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Efficacy of non-surgical treatments for androgenetic alopecia: a systematic review and network meta-analysis

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Running Head: Non-surgical treatments for Androgenetic Alopecia

Abstract

Androgenetic alopecia, or male/female pattern baldness, is the most common type of progressive hair loss disorder. The aim of this paper is to review recent advances in non-surgical treatments for androgenetic alopecia and identify the most effective treatments. A network meta-analysis (NMA) was conducted of the available literature of the six most common non-surgical treatment options for treating androgenetic alopecia in both men and women; dutasteride 0.5mg, finasteride 1mg, low level laser therapy (LLLT), minoxidil 2%, minoxidil 5% and platelet rich plasma (PRP). Seventy-eight studies met the inclusion criteria and twenty-two studies had the data necessary for a network meta-analysis. Relative effects show LLLT as the superior treatment. Relative effects show PRP, finasteride 1 mg (male), finasteride 1 mg (female), minoxidil 5%, minoxidil 2% and dutasteride (male) are approximately equivalent in mean change hair count following treatment. Minoxidil 5% and minoxidil 2% reported the most drug-related adverse events (*n*=45 and *n*=23, respectively). The quality of evidence of minoxidil 2% vs. minoxidil 5% was high; minoxidil 5% vs. placebo was moderate; dutasteride (male) vs. placebo, finasteride (female) vs placebo, minoxidil 2% vs. placebo, minoxidil 5% vs. LLLT was low and finasteride (male) vs. placebo, LLLT vs. sham, PRP vs. placebo, finasteride vs. minoxidil 2% was very low. Results of this NMA indicate the emergence of novel, non- hormonal therapies as effective treatments for hair loss; however, the quality of evidence is generally low. High quality randomized controlled trials and head to head trials are required to support these findings and aid in the development of more standardized protocols, particularly for PRP. Regardless, this analysis may aid physicians in clinical decision making and highlight the variety of non-surgical hair restoration options for patients.

Summary

Androgenetic alopecia (AGA) is a common hair loss condition that is characterized by the miniaturization of hair follicles in the frontal and parietal regions of the scalp[1]. This miniaturization may be driven by the conversion of testosterone to dihydrotestosterone (DHT) by 5-α reductase or alterations in the androgen receptor gene[2–4]. Treatments, such as hormone and biological response modifiers, have been used to combat this miniaturization and stabilize hair loss in AGA patients[5,6]. Hormone response modifiers, such as finasteride, promote hair growth by inhibiting type II 5-α reductase. This inhibition blocks the conversion of testosterone to DHT, promoting cell survival and proliferation[5,7]. Although the exact mechanism for biological response modifiers, such as minoxidil, are not yet known, minoxidil is thought to promote hair growth through vasodilation and/or stimulation of hair follicles into the growth phase[8–11].

As an alternative to traditional therapies, other non-surgical treatments such as platelet-rich plasma (PRP) and low level laser therapy (LLLT) have also shown promise[12]. Through isolating platelets found in whole blood, growth factors can be concentrated and injected into the hair follicle and surrounding area. Evidence has suggested that these concentrated growth factors can promote angiogenesis and vascularization, accelerate hair regrowth, increase the duration of the hair growth phase and stimulate catagen development[13–17]. Alternatively, through photobiomodulation, red light emitted by LLLT devices may encourage hair growth by accelerating keratinocyte and fibroblast mitosis, inhibiting nitric oxide and reducing inflammation[18–21] (Figure 1a, 1b, 1c and 1d).

Due to the limited number of head-to-head clinical trials and the limitations of published meta-analyses (e.g., comparisons limited to 2 treatments), comparing the efficacies of non-surgical treatments is predominately qualitative[22]. Quantitative comparisons of the efficacy of non-surgical AGA treatments that have not been directly compared in head-to-head trials would be a valuable tool for both clinicians and hair restoration surgeons, potentially aiding treatment decisions and influencing patient outcomes. To address this literature gap a network meta-analysis was conducted using randomized control trials (RCTs) of six main non-surgical AGA treatments; finasteride, dutasteride, minoxidil (2% and 5%), PRP and LLLT. Using placebo as a common comparator, the efficacy of non-surgical treatments was indirectly and directly compared, using the mean difference in hair count from baseline as the outcome measure[23].

Materials and methods

Systematic review

This systematic review and meta-analysis was conducted in agreement with the 2015 modified 32-item PRISMA extension statement for network meta-analysis (NMA)[24]. Studies were eligible for inclusion if they were randomized, placebo-controlled or head-to-head trials of non- surgical treatment for androgenetic alopecia published in English. Combination therapies were not included.

Details regarding the databases searched and study identification for this review are provided in Appendix S1 (see Supplementary Material). Treatment effects were evaluated based on the efficacy rates and safety parameters reported in the randomized trials identified during the systematic review. Hair count was selected as our primary outcome and the end point selected was the most commonly reported time per treatment regime (Table S1). Details regarding the quality of evidence and risk-of-bias assessment for this review are provided in Appendix S1[25]. Data extracted from trials were combined by a random-effects model, with effect sizes expressed as difference of means of achieving each outcome in the treatment arm versus the control arm. Total effect size was calculated by the Mantel-Haenszel method. Heterogeneity was evaluated with I^2 calculations. Statistical analysis was performed with RevMan 5.3 with two- tailed P-values < 0.05 considered significant. Forest plots and funnel plots were obtained for each outcome analyzed and included in the supplementary material.

Network meta-analysis

NMA was used to make mixed comparisons among the therapeutic options and to rank treatments, using the program *Aggregate Data Drug Information Software* (ADDIS) version 1.16.8 program[26]. Inconsistency between direct and indirect evidence in the network was analyzed using difference of means. A P-value < 0.05 indicated significant inconsistency between the direct and indirect evidence in the network.

Results

Results of the search

There were 10,484 records identified by our literature search (PubMed, Scopus, Embase, Cochrane Libraries, ClinicalTrials.gov and Medline) (Figure 2). Seventy-eight[27–45,45–48,17,49–103] met the inclusion criteria and were included in the quantitative analysis. A total of 15,888 participants (88.1% male) were included with an average age 36.0±7.3 (Table 1).

