases in hair shedding during first month [27]. In one RCT, pruritus, dermatitis, hypertrichosis, and scaling were found in 14% of women in the 5% topical minoxidil, 6% of patients in the 2% topical minoxidil group, and 4% in the placebo group [27]. A similar study in men found these dermatologic adverse events in 6% of the 5% topical minoxidil group, 2% in the 2% topical minoxidil, and 3% in the placebo group [28]. One study compared the use of LLLT monotherapy to LLLT combined with minoxidil and/or finasteride in males and females [10]. Monotherapy and both types of concomitant therapy showed improvement in patient condition, although none demonstrated significant advantage over the others. Another study compared their

LLLT results to separate minoxidil and finasteride studies and found that overall LLLT had comparable results to finasteride and minoxidil in the short term but was less efficacious in the long term [9].

Comparing and contrasting subject assessment/patient satisfaction with quantitative results is useful for defining realistic expectations for patients when using LLLT therapy. Several studies reported positive subject assessments, while a few studies did not find the same patient satisfaction despite positive objective findings. Two possible rationales for the discrepancy between the quantitative and qualitative subject outcomes are the presence of a placebo effect and/or the observed changes following laser therapy failed to meet the expectations of the patients. These findings emphasize the importance of setting realistic goals and expectations for patients when recommending LLLT as a possible therapy.

The importance of integrating personalized medicine when considering laser therapy was addressed in several studies. One prospective study found that patients with intermediate AGA (Hamilton-Norwood III and IV and Ludwig I and II) responded best because the amount of hair present in these individuals was sufficient for biostimulation while not surpassing the threshold for which the absorption of the laser is impeded by the existing hairs [10]. Another study investigated various subgroups that may experience varying benefits from LLLT therapy. They found that older subjects experienced a stronger linear trend of hair growth than younger subjects [15]. Secondly, they also reported that patients with Fitzpatrick skin type IV demonstrated a greater response to the LLLT therapy than patients with Fitzpatrick I, II, and III skin types [15]. One study found a greater improvement in the vertex area in men and temporal area in women, although both sexes showed significant benefit in all areas [7]. Further research with LLLT enrolling AGA patients with a broader clinical picture is needed to investigate the application of LLLT in these populations.

In addition to effectiveness, the cost and safety of LLLT therapy are important to consider. The majority of subjects did not report any serious adverse effects [8,9,13,16]. However, one study reported on a patient that developed two basal cell carcinomas on the scalp, but the authors did not equate this to the laser therapy [16]. The cost of the LLLT device is advantageous in that it is a one-time cost as opposed to medications that require lifelong refills. Additionally, the initial cost for the device is in an affordable range for some individuals who are unable to fund hair transplantation.

Light sources and dosimetry is an important discussion in LLLT. Wavelength, irradiance (Watts/cm^2), time, pulses, and possibly coherence and polarization influence the response to LLLT [29]. The ideal range for LLLT therapy is between 600 nm and 700 nm since this range has been used to treat superficial tissue. Insufficient irradiance (W/cm^2) or irradiation time that is too short can result in no response. On the other hand, if the irradiance is too high or irradiation time is too long, then the response can be inhibited [29]. The limited and varying information on irradiation parameters and treatment dose of each study made it difficult to identify patterns that may establish ideal dosimetry in LLLT for AGA. However, an interesting observation that may be of significance is found among the studies using the Hairmax Lasercomb. The study that did not find the device to be effective utilized the lowest irradiation time per session compared to all other studies using the same device [15]. This may be an example of short irradiance time as a cause for a lack of response to LLLT. Additionally, a second study that did not report effective results with LLLT therapy implemented a treatment frequency of two sessions per week, while all other studies recommended at least three sessions per week [16]. Although it is difficult to establish causality, highlighting these observations may aid in the direction for future research. In order to identify the most effective dosimetry, future studies must incorporate all irradiation parameters and treatment dose in order to compare them appropriately.

The pathogenesis of AGA is characterized by a stepwise miniaturization of the hair follicle, resulting in the vellus transformation of terminal hair [30]. The duration of the anagen phase (growing stage of hair cycle) in successive hairs becomes progressively shorter, resulting in the miniaturization of the hair follicle and ultimately a bald appearance [31,32]. This gradual miniaturization is thought to be due to the enzymatic conversion of testosterone into dihydrotestosterone (DHT) by 5α reductase, which then acts on receptors present on the hair follicle, resulting in early termination of anagen phase [30]. These changes in the hair cycle dynamics are mediated by the decreased expression of anagen-maintaining factors and increased expression of apoptosis-promoting cytokines [33–35].

The exact mechanism of the therapeutic effects on LLLT on hair growth and the hair cycle is not clearly defined. Laser/light therapy is thought to activate anagen re-entry in telogen hair follicles (resting stage of hair cycle), prolong the duration, and increase the rate of growth during the anagen phase and prevent entry into the catagen phase (regression stage of hair cycle) [36]. Studies have found 111 genes to be affected following LLLT therapy that coincides with increased rates of cell proliferation, migration, and tissue oxygenation as well as modulation of cytokines, growth factors, and inflammatory mediators [37,38]. The mechanism by which LLLT induces these changes may be explained by observations of increased ATP production, increased production of reactive oxygen species (ROS), increased nitric oxide (NO) release, and vasodilation following LLLT therapy [4,29,39–42].

Limitations to our systemic review include a limited amount of studies with large sample sizes. Additionally, it was difficult to assess the generalizability of these results and determine whether LLLT therapy may be more beneficial for certain populations since not all studies included detailed subject characteristics. Comparing and contrasting studies were also challenging in that there was extensive variability among each study. Most notably, there were various devices used, irradiation parameters,

treatment doses, length of treatment, and treatment frequencies described in each study making it difficult to assess standardization of treatment. Additionally, there is no gold standard for hair count and hair density measurements, and therefore a wide range of assessment tools were implemented. Hence, it would be beneficial for future studies to follow a more standardized approach. There are only two commercially available FDA-approved LLLT devices; therefore, future studies should focus on using these devices, the recommended treatment regimen, and implementing both phototrichogram and global photography as outcome-measuring tools for an objective and subjective assessment of hair growth. This will be advantageous in establishing effectiveness using comparable outcome measurements with consumer available LLLT devices and standardized treatment regimens. Furthermore, six out of the 11 studies reported a conflict of interest (four out of the six being RCT studies), which introduces another potential for bias. Future large sample RCT studies should be, if possible, conducted without any conflicts of interest to further minimize any source of bias.

CONCLUSION

Although we should be cautious when interpreting these findings, LLLT therapy is a promising monotherapy for MPHL and FPHL and may serve as an effective alternative for individuals unwilling to use medical therapy or undergo surgical options. The majority of studies covered in this review found an overall improvement in hair regrowth, thickness, and patient satisfaction following LLLT therapy. In general, LLLT devices are safe and seem to be effective; however, based on cost, and the number of studies, and minimal risks, the HairMax LaserComb seems to be the most favorable choice at this time. Additionally, it is important to recognize which patients are good candidates for LLLT therapy and establish realistic expectations of outcomes. More research is needed to identify which patients are the ideal candidates for LLLT and which patients would benefit from alternative strategies.

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