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[Intervention Review]

Interventions for female pattern hair loss

Esther J van Zuuren[1], Zbys Fedorowicz[2], Jan Schoones[3]

[1]Department of Dermatology, Leiden University Medical Center, Leiden, Netherlands. [2]Bahrain Branch, Cochrane, Awali, Bahrain. [3]Walaeus Library, Leiden University Medical Center, Leiden, Netherlands

Contact: Esther J van Zuuren, Department of Dermatology, Leiden University Medical Center, PO Box 9600, B1-Q, Leiden, 2300 RC, Netherlands. E.J.van_Zuuren@lumc.nl.

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A B S T R A C T

Background

Female pattern hair loss (FPHL), or androgenic alopecia, is the most common type of hair loss affecting women. It is characterised by progressive shortening of the duration of the growth phase of the hair with successive hair cycles, and progressive follicular miniaturisation with conversion of terminal to vellus hair follicles (terminal hairs are thicker and longer, while vellus hairs are soft, fine, and short). The frontal hair line may or may not be preserved. Hair loss can have a serious psychological impact on women.

Objectives

To determine the efficacy and safety of the available options for the treatment of female pattern hair loss in women.

Search methods

We updated our searches of the following databases to July 2015: the Cochrane Skin Group Specialised Register, CENTRAL in the Cochrane Library (2015, Issue 6), MEDLINE (from 1946), EMBASE (from 1974), PsycINFO (from 1872), AMED (from 1985), LILACS (from 1982), PubMed (from 1947), and Web of Science (from 1945). We also searched five trial registries and checked the reference lists of included and excluded studies.

Selection criteria

We included randomised controlled trials that assessed the efficacy of interventions for FPHL in women.

Data collection and analysis

Two review authors independently assessed trial quality, extracted data and carried out analyses.

Main results

We included 47 trials, with 5290 participants, of which 25 trials were new to this update. Only five trials were at 'low risk of bias', 26 were at 'unclear risk', and 16 were at 'high risk of bias'.

The included trials evaluated a wide range of interventions, and 17 studies evaluated minoxidil. Pooled data from six studies indicated that a greater proportion of participants (157/593) treated with minoxidil (2% and one study with 1%) reported a moderate to marked increase in their hair regrowth when compared with placebo (77/555) (risk ratio (RR) = 1.93, 95% confidence interval (CI) 1.51 to 2.47; moderate quality evidence). These results were confirmed by the investigator-rated assessments in seven studies with 1181 participants (RR 2.35, 95% CI 1.68 to 3.28; moderate quality evidence). Only one study reported on quality of life (QoL) (260 participants), albeit inadequately (low quality evidence). There was an important increase of 13.18 in total hair count per cm^2 in the minoxidil group compared to the placebo group (95% CI 10.92 to 15.44; low quality evidence) in eight studies (1242 participants). There were 40/407 adverse events in the twice daily

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minoxidil 2% group versus 28/320 in the placebo group (RR 1.24, 95% CI 0.82 to 1.87; low quality evidence). There was also no statistically significant difference in adverse events between any of the individual concentrations against placebo.

Four studies (1006 participants) evaluated minoxidil 2% versus 5%. In one study, 25/57 participants in the minoxidil 2% group experienced moderate to greatly increased hair regrowth versus 22/56 in the 5% group (RR 1.12, 95% CI 0.72 to 1.73). In another study, 209 participants experienced no difference based on a visual analogue scale (P = 0.062; low quality evidence). The assessments of the investigators based on three studies (586 participants) were in agreement with these findings (moderate quality evidence). One study assessed QoL (209 participants) and reported limited data (low quality evidence). Four trials (1006 participants) did not show a difference in number of adverse events between the two concentrations (RR 1.02, 95% CI 0.91 to 1.20; low quality evidence). Both concentrations did not show a difference in increase in total hair count at end of study in three trials with 631 participants (mean difference (MD) −2.12, 95% CI −5.47 to 1.23; low quality evidence).

Three studies investigated finasteride 1 mg compared to placebo. In the finasteride group 30/67 participants experienced improvement compared to 33/70 in the placebo group (RR 0.95, 95% CI 0.66 to 1.37; low quality evidence). This was consistent with the investigators' assessments (RR 0.77, 95% CI 0.31 to 1.90; low quality evidence). QoL was not assessed. Only one study addressed adverse events (137 participants) (RR 1.03, 95% CI 0.45 to 2.34; low quality evidence). In two studies (219 participants) there was no clinically meaningful difference in change of hair count, whilst one study (12 participants) favoured finasteride (low quality evidence).

Two studies (141 participants) evaluated low-level laser comb therapy compared to a sham device. According to the participants, the low-level laser comb was not more effective than the sham device (RR 1.54, 95% CI 0.96 to 2.49; and RR 1.18, 95% CI 0.74 to 1.89; moderate quality evidence). However, there was a difference in favour of low-level laser comb for change from baseline in hair count (MD 17.40, 95% CI 9.74 to 25.06; and MD 17.60, 95% CI 11.97 to 23.23; low quality evidence). These studies did not assess QoL and did not report adverse events per treatment arm and only in a generic way (low quality evidence). Low-level laser therapy against sham comparisons in two separate studies also showed an increase in total hair count but with limited further data.

Single studies addressed the other comparisons and provided limited evidence of either the efficacy or safety of these interventions, or were unlikely to be examined in future trials.

Authors' conclusions

Although there was a predominance of included studies at unclear to high risk of bias, there was evidence to support the efficacy and safety of topical minoxidil in the treatment of FPHL (mainly moderate to low quality evidence). Furthermore, there was no difference in effect between the minoxidil 2% and 5% with the quality of evidence rated moderate to low for most outcomes. Finasteride was no more effective than placebo (low quality evidence). There were inconsistent results in the studies that evaluated laser devices (moderate to low quality evidence), but there was an improvement in total hair count measured from baseline.

Further randomised controlled trials of other widely-used treatments, such as spironolactone, finasteride (different dosages), dutasteride, cyproterone acetate, and laser-based therapy are needed.

PLAIN LANGUAGE SUMMARY

Treatments for female pattern hair loss

Review question

Which treatments are effective and safe for female pattern hair loss (FPHL)?

Background

The most common type of hair loss in women is FPHL, also known as androgenic alopecia. Unlike men, women do not go bald, but have hair thinning predominantly over the top and front of the head. It can occur at any time, from puberty until later in life. However, it occurs more frequently in postmenopausal women.

The diagnosis is supported by careful history taking (including family history). Other causes should be considered; therefore, a clinical examination and laboratory tests may be necessary. FPHL can have a significant impact on self-consciousness, and the damage to a woman's self-confidence can affect her quality of life (QoL), leading to feelings of unattractiveness, shame, discomfort, emotional stress, and low self-esteem.

Study characteristics

We examined the available evidence up to 7 July 2015. Forty-seven studies, which included 5290 women, met the inclusion criteria of this Cochrane review. The mean age of participants in the studies varied from 27 to 57 years. We assessed over half of the included studies as at unclear risk of bias, 16 as high risk, and only five studies as low risk of bias. Funding was provided in 26 of the 47 studies, mainly by pharmaceutical companies.

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Key results

This Cochrane review found that minoxidil is more effective than placebo. In six studies, the proportion of women that experienced at least moderate hair regrowth was twice as high in the minoxidil group compared to the placebo group. This was confirmed by the investigators assessments in seven studies. In eight studies, there was an important increase in total hair count per cm^2 in the minoxidil group compared to the placebo group. QoL was only assessed in one study and it was unclear from the data if there was an important improvement. The number of adverse events was similar for both groups. These were mostly mild, consisting of itch, skin irritation, dermatitis, and additional hair growth on areas other than the scalp.

Four studies compared minoxidil (2%) to minoxidil (5%), but none of the studies indicated any benefit of the higher concentration over the lower concentration. The number of adverse events did not differ between the two groups. Minoxidil should not be used in pregnant or lactating women.

Three studies compared finasteride to placebo. Finasteride is only approved in men for treatment of hair loss as well as for enlarged prostate. In one of the three studies the opinion of both the participants and investigators were evaluated but finasteride was shown to be no more effective than placebo. Hair count improved only in the finasteride group in a small study with 12 participants, but not in the other two studies (219 participants). Adverse events were only addressed in one study and these were similar in both groups. The investigators of these studies did not assess QoL.

Laser comb therapy did not appear to be more effective than sham therapy according to the participants in two studies with 141 participants. Nonetheless an important increase in hair growth was reported in both these studies. QoL was not addressed, and adverse events were not reported per intervention group, making these data less usable.

Individual studies investigated most of the other interventions and comparisons, and we could not make any firm conclusions about the efficacy or safety of these other interventions.

Although it is generally acknowledged that renewed hair shedding occurs relatively soon after discontinuation of treatment, none of the included studies reported data on the sustainability of the treatment effect, nor on the possible impact of hair regrowth, reflected by a decrease in time spent by women on hair styling or the use of wigs.

Quality of the evidence

We rated the quality of evidence for most outcomes as moderate or low. The lower quality of evidence was mainly caused by risk of bias in studies (e.g. no blinding) or a small sample size making the results less precise.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Minoxidil versus placebo

Minoxidil (1%, 2% and 5%) compared to placebo for female pattern hair loss (FPHL)

Patient or population: women with FPHL
Intervention: minoxidil (1%, 2% and 5%)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with minoxidil				
The proportion of participants with self-rated clinically significant hair regrowth at the end of the study Assessed with: 3 to 7 point Likert scales Follow-up: range 24 weeks to 32 weeks	**Study population**		**RR 1.93** (1.51 to 2.47)	1148 (6 RCTs)	⊕⊕⊕⊖ moderate[1]	26.5% versus 13.9% experienced moderate to marked hair regrowth
	139 per 1000	**268 per 1000** (209 to 343)				
Change in quality of life Assessed with: VAS, 0 = negative, 50 = neutral and 100 = positive Scale from: 0 to 100	—	—	—	260 (1 RCT)	⊕⊕⊖⊖ low[2,3]	Standard deviations (SDs) were missing, therefore we could not calculate mean difference (MD). The VAS score was 54.4 for 5% minoxidil, 52.1 for 2% minoxidil, and 46.5 for placebo
Adverse events	**Study population**		**RR 1.24** (0.82 to 1.87)	727 (4 RCTs)	⊕⊕⊖⊖ low[4,5]	These are the data for the minoxidil 2% versus placebo. The RR for minoxidil 1% versus placebo was 1.12 (95% CI 0.61 to 2.06) and for minoxidil 5% versus placebo 2.05 (95% CI 0.96 to 4.37)
	88 per 1000	**109 per 1000** (72 to 164)				
Proportion of participants with investigator-rated clinically significant hair regrowth at the end of the study Assessed with: 4 to 7 point Likert scales	**Study population**		**RR 2.35** (1.68 to 3.28)	1181 (7 RCTs)	⊕⊕⊕⊖ moderate[6]	18.4% versus 7.7% had at least moderate hair regrowth
	77 per 1000	**181 per 1000** (129 to 253)				

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Follow-up: range 24 weeks to 32 weeks						
Change from baseline in total hair count Follow-up: range 24 weeks to 32 weeks	The mean change from baseline in total hair count ranged from **−3.25 to 20.4 hairs/cm²**	The mean change from baseline in total hair count in the intervention group was **13.18 hairs/cm² higher** (10.92 higher to 15.44 higher)	—	1242 (8 RCTs)[7]	⊕⊕⊝⊝ low[8,9]	The impact of excluding Price 1990 from this analysis had a marginal effect on the overall pooled result (RR 12.96, 95% 10.69 to 15.24)
Degree of hair shedding from baseline to the end of the study	**Study population**		Not estimable	380 (3 RCTs)	⊕⊝⊝⊝ very low[10,11,12]	Pazoki-Toroudi 2012: MD -37.85 hairs, 95% CI −54.22 to −21.48; P < 0.00001) in favour of minoxidil. Number of participants reporting decrease: Whiting 1992: RR 1.34, 95% CI 0.68 to 2.66; Tsuboi 2007: RR 1.13, 95% CI 0.95 to 1.33
	Not pooled	Not pooled				
Cosmetic appearance of the hair or participant satisfaction Assessed with: VAS with 0 = no benefit, 50 = moderate benefit, and 100 = great benefit Scale from: 0 to 100	—	—	—	260 (1 RCT)	⊕⊕⊝⊝ low[2,3]	VAS score was 60.0 (27.6) for 5% minoxidil, 50.5 (35.5) for 2% minoxidil and 41.8 (29.9) for placebo
Change in quality (or pattern) of hair regrowth (e.g. thickness) Assessed with: Savin Female Density scale and target area hair width was 0.87 (1.315) mm/cm²	Not estimable	Not estimable	—	372 (2 RCTs)	⊕⊕⊝⊝ low[2,13]	Investigators in Lucky 2004 reported statistically significant differences in hair density for both minoxidil concentrations compared to placebo. NCT01325350: MD 0.80, 95% CI 0.36 to 1.24; P = 0.004

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **FPHL:** female pattern hair loss;**RCT**: randomised controlled trial; **MD:** mean difference; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded 1 level for serious risk of bias as we judged 5/6 studies' key domains of risk of bias, i.e. sequence generation, allocation concealment, and blinding as 'unclear'. Tsuboi 2007 was at 'low risk'.
[2]Downgraded 1 level for serious imprecision due to small sample size, not meeting optimal information size.
[3]Downgraded 1 level for serious risk of bias due to high drop-out rate and per-protocol analysis.
[4]Downgraded 1 level for serious risk of bias as all 4 studies were at unclear to high risk of bias.
[5]Downgraded 1 level for serious imprecision due to low occurrence of events.
[6] Lucky 2004 had 3 treatment arms.
[7]Downgraded 1 level for serious risk of bias as we judged 6/7 studies' key domains of risk of bias, i.e. sequence generation, allocation concealment, and blinding as 'unclear'. Tsuboi 2007 was at 'low risk'.
[8]Downgraded 1 level for serious risk of bias as we judged 7/8 studies' key domains of risk of bias, i.e. sequence generation, allocation concealment, and blinding as 'unclear'. Tsuboi 2007 was at 'low risk'.
[9] Price 1990 was an outlier, with a small sample size (N = 8). There was possible publication bias, single participant with large treatment effect, and the result may be due to natural sampling variation.
[10]Downgraded 1 level for serious risk of bias as in 2/3 studies' key domains of risk of bias, i.e. sequence generation, allocation concealment, and blinding were judged 'unclear'. Tsuboi 2007 was at 'low risk'.
[11]Downgraded 1 level for serious inconsistency as only Pazoki-Toroudi 2012 showed a difference in favour of minoxidil whilst the other 2 studies did not.
[12]Downgraded 1 level for serious imprecision due to wide CIs, and the optimal information size is not met.
[13]Downgraded 1 level for serious risk of bias due to attrition bias in Lucky 2004 and unclear risk of selection, performance, and detection bias in NCT01325350.

Summary of findings 2. Minoxidil 2% versus minoxidil 5%

Minoxidil 2% compared to minoxidil 5% for female pattern hair loss (FPHL)

Patient or population: women with FPHL
Intervention: minoxidil 2%
Comparison: minoxidil 5%

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with minoxidil 5%	Risk with minoxidil 2%				
Proportion of participants with self-rated clinically significant hair regrowth Assessed with: 7 point Likert scale in Blume-Peytavi 2011a, VAS scale 0-100 in Lucky 2004	**Study population**		Not estimable	322 (2 RCTs)	⊕⊕⊝⊝ low[1,2]	In Blume-Peytavi 2011a moderate to greatly increased hair regrowth in minoxidil 2% group versus 5% RR 1.12, 95% CI 0.72 to 1.73. VAS in Lucky 2004 62.9 (16.7 standard deviation (SD)) versus 68.1 (17.9 SD), authors' reported P = 0.062
	Not pooled	Not pooled				

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Follow-up: range 24 weeks to 48 weeks						
Change in quality of life Assessed with: VAS Scale from: 0 to 100	—	—	—	209 (1 RCT)	⊕⊕⊝⊝ low[3,4]	Investigators reported "no statistically significant difference in impact of hair loss on quality of life between the two intervention groups"
Adverse events	**Study population**		**RR 1.02** (0.91 to 1.20)	1006 (4 RCTs)	⊕⊕⊝⊝ low[5,6]	Excluding Lucky 2004 from the analysis, reduced the degree of heterogeneity, with minimal impact on the pooled results
	369 per 1000	**376 per 1000** (335 to 442)				
Proportion of participants with investigator-rated clinically significant hair regrowth Assessed with: 7 point Likert scales in Blume-Peytavi 2011a and Sheng 2014. VAS scale in Lucky 2004 Follow-up: range 24 weeks to 52 weeks	**Study population**		Not estimable	586 (3 RCTs)	⊕⊕⊕⊝ moderate[7]	These outcomes in the 3 studies were in agreement with the participant assessments that there was no difference between the 2 concentrations of minoxidil
	Not pooled	Not pooled				
Change from baseline to study conclusion in total hair count Follow-up: range 26 weeks to 52 weeks	The mean change from baseline to study conclusion in total hair count ranged from **23.7 to 31.9 hairs/cm^2**	The mean change from baseline to study conclusion in total hair count in the intervention group was **2.12 hairs/cm^2 lower** (5.47 lower to 1.23 higher)	—	631 (3 RCTs)	⊕⊕⊝⊝ low[8,9]	No difference between the 2 concentrations of minoxidil
Degree of hair shedding from baseline to the end of the study - not measured	See comment	See comment	Not estimable	(0 studies)	—	This outcome was not assessed in any of the studies
Cosmetic appearance of the hair or participant satisfaction	**Study population**		Not estimable	322 (2 RCTs)	⊕⊕⊕⊝ moderate[2]	3/4 in Blume-Peytavi 2011a were more satisfied after minoxidil 2% versus > 50% on 5%. In Lucky 2004 the scores on the VAS were 50.5 (SD 32.5) in the 2% group versus 60.0 (SD 27.6) in the 5% group
	Not pooled	Not pooled				

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Change in quality (or pattern) of hair regrowth (e.g. thickness)	Not estimable	Not estimable	—	322 (2 RCTs)	⊕⊕⊕⊙ moderate[10]	No differences in both studies between the treatment arms

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **FPHL:** female pattern hair loss;**RCT**: randomised controlled trial; **MD:** mean difference; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded 1 level for serious risk of imprecision, due to wide CIs in Blume-Peytavi 2011a.
[2]Downgraded 1 level for serious risk of bias due to the fact participants were not blinded in Blume-Peytavi 2011a.
[3]Downgraded 1 level for serious risk of bias due to high drop-out rate and per-protocol analysis.
[4]Downgraded 1 level for serious imprecision due to small sample size, and not meeting the optimal information size.
[5]Downgraded 1 level for serious inconsistency, due to Lucky 2004 showing (as only study) a statistically significant difference in favour of minoxidil 2%.
[6]Downgraded 1 level for serious risk of bias as blinding was unclear in 3/4 studies.
[7]Downgraded 1 level for serious risk of bias, due to the fact the blinding of the investigators was not assured in Blume-Peytavi 2011a and Sheng 2014.
[8]Downgraded 1 level for serious risk of imprecision, due to wide CIs, and the optimal information size is not met.
[9]Downgraded 1 level for serious risk of bias, due to the fact that outcome assessors in NCT01145625 were not blinded.
[10]Downgraded 1 level for serious imprecision, due to low sample sizes not meeting optimal information sizes.

Summary of findings 3. Finasteride versus placebo

Finasteride compared to placebo for female pattern hair loss (FPHL)

Patient or population: women with FPHL
Intervention: finasteride
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with finasteride				
	Study population		**RR 0.95** (0.66 to 1.37)	137 (1 RCT)	⊕⊕⊙⊙ low[1,2]	Finasteride was no more effective than placebo

The proportion of participants with self-rated clinically significant hair regrowth at the end of the study Assessed with: Questionnaire (Barber 1998) Follow-up: mean 12 months	**471 per 1000**	**448 per 1000** (311 to 646)				
Change in quality of life - not measured	See comment	See comment	—	(0 studies)	—	This outcome was not assessed in any of the studies
Adverse events Follow-up: mean 12 months	**Study population**		**RR 1.03** (0.45 to 2.34)	137 (1 RCT)	⊕⊕⊝⊝ low[1,2]	
	786 per 1000	**809 per 1000** (354 to 1000)				
Proportion of participants with investigator-rated clinically significant hair regrowth Assessed with: 7-point rating scale (-3 = greatly decreased to +3 = greatly increased) Follow-up: mean 12 months	**Study population**		**RR 0.77** (0.31 to 1.90)	137 (1 RCT)	⊕⊕⊝⊝ low[1,2]	Finasteride was no more effective than placebo, this is consistent with the assessments of the participants
	186 per 1000	**143 per 1000** (58 to 353)				
Change from baseline to study conclusion in total hair count	**Study population**		Not estimable	231 (3 RCTs)	⊕⊕⊝⊝ low[3,4]	In two of the studies (Price 2000 and Whiting 1999) there was no clinically meaningful difference whilst in Keene 2011 there was a difference of around 17 hairs in favour of finasteride
	Not pooled	Not pooled				
Degree of hair shedding from baseline to the end of the study	—		—	137 (1 RCT)	⊕⊕⊝⊝ low[1,5]	Although the investigators in Price 2000 provided no data, they reported that there was no statistically significant difference in the slowing down of hair loss between the two groups
Cosmetic appearance of the hair or participant satisfaction Follow-up: mean 12 months	**Study population**		**RR 0.78** (0.40 to 1.53)	137 (1 RCT)	⊕⊕⊝⊝ low[1,2]	
	229 per 1000	**178 per 1000** (91 to 350)				

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Change in quality (or pattern) of hair regrowth (e.g. thickness) - not measured	See comment	See comment	Not estimable	(0 studies)	—	This outcome was not assessed in any of the studies

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **FPHL:** female pattern hair loss;**RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded 1 level for serious risk of bias as we judged key domains of risk of bias, i.e. sequence generation, allocation concealment, and blinding as 'unclear'.
[2]Downgraded 1 level for serious imprecision due to wide CIs, small sample size, and not meeting the optimal information size.
[3]Downgraded 1 level for serious risk of bias as in 2 studies key domains of risk of bias, i.e. sequence generation, allocation concealment, and blinding were judged 'unclear'. Furthermore in Whiting 1999 the drop-out ratio was > 30% and the analysis was per-protocol.
[4]Downgraded 1 level for serious inconsistency as in Price 2000 and Whiting 1999 there was no meaningful difference, while Keene 2011 did show a difference of around 19 hairs in favour of finasteride.
[5]Downgraded 1 level for serious imprecision due to small sample size not meeting the optimal information size.

Summary of findings 4. Low-level laser comb versus sham device

Low-level laser comb compared to sham device for female pattern hair loss (FPHL)

Patient or population: women with FPHL
Intervention: low-level laser comb
Comparison: sham device

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with sham device	Risk with low-level laser comb				
Proportion of participants with self-rated clinically significant hair regrowth Assessed with: 5 point Likert scale. However, minimally im-	**Study population**		Not estimable	141 (2 RCTs)	⊕⊕⊕⊖ moderate[1,2]	The participants did not consider the low-level laser comb to be more effective than the sham device (RR 1.54, 95% CI 0.96 to 2.49 for Jimenez 2014a and
	Not pooled	Not pooled				

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proved and improved data are combined by investigators Follow-up: mean 26 weeks						RR 1.18, 95% CI 0.74 to 1.89 for Jimenez 2014b
Change in quality of life - not measured	—	—	—	(0 studies)	—	This outcome was not assessed in any of the studies
Adverse events Follow-up: mean 26 weeks	**Study population**		Not estimable	141 (2 RCTs)	⊕⊕⊝⊝ low[3,4]	The investigators reported that there were "laser comb-related adverse events: dry skin (5.1%), pruritus (2.5%), scalp tenderness (1.3%), irritation (1.3%) & a warm sensation at the site (1.3%)"
	Not pooled	Not pooled				
Participants with investigator-rated clinically significant hair regrowth - not measured	See comment	See comment	Not estimable	(0 studies)	—	This outcome was not assessed in any of the studies
Change from baseline to study conclusion in total hair count Follow-up: mean 26 weeks	Not estimable	Not estimable	—	122 (2 RCTs)	⊕⊕⊝⊝ low[2,5]	There were statistically significant differences in favour of low-level laser comb. MD 17.40 hairs, 95% CI 9.74 to 25.06 (Jimenez 2014a); MD 17.60 hairs, 95% CI 11.97 to 23.23 (Jimenez 2014b)
Degree of hair shedding from baseline to the end of the study - not measured	—	—	—	(0 studies)	—	This outcome was not assessed in any of the studies
Cosmetic appearance of the hair or participant satisfaction Follow-up: mean 26 weeks	**Study population**		Not estimable	141 (2 RCTs)	⊕⊕⊕⊝ moderate[1,2]	Minimally improved or improved thickness or fullness of the hair: RR 1.46, 95% CI 0.86 to 2.49 for Jimenez 2014a and RR 1.33, 95% CI 0.76 to 2.33 for Jimenez 2014b
	Not pooled	Not pooled				
Change in quality (or pattern) of hair regrowth (e.g. thickness) - not measured	See comment	See comment	Not estimable	(0 studies)	—	This outcome was not assessed in any of the studies

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio; **ITT:** intention-to-treat; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **FPHL:** female pattern hair loss;**RCT**: randomised controlled trial; **MD:** mean difference

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

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[1]Not downgraded for risk of bias, due to the fact we recalculated the RR for the intention-to-treat (ITT) population, whilst in both studies (Jimenez 2014a; Jimenez 2014b) these were analysed as per-protocol.
[2]Downgraded 1 level for serious imprecision, due to wide CIs for both studies, due to small sample size, and not meeting optimal information size.
[3]Downgraded 1 level for serious risk of bias, due to the fact there was a drop-out rate of 19.2% in Jimenez 2014a and 9.5% in Jimenez 2014b, and data analysis was per-protocol. Furthermore, the trials did not provide exact data of adverse events per treatment arm.
[4]Downgraded 1 level for imprecision, due to small sample size, and not meeting optimal information size.
[5]Downgraded 1 level for serious risk of bias, due to the fact there was a drop-out rate of 19.2% in Jimenez 2014a and 9.5% in Jimenez 2014b, and data analysis was per-protocol.

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BACKGROUND

We have listed unfamiliar terms in the 'Glossary of terms' (Table 1).

Description of the condition

Definition and clinical features

Female pattern hair loss (FPHL) is an increasingly common clinical problem in women (Bienová 2005; Gan 2005; Hoffmann 2000), with over 21 million affected in the USA alone (Leavitt 2008). However, as the androgen-dependent (male hormone) nature of the condition has not been clearly established, it has been proposed that in women the commonly-used term 'androgenic alopecia' (AGA) should be replaced by 'female pattern hair loss' (FPHL) (Olsen 2001; Yip 2011). Both terms can be found in the literature and are often used interchangeably.

Hair growth occurs in cycles of various phases: anagen is the growth phase; catagen is the involuting or regressing phase; and telogen, the resting or quiescent phase (Dinh 2007). FPHL is characterised by the production of shorter and finer hairs due to progressive miniaturisation of hair follicles, so fine vellus hairs are produced instead of thicker terminal hairs (Trüeb 2002). Hair shedding can vary in intensity over time and from individual to individual. The onset of hair loss may precede menarche in young women or occur as late as the sixth decade of life (Olsen 2001; Olsen 2005; Yip 2011). Women who present to their doctor with a reduction in hair density often have thinning and widening of the area of hair loss on the central part of the scalp, which includes a breach of the frontal hairline. This sequence of symptoms is generally described as a 'Christmas tree' pattern (Blume-Peytavi 2011b; Olsen 2008) (see Figure 1 and Figure 2). The frontal hairline may or may not be preserved; however, as with male pattern hair loss, the degree of loss of hair from the temples does not necessarily correlate with the presence or severity of mid-frontal scalp hair loss (Sinclair 2005; Yip 2011).

Figure 1. Stage 1 on Ludwig scale (mild female pattern hair loss). Copyright © 2011 Department of Dermatology, Leiden University Medical Centre: reproduced with permission.

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Figure 2. Stage 3 on Ludwig scale (severe female pattern hair loss). Copyright © 2011 Department of Dermatology, Leiden University Medical Centre: reproduced with permission.

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The clinical evaluation and definition of the pattern of hair loss in women with FPHL has traditionally relied on the Ludwig (three-point) classification (Ludwig 1977); however, a five-point grading scale has been introduced more recently (Dinh 2007; Sinclair 2004). In all three Ludwig stages, there is hair loss in increasing severity on the front and top of the scalp, with relative preservation of the frontal hairline; the back and sides may or may not be involved (Ludwig 1977). In the five-point mid-frontal grading scale (visual analogue scale (VAS)), stage one represents the normal female hair pattern; stage two, mild hair loss; and the other stages, more severe hair loss (Gan 2005).

The diagnosis of FPHL in women is supported by a history of gradual thinning of the scalp hair over a period of months to years, which is characterised by a diffuse reduction of hair density over the crown and mid-frontal scalp region (Atanaskova Mesinkovska 2013; Birch 2002; Dinh 2007; Messenger 2006). In women with FPHL, a family history may not be as clearly defined as in men with AGA (Olsen 2005), and although there is often a positive association between family history and FPHL or AGA, a negative history should not specifically preclude a diagnosis of FPHL (Blume-Peytavi 2011b). A detailed history, including any family history of FPHL or AGA, and a thorough clinical examination should be undertaken, and this needs to include examination for features of hyperandrogenism (Atanaskova Mesinkovska 2013; Blume-Peytavi 2011b; Dinh 2007). Clinical evaluation should include examination of the scalp skin, hair density, and facial (including eyebrows and eyelashes) and body hair, as well as signs of acne, hirsutism, or both. If the medical history suggests hyperandrogenism, an examination for cliteromegaly should also be undertaken (Blume-Peytavi 2011b; Dinh 2007).

Women with menstrual cycle disturbances or those exhibiting marked acne, hirsutism, or both, should be investigated fully (Dinh 2007). The tests include the free androgen index test (FAI), and measurement of the levels of sex hormone-binding globulin (SHBG) and prolactin (Blume-Peytavi 2011b). More details on laboratory testing and excluding other causes of FPHL are found in the S1 guideline for diagnostic evaluation in androgenetic alopecia in men, women, and adolescents (Blume-Peytavi 2011b). Polycystic ovary syndrome is the most common cause of hyperandrogenism, and although virilizing tumours may be implicated, they tend to be rare and characterised by recent onset and rapidly progressing severe hair loss, among other features (Blume-Peytavi 2011b; Dinh 2007; Sinclair 2011; van Zuuren 2015). However, a lack of clinical evidence of hyperandrogenism does not necessarily rule out the presence of biochemical hyperandrogenism (Dinh 2007).

Loss of hair can also expose the scalp to sun damage and pose an increased risk of skin cancer (Yip 2011).

Other possible causes of hair loss must be considered; thus, the differential diagnosis of FPHL should include telogen effluvium (Sinclair 2005). Chronic telogen effluvium is defined as excessive shedding of hair for at least six months without a noticeable widening of the area of hair loss in the midfrontal scalp region (Dinh 2007). It can occur as a primary idiopathic event; secondary to thyroid disease, systemic lupus erythematosus, or end-stage renal disease; or it may be due to certain drugs or nutritional deficiencies (Camacho-Martínez 2009; Dinh 2007; Sinclair 2004). A sudden increase in hair loss is more consistent with a diagnosis of acute telogen effluvium, which may follow childbirth, severe systemic illness, or may be precipitated by certain medications (Dinh 2007). Alopecia areata diffusa is characterised by diffuse, patchy hair shedding in sharply defined areas (Leavitt 2008). It usually affects women over 40 years of age, many of whom are misdiagnosed as having telogen effluvium (Trüeb 2010).

Symptoms

Hair loss can have a significant negative psychological impact on both men and women (Dolte 2000; Hadshiew 2004; Levy 2013; Sinclair 2011). However, because hair has important social and psychological relevance to women, they tend to suffer more than men. A woman's hair is within her control to create her femininity, beauty, and sexuality. It is an "essential part of self-identity (or 'body-image')" (Cash 2001). For many people, hair is a "physical attribute that expresses individuality, and it is central to feelings of attractiveness or unattractiveness" (Cash 2001). In women it can be a source of concern in terms of feeling removed from what is considered a 'normal' female appearance (Cash 2001).

Studies have revealed that women with FPHL experience increased levels of self-consciousness, feelings of unattractiveness, shame, discomfort, and emotional stress; some of which can lead to social withdrawal (Cash 2001; Reid 2011; van der Donk 1991). The Women's Androgenetic Alopecia Quality of Life Questionnaire (WAA-QOL) is a validated instrument, which has been used to assess the impact of FPHL on quality of life (QoL) in women (Dolte 2000). However, recent research has indicated that the severity of a woman's hair loss is not a reliable predictor of QoL or perception of severity in hair loss (Reid 2011). People may often rate their hair loss more severely than a dermatologist (Biondo 2004); therefore, clinicians should be alert to the possible impact of a woman's perception of hair loss on her QoL.

Epidemiology and causes

Although FPHL is the most common type of hair loss in women, estimates of its true prevalence vary widely (Trüeb 2002). The fact that investigators tend to use different diagnostic criteria (and usually don't describe them clearly) may contribute to the variation in prevalence figures. However, it is generally recognised that the prevalence of FPHL increases with age (Dinh 2007). The prevalence of FPHL among women aged between 20 to 29 years increases from 12% to approximately 60% for women aged 80 and over (Gan 2005; Yip 2011). It is reported to be lower in Asian women, and although prevalence is considered to be less in African women, very limited data are available to support this contention (Blume-Peytavi 2011b).

Genetic predisposition as well as hormonal factors are involved in the cause of FPHL (Dinh 2007). Most women with FPHL do not have signs and symptoms of androgen excess, and systemic androgen levels are, in general, normal (Atanaskova Mesinkovska 2013; Blume-Peytavi 2011b; Olsen 2005; Yip 2011). In these women, the local conversion of testosterone into dihydrotestosterone in the hair follicles is supposed to initiate terminal to vellus transformation (Price 2003).

A complex pattern of inheritance and a number of genes are considered to be associated with FPHL (Ali 2008; Atanaskova Mesinkovska 2013; El-Samahy 2009; Richeti 2013; Sinclair 2011; Westberg 2001; Yip 2011). A variation of the androgen receptor gene has been identified in postmenopausal women, leading to increased serum levels of androgens (Ali 2008). In premenopausal women, certain variants of the androgen receptor gene and the

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oestrogen receptor beta gene seem to be involved (Westberg 2001). The role of oestrogens (female sex hormones) are probably of equal importance to that of androgens, but whether oestrogens have a stimulatory or an inhibitory effect is still a matter of debate (Yip 2011).

Low ferritin (iron-containing proteins) levels have been suggested as possible contributory factors in FPHL (Kantor 2003), although a more recent study did not support this (Olsen 2010).

"The demonstration of thyroid hormone receptor expression in hair follicle cells indicates that thyroid hormone may affect hair growth directly" (Messenger 2000). In view of the "similarity between hair loss in hypothyroidism and FPHL, the implications may extend to other forms of hair loss besides that seen in thyroid deficiency" (Messenger 2000).

Description of the intervention

Current treatment options for women with FPHL are either topical (applied to the scalp) or systemic (taken orally).

- Topical: minoxidil, aminexil, oestrogens, or alfatradiol (Atanaskova Mesinkovska 2013; Dinh 2007; Olsen 2005).
- Systemic: hormonal contraception, cyproterone acetate, finasteride, spironolactone, and flutamide (Atanaskova Mesinkovska 2013; Bienová 2005; Dinh 2007; Olsen 2005).

Minoxidil is an antihypertensive vasodilator (Atanaskova Mesinkovska 2013). The topical formulation is available in three concentrations (1%, 2%, and 5%), with the 2% concentration applied once daily and the 5% either once or twice daily as the most commonly prescribed treatments (Atanaskova Mesinkovska 2013; Blumeyer 2011; Dinh 2007). Minoxidil as a 1% concentration is less frequently used, and in most countries, the 5% concentration is only registered for the treatment of AGA in men (Rogers 2008). Common side-effects include scalp irritation and hypertrichosis on the cheeks and forehead (Rogers 2008). Minoxidil is contraindicated in pregnant and lactating women (Rogers 2008).

Aminexil is a derivative of minoxidil, which is available as a shampoo and in vials (Blumeyer 2011), but it has not been approved by either the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).

Twice daily applications of 1% to 5% tincture of progesterone (a major hormone in the female menstrual cycle) can be used, but not in concentrations greater than 2%, or more than 2 mL per day, as it may cause menstrual irregularities. Topical oestrogens include fulvestrant twice daily or topical estradiol valerate 0.03% once daily (Gassmueller 2008; Georgala 2004). Alfatradiol is a 5-alpha-reductase inhibitor, but it is not freely available in many countries (Blume-Peytavi 2007).

Systemic treatments that focus on antiandrogenic therapy include cyproterone acetate, spironolactone, finasteride, and flutamide (Atanaskova Mesinkovska 2013; Bienová 2005; Blumeyer 2011; Dinh 2007). As all of these treatments carry the risk of malformation in male foetuses, effective contraceptive advice should be provided to women of childbearing age (Blumeyer 2011; Olsen 2005).

Cyproterone acetate treatment is often used as a combination therapy of 2 mg in oral contraceptives plus cyproterone acetate up to 100 mg/day on days five to 15 of the menstrual cycle (Blumeyer 2011; Camacho-Martínez 2009). Important side-effects are depression, weight gain, breast tenderness, and loss of libido (Leavitt 2008).

Finasteride can be prescribed in varying doses, between 1 and 5 mg, and is generally well-tolerated, but some women may experience breast tenderness and increased libido (Dinh 2007). Furthermore, it is not registered by the FDA or EMA for use in women.

Spironolactone (a diuretic, which is also used as an antiandrogen) in a dose of 50 to 200 mg/day, is one of the most frequently prescribed medications for FPHL in the USA (Dinh 2007; Leavitt 2008). Well known side-effects are electrolyte imbalance, cycle disturbances, fatigue, drowsiness, urticaria, breast tenderness, hypotension, and haematological disturbances (Dinh 2007). Therefore, especially in the first weeks or months, blood pressure and electrolyte screening should be monitored (Dinh 2007).

Flutamide is not a first-line drug due to its potentially severe hepatotoxic effects, but it has been used as a last-resort treatment (Yazdabadi 2011).

There has also been a steadily increasing interest in a variety of low-level laser treatment options over recent years (Jimenez 2014a; Jimenez 2014b; Lanzafame 2014).

Other considered treatments include food and herbal supplements, hair transplantation, and less frequently used medical treatments (e.g. dutasteride, cimetidine, tretinoin, and ketoconazole) (Atanaskova Mesinkovska 2013; Blumeyer 2011; Dinh 2007). Cosmetic aids are other important management options and include hairstyling techniques, hair replacements, camouflage products, and hair accessories (Dinh 2007; Inui 2013).

As soon as treatment is stopped, shedding of hair may resume within weeks Dinh 2007). Women with FPHL need thoughtful evaluation and management as well as reassurance (Dinh 2007; Price 2003), especially when current options for the treatment of this condition do not appear to demonstrate any long-term or permanent benefits.

How the intervention might work

Strategies to improve scalp hair density include prolongation of anagen duration, reversal of terminal to vellus transformation, or generation of de novo hair induction from the inter-follicular epidermis (Ellis 2002). Minoxidil has a direct effect on the proliferation and differentiation of follicular keratinocytes (epidermal cells), leading to a prolongation of the anagen phase (Rogers 2008). In essence, it encourages hair to move from the resting stage to the active growth stage (Rogers 2008). Potassium channels found in human hair follicles may play a role in this process, but the exact mechanism of action is still unclear (Shorter 2008). Aminexil, a derivative of minoxidil, has a similar mode of action (Blumeyer 2011).

Cyproterone acetate is a progestin (synthetic hormone) with antiandrogen action. It acts by blocking androgen receptors, which prevents androgens (male hormones) from binding to these receptors and suppresses luteinizing hormone (which in turn reduces testosterone levels) (Dinh 2007; Leavitt 2008). It is often combined with oral contraceptives, especially ethinyl estradiol 35 µg with 2 mg cyproterone acetate (Blumeyer 2011; Dinh 2007; Leavitt 2008). Spironolactone reduces the activity of

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5-alpha-reductase, inhibits the biosynthesis of androgens, and has a direct antagonistic effect on androgen receptors (Dinh 2007; Leavitt 2008). Finasteride is a selective inhibitor of 5-alpha-reductase, which reduces the conversion of testosterone into dihydrotestosterone (DHT) (Bienová 2005; Rogers 2008), thereby lowering serum and scalp levels of DHT, while increasing scalp levels of testosterone. Low-level laser treatment options may increase anagen hairs by stimulating epidermal stem cells in the hair follicle bulge (Atanaskova Mesinkovska 2013; Avci 2013).

Why it is important to do this review

Although a range of options are available for the treatment of FPHL, it is unclear how effective they are and if any have a long-term beneficial effect. Many of these interventions may have important and undesirable side-effects. This Cochrane review is needed to clarify the best approach to treating this condition, to provide reliable decision-making information to clinicians and people with the condition about the benefits and harms of available treatments, and to be the basis for recommendations for future research.

OBJECTIVES

To determine the efficacy and safety of the available options for the treatment of female pattern hair loss in women.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Any woman of any age who had been diagnosed with female pattern hair loss (FPHL) or androgenic alopecia (AGA) by a dermatologist or clinician. We included women with increased circulating androgens, whether due to physiological causes, polycystic ovary syndrome, or any other causes. However, we excluded women with androgen-producing adrenal or ovary tumours.