Twenty-two studies[28,32,37,45,46,48,52,61,64,65,68,69,72,80,85,84,81,93,98,101–103] of the seventy-eight included in the quantitative analysis had the data necessary for a network meta-analysis. The included trials had 2,421 randomized participants, which were 64.2% male. The average age of participants was 37.7±7.1. The severity of disease was most commonly IV (n=273) and III vertex (n=497) on the Norwood-Hamilton Classification and II (n=381) on the Ludwig/Savin Scale. Detailed information for all the studies included in the network meta-analysis is presented in Table 1. A network graph summarizing the comparisons is provided in Figure 3.

Risk of bias

None of the included studies were judged to be low-risk across all six domains (Figure S1). With the exception of one domain (selective reporting), Hillmann *et al*.[52], was the only study to have a low-risk judgement across all domains. Four studies[64,65,69,72] (20%) were judged as low-risk on all but two domains. Detection bias (blinding of the outcome assessment) had the lowest risk of bias (64% of papers reported low risk). Incomplete outcome data (attrition bias – not reporting all participants and/or reasons for discontinuation) was the domain with the largest number of studies (50%) to be judged as high-risk, followed closely by selective reporting (reporting bias) (27%). Price *et al*.[84], was the only study to have an unclear judgement across all domains.

Quality of evidence

When considering mean hair count, evidence for treatment efficacy was generally low quality according to GRADEpro assessment. In treatment versus placebo studies: LLLT, PRP and finasteride (male) reported very low quality of evidence, finasteride (female), dutasteride (male) and minoxidil 2% had low quality evidence and minoxidil 5% had moderate quality evidence. When considering the treatment versus treatment: finasteride (male) versus minoxidil 2% had very low level quality of evidence, minoxidil 5% versus LLLT had low level of evidence and minoxidil 2% versus minoxidil 5% had high quality of evidence. Evidence was downgraded initially due to high risk of bias. Additionally, LLLT studies showed considerable inconsistency with high heterogeneity (I^2=93%). Dutasteride (male), LLLT, PRP, finasteride (male) vs minoxidil 2%, and minoxidil 5% vs LLLT analyzed less than 400 participants which contributed to the imprecision of the evidence.

Efficacy of direct comparisons

Meta-analysis of direct pair-wise comparisons showed that all non-surgical treatments exhibited greater efficacy over placebo with response to mean change hair count (Table 2, Figure S2). LLLT was the most effective treatment (mean difference [95% CI]: 66.70 [24.09, 109.31]), followed by PRP (23.51 [9.91, 37.11]) as demonstrated by their mean change hair count. Finasteride (female) was the least effective treatment (-1.93 [-5.27, 1.42]). Minoxidil 5% had the most drug- related adverse events (n=45) whereas PRP had the least (n=0), Table 1 and 5. Direct comparisons of treatments showed that finasteride was favoured over minoxidil 2% (8.10 [3.80, 12.40], minoxidil 5% was favoured over minoxidil 2% (4.69 [1.35, 8.04]) and LLLT was favoured over minoxidil 5% (1.53 [22.64, 25.70]) (Table 2, Figure S2-S5).

Results of the network meta-analysis indicate that the mean difference of LLLT is superior to all treatments. Additionally, finasteride (male) and minoxidil 2% indicated greater efficacy over placebo (21.140 [7.454, 35.465] and 16.615 [1.885, 33.023]) (Table 3). Otherwise relative effects showed that PRP, finasteride (male), finasteride (female), minoxidil 5%, minoxidil 2% and dutasteride (male) are approximately equivalent in mean change hair count following treatment (Table 3).

Inconsistency analysis

The indirect comparison of minoxidil 5% vs placebo, minoxidil 5% vs minoxidil 2%, minoxidil 5% vs LLLT and finasteride (male) vs placebo showed a treatment effect larger than the direct evidence. The indirect comparisons of minoxidil 2% vs placebo, LLLT vs sham and minoxidil 2% vs finasteride (male), showed a treatment effect smaller than the direct evidence (Table 4).

Model Fit

The mean deviance under the current model, relative to the deviance under a saturated model is referred to as the residual deviance. The residual deviance of our model was 50.5, the leverage (the influence of each data point) was 42.8 and the Deviance Information Criterion (model fit versus model complexity) was 93.3. The number of data points on which the fit is based was 46 (Figure S6).

Ranking of treatments by efficacy

Rank probabilities encode the probability for each treatment to be the best, second best, third best, etc. The probability that LLLT will be the most effective treatment option (rank 1) for our data is 92%, followed by PRP (5.2%). The probability that PRP will be the second most effective treatment option (rank 2) is 33.8%, followed by minoxidil 5% (21.8%). The probability that finasteride (male) will be the third most effective treatment option is 29.3%, and so on (Figure 4).

We used the surface under the cumulative ranking (SUCRA) probabilities to assess the efficacy of treatments. SUCRA expresses a percentage representing the efficacy of every intervention compared with a control. It is used to provide a hierarchy of the treatments and accounts both for the location and the variance of all relative treatment effects. A higher SUCRA score indicates a higher probability to be effective. The SUCRA scores demonstrate LLLT with the highest SUCRA (98.7%) followed by PRP, finasteride (male) and minoxidil 5% with similar scores (64.3%, 62.5% and 62.4%; respectively). Minoxidil 2%, dutasteride (male) and finasteride (female) report lower scores (51.0%, 32.9% and 14.4%; respectively) (Table 5).

Discussion

This network meta-analysis (NMA) compared the relative efficacy of finasteride, minoxidil 2% and 5%, low level laser therapy and platelet-rich plasma therapy in the treatment of androgenetic alopecia. Results indicate that the mean difference of LLLT is greater compared to all treatments. Additionally relative effects show PRP, finasteride 1 mg, minoxidil 5%, minoxidil 2% and dutasteride are approximately equivalent in mean change hair count following treatment. Minoxidil 5% and 2% reported the greatest amount of adverse events.

While results of this NMA indicate LLLT produced the largest increase in hair count, the quality of evidence is very low as determined by the risk of bias assessment. Further, these trials may require further scrutiny, as all five trials included in the NMA report funding and support from the device manufacturer or funding and/or affiliation of the author with the manufacturer. Nonetheless, these trials met the strict inclusion criteria of this NMA and analysis indicates LLLT is a highly effective treatment option.