Types of interventions

We considered any intervention for FPHL or AGA.

Types of outcome measures

Primary outcomes

- The proportion of participants with self-rated clinically significant hair regrowth at the end of the study.
- Change in quality of life (QoL) using any validated and recognised generic or disease-specific instrument, e.g. the Women's Androgenetic Alopecia Quality of Life Questionnaire (WAA-QOL) (Dolte 2000).
- Adverse effects: safety, tolerability, and any reported adverse events.

Secondary outcomes

- Proportion of participants with investigator-rated clinically significant hair regrowth at the end of the study.
- Mean change in total hair count from baseline to the end of the study.
- Degree of hair shedding from baseline to the end of the study.
- Cosmetic appearance of the hair or participant satisfaction.
- Change in quality (or pattern) of hair regrowth (e.g. thickness).

We defined 'clinically significant' outcomes as, for example, a single level change on the Sinclair scale (Messenger 2006; Sinclair 2004). We accepted all outcomes measures that used a recognised generic or validated scale (e.g. Ludwig scale, Sinclair scale).

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

Jan Schoones (JS) updated the following searches to 7 July 2015. Prior searches were done by JS and Skin Group's Information Specialist.

- The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2015, Issue 6) using the search strategy in Appendix 1.
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 2.
- EMBASE via Ovid (from 1974) using the strategy in Appendix 3.
- PsycInfo via Ovid (from 1872) using the strategy in Appendix 2.
- PubMed (from 1947) using the strategy in Appendix 4.
- Web of Science (from 1945) using the strategy in Appendix 5.

The Skin Group's Information Specialist updated the following searches to 15 July 2015.

- The Cochrane Skin Group Specialised Register using the following terms: (androgen* AND alopecia) OR (female AND pattern AND hair AND loss) OR (female and baldness) or (female AND pattern AND alopecia).
- AMED via Ovid (Allied and Complementary Medicine, from 1985) using the strategy in Appendix 6.
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 7.

Trial registries

We searched the following trial registries on 24 July 2015 (Esther J van Zuuren (EvZ) and JS) using the search terms: androgenic alopecia, androgenetic alopecia, and FPHL.

- The ISRCTN registry (www.controlled-trials.com).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

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Searching other resources

Adverse effects

We did not perform a separate search for adverse effects of the target intervention. However, we did examine data on adverse effects from the included studies we identified.

References from published studies

We examined the bibliographies of the included and excluded studies for further references to potentially eligible RCTs.

Correspondence

We contacted the trial investigators and asked them to provide missing data or clarify study details (see Table 2).

Data collection and analysis

We followed the previously published protocol (Cusmanich 2009) for this Cochrane review. This is the first update of the original published Cochrane review (van Zuuren 2012).

Selection of studies

Two review authors (EvZ and Zbys Fedorowicz (ZF)) assessed the titles and abstracts identified from the searches. We only included RCTs that evaluated FPHL in women in this Cochrane review. The two review authors independently assessed each included study to determine whether the predefined selection criteria were met, and they resolved any differences of opinion through discussion within the review team. We have listed the excluded studies and the reasons for their exclusion in the 'Characteristics of excluded studies' section of the review.

Data extraction and management

Two review authors (EvZ and ZF) extracted data using a previously developed data extraction form, and resolved any disagreements on data extraction by consensus. We contacted the trial authors and asked them to provide missing data where possible. Two review authors (EvZ and ZF) checked and entered the data into Review Manager (RevMan) (Review Manager (RevMan) 2014).

Assessment of risk of bias in included studies

Two review authors (EvZ and ZF) independently assessed the risk of bias in the included studies following the domain-based evaluation described in Chapter 8 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). They compared the evaluations, and resolved any inconsistencies by discussion.

We rated the following domains separately for each of the included studies as either 'low risk of bias', 'high risk of bias', or 'unclear' if the risk of bias was uncertain or unknown.

- Whether the allocation sequence was adequately generated ('sequence generation').
- Whether the allocation was adequately concealed ('allocation concealment').
- Whether knowledge of the allocated interventions was adequately prevented during the study ('blinding').
- Whether incomplete outcome data were adequately addressed.
- Whether reports of the study were free of suggestion of selective outcome reporting.
- Whether the study was apparently free of other sources of bias that could put it at high risk of bias, e.g. baseline imbalance.

We have reported these assessments in the 'Risk of bias' table for each individual study in the 'Characteristics of included studies' section of the review.

We also categorised and reported the overall risk of bias of each of the included studies according to the following.

- Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.
- Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were assessed as unclear.
- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

We reported these assessments in the 'Risk of bias in included studies' section.

Measures of treatment effect

We presented continuous outcomes on the original scale as reported in each individual study. In future updates, if included studies report similar outcomes using different scales, we will standardise these by dividing the estimated coefficient by its standard deviation (SD), to allow us to make comparisons between scales.

We presented dichotomous outcomes data as risk ratios (RR). We reported all outcome data with their associated 95% confidence intervals (CIs) and analysed them in RevMan (Review Manager (RevMan) 2014) using the Mantel-Haenszel test, unless we stated otherwise.

Unit of analysis issues

Cross-over studies

We included one cross-over study (Blume-Peytavi 2007), but as this study did not report any wash-out period, we only included data from the first treatment period.

Multi-armed studies

For continuous outcomes, we included participants from the control arms of within multi-arm studies approximately equally in the pair-wise comparisons with the active intervention arms. The mean and SD summary statistics for the placebo participants remained unchanged.

Dealing with missing data

We successfully contacted the investigators of several included trials (see Table 2). We re-analysed the data according to a treatment by allocation principle, whenever possible, and according to Section 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If study authors did not report data and had conducted a per-protocol analysis, we inspected the degree of imbalance in the dropout rate between the trial arms to determine the potential impact of bias. In the absence of a treatment by allocation population, we used an available case population and reported this accordingly.

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Assessment of heterogeneity

We assessed clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, and the interventions. Also, we determined the degree of heterogeneity between the studies using the I^2 statistic. We reported heterogeneity as important if it was at least moderate to substantial by an I^2 statistic value of greater than 60% (Higgins 2011). If we could explain this by clinical reasoning and could make a coherent argument for combining the studies, we entered these into a meta-analysis. In cases where we could not adequately explain the heterogeneity, we did not pool the data.

The clinical diversity between the studies included in this review, as well as the limited number of studies that we could combine for each intervention, only allowed us to make assessments of heterogeneity between the studies for two of the comparisons.

Assessment of reporting biases

We performed assessments of reporting bias following the recommendations on testing for funnel plot asymmetry (Egger 1997), as described in Section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), for primary and secondary outcomes where we performed meta-analysis (at least three studies needed). We only presented funnel plots where there was some evidence of asymmetry in the plots. We explored the possible sources of asymmetry with an additional sensitivity analysis.

Data synthesis

Two review authors (EvZ and ZF) analysed the data in RevMan (Review Manager (RevMan) 2014) and reported them in accordance with the advice in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We only performed a meta-analysis if we were able to identify an adequate number of studies ($n \geq 3$) that investigated similar interventions and reported data that exhibited not less than moderate heterogeneity (Treadwell 2006). We used a fixed-effect model to pool the data into a meta-analysis, and we fitted a random-effects model as part of a sensitivity analysis to explore the degree of heterogeneity between studies.

Subgroup analysis and investigation of heterogeneity

We analysed the different concentrations of the interventions as subgroups by comparing the RRs and 95% CI. If we observed differences in effect estimates between the subgroups, we analysed these separately.

In future updates of this Cochrane review and if a sufficient number of studies examining similar comparisons are available, we will consider if any further subgroup analyses are warranted, for example, age groups, pre- and postmenopausal, ethnic background, and the presence of hyperandrogenism.

Sensitivity analysis

We performed sensitivity analyses to assess the robustness of the results of this review; thus, we repeated all fixed-effect meta-analyses using random-effects models. We conducted an additional sensitivity analysis, which excluded one study (Price 1990) with suspected reporting bias in comparison one, i.e. minoxidil versus placebo, and a further sensitivity analysis in comparison two i.e. minoxidil (2%) versus minoxidil (5%), which excluded one study, which had twice the number of adverse events in the 5% treatment arm (Lucky 2004).

RESULTS

Description of studies

Results of the search

Our earlier searches retrieved 334 references to studies plus 10 references from other sources. The updated searches provided 563 references to studies in addition to 30 ongoing studies (of which seven appear to be completed and had data available on clinicaltrials.gov and we could include, and 11 were terminated or completed but no data available which are listed under Characteristics of studies awaiting classification) (see Figure 3). The total number of references retrieved for both sets of searches was therefore 937. There were 923 records after removal of duplicates. After examination of the titles and abstracts, we excluded 813 of these references from the review. We obtained full-text copies of the remaining 110 records for further evaluation. We translated several studies that were not published in the English language — two in Chinese (Li 1996; Sheng 2014), two in Farsi (Enshaieh 2005; Golpour 2013), three in Korean (Hong 2007; Kim 2009; Shin 2007), one in Spanish (Guerrero 2009), one in German (Gehring 2000), and three in Italian (Farella 1991; Minozzi 1997; Policarpi 1993) — prior to assessment for eligibility.

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Figure 3. Study flow diagram.

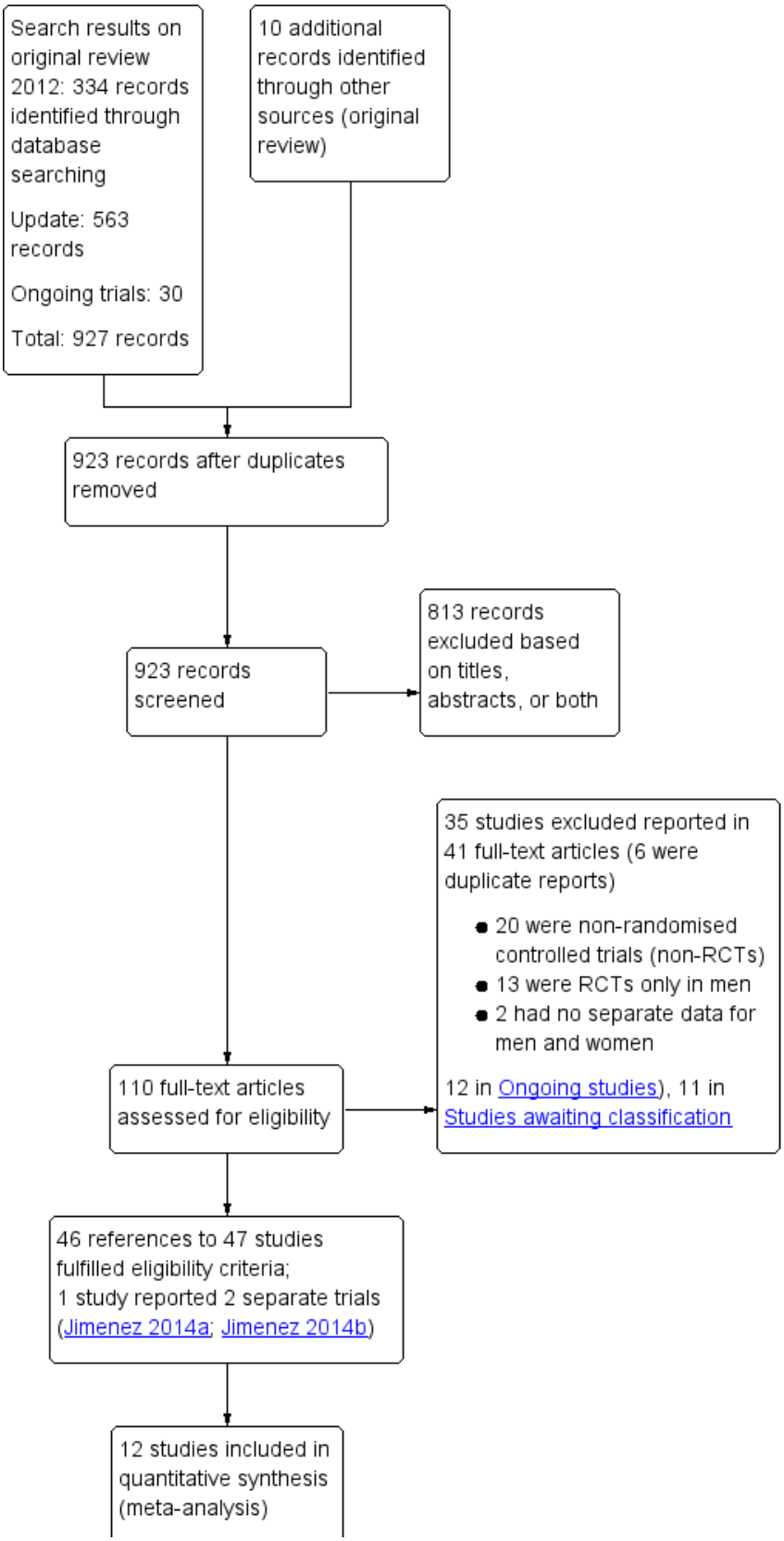

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Figure 3. (Continued)

(meta-analysis)

We excluded 35 studies reported in 41 records; six were duplicate reports of studies (see the 'Characteristics of excluded studies' section). We did not include 23 ongoing studies (seven of the 30 ongoing studies were already completed) in the analyses (see the 'Characteristics of ongoing studies' section), but we will include these in future updates of this review when data are available.

Overall, we included 46 references to 47 studies but with two separate trials included in one report (Jimenez 2014a; Jimenez 2014b). For further details, see the 'Study flow diagram' (Figure 3).

Included studies

This update added 25 further studies to the existing 22 studies included in the previous version of this review (van Zuuren 2012). The 47 studies comprised a total of 5290 participants (see the 'Characteristics of included studies' section).

Characteristics of the trial setting and methods

All of the included studies were randomised controlled trials, 29 had a placebo, 14 had an active control treatment arm, and four studies included both a placebo and an active control arm. Eleven studies were conducted prior to the year 2000. The duration of most studies was between six and 12 months, with a mean of 30.4 weeks. Twenty-two studies were conducted in Europe, 18 in the USA or Canada, two in Central- or South America, and 10 in Asia.

Characteristics of the participants

The number of participants included in the individual studies varied widely, from six to 404 women, with a mean of 112 participants. The age of the participants ranged from 18 to 89 years, with most between 18 and 60 years and a mean of 40.5 years. All women had been diagnosed with androgenic alopecia (AGA) or female pattern hair loss (FPHL), and two studies included hyperandrogenic women (Carmina 2003; Vexiau 2002).

Characteristics of the interventions

The included studies evaluated a wide range of interventions: 17 studies assessed minoxidil (Blume-Peytavi 2007; Blume-Peytavi 2011a; DeVillez 1994; Jacobs 1993; Lucky 2004; NCT01145625; NCT01226459; NCT01655108; NCT01900041; Olsen 1991; Pazoki-Toroudi 2012; Price 1990; Rietschel 1987; Sheng 2014; Tsuboi 2007; Vexiau 2002; Whiting 1992), and six studies examined the effects of finasteride (Carmina 2003; Keene 2011; Mazzarella 1997; Price 2000; Ukşal 1999; Whiting 1999). Two studies included cyproterone acetate in one treatment arm (Carmina 2003; Vexiau 2002), and two other studies evaluated flutamide (Carmina 2003; Ukşal 1999). Five studies investigated laser treatment (Jimenez 2014a; Jimenez 2014b; Kim 2013; Lanzafame 2014; NCT01967277). Two studies examined bimatoprost (NCT01189279; NCT01325350).

A total of 17 studies addressed other interventions: alfatradiol (Blume-Peytavi 2007); essential oil (Bureau 2003); 0.5% octyl nicotinate and 5.0% myristyl nicotinate (Draelos 2005); topical melatonin-alcohol solution (Fischer 2004); topical fulvestrant solution (Gassmueller 2008); an oral combination product of millet seed extract, L-cystine, and calcium pantothenate (Gehring 2000); oestrogen ointment (Georgala 2004; Guerrero 2009); cytopurine/pentadecanoic glyceride (Hong 2007); red ginseng powder capsules (Kim 2009); nutritional supplement (Le Floc'h 2015); systemic oestrogens (Minozzi 1997); oral gelatin cystine and lotion based on gelatine cystine and *Serenoa repens* (Morganti 1998); 0.75% adenosine lotion (Oura 2008); the application of a pulsed electrostatic field (Policarpi 1993); AP-FHG0604T (plant extracts; Shin 2007) and spironolactone (Ukşal 1999). Several trials compared and evaluated a number of these interventions in the different treatment arms.

Characteristics of the outcome measures

Half of the included studies evaluated 'hair regrowth' as assessed by the participants (Blume-Peytavi 2011a; Bureau 2003; Carmina 2003; DeVillez 1994; Hong 2007; Jacobs 1993; Jimenez 2014a; Jimenez 2014b; Kim 2013; Le Floc'h 2015; Lucky 2004; Mazzarella 1997; NCT01226459; NCT01325350; NCT01655108; Olsen 1991; Oura 2008; Pazoki-Toroudi 2012; Policarpi 1993; Price 2000; Shin 2007; Tsuboi 2007; Whiting 1992), which was the primary outcome for this review. However, none of these outcomes were measured or reported according to the definition of 'clinically significant' hair regrowth, which was prespecified for this review (see the 'Types of outcome measures' section).

The outcome measures used to assess hair regrowth consisted of questionnaires that assessed these outcomes using three- to seven-point scales. They included a wide range of scaling items, many of which were inadequately defined, i.e. 'none, mild, moderate improvement' or 'worsened to marked improved', and were not matched across the included studies. Three studies reported that they had applied a "modified version of a validated self-administered hair growth questionnaire" (Carmina 2003; Oura 2008; Price 2000), which was developed in a previous study (Barber 1998). The investigators provided no details of how and if their 'modified version' was tested prior to its use, and as it was originally designed for the evaluation of interventions for male pattern baldness, its validity as an assessment tool for FPHL is unclear. Two studies utilised a standard 100 mm visual analogue scale (VAS) for participant assessments of hair growth (Lucky 2004; Shin 2007). Benefit from treatment was scored: 0 = "no benefit" to 100 = "great benefit". Lucky 2004 was also the only included study to assess the effects of two of the interventions on quality of life (QoL), a key primary outcome for this review. The study used a six-item VAS-based questionnaire for these assessments, but did not indicate if the instrument had been previously tested or validated.

A large proportion of the trials (32) assessed treatment-associated adverse events either through questionnaires that rated the "tolerability of treatment" (Blume-Peytavi 2007) or "dermal reactions", such as erythema, scaling, and itching (Gassmueller 2008), or these were reported as incidental events by the participants during the course of the individual study.

Several included studies assessed the secondary outcomes for this review, but in general, the methods of measurement and the timing of the assessments were not uniform across these studies. Over half of the studies included two of the secondary outcomes,

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i.e. investigator-rated clinically significant hair regrowth and the change in total hair count from baseline to study conclusion. Eleven studies addressed hair shedding (Carmina 2003; Guerrero 2009; Hong 2007; Kim 2009; Le Floc'h 2015; Mazzarella 1997; Oura 2008; Pazoki-Toroudi 2012; Tsuboi 2007; Vexiau 2002; Whiting 1992). Twelve studies assessed cosmetic appearance and 'patient' satisfaction (Blume-Peytavi 2011a; Carmina 2003; Draelos 2005; Kim 2009; Kim 2013; Le Floc'h 2015; Lucky 2004; NCT01655108; Oura 2008; Price 2000; Thom 2001; Thom 2006).

Fourteen studies evaluated one of the secondary outcomes for this review, i.e. quality and pattern of hair regrowth (Blume-Peytavi 2007; Blume-Peytavi 2011a; Bureau 2003 ; Carmina 2003; Gassmueller 2008; Jimenez 2014a; Jimenez 2014b; Kim 2009; Kim 2013; Le Floc'h 2015; NCT01325350; NCT01655108; NCT01900041; Oura 2008).

We examined any of the patient-reported outcomes (PROs) presented in the included studies against the 'checklist for describing and assessing PRO's in clinical trials' (see Table 3), which is provided in Chapter 17.6.a of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Excluded studies

We excluded 35 studies, and reported the reasons for their exclusion in the 'Characteristics of excluded studies' tables. We excluded all of these studies only after assessment of the full-text reports. The most frequent reason for their exclusion was that they were non-RCTs, or because they included only male participants.

Risk of bias in included studies

We assessed each included study for risk of bias and reported the judgements for the individual domains in the 'Risk of bias' table associated with each study. We have also presented these in the 'Risk of bias' graph in Figure 4 and the 'Risk of bias' summary in Figure 5.

Figure 4. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

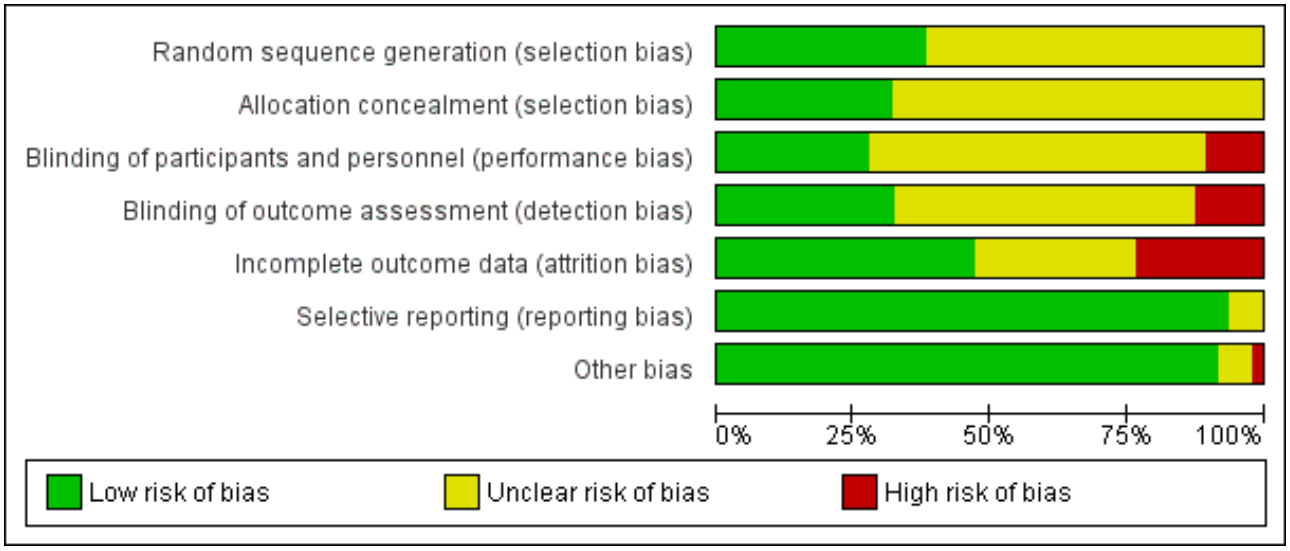

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Figure 5. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

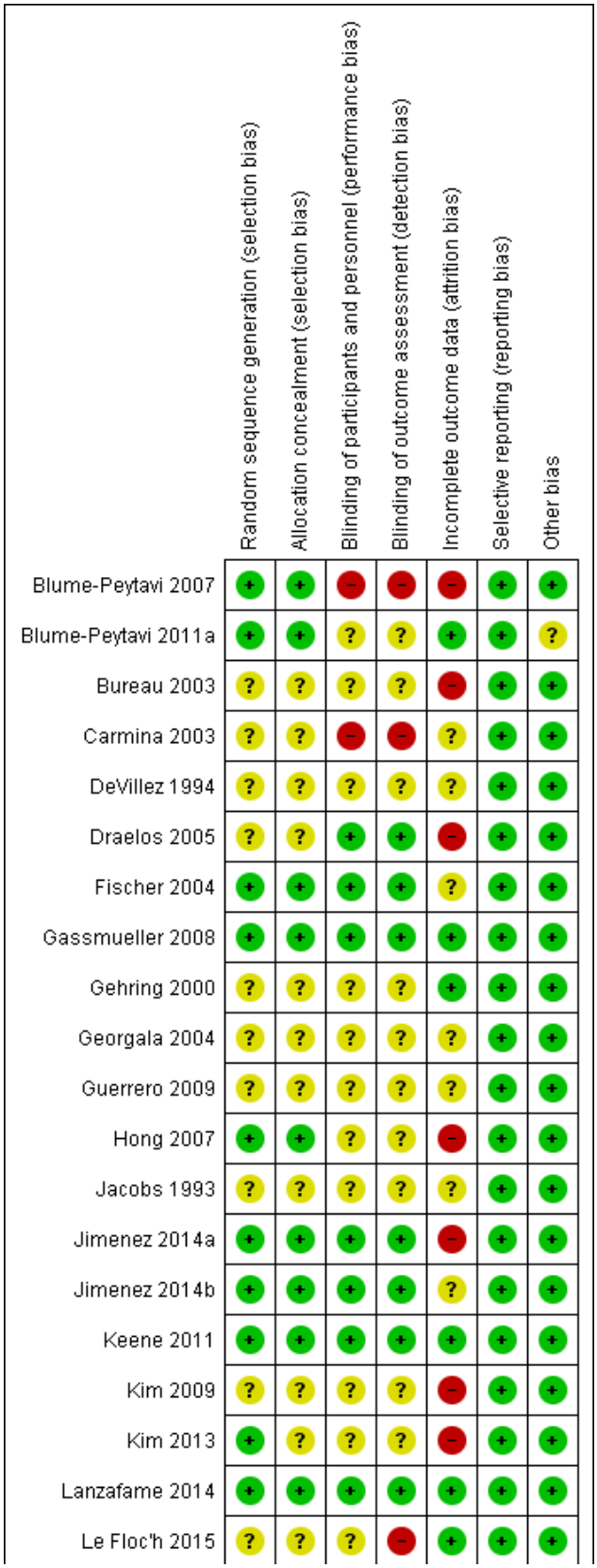

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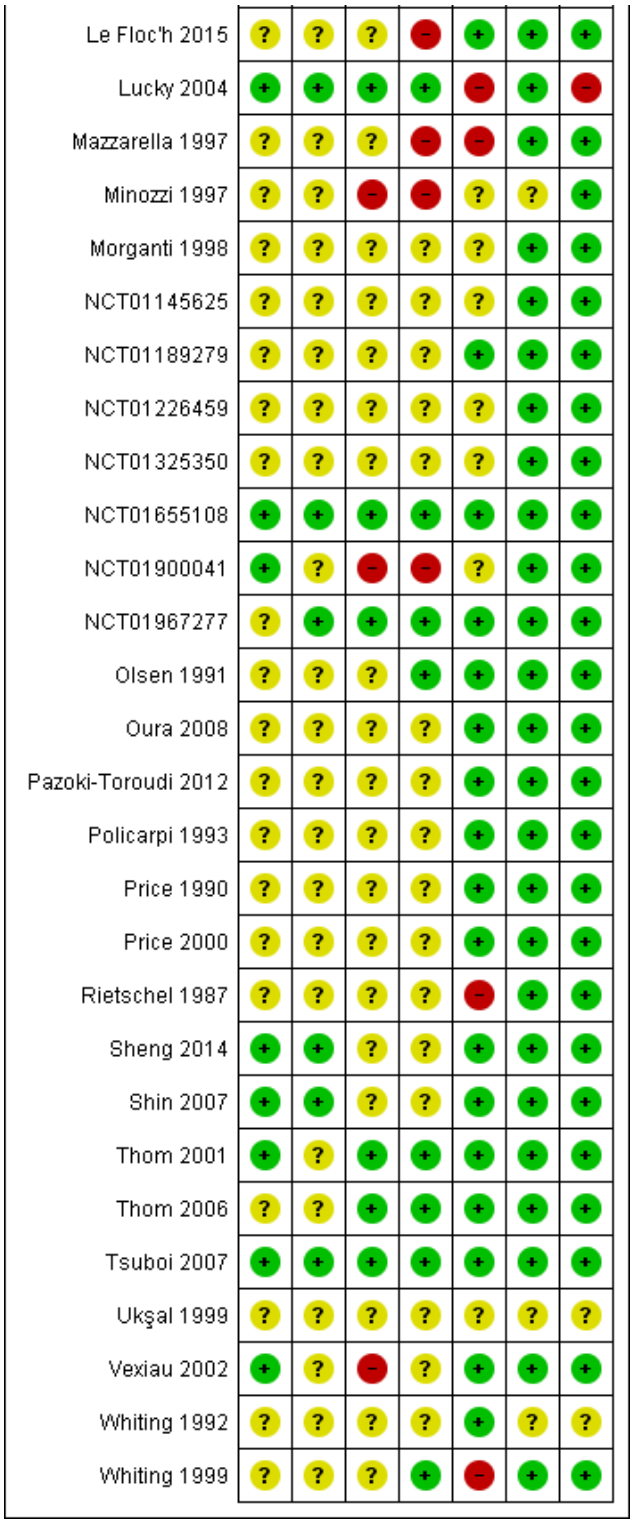
Figure 5. (Continued)



We assessed the overall risk of bias for each included study, and we considered five studies to be at 'low risk of bias' as they met all criteria across all domains in the Cochrane 'Risk of bias' assessment tool (plausible bias unlikely to seriously alter the results) (Gassmueller 2008; Keene 2011; Lanzafame 2014; NCT01655108; Tsuboi 2007). We categorised 16 studies as at high risk of bias (plausible bias that seriously weakens confidence in the results) because one or more domains received a judgement of high risk (Blume-Peytavi 2007; Bureau 2003; Carmina 2003; Draelos 2005; Hong 2007; Jimenez 2014a; Kim 2009; Kim 2013; Le Floc'h

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2015; Lucky 2004; Mazzarella 1997; Minozzi 1997; NCT01900041; Rietschel 1987; Vexiau 2002; Whiting 1999). We rated the remaining 26 studies as at unclear risk of bias (plausible bias that raises some doubt about the result) because we assessed one or more criteria as unclear.

Some of these assessments were, to a certain extent, based on the inadequate reporting of the criteria that are a prerequisite in the evaluation of methodological rigour, in terms of trial design and conduct. Concealment of the allocation sequence and blinding are key domains in the assessment of risk of bias, and a number of included studies provided insufficient detail to enable us to make accurate judgements. Protocol deviation, losses to follow-up with incomplete data, and subsequent per-protocol analyses were other important sources of potential bias in a number of the included studies. We were able to amend the judgements for a number of the domains after we successfully contacted several trial investigators. For these and further details, see the 'Risk of bias' tables in the 'Characteristics of included studies' section.

Allocation

The methods used to generate the allocation sequence and how the sequence was concealed, such that participants and investigators enrolling participants could not foresee the upcoming assignment, are the most important and sensitive indicators that bias has been minimised in a clinical trial (Schulz 1995).

Sequence generation

Eighteen studies described in sufficient detail the method used to generate the allocation sequence (Blume-Peytavi 2007; Blume-Peytavi 2011a; Fischer 2004; Gassmueller 2008; Hong 2007; Jimenez 2014a; Jimenez 2014b; Keene 2011; Kim 2013; Lanzafame 2014; Lucky 2004; NCT01655108; NCT01900041; Sheng 2014; Shin 2007; Thom 2001; Tsuboi 2007; Vexiau 2002). Therefore, we judged these studies as at low risk of bias for this domain. We considered the remaining 29 studies as at unclear risk of bias.

Allocation concealment

Pharmacy-controlled, central allocation or sequentially numbered, opaque, sealed envelopes/packets ensured that the intervention allocations could not have been foreseen in advance of, or during, enrolment in 15 studies (Blume-Peytavi 2007; Blume-Peytavi 2011a; Fischer 2004; Gassmueller 2008; Hong 2007; Jimenez 2014a; Jimenez 2014b; Keene 2011; Lanzafame 2014; Lucky 2004; NCT01655108; NCT01967277; Sheng 2014; Shin 2007; Tsuboi 2007), which we judged low risk of bias for this domain. The remaining trials did not report the method used to conceal the allocation sequence; thus, they received a judgment of unclear risk of bias for this domain.

Blinding

Thirteen studies described in sufficient detail the measures used to blind study participants and personnel from knowledge of which intervention a participant received (Draelos 2005; Fischer 2004; Gassmueller 2008; Jimenez 2014a; Jimenez 2014b; Keene 2011; Lanzafame 2014; Lucky 2004; NCT01655108; NCT01967277; Thom 2001; Thom 2006; Tsuboi 2007). Blinding was achieved by identical pre-labelled bottles, tablets, devices, or packages. As five studies were open label (Blume-Peytavi 2007; Carmina 2003; Minozzi 1997; NCT01900041; Vexiau 2002), the outcome or outcome measurement was likely to be influenced by lack of blinding. In these studies, we judged this domain as at high risk of bias. Inadequate reporting did not permit us to make a clear judgement for this domain in the other 29 studies.

Fifteen studies ensured blinding of outcome assessment (Draelos 2005; Fischer 2004; Gassmueller 2008; Jimenez 2014a; Jimenez 2014b; Keene 2011; Lanzafame 2014; Lucky 2004; NCT01655108; NCT01967277; Olsen 1991; Thom 2001; Thom 2006; Tsuboi 2007; Whiting 1999). In six studies, we judged that there was a high risk of detection bias mainly due to the open-label design (Blume-Peytavi 2007; Carmina 2003; Le Floc'h 2015; Mazzarella 1997; Minozzi 1997; NCT01900041), whilst for the remainder (26 studies), we judged this domain as at unclear risk of bias.

Incomplete outcome data

In slightly less than half of the included studies (22), incomplete outcome data appear to have been adequately addressed. The losses to follow-up were reasonably well-balanced across intervention groups, with similar reasons for missing data across the groups. However, in 11 studies, the high dropout rate and subsequent per-protocol analysis of the data resulted in a judgement of high risk of bias for this domain (Blume-Peytavi 2007; Bureau 2003; Draelos 2005; Hong 2007; Jimenez 2014a; Kim 2009; Kim 2013; Lucky 2004; Mazzarella 1997; Rietschel 1987; Whiting 1999).

The remaining 14 studies reported insufficient information to permit a clear judgment of the risk of bias for this domain (Carmina 2003; DeVillez 1994; Fischer 2004; Georgala 2004; Guerrero 2009; Jacobs 1993; Jimenez 2014b; Minozzi 1997; Morganti 1998; NCT01145625; NCT01226459; NCT01325350; NCT01900041; Ukşal 1999).

Selective reporting

Protocols were available for only 13 included studies (Blume-Peytavi 2011a; Jimenez 2014a; Jimenez 2014b; Keene 2011; Lanzafame 2014; Le Floc'h 2015; NCT01145625; NCT01189279; NCT01226459; NCT01325350; NCT01655108; NCT01900041; NCT01967277). Based on this information as well as on the details provided in the methods section of the reports, 44 of the 47 studies appear to have reported all prespecified outcomes and we therefore judged them to be free of selective reporting. We considered the remaining three studies to be at unclear risk of bias (Minozzi 1997; Ukşal 1999; Whiting 1992). One of these studies, Ukşal 1999, was reported only as an abstract to conference proceedings, which provided insufficient information to make a clear judgement for this domain. Although Whiting 1992 did not fully report the primary outcomes of participant and investigator assessments of hair regrowth, this did not appear to be intentional; and as the impact of this was unclear, we judged this domain as at unclear risk of bias. The investigators in Minozzi 1997 did not report all of their prespecified outcomes, but it was uncertain to what extent the lack of data for anything other than sex hormone-binding globulin (SHBG) had any impact on their reported results; therefore, we judged this domain as at unclear risk of bias.

Other potential sources of bias

We judged this domain as at 'low risk of bias' in most of the included studies (43). Although the impact of study sponsorship in Lucky 2004 was unclear, the "protocol-prohibited concomitant

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medications" used by a number of participants, mostly in the active intervention group, represented a high risk of bias for this domain in this study. In Blume-Peytavi 2011a, the baseline imbalance between the intervention groups, i.e. a higher proportion of participants with more extensive hair thinning in the 5% minoxidil group, posed a risk of bias for this domain in this study. In Whiting 1992, the potential impact of the wide range in duration (six months to 25 years) of hair loss at baseline was unclear. In Ukşal 1999, which was reported as an abstract, we had insufficient information to permit a judgement.

Effects of interventions

See: **Summary of findings for the main comparison** Minoxidil versus placebo; **Summary of findings 2** Minoxidil 2% versus minoxidil 5%; **Summary of findings 3** Finasteride versus placebo; **Summary of findings 4** Low-level laser comb versus sham device

Fifteen studies provided no usable or retrievable data, and did not contribute further to the results of this review (see Table 4). The main reasons why we could not use data were: studies did not report data separately for men and women, there were very limited data available in abstracts to conference proceedings, or studies did not address any of our outcomes.

We have categorised comparisons as follows.

- Treatments with topical minoxidil (comparisons 1 to 8).
- Other topical treatments (comparisons 9 to 15).
- Oral treatments (comparisons 16 to 18).
- Laser-based treatments and electrostatic field (comparisons 19 to 22).

1. Minoxidil (1%, 2%, and 5%) versus placebo

Nine trials provided data for some outcomes for this comparison (DeVillez 1994; Jacobs 1993; Lucky 2004; NCT01325350; Olsen 1991; Pazoki-Toroudi 2012; Price 1990; Tsuboi 2007; Whiting 1992). Seven of these trials examined the effects of a 2% concentration of minoxidil, whereas Tsuboi 2007 compared a 1% concentration with placebo, one study included an additional 5% arm (Lucky 2004), and one three-armed study compared minoxidil 5% with placebo as one of the three comparisons within that study (Pazoki-Toroudi 2012). See also 'Summary of findings' table 1 (Summary of findings for the main comparison).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

Six studies (1148 participants) reported participant-rated clinically significant (moderate to marked) hair regrowth (DeVillez 1994; Jacobs 1993; NCT01325350; Olsen 1991; Pazoki-Toroudi 2012; Tsuboi 2007). Pooled data, using a fixed-effect model, from these studies indicated that a greater proportion of participants (157/593) treated with minoxidil reported a statistically significant moderate increase in hair regrowth when compared with placebo (77/555) (risk ratio (RR) 1.93, 95% confidence interval (CI) 1.51 to 2.47; six trials, 1148 participants; P < 0.00001; I^2 statistic = 24%, Analysis 1.1). We compared the effect size and the precision estimates of 1% minoxidil versus placebo, 2% minoxidil versus placebo, and 5% minoxidil versus placebo. Thus, we conclude that although the difference would appear to favour minoxidil (2%), this was relatively small and provides no evidence of any genuine difference with the 1% concentration, whilst the higher concentration of 5% did not show a statistically significant difference compared to placebo. Although there was little suggestion of heterogeneity, we repeated this analysis using a random-effects model to assess the extent of the between-study heterogeneity (see Table 5). One other study, Lucky 2004 (381 participants, data on 260 participants), which also reported data for this outcome, used a VAS rated zero to 100 to measure change in hair growth/scalp coverage, with a higher score indicating more scalp coverage. The VAS score was 58.3 (18.2 standard deviation (SD)) in the placebo group, 62.9 (16.7 SD) in the 2% minoxidil group, and 68.1 (17.9 SD) in the 5% minoxidil group. According to the principal investigators only the self assessments of 5% minoxidil versus placebo reached a statistically significant difference (P < 0.001).

Change in QoL

Lucky 2004 rated the impact of hair loss on QoL on a VAS (data on 260 participants), and at 48 weeks the mean score in the 2% minoxidil group was 52.1 and 46.5 in the placebo group (study authors reported P = 0.04, Student t-test), where a score of 50 indicates "neutral" impact, ranging up to 100 as "positive" impact. In the 5% minoxidil group, the mean VAS score was 54.4 (slightly more than no change) compared to 46.5 with placebo (study authors reported P = 0.004, Student t-test). Although the study investigators reported these scores without SDs and stated them as being statistically significant, the mean differences (MDs) between intervention groups were marginal and can be considered not clinically important. The other included studies did not assess this outcome.

Adverse effects, safety, and tolerability

Comparison of the effect size and precision estimates for minoxidil (1%) versus placebo (RR 1.12, 95% CI 0.61 to 2.06; one trial, 280 participants), minoxidil (2%) versus placebo (RR 1.24, 95% CI 0.82 to 1.87), and minoxidil (5%) versus placebo (RR 2.05, 95% CI 0.96 to 4.37; four trials, 427 participants) reveals that although the difference between the adverse effects favours the minoxidil (1%) concentration, this is small and provides limited evidence of any genuine difference between the three concentrations (see Analysis 1.2). The interaction between the subgroups of dose and effect size did not provide adequate evidence to demonstrate a difference, but this is likely to be due to a lack of power (P value = 0.43).

In most instances, the adverse events reported were mild and consisted of pruritus, skin irritation, and dermatitis. Additional hair growth on areas other than the scalp, e.g. sideburns and forehead, was reported in 71/153 participants in the minoxidil (5%) group compared to 34/154 in the minoxidil (2%) group and 12/74 in the placebo group (Lucky 2004). The data for adverse events were incompletely reported in DeVillez 1994, with the investigators indicating only that "no serious or unexpected medical events were reported during the study", and Whiting 1992 reported that no serious side effects were encountered.

Pooled adverse events data for all of the concentrations of minoxidil versus placebo showed a RR of 1.34 (95% CI 0.98 to 1.83; five trials, 1301 participants; I^2 statistic = 0%), with no statistically significant difference between groups.