PRP is also an effective treatment for AGA. However, quality of evidence of PRP is “very low” according to GRADEpro assessment. There are few randomized controlled trials examining the efficacy of PRP in AGA. Half head studies are common in the literature, however, this design may be considered problematic as each patient contributes to the treatment and control arm of the study. There is also a high degree of variability in study design among PRP trials. Studies have reported treatment administration weekly, monthly, and bimonthly and range in the total number of treatment sessions. Further, unlike oral or topical formulations such as finasteride or minoxidil, which are prescribed at standard doses, there is significant variability in the preparation and administration of PRP. Individual preparation systems and added activators can influence the concentration of growth factors[17]. Coupled to variability in frequency and volume of injections, this creates substantial differences in dosing across studies. We included trials in which activated PRP was administered.

Finasteride 1 mg and minoxidil 5% demonstrated similar efficacy. As such, other factors including the risk of adverse events (AEs) may contribute to clinical decision making. AEs reported with finasteride use are predominantly related to sexual dysfunction. Decreased libido, erectile dysfunction, and sexual adverse events are reported in several of the trials included in this NMA. The prevalence of sexual adverse events associated with finasteride use is widely discussed in the literature. We have previously demonstrated an increase in reports of sexual dysfunction with finasteride as the primary suspect in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS)[104]. Others report persistent sexual dysfunction up to one year after cessation of finasteride treatment[105]. The side effects of minoxidil 5% ranged from dermatologic in nature, such as hypertrichosis, and burning and itching of the skin, to cardiovascular AEs. The mechanism of action of minoxidil may contribute to the cardiovascular AEs, as it is a vasodilator. While the results of this NMA indicate finasteride 1 mg and minoxidil 5% demonstrate similar efficacy, considering the AEs associated with each treatment may aid in clinical decision making.

We included data for male and female participants from trials for minoxidil, LLLT and PRP. However, we separated the males and females for finasteride and dutasteride as we felt the results would have been skewed if we combined them. There were no studies reporting females taking dutasteride. In AGA, dihydrotestosterone (DHT) binding to androgen receptors in the scalp contributes to hair loss. DHT is formed by enzymatic conversion of testosterone to DHT by 5α- reductase, and these enzymes are inhibited by finasteride and dutasteride. Given the hormonal mechanism of action of 5α-reductase inhibitors, they are not approved for the treatment of hair loss in female patients. Finasteride has been associated with negative effects on the fetus as well as menstrual and endometrial abnormalities among others[106]. Dutasteride is a dual 5α-reductase inhibitor, which is approved for use in the treatment of benign prostatic hyperplasia and is used off- label for hair loss. Therefore, data for female participants was separated from the males.

A potential limitation of this analysis was the use of hair count as a primary outcome measure. AGA treatment efficacy can be determined with a variety of different assessments. Expert assessment of global photographs, hair counts using phototrichogram and manual hair counts using clippings have all been reported in the literature. Our rationale for selecting hair count was twofold: first, this is a more quantitative measure than global photographic assessment; studies reporting only global photographic assessment were not included. Second, some studies reported hair density (the number of hairs per predefined area). It is possible to convert hair count to hair density when provided a target area, however it is not possible if the area is not specified. Therefore, in order to maximize the number of included trials

in this NMA we selected hair count as our primary outcome measure. Unfortunately, this may be a limiting factor, as larger target areas would in theory have greater hair counts. This presents a point of consideration in the development and initiation of new trials. The use of a consistent outcome measure may aid in the comparison of treatment efficacy across many different treatments for hair loss or other dermatological conditions.

Another limitation to this study is the comparison of drugs with different routes of administration. Oral (finasteride), topical (LLLT, minoxidil) and intradermal injection (PRP) were all compared in this NMA. These treatments function through unique mechanisms of action and may have different metabolism and durations of effect. Despite this, all treatments compared in this analysis are FDA approved for use in the treatment of AGA. Therefore, these findings are relevant to clinicians and patients in the development of a treatment plan.

In addition to these limitations, the measurement of efficacy for AGA treatments has not yet been standardized; leading to multiple units of analysis reported across studies and therapies (e.g. hair density, hair count, hair shedding etc.). Furthermore, of the 20 studies included in the analysis, only six (30%) did not have obvious links to industry[28,38,45,80,93,102]. Most studies included in the analysis (14/20 = 70%) were supported or funded by invested parties (e.g., drug manufacture, patent owner, etc.). This may have contributed to the high number of studies judged to have a high risk of reporting bias and/or attrition bias. Industry funding for studies is often inevitable and appreciated; high-quality trials with low risk of bias counters perceptions of conflicted interests.

Systematic reviews as well as clinical trials must be designed rigorously in order to ensure the validity of the finding of the network meta-analysis. Interpreting the results of a NMA can prove challenging for the non-expert statistician. One of the most commonly misinterpreted parts of a NMA is the probability rankings. Ranking done in medical statistics will always depend on the criteria; one treatment may be best for efficacy but worse for long term safety. A risk subsists that one may incorrectly accentuate the probabilities as being clinically useful. That is why it is important to consider the numerical values of the rankings themselves, not only their probability ranks. The SUCRA scores also can be misleading as the SUCRA is most meaningful when the difference in preference between successive ranks remains the same across the entire ranking scale[107]. Our data does not have such interval scaling, thus weakening the SUCRA evidence. For clinical application, greater emphasis on the treatment effects and their uncertainty are crucial. As new trials are published, the network will expand and treatment rankings may change considerably. Consideration should also be issued to cost and a clinician's familiarity with use of a particular treatment.

In summary, results of this NMA indicate the emergence of more novel, non-hormonal therapies as effective treatments for hair loss. Further randomized controlled trials and head to head trials limiting risk of bias are required to support these findings and aid in the development of more standardized protocols, particularly for PRP. The data may provide guidance to physicians when counselling patients with AGA regarding non-surgical options.

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Table 1 Studies included in the network meta-analysis for non-surgican treatment sfor AGA

Author	Agent	Dose	*N* at randomization	Male (%)	Ludwig/ Savin Scale (*n*)	Norwood-Hamilton classification (*n*)	Age Mean ± SD, (Range)	Mean change hair count Mean ± SD	Drug-related adverse events (AEs) Number of patients
Dutasteride vs. placebo (*n* = 153)									
Eun *et al.* 2010[40]	Dutasteride	0.5 mg	153	100	NA	III vertex: 38, IV:14, V:21	37.8 ± 7.1	12.2 ± 23.6	Drug-related AEs: 5, sexual dysfunction: 3
	Placebo					III vertex: 36, IV:15, V:22	38.4 ± 6.6	4.7 ± 16.8	Drug-related AEs: 7, sexual dysfunction: 2, erectile dysfunction: 1, ejaculation disorder: 1
Finasteride vs. placebo (*n* = 976)									
Leyden *et al.* 1999[39]	Finasteride	1.0 mg	326	100	NA	II vertex*: 60; II A: 8; III: 27; III vertex: 71	33.0 ± 5.2	9.6 ± 19.32	Decreased libido: 2, impotence: 1
	Placebo					II vertex*: 79; II A: 5; III: 35; III vertex: 41	32.0 ± 5.1	−2.06 ± 18.97	Decreased libido: 2, ejaculation disorder: 1
Prasad *et al.* 2005[82]	Finasteride	1.0 mg	80	100	NA	II: 22; II A: 4; III: 8; III A:1; III vertex: 2; IV:1; IV A:2	24.6 ± 2.8	20.56 ± 29.92	Erectile dysfunction and decreased libido: 5, erectile dysfunction: 4, decreased libido: 1
	Placebo					II:18; II A:3; III:11; III A:4; III vertex:0; IV:2; IV A:2	24.6 ± 2.5	−9.56 ± 34.97	
Price *et al.* 2002[84]	Finasteride	1.0 mg	66	100		II: 8; II A:1; II	32.9 ± 4.8	32.12 ± 25.51	0
	Placebo							7.01 ± 13.93	
Price *et al.* 2000[85]	Finasteride	1.0 mg	137	0	I:22; II: 45	NA	53 ± 4	−8.7 ± 26.44	Folliculitis: 1
	Placebo				I: 31; II:39		53 ± 5	−6.6 ± 26.64	Increased body hair growth: 2, sweating and hot flashes: 1, hot flashes: 1, headache: 1
Slough *et al.* 2002[86]	Finasteride	1.0 mg	18	100	NA	II vertex*: 0; III vertex: 6; IV:1; V:2	38.6 ± 2.5	16 ± 11.31	0
	Placebo					II vertex*: 0; III vertex: 6; IV:1; V:2	38.6 ± 2.5	−4 ± 15	
Van Neste *et al.* 2000[101]	Finasteride	1.0 mg	212	100	NA	II vertex*: 40; III vertex: 25; IV: 29; V: 12	30.2 ± 6.2	7.2 ± 16.99	
	Placebo					II vertex*: 35; III vertex: 35; IV: 18; V:18	29.3 ± 6.2	−10.1 ± 16.81	Sexual adverse event: 1
Whiting *et al.* 1999[120]	Finasteride	1.0 mg	137	0	ND	ND	(41-60)	−1.9 ± 1.3	0
	Placebo							0.0 ± 1.3	
Minoxidil (2% and 5%) vs. placebo (*n* = 886)									
Price & Menefee, 1990[81]	Minoxidil 2%	1 mL 2× a day	9	0	I: 2, II: 3	NA	(22-41)	38.75 ± 24.8	
	Placebo				I: 1, II: 3		(22-41)	−3.25 ± 10.2	0

Author	Agent	Dose	*N* at randomization	Male (%)	Ludwig/ Savin Scale (*n*)	Norwood-Hamilton classification (*n*)	Age Mean ± SD, (Range)	Mean change hair count Mean ± SD	Drug-related adverse events (AEs) Number of patients
Whiting & Jacobson, 1992[108]	Minoxidil 2%	1 mL 2× a day (12 h intervals)	33	0	I: 13, II: 4	NA	34.0, (22–44)	28 ± 29	0
	Placebo				I: 9, II: 7		34.0, (22–44)	20 ± 18	
Lucky *et al.* 2004[69]	Minoxidil 2%	1 mL 2× a day (12 h intervals)	381	0	I: 56, II: 96, III: 2		37.0	20.7 ± 17.6	Dermatologic adverse events: 10, headache: 6, cardiovascular: 2
	Minoxidil 5%				I: 55, II: 92, III: 6	NA	37.0	24.5 ± 21.9	Dermatologic adverse events: 22, hypertrichosis: 4, headache: 3, cardiovascular: 2
	Placebo				I: 27, II: 44, III: 3		37.0	9.4 ± 14.6	Dermatologic adverse events: 3, cardiovascular: 2
Olsen *et al.* 2002[70]	Minoxidil 2%	1 mL 2× a day (12 h intervals)	393	100	NA	IIA: 0, III: 3, III vertex: 69, IV: 53, V: 18, VA: 10, VI: 4, VII: 1	36.5 ± 8.5	12.7 ± 20.7	Dermatologic adverse events: 4, headache: 1
	Minoxidil 5%					IIA: 1, II:1, III vertex: 64, IV: 55, V: 19, VA: 11, VI: 4, VII: 2	36.2 ± 8.4	18.6 ± 25.4	Dermatologic adverse events: 9, headache: 5
	Placebo					IIA: 0, III: 0, III vertex: 29, IV: 32, V: 7, VA: 6, VI: 4, VII: 0	36.8 ± 8.4	3.9 ± 21.7	Dermatologic adverse events: 2, headache: 1
Hillmann *et al.* 2015[22]	Minoxidil 5%	½ capful 2× a day	70	100	NA	III vertex: 11, IV: 10, V: 13, VA: 0, VI: 1	43.2 ± 12.2	7.8 ± 24.1	Drug-related AEs: 3† Intolerance events considered to be drug-related†: erythema: 2, pruritus: 5, burning/ stinging: 3, desquamation /dandruff: 3, papules: 1, folliculitis: 1, feeling of skin tension: 1
	Placebo				NA	III vertex: 12, IV: 11, V: 10, VA: 1, VI: 1	43.8 ± 11.4	−1.5 ± 15.0	Drug-related AEs: 1† Intolerance events considered to be drug-related†: pruritus: 5, burning/stinging: 4, desquamation/dandruff: 2