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Secondary outcomes

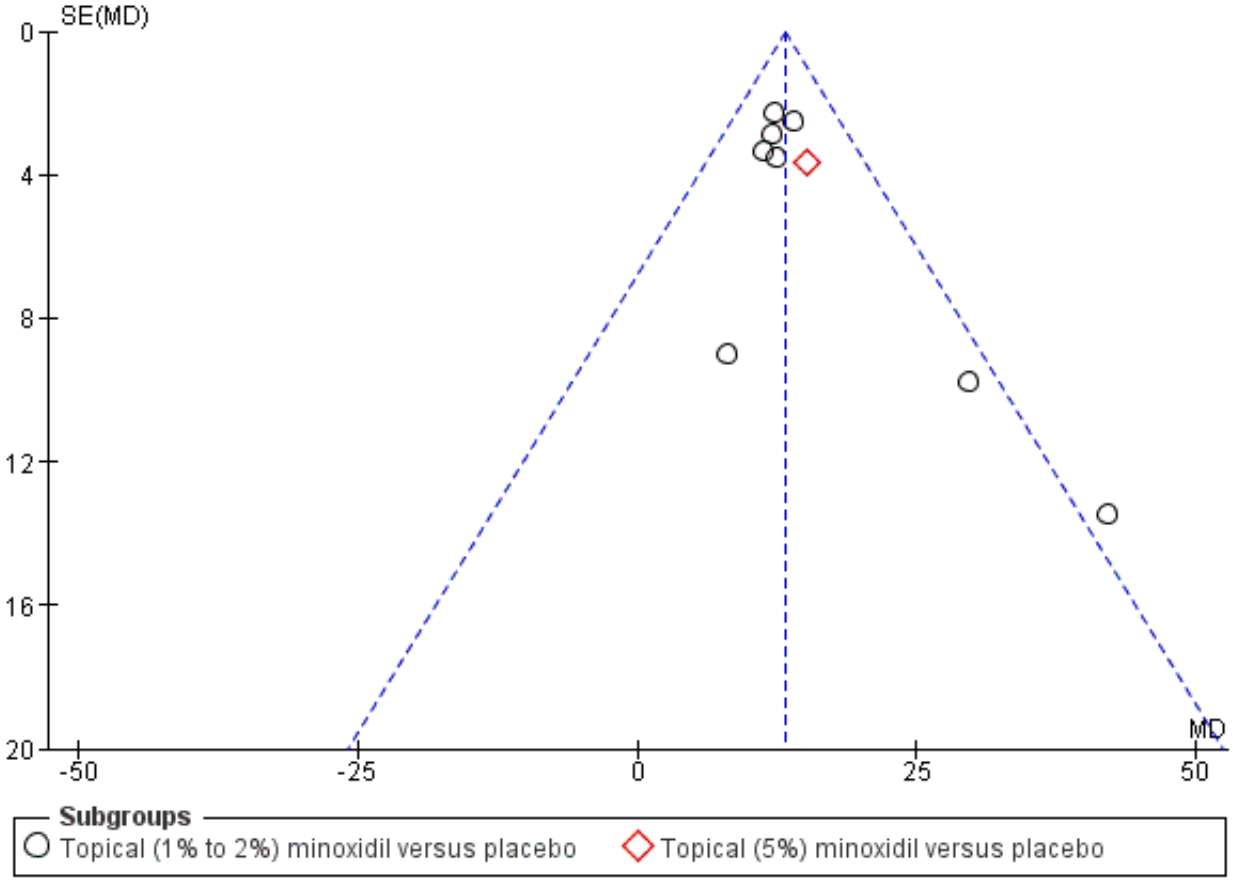
Proportion of participants with investigator-rated hair regrowth

Seven studies (1181 participants) comparing one or more of these interventions provided data for this outcome (DeVillez 1994; Jacobs 1993; NCT01325350; Olsen 1991; Pazoki-Toroudi 2012; Tsuboi 2007; Whiting 1992). The investigator-rated assessments were in agreement with the participant self-rated assessments, both of which reported and confirmed a statistically significant increase in moderate to marked hair regrowth with minoxidil (112/610) compared to placebo (44/571) (RR 2.35, 95% CI 1.68 to 3.28; seven trials, 1181 participants; P < 0.00001 I^2 statistic = 2%; Analysis 1.3). A comparison of the effect size and precision of estimates for minoxidil (1%) versus placebo, and minoxidil (2%) versus placebo revealed that there was no appreciable difference between the two concentrations of minoxidil for this outcome. Pazoki-Toroudi 2012 showed no statistically significant difference between the minoxidil (5%) group and placebo, but the effect estimate was very imprecise with wide CIs, due to a lack of events in the placebo group. One other study, Lucky 2004 (data on 260 participants), used a VAS, rated zero to 100, to evaluate change in hair growth/scalp coverage with a higher score indicating better coverage. The changes were 2.2 (17.9 SD) in the placebo group, 10.3 (17.0 SD) in the minoxidil (2%) group and 11.7 (17.2 SD) in the minoxidil (5%) group.

Change from baseline in total hair count

Eight studies including 1242 participants reported data for the mean change in total hair count from baseline (DeVillez 1994; Jacobs 1993; Lucky 2004; NCT01325350; Olsen 1991; Price 1990; Tsuboi 2007; Whiting 1992). The MD across the studies favoured minoxidil and ranged from eight to 42 hairs (total hair count). The pooled data illustrated that the increase in total hair count in the minoxidil group when compared to the placebo group was 13.18 (95% CI 10.92 to 15.44; eight trials, 1242 participants; P < 0.00001; I^2 statistic = 9%; Analysis 1.4). A comparison of the effect size and precision of the estimates indicated that there was no evidence of any systematic difference between the three concentrations of minoxidil. In addition, we observed funnel plot asymmetry that was attributable to a single study of eight participants (Price 1990) (see Figure 6). It remains unclear whether this asymmetry was the result of publication bias, small-study effects, or an artefact of natural variability. The impact of excluding this study from Analysis 1.4 had a marginal effect on the overall pooled result (RR 12.96, 95% CI 10.69 to 15.24; seven trials, 1108 participants; P < 0.00001; I^2 statistic = 0%), which we report as a sensitivity analysis (see Analysis 1.5); however, it did remove any suggestion of heterogeneity. In an attempt to assess the between study heterogeneity, we repeated both of these analyses using a random-effects model, and presented the results in Table 5. We found little difference between the two sets of analyses.

Figure 6. Funnel plot of comparison: 1 Minoxidil versus placebo, outcome: 1.4 Mean increase in total hair count from baseline.



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Degree of hair shedding from baseline to the end of the study

Three studies reported data on this outcome (Pazoki-Toroudi 2012; Tsuboi 2007; Whiting 1992). In Pazoki-Toroudi 2012 there was a reduction in the number of shed hair of 38.32 (40.98 SD) in the minoxidil (5%) group (43 participants) compared to a reduction of 0.47 (23.50 SD) in the placebo group (18 participants) with a MD of −37.85 (95% CI −54.22 to −21.48; P < 0.00001).

Two thirds (10/17) of the participants in the minoxidil (2%) group reported a decrease in hair shedding compared with less than half (7/16) in placebo group, and that this was more noticeable at the second month of treatment in Whiting 1992 (RR 1.34, 95% CI 0.68 to 2.66; one trial, 33 participants).

However, there was no statistically significant difference in the number of participants in Tsuboi 2007 that reported a decrease in hair loss, and 98/140 participants in the minoxidil (1%) group compared to 87/140 demonstrated a large placebo effect (RR 1.13, 95% CI 0.95 to 1.33, one trial, 180 participants).

Cosmetic appearance of the hair or participant satisfaction

One study measured participants' satisfaction as a 'benefit of treatment' and rated it using a VAS (zero = no benefit, 50 = moderate benefit, and 100 = great benefit) (Lucky 2004). Participant satisfaction in the two minoxidil groups compared to placebo was 18.2 for the minoxidil (5%) group (principal investigators reported P < 0.001, Student t-test) and 8.7 for the minoxidil (2%) group (P = 0.09, Student t-test). The score for the minoxidil (5%) group was 60.0 (27.6 SD), for the (2%) group 50.5 (32.5 SD), and 41.8 (29.9 SD) for the placebo group, and was rated using a VAS score (0 = no benefit, 50 = moderate benefit, and 100 = great benefit). The investigators concluded that there was evidence of increased participant satisfaction with the higher, rather than with the lower, concentration. However, there was a 32% loss to follow-up in this study and the data analysis was per-protocol.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The mean change in hair density, assessed on the Savin Female Density scale at 48 weeks, was −0.9 in the minoxidil (2%) group compared to −0.4 in the placebo group (investigators reported P = 0.012, Student t-test), and a lower score represented a more beneficial effect (Lucky 2004). The mean change in hair density in the minoxidil (5%) group was −0.8 (P value = 0.015, Student t-test) compared to placebo. In NCT01325350 the mean change from baseline in target area hair width was 0.87 (1.315) mm/cm^2 in the minoxidil (2%) group versus 0.07 (1.183) mm/cm^2 in the placebo group with a MD of 0.80 (95% CI 0.36 to 1.24; P = 0.0004) which favoured minoxidil (2%).

2. Minoxidil (2%) versus minoxidil (5%)

Four studies compared these interventions (Blume-Peytavi 2011a; Lucky 2004; NCT01145625; Sheng 2014). One study, Blume-Peytavi 2011a, used a 2% concentration applied twice daily and the 5% concentration once daily, whereas Lucky 2004 and Sheng 2014 applied both concentrations twice daily. In NCT01145625 both treatment arms received a single dose each day. None of the four studies reported any significant difference in efficacy between either of the two concentrations of minoxidil. See also 'Summary of findings' table 2 (Summary of findings 2).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

Two of the studies did not assess this outcome (NCT01145625; Sheng 2014). In Blume-Peytavi 2011a 44% (25/57) of the participants in the minoxidil (2%) group, as opposed to 39% (22/56) of those in the minoxidil (5%) group, experienced moderate to greatly increased hair regrowth (RR 1.12, 95% CI 0.72 to 1.73; one trial, 113 participants). In Lucky 2004 (209 participants for this comparison) the VAS score showed a change in hair growth/scalp coverage of 62.9 (16.7 SD) in the minoxidil (2%) group, compared to a score of 68.1 (17.9 SD) in the minoxidil (5%) group (investigators reported P = 0.062).

Change in QoL

Only one study evaluated this outcome (Lucky 2004). The trial investigators reported that at week 48 there was no statistically significant difference in impact of hair loss on QoL between the two intervention groups.

Adverse effects, safety, and tolerability

There was no statistically significant difference in the number of adverse events reported in either intervention group in three of the studies (Blume-Peytavi 2011a; NCT01145625; Sheng 2014). However, in Lucky 2004 the number of participants that reported adverse events appeared to favour the lower concentration. These were reported by 10/154 participants in the minoxidil (2%) twice daily group compared to 22/153 in the minoxidil (5%) twice daily group (RR 0.45, 95% CI 0.22 to 0.92, one trial, 307 participants). Hypertrichosis (more hair growth on areas other than the scalp), dermatitis, and pruritus were also reported more frequently in the minoxidil (5%) group. Pooling of the data indicated a RR of 1.02 (95% CI 0.91 to 1.15; four trials, 1006 participants; I^2 statistic = 76%; Analysis 2.1). Exclusion of this single study, Lucky 2004, from the analysis slightly altered the pooled results and reduced the degree of heterogeneity (RR 1.10, 95% CI 0.99 to 1.23; three trials, 699 participants; I^2 statistic = 50%; Analysis 2.2). The twice daily dose of 5% in this study resulted in double the number of adverse events compared to the twice daily dosage of minoxidil (2%). We repeated the analyses using a random-effects model and found little difference between the two sets of analyses (Table 5).

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The investigator- and participant-rated assessments were largely in agreement in three of the studies, i.e. there was no evidence of a difference between the two concentrations of minoxidil for stimulating hair growth. In Blume-Peytavi 2011a the investigator-rated assessments revealed that 12/57 participants in the minoxidil (2%) group had moderate to greatly increased hair growth compared to 14/56 in the minoxidil (5%) group (RR 0.84, 95% CI 0.43 to 1.66; one trial 113 participants). These results were confirmed by the investigator-rated VAS scores in Lucky 2004, which showed no statistically significant difference in efficacy between either concentration of minoxidil (principal investigators' reported P = 0.608). In Sheng 2014 27/132 participants in the minoxidil (2%) group had a moderate to marked improvement compared to 34/132

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in the minoxidil (5%) group (RR 0.79, 95% CI 0.51 to 1.24; one trial 264 participants). NCT01145625 did not assess this outcome.

Change from baseline to study conclusion in total hair count

The pooled data from three studies (631 participants) (Blume-Peytavi 2011a; Lucky 2004; NCT01145625) indicated that there was no statistically significant difference in the change in total hair count from baseline to the end of study between the two treatment groups (MD −2.12, 95% CI −5.47 to 1.23; I^2 statistic = 0%; see Analysis 2.3 and Table 5).

Degree of hair shedding from baseline to the end of the study

None of the studies assessed this outcome.

Cosmetic appearance of the hair or participant satisfaction

Almost three quarters of the participants in the minoxidil (2%) group were more satisfied with the appearance of their hair at the end of treatment compared to more than half of those in the minoxidil (5%) group (Blume-Peytavi 2011a). Assessments of 'benefit of treatment' in Lucky 2004 rated on a VAS scored 50.5 (32.5 SD) in the 2% group versus 60.0 (27.6 SD) in the 5% group (principal investigators' reported P = 0.29, Student t-test). The two other studies did not assess this outcome (NCT01145625; Sheng 2014).

Change in quality (or pattern) of hair regrowth (e.g. thickness)

There was no statistically significant difference in the non-vellus cumulative target area hair width (mm/cm^2 between the minoxidil (2% and 5%) applications in Blume-Peytavi 2011a, and similarly in Lucky 2004 for hair density, assessed as the mean change from baseline based on the Savin Female Density scale. The other two studies did not assess this outcome (NCT01145625; Sheng 2014).

3. Minoxidil 12.5% + azelaic acid + betamethasone 17-valerate 0.025% versus placebo

One three-armed study at unclear risk of bias conducted over a period of 24 weeks, which included 75 participants, evaluated this comparison (Pazoki-Toroudi 2012).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

In the minoxidil high extra combination (MHEC) group, as named by the principal investigators, 21/57 of participants reported moderate to marked improvement compared to 0/18 in the placebo group (RR 14.09, 95% CI 0.90 to 221.58; one trial, 75 participants).

Change in QoL

This study did not assess this outcome.

Adverse effects, safety, and tolerability

The number of adverse events were 14/57 in the MHEC group and 4/18 in the placebo group (RR 1.11, 95% 0.42 to 2.94; one trial, 75 participants). Adverse events included irritation, hypertrichosis, pruritus, and headache.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The judgements regarding improvement (moderate and marked) were 100% in agreement with the participant assessments (RR 14.09, 95% CI 0.90 to 221.58; one trial 75 participants).

Change from baseline to study conclusion in total hair count

This study did not assess this outcome.

Degree of hair shedding from baseline to the end of the study

The mean decrease in number of shed hairs was 53.80 (40.94 SD) in the MHEC group versus 0.47 (23.50 SD) in the placebo group with a MD of −53.33 hairs (95% CI −68.66 to −38.00; P < 0.00001) in favour of MHEC.

Cosmetic appearance of the hair or participant satisfaction

This study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

This study did not assess this outcome.

4. Minoxidil 12.5% + azelaic acid + betamethasone 17-valerate 0.025% versus minoxidil 5%

This is the third comparison, which included 106 participants, that Pazoki-Toroudi 2012 evaluated.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

In the MHEC group, 21/57 participants considered themselves to have moderate to marked improvement compared to 16/49 in the minoxidil (5%) group (RR 1.13, 95% CI 0.67 to 1.91; one trial, 106 participants).

Change in QoL

This study did not assess this outcome.

Adverse effects, safety, and tolerability

There were 14 adverse events in 57 participants in the MHEC group and 11/49 in the minoxidil (5%) group (RR 1.09, 95% 0.55 to 2.18; one trial, 106 participants). Adverse events included irritation, hypertrichosis, pruritus, and headache.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

According to the investigators, 21/57 participants in MHEC group versus 16/49 in the minoxidil (5%) group showed a moderate to marked improvement of hair regrowth (RR 1.13, 95% CI 0.67 to 1.91; one trial, 106 participants), which is in concordance with the participants' assessments.

Change from baseline to study conclusion in total hair count

This study did not assess the outcome.

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Degree of hair shedding from baseline to the end of the study

The mean decrease in number of shed hairs was 53.80 (40.94 SD) in the MHEC group, which was better than 38.32 (40.98 SD) in the minoxidil (5%) group with a MD of −15.48 hairs (95% CI −31.82 to 0.86).

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The study did not assess this outcome.

5. Minoxidil (2%) versus alfatradiol

One study (103 participants), which we assessed as at high risk of bias, reported limited data for this comparison (Blume-Peytavi 2007).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

The study did not assess this outcome.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

No adverse effects were reported for either intervention in this study (Blume-Peytavi 2007). "Tolerability of treatment" was participant- and investigator-assessed, and, although inadequately defined, the investigators referred to it in further similar studies as "pruritus and local intolerance". No relevant data were reported at 6 months, and the data at 12 months were incomplete and implausibly analysed (see the 'Risk of bias in included studies' section). Therefore, we have not included these in the meta-analysis.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The study did not assess this outcome.

Change from baseline to study conclusion in total hair count

At 12 months the increase in hair density was 17.20 (SD 32.95) hairs/cm² in the minoxidil group compared to 9.8 (SD 31.79) hairs/cm² in the alfatradiol group with a MD of 7.40 hairs/cm² (95% CI −8.98 to 23.78), which was not statistically significant.

Degree of hair shedding from baseline to the end of the study

The study did not assess this outcome.

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The mean change in cumulative hair thickness from baseline to 12 months was 2.10 (3.10 SD) mm/cm² in the minoxidil group compared to 0.40 (3.31 SD) mm/cm² in the alfatradiol group with a MD of 1.70 mm/cm² (95% CI 0.07 to 3.33, P = 0.04).

6. Intradermal applications (mesotherapy) with minoxidil 0.5% per 2 mL versus intradermal applications (mesotherapy) with saline 0.9%

A single study, NCT01655108, at low risk of bias with 54 participants compared these interventions over 10 sessions and at weekly intervals.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

In the mesotherapy plus minoxidil group 7/27 participants reported a moderate to sharp increase in hair volume compared to 1/27 in the mesotherapy plus saline group (RR 7.00, 95% CI 0.92 to 53.10; one trial 54 participants).

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

All participants in both groups reported pain, but there were more reports in the mesotherapy plus minoxidil group (authors' reported P < 0.10). The investigators also indicated that there was no difference between the groups regarding the nature of other adverse events such as headache, burning, and itching.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The study did not assess this outcome.

Change from baseline to study conclusion in total hair count

The study did not assess this outcome.

Degree of hair shedding from baseline to the end of the study

In the mesotherapy plus minoxidil group 18/27 participants noticed a decrease in the extent of hair loss compared to 8/27 in the mesotherapy plus saline group (RR 2.25, 95% CI 1.19 to 4.27; one trial 54 participants; P = 0.01), which was in favour of mesotherapy plus minoxidil.

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The study did not assess this outcome.

7. Pantovigar one capsule three times a day plus minoxidil 2% twice daily versus minoxidil 2% twice daily

Pantovigar is a natural hair loss supplement. One study, at high risk of bias, evaluated it in combination with topical minoxidil versus minoxidil (2%) monotherapy (NCT01900041). It was conducted over 26 weeks and included 74 participants.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

The study did not assess this outcome.

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Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

In the Pantovigar plus minoxidil group 15 adverse events were reported in 37 participants versus 19 adverse events in 37 participants in the minoxidil "only" group (RR 0.79, 95% CI 0.48 to 1.30; one trial 74 participants).

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The study did not assess this outcome.

Change from baseline to study conclusion in total hair count

The study did not assess this outcome.

Degree of hair shedding from baseline to the end of the study

The investigators reported that "changes in percentage telogen rate were comparable between both groups. No statistically significant difference was observed (P = 0.45)."

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The study did not assess this outcome.

8. Minoxidil and oral contraceptive pill (OCP) versus cyproterone acetate and OCP

One study, including 66 participants and assessed as high risk of bias, compared the effects of these interventions (Vexiau 2002).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

The study did not assess this outcome.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

Three participants in the minoxidil combined with OCP group reported pruritus, and one reported weight gain. A further participant in the cyproterone acetate group reported weight gain.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The study did not assess this outcome.

Change from baseline to study conclusion in total hair count

Minoxidil combined with the OCP was more effective than cyproterone acetate. Mean change from baseline in the combination group was 7.7 hairs (9.3 SD) and in the cyproterone acetate group −0.2 hairs (6.7 SD). The MD in total number of hairs per 0.36 cm^2 between the minoxidil group was 7.90 (95% CI 3.70 to 12.10).

Degree of hair shedding from baseline to the end of the study

Both groups reported large decreases in self-assessed mean hair loss; rated on a VAS, these were −28 (24 SD) for the minoxidil group versus −24 (26 SD) mm for the cyproterone acetate group. These found there was no difference in the reduction of hair loss between the 2 treatment groups (MD −4.00, 95% CI −17.52 to 9.52)

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (thickness and density)

The study did not assess this outcome.

9. Estradiol valerate topical ointment (3%) for 12 weeks versus estradiol valerate topical ointment (3%) for 24 weeks versus placebo vehicle only for 24 weeks

A single study (75 participants) at unclear risk of bias provided minimal data for this comparison (Georgala 2004).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

The study did not assess this outcome.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

Two of 25 participants in the 12-week group reported mild pruritus itching on the scalp compared to 4/25 in the 24-week group and 2/25 in the placebo group. In the 24-week treatment group, two participants experienced postmenopausal uterine bleeding, which resulted in their withdrawal from the study.

Secondary outcomes

The study did not assess any of our secondary outcomes.

10. Octyl nicotinate (0.5%) and myristyl nicotinate (5%) versus placebo

A single study (60 participants) at unclear risk of bias compared the safety and efficacy of octyl nicotinate (0.5%) and myristyl nicotinate (5%) versus placebo over six months (Draelos 2005).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

The study did not assess this outcome.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

Draelos 2005 did not report data separately for adverse events for each intervention, only cumulatively as scalp stinging (9), scalp burning (2), scalp itching (12), scalp redness (4), and eye irritation (7). These occurred in both placebo and active intervention groups, and the study authors concluded that they were related to the volatile vehicle, and not the active constituent.

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Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

At six months, 22/40 participants treated with the combination therapy showed an increase in hair fullness compared to 4/20 of those treated with placebo (RR 2.75, 95% CI 1.10 to 6.90; one trial, 60 participants).

Change from baseline to study conclusion in total hair count

The study did not assess this outcome.

Degree of hair shedding from baseline to the end of the study

The study did not assess this outcome.

Cosmetic appearance of the hair or participant satisfaction

Although no data were reported, the investigators referred to a "positive trend" in the participants' assessments of the appearance of their hair, but indicated that this did not reach significance (investigators' reported P value = 0.05).

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The study did not assess this outcome.

11. Fulvestrant 70 mg/mL versus placebo

A single study (70 participants) at low risk of bias provided limited outcome data for this comparison (Gassmueller 2008), and concluded that fulvestrant was ineffective after 16 weeks in the treatment of FPHL.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

The study did not assess this outcome.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

There was no statistically significant difference in the number of adverse events between the interventions. These were mild, i.e. cold and headache, and similar in the fulvestrant group (10/34) and the placebo group (16/36) (RR 0.66, 95% CI 0.35 to 1.25; one trial, 70 participants). The study reported that both fulvestrant and the vehicle were well-tolerated.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The study did not assess this outcome.

Change from baseline to study conclusion in total hair count

The study did not assess this outcome.

Degree of hair shedding from baseline to the end of the study

The study did not assess this outcome.

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

No statistically significant differences were reported in terms of percentage change from baseline in cumulative hair thickness, nor in hair density. So there was no evidence in favour of fulvestrant over placebo.

12. Adenosine versus placebo

Only one study, which was at unclear risk of bias and included 30 participants, evaluated the effect of this intervention in the treatment of FPHL for a 12-month duration (Oura 2008).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

The study evaluated self-assessments with a questionnaire, however the investigators only provided P values. These indicated that for hair growth there was no statistically significant difference between the two treatment groups at month 12 (investigators reported "P value = 0.081, Mann–Whitney U-test")

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

There were no adverse events in either group.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The dermatologist-rated assessments indicated that four out of 15 participants in the adenosine treatment group improved compared to 2/15 in the placebo group (RR 2.00, 95% CI 0.43 to 9.32; one trial, 30 participants), and that these results were reasonably consistent with the investigator-rated assessments.

Change from baseline to study conclusion in total hair count

The investigators reported that "hair density did not change significantly between the groups at any time point".

Degree of hair shedding from baseline to the end of the study

The investigators reported that at the end of the study there was a statistically significant difference in favour of the adenosine group regarding the prevention of hair loss (authors' reported "P value = 0.036, Mann–Whitney U-test"). However, they did not provide any data to support this conclusion.

Cosmetic appearance of the hair or participant satisfaction

Although the 'change in appearance' at 12 months appeared to favour adenosine (investigators' reported "P value = 0.048, Mann–Whitney U-test"), there was no statistically significant difference in satisfaction between the two groups at the end of the study.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The thick hair ratio (number of hairs thicker than 80 µm in diameter/thinner hairs) did not improve in the adenosine group over 12 months, but it did show a decrease in the placebo group (investigators reported "P value = 0.002, Student t-test") with a difference between the two groups in favour of adenosine (investigators reported "P value = 0.04, Student t-test").

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13. Botanical tincture versus placebo

One study compared a botanical tincture (which contained *Thuja occidentalis* extract, *Swertia* extract, pantotenilethylether, 4-pyrrolidine 2,6-diaminopyrimidine 1-oxide, cyanocobalamin, 95% ethanol, saline) to placebo (Shin 2007). Both were applied twice daily for 18 weeks in 33 participants. The limited data that were reported for this study, which we assessed as at unclear risk of bias, indicated a lack of efficacy for this treatment.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

The improvement score based on a VAS scale, rated from zero to 10, did not show a statistically significant difference between the groups (with a score of 4.4 (2.47 SD) in the botanical tincture group versus 4.5 (2.80 SD) in the placebo group.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

There were no adverse events reported in either group.

Secondary outcomes

Participants with investigator-rated clinically significant hair regrowth

After 18 weeks the score in the botanical tincture group was 1.0 (0.82 SD) with a score of 1 representing a 0 to 25% improvement. In the placebo group the score was 0.8 (0.80 SD), which indicated no change or worse.

Change from baseline to study conclusion in total hair count

The investigators reported no statistically significant change in hair count compared to baseline for either group.

Degree of hair shedding from baseline to the end of the study

According to the investigators the degree of hair shedding, which was assessed using a VAS, was 5.0 (2.89 SD) in the botanical tincture group compared to 4.4 (3.20 SD) in the placebo group. There was no statistically significant difference between the groups.

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The investigators reported no statistically significant change in hair diameter compared to baseline for either group.

14. Bimatoprost different concentrations versus vehicle

One five-armed study at unclear risk of bias, which included a total of 306 participants, evaluated the different concentrations of bimatoprost topical applications versus vehicle (NCT01325350). Three arms included bimatoprost formulation A, B, and C without further specification, and the other two arms were minoxidil and vehicle. We have reported the comparisons versus minoxidil under comparison 22, and minoxidil versus vehicle under comparison 1.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

This was rated on a seven-point scale of the Subject Self Assessment in Alopecia (SSA) score. Accordingly, 12/61 participants considered they had a moderate to great increase in hair regrowth in bimatoprost formulation A, 14/61 in formulation B, and 14/61 in formulation C versus 13/61 in the vehicle group. None of the comparisons showed a statistically significant difference compared to vehicle or compared to any of the bimatoprost concentration, which suggested that according to participants the treatment is ineffective.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

In the bimatoprost formulation A group 21/61 participants reported adverse events, with five experiencing hypertrichosis; 21/61 in formulation B (one hypertrichosis), 18/61 in formulation C (no hypertrichosis); and 21/61 in the vehicle group (one hypertrichosis). There was no statistically significant difference between any of the treatment arms.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

Based on the Investigator's Global Assessment scale, the investigators judged that 10/61 in the bimatoprost formulation A group had a moderate to greatly increased hair regrowth, 8/61 in formulation B group, 10/61 in formulation C group, and 10/61 in the vehicle group, with no statistically significant difference between any of the groups. These assessments were in agreement with the participants' judgements.

Change from baseline to study conclusion in total hair count

The mean change in hair count was not clinically meaningful in any group. The mean change from baseline in hair count was 0.4 (17.10 SD) in the bimatoprost formulation A group, 3.5 (18.21 SD) in formulation B group, 4.3 (16.82 SD) in the formulation C group, and 1.1 (20.44 SD) in the vehicle group.

Degree of hair shedding from baseline to the end of the study

The study did not assess this outcome.

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The mean change from baseline in target area hair width was 0.13 (1.198 SD) mm/cm^2 in the bimatoprost formulation A group, 0.19 (1.067 SD) mm/cm^2 in group B, 0.30 (1.263 SD) mm/cm^2 in group C, and 0.07 (1.1183 SD) mm/cm^2 in the vehicle group. No treatment arm showed a statistically significant difference of vehicle or against the other formulations.

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15. Bimatoprost different concentrations versus minoxidil

The same five-armed study as in comparison 21 evaluated the different concentrations of topical applications versus minoxidil 2% (NCT01325350).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

This was rated on a seven-point scale of the SSA. Accordingly, 12/61 participants considered that they had a moderate to great increase in hair regrowth with the bimatoprost formulation A, 14/61 in formulation B, 14/61 in formulation C, versus 20/61 in the minoxidil group. Although the minoxidil group scored better on the SSA score, there was no statistically significant difference between any of the comparisons.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

Adverse events reported were 21/61 in bimatoprost formulation A, with five experiencing hypertrichosis; 21/61 in formulation B (one hypertrichosis), 18/61 in formulation C (no hypertrichosis); and 25/62 in the minoxidil group (three hypertrichosis). There was no statistically significant difference between any of the treatment arms.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

Based on the Investigator's Global Assessment scale, the investigators judged that 10/61 in the bimatoprost formulation A group had a moderate to greatly increased hair regrowth, 8/61 in formulation B group, 10/61 in formulation C group, and 10/61 in the minoxidil group, with no statistically significant difference between any of the groups. This is in agreement with the participants judgements.

Change from baseline to study conclusion in total hair count

In the bimatoprost formulation A group, the mean change in hair count from baseline was 0.4 (17.10 SD) in the bimatoprost formulation A group, 3.5 (18.21 SD) in formulation B group, 4.3 (16.82 SD) in the formulation C group, and 13.6 (18.72 SD) in the minoxidil group. There was a statistically significant MD for each of the comparisons bimatoprost versus minoxidil in favour of minoxidil. The MD that compared formulation A versus minoxidil was −13.20 (95% CI −19.53, to −6.87; P < 0.0001). For formulation B versus minoxidil the MD was −10.10 (95% CI −16.63 to −3.57; P = 0.002), and for formulation C versus minoxidil the MD was −9.30 (95% CI −15.59 to −3.01; P = 0.004).

Degree of hair shedding from baseline to the end of the study

The study did not assess this outcome.

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The mean change from baseline in target area hair width was 0.13 (1.198 SD) mm/cm^2 in the bimatoprost formulation A group, 0.19 (1.067 SD) mm/cm^2 in group B, 0.30 (1.263 SD) mm/cm^2 in group C, and 0.87 (1.315 SD) mm/cm^2 in the minoxidil group. There was a statistically significant difference in favour of minoxidil in all comparisons. The MD of bimatoprost formulation A versus minoxidil was −0.74 (95% CI −1.18 to −0.30; P = 0.001), bimatoprost formulation B versus minoxidil MD −0.68 (95% CI −1.10 to −0.26; P = 0.002), and formulation C versus minoxidil MD −0.57 (95% CI −1.01 to −0.13; P = 0.01).

16. Cyproterone versus flutamide versus finasteride

One study that included 36 participants examined these comparisons (Carmina 2003), but we assessed it as at high risk of bias. The investigators reported that flutamide at a dose of 250 mg daily provided a modest improvement in alopecia after one year, whereas cyproterone acetate 50 mg and finasteride 5 mg were not considered effective.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

Hair regrowth was participant-assessed with a standardised questionnaire (Barber 1998). Two of 12 participants in the cyproterone group reported improvement in hair growth compared to 3/12 in the flutamide group and 1/12 in the finasteride group.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

No adverse events were reported for these comparisons; however, in the flutamide group, 2/12 participants had a slight increase in liver enzymes, which is considered to be a common side-effect of this intervention.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The study did not assess this outcome.

Change from baseline to study conclusion in total hair count

The study did not assess this outcome.

Degree of hair shedding from baseline to the end of the study

In the flutamide group, 8/12 participants reported an improvement in slowing down of hair loss versus 3/12 in the cyproterone acetate group and 1/12 in the finasteride group.

Cosmetic appearance of the hair or participant satisfaction

Improvement of hair appearance was reported by 3/12 participants in the flutamide group compared to 1/12 in the cyproterone acetate and none in the finasteride group. The flutamide participants were also more satisfied with their therapy (5/12) versus 3/12 in the cyproterone acetate and the finasteride group (1/12).

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Change in quality (or pattern) of hair regrowth (e.g. thickness)

Baseline to end of study hair density was investigator-assessed on a seven-point scale (−3 = greatly decreased to 3 = greatly increased). In the cyproterone group, this scale was rated after 12 months as 0.5 (0.2 SD) in the flutamide group 0.9 (0.2 SD) and in the finasteride group 0.1 (0.2 SD).

17. Finasteride (1 mg) versus placebo

Three studies examined this comparison (Keene 2011; Price 2000; Whiting 1999). We assessed Keene 2011 as at low risk of bias, Price 2000 at unclear risk of bias, and Whiting 1999 at high risk of bias. See also 'Summary of findings' table 3 (Summary of findings 3).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

Participant- and investigator-rated assessments in Price 2000 were largely in agreement that finasteride was no more effective than placebo. In the finasteride group, 30/67 participants considered themselves improved versus 33/70 in the placebo group (RR 0.95, 95% CI 0.66 to 1.37; one trial, 137 participants). Keene 2011 and Whiting 1999 did not assess this outcome.

Change in QoL

None of the studies assessed this outcome.

Adverse effects, safety, and tolerability

Both groups in Price 2000 reported a similar number of adverse events: 53/67 in the finasteride group versus 55/70 in the placebo group (RR 1.03, 95% CI 0.45 to 2.34; one trial, 137 participants). Several of the adverse events reported in this study are common in postmenopausal women and are not necessarily drug-related. The placebo group reported more adverse events, such as headache and depression. Keene 2011 and Whiting 1999 did not assess this outcome.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

Only one study provided data for this outcome (Price 2000). The investigators reported that 10/67 participants in the finasteride group showed a moderate increase versus 13/70 in the placebo group, which included one participant with a greatly increased change in hair growth (RR 0.77, 95% CI 0.31 to 1.90; one trial, 137 participants). Keene 2011 and Whiting 1999 did not assess this outcome.

Change from baseline to study conclusion in total hair count

At 12 months, both treatment groups in Price 2000 (data on 125 participants for this outcome) demonstrated a similar degree of hair loss by hair count, with a mean decrease from baseline in hair count of 8.7 hairs in the finasteride group versus 6.6 in the placebo group, but no SDs were reported. Individual patient data were provided in Keene 2011 for two different hair counts. The mean increase from baseline in hair count 1 was 17.86 hairs/cm^2, and 11.86 hairs/cm^2 in hair count 2 for seven participants on finasteride, and one hair, and -4.4 hairs for the two hair counts for the five participants on placebo. In Whiting 1999, there was an increase of 0.2 (0.9 SD) in change from baseline in total hair count of terminal hairs in the finasteride group (44 participants) versus 1.1 (0.9 SD) in the placebo group (50 participants) (MD −0.90, 95% CI −1.2 to −0.54; P < 0.00001), which was in favour of placebo. However, the difference of one hair in a 4 mm punch biopsy is not clinically important.

Degree of hair shedding from baseline to the end of the study

Although the investigators in Price 2000 provided no data, they reported that there was no statistically significant difference in the slowing down of hair loss between the two groups at the end of the study. The other two studies did not assess this outcome.

Cosmetic appearance of the hair or participant satisfaction

Twelve out of 67 participants on finasteride were satisfied with their hair overall compared to 16/70 in the placebo group (RR 0.78, 95% CI 0.40 to 1.53; one trial, 137 participants), which was not a statistically significant difference (Price 2000). The other two studies did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g thickness)

The studies did not assess this outcome

18. Nutritional supplement versus no supplement

One study, which we assessed as at high risk of bias and included 120 participants, investigated the efficacy of a nutritional supplement that contained 460 mg fish oil, 460 mg black currant seed oil, 5 mg vitamin E, 30 mg vitamin C, and 1 mg lycopene versus no supplement during six months (Le Floc'h 2015).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

Only data were reported for the group that received the supplement and 69/80 participants reported a moderate to large increase in hair density, and the investigators reported P < 0.001. These data would suggest a huge beneficial effect for the supplement. However, these numbers are unusable without the data from the comparator group. As we were unable to retrieve these from the investigators, they cannot be further analysed.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

There were no adverse events reported in either group.

Secondary outcomes

Participants with investigator-rated clinically significant hair regrowth

The study did not assess this outcome.

Change from baseline to study conclusion in total hair count

The study did not assess this outcome.

Degree of hair shedding from baseline to the end of the study

Hair loss according to the self-assessments of the participants decreased in 71/80 women in the supplement group compared to 27/40 in the group that received no treatment (RR 1.31, 95% CI 1.05 to 1.65; one trial, 120 participants; P = 0.02) in favour of the supplement group.

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Cosmetic appearance of the hair or participant satisfaction

Data were only reported for the supplement group, which indicated that 68/80 women were satisfied, but data for the untreated group were missing.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The study assessed hair density on a seven-point Likert scale, rated from −3 to 3, and showed that 22 women had a moderate increase in hair density and just one patient in the supplement group experienced a "great increase" versus no improvement at all in the 'no-treatment' group (RR 23.79, 95% CI 1.48 to 381.88; one trial, 120 participants; P = 0.03).

19. Low level laser comb versus sham device

Two studies evaluated laser combs versus sham device therapy for three times a week for 12 minutes for a period of 26 weeks. Jimenez 2014a (78 participants) used a nine-beam laser comb, and Jimenez 2014b (63 participants) used a dual 12-beam laser comb. We assessed the studies as at high risk and unclear risk of bias, respectively. Although there appeared to be a statistically significant difference in the increase in hair count, this was not reflected in the participant assessments. See 'Summary of findings' table 4 (Summary of findings 4).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

Both studies combined the data that reported minimally improved and improved hair regrowth, and therefore we cannot be certain to what extent participants considered these improvements to be clinically relevant. In Jimenez 2014a 36/53 in the nine-beam laser comb group reported minimal improvement of their hair loss versus 11/25 in the sham device group (RR 1.54, 95% CI 0.96 to 2.49; one trial, 78 participants). In Jimenez 2014b 26/42 participants in the 12-beam laser comb group considered their hair loss minimally improved or improved versus 11/21 in the sham device group (RR 1.18, 95% CI 0.74 to 1.89, one trial, 63 participants).

Change in QoL

The studies did not assess this outcome.

Adverse effects, safety, and tolerability

The report in both studies also included two studies in men. The adverse events were not addressed per study, and the investigators reported that there were "no serious adverse events in any study and laser comb-related adverse events consisted of dry skin (5.1 %), pruritus (2.5 %), scalp tenderness (1.3 %), irritation (1.3 %), and a warm sensation at the site (1.3 %)."

Secondary outcomes

Participants with investigator-rated clinically significant hair regrowth

The studies did not assess this outcome.

Change from baseline to study conclusion in total hair count

The mean change from baseline in the nine-beam laser comb group was 20.2 (11.2 SD) hairs/cm^2 versus 2.8 (16.5 SD) in the sham device group with a MD of 17.40 hairs/cm^2 (95% CI 9.74, to 25.06; P < 0.00001), which is a statistically significant difference (Jimenez 2014a). The data in Jimenez 2014b were similar with an increase of 20.6 (11.6 SD) hairs/cm^2 in the 12-beam laser comb group and 3.0 (9.3 SD) in the sham device group (MD 17.60 hairs/cm^2, 95% CI 11.97, to 23.23; P < 0.00001).

Degree of hair shedding from baseline to the end of the study

The studies did not assess this outcome.

Cosmetic appearance of the hair or participant satisfaction

At 26 weeks 31/53 participants in the nine-beam laser comb group felt there was minimally improved or improved thickness or fullness of the hair compared to 10/25 in the sham device group (RR 1.46, 95% CI 0.86 to 2.49; one trial 78 participants) (Jimenez 2014a). In Jimenez 2014b 24/42 in the nine-beam laser comb group experienced minimal improvement or improvement versus 9/21 in the sham device group (RR 1.33, 95% CI 0.76 to 2.33; one trial, 63 participants).

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The studies did not assess this outcome.

20. Low level laser in bicycle-helmet like apparatus versus sham helmet

One study at low risk of bias in 47 participants evaluated these interventions for 25 minutes every other day over 16 weeks (Lanzafame 2014). The helmet in the active treatment group contained 21, 5 mW diode lasers (655 ± 5 nm) and 30 LEDS (655 ± 20 nm), and showed that the helmet with the low level laser improved hair count.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

The study did not assess this outcome.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

No adverse events were reported in either intervention arm.