Author	Agent	Dose	*N* at randomization	Male (%)	Ludwig/ Savin Scale (*n*)	Norwood-Hamilton classification (*n*)	Age Mean ± SD, (Range)	Mean change hair count Mean ± SD	Drug-related adverse events (AEs) Number of patients
Low-level laser therapy vs. placebo (*n* = 242)									
Barikbin *et al.*, 2017[32]	LLLT (650 nm)	3 times a week for 4 months	30	67	I: 3, II: 6, III: 1	II: 2, III: 3, III vertex:1IV: 2, V: 6, V vertex: 1, VI: 4, VII: 1	40.9 ± 14.01	10.13 ± 10.44	
	LLLT (650 + 808 nm)		30		I: 8, II: 1, III: 1	II: 2, III: 7, III vertex: 1, IV: 2, V: 3, V vertex: 2, VI: 2, VII: 1	39.57 ± 14.75	9.86 ± 9.53	0
	Sham		30		I:10	II: 3, III: 6, IV: 1, V: 7, VI: 1, VII: 2	35.10 ± 14.36	−1.2 ± 2.15	
Friedman & Schnoor, 2017[48]	LLLT	30 min every other day	40	0	I: 8, II: 14	NA	48.4 ± 5.3	89.89 ± 63.31	0
	Sham				I: 13, II: 9		47.1 ± 11.6	18.52 ± 24.43	
Kim *et al.* 2013[31]	LLLT	18 min/day	29	52	I: 5, II: 1	III: 6, IV: 2, V: 1, VI: 5	43.9 ± 12.2	120.40 ± 85.08	0
	Sham				I: 8	III: 4, IV: 4, V: 3, VI: 1	44.5 ± 11.4	−15 ± 128.10	
Lanzafame *et al.* 2013[34]	LLLT	25 min every other day	41	100		IIa-V	(18-48)	86.64 ± 46.20	0
	Sham						(18-48)	14.63 ± 53.62	
Lanzafame *et al.* 2014[33]	LLLT	25 min every other day	42	0	I: 7, II: 11	NA	46.3 ± 9.2	100.33 ± 53.38	0
	Sham				I: 11, II: 13		51.0 ± 7.1	23.94 ± 30.13	
Platelet-rich plasma vs. placebo (*n* = 35)									
Cervelli *et al.* 2014[47]	PRP (activated)	3 sessions at 30-day intervals	10	100	NA	IIA-IV	32.7 ± 10.57	27 ± 15.3	0
	Placebo							−2.1 ± 12.4	
Alves & Grimalt, 2016[35]	PRP (activated)	3 sessions at 30-day intervals	25	48	NA	II-IV	39 (21-62)	12.8 ± 32.6	0
	Placebo							−2.1 ± 31.3	
Minoxidil 2% vs. finasteride (*n* = 99)									
Saraswat & Kumar, 2003[43]	Minoxidil 2%	1 mL 2× a day	99	100	NA	IIIA: 5, III vertex: 23, IV: 14, V: 5	27.7 ± 3.4	9.6 ± 6.04	0
	Finasteride	1 mg				IIIA: 5, III vertex: 26, IV: 13, V:8	29.0 ± 4.3	17.7 ± 14	0
Minoxidil 5% vs. LLLT (*n* = 30)									
Esmat *et al.*, 2017[49]	Minoxidil 5%	Twice daily	15	0	I: 6, II: 6, III: 3	NA	31.27 ± 5.57	18.67 ± 3.54	0
	LLLT	25 min every 3 days	15		I: 2, II: 10, III: 3		35.67 ± 7.17	20.2 ± 6.36	

*Rating based on a modified version of the Norwood-Hamilton classification scale

†Unit of analysis: number of adverse events

Table 2 Direct comparison of each non-surgical treatment included in the network

Treatment 1	Treatment 2	Mean change hair count	Number of trials making direct comparison
Treatment vs. Placebo			
LLLT	Placebo	66.70 [24.26, 109.13]	5
PRP	Placebo	23.51 [9.91, 37.11]	2
Finasteride 1 mg (male)	Placebo	17.37 [11.67, 23.07]	5
Minoxidil 5%	Placebo	14.24 [10.72, 17.75]	3
Minoxidil 2%	Placebo	11.51 [5.34, 17.67]	4
Dutasteride 0.5 mg (male)	Placebo	7.50 [0.76, 14.24]	1
Finasteride 1 mg (female)	Placebo	−1.93 [−5.27, 1.42]	2
Treatment vs. Treatment			
Finasteride 1 mg (male)	Minoxidil 2%	8.10 [3.80, 12.40]	1
Minoxidil 2%	Minoxidil 5%	4.69 [1.35, 8.04]	2
Minoxidil 5%	LLLT	1.53 [−22.64, 25.70]	1

Table 3. Relative effects table. Comparison of the included interventions: mean difference (95% Credible Intervals). Each cell gives the effect of the column-defining intervention relative to the row-defining intervention.

LLLT[48,61,64,65] **week 16-24**	-25.317 (-49.628, -4.692)	-46.642 (-67.444, -29.365)	-25.184 (-50.989, -4.318)	-29.729 (-55.303, -8.590)	-23.790 (-57.495, 5.807)	-48.270 (-81.057, -21.108)	-38.930 (-80.913, -4.799)
	Minoxidil 5%[52,69,72] **week 24-48**	-20.912 (-39.152, -5.233)	0.187 (-21.937, 20.564)	-4.204 (-23.957, 14.404)	1.777 (-30.053, 30.773)	-22.682 (-52.705, 5.631)	-13.924 (-51.536, 22.640)
		Placebo or sham[28,37,46,68,80,85,84,98,101,81,102,69,72,52,48,61,64,65,103]	21.140 (7.454, 35.465)	16.615 (1.885, 33.023)	22.794 (-2.165, 48.520)	-1.891 (-25.046, 21.287)	7.380 (-25.890, 39.535)
			Finasteride 1 mg (male)[68,80,84,93,98,101] **week 14-26**	-4.415 (-22.822, 14.910)	1.740 (-28.043, 30.343)	-22.927 (-50.120, 3.679)	-13.741 (-50.404, 20.258)
				Minoxidil 2%[69,72,81,93,102] **week 32-52**	6.211 (-23.988, 35.338)	-18.508 (-46.960, 8.961)	-9.341 (-47.301, 25.836)
					PRP[28,37] **week 14-26**	-24.772 (-59.363, 9.575)	-15.516 (-57.572, 25.393)
						Finasteride 1 mg (female)[85,103] **week 52**	9.090 (-32.980, 48.968)
							Dutasteride 0.5mg (male)[45] **week 26**

Table 4. Results from the node-splitting analysis of consistency/inconsistency comparisons.