Secondary outcomes

Participants with investigator-rated clinically significant hair regrowth

The study did not assess this outcome.

Change from baseline to study conclusion in total hair count

The mean change from baseline was 100.3 hairs per 2.85 cm^2 (53.4 SD) in the laser helmet group versus 23.9 (30.1 SD) in the sham device group with a MD of 76.40 hairs per 2.85 cm^2 (95% CI 50.91 to 101.89; P < 0.00001), which favours the laser helmet group

Degree of hair shedding from baseline to the end of the study

The study did not assess this outcome.

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

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Change in quality (or pattern) of hair regrowth (e.g. thickness)

The study did not assess this outcome.

21. Handi-Dome laser versus incandescent red light source

One study in 44 women, which we assessed as at unclear risk of bias, compared these interventions which consisted of a single, 30 minute treatment, every other day over 16 weeks (NCT01967277) .

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

The study did not assess this outcome.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

No adverse events were reported in either intervention arm.

Secondary outcomes

Participants with investigator-rated clinically significant hair regrowth

The study did not assess this outcome.

Change from baseline to study conclusion in total hair count

The Handi-Dome laser group showed a larger increase in hair count than the red light group with a mean change of 89.9 (63.3 SD) in the Handi-Dome laser group versus 18.5 (24.4 SD) in the red light group (MD 71.40, 95% CI 41.08 to 101.72; P < 0.00001).

Degree of hair shedding from baseline to the end of the study

The study did not assess this outcome.

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The study did not assess this outcome.

22. Pulsed electrostatic field versus sham

One poorly reported trial, which we assessed as at unclear risk of bias, provided independent patient data (IPD) for the six female participants (Policarpi 1993).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

Two out of four participants in the active treatment group showed a "significant improvement" at 36 weeks compared to neither of the two participants in the sham group.

Change in QoL

The study did not assess this outcome.

Adverse effects, safety, and tolerability

The study did not assess this outcome.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The investigator-rated assessments indicated there was no clinically "significant hair growth" observed in the participants in both treatment arms.

Change from baseline to study conclusion in total hair count

The percentage change in mean hair count from baseline at 36 weeks in the active group was 2.96 in the first participant, and 16.95%, 4.67%, and 3.37% in subsequent participants. In the two participants in the sham group, the percentage change was 1.15% and 1.45%.

Degree of hair shedding from baseline to the end of the study

The study did not assess this outcome.

Cosmetic appearance of the hair or participant satisfaction

The study did not assess this outcome.

Change in quality (or pattern) of hair regrowth (e.g. thickness)

The study did not assess this outcome.

DISCUSSION

Summary of main results

Forty-seven studies, which examined 5290 participants, met the inclusion criteria of this Cochrane review. Only one included study assessed one of our key patient-preferred outcomes, 'quality of life' (QoL) (Lucky 2004). Most included studies focused on change in total (non-vellus) hair count. However, although this may provide a quantifiable, objective, and more readily intelligible outcome, it is considered to be physician-preferred, rather than an outcome directed towards addressing participants' preferences. Other frequently-reported outcomes included participant-assessed improvement of hair regrowth, as well as physician-assessed improvement, and adverse events. Female pattern hair loss (FPHL) can be distressing, and is known to impact on QoL. Thus, the importance of assessing the efficacy of interventions targeted at improving this key outcome should not be underestimated (Biondo 2010). Pooling of data was only feasible for a limited number of the outcomes reported in the included studies and was confined to those that evaluated the efficacy of minoxidil compared to placebo and minoxidil (2%) versus minoxidil (5%).

Based on the findings of this review, the only interventions that appeared to demonstrate a measure of efficacy were minoxidil (2% and 5% concentrations) with the quality of evidence being mainly moderate to low ('Summary of findings' table 1; 'Summary of findings' table 2). Both concentrations illustrated a good safety profile, but there is wide acknowledgement that doses in excess of 60 mg a day may lead to an increase in the number of adverse effects. Therefore, the application of 1 mL minoxidil 2% (20 mg/mL) twice daily or 1 mL minoxidil 5% (50 mg/mL) once daily should not be exceeded and the threshold is reached quicker with the 5% dosage. After discontinuation of treatment, renewed hair loss is likely to reoccur within three months and all beneficial effects will have disappeared in six months (Olsen 2005; Torres 2015).

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Finasteride appeared to have a limited to no effect, but the results were inconsistent across the three studies with the quality of evidence rated low ('Summary of findings' table 3). Finasteride is not approved for use in women and has well known side effects such as libido reduction, breast tenderness, depression, and abnormalities of the external genitalia of a male foetus when used in pregnant women. Low-level laser therapy showed an increase in total hair count, but this was not supported by both the participant-assessments of improvement ('Summary of findings' table 4; moderate to low quality evidence).

For further details see the 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4).

Overall completeness and applicability of evidence

The studies included in this review, which evaluated a range of interventions, did not provide sufficient data to enable fair and reliable comparisons to be made for any one single intervention against another for a specific outcome, with the exception of minoxidil 2% and 5%, which, based on the evidence available, appeared to be safe and effective in the treatment of FPHL.

Most interventions were evaluated in a single study, and none of the studies addressed more than a very limited number of our outcomes, which illustrates gaps in the overall completeness of the evidence. The quality of data reporting and its analysis was variable across the included studies.

Mean change in hair count and adverse events were the most commonly addressed outcomes, followed by participant- and physician-assessments of improvement of hair regrowth. However, there was a lack of consistency in the choice and assessment of other outcomes across the studies. Although it is generally acknowledged that renewed hair shedding occurs relatively soon after discontinuation of treatment, none of the studies reported data on the sustainability of the treatment effect after the end of the study, which is an outcome of some considerable importance to participants. Furthermore, none of the studies, except Lucky 2004, reported the possible impact of hair regrowth reflected by a decrease in time spent by the women on hair styling, or the use of wigs.

We identified several ongoing studies that may eventually help to fill in some of the gaps in the evidence for the efficacy or otherwise of some of the other interventions, e.g. spironolactone, plasma rich in growth factors, and injections of autologous dermal and epidermal cells into the balding scalp (see the 'Characteristics of ongoing studies' section). However, the research institute that was conducting these 10 studies on these cell injections has gone into liquidation and we were unable to access further details.

Quality of the evidence

Limitations in study design and implementation

Although the study design in the included studies appeared to have been at best adequate, our study-level assessments of the risk of bias for a number of the domains in several of these studies revealed some of the limitations in their implementation, which we have reported in the 'Risk of bias in included studies' section of this review.

There was considerable variation in how well the studies were reported, and in particular the methods trials used to generate the sequence, to conceal the allocation, and the measures taken to blind investigators and participants. These factors, compounded with our unsuccessful attempts to contact many of the investigators for additional information, created difficulties in making accurate assessments of the risk of bias in more than 60% of the included studies.

In many instances, the key outcomes assessed in the included studies provided limited data, much of which we could not pool except for minoxidil 2% and 5%, and, consequently, did not allow any wider assessment or comparison of the effects of the interventions across the studies.

Indirectness of the evidence

The participants in the included studies were, in general, a clinically representative sample matching the inclusion criteria; therefore, we did not have any significant concerns about the appropriateness of participants identified in the review (see the 'Characteristics of included studies' section).

Twenty-nine of the 47 studies included in this review were placebo-controlled trials, which may only provide limited evidence on the advantages or disadvantages of new relative to existing interventions. Physicians need to have access to information about the benefits and harms of individual treatments, as well as the comparative efficacy of these interventions, and direct comparison trials are more likely to provide additional evidence that is both relevant and direct.

Patient-reported outcomes (PROs) are a prerequisite for informing evidence-based decision-making, but the importance of PROs — specifically those used in evaluating the impact of interventions on QoL and which are of direct relevance to patients — appears to have been underestimated by the investigators in most included studies. A validated disease-specific tool for the assessment of QoL in women with FPHL (Dolte 2000) has been available for many years, yet none of the included studies appear to have recognised its value as a reliable instrument that can be used for assessment of this crucially important outcome. The one study that evaluated the impact of the interventions on QoL utilised a simple questionnaire (Lucky 2004), and, as with most of the PROs assessed in the included studies, this did not satisfy some of the more fundamental criteria provided in the 'checklist for describing and assessing PROs in clinical trials' (see Table 3).

Inconsistency of the results

The low number of studies investigating similar interventions, with the exception of minoxidil versus placebo, and minoxidil (2%) versus minoxidil (5%) did not permit pooling of data for most of the comparisons. Therefore, any inferences about the inconsistency of the results could only be drawn from these comparisons. We investigated the heterogeneity between the studies for these comparisons and report these in the Effects of interventions as well as in Sensitivity analysis. sections of this review.

Imprecision of the results

Of the 47 studies included in this review, nine studies provided data for the comparison of minoxidil versus placebo. We downgraded the quality of evidence for serious imprecision for three of the

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separate outcomes, i.e. QoL, adverse events and degree of hair shedding, due to low sample size or low occurrence of events. In the comparison minoxidil 2% versus minoxidil 5% that covered four studies, we downgraded the quality of evidence for serious imprecision for the proportion of participants with self-rated clinically significant hair regrowth, QoL, and change from baseline to study conclusion in total hair count for having wide CIs or low sample size. In the comparison finasteride versus placebo and the comparison of low-level laser comb versus sham device, we downgraded the quality of evidence several times for serious imprecision for not meeting the optimal information size (see the 'Summary of findings' tables; Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4).

Publication bias

Based on a visual assessment of funnel plots in each case, there was no evidence of asymmetry in Analysis 1.1, Analysis 1.2, and Analysis 1.3. However, in Analysis 1.4, examination of the funnel plot (Figure 6) revealed asymmetry, which was caused by the inclusion of one small study that randomised eight participants and reported extremely positive results favouring minoxidil (Price 1990). After we investigated the individual participant data from the study, it remained unclear if the large treatment effect was the result of publication bias, small-study effects, or an artefact of natural variability (see Section 10.4.1 of the *Cochrane Handbook for Systematic Reviews of Interventions*, Higgins 2011). To assess the impact of this study, we performed a sensitivity analysis, which, after exclusion of the study, resulted in little change to the overall treatment effect (see Analysis 1.5).

Potential biases in the review process

We made every attempt to limit bias in the review process by ensuring a comprehensive search for potentially eligible studies. The review authors' independent assessments of eligibility of studies for inclusion in this review and extraction of data minimised the potential for additional bias beyond that detailed in the 'Risk of bias in included studies' tables. The incompleteness of some of the reports and our inability to obtain clarification of certain trial details or to resolve ambiguities in the reports may have contributed to some bias in their assessment, but, where these conditions applied, we explicitly stated this in the review text. The effects of language bias on the identification and selection of studies for inclusion in a systematic review is widely recognised; therefore, we ensured that any studies not in the English language were translated so that we could assess them for eligibility.

Agreements and disagreements with other studies or reviews

We retrieved one systematic review, Hassani 2012, which although published in 2012 only searched up to August 2008, excluded studies with small sample size and studies not in the English language, and did not reflect the extent of our current up-to-date searches. The review also lacked methodological rigour i.e. did not report prespecified outcomes, included an incomplete 'Risk of bias' assessment, and lacked a rating of the quality of the evidence.

We also identified several literature reviews (Avci 2013; Birch 2002; Camacho-Martínez 2009; Dinh 2007; Leavitt 2008; Olsen 2005; Price 2003; Trüeb 2010; Varothai 2014) and three guidelines (Blumeyer 2011; Drake 1996; Lee 2013b) that covered aspects of the diagnosis and management of FPHL in women. Although the reviews were a valuable resource to answer background questions covering the pathogenesis, classification, and epidemiology of the condition, none included a systematic search of the literature, nor a critical appraisal of the studies cited as references in support of the various treatment options described. The two guidelines provided comprehensive clinical recommendations on the effectiveness of a range of interventions for both men and women. However, to ensure that a guideline provides balanced information on the benefits and limitations of the therapeutic interventions being evaluated, its process of development should be transparent, robust, and reproducible; it should also clearly demonstrate that the supporting evidence was systematically reviewed (Nasser 2011).

The earlier of the three guidelines, Drake 1996, which was produced by the American Academy of Dermatology's Guidelines/Outcomes Committee, lacked transparency and reproducibility, in that it did not report on the methodological approach used by its developers but only that the guideline reflected the "best data available at the time the report was prepared". However, the developers wisely cautioned that "the results of future studies may require alteration of its conclusions and recommendations."

The guideline by Lee 2013b targeted Asian participants, both male and female, and provided little to no detail of how the evidence was gathered and summarized, and no indication of how the recommendations made were based on the evidence.

The 'Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men' (Blumeyer 2011) was commissioned by the European Dermatology Forum to evaluate the "efficacy of the currently available therapeutic options". Although its development relied heavily on a formal consensus process negotiated between members of the guideline group and was therefore deemed reasonably transparent, we are in disagreement over the robustness of the methodological approach used in its development. Lack of clarity in the process, and ultimately its reproducibility, was illustrated by the incomplete reporting of some important steps taken in study assessment, handling of missing trial data, analysis and interpretation of results, and summary of the adverse events.

We recognise an important area of discord with the method of grading of evidence for this guideline, which was based on study design and "summarised in a level of evidence" that combined the study design with a quality measure described by the developers as "mainly consistent results". However, these consistencies or inconsistencies, or indeed how they were defined or assessed in any of the individual studies, were unreported. It remains unclear if these factors were a potential source of bias, because, unlike in our systematic review, no 'Risk of bias' assessments were undertaken and the guideline developers did not report anything. Critically, four of the key studies underpinning the guideline recommendations for minoxidil were graded as "A_2 evidence resulting in an evidence level 1", which was inconsistent with our judgment that they were all categorised as at high risk of bias. A further seven studies were graded as B level evidence ("randomised, clinical studies of lesser quality"), but these quality criteria were also not clearly reported. Also, from the rather limited detail provided by the developers, a number of these assessments were not in agreement with the 'Risk of

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bias' assessments performed in this Cochrane review (see the 'Assessment of risk of bias in included studies' section).

In making their study level assessments of evidence, the guideline developers also did not appear to have taken into consideration the conceptual differences between methodological quality and reporting quality. Thus, the "level of evidence" in the guidelines was based solely on the methodological quality of the individual trial as reported, with no clear indication if the developers had attempted to contact investigators to clarify missing trial details and data, which would have enabled more robust and exhaustive 'Risk of bias' assessments to be carried out.

We specifically question and are at variance with the guideline developers' decision to summarise studies that combine data from men and women and narratively describe the treatment efficacy directed towards women. More importantly, we draw attention to the data analysis for the efficacy of minoxidil that included only the participants within the active treatment arms, ignorant of any placebo effect, which we have demonstrated can be considerable and is a further point of disagreement with our review. The, possibly unintentional, effect of this (as reported in the guideline) is an implied superiority in efficacy of the minoxidil (2% and 5%) concentrations compared to minoxidil (1%). However, in our systematic review, after accounting for the placebo participants in the analysis, the study that evaluated minoxidil (1%) (Tsuboi 2007) provided results that were the fourth largest treatment effect out of the eight included studies in Analysis 1.4 and, similarly, in Analysis 1.3. Notably, whilst the guideline provided a narrative synthesis of the data, the conclusions in this Cochrane review are inferences derived from a systematic and evidence-based approach.

In this systematic review, a closer examination of the primary research clearly indicated that the lower concentration of minoxidil was well-tolerated and without the adverse events associated with the higher concentration (Tsuboi 2007). Benefits and harms are equally important for decision-making; thus, we noted the rather limited emphasis placed on the discussion of harms in the S3 guideline, in which the adverse events were only reported in a generic narrative as "instruction for use/practicability", lacked a structured analysis, and was in sharp contrast with the more detailed exploration undertaken in this review.

The strength of clinical recommendations in the S3 guideline was based on the level of evidence and a number of other factors, none of which were clearly defined, nor appeared to correspond to the widely-recognised GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to developing and presenting recommendations for management of patients (Guyatt 2008). In contrast, we used this method in this review to examine and categorise the quality level of a body of evidence.

Therefore, whilst we concur with the general conclusions reached in both guidelines in terms of direction of treatment effect, we express a level of disagreement with the magnitude, and, more specifically, as reported in the S3 guideline, where it underpins the relevant clinical recommendations for minoxidil.

AUTHORS' CONCLUSIONS

Implications for practice

Based on only those studies that are most likely to have provided reliable results (i.e. reproducible, repeatable, and therefore valid), and selecting the most rigorously described and conducted studies, we conclude that there is mainly moderate to low quality evidence to support the efficacy of only one of the interventions for female pattern hair loss (FPHL), notably minoxidil.

Minoxidil (2%) topical solution twice daily appears to be effective and safe, and minoxidil (5%) used once daily may be as effective as minoxidil (2%) used twice daily, which is likely to result in improved adherence. However, the higher concentration of minoxidil (5%) is only registered for therapeutic management of FPHL in a small number of countries worldwide.

Although finasteride continues to be prescribed for treatment of women with FPHL, this therapeutic option does not appear to be supported by current research based on randomised controlled trials. Low-level laser therapy options are attracting interest but the results so far have been inconsistent.

Clinical decision-making on the choice of intervention for FPHL should be based on high-level evidence if it is available, but in the absence of such evidence for any other specific intervention, these decisions should continue to be guided by clinical experience and peoples' individual characteristics and preferences until further evidence for these other interventions becomes available.

In view of the fact that there may be a delay before any treatment effect can be noticed, and as most of the available treatments fail to achieve the desired end result, cosmetic aids and hair transplant surgery need to be included in the decision-making process. Furthermore, physicians should also try to address the psychosocial impact, coping mechanisms, and QoL issues when treating women with FPHL.

Implications for research

It is widely perceived that 2% minoxidil is more effective than the 1% concentration, and this is reflected in the fact that the 2% concentration is most frequently registered worldwide for FPHL. However, the results from one study included in this review indicate that 1% minoxidil does not appear any less effective than 2% minoxidil and is also associated with a potentially lower number of adverse events. There was also evidence (mainly moderate to low quality) that 5% minoxidil once daily was as effective as 2% minoxidil twice daily; a factor which may be important in improving adherence in future clinical trials.

There is also an urgent need for high-quality, well-designed, and rigorously-reported studies of other widely-used treatments, such as spironolactone, finasteride (at different dosages), dutasteride, cyproterone acetate, and laser-based therapy. Conceivably, some studies listed in the 'Characteristics of ongoing studies' section of this review will be able to provide answers to these remaining questions in the future.

There was wide variability in the conduct and the quality of reporting of many trials. A major area for improvement would be in the standardisation of outcome reporting in any future research. The use of proprietary severity scales and non-standardised scales

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significantly hampered our ability to combine study results for a meta-analysis. Outcomes collected in future trials should be primarily based on a standardised scale of the participant's assessment of the treatment efficacy, and they should also have a greater emphasis on changes in QoL as a result of the interventions. Standardised and uniform scales should be developed and used for physicians' assessments, and these should reliably reflect the proportion of participants with investigator-rated clinically significant hair regrowth and mean change in total hair count from baseline to the end of the study. Follow-up studies addressing the sustainability of hair regrowth after discontinuation of treatment should be taken into account as they constitute an important outcome for participants. Another important patient-reported outcome should be the impact of the hair regrowth reflected by a decrease in the time spent by women on hair styling, including the use of wigs.

Future randomised controlled trials must be well-designed, well-conducted, and adequately delivered, with subsequent reporting, including high-quality descriptions of all aspects of methodology. Rigorous reporting needs to conform to the Consolidated Standards of Reporting Trials (CONSORT) statement, and this will enable appraisal and interpretation of results, and accurate judgements to be made about the risk of bias and the overall quality of the evidence. Although it is uncertain whether reported quality mirrors actual study conduct, it is noteworthy that studies with unclear methodology have been shown to produce biased estimates of treatment effects (Schulz 1995). Adherence to guidelines, such as the CONSORT statement, would help ensure complete reporting.

For further research recommendations based on the EPICOT (evidence, population, intervention, comparison, outcomes, and time) format (Brown 2006), see Table 6.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Blume-Peytavi 2007

Methods	This was a randomised, parallel group comparative phase IV study for the first 6 months, then those in the comparator group were crossed over to minoxidil for months 7 to 12 **Setting** Multicentre (4), Germany **Date of study** Unspecified (12-month duration)
Participants	103 women Mean age = 50.7 years in group I, 45.6 years in group II **Inclusion criteria** • FPHL grade I or II (Ludwig 1977). **Exclusion criteria** Nothing was reported **Randomised** 103 participants were randomised (minoxidil 2% group = 52, alfatradiol 0.025% = 51) **Withdrawals/losses to follow-up** • Time of randomisation - start of study: total = 28/103 (27%) (14/52 (27%) in group I, 14/51 (27%) in group II). • At 6 months: 14/52 in group I, 14/51 in group II. • At 12 months: 21/52 (40%) in group I, 22/51 (43%) in group II. Non-compliant participants were excluded from the analysis **Baseline data** There was a minimal data set, and baseline data for early withdrawals were unreported
Interventions	**Intervention** • Minoxidil 2% 1 mL twice daily to central parietal scalp for 12 months. **Comparator** • Alfatradiol 0.025% solution 3 mL once daily (months 1 to 6); cross-over (months 7 to 12) to minoxidil 2%. No wash-out period was specified.

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Blume-Peytavi 2007 *(Continued)*

Outcomes	Assessments (4): at baseline 3-, 6-, 12-month recall of the central parietal region of the scalp, defined and marked with a semipermanent tattoo. The area was shaved and assessed by TrichoScan® (Hoffmann 2002), epiluminescence microscopy and digital image analysis. **Outcomes** (as reported) • Cumulative hair thickness (mm/cm^2).[1] • Hair density (number of hairs/cm^2).[1] • Terminal hair density. • Vellus hair density. • "Tolerability of treatment" by participant and investigator on a scale of 1 (excellent) to 5 (unsatisfactory).[1] • "Unwanted event or side effect".[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared. Although they did not confirm what, if any, support was provided, the intervention under investigation was Regaine ® Frauen (Pfizer Consumer Healthcare).
Declaration of interest	The Principal Investigator, Ulrike Blume-Peytavi, was an advisor for Pfizer and Galderma R&D. Three investigators; Christian Kunte, Natalie Garcia Bartels, and Rolf Hoffmann were advisors for Pfizer.
Notes	This is a comparative study of minoxidil versus alfatradiol alone for 6 months, with a cross-over to minoxidil alone for 6 months. No wash-out period was reported. We only included the first 6 months. It was unclear whether "tolerability of treatment" referred to the satisfaction of the participant, physician, or both. It was rated on a scale of 1 (excellent) to 5 (unsatisfactory). E-mail contact with the Principal Investigator (PI) suggests that this outcome refers to adverse/side-effects, rather than satisfaction. We requested that the investigators provide individual patient data, but none were unavailable.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 392): "were randomized online into two treatment groups." Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	The method used to generate the sequence would appear to indicate that intervention allocations could not have been foreseen in advance of, or during, enrolment. Comment: this was probably done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 392): "open randomized study" Comment: the outcome is likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 392): "open randomized study" Comment: the outcome measurement is likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote (page 392): "Included in the statistical analysis were all patients who appeared at least at visit 1 (baseline) and visit 3 (6 months)"

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Blume-Peytavi 2007 *(Continued)*

		There was a significant amount of incomplete and missing outcome data; it was unclear if these were withdrawals or losses to follow-up. • Early losses (baseline) and 6-month follow-up ≥ 27% in each group, and > 40% in each group at 12-month follow-up. • Timing and reasons for losses or withdrawals, other than "non compliance" or "personal reasons", were inadequately reported, and data analysis was per-protocol. Comment: the analysis did not account for the large number of postrandomisation losses of participants, nor the potential carry-over and period effects due to the cross-over design in 1 treatment arm. The high attrition rate and the per-protocol analysis of these data may raise concerns about the reliability of the data as reported.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Blume-Peytavi 2011a

Methods	This was a randomised, investigator-blind, active-controlled trial **Setting** Departments of Dermatology and Allergy, Clinical Research Center for Hair and Skin Science, Charité-Universitätsmedizin Berlin, Germany **Date of study** June 2008 to January 2009 (24-week duration)
Participants	114 women Mean age (range) = 49.9 years (23 to 75 years) **Inclusion criteria** • > 18 years. • Savin grade D3 to D6 female pattern androgenetic alopecia. • Hair density ≤ 220 hairs/cm^2 as measured by TrichoScan. **Exclusion criteria** • Ferriman-Gallwey score > 6 (scores > 8 indicate excess androgen production). • Hypersensitivity to minoxidil or other study ingredients. • Local scalp treatments during previous 4 weeks. • Systemic treatment 3 months prior to study that could interfere with the study medications. • Use of non-breathable wigs or hair transplants. • Participation in another study in previous 4 weeks • Chemotherapy, radiation therapy, or laser therapy (on the scalp) within the last 6 months. • Pregnancy or desire to become pregnant. • Presence of other dermatologic disorders. • Severe medical conditions or hair loss diseases.

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Blume-Peytavi 2011a *(Continued)*

	Randomised 113 participants were randomised (minoxidil 5% group = 56, minoxidil 2% group = 57) **Withdrawals/losses to follow-up** There were 13/113 (11.5%) withdrawals/losses to follow-up: 6/56 (10.7%) in the 5% minoxidil group, and 7/57 (12.3%) in the 2% minoxidil group • Minoxidil 5% group: 1 participant preference, 1 lost to follow-up, 3 to adverse events, 1 serious adverse event. • Minoxidil 2% group: 4 participant preference, 2 lost to follow-up, 1 to adverse events. **Baseline data** The mean Savin hair density score was 4.13 in the minoxidil 5% group, and 3.84 in the minoxidil group 2%. There was a higher proportion of participants with more extensive hair thinning (Savin scores of D5 or D6) in the minoxidil 5% group (N = 19) compared to the minoxidil 2% group (N = 9).
Interventions	**Intervention** • Minoxidil 5% topical foam (MTF) once daily for 24 weeks. **Comparator** • Minoxidil 2% topical solution (MTS) twice daily for 24 weeks.
Outcomes	Assessments (3): at baseline, week 12 and 24 **Primary outcomes** (as reported) • Change from baseline in non-vellus target area hair count at week 24.[1] **Secondary outcomes** (as reported) • Change in non-vellus target area hair width. • Overall efficacy by global photographic review as assessed by treatment-blinded evaluators and the subject herself.[1] • Adverse events.[1] • Participants' assessment of product aesthetics. [1]Denotes outcomes prespecified for this review.
Funding source	Quote (page 1126): "Supported by a medical grant application, Johnson & Johnson Consumer Co Inc."
Declaration of interest	Quote (page 1126): "Dr Blume-Peytavi is a consultant for Johnson & Johnson Consumer Co Inc. Dr Garcia Bartels was a consultant for Pfizer GmbH Germany until 2008."
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1127): "24-week, randomized, investigator initiated and -blinded, 2-arm comparative study" "Participants were randomized (1:1) to treatment with either half a capful of 5% MTF applied once daily or 1 mL of 2% MTS applied twice daily."

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Blume-Peytavi 2011a *(Continued)*

		After e-mail communication with investigators: the allocation was performed using block randomisation (27 blocks, sequences 4 and 6). Comment: we judged this as adequate.
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement. After e-mail communication with investigators: in this study, the allocation concealment was "performed using sequentially numbered, sealed, opaque envelopes, and kept by the project manager of the CRC." Comment: we judged this as adequate.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1128): "investigator-blinded." "To ensure investigator blinding, participants were instructed to speak in the presence of an investigator only about 'the product' and not to use the terms 'foam' or 'solution' or to mention how many times per day they used the study product. In addition, each participant was instructed to wash their hair before each study visit to avoid providing the study investigators with any indication as to which product they were using." Comment: the blinding of investigators appeared to have been adequate, but the impact of lack of blinding of participants was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1127): "investigator-blinded." Both investigator and participants were the outcomes assessors. Quote (page 1128): "To ensure investigator blinding, participants were instructed to speak in the presence of an investigator only about 'the product' and not to use the terms 'foam' or 'solution' or to mention how many times per day they used the study product. In addition, each participant was instructed to wash their hair before each study visit to avoid providing the study investigators with any indication as to which product they were using." Comment: reasonable attempts were made to blind outcomes assessors (personnel), but it was not possible to blind participants. It's unclear to what extent the lack of blinding had any impact on the participant-assessed outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The reasons and number of dropouts/withdrawals (13/113 = 11%) from each group were reported and balanced across both active intervention groups. The data analysis was per-protocol. Comment: although there was per-protocol analysis, the low percentage of dropouts posed a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT00958750 and EUCTR2008-001770-33-DE and MINALO3005). The prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Unclear risk	There was baseline imbalance, with a higher proportion of participants with more extensive hair thinning in the minoxidil (5%) group. We cannot exclude a potential risk of bias.

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Bureau 2003

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Multicentre (4), France **Date of study** Unspecified (6-month duration)
Participants	93 men/women Mean age = 38.6 ± 8.14 years (standard deviation (SD)) in group I, 40.6 ± 9.32 years (SD) in group II **Inclusion criteria** • Female: stage I and II alopecia Ludwig scale (Ludwig 1977). (Male: I to VII alopecia; Hamilton-Norwood scale). **Exclusion criteria** Nothing was reported **Randomised** 93 participants were randomised, data on 69 participants (group I = 31 men/9 women, group II = 21 men/8 women) **Withdrawals/losses to follow-up** There were 24/93 (26%) withdrawals/losses to follow-up. • Cutaneous intolerance (1). • For "reasons unrelated to treatment" (23). The losses in each group and number of men/women were unreported **Baseline data** Average hair density: group I = 152 h/cm^2, group II = 165 h/cm^2
Interventions	**Intervention** • Group I = 3 times/week, light scalp massage, and 20 drops essential oil solution (E2F7) and electro-magnetic pulses (12.5 V/m at 1 cm,10 MHz) delivered by a synthetic resin helmet for 30 mins (E2F7 essential oil solution contains:*Pimenta racemosa*, *Rosmarinus officinalis*, *Myrtus communis*, *Salvia officinalis*, *Cedrus atlantica*, *Salvia sclarea*, *Laurus nobilis*, *Thymus satureioides*, *Pogostemon patchouli*, *Cananga odorata*) **Comparator** • Group II = 3 times/week, light scalp massage and application of placebo solution (neopentyl glycol dictanoate and essence of *Calamus*), followed by electromagnetic pulses (12.5 V/m at 1 cm,10 MHz) for 30 mins.
Outcomes	Assessments were monthly (6) **Primary outcomes** (as reported) • Mean hair counts.[1] • Hair density via macro-photography.[1]

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Bureau 2003 *(Continued)*

- Biopsy/histo-chemical examination of hairs.

Secondary outcomes (as reported)

- Tolerability (side-effects).[1]
- Acceptability of treatment and hair quality evaluation: participant-assessed VAS (monthly) and investigator-assessed clinically.[1]

[1]Denotes outcomes prespecified for this review

Funding source	None declared
Declaration of interest	None declared
Notes	Data were not stratified for gender. We sent e-mails to the PI, but unfortunately they were unable to help us. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 221): "were placed into either group A (treatment, n=40) or group B (control placebo, n=29) according to a statistical randomization plan". Comment: the study authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 221): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit clear judgement of risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 24/93 (26%) withdrawals/losses to follow-up, with reasons reported. The data analysis was per-protocol. Comment: the large number of dropouts (26%), incomplete outcome data, and inappropriate analysis were potential sources of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

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Carmina 2003

Methods	This was a randomised "unmasked" study with 2 active control groups and an observation/no treatment group **Setting** Endocrinology outpatient practice in Italy **Date of study** Unspecified (12 month-duration)
Participants	48 hyperandrogenic women with alopecia Mean age = 25 ± 2 years **Inclusion criteria** • FPHL Ludwig scale grade I to III (Ludwig 1977). • Premenopausal with increased serum androgens. **Exclusion criteria** The trial did not report any exclusion criteria **Randomised** 36 participants were randomised (group I = 12, group II = 12, group III = 12) (Untreated controls (12), these were enrolled, not randomised, but refused treatment and served as an observation group) **Withdrawals/losses to follow-up** None were reported **Baseline data** Ludwig scale (mean) • Cyproterone acetate group = 2.1 (0.2). • Flutamide group = 2.3 (0.2). • Finasteride group = 2.2 (0.1). • Observation group = 2.1 (0.3).
Interventions	**Intervention** • Group I = cyproterone acetate (CPA) 50 mg/day with 25 µg of ethinyl estradiol in a reverse sequential regimen (CPA from day 5 to 15 of the cycle, and ethinyl estradiol from day 5 to 25 of the cycle). **Comparator 1** • Group II = flutamide (250 mg/day). **Comparator 2** • Group III = finasteride (5 mg/day). **Comparator 3** • Control group = no treatment (observational, not randomised). The duration of treatment for groups I, II, and III was 1 year

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Carmina 2003 *(Continued)*

Outcomes	There was inadequate and unclear information on the frequency and timing of the following assessments **Primary outcomes** (as reported) • Hair thinning (frontal) on Ludwig scale (Ludwig 1977). • Hair growth: self-assessed questionnaire based on a 7-item questionnaire (Barber 1998) (appearance and growth of the hair, slowing down of hair loss, general satisfaction with therapy).[1] • Hair density: investigator-assessed (frontal–parietal region) before and after treatment rated on 7-point scale: greatly decreased (-3) to greatly increased (+3).[1] **Secondary outcomes** (as reported) • Possible side-effects and liver function tests assessed at 3-month intervals.[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 92): "Thirty-six women were randomized to one of three treatments, each composed of 12 subjects." Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 91): "unmasked trial of three treatments." Comment: the outcome was likely to be influenced by the lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 91): "unmasked trial of three treatments." Quote (page 92): "All assessments were carried out by one of the authors." Comment: the outcome measurement was likely to have been influenced by the lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts, withdrawals, or missing outcome data were reported. The time points of outcome assessments were unclear, and only end of study data were reported. Comment: There was insufficient information to permit a clear judgement of the risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported.

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Carmina 2003 *(Continued)*

		Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

DeVillez 1994

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Multicentre (11), USA, but no further details reported **Date of study** Unspecified (32-week duration)
Participants	308 women Mean age (SD) = 33.6 years (6.67) in the minoxidil group, 34.4 years (6.32) in the placebo group **Inclusion criteria** • Age 18 to 45 years. • FPHL Ludwig scale grade I or II (Ludwig 1977). • Good general health; no evidence of cardiac, systemic, psychiatric, or scalp disease. **Exclusion criteria** • Previous exposure to minoxidil solution. • Pregnant or at risk of pregnancy, < 12 months postpartum, or breast feeding. • Prior use of hair restorers or systemic drugs, e.g. steroids, antihypertensives, cytotoxic compounds, vasodilators, anticonvulsant drugs, ß-blockers, spironolactone, cimetidine, diazoxide, cyclosporin, ketoconazole, cyproterone acetate, oestrogens, or progesterones, in previous 3 months. **Randomised** 308 participants were randomised (minoxidil group = 157, placebo group = 151) **Withdrawals/losses to follow-up** There were 52/308 (17%) withdrawals/losses to follow-up: 27/157 (16.6%) in the minoxidil group, and 25/151 (14.8%) in the placebo group • Voluntary withdrawal: minoxidil group = 18 (11.5%), placebo group = 17 (11.3%). • Local irritation: minoxidil group = 1 (0.1%), placebo group = 1 (0.1%). • Pregnancy: minoxidil group = 2, placebo group = 0. • Other health problems: minoxidil group = 6 (3.8%), placebo group = 6 (3.3%). • Use of prohibited medication: minoxidil group = 0, placebo group = 1. **Baseline data** Duration of hair loss (SD): minoxidil group = 9.5 years (6.67), placebo group = 9.0 years (6.68) Age at onset (SD) : minoxidil group = 24.1 years (7.26), placebo group = 25.4 years (7.14) Degree of thinning, Ludwig scale (% of participants by grade and group) • Grade I: minoxidil group = 48, placebo group = 53. • Grade II: minoxidil group = 52, placebo group = 47.

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DeVillez 1994 *(Continued)*

Interventions	**Intervention** • Minoxidil 2% topical solution (minoxidil powder, propylene glycol, alcohol, and water). Applied 1 mL twice daily at 12 hour-intervals to the scalp for 32 weeks. **Comparator** • Placebo (propylene glycol, alcohol and water). Applied 1 mL twice daily at 12 hour-intervals to the scalp for 32 weeks.
Outcomes	Assessments (9): at baseline and every 4 weeks **Primary outcomes** (as reported) • Hair counts (combination photography and computer-assisted image counting).[1] **Secondary outcomes** (as reported) • Investigator- and participant-assessed new hair growth, rated as none/minimal or moderate/dense compared to baseline.[1] • Participant-assessed hair shedding (degree), rated as increased/decreased/unchanged.[1] • Adverse events.[1] [1]Denotes outcomes prespecified for this review
Funding source	The report was unclear about the extent and level of any funding or support, but as three of the investigators were employed by the manufacturer, a level of support and possibly funding is most probable.
Declaration of interest	Three of the four investigators were from the Dermatology Division of Upjohn Laboratories, the manufacturer of the intervention under investigation
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 304): "randomized to receive either". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 304): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 304): "Both the investigator and the patient assessed visible new hair growth."

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DeVillez 1994 *(Continued)*

		Comment: there was uncertainty with effective blinding of outcomes assessors (participants/healthcare providers) during the study. There was insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	52/308 participants "discontinued"; most were voluntary withdrawals and were balanced across both groups. The data analysis was per-protocol. Comment: the number of dropouts (17%) and incomplete outcome data, combined with per-protocol analysis were potential sources of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Draelos 2005

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** A "research center" in the USA **Date of study** Unreported (6-month duration)
Participants	60 women **Inclusion criteria** • Age 20 to 80 years. • FPHL Ludwig scale grade I to III (Ludwig 1977). **Exclusion criteria** Nothing was reported **Randomised** 60 participants were randomised (active intervention group = 40, placebo group = 20) **Withdrawals/losses to follow-up** There were 8/40 (20%) withdrawals/losses to follow-up in the active intervention group, and 8/20 (40%) in the placebo group. • The timing and reasons for withdrawal were unreported. **Baseline data** The duration and extent of thinning was unreported
Interventions	**Intervention** • Octyl nicotinate 0.5% and myristyl nicotinate 5.0% in vehicle. 6 drops/night to the scalp (right anterior/right-middle top/left-middle top/right posterior/left posterior) for 6 months.

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Draelos 2005 *(Continued)*

	Comparator • Vehicle only. 6 drops/night to the scalp (right anterior/right-middle top/left-middle top/right posterior/left posterior) for 6 months.
Outcomes	Assessments (4): at baseline, 2, 4, and 6 months **Outcomes of the trial** (as reported) • Investigator-assessed hair growth by standardised photographic techniques (baseline and end points), rated as follows: -1 = decrease/no change, +1 = increased.[1] • Appearance of hair (participant-assessed).[1] • Adverse events.[1] [1]Denotes outcomes prespecified for this review
Funding source	Quote (page 261): "This research was supported in part by NIH grantR43CA90085 and a grant from Niadyne Inc."
Declaration of interest	Quote (page 261): "MKJ and ELJ are principals in Niadyne Inc., whose sponsored research is managed in accordance with the University of Arizona conflict-of-interest policies. Dr Draelos owns no stock in Niadyne and has no other financial interest in the corporation."
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 259): "Subjects were assigned randomly to the placebo (20, vehicle only) or active groups." Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 259): "Dispensed products were packaged in identical containers." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were participant- and investigator-assessed. Blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken. Comment: we judged this as at a low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 8/40 (20%) withdrawals/losses to follow-up in the active intervention group, and 8/20 (40%) in the placebo group. Incomplete outcome data were not adequately addressed; timing of, and reasons for, withdrawal were unreported; and there were substantial differences in attritional losses between the 2 groups.

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Draelos 2005 *(Continued)*

		Comment: we judged this as at a high risk of bias.
Selective reporting (reporting bias)	Low risk	Although only minimal data were reported, the outcomes listed in the 'Methods' section were comparable to the reported results. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Fischer 2004

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Friedrich-Schiller-University, Jena, Germany **Date of study** Unspecified (6-month duration)
Participants	40 women (28 with diffuse alopecia, 12 with androgenetic alopecia) Age = 20 to 70 years **Inclusion criteria** • AGA Ludwig scale (Ludwig 1977). • Diagnosis of diffuse alopecia; hair thinning all over the scalp. **Exclusion criteria** • Thyroid disease or iron deficiency. **Randomised** 40 participants were randomised (melatonin group = 20, placebo group = 20) **Withdrawals/losses to follow-up** None were reported **Baseline data** % anagen hairs, trichogram-assessed • Frontal: placebo group = 79.9%, melatonin group = 78.0%. • Occipital: placebo group = 78.2%, melatonin group = 76.3%.
Interventions	**Intervention** • Melatonin 0.1% alcohol solution. 1mL as a spray once daily in the evening for 6 months. **Comparator** • Alcohol solution alone. 1 mL as a spray once daily in the evening for 6 months.
Outcomes	Assessments (3): at baseline, 3, and 6 months **Outcomes** (as reported) • Hair counts by frontal and occipital Trichograms.[1]

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Fischer 2004 *(Continued)*

	[1]Denotes outcomes prespecified for this review
Funding source	Quote (page 344): "This study was performed with kind support of ASAT Applied Science and Technology, Zug, Switzerland. Special thanks are given to Dr D.Menne, BiomedicalSoftware, Tübingen, Germany, for the statistical analysis."
Declaration of interest	None declared
Notes	There was separate analysis for AGA and diffuse alopecia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (pg 342): "double-blind randomized". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups. After e-mail communication with investigators: "Randomisation was performed in two groups (placebo/verum) of 20 cards by drawing the cards and allocating them to the numeric numbers 1 to 40." Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement. After e-mail communication with investigators: "The bottles in which the test solutions were filled up were numbered and randomly allocated by the producer/sponsor to verum and placebo." "The patients received the test numbers in order of their recruitment." Comment: as a form of central randomisation, this was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement. After e-mail communication with investigators: "The bottles in which the test solutions were filled up were numbered and randomly allocated by the producer/sponsor to verum and placebo. The study was double-blind, so there was no code except the emergency code to identify the numbers with their respective ingredients." Comment: it appears that reasonable attempts were made to blind participants and personnel from knowledge of which intervention a participant received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	There was insufficient information in the report to permit a clear judgement. After e-mail contact with the investigators (see above), we judged the blinding to be adequate.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts, withdrawals, or missing outcome data were reported. Comment: there was insufficient information to permit a clear judgement of the risk of bias.