Treatment 1	Treatment 2	Direct estimate	Indirect estimate	Random effects standard deviation	Inconsistency P-value[a]	DIC[b]
Minoxidil 5%	Placebo	-15.516 (-37.865, 7.362)	-53.150 (-105.110, -5.456)	17.499 (10.752, 30.459)	0.155	87.2
Minoxidil 2%	Placebo	17.572 (-3.533, 39.387)	12.568 (-32.362, 58.046)	18.613 (10.941, 32.629)	0.829	88.0
Minoxidil 5%	Minoxidil 2%	-4.341 (-33.730, 24.290)	-6.740 (-50.813, 32.868)	18.633 (10.920, 32.716)	0.913	88.5
Minoxidil 5%	LLLT	-1.479 (-42.992, 38.260)	-35.792 (-66.252, -10.702)	15.544 (9.517, 26.274)	0.144	91.6
LLLT	Sham	-52.419 (-75.594, -33.765)	-17.838 (-63.381, 27.334)	15.465 (9.535, 26.203)	0.142	91.7
Finasteride 1 mg (male)	Placebo	20.291 (3.874, 37.067)	26.275 (-11.929, 67.835	16.185 (9.588, 27.988)	0.752	92.6
Minoxidil 2%	Finasteride 1 mg (male)	-8.254 (-43.057, 26.829)	-2.256 (-25.948, 22.639)	16.054 (9.454, 27.989)	0.760	92.9

A *p* value < .05 indicated significant inconsistency between the direct and indirect evidence in the network

[a]The p-value measures consistency by calculating the probability of observing the results from your sample of data or a sample with results more extreme, assuming the null hypothesis is true. The smaller the p-value, the greater the inconsistency

[b]The deviance information criterion (DIC), is a measure of model fit that penalizes model complexity. The DIC is used to compare fit between models for the same data; differences in DIC of 3 or greater are often considered relevant.

Table 5. Ranking of competing non-surgical treatments for AGA.

Treatment	**SUCRA** *(%)*	**PrRank 1** *(%)*	**PrRank 2** *(%)*	**PrRank 3** *(%)*	**Drug-related adverse events** *(n)*
LLLT, week 16-24	98.7	92.0	7.1	0.7	0
PRP, week 14-26	64.3	5.2	33.8	17.7	0
Finasteride 1 mg (male), week 48-52	62.5	1.2	8.3	7.5	15
Minoxidil 5%, week 17-48	62.4	0.8	21.8	27.2	45*
Minoxidil 2%, week 32-52	51.0	0.2	7.3	16.3	23
Dutasteride 0.5mg (male), week 26	32.9	1.2	8.3	7.5	8
Finasteride 1 mg (female), week 52	14.4	1.2	8.3	7.5	1
Placebo or sham	13.4	0.0	0.0	0.0	27*

SUCRA: surface under the cumulative ranking curve, PrRank: probability of best treatment and rank 1, 2 and 3.
*Minoxidil 5% additionally reported 16 individual events of AEs and placebo or sham had 11 individual events

Figure 1a. Working hypotheses of anti-androgens in AGA.

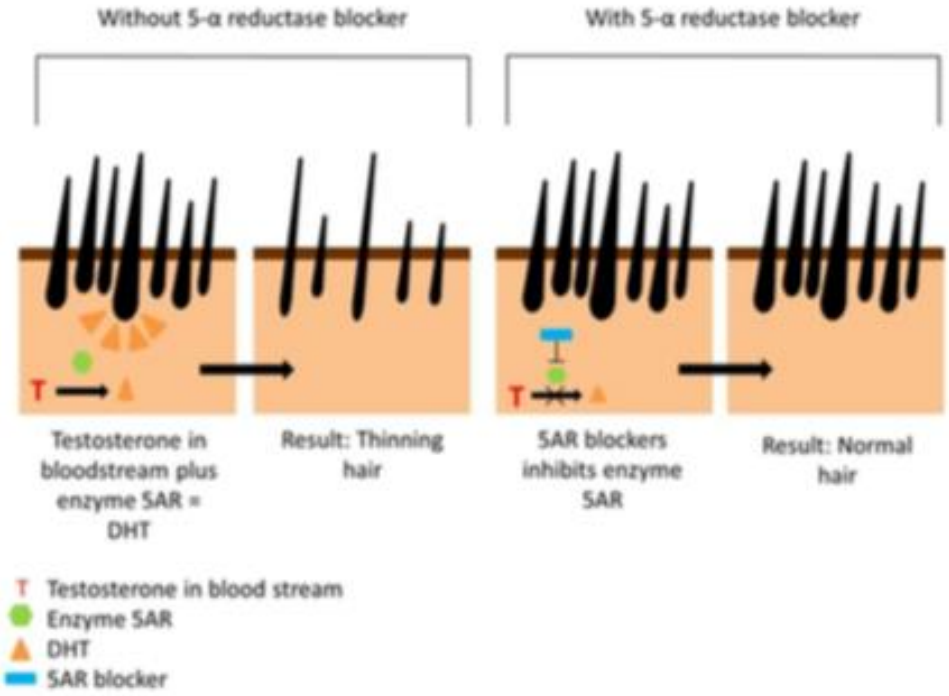

Figure 1b. Working hypotheses of minoxidil in AGA.