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Fischer 2004 *(Continued)*

Selective reporting (reporting bias)	Low risk	Although only minimal data were reported, the outcomes listed in the 'Methods' section were comparable to the reported results. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Gassmueller 2008

Methods	This was a randomised, double-blind, placebo-controlled trial (please see the Notes section) **Setting** 2 centres in Germany **Date of study** Unspecified (16-week duration)
Participants	70 women Age = 49 to 72 years **Inclusion criteria** • Postmenopausal. • AGA Ludwig scale grade I or II (Ludwig 1977). **Exclusion criteria** • Previous surgical correction of scalp hair loss. • Hair loss due to disease or drug treatment. • Known allergy to components of the study preparations or hair dye. • Clinically significant disease. • Treatment for arterial hypertension. • Known hyper- or hypothyroidism. • Treatment with minoxidil in previous 6 months. • Treatment with other hair growth products in previous 3 months. • Treatment with ß-blockers, cimetidine, angiotensin-converting enzyme inhibitors, amphetamines, retinoids, ketoconazole, or lithium preparations. **Randomised** 70 participants were randomised (topical fulvestrant group = 34, vehicle only group = 36) **Withdrawals/losses to follow-up** 3/70 (4%) withdrawals/losses to follow-up. It was unclear from which of the groups the losses were: 2 for personal reasons (on days 15 & 17), and 1 for protocol deviation (use of prohibited concomitant medication). **Baseline data** Mean hair density as hairs per cm^2 (range) • Fulvestrant group = 214.4 (97 to 312), vehicle group = 195.4 (57 to 327). Mean cumulative hair thickness in mm per cm^2 (range) • Fulvestrant group = 21.35 (7.6 to 29.5), vehicle group = 19.61 (5.4 to 32.5).

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Gassmueller 2008 *(Continued)*

	Mean hair growth rate in mm per day (range) • Fulvestrant group = 0.38 (0.27 to 0.49), vehicle group = 0.39 (0.18 to 0.56).
Interventions	**Intervention** • Fulvestrant 30 µL per cm^2, 70 mg per mL (0.115 mol per L) solution. Applied topically twice daily for 16 weeks. **Comparator** • Vehicle (40% propylene glycol, 40% isopropanol, 20% water). Applied topically twice daily for 16 weeks.
Outcomes	Assessments (5): at baseline, day 29, 57, 85, and 113 **Outcomes of the trial** (as reported) • Hair density, TrichoScan analysis of digital images of test area.[1] • Hair thickness and hair growth rate by TrichoScan analysis.[1] • Level of systemic exposure to fulvestrant and tolerability of topical fulvestrant.[1] [1]Denotes outcomes prespecified for this review
Funding source	Quote (page 115): "This study (including editorial assistance provided by Dr Keri Wellington of Mudskipper Bioscience) was supported financially by AstraZeneca."
Declaration of interest	None declared. One investigator (A. Webster) was associated with AstraZeneca
Notes	Of two phase II randomised controlled trials (RCTs) of men and women with AGA, we only considered the trial that included women

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 110): "randomized (via a randomization list generated by AstraZeneca)." Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. After e-mail contact with the investigators: "Randomization was performed centrally by the sponsor of the study in a balanced manner." "The random assignment for each subject was kept in a sealed envelope at the site which was only to be opened in case of an emergency." Comment: although the sponsor generated the sequence, this was a form of central randomisation. This was probably done; therefore, we judged this as at a low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 110): "The female study was double blind." The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.

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Gassmueller 2008 *(Continued)*

		After e-mail contact with the investigators: "The study medication was labelled with the respective subject (randomisation) number by the sponsor, before delivery to the test sites." Comment: we judged this as at a low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 111): "TrichoScan analysis...images analysed at the end of the study by an independent observer who was blinded to the treatment received and who was also unaware of the time point in the study for each image". Comment: the measures used to blind the outcome assessor from knowledge of which intervention a participant received was adequately reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/70 participants dropped out (unclear which group); the reasons for withdrawal were reported. There was an intention-to-treat (ITT) analysis. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Gehring 2000

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Dermatology Clinic in Karlsruhe, Germany **Date of study** Unspecified (6-month duration - late autumn until summer)
Participants	41 women Mean age (range) = 38.1 years (19 to 57) in the active treatment group, 39.2 years (23 to 54) in the placebo group **Inclusion criteria** • Female 18 to 65 years. • Anagen hair ratio < 80%. **Exclusion criteria** • Pregnant or lactating women. • < 6 months postpartum. • Acute infectious diseases and febrile infections or surgery < 3 months before enrolment. • Medication that can induce hair loss (cytostatics, lipid-lowering agents, antithyroid drugs, anticoagulants, H^2 blockers, tricyclic antidepressants). • Medication that can influence hair growth disorders (e.g. oral contraceptives, topical corticosteroids). • Diseases resulting in cachexia (e.g. acquired immune deficiency syndrome (AIDS), cancer). • Malnutrition (iron deficiency, anorexia nervosa).

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Gehring 2000 *(Continued)*

- Acute liver, renal, or metabolic disease.

Randomised

41 participants were randomised (active treatment group = 21, placebo group = 20)

Withdrawals/losses to follow-up

There was 1 in the placebo group; the reason was unreported

Baseline data

Anagen hairs (%)

- Active treatment group = 75.5, placebo group = 74.5.

Interventions	**Intervention** • Oral combination product of millet seed extract, L-cystine, and calcium pantothenate. 2 capsules 3 times a day for 6 months. **Comparator** • Vehicle. 2 capsules 3 times a day for 6 months.
Outcomes	Assessments (3): at baseline, 3, and 6 months **Outcomes of the trial** (as reported) • Anagen hair rate, change from baseline by phototrichogram.[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared. Quote (page 420): "Medication provided by Company Roche Nicholas, Germany"
Declaration of interest	None declared
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 419): "randomized, double-blind". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 419): "double-blind". The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 419): "double-blind".

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Gehring 2000 *(Continued)*

All outcomes		Comment: uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was 1 dropout in the placebo group; the reason was unreported. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Georgala 2004

Methods	This was a randomised, placebo-controlled trial **Setting** Hospital in Athens, Greece **Date of study** 1998 to 2000 (the duration in group I was 12 weeks, in group II & III it was 24 weeks)
Participants	75 women Age = 48 to 71 years **Inclusion criteria** • Postmenopausal female with clinical diagnosis AGA. • AGA telogen rate > 20%. • Good general health, absence of other causes of alopecia. **Exclusion criteria** • Other treatment for AGA in previous 3 months. • Participants assessed as at high risk for breast cancer. **Randomised** 75 participants were randomised into 3 treatment groups (group I = 25, group II = 25, group III = 25) **Withdrawals/losses to follow-up** There were 13/75 (17%) withdrawals/losses to follow-up: 3 in group I, 5 in group II, and 5 in group III. • The reasons were poor compliance and loss to follow-up. **Baseline data** The duration and extent of thinning was unreported. Anagen/telogen ratio at baseline. • Group I = 1.68. • Group II = 1.57. • Group III = 1.61.

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Georgala 2004 *(Continued)*

Interventions	**Intervention** • Group I = estradiol valerate topical ointment (3%) for 12 weeks. 15 drops/night on the affected area of the scalp for 4 weeks and then alternate nights until the end of the study period. **Comparator 1** • Group II = estradiol valerate topical ointment (3%) for 24 weeks. 15 drops/night on the affected area of the scalp for 4 weeks and then alternate nights until the end of the study period. **Comparator 2** • Group III = placebo vehicle only for 24 weeks. 15 drops/night on the affected area of the scalp for 4 weeks and then alternate nights until the end of the study period.
Outcomes	Assessments (3): at baseline, 3, and 6 months **Outcomes of the trial** (as reported) Trichograms were taken at baseline and the completion of the study. • Ratio of anagen/telogen compared to baseline. • Adverse events and side-effects.[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	This report was a Letter to "Dermatology". Data reporting were inadequate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 178): "Patients were randomised into three treatment groups." Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of the risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement of the risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The ratio of dropouts/withdrawals was as follows: 13/75 (17%). The reasons and number from each group were reported and balanced across active intervention groups only.

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Georgala 2004 *(Continued)*

		The data analysis was per-protocol. Comment: although the numbers of dropouts were balanced between the groups, the percentage of dropouts and subsequent per-protocol analysis poses an unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Guerrero 2009

Methods	This was a randomised, active-controlled trial **Setting** 3 centres in Chile **Date of study** November 2007 to April 2008 (12-week duration)
Participants	40 men and women (22 men, 18 women) Mean age = 43.7 years (range 20 to 69) **Inclusion criteria** • Androgenetic alopecia according to Hamilton for men and Ludwig for women (Ludwig 1977). • Informed consent, and willing to comply and attend visits to the clinic. **Exclusion criteria** • Hormonal treatment in previous 3 months. • Diseases interfering with alopecia. • Pregnant and lactating women. • Hair diseases that worsen with topical applications. • Treatments that affect hair growth such as lithium and methotrexate. • Hypersensitivity to 1 of the ingredients. • Hair transplant. **Randomised** 40 participants were randomised (minoxidil group = 15, estradiol group 18, unclear = 7) **Withdrawals/losses to follow-up** 7/40 (18%) withdrawals/losses to follow-up: unclear how many from each group • Not attending primary visit (2) control visits (3), adverse events (1), pregnancy and subsequent spontaneous abortion (1). **Baseline data** Most men had Hamilton II/III and most women Ludwig II
Interventions	**Intervention**

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Guerrero 2009 *(Continued)*

	• Minoxidil 2% once daily application for 12 months. **Comparator** • 17-alfa-estradiol 0.025% once daily application for 12 months.
Outcomes	Assessments (4): at baseline, days 30, 60, and 90 **Outcomes of the trial** (as reported) • Percentage hair in telogen and anagen phase.[1] • Adverse events.[1] • Hair loss, and hair growth.[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	The sample comprised of participants of both genders, and the sequence was generated according to simple randomisation (specific method unreported, but without stratification). The results did not consider gender as a factor or covariate, and the data reported and subsequent analysis is not gender-specific. We e-mailed the PI, but received no response. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 22): "un estudio randomizado" and "en forma aleatoria mediante randomización simple en dos grupos" (randomised through simple randomisation). Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: there was insufficient information to permit a clear judgement of the risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 22): "triple ciego" (triple-blind). Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 22): "triple ciego" (triple-blind). Comment: uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. There was insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/40 (18%) withdrawals/losses to follow-up: unclear how many from each group.

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Guerrero 2009 *(Continued)*

		The data analysis was per-protocol. Comment: although the numbers of dropouts appear balanced between the groups, the percentage of dropouts and subsequent per-protocol analysis poses an unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the trial appears to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Hong 2007

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Dermatology Department at Chung-Ang University Medical Center, Seoul, Korea **Date of study** Unspecified (16-week duration)
Participants	95 men and women (74 men, 21 women) Mean (SD) age = 38.8 (8.9) years in active treatment group, 41.7 (8.9) years in placebo group **Inclusion criteria** • Those with male pattern hair loss of Hamilton-Norwood grades II to V or with female pattern hair loss (FPHL) of Ludwig grades I to II. • 19 to 55 years. **Exclusion criteria** • Scalp or systemic disease that may affect the study results. • Hair loss treatment within 4 weeks prior to enrolment; such as carpronium chloride treatment, minoxidil use, other hair growth products, adrenal corticosteroid use, ultraviolet (UV) treatment, and immunosuppressive drugs. **Randomised** 95 participants were randomised (active treatment group = 33, placebo group 40, unclear = 22) **Withdrawals/losses to follow-up** 22/95 (23.2%) withdrawals/losses to follow-up: unclear how many from each group **Baseline data** Hair shed per (mean): active treatment group 250, placebo group 300
Interventions	**Intervention** • Cytopurine, pentadecanoic glyceride, 95% ethanol topical solution. **Comparator**

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Hong 2007 *(Continued)*

	• Vehicle solution.
Outcomes	Assessments (3): at baseline, week 8, and week 16 **Outcomes of the trial** (as reported) • Counting the number of hair shed when washing hair every other day for 5 times before the visit. • Phototrichogram evaluation of total hair count, anagen hair count, and mean hair diameter in the 1 cm^2 area on the vertex (defined as 15 cm from the glabella) at 3 days after shaving the area.[1] • Physician evaluation of dandruff, itching, sebum production, and scalp erythema on a 3-point Likert scale (exacerbation, no change, improvement).[1] • Patient evaluation of overall improvement (5-point Likert scale (exacerbation, no change, a little improvement, some improvement, definite improvement)).[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	The trial did not stratify data by gender. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1233): "randomized". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups. After e-mail communication: "We used computer software program that generates the random sequence" Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	The trial did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of the risk of bias. After e-mail communication: "We used sequentially numbered, opaque, sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1233): "double-blind". The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1233): "double-blind". Comment: uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. There was insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias)	High risk	22/95 (23.2%) withdrawals/losses to follow-up: unclear how many from each group. Data analysis was per-protocol.

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Hong 2007 *(Continued)*

All outcomes		Comment: we judged this as at a high risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the trial appear to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Jacobs 1993

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Multicentre (10), Europe (France/Belgium/UK/Holland/Switzerland) **Date of study** Unspecified (32-week duration)
Participants	346 women Mean age (SD) = 33.1 years (6.93) in the minoxidil group, 34.2 years (6.35) in the placebo group **Inclusion criteria** • Age 18 to 45 years. • AGA Ludwig scale grade I or II (Ludwig 1977). • Good general health; no evidence of cardiac, systemic, psychiatric, or scalp disease. **Exclusion criteria** • Previous exposure to minoxidil solution. • Pregnant or at risk of pregnancy, < 12 months postpartum, or breast feeding. • Prior use of hair restorers or systemic drugs, e.g. steroids, antihypertensives, cytotoxic compounds, vasodilators, anticonvulsant drugs, ß-blockers, spironolactone, cimetidine, diazoxide, cyclosporin, ketoconazole, cyproterone acetate, oestrogens, or progesterones in previous 3 months. **Randomised** 346 participants were randomised (minoxidil group = 176, placebo group = 170) **Withdrawals/losses to follow-up** There were 52/346 (15%) withdrawals/losses to follow-up: 21/176 (11.9%) in the minoxidil group, and 31/170 (18.2%) in the placebo group **Baseline data** Duration hair loss (SD): minoxidil group = 8.0 years (6.31), placebo group = 8.6 years (5.91) Age at onset of hair loss (SD): minoxidil group = 25.1 years (7.19), placebo group = 25.6 years (6.99) Degree of thinning Ludwig scale (% of participants by grade and group) • Grade I: minoxidil group = 52, placebo group = 47. • Grade II: minoxidil group = 48, placebo group = 53.
Interventions	**Intervention**

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Jacobs 1993 *(Continued)*

- Minoxidil 2% topical solution (minoxidil powder, propylene glycol, alcohol, and water). Applied 1 mL twice daily at 12-hour intervals to the scalp for 32 weeks.

Comparator

- Placebo (propylene glycol, alcohol, and water). Applied 1 mL twice daily at 12-hour intervals to the scalp for 32 weeks.

Outcomes	Assessments (9): at baseline and every 4 weeks **Primary outcomes** (as reported) • Hair counts (non-vellus) by standardised photographic techniques and computer-assisted image counting.[1] **Secondary outcomes of the trial** (as reported) • New hair growth (investigator- and participant-assessed) from baseline, rated minimal/moderate/dense.[1] • Safety evaluation (electrocardiogram (ECG)/serum chemical tests/blood count/platelet count/serum ferritin level/urinalysis).[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared, but the three trial authors are employed by Upjohn Laboratories, the manufacturer of minoxidil.
Declaration of interest	The three PIs were from the Dermatology Division of Upjohn Laboratories, Kalamazoo
Notes	Although adverse events are not mentioned as an outcome by the investigators, 2 adverse events were reported regarding withdrawals in the minoxidil group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 759): "randomized to receive either". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: there was insufficient information to permit a clear judgement of the risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 758): "double-blind trial." Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 758): "double-blind trial." Comment: there was uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. There was insufficient information to permit a clear judgement.

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Jacobs 1993 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was a 15% rate of withdrawals and losses to follow-up: 21/176 withdrew in the minoxidil group, and 31/170 in the placebo group. The trial reported the reasons for withdrawal, and the numbers were reasonably balanced across the groups. The data analysis was per-protocol. Comment: although the numbers of dropouts appear balanced between the groups, the percentage of dropouts and subsequent per-protocol analysis poses an unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Jimenez 2014a

Methods	This was a randomised, double-blind, sham-controlled trial **Setting** Multicentre (5), Europe and USA **Date of study** The recruitment period was from 29 October 2008 to 2 March 2009 (26-week duration)
Participants	78 women Mean age (SD) = 49.3 years (9.1) in the laser comb group, 49.8 years (7.3) in the sham group **Inclusion criteria** • Diagnosis of androgenetic alopecia. • Fitzpatrick Skin Types I-IV. • Ludwig I-4, II-1, II-2, or frontal. • Active hair loss within last 12 months. **Exclusion criteria** • Photosensitivity to laser light. • Malignancy in the target area. • Pregnancy. • Lactating females. **Randomised** 78 participants were randomised (laser comb group = 53, sham group = 25) **Withdrawals/losses to follow-up** There were 15/78 (19.2%) withdrawals/losses to follow-up: 11/53 (21%) in the laser comb group, and 4/25 (16%) in the placebo group **Baseline data**

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Jimenez 2014a *(Continued)*

	• Ludwig 1-4: laser comb group = 12, sham group = 3. • Ludwig II-1: laser comb group = 11, sham group = 7. • Ludwig II-2: laser comb group = 15, sham group = 9. • Frontal: laser comb group = 5, sham group = 3.
Interventions	**Intervention** • HairMax LaserComb 2009 9 Beam three times a week for 12 minutes for 26 weeks. **Comparator** • Sham device 3 times a week for 12 minutes for 26 weeks.
Outcomes	Assessments (3): at baseline, week 16, and week 26 **Primary outcomes** (as reported) • Changes in terminal hair count from baseline (The Canfield Epilume System was used for digital imaging and the TrichoScience software (Tricholog, Moscow, Russia).[1] • Categorical change in terminal hair density from baseline. **Secondary outcomes** (as reported) • Subject self-evaluation (questionnaire).[1] • Adverse events.[1] [1]Denotes outcomes prespecified for this review
Funding source	Quote (page 126): "Lexington International, LLC partially funded the study, and provided the treatment and sham devices and equipment (including the digital imaging system)".
Declaration of interest	Quote (page 126): "M.R. Hamblin has received honorarium/consulting fees, and L.A. Schachner has received fees for participation from Lexington International, LLC. M. Hordinsky has received, on behalf of the Department of Dermatology at the University of Minnesota, a grant to conduct part of this study. J.J. Jimenez, T.C. Wikramanayake, W.F. Bergfeld, and J.G.Hickman have no conflicts of interest that are directly relevant to this study. M.R. Hamblin was supported by a NIH grant R01AI050875".
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 118): "Randomization was generated by EugeneR. Heyman (http://www.erhstats.com) using the SASPROC RAND method...randomization was 2:1 with a block size of 3." Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	Quote (page 118); "The lasercomb and sham devices, along with instructions, were provided to the site investigator in sealed, sequentially numbered opaque packets in a blinded manner, and were dispensed sequentially. Both the site investigators and the subjects remain blinded to the type of device they dispensed/received throughout the trial." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done.

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Jimenez 2014a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 118): "An independent evaluator not connected to the clinical trials analyzed the uploaded images and performed computer-assisted hair counts…The evaluator…… was blinded to which trial arm the subject belonged, as well as which images were from baseline and which were from follow-up." After e-mail contact: "the study site evaluators never observed or knew which device the subject was using at any evaluation point, only knew by a randomization code numbers which device each subject was using. The sealed bag containing the device the subject were to use, was only opened at the subject's home and was never brought to the study center during the course of the study. Since the subject used the device assigned and had no comparator, they did not have any way of knowing if the device was active or not, since both the active and sham device emitted light." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken. Comment: we judged this as at a low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	15/78 (19.2%) unspecified withdrawals/losses to follow-up: 11/53 in the laser comb group (21%), and 4/25 in the placebo group (16%). The data analysis was per-protocol. Comment: we judged this as at high risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT00981461). The prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Jimenez 2014b

Methods	This was a randomised, double-blind, sham-controlled trial **Setting** Multicentre (5), Europe and USA **Date of study** The recruitment period was from 1 February to 28 September 2010 (26-week duration)
Participants	63 women Mean age (SD) = 48.7 years (10.2) in the laser comb group, 49.1 years (8.3) in the sham group **Inclusion criteria** • Diagnosis of androgenetic alopecia. • Fitzpatrick Skin Types I-IV.

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Jimenez 2014b *(Continued)*

- Ludwig I-4, II-1, II-2, or frontal.
- Active hair loss within last 12 months.

Exclusion criteria

- Photosensitivity to laser light.
- Malignancy in the target area.
- Pregnancy.
- Lactating females.

Randomised

63 participants were randomised (laser comb group = 42, sham group = 21)

Withdrawals/losses to follow-up

There were 6/63 (9.5%) withdrawals/losses to follow-up: 3/42 (7.1%) in the laser comb group, and 3/21 (14.3%) in the placebo group (14.3%)

Baseline data

- Ludwig 1-4: laser comb group = 21, sham group = 6.
- Ludwig II-1: laser comb group = 11, sham group = 6.
- Ludwig II-2: laser comb group = 6, sham group = 4.
- Frontal: laser comb group = 1, sham group = 2.

Interventions	**Intervention** • HairMax LaserComb 2009 12 Beam 3 times a week for 12 minutes for 26 weeks. **Comparator** • Sham device 3 times a week for 12 minutes for 26 weeks.
Outcomes	Assessments (3): at baseline, week 16, and week 26 **Primary outcomes** (as reported) • Changes in terminal hair count from baseline (The Canfield Epilume System was used for digital imaging and the TrichoScience software (Tricholog, Moscow, Russia).[1] • Categorical change in terminal hair density from baseline. **Secondary outcomes of the trial** (as reported) • Subject self-evaluation (questionnaire).[1] • Adverse events.[1] [1]Denotes outcomes prespecified for this review
Funding source	Quote (page 126): "Lexington International, LLC partially funded the study, and provided the treatment and sham devices and equipment (including the digital imaging system)".
Declaration of interest	Quote (page 126): "M.R. Hamblin has received honorarium/consulting fees, and L.A. Schachner has received fees for participation from Lexington International, LLC. M. Hordinsky has received, on behalf of the Department of Dermatology at the University of Minnesota, a grant to conduct part of this study. J.J. Jimenez, T.C. Wikramanayake, W.F. Bergfeld, and J.G.Hickman have no conflicts of interest that are directly relevant to this study. M.R. Hamblin was supported by a NIH grant R01AI050875".
Notes	—
Risk of bias	

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Jimenez 2014b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 118): "Randomization was generated by Eugene R. Heyman (http://www.erhstats.com) using the SASPROC RAND method...randomization was 2:1 with a block size of 3." Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	Quote (page 118): "The lasercomb and sham devices, along with instructions, were provided to the site investigator in sealed, sequentially numbered opaque packets in a blinded manner, and were dispensed sequentially. Both the site investigators and the subjects remain blinded to the type of device they dispensed/received throughout the trial." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 118): "An independent evaluator not connected to the clinical trials analyzed the uploaded images and performed computer-assisted hair counts…The evaluator…… was blinded to which trial arm the subject belonged, as well as which images were from baseline and which were from follow-up." After e-mail contact: "the study site evaluators never observed or knew which device the subject was using at any evaluation point, only knew by a randomization code numbers which device each subject was using. The sealed bag containing the device the subject were to use, was only opened at the subject's home and was never brought to the study center during the course of the study. Since the subject used the device assigned and had no comparator, they did not have any way of knowing if the device was active or not, since both the active and sham device emitted light." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken. Comment: we judged this as at a low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 6/63 (9.5%) unspecified and unbalanced withdrawals/losses to follow-up: 3/42 in the laser comb group (7.1%), and 3/21 in the placebo group (14.3%). The data analysis was per-protocol. Comment: we judged this as at unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT01016964). The trial appears to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

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Keene 2011

Methods	This was a randomised, blinded, sham-controlled trial **Setting** Unspecified USA **Date of study** December 2008 to December 2009 (6-month duration)
Participants	13 women Mean age (SD) = not reported **Inclusion criteria** • Postmenopausal women with frontal or vertex hair loss. **Exclusion criteria** • Active depression. • Hair loss caused by metabolic or hormonal abnormalities. • Hair loss because of medication or other dermatologic conditions that were not apparently androgenetic alopecia (AGA), including diffuse unpatterned hair loss. **Randomised** 13 participants were randomised (finasteride group = 8, placebo group = 5) **Withdrawals/losses to follow-up** None were reported **Baseline data** None reported
Interventions	**Intervention** • Finasteride 1 mg for 6 months. **Comparator** • Placebo for 6 months.
Outcomes	Assessments (7): at baseline and every month **Outcomes of the trial** (as reported) • Hair counts (two 1 cm^2 areas along the leading edge of hair loss which were tattooed for reproducible reference Microphotographs were then taken using a Nikon D80, Speedlight600 camera, 10.2 megapixels, with a Dermlite lens and Global photographs were taken using a Nikon Coolpix 995, 3.24-megapixel digital camera (Nikon Corporation, Shinjuku, Tokyo, Japan).[1] • Beck Depression Inventory survey. [1]Denotes outcomes prespecified for this review
Funding source	Quote (page 268): "study was funded by DermaGenoma, Inc"
Declaration of interest	Quote (page 268): "Both authors are employed by DermaGenoma, Inc"
Notes	Study participants used buccal swabs to obtain DNA for identification of their AR gene polymorphism. This involved evaluation of the number of CAG nucleotide repeats in the first exon of the AR gene in

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Keene 2011 *(Continued)*

each X chromosome. Subsequently, each participant who was not homozygous in the AR-CAG allele underwent determination of percentage of X inactivation for each allele based on the method of quantitative polymerase chain reaction (PCR) product (inactive allele) following digestion of unmethylated (activated) DNA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 297): "Patients who met the inclusion criteria were randomized to either placebo or 1-mg finasteride". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups. After e-mail communication: "For each subject, the site supervisor picked from a bowl a random letter A or B". Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: there was insufficient information to permit a clear judgement. After e-mail communication: "The study was conducted for a sponsor. The sponsor recruited an independent site monitor (Registered Nurse) who had the sole access to the information during the course of the study". Comment: this is a form of central allocation, which was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 297): "6-month blinded". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement. After e-mail communication: "Tablets were compounded at a pharmacy to look exactly the same".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 297): "6-month blinded". Comment: there was uncertainty with effective blinding of outcomes assessors (participants/healthcare providers) during the study. There was insufficient information to permit a clear judgement. After e-mail communication: "Tablets were compounded at a pharmacy to look exactly the same". Comment: it was unlikely that the blinding was broken.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported and data are available for all individual participants. Comment: we judged this as at low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT01052870). The trial appeared to report the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.

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Keene 2011 *(Continued)*

Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Kim 2009

Methods	This was a randomised, placebo-controlled trial **Setting** Department of Dermatology, College of Medicine, Korea University, Seoul, Korea **Date of study** Unspecified (24-week duration)
Participants	40 men and women (28 men, 12 women) Mean age = 43.1 years **Inclusion criteria** • Ability to understand the purpose and design of the study and ability to give informed consent. • Korean male or female patients who have been diagnosed with androgenic alopecia (AGA) for longer than 3 months. **Exclusion criteria** • Receiving therapy for other disease (not clear if it only applies to systemic therapy or if it includes topical treatment as well). • Pregnant or lactating female. • Known allergic reaction to ginseng. • Participated in another trial within 3 months prior to being considered for this study. • Inability to understand purpose and methodology of the study. • Illiteracy. • Received other treatment for alopecia within 2 weeks prior to randomisation. • Clinical judgment that enrolment may not be appropriate. **Randomised** 40 men and women were randomised (ginseng group = 20, placebo group = 20) **Withdrawals/losses to follow-up** 8/40 (20%) withdrawals/losses to follow-up, 3/20 (15%) in ginseng group and 5/20 (25%) in placebo group, reasons unreported **Baseline data of the females** 7 had Ludwig Grade I female pattern alopecia, and 5 had Grade II. None had Grade III
Interventions	**Intervention** • Korean red ginseng powder capsule 1000 mg 3 times a day for 24 weeks. **Comparator** • Placebo 3 times a day for 24 weeks.
Outcomes	Assessments (3): at baseline, 12 weeks, and 24 weeks **Outcomes of the trial** (as reported)

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Kim 2009 *(Continued)*

- Hair density measured by Folliscope.[1]
- Hair thickness measured by Folliscope.[1]
- Patient-reported outcome for a) size of vertex bald spot, b) hair loss on the vertex, c) receding temporal hairline, d) hair shedding, e) hair quality and f) overall satisfaction.[1]
- Physician's assessment of improvement or worsening of alopecia, based on photographs of the study participants and graded on a 7-point scale.[1]

[1]Denotes outcomes prespecified for this review

Funding source	The Korean Ginseng Corporation funded the study and provided the medications used in the intervention group
Declaration of interest	None declared
Notes	The trial did not stratify data by gender. We sent e-mails were sent to the PI, but received no reply. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 223): "randomly". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of the risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 223): "double-blind trial." Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 758): "double-blind trial." Comment: there was uncertainty regarding the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. There was insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	8/40 (20%) withdrawals/losses to follow-up, 3/20 (15%) in ginseng group and 5/20 (25%) in placebo group (unbalanced), but the reasons were unreported. Comment: we judged this as at a high risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

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Kim 2013

Methods	This was a randomised, double-blind, sham device-controlled trial **Setting** Multicentre (2), Korea **Date of study** Unspecified (24-week duration)
Participants	40 men and women (26 men, 14 women) Mean age (SD) = 43.9 years (12.2) in the low level light therapy group, 44.5 years (11.4) in the sham device group **Inclusion criteria** • Diagnosis of androgenetic alopecia. • Norwood-Hamilton classification of III to VII for men or a Ludwig classification of I to III for women. **Exclusion criteria** • Topical or systemic medications affecting hair growth, such as finasteride, cyclosporine, or minoxidil, within the past 6 months. • Hair disorders other than AGA or systemic diseases that might affect the results. **Randomised** 40 participants were randomised (low level light therapy group = 20, sham group = 20) **Withdrawals/losses to follow-up** There were 11/40 (27.5%) withdrawals/losses to follow-up: 5/20 (25%) in the low-level light therapy group, and 6/20 (30%) in the sham group • Withdrawal of consent: low-level light therapy group (0), sham group (2). • Non adherence: low-level light therapy group (5), sham group (4). **Baseline data** Duration hair loss (SD): low level light therapy group = 114.3 months (86.2), sham group = 100.55 months (84.8) • Norwood-Hamilton III: low level light therapy group = 6, sham group = 4. • Norwood-Hamilton IV: low level light therapy group = 2, sham group = 4.Norwood-Hamilton V: low level light therapy group = 1, sham group = 3. • Norwood-Hamilton VI: low level light therapy group = 5, sham group = 1. • Ludwig I: low level light therapy group = 5, sham group = 8. • Ludwig II: low level light therapy group = 1, sham group = 0.
Interventions	**Intervention** • Helmet-type, home-use low-level light therapy device emitting wavelengths of 630, 650, and 660 nm for 18 minutes daily for 24 weeks. **Comparator** • Sham device daily for 18 minutes for 24 weeks.
Outcomes	Assessments (3): at baseline, week 12, and week 24 **Primary outcomes** (as reported)

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Kim 2013 *(Continued)*

- Changes in hair density from baseline (phototrichogram, Folliscope, LeadM, Seoul, Republic of Korea).[1]

Secondary outcomes (as reported)

- Changes in the hair shaft.[1]
- Global assessment of hair regrowth according to the participant and the investigator.[1]
- Subjective satisfaction.[1]
- Adverse events.[1]

[1]Denotes outcomes prespecified for this review

Funding source	Quote (page 1177): "This study was supported by Won Technology, Daejeon, Republic of Korea."
Declaration of interest	Quote (page 1177): "The authors have indicated no significant interest with commercial supporters"
Notes	The trial did not stratify data by gender. We sent e-mails to the PI, but received no reply. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1177): "randomized" and "We randomly assigned". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups. After e-mail communication: "coin throw method for the allocation" Comment: this was probably done.
Allocation concealment (selection bias)	Unclear risk	The trial did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1177): "double-blind" and "The sham device was identical in appearance and its regulator operated, although it emitted no light", and (page 1179) " they were totally blinded". Comment: we judged this as at an unclear risk of bias in view of the fact that the helmet did not emit light.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1177): "double-blind", (page 1179 " the investigators in charge of efficacy assessment were totally blinded". Comment: both investigators and participants were outcome assessors. We judged this as at an unclear risk of bias as the helmet did not emit light and might have influenced the outcome assessment by the participants.
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 11/40 (27.5%) withdrawals/losses to follow-up: 5/20 in the low-level light therapy group (25%), and 6/20 in the sham group (30%). The data analysis was per-protocol. Comment: the large number of dropouts (26%), incomplete outcome data, and inappropriate analysis were potential sources of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the trial appeared to report the prespecified outcomes and those mentioned in the methods section.

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Kim 2013 *(Continued)*

		Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Lanzafame 2014

Methods	This was a randomised, double-blind, sham-controlled trial **Setting** Multicentre (2), USA **Date of study** Unspecified (16-week duration)
Participants	47 women Mean age (SD) = 46.3 years (9.2) in the visible red light laser and LED sources group, 51.0 years (7.05) in the sham device group **Inclusion criteria** • Women with Ludwig–Savin Baldness Scale I-2, I-3, I-4, II-1, II-2 baldness patterns. • 18 to 60 years. **Exclusion criteria** • None reported. **Randomised** 47 participants were randomised (unclear how many to each arm) **Withdrawals/losses to follow-up** There were 5/47 (0.6%%) withdrawals/losses to follow-up: prior to treatment, reasons unknown **Baseline data** Duration hair loss (SD): low level light therapy group = 114.3 months (86.2), sham group = 100.55 months (84.8) • Ludwig I: visible red light laser and LED sources group = 11, sham group = 7. • Ludwig II: visible red light laser and LED sources group = 13, sham group = 11.
Interventions	**Intervention** • TOPHAT655" unit containing 21, 5 mW diode lasers (655 ± 5 nm) and 30 LEDs (655 ± 20 nm), in a bicycle-helmet like apparatus for 25 minutes every other day for 16 weeks. **Comparator** • Identical, containing incandescent red lights for 25 minutes every other day for 16 weeks.
Outcomes	Assessments (2): at baseline and week 16 **Primary outcomes** (as reported) • Percent increase in hair counts from baseline at the end of 16 weeks (photography Canon Rebel T3i 18 Megapixel camera system (Canon USA, Melville, NY)).[1]

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Lanzafame 2014 *(Continued)*

	Secondary outcomes (as reported) • Adverse events.[1] [1]Denotes outcomes prespecified for this review
Funding source	Quote (page 601): "This study was funded by Apira Science, Inc"
Declaration of interest	RP Chiacchierini, E Kazmirek and JA Sklar have no disclosures. RR Blanche received consulting fees, had study-related travel expenses paid and has ownership interest in Apira Science. RJ Lanzafame received consulting fees, fees for manuscript preparation, and has ownership interest in Apira Science.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 602): "Subjects were randomly assigned". Comment:the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups. After e-mail communication: "Central allocation, blocks of six." Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	Quote (page 602): "A serial number was assigned to each helmet, which was recorded in a device log that contained the reference code for placebo and actual test unit. This log was not revealed to any investigator, subject, office staff, hair counter or sponsor employee." Comment: the method used to generate the sequence would appear to indicate that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 602): "The sham group received a unit that was identical in appearance and function to the laser group devices, with the exception that the light sources were incandescent wheat lights that were painted red to mimic the appearance and configuration of the functioning device". Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 601): "These baseline images were coded and then forwarded to the photographic consultant. The photographic consultant verified that the images were of acceptable quality and processed the images for transmission to the investigator responsible for conducting the hair counts. The transmitted images were masked using a black mask to produce a 1.9 cm diameter circle centered on the tattoo, which provided a consistent 2.85 cm2 area for hair counts. Neither the photographic consultant nor the investigator performing the hair counts was aware of the identity of the subject or the subjects' study group assignment". Comment: the measures used to blind the outcome assessor from knowledge of which intervention a participant received were adequately reported.
Incomplete outcome data (attrition bias)	Low risk	There were 5/47 (10.6%) withdrawals/losses to follow-up, but it was unclear from which group. The data analysis was per-protocol.

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Lanzafame 2014 *(Continued)*

All outcomes		Comment: although unclear from which group the low number of drop-outs occurred, we judged it as at low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was available (NCT01437163), and the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Le Floc'h 2015

Methods	This was a RCT **Setting** One centre in Italy **Date of study** January to September 2012 (6-month duration)
Participants	120 women Mean age (SD) = 48.6 years (11.2) in supplement group, 46.0 years (14.9) in the control group **Inclusion criteria** • Women with hair loss according to Ludwig scale of I. • 18 to 65 years with a body mass index between 18 and 27 kg/m^2. **Exclusion criteria** • Telogen effluvium. • Any condition inducing hair disorders. • Vitamin deficiencies. • Hyper or hypo-thyroidism. • Metabolism of lipid absorption disorders. • Recent modification of diet. • Used oral or topical drug that might affect hair or scalp. • Pregnant or lactating women. • Or first 6 months post-partum. **Randomised** 120 participants were randomised (nutritional supplement = 80, control group = 40) **Withdrawals/losses to follow-up** There were 2/120 (1.6%) withdrawals/losses to follow-up: one in each group for personal reasons **Baseline data** • Telogen hair % (mean (SD): supplement group 20.0 (4.1), control group 21.1 (3.4). • Trichometer index: supplement group 75.71 (16.56), control group 78.01 (16.95).
Interventions	**Intervention**

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Le Floc'h 2015 *(Continued)*

	• Nutritional supplement (fish oil 460 mg, blackcurrant seed oil 460 mg, vitamin E 5 mg, vitamin C 30 mg, lycopene 1 mg) for 6 months. **Comparator** • No supplement for 6 months. Each participant was provided with a neutral shampoo to be used every other day
Outcomes	Assessments (2): at baseline and month 6 **Primary outcomes** (as reported) • Change in hair density (global photographs); 7-point Likert scale from -3 greatly decreased to + 3 greatly increased.[1] • Self assessment (same photographs and Likert scale).[1] **Secondary outcomes** (as reported) • Trichogram technique (hair loss hair diameter distribution). • Trichometer.[1] [1]Denotes outcomes prespecified for this review
Funding source	None reported, but the first author is employed by Innéov (L'Oréal) the manufacturer of the supplement
Declaration of interest	None reported, but the first author is employed by Innéov (Loreal) the manufacturer of the supplement
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 77): "were randomly assigned". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 77): "expert-blinded". Comment: the report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Both investigators and participants were the outcomes assessors. Participants did not receive a substitute for the nutritional supplement, which is likely to influence their outcome assessment. Comment: we judged this as at high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 2/120 (1.6%%) withdrawals/losses to follow-up: one in each group for personal reasons. The data analysis was per-protocol.

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Le Floc'h 2015 *(Continued)*

		Comment: we judged this as at low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was available (NCT01437163), and the trial appeared to report the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Lucky 2004

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Multicentre (9), USA **Date of study** May 1992 to 1993 (48-week duration)
Participants	381 women **Inclusion criteria** • Age 18 to 49 years. • Naturally dark hair. • Gradual/conspicuous hair loss in the frontoparietal region with/without front hairline recession. • Hair density rating (4 to 7) using the Savin female density scale (Trancik 1996) (please see the Notes section). • Good general health; no evidence of cardiac, systemic, psychiatric, or scalp disease. **Exclusion criteria** • Pregnant, at risk of pregnancy, < 12 months postpartum, or breast feeding. • Hypersensitivity to minoxidil. • Concomitant use of hair restorers, systemic drugs (steroids, cytotoxic agents, vasodilators, antihypertensives, anticonvulsant drugs, ß-blockers, diuretics, spironolactone, cimetidine, diazoxide, cyclosporine, ketoconazole, or replacement hormonal therapy). **Randomised** 381 participants were randomised (minoxidil 5% group = 153, minoxidil 2% = 154, placebo group = 74) **Withdrawals/losses to follow-up** There were 121/381 (32%) withdrawals/losses to follow-up: 52/153 (33.9%) in the minoxidil 5% group, 46/154 (29.8%) in the minoxidil 2% group, and 23/74 (31.1%) in the placebo group • Voluntary withdrawal: minoxidil 5% group = 14/153, minoxidil 2% group = 13/154, placebo group = 8/74. • Adverse events: minoxidil 5% group = 21/153, minoxidil 2% group = 16/154, placebo group = 3/74. • Lost to follow-up: minoxidil 5% group = 10/153, minoxidil 2% group = 9/154, placebo group = 7/74. **Baseline data** Degree of thinning Ludwig scale (% of participants by grade and group) • Grade I: minoxidil 5% group = (35.9), minoxidil 2% group = (36.4), placebo group = (36.5).