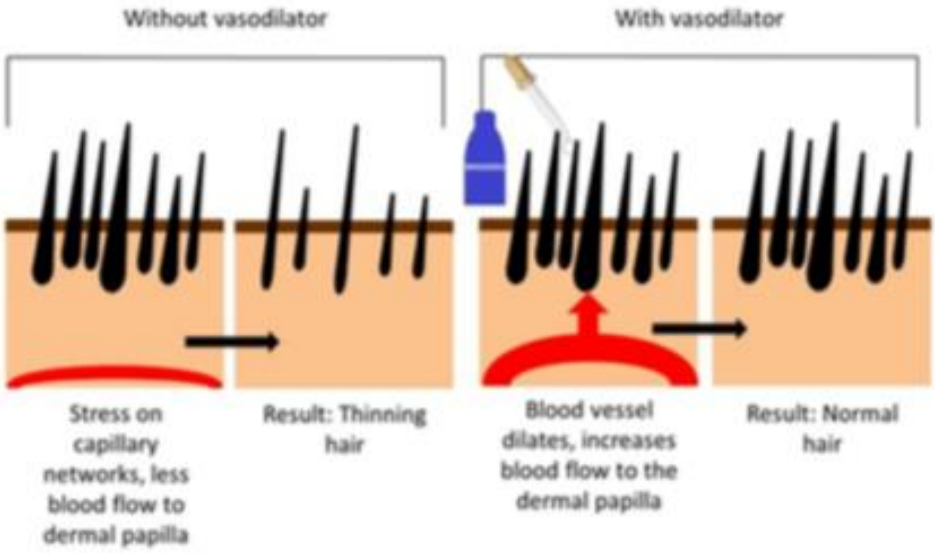

Figure 1c. Working hypotheses of PRP in AGA.

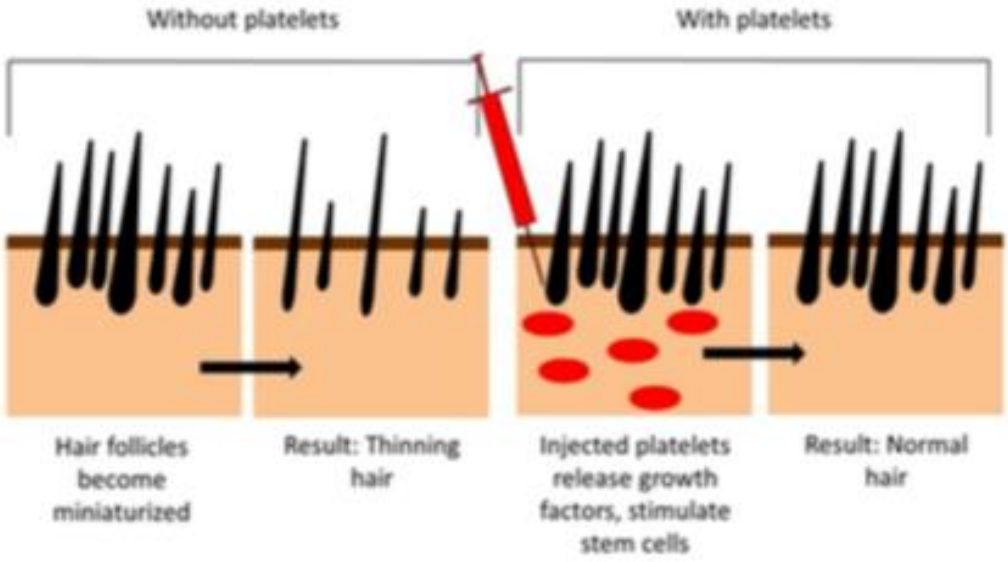

Figure 1d. Working hypotheses of LLLT in AGA.

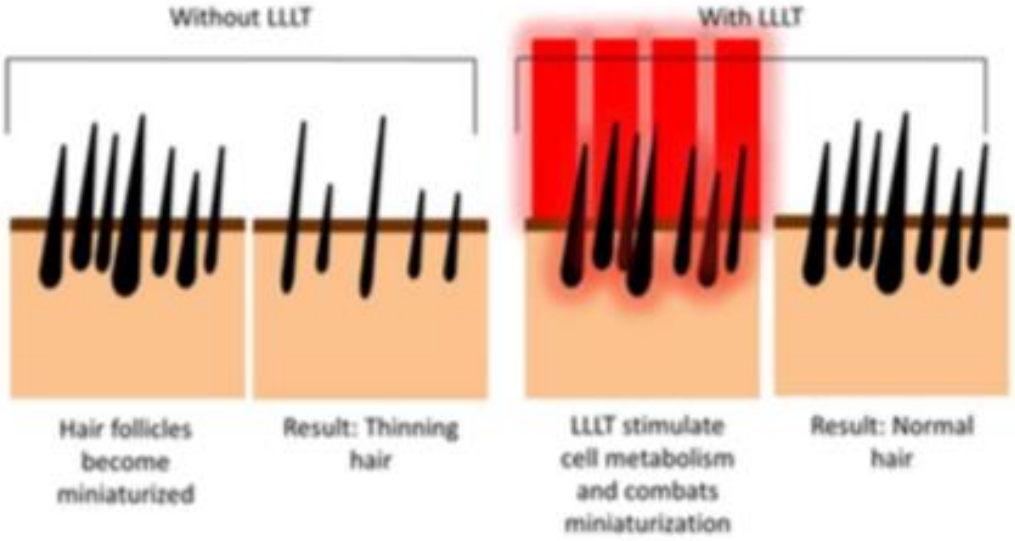

Figure 2. Summary of literature search for RCTs.

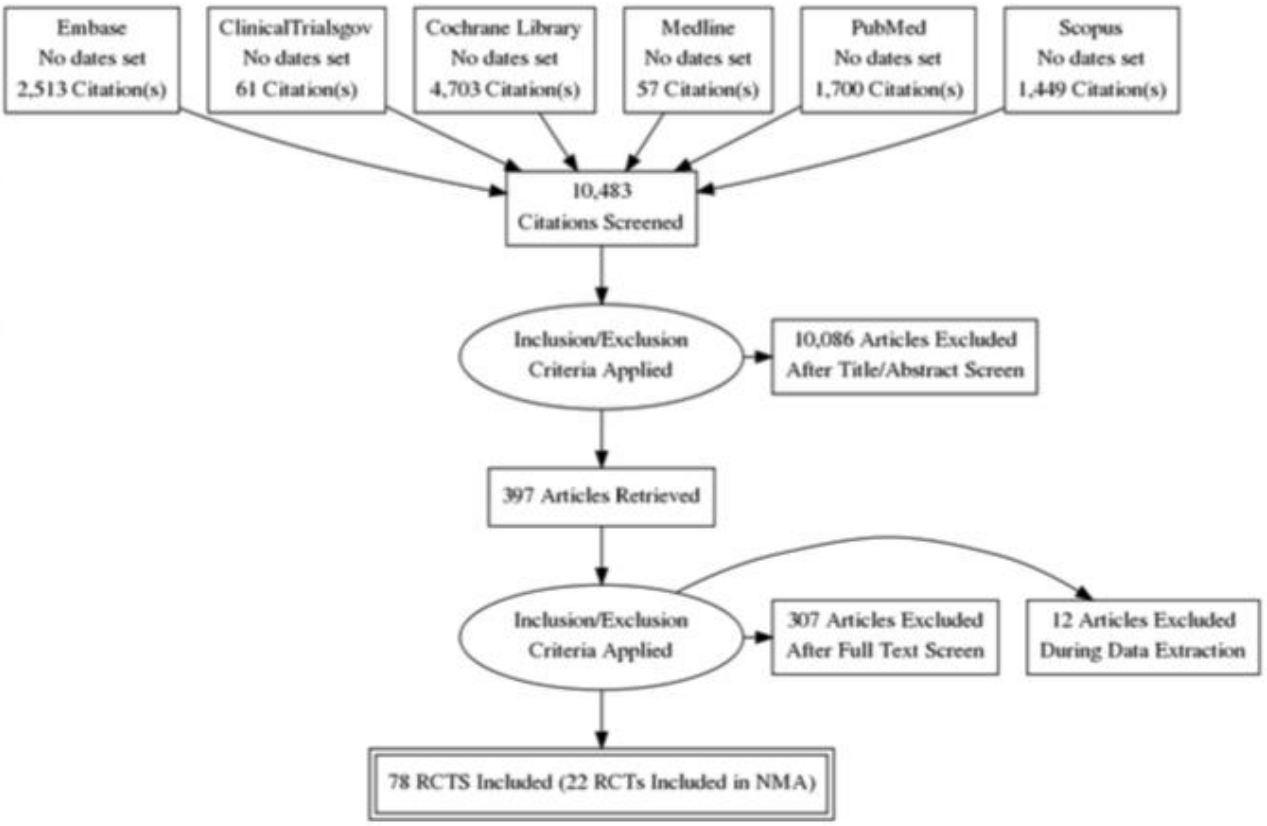

Figure 3. Network graph. The network graph shows the evidence network for all selected interventions. The size of an intervention's circle reflects the total number of participants for that intervention. Lines signify that interventions are connected through at least one study, with thicker lines indicating more connecting studies.

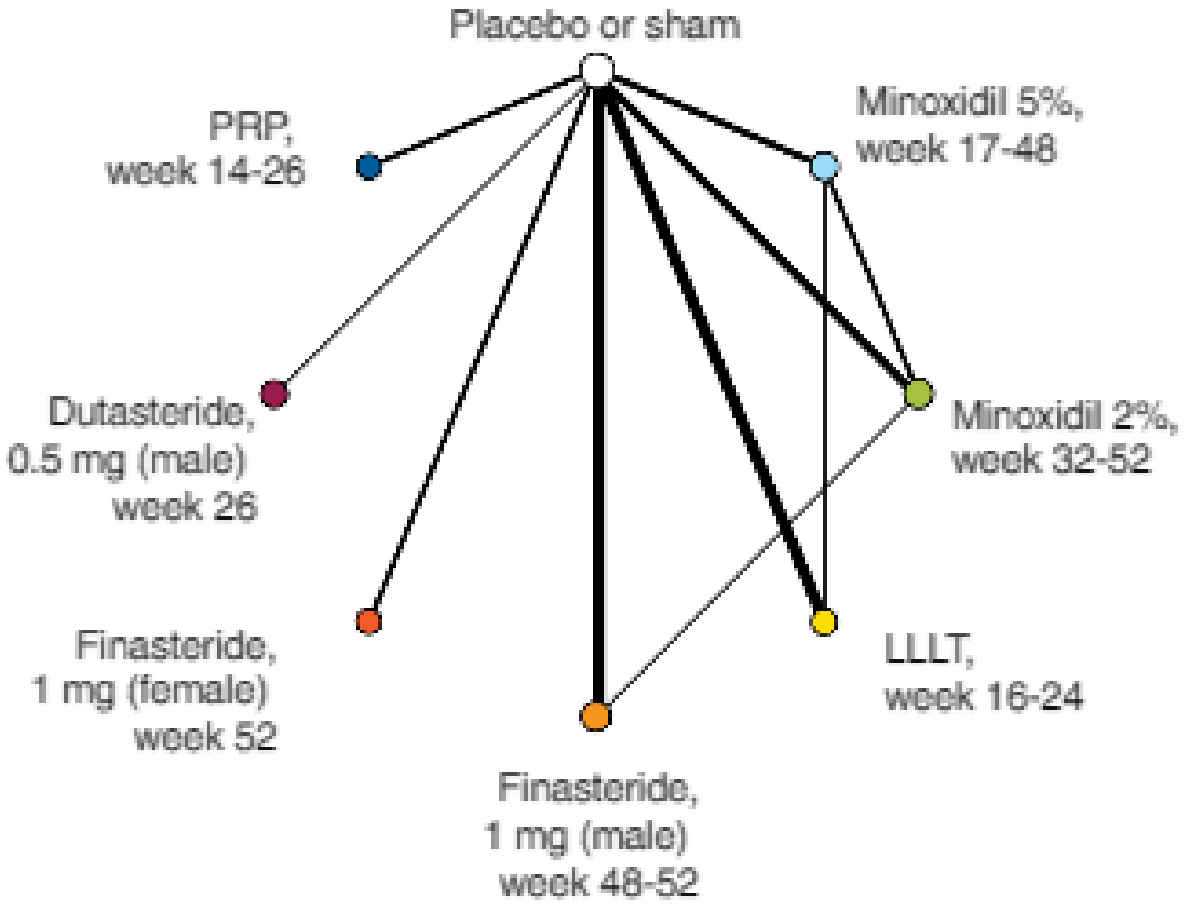

Figure 4. Bar plots for the ranking probabilities of competing non-surgical treatments for AGA. On the horizontal axis is the possible rank of each treatment (from best to worst according to the outcome). The size of each bar corresponds to the probability of each treatment to be at a specific rank.