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Lucky 2004 *(Continued)*

- Grade II: minoxidil 5% group = (60.1), minoxidil 2% group = (62.3), placebo group = (59.5).
- Grade III: minoxidil 5% group = (3.9), minoxidil 2% group = (1.3), placebo group = (4.1).

Hair density Savin female density scale (% of participants by score and group)

- Score 4: minoxidil 5% group = (38.9), minoxidil 2% group = (45.8), placebo group = (39.2).
- Score 5: minoxidil 5% group = (38.9), minoxidil 2% group = (39.9), placebo group = (47.3).
- Score 6: minoxidil 5% group = (18.8), minoxidil 2% group =(13.7), placebo group = (12).

Interventions	**Intervention** • Minoxidil 5% topical solution. 1 mL of assigned solution twice daily at approximately 12-hour intervals (total daily dose of 2 mL) for 48 weeks. **Comparator** • Minoxidil 2% topical solution. 1 mL of assigned solution twice daily at approximately 12-hour intervals (total daily dose of 2 mL) for 48 weeks. **Placebo** • Placebo (vehicle only). 1 mL of assigned solution twice daily at approximately 12-hour intervals (total daily dose of 2 mL) for 48 weeks.
Outcomes	Assessments (2): at baseline and week 48 **Primary outcomes** (as reported) • Hair count (non-vellus) (change from baseline) at 48 weeks.[1] • Hair growth/scalp coverage (participant-assessed) at 48 weeks.[1] • Hair growth/scalp coverage (investigator-assessed) at 48 weeks.[1] **Secondary outcomes** (as reported) • Participant-assessed by 12-item questionnaire: quality of life (QoL) (6), global benefit (6), i.e. hair growth and hair styling measures.[1] • Safety evaluation.[1] [1]Denotes outcomes prespecified for this review
Funding source	Quote (page 541): "Supported by Pfizer Inc (formerly Pharmacia Corporation, formerly The Upjohn Company)."
Declaration of interest	Quote (page 541): "Disclosure: All authors were the clinical investigators involved in the conduct of the trial."
Notes	The Savin female density scale appears to be validated. It was developed by Dr Trancik of Upjohn Laboratories. There were concomitant prohibited medications in 13/153 in the 5% topical minoxidil group; 5/154 in the 2% topical minoxidil group; and 3/74 participants in the placebo group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 542): "Randomization occurred in a 2:2:1 design...according to a predetermined, computerized randomization plan." Comment: this was probably done.

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Lucky 2004 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote (page 542): "Each trial site was provided with a unique list of randomization code numbers". Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 542): "double blind". "The investigational medications were provided to each trial site in identically appearing, prepackaged, and pre-labelled bottles" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were participant- and investigator-assessed. Blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken. Comment: we judged this as at a low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	Although a flow chart tracked participants through the study, losses to follow-up/withdrawals were substantial (> 30%) in all treatment groups. Quote (page 544): "261 patients were included in the efficacy evaluable population." The data analysis was per-protocol (261/381). Comment: we judged this as at a high risk of bias.
Selective reporting (reporting bias)	Low risk	Although the study protocol was unavailable, the outcomes listed in the 'Methods' section were comparable to the reported results. Comment: we judged this as at a low risk of bias.
Other bias	High risk	There was an influence of co-interventions as effect modifiers. Quote (page 545): "21 patients used protocol-prohibited concomitant medications (systemic corticosteroids)." Comment: potential effects of co-interventions represented a possible risk of bias.

Mazzarella 1997

Methods	This was a randomised, single-blind, placebo-controlled study **Setting** Department of Dermatology, University of Bari, Bari, Italy **Date of study** Unspecified (16-month duration)
Participants	52 men and women (28 male and 24 women) Mean age (range) = 28 years (18 to 38)

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Mazzarella 1997 *(Continued)*

	Inclusion criteria • AGA. **Exclusion criteria** • Treatment for alopecia or other cutaneous and non-cutaneous diseases one month prior to commencing the protocol. • Women taking oral contraceptives in previous year. **Randomised** 52 participants were randomised (finasteride group = 26, vehicle group = 26) **Withdrawals/losses to follow-up** There were 16/52 (30.7%) withdrawals/losses to follow-up: 0/26 (0%) in the finasteride group, 16/26 (61.5%) in the vehicle group (61.5%), reasons and gender not reported **Baseline data** Hamilton stage II: 13 male; stage III 15 male Ludwig stage I: 11 female; stage II 13 female
Interventions	**Intervention** • Finasteride 0.005% solution 1 ml twice daily for 16 months. **Comparator** • Vehicle (50% ethyl alcohol, 25% propylene glycol, and 25% distilled water) 1 mL twice daily for 16 months.
Outcomes	Assessments (5): at baseline, week 4, 8, 12, and 16 **Outcomes of the trial** (as reported) • Photographs at monthly intervals.[1] • End of study assessment of hair regrowth according to a 6-point scale and hair loss by performing a 'wash test' at 2-month intervals. Collect all hairs lost during shampooing. Bimonthly hair counts recorded.[1] • At the end of treatment the patients' opinions and self-perceived changes in the status of the scalp hair were recorded and categorized 4-point scale of effectiveness (3 = high effectiveness, 0 = no effect).[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	There were no separate data for women. There were 16 dropouts (61.5%) in the placebo group only. We e-mailed the PI, but received no response. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 189): "were randomly allocated".

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Mazzarella 1997 *(Continued)*

		Comment: the trial did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: There was insufficient information to permit a clear judgement of the risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 189): "single-blind trial" Comment: the investigators were not blinded. The report did not provide sufficient detail about the measures used to blind study participants from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 189): "single-blind trial". Both investigators and participants were outcome assessors and the investigators were not blinded. Comment: the outcome measurement by the investigators is likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 16/52 (30.7%) withdrawals/losses to follow-up: 0/26 in the finasteride group (0%), 16/26 in the vehicle group (61.5%), reasons were not reported. There were unbalanced withdrawals. The data analysis was per-protocol. Comment: we judged this as at a high risk of bias
Selective reporting (reporting bias)	Low risk	Although the study protocol was unavailable, the outcomes listed in the 'Methods' section were comparable to the reported results. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Minozzi 1997

Methods	This was a randomised, active-controlled trial **Setting** Center for Climacteric and Menopause of the Institute of Obstetrics and Gynecology, Policlinico Umberto l, Rome, Italy **Date of study** Unspecified (12-month duration)
Participants	63 women Age = 52 to 63 years **Inclusion criteria** • Postmenopausal women with excessive hair loss as a predominant symptom. **Exclusion criteria**

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Minozzi 1997 *(Continued)*

- Hormonal therapy.
- Endocrine diseases.
- Drug intake.
- Premenopausal alopecia.
- Disease of the scalp.

Randomised

63 participants were randomised (group I = 21, group II = 21, group III = 21)

Withdrawals/losses to follow-up

None were reported

Baseline data

Minimal data, blood tests: routine blood tests, serum follicle-stimulating hormone (FSH), LH, estradiol, testosterone, free testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), delta-4-androstenedione, dihydrotestosterone, SHBG. Hormonal status consistent with menopause

Interventions	**Intervention** • Group I = ethinyl estradiol (0.02 mg/day) on days 1 to 25 each month, a daily dose of 10 mg medroxyprogesterone acetate (MPA) added for the last 10 days of oestrogen administration. Repeated for 12 cycles. **Comparator 1** • Group II = transdermal estradiol (0.05 mg/day) associated with medroxyprogesterone acetate (MPA) for the last 10 days of oestrogen administration. Repeated for 12 cycles. **Comparator 2** • Group III = ethinyl estradiol (0.02 mg/day) on days 1 to 25 each month. A daily dose of 12.5 mg cyproterone acetate was added for the first the 10 days of oestrogen administration. Repeated for 12 cycles.
Outcomes	Assessments (2): at baseline and month 12 **Outcomes** (as reported) • Hormonal assays. • Trichogram (with microscope).[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	Diagnosis of FPHL was not clearly defined/stated We sent several e-mails to the PI but received no response. None of our outcomes were assessed. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 341): "The patients have been randomized in three equal groups to which a different treatment had been administered."

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Minozzi 1997 *(Continued)*

		Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open. The nature of the treatment interventions precludes any possibility of blinding of participants and personnel. Comment: the outcome is likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was open. The nature of the treatment interventions precludes any possibility of blinding of participants and personnel. Comment: the outcome measurement is likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts were reported. It was unclear if data analysis was per-protocol or intention-to-treat. Comment: there was insufficient information to permit a clear judgement of risk of bias.
Selective reporting (reporting bias)	Unclear risk	The investigators did not report all of their prespecified outcomes of the hormonal screening (only SHBG), but it was uncertain to what extent the lack of data for other than SHBG had any impact on their reported results. Therefore, we judged this domain as at an unclear risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Morganti 1998

Methods	This was a randomised, double-blind, placebo-controlled study **Setting** Department of Cosmetic Dermatology, Accademia di Storia dell'Arte Sanitaria, Rome, Italy **Date of study** Unspecified (50-week duration)
Participants	60 men and women (at least 24 men and 24 women; for 12, the gender was not reported). Age = 21 to 38 years **Inclusion criteria** • Androgenetic alopecia, type III or IV Hamilton scale. **Exclusion criteria** • Nothing was reported. **Randomised**

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Morganti 1998 *(Continued)*

	60 participants were randomised (12 to each group) **Withdrawals/losses to follow-up** None were reported **Baseline data** Nothing reported
Interventions	**Intervention** • Group I = active lotion (gelatine-cystine and *Serenoa repens*) (N = 12). **Comparator 1** • Group II = placebo lotion (N = 12). **Comparator 2** • Group III = active diet supplement (gelatine-cystine) (N = 12). **Comparator 3** • Group IV = placebo supplement (N =12). **Comparator 4** • Group V = active lotion and active supplement (N = 12) The lotion was applied twice a day, and the pills were administered 4 times per day
Outcomes	Assessments (6): at baseline and every 10 weeks **Outcomes of the trial** (as reported) • Efficacy of oral gelatin cystine and lotion based on gelatine cystine and *Serenoa repens* on hair growth promotion and retarding of hair loss.[1] • Quantify the radical oxygen species (ROS) before, during, and after the diet supplementation. [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	There were no separate data for women. Dropouts were not reported. We were unable to contact the investigators. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 59): "assigned in a randomized double-blind manner". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.

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Morganti 1998 *(Continued)*

		Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 59): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 59): "double-blind". Comment: there was uncertainty with effective blinding of outcomes assessors (healthcare providers) during the study. There was insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts, withdrawals, or missing outcome data were reported. The reporting was overall incomplete and inconsistent. Comment: there was insufficient information to permit a clear judgement of the risk of bias.
Selective reporting (reporting bias)	Low risk	Although the study protocol was unavailable, the outcomes listed in the 'Methods' section were comparable to the reported results. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

NCT01145625

Methods	This is a randomised, single-blind, active-controlled trial **Setting** Multicentre (UK, USA, and Canada) **Date of study** June 2010 to February 2012 (52-week duration)
Participants	322 women **Inclusion criteria** • Females, age 18 or older in general good health. • Exhibits FPHL. • Signs and dates an informed consent document. • Agrees to use an adequate method of birth control; if of childbearing potential. • Shows a negative urine pregnancy test at screening visit. • Willing to maintain the same hair style, hair colour, and hair regimen throughout the study. • Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures. **Exclusion criteria** • Hypersensitivity to the study product, or any ingredients of the study product. • Known allergy to hair dye, or hair dye components. • Clinically relevant history of hypotension. • Untreated or uncontrolled hypertension.

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NCT01145625 *(Continued)*

- Pregnant, planning a pregnancy or nursing a child.
- History of hair transplants.
- Currently use hair weaves or non-breathable wigs.
- Dermatological disorders of the scalp that require chronic use of medication for control.
- Other types or history of hair loss.
- Enrolled in any other investigational medication (drug) study currently, or within the last 6 months.

Randomised

322 participants were randomised (minoxidil 2% group = 161, minoxidil 5% group = 161)

Withdrawals/losses to follow-up

There were 55/322 (17.1%) withdrawals/losses to follow-up: 24/161 (14.9%) minoxidil 2% group, 31/161 (19.3%) in the minoxidil 5% group

- Lost to follow-up: minoxidil 2% group = 8 (5.0%), minoxidil 5% group = 9 (5.6%).
- Adverse event: minoxidil 2% group = 6 (3.7%), minoxidil 5% group = 4 (2.5%).
- Protocol violation: minoxidil 2% group = 3 (1.9%), minoxidil 5% group = 1 (< 1%).
- Withdrawal by participant: minoxidil 2% group = 7 (4.3%), minoxidil 5% group = 16 (9.9%).
- Pregnancy: minoxidil 2% group = 0 (0%), minoxidil 5% group = 1 (< 1%).

Baseline data

Target area hair count hairs/cm^2 (SD): minoxidil 2% group 167.3 (55.0), minoxidil 5% group 169.7 (58.6)

Interventions	**Intervention** • 2% minoxidil solution 1 mL twice daily for 52 weeks. **Comparator** • 5% minoxidil foam 1 g once daily for 52 weeks.
Outcomes	Assessments (4): at baseline, week 12, 24, and 52. **Primary outcomes** (as reported) • Change in target area hair count at week 24 (i.e. change in the number of hairs in the area being examined between baseline and week 24).[1] **Secondary outcomes** (as reported) • Change in target area hair count at week 12 (i.e. change in the number of hairs in the area being examined between baseline and week 12).[1] • Change in target area hair count at week 52 (i.e. change in the number of hairs in the area being examined between baseline and week 52).[1] • Adverse events.[1] [1]Denotes outcomes prespecified for this review
Funding source	**Sponsor:** Johnson & Johnson Healthcare Products Division of McNEIL-PPC, Inc
Declaration of interest	This was unclear from clinicaltrials.gov, but some investigators appear to be employees of Johnson & Johnson Consumer Companies Inc
Notes	We accessed the website on 17 July 2015
Risk of bias	

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NCT01145625 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (clinicaltrials.gov): "randomized". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (clinicaltrials.gov): "single-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (clinicaltrials.gov): "single-blind". Comment: there was uncertainty with effective blinding of outcomes assessors (healthcare providers) during the study. There was insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 55/322 (17.1%) withdrawals/losses to follow-up: 24/161 minoxidil 2% group (14.9%), 31/161 in the minoxidil 5% group (19.3%). Data analysis was intention-to-treat. Comment: we judged this as at an unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was available (NCT01145625), and the trial reported all outcomes listed. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

NCT01189279

Methods	This is a randomised active-controlled trial **Setting** Unspecified, Tempe, Arizona, USA **Date of study** October 2010 to January 2011 (17-day duration)
Participants	42 men and women (21 men/21 women) Age = 18 to 64 years **Inclusion criteria** • Males with moderate male-pattern baldness (AGA). • Females with moderate FPHL.

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NCT01189279 *(Continued)*

- Non-smoker or smoker with at least 30 days abstinence from smoking/using nicotine-containing products.

Exclusion criteria

- Any dermatological condition of the scalp other than AGA (males) or FPHL (females).
- Use of bimatoprost or other prostaglandin analogues within 3 months.
- Prior use of scalp hair growth treatment (e.g. finasteride, minoxidil) within 6 months.
- Any prior hair growth procedures (e.g. hair transplant or laser).
- Blood donation or equivalent blood loss within 90 days.
- History of alcohol or drug addiction.

Randomised

42 participants were randomised (bimatoprost formulation A group = 14, bimatoprost formulation B group = 14, bimatoprost formulation C group = 14)

Withdrawals/losses to follow-up

There were 2/42 (4.8%) withdrawals/losses to follow-up: 1/14 (7.1%) in the bimatoprost formulation A group, 1/14 (7.1%) in the bimatoprost formulation C group

Baseline data

Nothing reported

Interventions	**Intervention** • Bimatoprost (formulation A) 1 mL/day for 14 days followed by multiple doses a day. **Comparator** • Bimatoprost (formulation B) 1 mL/day for 14 days followed by multiple doses a day. **Comparator 2** • Bimatoprost (formulation C) 1 mL/day for 14 days followed by multiple doses a day (2nd phase of the study).
Outcomes	Assessments (2): at day 1 and 17 **Primary outcomes** (as reported) • Pharmacokinetics following single dose of bimatoprost. • Pharmacokinetics following multiple doses of bimatoprost. **Secondary outcomes** (as reported) • 12-lead electrocardiogram (ECG). • Local scalp tolerability assessment. [1]Denotes outcomes prespecified for this review
Funding source	Sponsor is Allergan
Declaration of interest	No information, probably Allergan
Notes	None of our outcomes were addressed, and there were no separate data for men and women. See Table 4. We e-mailed Allergan several times, without any response
Risk of bias	

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NCT01189279 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (clinicaltrials.gov): "randomized". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (clinicaltrials.gov): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (clinicaltrials.gov): "double-blind". Comment: there was uncertainty with effective blinding of outcomes assessors (healthcare providers) during the study. There was insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 2/42 (4.8%) withdrawals/losses to follow-up: 1/14 in the bimatoprost formulation A group (7.1%), 1/14 in the bimatoprost formulation C group (7.1%), Data analysis was per-protocol. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was available (NCT01189279), and the outcomes listed were all reported. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

NCT01226459

Methods	This is a randomised double-blind placebo-controlled trial **Setting** Multicentre (17) in USA, UK, France and Germany **Date of study** September 2010 to August 2011 (24-week duration)
Participants	404 women **Inclusion criteria** • Females, age 18 or older in general good health. • Exhibits FPHL. • Signs and dates an informed consent document. • Agrees to use an adequate method of birth control; if of childbearing potential.

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NCT01226459 *(Continued)*

- Shows a negative urine pregnancy test at screening visit.
- Is willing to maintain the same hair style, hair colour, and hair regimen throughout the study.
- Is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.

Exclusion criteria

- Hypersensitivity to the (study product), or any ingredients of the (study product).
- Known allergy to hair dye, or hair dye components.
- Clinically relevant history of hypotension.
- Untreated or uncontrolled hypertension.
- Pregnant, planning a pregnancy, or nursing a child.
- History of hair transplants.
- Currently use hair weaves or non-breathable wigs.
- Dermatologic disorders of the scalp that require chronic use of medication for control.
- Other types or history of hair loss.
- Enrolled in any other investigational medication (drug) study currently, or within the last 6 months.

Randomised

404 participants were randomised (minoxidil 5% foam group = 203, vehicle foam group = 201)

Withdrawals/losses to follow-up

There were 53/404 (13.1%) withdrawals/losses to follow-up: 32/203 in the minoxidil 5% foam group (15.8%), 21/201 in the vehicle foam group (10.4%)

- Adverse events; (8) in minoxidil 5% foam group (3.9%), (2) in vehicle foam group (< 1%).
- Protocol violation; (3) in minoxidil 5% foam group (1.5%), (4) in vehicle foam group (2.0%).
- Withdrawal by participant; (13) in minoxidil 5% foam group (6.4%), (10) in vehicle foam group (5.0%).
- Lost to follow-up; (8) in minoxidil 5% foam group (3.9%), (4) in vehicle foam group (2.0%).
- Pregnancy; (0) in minoxidil 5% foam group (0%), (1) in vehicle foam group (< 1%).

Baseline data

Target area hair count hairs/cm^2 (SD): minoxidil 5% foam group 158.6 (61.6), vehicle foam group 152.7 (59.7)

Interventions	**Intervention** • Minoxidil 5% topical foam once daily for 24 weeks. **Comparator** • Vehicle topical foam once daily for 24 weeks.
Outcomes	Assessments (3): at baseline, week 12, and week 24 **Primary outcomes** (as reported) • Change in target area hair count from baseline to week 24.[1] • Subject Assessment of Scalp Coverage (7-point Likert scale from -3 to +3).[1] **Secondary outcomes** (as reported) • Change in target area hair count from baseline to week 12. • Adverse events.[1]
Funding source	Johnson & Johnson Healthcare Products Division of McNEIL-PPC, Inc

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NCT01226459 *(Continued)*

Declaration of interest	This was unclear from clinicaltrials.gov, but collaborators are Johnson & Johnson Consumer and Personal Products Worldwide
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (clinicaltrials.gov): "randomly assigned in a 1:1 ratio to use either 5% MTF OD or foam vehicle OD". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (clinicaltrials.gov): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (clinicaltrials.gov): "double-blind". Comment: there was uncertainty with effective blinding of outcomes assessors (healthcare providers) during the study. There was insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 53/404 (13.1%) withdrawals/losses to follow-up: 32/203 in the minoxidil 5% foam group (15.5%), 21/201 in the vehicle foam group (10.4%). Data analysis was per-protocol. Comment: we judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The study protocol was available (NCT01226459 as well as MINALO3005, EudraCT 2010-019881-96), and the trial reported all outcomes listed. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

NCT01325350

Methods	This was a randomised, double-blind, placebo and active-controlled study **Setting** Multicentre (2) USA and Germany **Date of study** June 2011 to July 2012 (6-month duration)

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NCT01325350 *(Continued)*

Participants	306 women Age = 18 to 59 years **Inclusion criteria** • Mild to moderate FPHL with ongoing hair loss for at least 1 year. • Willingness to have micro-dot-tattoo applied to scalp. • Willingness to maintain same hair style, length and hair colour during study. **Exclusion criteria** • Drug or alcohol abuse within 12 months. • Human immunodeficiency virus (HIV)-positive. • Received hair transplants or had scalp reductions. • Use of hair weaves, hair extensions or wigs within 3 months. • Oral or topical minoxidil treatment within 6 months. • Application of topical steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) to scalp within 4 weeks. **Randomised** 306 participants were randomised (bimatoprost A = 61, bimatoprost B = 61, bimatoprost C = 61, bimatoprost vehicle = 61, minoxidil 2% = 62) **Withdrawals/losses to follow-up** There were 49/306 (16.0%) withdrawals/losses to follow-up: 6/61 (9.8%) bimatoprost A group, 5/61 (8.2%) bimatoprost B group, 17/61 (27.9%) bimatoprost C group, 9/61 (14.8%) bimatoprost vehicle group, 12/62 (19.4%) minoxidil 2% group. • Adverse events: bimatoprost A (3), bimatoprost B (3), bimatoprost C (3), bimatoprost vehicle (1), minoxidil 2% (2). • Pregnancy: bimatoprost A (0), bimatoprost B (0), bimatoprost C (1), bimatoprost vehicle (0), minoxidil 2% (1). • Lost to follow-up: bimatoprost A (1), bimatoprost B (0), bimatoprost C (5), bimatoprost vehicle (1), minoxidil 2% (5). • Personal reasons: bimatoprost A (2), bimatoprost B (1), bimatoprost C (6), bimatoprost vehicle (5), minoxidil 2% (3). • Withdrawal by participant: bimatoprost A (0), bimatoprost B (0), bimatoprost C (1), bimatoprost vehicle (1), minoxidil 2% (0). • Did not receive treatment: bimatoprost A (0), bimatoprost B (1), bimatoprost C (1), bimatoprost vehicle (0), minoxidil 2% (1). **Baseline data** Target area hair count hairs/cm^2 (SD): bimatoprost 153.1 (54.78), bimatoprost B 161.1 (63.85), bimatoprost C 145.2 (63.42), bimatoprost vehicle 163.0 (57.28), minoxidil 2% 156.3 (55.46)
Interventions	**Intervention** • Bimatoprost (formulation A) 1 mL/day once daily for 6 months. **Comparator** • Bimatoprost (formulation B) 1 mL/day once daily for 6 months. **Comparator 2** • Bimatoprost (formulation C) 1 mL/day once daily for 6 months. **Comparator 3**

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NCT01325350 *(Continued)*

	• Bimatoprost vehicle 1 mL/day once daily for 6 months. **Comparator 4** • Minoxidil 2% 1 mL/day twice daily for 6 months.
Outcomes	Assessments (2): at baseline and month 6 **Primary outcomes** (as reported) • Change from baseline in target area hair count.[1] • Percentage of participants in each response category of the subject self assessment in alopecia (SSA) score.[1] **Secondary outcomes** (as reported) • Percentage of participants in each response category of the Investigator Global Assessment (IGA) score.[1] • Percentage of participants in each response category of the Global Panel Review (GPR) score.[1] • Change from baseline in target area hair width (TAHW).[1] • Change from baseline in target area hair darkness (TAHD). [1]Denotes outcomes prespecified for this review
Funding source	Sponsor is Allergan
Declaration of interest	No information, probably Allergan
Notes	We e-mailed Allergan several times, without any response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (clinicaltrials.gov): "randomized". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (clinicaltrials.gov): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (clinicaltrials.gov): "double-blind". Comment: there was uncertainty with effective blinding of outcomes assessors (healthcare providers) during the study. There was insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 49/306 (16.0%) withdrawals/losses to follow-up: 6/61 (9.8%) bimatoprost A group, 5/61 (8.2%) bimatoprost B group, 17/61 (27.9%) bimatoprost C group, 9/61 (14.8%) bimatoprost vehicle group, 12/62 (19.4%) minox-

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NCT01325350 *(Continued)*

		idil 2% group. Reasons were reported, and there was an unbalanced number of drop-outs. However, the higher percentage of drop-outs in bimatoprost C group was unrelated to adverse events or lack of effect. Data analysis was per-protocol. Comment: we judged this as at unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was available (NCT01325350 as well as EudraCT 2011-000380-27), and trial reported all outcomes listed. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

NCT01655108

Methods	This is a double-blind randomised active-controlled trial **Setting** Brasilia University Hospital, Brasilia, Brazil **Date of study** March 2012 to October 2013 (10-week duration)
Participants	54 women **Inclusion criteria** • 18 to 65 years of age. • AGA (FPHL). **Exclusion criteria** • Patients with alopecia areata or cicatricial alopecia. • Pregnancy and breastfeeding. • Have undergone any specific treatment in the last 6 months. • Use of drugs with anti-androgenic properties. • Patients with signs or symptoms of hyperandrogynism. **Randomised** 54 participants were randomised (minoxidil group = 27, placebo group = 27) **Withdrawals/losses to follow-up** There were 4/54 (7.4%) withdrawals/losses to follow-up: 3/27 (11.1%) minoxidil group, 1/27 (3.7%) placebo group • Headache: minoxidil group (1). • Protocol drop-out: minoxidil group (2), placebo (1). **Baseline data** Not clearly reported
Interventions	**Intervention** • Intradermal applications (mesotherapy) with minoxidil 0.5%/2 mL 10 sessions at weekly intervals.

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NCT01655108 *(Continued)*

	Comparator • Intradermal applications (mesotherapy) of saline 0.9% 10 sessions at weekly intervals.
Outcomes	Assessments (3): at baseline, week 10, and week 18 **Primary outcomes** (as reported) • Increase in hair density.[1] **Secondary outcomes** (as reported) • Mesotherapy safety [1]Denotes outcomes prespecified for this review
Funding source	Unclear
Declaration of interest	Unclear
Notes	We last accessed the website on 29 July 2015, and the study was completed. We received data from the PI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (clinicaltrials.gov): "randomized". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups. After e-mail contact: "We made the allocation using the random function of Microsoft Excel, version 6.1.7601 (Microsoft Corporation, Santa Rosa, U.S.A)...The clinical record of the patient was developed / created on a computer, where it was connected to the randomization Excel spreadsheet described above so that upon being selected for the study (control group?) , the patient would be randomized by the system itself, therefore eliminating the possibility of interference from the investigators / researchers". Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement. After e-mail contact: central allocation, which was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (clinicaltrials.gov): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement. After e-mail contact: "The medications utilized in the study (minoxidil 0,5%) and placebo (0,9% saline) were produced by a compounding pharmacy (Health Tech Farmácia de Manipulação LTDA - Rusa Teresina 208/210, Vila Bertioga, São Paulo - SP) in identical bottles. The bottles were labelled with number only: 1 (0,9% Saline) and 2 (Minoxidil 0,5%) so that identification of the original medication was not possible".

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NCT01655108 *(Continued)*

		Comment: we judged this as at low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (clinicaltrials.gov): "double-blind". Comment: there was uncertainty with effective blinding of outcomes assessors (healthcare providers) during the study. There was insufficient information to permit a clear judgement. After e-mail contact (see above): the trial authors adequately reported the measures used to blind the outcome assessor from knowledge of which intervention a participant received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 4/54 (7.4%) withdrawals/losses to follow-up: 3/27 (11.1%) minoxidil group, 1/27 (3.7%) placebo group). Data analysis was per-protocol. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was available (NCT01655108), and the trial reported all outcomes listed. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

NCT01900041

Methods	This is a open-label randomised active-controlled trial **Setting** Multicentre, Moscow Scientific Clinical Center of Dermatology and Cosmetology, Moscow, Russian Federation **Date of study** April 2012 to July 2013 (26-week duration)
Participants	74 women Age = 18 to 45 years **Inclusion criteria** • Complaint of hair loss and/or hair density reduction for more than 3 months. • Female hair loss including androgenetic alopecia Ludwig type I and II. • More than 15% of telogen frontoparietal hair as shown in the phototrichogram. **Exclusion criteria** • Symptomatic diffuse alopecia (screening for iron and thyroid function, thyroid stimulating hormone, triiodothyronine, ferritin , total iron-binding capacity). • Active or history of autoimmune disorder, e.g. systemic lupus erythematosus. • Hyperandrogenic alopecia (polycystic ovary syndrome, adrenogenital syndrome, tumours with androgenic activity) (testosterone, prolactin hormone, androstenedione, dehydroepiandrosterone). • Initiation or termination of hormone therapy within 6 months prior to entering study. • Hormone therapy with androgenic action, e.g. norethisterone etc. • Pregnancy or lactation within 6 months prior to entering study. • Alopecia areata. • Scarring alopecia.

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NCT01900041 *(Continued)*

- Treatment with hair promoting agent within 3 months prior to entering the study.
- Known hair loss after drug intake.
- Concomitant use of drugs known to cause hair loss (e.g. aromatase inhibitors, thyreostatics, cytostatics, etc.).

Randomised

74 participants were randomised (37 in each treatment arm)

Withdrawals/losses to follow-up

There were 13/74 (17.6%) withdrawals/losses to follow-up: 7/37 (18.9%) Pantovigar + minoxidil group, 6/37 (16.2%) minoxidil group)

- Adverse events/lack of efficacy: Pantovigar + minoxidil (2), minoxidil (3).
- Refusal to participate: Pantovigar + minoxidil (4), minoxidil (2).
- Protocol deviation: Pantovigar + minoxidil (1), minoxidil (1).

Baseline data

Nothing reported

Interventions	**Intervention** • Pantovigar 1 capsule 3 times a day + minoxidil 2% 1 mL twice daily applied to scalp for 26 weeks. **Comparator** • Minoxidil 2% 1 mL twice daily applied to scalp for 26 weeks.
Outcomes	Assessments (4): at baseline, 4, 6, and 9 months **Primary outcomes** (as reported) • Rate of responders to the treatment (assessed by the Investigator using the results phototrichogram (TrichoScience). Includes: reduction in the amount of telogen hair to 15% and below; increasing hair growth density; thickening of average hair diameter; reduction in the amount of vellus hair in comparison with initial indicators).[1] **Secondary outcomes** (as reported) • Global photographic assessments.[1] [1]Denotes outcomes prespecified for this review
Funding source	Merz Pharmaceuticals GmbH, Frankfurt, Germany
Declaration of interest	Unclear, not full publication
Notes	Website accessed 3 August 2015, and last updated December 2013. Pantovigar consists of medicinal yeast 100 mg, thiamine mononitrate 60 mg, calcium pantothenate 60 mg, cystine 20 mg, para-aminobenzoic acid 20 mg, and keratin 20 mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (clinicaltrials.gov): "randomized". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.

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NCT01900041 *(Continued)*

		After e-mail communication: "The patients were randomized by the block method. The randomization sequence was formed using computer." Comment: this was probably done.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (clinicaltrials.gov): "open label". Comment: the outcome is likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (clinicaltrials.gov): "open label". Comment: the outcome measurement is likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 13/74 (17.6%) withdrawals/losses to follow-up: 7/37 (18.9%) Pantovigar + minoxidil group, 6/37 (16.2%) minoxidil group. Data analysis was per-protocol. Comment: we judged this as at an unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was available (NCT01900041), and the trial reported all outcomes listed. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

NCT01967277

Methods	This is a double-blind randomised active-controlled trial **Setting** Two centres USA **Date of study** March 2014 to August 2014 (16-week duration)
Participants	44 women Mean age = 49 years **Inclusion criteria** • Female (18 to 60 years) with androgenetic alopecia/FPHL Fitzpatrick skin phototypes of I to IV Ludwig-Savin Hair Loss scale I to II. • In overall good health as determined by the physician investigator. • Active hair loss within the last 12 months. • Willingness to refrain from using all other hair growth products or treatments. **Exclusion criteria** • Photosensitivity to the specific wavelength of light - 650 nm.

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NCT01967277 *(Continued)*

- Malignancy in the target treatment area.
- Other forms of alopecia of the head.
- Past medical history of a collagen-vascular disease, thyroid disease, or other cutaneous or systemic disease that seriously affects the scalp.
- Willing to remove hair replacement products during the 16 weeks of therapy.
- Using any medications deemed to inhibit hair growth as determined by the physician investigator.

Randomised
44 participants were randomised (Handi-Dome Laser One group = 22, Incandescent Red Light Source group = 22)

Withdrawals/losses to follow-up

There were 4/44 (9%) withdrawals/losses to follow-up: 3/22 (13.6%) Handi-Dome Laser One group, 1/22 (4.5%) Incandescent Red Light Source group)

- Lost to follow-up: Handi-Dome Laser One group (2), Incandescent Red Light Source group (1).
- Unrelated illness: Handi-Dome Laser One group (1), Incandescent Red Light Source group (0).

Baseline data

Hair count on 25 mm area (SD): Handi-Dome Laser One group 189.3 (85.8), Incandescent Red Light Source group 216.9 (109.1)

Interventions	**Intervention** • Handi-Dome Laser. One 30-minute treatment every other day for 16 weeks. **Comparator** • Incandescent red light source. One 30-minute treatment every other day for 16 weeks.
Outcomes	Assessments (2): at baseline and week 16 **Primary outcomes** (as reported) • Percentage increase in terminal hair counts from pre-treatment, baseline for active test participants over the placebo test participants.[1] • Absolute increase in terminal hair counts from pre-treatment, baseline for active test subjects over the placebo test participants.[1] • Adverse events.[1] [1]Denotes outcomes prespecified for this review
Funding source	Study is sponsored by Capillus LLC
Declaration of interest	Unclear
Notes	We last accessed the website on 4 August 2015, which was last updated on 5 May 2015. The study is completed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (clinicaltrials.gov): "randomized". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.

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NCT01967277 *(Continued)*

		After e-mail communication: we did not receive any additional information to enable a clear judgement.
Allocation concealment (selection bias)	Low risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement. After e-mail communication: "These devices were then logged in, tested for function and segregated by actual and sham models. A serial number was written on each helmet top with a permanent marker. This procedure was performed by a technical assistant who had no contact with any other member of the clinical trial, subject or investigator and staff. The helmets were then packed in boxes of twelve (12) and delivered to each site, as required by appointment". Comment: this was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (clinicaltrials.gov): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement. After e-mail communication: "All test devices, per the IRB approved protocol were unmarked, unadorned with labels (unless required by law), paints or signage. The devices were differentiated from internationally available similar devices by assigning the fictitious name of Handi-Dome 650...The helmets were then packed in boxes of twelve (12) and delivered to each site, as required by appointment". Comment: it appears that the trial made reasonable attempts to blind participants and personnel from knowledge of which intervention a participant received. We judged this as at a low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (clinicaltrials.gov): "double-blind". Comment: there was uncertainty with effective blinding of outcomes assessors (healthcare providers) during the study. There was insufficient information to permit a clear judgement. After e-mail communication: see above. We judged this as at a low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 4/44 (9%) withdrawals/losses to follow-up: 3/22 (13.6%) Handi-Dome Laser One group, 1/27 (4.5%) Incandescent Red Light Source group). The trial reported the reasons, and performed data analysis per-protocol. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was available (NCT01967277), and the trial reported all outcomes listed. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Olsen 1991

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting**

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Olsen 1991 *(Continued)*

	Duke University Medical Center, Durham, USA **Date of study** Not reported (32-week duration)
Participants	30 women Mean age (range) = 36.0 years (19 to 45) in the minoxidil group, 38.9 years (33 to 43) in the placebo group **Inclusion criteria** • Female age 18 to 45 years. • Dark hair. • FPHL Ludwig scale grade I or II (Ludwig 1977), diagnosis based on clinical history/scalp hair loss pattern. **Exclusion criteria** • Advanced hair loss. • Using hormone therapy, oral contraceptives. • Use of hair growth promoter, antihypertensives, anticonvulsants, ß-blockers, steroids, cytotoxic drugs, vasodilators, diazoxide, or any drug with antiandrogen effects in prior 3 months. • Concurrent evidence of anaemia, iron deficiency, or thyroid disease. **Randomised** 30 participants were randomised (15 to each of 2 groups) **Withdrawals/losses to follow-up** There were 2/30 (6.7%) (1/group) withdrawals/losses to follow-up. The time and reasons were unreported **Baseline data** Duration of hair thinning in mean (SD) years • Minoxidil group = 10.07 (8.72), placebo group = 7.21 (1.06). Degree of thinning Ludwig scale (participants by grade and group) • Grade I: minoxidil group = 9, placebo group = 9. • Grade II: minoxidil group = 5, placebo group = 5. Number of non-vellus hairs in the target area, mean (SD) • Minoxidil group = 160.1 (34.63), placebo group = 154.2 (35.96).
Interventions	**Intervention** • Minoxidil 2% solution. 1 mL of assigned solution applied to involved scalp twice daily for 32 weeks. **Comparator** • Placebo (vehicle: propylene glycol, alcohol, water) solution. 1 mL of assigned solution applied to involved scalp twice daily for 32 weeks.
Outcomes	Assessments (9): at baseline, 4, 8, 12, 16, 20, 24, 28, and 32 weeks **Primary outcomes** (as reported) • Hair counts at target area (frontoparietal tattooed), macro-photography assessed.[1]

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Olsen 1991 *(Continued)*

- Regrowth: subjective assessment (investigator/participant), rated none/minimal/moderate/dense regrowth.[1]

Secondary outcomes (as reported)

- Adverse events: investigator-assessed by clinical exam and questionnaire.[1]

[1]Denotes outcomes prespecified for this review

Funding source	Quote (page 248): "This work was supported in part by a grant from the Upjohn Company"
Declaration of interest	None declared
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 243): "were randomly assigned to apply". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of the risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 244): "Both subjects and investigators remained blinded during the entire study." Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 245): "One technician at Duke University Medical Center blinded as to treatment counted the nonvellus target areas hairs on each set of before and after photographs." Comment: this was probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a balanced and low number (1 in each group) of losses to follow-up. The data analysis was per-protocol. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the trial appears to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

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Oura 2008

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Department of Dermatology, University of Tokushima, Japan **Date of study** Unreported (12-month duration)
Participants	30 women Mean age (range) = 38.9 years (22 to 53) **Inclusion criteria** • Clinical diagnosis of FPHL. • No systemic disease. **Exclusion criteria** Nothing was reported **Randomised** 30 women participants were randomised into 2 equal groups **Withdrawals/losses to follow-up** There were 3/30 (10%) withdrawals/losses to follow-up: adenosine group 2/15, placebo group 1/15: 1 in each group before intervention, and voluntary withdrawal in the adenosine group (1) **Baseline data** Participants had a clinical diagnosis of FPHL that was rated > 1.5 (6-point scale 1 = no hair loss, to 6 = detectable hair loss) (Tajima 2007)
Interventions	**Intervention** • Adenosine (0.75%) solution. 3 mL of assigned lotion applied twice daily over 12 months. **Comparator** • Vehicle solution. 3 mL of assigned lotion applied twice daily over 12 months.
Outcomes	Assessments (3): at baseline, 6, and 12 months **Outcomes** (as reported) • Hair loss (dermatologist-assessed) via standardised photographic techniques (6-point scale: 1 = no hair loss, 6 = detectable hair loss) (Tajima 2007).[1] • Improvement in hair loss (investigator-assessed) via standard photography (6-point scale: 1 = no hair loss, 6 = detectable hair loss).[1] • Phototrichograms (counting hair numbers, anagen hair growth, hair thickness, hair density).[1] • Self-assessments by 7-item questionnaire (Barber 1998).[1] [1]Denotes outcomes prespecified for this review
Funding source	Quote (page 767): "Shiseido Research Centre were cooperative investigators."
Declaration of interest	None declared

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Oura 2008 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 764): "Randomization was carried out to divide the volunteers into two groups". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 764): "a double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement of risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a low number of withdrawals (3/30, 10%): 1 in each group before using the test lotion. There was 1 voluntary withdrawal from the adenosine group at month 12. The data analysis was per-protocol. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the trial appears to have reported all prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Pazoki-Toroudi 2012

Methods	This was a randomised placebo-controlled trial **Setting** Iran University of Medical Sciences, Tehran, Iran **Date of study** Unspecified (24-week duration)
Participants	124 men and women (62 men, 62 women)

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Pazoki-Toroudi 2012 *(Continued)*

Mean age (SD) = 33.63 (7.32) minoxidil 5% group, 32.81 (8.24) in minoxidil high extra combination (MHEC) 37.17 (6.40) years in placebo group

Inclusion criteria

- Men with AGA with grade I to IVa on Hamilton scale and women with grade I to III on Ludwig scale.

Exclusion criteria

- Concomitant dermatological disease on the scalp other than AGA.
- Serious heart, renal, or hepatic diseases.
- Collagen disorders.
- Hormone replacement therapy.
- Pregnancy or lactation, or intention to conceive.
- Drug hypersensitivity.
- History of treatment with minoxidil or MHEC.

Randomised
124 participants were randomised (minoxidil group = 49, MHEC group = 57, placebo group = 18)

There were 8/124 (6.5%) withdrawals/losses to follow-up: 6/49 in minoxidil group and 2/57 in MHEC group, all due to adverse events

Baseline data
Hamilton scale II: minoxidil group 2, MHEC group 1, placebo group 0

Hamilton scale IIa: minoxidil group 3, MHEC group 6, placebo group 1

Hamilton scale III: minoxidil group 5, MHEC group 4, placebo group 2

Hamilton scale IIIa: minoxidil group 3, MHEC group 4, placebo group 1

Hamilton scale III vertex: minoxidil group 6, MHEC group 5, placebo group 3

Hamilton scale IV: minoxidil group 3, MHEC group 3, placebo group 1

Hamilton scale IVa: minoxidil group 2, MHEC group 1, placebo group 1

Ludwig scale I: minoxidil group 4, MHEC group 2, placebo group 2

Ludwig scale II: minoxidil group 13, MHEC group 28, placebo group 7

Ludwig scale III: minoxidil group 2, MHEC group 1, placebo group 0

Interventions	**Intervention** • Minoxidil 5% twice daily for 24 weeks. **Comparator** • Minoxidil 12.5%, azelaic acid 5%, and betamethasone 0.025% in ethyl alcohol 98%, propylene glycol, and deionised water once daily for 24 weeks. **Comparator 2** • Placebo twice daily for 24 weeks.
Outcomes	Assessments (5): at baseline, week 6, 12, 18, and 24 **Outcomes** (as reported) • Hair count of shed hair.[1] • Investigators assessments of hair growth (5 point Likert scale from −1 (worsening) to 3 (marked improved).[1]

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Pazoki-Toroudi 2012 *(Continued)*

- Participants assessments of hair growth (5 point Likert scale from −1 (worsening) to 3 (marked improved).[1]
- Adverse events.[1]

[1]Denotes outcomes prespecified for this review

Funding source	None declared but one PI is employed by Nano Vichar Pharmaceutical Co.Ltd
Declaration of interest	None declared
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 277): "were randomly allocated". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 277): "blinded investigators (specialists) made observations; therefore neither investigators nor patients knew about the group of study". The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement of risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigators and participants were both outcome assessors. MHEC treatment was applied once a day versus minoxidil and placebo twice a day. Comment: there was uncertainty with effective blinding of outcomes assessors (healthcare providers) during the study. There was insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 8/124 (6.5%) withdrawals/losses to follow-up: 6/49 in minoxidil group and 2/57 in MHEC group, all due to adverse events. Data analysis was per-protocol. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the trial appears to have reported all prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

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Policarpi 1993

Methods	This was a randomised controlled (sham treatment) trial **Setting** Departments of Dermatology, University of Florence, Italy **Date of study** Unreported (36-week duration)
Participants	30 (24 male, 6 female) Mean age (range) = 29.1 years (17 to 58) **Inclusion criteria** • Female: Ludwig scale grade II or III (Ludwig 1977). (Male: II to IV alopecia; Hamilton-Norwood scale). **Exclusion criteria** • Cardiac pacemakers or with cardiac problems in which the intervention may have a negative effect. • No topical or systemic agents that can stimulate hair growth or prevent hair loss in the prior 3 months. **Randomised** Participants were randomised into 2 groups (active intervention group = 20, sham intervention group = 10) **Withdrawals/losses to follow-up** There were 6/30 (20%) withdrawals/losses to follow-up: 5/20 (25%) in the active intervention group, and 1/10 (10%) in the sham intervention group • 1 withdrew because his condition worsened, and 5 were voluntary withdrawals. None of the 6 women withdrew. **Baseline data** Degree of thinning Ludwig scale • 6 women classed as grade II or III (no further specification).
Interventions	**Intervention** • Pulsed electrostatic field applied in a 12-minute session/week for 36 weeks. **Comparator** • Sham treatment for 36 weeks. Very limited information was reported
Outcomes	Assessments (3): at baseline, 8, and 16 weeks **Outcomes** (as reported) • Hair count (anagen) using standardised photographic technique.[1] • Self-assessment with clinical condition (4-point scale: 0 = worse, 1= unchanged, 2 = slightly improved, 3 = significantly improved).[1] • Investigator-assessed satisfaction with clinical condition (4-point scale).[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared

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Policarpi 1993 *(Continued)*

Declaration of interest	None declared
Notes	Individual patient data were available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 228): "in modo random in 2 gruppi." Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement. Comment: there was insufficient information to permit judgement of whether there was low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing outcome data for women. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the trial appears to have reported all prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Price 1990

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Departments of Dematology of Kaiser Permanente Medical Center and University, San Francisco, and Trichos Research, Richmond, USA **Date of study** Unreported (40-week duration)
Participants	9 women

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Price 1990 *(Continued)*

	Age = 22 to 41 years **Inclusion criteria** • Female 18 to 45 years. • Ludwig scale grade I and II (Ludwig 1977). • Good health. • Regular menses. • Dark undyed hair. **Exclusion criteria** • Pregnancy. • < 12 months postpartum or breastfeeding. • Previous use of topical minoxidil. • < 3 months before start of study use of the following: oral contraceptives, steroid hormones, vasodilators, antihypertensives, anticonvulsants, cytotoxic agents, ß-blockers, spironolactone, cimetidine, cyclosporin, ketoconazole, or hair restorers. **Randomised** 9 participants were randomised (minoxidil group = 5, placebo group = 4) **Withdrawals/losses to follow-up** There was 1 withdrawal in the minoxidil group due to hyperprolactinaemia **Baseline data** Degree of thinning Ludwig scale (participants by grade, intervention group) • Grade I: minoxidil group = 2, placebo group = 1. • Grade II: minoxidil group = 3, placebo group = 3.
Interventions	**Intervention** • Minoxidil 2% solution. 1 mL of solution twice daily on scalp (frontal parietal) at clipped site over 32 weeks. **Comparator** • Vehicle solution. 1 mL of solution twice daily on scalp (frontal parietal) at clipped site over 32 weeks. The study duration was 40 weeks, and treatment was started after the 2nd visit at 4 weeks from baseline
Outcomes	Assessments (6): at baseline and at 8-week intervals **Outcomes** (as reported) • Hair weight of clipped sample. • Hair count of clipped sample.[1] • Hair width/length of clipped sample. [1]Denotes outcomes prespecified for this review
Funding source	Quote (page 683): "The Upjohn Company provided support and encouragement of this research."
Declaration of interest	None declared
Notes	Individual patient data were reported, but there were small sample sizes

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Price 1990 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 684): "The subjects were given test solutions in a random, double-blind manner." Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 683): "double-blind protocol". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement of risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a small number of withdrawals: 1/9 in the minoxidil group (hyperprolactinaemia). Individual patient data were reported. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was unavailable, but the trial appears to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Price 2000

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** 8 investigational sites in the USA **Date of study** Unreported (12-month duration)
Participants	137 women Mean age (range) = 53 years (41 to 60)

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Price 2000 *(Continued)*

Inclusion criteria

- < 59 years of age in good physical and mental health, postmenopausal (and amenorrhoeic > 1 year, but > 10 years).
- Serum follicle-stimulating hormone (FSH) level of > 40 mIU/mL.
- Mild to moderate frontal hair thinning Ludwig scale grade I or II (Ludwig 1977); and Savin female density scale 3, 4, or 5 (Trancik 1996).

Exclusion criteria

Nothing was reported

Randomised

137 participants were randomised (finasteride group = 67, placebo group = 70)

Withdrawals/losses to follow-up

There were 12/137 (8.8%) withdrawals/losses to follow-up: 5/67 (7.5%) in the finasteride group, and 7/70 (10%) in the placebo group

- Clinical adverse event: finasteride group = 2, placebo group = 1.
- Lost to follow-up: finasteride group = 1, placebo group = 3.
- Withdrew consent: finasteride group = 0, placebo group = 3.
- Noncompliance: finasteride group = 1, placebo group = 0.
- Lack of efficacy: finasteride group = 1, placebo group = 0.

Baseline data

Mean baseline hair count measured in a 1 cm^2 circular area at the anterior/mid area of the scalp ± SD

- Finasteride group = 151 ± 49, placebo group = 164 ± 53.

Savin score (number [%] of women)

- 3: finasteride group = 21 (31.3), placebo group = 30 (42.9).
- 4: finasteride group = 30 (44.8), placebo group = 21 (30.0).
- 5: finasteride group = 16 (23.9), placebo group = 19 (27.1).

Ludwig scale (number (%) of women)

- Grade I: finasteride group = 22 (32.8), placebo group = 31 (44.3).
- Grade II: finasteride group = 45 (67.2), placebo group = 39 (55.7).

Concomitant hormone replacement therapy (number (%) of women)

- Finasteride group = 35 (52.2), placebo group = 37 (52.9).

Interventions	**Intervention** • Oral finasteride 1 mg/day during 12 months. **Comparator** • Placebo during 12 months.
Outcomes	Assessments (6): at baseline, 1, 3, 6, 9, and 12 months **Primary outcomes** (as reported) • Hair counts, computer-assisted scans of macro-photographs of clipped hair in a defined (dot tattoo) circular target area (1 cm^2) frontal/parietal (anterior/mid) scalp. Macro-photographs converted into dot maps at baseline and at months 3, 6, and 12.[1]

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Price 2000 *(Continued)*

	Secondary outcomes (as reported) • Participant/self-assessed hair growth, modified version of a validated questionnaire (4 questions: appearance of hair, growth of hair, slowing down of hair loss, and satisfaction with appearance of hair) (Barber 1998).[1] • Investigator-assessed hair growth, a standardised 7-point rating scale (−3 = greatly decreased to +3 = greatly increased).[1] • Scalp biopsies; terminal hair bulbs; terminal anagen, catagen, and telogen hairs; and vellus and vellus-like (miniaturised) hair counts. • Laboratory tests; haematology, urinalysis, serum chemistry, hormone analysis, and bone marker analyses. [1]Denotes outcomes prespecified for this review
Funding source	Quote (page 768): "supported by Merck Research Laboratories."
Declaration of interest	None declared but almost half of the investigators indicated an affiliation with Merck Research Laboratories
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 769): "randomized to receive either". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 769): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement of risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 770): "At the end of the study, an expert panel of 3 dermatologists (E. Olsen, R. Savin, and D. Whiting), blinded as to treatment, independently evaluated hair growth or loss by comparing baseline photographs." Comment: participants and the 3 dermatologists (investigators) were assessors for several outcomes, and, although stated to be "blinded", the measures used were not reported. There was insufficient information to permit clear judgement of bias across all outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 12/137 (8.8%) dropouts; and the reasons were reported. Intention-to-treat analysis (ITT) analysis was done. Comment: we judged this as at a low risk of bias.

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Price 2000 *(Continued)*

Selective reporting (reporting bias)	Low risk	The study protocol was unavailable, but the study appeared to have reported the prespecified outcomes and those mentioned in the methods section. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Rietschel 1987

Methods	This was a randomised, double-blind, controlled study **Setting** 2 centres in the USA **Date of study** Unspecified (2-year duration)
Participants	149 with men and women (142 men and 7 women) Age (range) = 34.1 years (18 to 49) **Inclusion criteria** • Participants were required to have a distinct pattern of balding consistent with androgenetic alopecia. **Exclusion criteria** • Lack of other scalp pathologic processes. **Randomised** 149 participants (minoxidil 2% = 48, minoxidil 3% = 51, placebo to 3% minoxidil = 50) **Withdrawals/losses to follow-up** There were 47/149 (31.9%) withdrawals/losses to follow-up: 14/48 (29.2%) minoxidil 2% group, 18/51 (35.3%) minoxidil 3%, 15/50 (30%) placebo to 3% minoxidil, reasons unreported **Baseline data** Duration of baldness ranged from 1 to 32 years, averaging 10.2 years. The average diameter of the vertex bald spot at its widest measurement was 10.7 cm (range = 3.81 to 24.13). All participants had a receding hairline and bitemporal recession
Interventions	**Intervention** • Minoxidil 2% solution 1 mL twice a day. **Comparator** • Minoxidil 3% solution 1 mL twice a day. **Comparator 2** • Placebo (vehicle) solution 1 mL twice a day. At the end of 4 months, the placebo group switched to a 3% minoxidil solution for the duration of the study. At 12 months, the 2% minoxidil group also switched to a 3% solution. Thus, all participants that

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Rietschel 1987 *(Continued)*

	continued past 12 months were using the 3% solution. Participants applied 1 mL of solution to the balding area of the scalp in the morning and in the evening.
Outcomes	Assessments: at baseline, week 2, and then at monthly intervals in the first year and after a year at 3 monthly intervals **Outcomes** (as reported) • Hair counts according to 3 classifications: (1) terminal, (2) intermediate, and (3) vellus. Total hair counts were the sum of the 3 categories.[1] • Laboratory parameters, monitored at baseline, at 4 months, and at 12 months, included complete blood cell count, urinalysis, multiple automated blood screening analysis, chest x-ray, electrocardiogram, and M-mode echocardiogram. • Physical findings measured at each examination included weight; pulse; systolic and diastolic blood pressures; and the presence or absence of edema, arrhythmia, pericardial friction rub, and pulmonary rales. [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	There were no separate data for the 7 women. We were unable to contact the trial investigators. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 678): "Subjects were randomly assigned to use one of three topical solutions" Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 678): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement of risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 47/149 (31.9%) withdrawals/losses to follow-up: 14/48 (29.2%) minoxidil 2% group, 18/51 (35.3%) minoxidil 3%, 15/50 (30%) placebo to 3% minoxidil, reasons unreported. Comment: we judged this as at a high risk of bias.

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Rietschel 1987 *(Continued)*

Selective reporting (reporting bias)	Low risk	The study protocol was unavailable, but the trial appeared to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Sheng 2014

Methods	This was a randomised, double-blind, active-controlled study **Setting** Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, China **Date of study** Unspecified (6-month duration)
Participants	264 women Mean age (SD) = 32.16 (7.07) years in 2% minoxidil group and 33.08 (2.68) in 5% minoxidil group **Inclusion criteria** • FPHL, Ludwig grade II and III. • 18 to 48 years. **Exclusion criteria** • Had heart, lung, liver, kidney, endocrine, neurological, or psychiatric diseases. • Pregnant or lactating. • Seborrhoeic dermatitis, eczema, or psoriasis of the scalp. • Received minoxidil or other drugs affecting hair growth (anti-androgen, glucocorticoids, cytotoxic drugs, and immunomodulators) within 6 months before screening. **Randomised** 264 participants (minoxidil 2% = 132, minoxidil 5% = 132) **Withdrawals/losses to follow-up** There were 13/264 (4.9%) withdrawals/losses to follow-up: 1/132 (<1%) minoxidil 2% group, 11/132 (8.3%), minoxidil 5% group **Baseline data** Ludwig grade II: minoxidil 2% group (103), minoxidil 5% group (85) Ludwig grade III: minoxidil 2% group (28), minoxidil 5% group (36)
Interventions	**Intervention** • Minoxidil 2% solution twice a day for 6 months. **Comparator** • Minoxidil 5% solution twice a day for 6 months.
Outcomes	Assessments (3): at baseline, month 3, and month 6

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Sheng 2014 *(Continued)*

Outcomes (as reported)

- Improvement in hair growth (7-point Likert scale from -3 marked decrease to + 3 marked increase).
- Adverse events.[1]

[1]Denotes outcomes prespecified for this review

Funding source	None declared
Declaration of interest	None declared
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (translated): "Using randomisation, 264 patients with FPHL were allocated to 2% and 5% minoxidil solution." Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups. After e-mail communication: "In the study design, randomization (completely randomized design) was done with SPSS. Since FPHL patients were not enrolled simultaneously, they were sorted by the enrolment time (1st, 2nd, 3rd, …, 264th). Then, each subject was allocated according to the random assignment table generated by SPSS." Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias. After e-mail communication: "Random assignment table from SPSS was generate and kept by a separate colleague, and therefore, other participants and investigators enrolling patients could not foresee the assignment." Comment: this was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 583): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement of risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 13/264 (4.9%) withdrawals/losses to follow-up: 1/132 (< 1%) minoxidil 2% group, 11/132 (8.3%), minoxidil 5% group. Data analysis was per-protocol. Comment: we judged this as at a low risk of bias.

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Sheng 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	The study protocol was unavailable, but the trial appeared to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Shin 2007

Methods	This was a randomised, double-blind,placebo-controlled study **Setting** Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea **Date of study** Unspecified (18-week duration)
Participants	36 women Mean age (SD) = 34.1 (4.8) years in the AP-FHG0604T group 32.2 (7.3) years in placebo group **Inclusion criteria** • FPHL, Ludwig grade I. • 20 to 45 years of age. **Exclusion criteria** • Acute illness in 6 months prior to enrolment or chronic illness that may affect the study results. • Prior surgical process to treat alopecia. • Minoxidil use within 3 months prior to enrolment. • Anti-androgen or other treatments that many affect hair growth cycle. • Alopecia type other than FPHL. • Pregnancy or lactation. **Randomised** 36 participants (AP-FHG0604T group = 17, placebo group = 16, 3 unclear) **Withdrawals/losses to follow-up** There were 3/36 (8.3%) withdrawals/losses to follow-up: lost to follow-up, did not want to shave, unclear from which group **Baseline data** Total hair count (n/cm^2(SD)): 100.2 (5.4) in AP-FHG0604T group, 100.8 (4.1)
Interventions	**Intervention** • AP-FHG0604T (*Thuja occidentalis* extract, *Swertia* extract, pantotenilethylether, 4-pyrrolidine 2,6-diaminopyrimidine 1-oxide, cyanocobalamin, 95% ethanol, saline) twice a day for 18 weeks. **Comparator** • Vehicle twice a day for 18 weeks.
Outcomes	Assessments (3): baseline, week 9, and week 18 **Outcomes** (as reported)

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Shin 2007 *(Continued)*

- Hair count (photo trichogram).[1]
- Global evaluation by investigator (photos, 5-point Likert scale (0 = no improvement, 4 ≥ 75% improvement).[1]
- Participants assessments (questionnaire, hair-loss and improvement on a VAS from 0-10, with 10 being best score).[1]
- Adverse events.[1]

[1]Denotes outcomes prespecified for this review

Funding source	None declared
Declaration of interest	None declared
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 119): "randomized." Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups. After e-mail communication: "We used a block randomization method. Random numbers were generated by SAS program" Comment: this was probably done.
Allocation concealment (selection bias)	Low risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias. After e-mail communication: "The allocation sequence was kept in an envelop secretly by a third staff (a pharmacist who was not involved in the intervention and analysis). This concealment was maintained until the completion of the last follow up and evaluation of all results." Comment: this was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 119): "double-blind". Comment: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement of risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 3/36 (8.3%) withdrawals/losses to follow-up: lost to follow-up, did not want to shave, unclear from which group. Data analysis per-protocol. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was unavailable, but the trial appears to have reported the prespecified outcomes and those mentioned in the methods section.

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Shin 2007 *(Continued)*

		Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Thom 2001

Methods	This was a randomised, placebo-controlled, double-blind study **Setting** Norway **Date of study** Unspecified (6-month duration)
Participants	60 (55 men and 5 women) Mean age (SD) = 37.8 (3.9) years in Hairgain® group and 38.6 (3.4) years in placebo group **Inclusion criteria** • > 18 years of age. • Hair-loss for > 1 year. **Exclusion criteria** • Nothing reported. **Randomised** 60 participants (30 in both groups) **Withdrawals/losses to follow-up** There were no withdrawals/losses to follow-up **Baseline data** AGA (56), alopecia totalis (4) Duration of hair loss: 18.6 months in the Hairgain® group, 20.4 in the placebo group
Interventions	**Intervention** • Hairgain® (dietary supplement of marine protein extract, vitamins, and minerals), 2 capsules/day (< 80 kg in body weight) or 3 capsules/day (> 80 kg) for 6 months. **Comparator** • Placebo 2 capsules/day (< 80 kg in body weight) or 3 capsules/day (> 80 kg) for 6 months.
Outcomes	Assessments (4): baseline, month 2, 4, and 6 **Outcomes** (as reported) • Hair growth by hair counts assessed by standardised photographic techniques at baseline and completion of study.[1] • Participant-assessed satisfaction VAS (0 to 10).[1] • Tolerability, i.e. adverse effects.[1] • Compliance verified.

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Thom 2001 *(Continued)*

	[1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared, but PI is employed by PAREXEL Medstat AS, Lillestrøm, Norway
Notes	The 6-month blinded phase was followed by an open phase on active treatment. There were no separate data for women. We e-mailed the PI but received no response. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2 to 3): "randomized" "simple block-randomization procedure (blocks of six)" Comment: this was probably done.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 3): "Hairgain® and placebo capsules had the same appearance and were packed in similar plastic bottles in order to keep the study blind. The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators and participants were outcome assessors. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was unavailable, but the trial appears to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Thom 2006

Methods	This was a randomised, placebo-controlled, double-blind study **Setting** Norway

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Thom 2006 *(Continued)*

	Date of study Unspecified (6-month duration)
Participants	60 (51 men and 4 women, 5 gender unclear) Mean age (SD) = 40.4 (5.4) years in Hairgain® group and 41.7 (6.0) years in placebo group **Inclusion criteria** • > 18 year. • Hair-loss for > 1 year. **Exclusion criteria** • Nothing reported. **Randomised** 60 participants (30 in both groups) **Withdrawals/losses to follow-up** There were 5/60 (8.3%) withdrawals/losses to follow-up: 3/30 (10%) in Nourkrin® group, 2/30 (6.7%) placebo group for not attending follow-up visits not related to side effects **Baseline data** Duration of hair loss in months (SD): 20.2 (6.7) in Nourkrin® group and 18.7 (5.6) in placebo group
Interventions	**Intervention** • Nourkrin® (Pharma Medico International, Aarhus, Denmark) food supplement marine proteins extract, acerola cherry extract, silica kieselguhr, horsetail extract, and immunoglobulins. 2 capsules/day (< 80 kg in body weight) or 3 capsules/day (> 80 kg) for 6 months. **Comparator** • Placebo 2 capsules/day (< 80 kg in body weight) or 3 capsules/day (> 80 kg) for 6 months.
Outcomes	Assessments (4): at baseline, month 2, 4, and 6 **Outcomes** (as reported) • Hair count by magnifying glass of pre-defined areas of scalp.[1] • Participant-assessed satisfaction VAS (0 to 10).[1] • Tolerability, i.e. adverse effects/side-effects.[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	The 6-month blinded phase was followed by an open phase on active treatment. There were no separate data for women. We e-mailed the PI but received no response. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 515): "The subjects were first randomized to receive".

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Thom 2006 *(Continued)*

		Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 515): "Nourkrin® and placebo capsules had the same appearance and were packed in similar plastic bottles". Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement. We judged this as at a low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators and participants were outcome assessors. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 5/60 (8.3%) withdrawals/losses to follow-up: 3/30 (10%) in Nourkrin® group, 2/30 (6.7%) placebo group. Data analysis was per-protocol. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was unavailable, but the trial appears to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Tsuboi 2007

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Multicentre, Japan **Date of study** January 2001 to January 2002 (24-week duration)
Participants	280 women Mean age (SD) = 56.3 years (10.4) in the minoxidil group, 57.2 years (9.7) in the placebo group **Inclusion criteria** • > 20 years. • Ludwig scale grade I or II (Ludwig 1977). **Exclusion criteria**

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Tsuboi 2007 *(Continued)*

- Concomitant dermatological scalp disorders other than AGA.
- Serious heart disease (angina pectoris, myocardial infarction), renal, or hepatic diseases.
- Pituitary, thyroid, or collagen diseases (particularly systemic lupus erythematosus).
- Receiving hormone replacement therapy.
- Pregnancy, participants < 12 months after giving birth, or lactating mothers.
- Drug hypersensitivity (including contact dermatitis to cosmetics).
- Participants wearing a wig or with hair transplants.
- Previously treated with minoxidil.

Randomised

280 participants were randomised (minoxidil group = 140, placebo group = 140).

Withdrawals/losses to follow-up

There were 25/280 (8.9%) withdrawals/losses to follow-up: 11/140 in the minoxidil group (7.8%), and 14/140 in the placebo group (10%).

- Adverse events: minoxidil group = 3, placebo group = 8.
- Voluntary withdrawal: minoxidil group = 5, placebo group = 2.
- Other: minoxidil group = 3, placebo group = 4.

3 participants in the minoxidil group and 4 in the placebo group had concomitant or suspected thyroid disease and were considered ineligible for efficacy analyses.

Baseline data

History of hair loss (years)

- Minoxidil group = 6.86 ± 4.53, placebo group = 7.03 ± 5.62.

Degree of thinning Ludwig scale (% of participants by grade and group)

- Grade I: minoxidil group = 78 (56.9), placebo group = 84 (61.8).
- Grade II: minoxidil group = 59 (43.1), placebo group = 52 (38.2).

Non-vellus hair count (mean ± SD)

- Minoxidil group = 133.75 ± 49.62, placebo group = 139.72 ± 46.45.

Vellus hair count (mean ± SD)

- Minoxidil group = 55.53 ± 28.69, placebo group = 52.77 ± 27.82.

Total hair count (mean ± SD)

- Minoxidil group = 189.27 ± 47.26, placebo group = 192.49 ± 40.85.

Interventions	**Intervention** • Minoxidil 1% (10 mg/mL) solution. 1 mL twice daily for 24 weeks. **Comparator** • Vehicle only. 1 mL twice daily for 24 weeks.
Outcomes	Assessment was every 4 weeks. **Outcomes** (as reported) • Hair counts assessed with photography/microscopy.[1] • Investigator-assessed hair growth, photographic comparison (5-point Likert scale: 1 = markedly improved, 5 = worsened).[1]

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Tsuboi 2007 *(Continued)*

- Participant-assessed hair growth (5-point Likert scale) compared to baseline every 4 weeks.[1]
- Participant-assessed hair loss (3-point Likert scale: 1 = good, i.e. decreased hair loss; 2 = unchanged; 3 = worsened, i.e. increased hair loss).[1]
- Adverse events as reported and investigator-assessed dermatological and abnormal changes in laboratory values.[1]

[1]Denotes outcomes prespecified for this review.

Funding source	Quote (page 43): "The authors received financial support from: Taisho Pharmaceutical Co.,ltd."
Declaration of interest	Quote (page 43): "Conflict of interest: None"
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 38): "were randomly allocated to either of two groups (n = 140 in each group)." "The person responsible for study drug allocation assigned patients to either the TMS or PBO group at a ratio of 1:1, and disclosed the allocation codes to no one until the end of the trial." After e-mail communication with investigators: in order to obtain the random allocation sequence for making intervention assignments, a computerised random-number generator was used. Blocked randomisation was used for the generation of the allocation sequence. Comment: we judged this as adequate.
Allocation concealment (selection bias)	Low risk	Quote (page 38): "The person responsible for study drug allocation assigned patients to either the TMS or PBO group at a ratio of 1:1, and disclosed the allocation codes to no one until the end of the trial." After e-mail communication with investigators: a third party, who was independent of the investigator and the sponsor, assigned drugs to either the TMS or PBO group at a ratio of 1:1. The study drug was indistinguishable in appearance and had indistinguishable packaging, and a third party identified indistinguishably in appearance at the time of drug allocation and the end of the trial. A third party disclosed the allocation tables to no one until the end of data lock for analysis, and identified that it had been unopened. Therefore, the allocation sequence was kept blinded to participants, investigators, and sponsor staff who were involved in the treatment or clinical evaluation, until the end of data lock. Comment: this was probably done; we judged this as at a low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 37): "double-blind". Quote (page 38): "The active drug and placebo were indistinguishable in appearance and had indistinguishable packaging." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement. We judged this as a low risk of bias.

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Tsuboi 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were participant- and investigator-assessed. Blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken. Comment: we judged this as at a low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The incomplete outcome data was as follows:17/140 (12.1%) in the minoxidil group, and 18/140 (12.9%) in the placebo group. Reasons were stated and equally balanced. The data analysis was per-protocol. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was unavailable, but the trial appears to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Ukşal 1999

Methods	This was a randomised, active-controlled trial **Setting** Departments of Dermatology and Endocrinology, Kayseri, Turkey **Date of study** Unspecified (3-month duration)
Participants	Number unclear Age = unclear **Inclusion criteria** • Androgenetic alopecia Ludwig scale grade II or III (Ludwig 1977). **Exclusion criteria.** Nothing was reported **Randomised** It was unclear how many participants were randomised **Withdrawals/losses to follow-up** This was unclear **Baseline data** This was unclear
Interventions	**Intervention** • Spironolactone 100 mg/day during 3 months.

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Ukşal 1999 *(Continued)*

	Comparator • Flutamide 125 mg/day during 3 months. **Comparator 2** • Finasteride 2.5 mg/day during 3 months.
Outcomes	The trial authors did not state these
Funding source	None declared
Declaration of interest	None declared
Notes	The poster abstract had minimal reporting of trial details. We sent 3 e-mails to the PI, but received no response. See Table 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page S238): "Patients were randomly divided into three groups." Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of the risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias.
Other bias	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias.

Vexiau 2002

Methods	This was a randomised, active-controlled trial **Setting**

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Vexiau 2002 *(Continued)*

	Endocrinology Department, Hôpital Saint-Louis, Paris, France **Date of study** July 1993 to November 1995 (6-month duration)
Participants	66 women Mean age = 26.4 years (range 18 to 34) (25.7 years in the cyproterone acetate group (CPA), 27.1 years in the minoxidil group) **Inclusion criteria** • Age 18 to 35 years. • Female pattern AGA. **Exclusion criteria** • Contraindications for taking cyproterone acetate or combined oral contraceptive. • Minoxidil therapy < 3 months preceding the study. • Postmenopausal women. • < 6 months postpartum. • Presenting with male-pattern alopecia. • Alopecia associated with hypothyroidism. • Hyperprolactinaemia. • Cushing's disease or syndrome. • Major iron deficiencies. • Hormone treatment, including oral contraceptives, < 3 months immediately prior to investigation. **Randomised** 66 participants were randomised (minoxidil group = 33, CPA group = 33) **Withdrawals/losses to follow-up** There were 14/66 (21.2%) withdrawals/losses to follow-up: 6/33 (18%) in the minoxidil group, and 8/33 (24.2%) in the CPA group • 1 in each group before start of treatment. • Minoxidil group: 3 due to the restrictive nature of treatment, 1 due to mastodynia,1 due to nausea. • CPA group: 2 due to dyspareunia, 2 due to weight gain, 1 due to migraine headache, 2 no reasons given. **Baseline data** Degree of thinning Ludwig scale (participants by grade and group) • Grade I: minoxidil group = 20, CPA group = 15. • Grade II: minoxidil group = 8, CPA group = 12. • Grade III: minoxidil group = 2, CPA group = 0. Mean duration of alopecia • 5.5 ± 4.2 years. Presence of acne, hirsutism, or both • Minoxidil group = 70%, CPA group = 61%. Menstrual cycle irregularities • Minoxidil group = 61%, CPA group = 58%.

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Vexiau 2002 *(Continued)*

Interventions	**Intervention** • Topical minoxidil 2% 1mL twice daily in association with combined oral contraceptive consisting of ethinyl oestradiol 30 µg and gestodene 75 µg/day for 21 of 28 days. Repeated for 12 cycles. **Comparator** • Cyproterone acetate 50 mg/day for 20 of 28 days, plus a combination of ethinyl oestradiol 35 µg and cyproterone acetate, 2 mg/day for 21 of 28 days. Repeated for 12 cycles.
Outcomes	Assessments (3)**:** at baseline, 6 months, and 12 months **Primary outcomes** (as reported) • Number of hairs > 40 µm in diameter measured with phototrichogram.[1] **Secondary outcomes** (as reported) • Total number of hairs.[1] • Number of hairs in the anagen and telogen phases. • Participant assessment (VAS) of cosmetic effectiveness of treatment (hair loss and degree of seborrhoea at the beginning and end of the study).[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared, after e-mail contact. "The study was sponsored by Schering Laboratories."
Declaration of interest	None declared
Notes	The trial authors did not provide baseline data for all randomised participants. women with hyperandrogenic profile included. The trial authors provided intergroup data as well as intragroup (women with versus women without hyperandrogenism), although they did not specify this in the methods section.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 993): "Patients were randomly assigned to one of two groups with stratification every six patients." Comment: this appeared to be block (6) randomisation. This was probably done.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement of risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open. The nature of the treatment interventions precludes any possibility of blinding of participants and personnel. Comment: the outcome or outcome measurement is likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 993): "Upon completion of the study, all phototrichograms were read in a blind manner by two independent dermatologists. Conflicting results between the two primary dermatologists were agreed with a third dermatologist."

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Vexiau 2002 *(Continued)*

		However, participant assessments are likely to be influenced by lack of blinding. Comment: we judged this as at an unclear risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (page 993): "We had intended to analyse only the results of patients who fully completed the study; however, in cases in which the final measurements at M12 were not carried out, the last documented measurement after day zero (M6) was taken as the final measurement." Quote (page 993): "We were able to analyse the results obtained from the last measurement in 58 of the 66 patients (30 in the CPA group and 28 in the minoxidil group), who were evaluated at least once in addition to d0. A total of 12 patients left the study after the beginning of the treatment, 7 in the CPA group and 5 in the minoxidil group." Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was unavailable, but the trial authors appear to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Whiting 1992

Methods	This was a randomised, double-blind, placebo-controlled trial **Setting** Departments of Dermatology and Pediatrics, University of Texas, Dallas, Texas; and the Baylor Hair Research and Treatment Center, Baylor University Medical Center, Dallas, Texas, USA **Date of study** Unspecified (32-week duration)
Participants	33 women Mean age (range) = 34 years (20 to 44) **Inclusion criteria** • Good general health; no evidence of cardiac, scalp, systemic, or psychiatric disease. • No previous treatment with topical minoxidil solution. **Exclusion criteria** • Pregnancy or risk of pregnancy. • A postpartum period < 12 months. • Breast-feeding. • Use within the preceding 3 months: hair restorers or systemic drugs, e.g. anticonvulsants, antihypertensives, ß-blockers, cimetidine, cyclosporine, cyproterone acetate, cytotoxic compounds, diazoxide, oestrogens or progesterones, ketoconazole, spironolactone, steroids, and vasodilators. **Randomised** 33 participants were randomised (minoxidil group = 17, placebo group = 16)

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Whiting 1992 *(Continued)*

	Withdrawals/losses to follow-up Because of other health problems, relocation, or noncompliance with follow-up 2 withdrew/were lost to follow-up in the minoxidil group and 3 in the placebo group **Baseline data** Mean duration of hair loss • 7.25 years (range = 6 months to 25 years). Degree of thinning Ludwig scale (participants by grade and group) • Grade I: minoxidil group = 13, placebo group = 9. • Grade II: minoxidil group = 4, placebo group = 7.
Interventions	**Intervention** • Minoxidil 2% solution. 1 mL twice daily to the scalp for 32 weeks. **Comparator** • Vehicle. 1 mL twice daily to the scalp for 32 weeks.
Outcomes	Assessment was every 4 weeks. **Outcomes** (as reported) • Hair counts: macro-photograph pre-defined tattooed area and count with Quantimet 920 Image Analyzer Cambridge Instrument, Cambridge, MA.[1] • Overall growth: a global photograph of the affected area.[1] • Regrowth: investigator- and participant-assessed (subjective).[1] • Participant-assessed hair shedding between visits.[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	Adverse events were not an outcome, but the trial reported that local side-effects were not severe, and no participants stopped using the medication because of irritation (page 803)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 801): "randomized". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 801): "double-blind".

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Whiting 1992 *(Continued)*

All outcomes		The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit clear a judgement of the risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a low number (5/33) of dropouts: 2 in the minoxidil group and 3 in the placebo group. Reasons were reported and balanced across groups. The data analysis was per-protocol. Comment: we judged this as at a low risk of bias.
Selective reporting (reporting bias)	Unclear risk	The study protocol was unavailable. Quote (page 802): "The investigator and patient subjectively evaluated visible hair regrowth." Comment: No data were reported for these participant- and investigator-subjective assessments of hair, only that these "correlated poorly with the actual hair counts in the test area." The primary outcomes for this review were under-reported, so judged this as at unclear risk of bias.
Other bias	Unclear risk	The potential impact of the wide range in duration (6 months to 25 years) of hair loss at baseline was unclear. Comment: there was insufficient information to permit a clear judgement of the risk of bias.

Whiting 1999

Methods	This was a randomised, placebo-controlled trial (phase II study) **Setting** Multicentre, USA **Date of study** Unspecified (12-month duration)
Participants	137 women Age = 41 to 60 years **Inclusion criteria** • Postmenopausal women with AGA. **Exclusion criteria** • Nothing was reported. **Randomised**

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Whiting 1999 *(Continued)*

	137 participants were randomised. Data including information on allocation was only available for 94 (finasteride group = 44, placebo group = 50) participants who underwent biopsy at baseline and 12 months **Withdrawals/losses to follow-up** 43/137 (31.3%) participants were not analysed, and the reasons for why there was no biopsy (baseline, 12 months) were unreported **Baseline data** Total terminal anagen hairs (SD) • Finasteride group = 17.6 (1.1), placebo group = 17.8 (1.1). Total terminal telogen hairs (SD) • Finasteride group = 2.9 (0.3), placebo group = 3.1 (0.3). Total terminal hairs (SD) • Finasteride group = 20.5 (1.2), placebo group = 20.9 (1.1). Total vellus or miniaturised hairs (SD) • Finasteride group = 11.9 (1.1), placebo group = 11.0 (0.9). Total terminal and vellus hairs (SD) • Finasteride group = 32.4 (1.5), placebo group = 31.9 (1.2). Ratio (± SE) anagen/telogen • Finasteride group = 6.1 (0.7), placebo group = 5.7 (0.7). Ratio (± SE) terminal/vellus • Finasteride group = 1.7 (0.2), placebo group = 1.9 (0.2).
Interventions	**Intervention** • Finasteride 1 mg/day. Duration of 12 months. **Comparator** • Placebo. Duration of 12 months.
Outcomes	Assessments (2): at baseline and 12 months **Outcomes** (as reported) 1. Scalp biopsy: all terminal hair bulbs; terminal anagen, catagen, and telogen hairs; vellus hairs and vellus-like hairs (miniaturised); stelae (streamers); and follicular units counted.[1] [1]Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	—
Risk of bias	

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Whiting 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 282): "137 patients randomized". Comment: the trial authors did not report the method used to generate the allocation sequence in sufficient detail to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Comment: there was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The report did not provide any detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 282): "Horizontal sections of reticular and papillary dermis were read by one observer blinded to patient, treatment and time." Comment: this was probably done.
Incomplete outcome data (attrition bias) All outcomes	High risk	The dropout rate was > 30%; the reasons were not stated. The data analysis was per-protocol. Comment: the large number of dropouts (> 30%), incomplete outcome data, and inappropriate analysis were potential sources of bias.
Selective reporting (reporting bias)	Low risk	The study protocol was unavailable, but the study appears to have reported the prespecified outcomes and those mentioned in the methods section. Comment: we judged this as at a low risk of bias.
Other bias	Low risk	Comment: the study appeared to be free of other forms of bias.

Abbreviations: AGA: androgenetic alopecia; CPA: cyproterone acetate; RCT: randomised controlled trial; FPHL: female pattern hair loss.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahn 2006	This was a non-randomised controlled trial (RCT).
Bazzano 1986	This was a controlled clinical trial (CCT).
Bezzola 2009	This was a quasi-randomised CCT study (3 groups, each with 15 men and 15 women). In van Zuuren 2012, the former version of the review, we excluded the study because there were no separate data for men and women, but should excluded it for being a CCT.
Califano 1991	This was published in Italian; the language abstract was in English, and the study only included male participants.
Caserini 2013	The study only included male participants.

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Study	Reason for exclusion
DDI 2008	This was a non-RCT. All women received the same treatment.
Dhurat 2013	The study only included male participants.
Enshaieh 2005	Mona Nasser translated this study from Farsi into English (see Acknowledgements). The full study is available in Farsi: Journal of Arak University of Medical Sciences 2003; 6(23)):1-6.IRANMEDEX http://www.iranmedex.com/English/ (accessed 29 March 2011). The study only included male participants.
Farella 1991	The Italian Cochrane Centre translated and assessed this study, but it was a CCT, so we excluded it.
Fisher 2012	The study describes five studies, but none is a RCT.
Golpour 2013	ZF translated this study, which only included male participants.
Greenberg 1996	This study only included male participants.
Gómez Grau 2015	This was a non-RCT.
Inui 2007	This study only included male participants.
Kohler 2007	This was a non-RCT (retrospective study).
Lee 2013a	This was a non-RCT (case-series).
Lee 2015	This was a non-RCT.
Li 1996	This was a quasi-randomised (CCT) study, which assigned participants into two treatment groups by odd-even visit number.
Moftah 2013	This was a CCT (quasi-randomised).
Navadeh 2002	This was a CCT (quasi-randomised).
Orfanos 1980	This study included both male and female participants (9), but there was no separate analysis. The study is more than 35 years old, so it was unlikely that we would receive individual patient data.
Panahi 2015	This study only included male participants.
Peereboom-Wynia 1989	This was a non-RCT.
Piérard 1996	This was a non-RCT.
Piérard-Franchimont 1998	This study only included male participants.
Prager 2002	This study only included male participants.
Rinaldi 2006	Allocation was by alternation on arrival. There was an inadequate method of sequence generation, which allows for knowledge of intervention assignment among those recruiting participants to the study. It was quasi-randomised.
Roberts 1987	Although this was a RCT, the study randomised 60 participants, but only included 1 woman (with male pattern baldness).
Satino 2003	This was a CCT.

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Study	Reason for exclusion
Sinclair 2002	Allocation was according to month of birth, so the study was a CCT (quasi-randomised). The study used an inadequate method of sequence generation.
Sinclair 2005	This study used the same data set as Sinclair 2002. It was a non-RCT.
Sisto 2013	The study only included male participants.
Slaught 2013	This was a non-RCT (case-series). Retrospective cohort, chart review, study.
Takeda 2014	The study only included male participants.
Yang 2002	The study only included male participants.

Abbreviations: RCT: randomised controlled trial; CCT: controlled clinical trial (quasi-randomised).

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01292746

Methods	This is a RCT
Participants	**Inclusion criteria** • 70 women with androgenetic alopecia (18 to 60 years).Notable hair loss/thinning onset within the past 5 years. • Progressive/active hair loss/thinning within the last 12 months. • Skin type I through IV according to the Fitzpatrick Skin Type Scale. • Healthy, balanced scalp, determined as one that shows no indication of notable: dryness, flaking, dandruff (pityriasis), redness, irritation, inflammation, itching, greasy/oily texture, odour, lesions, scalp acne, or other significant dermatological conditions. • PI or P2 on the American Society of Anesthesiologists (ASA) Physical Status Classification System. • Willing and able to maintain same hair style, length, colour, and hair care regimen throughout study participation. **Exclusion criteria** • Hair loss attributable to one or more of the following conditions: tinea capitis, secondary syphilis, discoid lupus erythematosus: Inflammation, alopecia areata, trichotillomania, telogen effluvium, anagen effluvium, traumatic alopecia. • Use of any of the following medications presently or during the prior 6 months: minoxidil, finasteride (or any other 5α-reductase inhibitor medications), medication with anti-androgenic properties (e.g. cyproterone, spironolactone, ketoconazole, flutamide and bicalutamide), topical estrogens, progesterone, tamoxifen, anabolic steroids, medications that can potentially cause hypertrichosis (e.g. ciclosporin, diazoxide, phenytoin, and psoralens), oral glucocorticoids (inhaled glucocorticoids permitted), lithium, phenothiazines • Current use of other prescription or over-the-counter products known to affect hair growth and distribution (e.g. saw palmetto, fish oil, corticosteroids, antineoplastic agents, beta blockers, diazoxide, heparin, verapamil, warfarin, etc.), or both. • Medical, physical, or other contraindications for, or sensitivity to, light therapy (e.g. porphyria, photo sensitizing drug therapies). • Taking hormonal replacement therapy. • Conditions that may worsen with light therapy. • History of poor wound healing. • History of keloid formation. • Prior hair restoration/transplantation surgery.

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NCT01292746 *(Continued)*

	• Prior scalp reduction procedure(s). • Other surgery to the scalp region (e.g. to remove a skin cancer lesion). • Active skin infection, wound, or other external trauma to the scalp evaluation area. • Active malignancy or any malignancy in the past five years in the scalp evaluation area. • Dermatological condition (dermatitis, eczema, psoriasis, etc.) of the scalp other than FPHL • Significant scarring (e.g. from burns) in the scalp evaluation area. • History of thyroid condition that may influence hair growth and loss. • Underlying medical condition(s) known to adversely affect hair growth or hair pattern, such as HIV, connective tissue disease, inflammatory bowel disease. • Current hair weaves. • Use of non-breathable wigs. • Hairstyle is a "buzz" cut, defined as hair cut to < 1 inch in length. • Tattooing of the scalp target evaluation area. • Participant is pregnant, nursing, planning a pregnancy, or less than 6 months postpartum. • Serious mental health illness such as dementia or schizophrenia; psychiatric hospitalization in the past 2 years. • Developmental disability or cognitive impairment that would preclude adequate comprehension of the informed consent form and/or ability to record study measurements. • Involvement in litigation/receiving disability benefits related in any way to the parameters of the study. • Participation in research in the past 30 days.
Interventions	• Erchonia® ML Scanner (MLS) (low level laser scanner) device. • Placebo device.
Outcomes	**Primary outcomes** • Per cent change in non-vellus terminal hair count across a 3 cm diameter scalp area **Secondary outcomes** • Stage on the Ludwig-Savin hair loss classification scale for female AGA. • Participant global assessment of new hair growth. • Investigator global assessment of new hair growth. • Participant satisfaction with procedure outcomes ratings.
Notes	We accessed the website on 24 July 2015. Last updated April 2013. This study has been terminated. (Recruitment and participant study compliance was difficult)

NCT01451021

Methods	This is a investigator-blind RCT
Participants	**Inclusion criteria** • 21 male and female volunteers 18 to 65 years old, inclusive. • Hair loss consistent with ≥ Grade III-Vertex, IV, VA, V, and VI, based on Norwood-Hamilton Scale providing there is bridging of hair in the anterior edge of the vertex circle. • Have no clinically significant disease or abnormal laboratory results taken at the screening visit. **Exclusion criteria** • Known sensitivity to DMEM/F-12 or any component of the study material. • Known hypersensitivity to clindamycin hydrochloride, amphotericin B or streptomycin sulfate.

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NCT01451021 *(Continued)*

	• Participants who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening. • A history of drug or alcohol abuse within 1 year of study enrolment. • Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator. • Any clinically significant abnormal laboratory parameters. • A positive result at screening for HIV 1 or 2, Hepatitis B or C, HTLV I/II. • Dermatological condition in donation or study areas, or both. • Prior surgery in the treatment area. • Insufficient hair or scarring in the donor area that might impact cell growth. • Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematological, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or central nervous system (CNS) function; or any condition that would place the participant at increased risk.
Interventions	• A piece of occipital scalp is taken from the participant. The epidermal and dermal cells from this tissue are expanded in culture. The cells are then harvested and, for certain types of product, combined. These cells are then injected into the balding area of the scalp of the original participant. • Dermal cells only.
Outcomes	**Primary outcomes** • Change from baseline in hair number. • Change from baseline in hair width. • Time course of any treatment benefit.
Notes	We accessed the website on 4 August 2015, which was last updated on 28 February 2012. The study has been completed

NCT01451047

Methods	This is a investigator-blind RCT
Participants	**Inclusion criteria** • 31 male and female volunteers 18 to 65 years old, inclusive. • Hair loss consistent with ≥ Grade III-Vertex, IV, VA, V, and VI, based on Norwood-Hamilton Scale providing there is bridging of hair in the anterior edge of the vertex circle. • Have no clinically significant disease or abnormal laboratory results taken at the screening visit. **Exclusion criteria** • Known sensitivity to DMEM/F-12 or any component of the study material. • Known hypersensitivity to clindamycin hydrochloride, amphotericin B, or streptomycin sulfate. • Participants who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening. • A history of drug or alcohol abuse within 1 year of study enrolment. • Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator. • Any clinically significant abnormal laboratory parameters. • A positive result at screening for HIV 1 or 2, Hepatitis B or C, HTLV I/II. • Dermatological condition in donation or study areas, or both. • Prior surgery in the treatment area.

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NCT01451047 *(Continued)*

	• Insufficient hair or scarring in the donor area that might impact cell growth. • Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or CNS function; or any condition that would place the participant at increased risk.
Interventions	• A piece of occipital scalp is taken from the participant. The epidermal and dermal cells from this tissue are expanded in culture. The cells are then harvested and, for certain types of product, combined. These cells are then injected into the balding area of the scalp of the original participant. • Dermal cells only.
Outcomes	**Primary outcomes** • Change from baseline in hair number. • Change from baseline in hair width. • Time course of any treatment benefit.
Notes	We accessed the website on 4 August 2015, which was last updated on 28 February 2012. The study has been completed

NCT01451073

Methods	This is a investigator-blind RCT
Participants	**Inclusion criteria** • 33 male and female volunteers 18 to 65 years old, inclusive. • Hair loss consistent with ≥ Grade III-Vertex, IV, VA, V, and VI, based on Norwood-Hamilton Scale providing there is bridging of hair in the anterior edge of the vertex circle. • Have no clinically significant disease or abnormal laboratory results taken at the screening visit. **Exclusion criteria** • Known sensitivity to DMEM/F-12 or any component of the study material. • Known hypersensitivity to clindamycin hydrochloride, amphotericin B, or streptomycin sulfate. • Participants who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening. • A history of drug or alcohol abuse within 1 year of study enrolment. • Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator. • Any clinically significant abnormal laboratory parameters. • A positive result at screening for HIV 1 or 2, Hepatitis B or C, HTLV I/II. • Dermatological condition in donation or study areas, or both. • Prior surgery in the treatment area. • Insufficient hair or scarring in the donor area that might impact cell growth. • Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or CNS function; or any condition that would place the participant at increased risk.
Interventions	• Injection of ex vivo expanded cultured autologous occipital dermal and epidermal cells (same day as cell culture harvest) into the balding scalp. • Repeat injections of ex vivo expanded cultured autologous occipital dermal and epidermal cells (same day as cell culture harvest) into the balding scalp.
Outcomes	**Primary outcomes**

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NCT01451073 *(Continued)*

	• Change from baseline in hair number. • Change from baseline in hair width. • Time course of any treatment benefit.
Notes	We accessed the website on 4 August 2015, which was last updated on 28 February 2012. The study has been completed

NCT01451099

Methods	This is a investigator-blind RCT
Participants	**Inclusion criteria** • 21 male and female volunteers 18 to 65 years old, inclusive. • Hair loss consistent with ≥ Grade III-Vertex, IV, VA, V, and VI, based on Norwood-Hamilton Scale providing there is bridging of hair in the anterior edge of the vertex circle. • Have no clinically significant disease or abnormal laboratory results taken at the screening visit. **Exclusion criteria** • Known sensitivity to DMEM/F-12 or any component of the study material. • Known hypersensitivity to clindamycin hydrochloride, amphotericin B or streptomycin sulfate. • Participants who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening. • A history of drug or alcohol abuse within 1 year of study enrolment. • Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator. • Any clinically significant abnormal laboratory parameters. • A positive result at screening for HIV 1 or 2, Hepatitis B or C, HTLV I/II. • Dermatological condition in donation or study areas, or both. • Prior surgery in the treatment area. • Insufficient hair or scarring in the donor area that might impact cell growth. • Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or CNS function; or any condition that would place the participant at increased risk.
Interventions	• Autologous cultured dermal cells, a piece of occipital scalp is taken from the participant. The dermal cells from this tissue are expanded in culture. The cells are then harvested. These cells are then injected into the balding area of the scalp of the original participant. • Comparator not stated.
Outcomes	**Primary outcomes** • Change from baseline in hair number. • Change from baseline in hair width. • Time course of any treatment benefit.
Notes	We accessed the website on 4 August 2015, which was last updated on 28 February 2012. The study has been completed

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NCT01451112

Methods	This is a investigator-blind RCT
Participants	**Inclusion criteria** • 30 male and female volunteers 18 to 65 years old, inclusive. • Hair loss consistent with ≥ Grade III-Vertex, IV, VA, V, and VI, based on Norwood-Hamilton Scale providing there is bridging of hair in the anterior edge of the vertex circle. • Have no clinically significant disease or abnormal laboratory results taken at the screening visit. **Exclusion criteria** • Known sensitivity to DMEM/F-12 or any component of the study material. • Known hypersensitivity to clindamycin hydrochloride, amphotericin B or streptomycin sulfate. • Participants who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening. • A history of drug or alcohol abuse within 1 year of study enrolment. • Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator. • Any clinically significant abnormal laboratory parameters. • A positive result at screening for HIV 1 or 2, Hepatitis B or C, HTLV I/II. • Dermatological condition in donation or study areas, or both. • Prior surgery in the treatment area. • Insufficient hair or scarring in the donor area that might impact cell growth. • Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematological, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or CNS function; or any condition that would place the participant at increased risk.
Interventions	• A piece of occipital scalp is taken from the participant. The epidermal and dermal cells from this tissue are expanded in culture. The cells are then harvested and, for certain types of product, combined. These cells are then injected into the balding area of the scalp of the original participant. • Dermal cells only.
Outcomes	**Primary outcomes** • Change from baseline in hair number. • Change from baseline in hair width. • Time course of any treatment benefit.
Notes	We accessed the website on 4 August 2015, which was last updated in July 2013. The study has been completed

NCT01451125

Methods	This is a investigator-blind RCT
Participants	**Inclusion criteria** • 43 male and female volunteers 18 to 65 years old, inclusive. • Hair loss consistent with ≥ Grade III-Vertex, IV, VA, V, and VI, based on Norwood-Hamilton Scale providing there is bridging of hair in the anterior edge of the vertex circle. • Have no clinically significant disease or abnormal laboratory results taken at the screening visit. • Agree to abstain from use of any hair growth affecting oral or topical medication including over the counter and herbal medications, finasteride or dutasteride during the course of this study (other than minoxidil as required in this study).

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NCT01451125 *(Continued)*

	Exclusion criteria • Known sensitivity to DMEM/F-12 or any component of the study material. • Known hypersensitivity to clindamycin hydrochloride, amphotericin B, or streptomycin sulfate. • Participants who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening. • A history of drug or alcohol abuse within 1 year of study enrolment. • Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator. • Any clinically significant abnormal laboratory parameters. • A positive result at screening for HIV 1 or 2, Hepatitis B or C, HTLV I/II. • Dermatologic condition in donation or study areas, or both. • Prior surgery in the treatment area. • Insufficient hair or scarring in the donor area that might impact cell growth. • Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematological, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or CNS function; or any condition that would place the participant at increased risk. • Hypersensitivity to minoxidil or the ingredients in the topical solution or foam formulations.
Interventions	• A piece of occipital scalp is taken from the participant. The epidermal and dermal cells from this tissue are expanded in culture. The cells are then harvested and, for certain types of product, combined. These cells are then injected into the balding area of the scalp of the original participant and synergy with application of topical minoxidil. • Dermal cells and synergy with application of topical minoxidil (not totally clear).
Outcomes	**Primary outcomes** • Change from baseline in hair number. • Change from baseline in hair width. • Time course of any treatment benefit. **Secondary outcomes** • Effect of minoxidil.
Notes	We accessed the website on 4 August 2015, which was last updated in July 2013. This study has been completed

NCT01451138

Methods	This is a investigator-blind RCT
Participants	**Inclusion criteria** • 40 male and female volunteers 18 to 65 years old, inclusive. • Hair loss consistent with ≥ Grade III-Vertex, IV, VA, V, and VI, based on Norwood-Hamilton Scale providing there is bridging of hair in the anterior edge of the vertex circle. • Able to provide informed consent after risks and benefits of the study have been explained. • Be willing to undergo all study procedures. • Ability to communicate effectively with study personnel. • Have no clinically significant disease or abnormal laboratory evaluations taken at the screening visit.

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NCT01451138 *(Continued)*

	• Agree to abstain from use of any hair growth affecting oral or topical medication including over the counter and herbal medications, minoxidil, finasteride or dutasteride during the course of this study. **Exclusion criteria** • Known sensitivity to DMEM/F-12 or any component of the study material • Known hypersensitivity to clindamycin hydrochloride, amphotericin B or streptomycin sulfate. • Participants who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening. • A history of drug or alcohol abuse within 1 year of study enrolment. • Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator. • Any clinically significant abnormal laboratory parameters. • A positive result at screening for HIV 1 or 2, Hepatitis B or C, HTLV I/II. • Dermatologic condition in donation or study areas, or both. • Prior surgery in the treatment area. • Insufficient hair or scarring in the donor area that might impact cell growth. • Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematological, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or CNS function; or any condition that would place the participant at increased risk.
Interventions	• A piece of occipital scalp is taken from the participant. The epidermal and dermal cells from this tissue are expanded in culture. The cells are then harvested and, for certain types of product, combined. These cells are then injected into the balding area of the scalp of the original participant. • Dermal cells only.
Outcomes	**Primary outcomes** • Change from baseline in hair number. • Change from baseline in hair width. • Time course of any treatment benefit.
Notes	We accessed the website on 4 August 2015, which was last updated in July 2013. This study has been completed

NCT01451151

Methods	This is a investigator-blind RCT
Participants	**Inclusion criteria** • 33 male and female volunteers 18 to 65 years old, inclusive. • Hair loss consistent with ≥ Grade III-Vertex, IV, VA, V, and VI, based on Norwood-Hamilton Scale providing there is bridging of hair in the anterior edge of the vertex circle. • Able to provide informed consent after risks and benefits of the study have been explained. • Be willing to undergo all study procedures. • Ability to communicate effectively with study personnel. • Have no clinically significant disease or abnormal laboratory evaluations taken at the screening visit. • Agree to abstain from use of any hair growth affecting oral or topical medication including over the counter and herbal medications, minoxidil, finasteride, or dutasteride during the course of this study.

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NCT01451151 *(Continued)*

	Exclusion criteria • Known sensitivity to DMEM/F-12 or any component of the study material. • Known hypersensitivity to clindamycin hydrochloride, amphotericin B or streptomycin sulfate. • Participants who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening. • A history of drug or alcohol abuse within 1 year of study enrolment. • Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator. • Any clinically significant abnormal laboratory parameters. • A positive result at screening for HIV 1 or 2, Hepatitis B or C, HTLV I/II. • Dermatologic condition in donation or study areas, or both. • Prior surgery in the treatment area. • Insufficient hair or scarring in the donor area that might impact cell growth. • Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematological, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or CNS function; or any condition that would place the participant at increased risk.
Interventions	• A piece of occipital scalp is taken from the participant. A mixed population of dermal cells from this tissue are expanded in culture. The cells are then harvested. These cells are then injected into the balding area of the scalp of the original participant. • Comparator not stated.
Outcomes	**Primary outcomes** • Change from baseline in hair number. • Change from baseline in hair width. • Time course of any treatment benefit.
Notes	We accessed the website on 4 August 2015, which was last updated in July 2013. This study has been completed

NCT01451177

Methods	This is a investigator-blind RCT
Participants	**Inclusion criteria** • 43 male and female volunteers 18 to 65 years old, inclusive. • Hair loss consistent with ≥ Grade III-Vertex, IV, VA, V, and VI, based on Norwood-Hamilton Scale providing there is bridging of hair in the anterior edge of the vertex circle. • Able to provide informed consent after risks and benefits of the study have been explained. • Be willing to undergo all study procedures. • Ability to communicate effectively with study personnel. • Have no clinically significant disease or abnormal laboratory evaluations taken at the screening visit. • Agree to abstain from use of any hair growth affecting oral or topical medication including over the counter and herbal medications, minoxidil, finasteride or dutasteride during the course of this study. **Exclusion criteria** • Known sensitivity to DMEM/F-12 or any component of the study material. • Known hypersensitivity to clindamycin hydrochloride, amphotericin B, or streptomycin sulfate.

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NCT01451177 *(Continued)*

	• Participants who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening. • A history of drug or alcohol abuse within 1 year of study enrolment. • Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator. • Any clinically significant abnormal laboratory parameters. • A positive result at screening for HIV 1 or 2, Hepatitis B or C, HTLV I/II. • Dermatologic condition in donation or study areas, or both. • Prior surgery in the treatment area. • Insufficient hair or scarring in the donor area that might impact cell growth. • Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematological, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or CNS function; or any condition that would place the participant at increased risk.
Interventions	• A piece of occipital scalp, plucked of hairs prior to excision, is taken from the participant. The epidermal and dermal cells from this tissue are expanded in culture. The cells are then harvested and, for certain types of product, combined. The cells are then injected into the balding area of the scalp of the original participant. • Dermal cells only
Outcomes	**Primary outcomes** • Change from baseline in hair number. • Change from baseline in hair width. • Time course of any treatment benefit.
Notes	We accessed the website on 4 August 2015, which was last updated in July 2013. This study has been completed

NCT01451190

Methods	This is a investigator-blind RCT
Participants	**Inclusion criteria** • 88 male and female volunteers 18 to 65 years old, inclusive. • Hair loss consistent with ≥ Grade III-Vertex, IV, VA, V, and VI, based on Norwood-Hamilton Scale providing there is bridging of hair in the anterior edge of the vertex circle. • Able to provide informed consent after risks and benefits of the study have been explained. • Be willing to undergo all study procedures. • Ability to communicate effectively with study personnel. • Have no clinically significant disease or abnormal laboratory evaluations taken at the screening visit. • Agree to abstain from use of any hair growth affecting oral or topical medication including over the counter and herbal medications, minoxidil, finasteride or dutasteride during the course of this study. **Exclusion criteria** • Known sensitivity to DMEM/F-12 or any component of the study material. • Known hypersensitivity to clindamycin hydrochloride, amphotericin B, or streptomycin sulfate. • Participantss who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening.

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NCT01451190 *(Continued)*

	• A history of drug or alcohol abuse within 1 year of study enrolment. • Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator. • Any clinically significant abnormal laboratory parameters. • A positive result at screening for (HIV 1 or 2, Hepatitis B or C, HTLV I/II. • Dermatologic condition in donation or study areas, or both. • Prior surgery in the treatment area. • Insufficient hair or scarring in the donor area that might impact cell growth. • Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematological, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or CNS function; or any condition that would place the participant at increased risk.
Interventions	• A piece of occipital scalp is taken from the participant. A mixed population of dermal cells from this tissue are expanded in culture. The cells are then harvested. These cells are then injected into the balding area of the scalp of the original participant. • Comparator not stated.
Outcomes	**Primary outcomes** • Change from baseline in hair number. • Change from baseline in hair width. • Time course of any treatment benefit.
Notes	We accessed the website on 4 August 2015, which was last updated on July 2013. This study has been completed

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12607000027415

Trial name or title	Double blind placebo controlled trial into the treatment of female pattern hair loss with spironolactone and minoxidil
Methods	This is a randomised controlled trial (RCT)
Participants	**Inclusion criteria** • Women from 18 to 40 years with diagnosis of female pattern hair loss (FPHL), with a hair loss greater than 6 months with biopsy-proven follicle miniaturisation.
Interventions	• Control group = oral spironolactone 200 mg/day plus topical placebo once a day. • Experimental group = oral spironolactone 200 mg/day plus 2% topical minoxidil. Both groups are treated for 12 months.
Outcomes	**Primary outcomes** • Hair counts (measured at baseline and at 6-month intervals). **Secondary outcomes** • Mid-scalp clinical grading system. • Participant self-evaluation of hair density.
Starting date	1 February 2007

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ACTRN12607000027415 *(Continued)*

Contact information	Dr. A Yazdabadi (yazdaa27@gmail.com) Department of Dermatology St Vincent's Hospital Fitzroy Australia Telephone: (03) 9288 2211, yazdaa27@gmail.com
Notes	At 24 July 2015, the trial was "not yet recruiting". Contact: Rod.SINCLAIR@svhm.org.au

EUCTR2013-002740-85-ES

Trial name or title	A Pilot Randomized, Double-blind, Placebo-controlled Clinical Trial to Obtain Preliminary Data on Efficacy and Safety in the Application of PRGF-Endoret by Mesotherapy, in the Treatment of Male and Female Androgenetic Alopecia of Over 6 Months Duration
Methods	This is a double-blind randomised placebo-controlled trial
Participants	**Inclusion criteria** • 24 women and men (18 to 64 years) with androgenetic alopecia (if male, have Norwood-Hamilton classifications of II-VI male pattern baldness, If female, have Ludwig Scale classifications I-II. **Exclusion criteria** • No androgenetic alopecia. • Telogen and anagen effluvium. • Active inflammation or infection in the intervention area. • Presence of active systemic infections. • Background of cancerous or precancerous lesions. • Background of connective or rheumatic diseases. • Suffering from any serious blood disorders. • To have undergone treatments for alopecia in the previous 6 months. • Previous hair implants. • Intake of drugs that affect hair loss. • Be undergoing immunosuppressive therapy, or anticoagulants, or both. • Known intolerance to mesotherapy. • Taking contraceptives containing cyproterone acetate. • Pregnancy. • In general, any limitations that would prevent the proper application of both treatments and the right monitoring of the efficacy variable.
Interventions	• Plasma rich in growth factors (PRGF-Endoret). • Saline solution.
Outcomes	**Primary outcomes** • Change from baseline in hair density at three months (number of hairs per cm^2). **Secondary outcomes**

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EUCTR2013-002740-85-ES *(Continued)*

	• Hair width (µm). • Anagen/telogen ratio. • Terminal hair density. • Vellus hair density.
Starting date	11 February 2014
Contact information	virginia.cuadrado@bti-implant.es
Notes	It looks exactly like NCT01885676 and has the same sponsor, but has different contact people

NCT00175617

Trial name or title	Efficacy of Therapy With the Anti-androgen Spironolactone Compared to Topical Minoxidil in Female Pattern Hair Loss
Methods	This is a open-label RCT
Participants	**Inclusion criteria** • Women aged 18 to 75 years with a diagnosis of FPHL. **Exclusion criteria** • Androgen excess. • Other scalp or hair disorders. • Contraindications to spironolactone treatment, especially pregnancy, electrolyte imbalances, history of breast cancer, or intake of interfering drugs. • Contraindications to minoxidil treatment, especially patients who are allergic to this treatment or have a history of low blood pressure or irregular heart beats.
Interventions	• Oral spironolactone. • Topical minoxidil.
Outcomes	**Primary outcomes** • Hair density (measured at baseline, and after 3, 6, and 9 months) **Secondary outcomes** • Percentage of participants who experience side-effects. • Participant assessment of treatment effect.
Starting date	September 2005
Contact information	Andreas Finner UBC Division of Dermatology Hair Research and Treatment Centre Vancouver British Columbia Canada V6G 1Y6

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NCT00175617 *(Continued)*

	Telephone: 604 875 4747, e-mail andreas.finner@vch.ca and Jerry Shapiro jerry.shapiro@vch.ca
Notes	Recruitment status unknown because information has not been verified recently (website accessed 17 July 2015)

NCT00197379

Trial name or title	The Study for New Effect of Roxithromycin on Androgenetic Alopecia
Methods	This is a cross-over, open-label RCT
Participants	**Inclusion criteria** • Women and men older than 20 years with androgenetic alopecia. **Exclusion criteria** • Cicatricial alopecia. • Allergy to roxithromycin. • Children (19 years old or younger). • Pregnant female.
Interventions	• Topical roxithromycin 0.05% lotion. • Placebo.
Outcomes	**Primary outcomes** • No primary outcomes reported **Secondary outcomes** • Pathological study taken from lesional scalp skin
Starting date	May 2005
Contact information	Department of Dermatology Hamamatsu University School of Medicine Hamamatsu Japan 431-3192 E-mail: itoutai@hama-med.ac.jp
Notes	The recruitment status of this study is unknown because the information has not been verified recently; it was last updated in July 2010 (website accessed 17 July 2015). See Table 2

NCT00418249

Trial name or title	Topical AS101 for Treatment of FAGA (Female Androgenetic Alopecia) in Menopause Women
Methods	This is a randomised placebo-controlled trial

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NCT00418249 *(Continued)*

Participants	**Inclusion criteria** • Women aged 50 years or older in menopause, clinically diagnosed for AGA according to Ludwig scale I to II. **Exclusion criteria** • Women treated with chronic medication. • Use of Minoxidil within 3 months prior to entering study. • Women who have underwent hair transplantation. • Use of drugs with androgenic or anti-androgenic effects. • Any other type of hair loss.
Interventions	• Experimental group = topical AS101. • Control group = placebo.
Outcomes	**Primary outcomes** • Hair density. **Secondary outcomes** • Hair diameter. • Anagen/telogen ratio. • Hair growth rate. • Global photographic assessment according to female Ludwig scale. • Self-administered satisfaction questionnaire.
Starting date	January 2007
Contact information	Raziel Lurie, MD, rlurie@bezeqint.net or Danny Ben Amitai danb@clalit.org.il
Notes	The recruitment status of this study is unknown because the information has not been verified recently (website accessed 17 July 2015). We received no response from the contact person

NCT01286649

Trial name or title	Safety and Efficacy Study of Human Autologous Hair Follicle Cells to Treat Androgenetic Alopecia
Methods	This is a double-blind randomised placebo-controlled trial
Participants	**Inclusion criteria** • 19 male or female between the age of 18 and 55 years and in good health having evidence of mild to moderate androgenetic alopecia (AGA) involving the vertex area of the scalp. Female patients with AGA characterized as vertex pattern type II or type III of the Ludwig Scale qualify for inclusion in this study. Males with AGA involving the vertex area of the scalp, characterized as type III vertex-type VI on the Norwood Scale qualify for inclusion in the study. • Willingness to provide written informed consent for participation in the study, attend all study visits and complete all procedures required by this protocol. • The test areas (areas to be injected) are of uniform skin colour without erythema, dark pigmentation, or scars that may confound study results. • Willingness to forego the use cosmetic or medical products for hair loss throughout the course of the study.

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NCT01286649 *(Continued)*

	• Females must be postmenopausal for at least 1 year, surgically sterile, or, if of childbearing potential, using highly-effective methods of birth control. This method of contraception must be used at least 4 weeks prior to and during the entire duration of the clinical trial. **Exclusion criteria** • Use of any product (medication or otherwise) which interferes with the hair growth cycle. • Any systemic medical treatment for hair loss (e.g. finasteride, minoxidil, dutasteride, or antiandrogens) within the last 12 months. • Start of contraception treatments containing chlormadinone or cyproterone acetate within the last 12 months. • Women who are pregnant or nursing. • Presence of any medical condition that influences the hair growth cycle (e.g. alopecia areata, lichen planopilaris, lupus erythematosus, severe seborrhoeic eczema, psoriasis capitis or tinea capitis, untreated thyroid gland disease/goitre development, auto-immune diseases, etc.). • Any condition that, in the investigator's opinion would impact patient safety or a patient's ability to complete all study related procedures, or both (e.g. psychiatric illness, drug addiction, alcoholism, etc.). • Infection with human immunodeficiency virus (HIV), hepatitis, or syphilis. • Participants diagnosed with cancer with or without chemotherapy treatment. • Sudden hair loss within the last 4 months unrelated to normal seasonal hair shedding or AGA. • Participants in the process of or having completed surgical correction of hair loss in the past 24 months. • Participation in a cosmetic and/or pharmaceutical research study.
Interventions	• Human autologous hair follicle cells. • Medium alone.
Outcomes	**Primary outcomes** • Incidence of local adverse events six months postinjection. **Secondary outcomes** • Incidence of local adverse events 12, 24, and 60 months postinjection. • Systemic adverse events. • Histopathological analysis. • Complete safety profile. • Hair growth.
Starting date	December 2010
Contact information	RepliCel Life Sciences, Inc. Principal investigator Nino Lortkipanidze, Scientific Research Institute for Skin and Venereal Diseases, Tbilisi Georgia
Notes	This trial is expected to be completed October 2016. We accessed the website on 29 July 2015. No e-mail address

NCT01662089

Trial name or title	The Efficacy in Treatment of Female Pattern Hair Loss Using 5% Minoxidil Solution Combined With Zinc Supplement

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NCT01662089 *(Continued)*

Methods	This is a double-blind RCT
Participants	**Inclusion criteria** • 20 women with FPHL (Ludwig classification grade 1 and 2). **Exclusion criteria** • Underlying disease; anaemia, diabetes, chronic alcoholism, previous gastrointestinal surgery, short bowel syndrome, Crohn's disease, digestive disorder, hypo/hyperthyroidism, sickle cell disease, autoimmune disease, iron deficiency. • Psychologic disorder trichotillomania. • Diet control. • Pregnancy or lactation. • On supplement diet within 3 months prior to trial.
Interventions	• 15 mg chelate zinc additional to standard 5% minoxidil. • Placebo drug supplement additional to standard 5% minoxidil.
Outcomes	**Primary outcomes** • Compare clinical improvement before and after treatment. • Compare hair density before and after treatment. • Compare average hair shaft diameter before and after treatment. **Secondary outcomes** • Number of patients with side effect.
Starting date	January 2012
Contact information	Rattapon Thuangtong, MD, rattapongthuangtong@yahoo.com Siriraj Hospital Bangkok Thailand
Notes	We accessed the website on 4 August 2015, which was last updated on 7 August 2012

NCT01686295

Trial name or title	24 Week Clinical Trial to Evaluate Safety and Effectiveness of a Hair Growth System to Treat Male and Female Baldness
Methods	This is a double-blind RCT
Participants	**Inclusion criteria** • 100 male or female, 25 to 60 years of age. • If male, have Norwood-Hamilton classifications of IIa to V male pattern baldness. • If female, have Ludwig Scale classifications I-4, II-1, II-2, or frontal. • Are willing to have a tattoo created on the target area. • Have been experiencing active hair loss within the last 12 months. • In the case of females of childbearing potential, are using an acceptable form of birth control (oral/implant/injectable/transdermal contraceptives, intrauterine device, condom with spermicide, diaphragm with spermicide, abstinence or partner's vasectomy: abstinence or partner's vasectomy are acceptable if the female agrees to implement one of the other acceptable methods of birth control if her lifestyle or partner changes). • Have Fitzpatrick Skin Type I-IV. • Are willing to have the target area hair clipped.

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NCT01686295 *(Continued)*

	• Read, understand, and sign a photographic release form(s). • Read, understand, and sign an informed consent document after being advised of the nature of the study. **Exclusion criteria** • Individuals who have used any of the following medications within 6 months prior to enrolment: minoxidil, finasteride (or any other 5α-reductase inhibitor medications); medications with anti-androgenic properties (e.g. cyproterone, spironolactone, ketoconazole, flutamide, and bicalutamide); topical estrogens, progesterone, tamoxifen, anabolic steroids medications that can potentially cause hypertrichosis (e.g. ciclosporin, diazoxide, phenytoin, and psoralens); oral glucocorticoids (inhaled glucocorticoids are permitted); lithium or phenothiazines; medications of known or suspected phototoxicity (eg, tetracyclines, thiazides, certain NSAIDs); other medications which, in the opinion of the investigator, may interfere with the performance of study assessments or place the participant at undue risk. • Will not agree to refrain from changing hair colour and hair style during the course of the study. • Have had a hair transplant, scalp reduction, hair weave, or tattoo which, in the opinion of the investigator, may interfere with the performance of the study assessments. • Are using or have used depilatories, razors, or wax on the scalp to an extent which, in the opinion of the investigator, may interfere with the performance of the study assessments. • Have psoriasis, active dermatitis/eczema, or severe acne on the scalp area. • Have diabetes requiring exogenous insulin. • Have cataracts. • Have any medical condition which, in the opinion of the investigator, could affect hair growth (e.g. HIV, connective tissue disease, inflammatory bowel disease). • Have very little contrast between hair colour and scalp, e.g. are of a fair hair colour (e.g. white or very blond) and have very pale skin. • Are females who are pregnant, planning to become pregnant during the study, or breastfeeding. • Are, in the opinion of the investigative personnel, unable to comprehend or otherwise comply with any aspect of study requirements, or both.
Interventions	• iRestore Hair Rejuvenation System (the device irradiates the scalp with visible light using 5 mW (class 3a) lasers. It is to be used approximately 3 times per week for approximately 30 minutes at each session). • Sham device (it is to be used approximately 3 times per week for approximately 30 minutes at each session).
Outcomes	**Primary outcomes** • Change from Screening/Baseline Hair Growth at Week 12 and Week 24 (standardized global scalp photographs will be taken of each participant prior to hair clipping for hair count macrophotography). **Secondary outcomes** • Visual scalp assessment.
Starting date	July 2012
Contact information	C Andresen, candresen@tklresearch.com J Dosik Jdosik@tklresearch.com
Notes	We accessed the website on 4 August 2015, which was last updated on 12 September 2012

NCT01885676

Trial name or title	Plasma Rich in Growth Factors (PRGF-Endoret) in the Treatment of Androgenetic Alopecia

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NCT01885676 *(Continued)*

Methods	This is a double-blind randomised placebo-controlled trial
Participants	**Inclusion criteria** • 24 men and women with androgenetic alopecia (18 to 65 years) (Ludwig scale I and II, and the Hamilton-Norwood score II-VI). **Exclusion criteria** • No androgenetic alopecia. • Telogen and anagen effluvium. • Active inflammation or infection in the intervention area. • Presence of active systemic infections. • Background of cancerous or precancerous lesions. • Background of connective or rheumatic diseases. • Suffering from any serious blood disorders. • To have undergone treatments for alopecia in the previous 6 months. • Previous hair implants. • Intake of drugs that affect hair loss. • Be undergoing immunosuppressive therapy or anticoagulants, or both. • Known intolerance to mesotherapy. • Taking contraceptives containing cyproterone acetate. • Pregnancy. • In general, any limitations that would prevent the proper application of both treatments and the right monitoring of the efficacy variables.
Interventions	• Plasma Rich in Growth Factors (PRGF-Endoret). • Saline solution.
Outcomes	**Primary outcomes** • Change from baseline in hair density at three months (number of hairs per cm^2). **Secondary outcomes** • Hair width (µm). • Anagen/telogen ratio. • Terminal hair density. • Vellus hair density.
Starting date	Not stated
Contact information	Eduardo Anitua, MD, DDS, PhD, eduardoanitua@eduardoanitua.com
Notes	We accessed the website on 3 August 2015, which was last updated on 24 December 2013. This is same as EUCTR2013-002740-85-ES above. Both are known under 'BTI-01D-EC/12/ALO', but with another contact name virginia.cuadrado@bti-implant.es

NCT02074943

Trial name or title	Efficacy and Safety of Platelet Rich Plasma in Androgenetic Alopecia
Methods	This is a double-blind randomised placebo-controlled trial
Participants	**Inclusion criteria**

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NCT02074943 *(Continued)*

	• 20 men and women with mild to moderate androgenetic alopecia (18 to 70 years) (Ludwig alopecia score I and II, and the Hamilton-Norwood score 1 to 4). **Exclusion criteria** • Treatments for AGA within the last 3 months. • Active or history of malignancies. • Platelets disorders, anaemia and or bleeding disorders. • Women who are pregnant or breast-feeding. • Uncooperative patients or patients who are unable to understand the protocol or give informed consent. • Participants who are known to be HIV, hepatitis B or C positive or otherwise immunocompromised. • Participants who have active skin disease or skin infection at the intended treatment area. • Non-steroidal anti-inflammatory medications. • Participants with a propensity for keloids.
Interventions	• Platelet rich plasma on one half of the head. • Saline on other half of the head.
Outcomes	**Primary outcomes** • The degree of hair regrowth based on the hair regrowth score (RGS) for each side of scalp. **Secondary outcomes** • Changes in hair count and caliber.
Starting date	April 2014. Currently recruiting
Contact information	Jerry Shapiro, MD Jerry.Shapiro@vch.ca
Notes	We accessed the website on 29 July 2015, which was last updated on 10 December 2014

NCT02483195

Trial name or title	The Use of 5mg Finasteride Versus 200mg Spironolactone and Topical 5% Minoxidil in Treating Postmenopausal Female Androgenetic Alopecia
Methods	This is a double-blind randomised active-controlled trial
Participants	**Inclusion criteria** • 50 female. • Postmenopausal (> 60 years old or with total hysterectomy). • Diagnosed with androgenetic alopecia. • No chemical processing or changes in hair products throughout the study. **Exclusion criteria** • Men. • Premenopausal women (< 60 or without hysterectomy). • Participants allergic to any of the study medications (minoxidil, finasteride, spironolactone). • Participants with other co-existing forms of alopecia (traction, alopecia areata, or scarring alopecias). • Participants with obstructive uropathy or advanced liver disease.

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NCT02483195 *(Continued)*

	• Prior hair loss treatment within the last 6 months. • Hair loss from the chemotherapy or other medication-induced alopecia. • Hair loss for greater than 5 years, as medical therapy is unlikely to have much effect at restoring hair follicles inactive for that long of a period.
Interventions	• Combination 5% minoxidil and 200 mg spironolactone. • 5 mg finasteride with placebo topical preparation.
Outcomes	**Primary outcomes** 1. The Savin Scale will be used to determine hair growth or hair loss between the groups, or both. 2. The Ludwig Scale will be used to determine hair growth or hair loss between the groups, or both. 3. Alopecia improvement assessment will be used to determine hair growth and/or hair loss between the groups (7-point Likert scale).
Starting date	Not yet recruiting
Contact information	Andrea L Taylor, MD andrea.taylor@medicine.ufl.edu and Mark Correa mcorrea@ufl.edu
Notes	We accessed the website on 3 August 2015, which was last updated on 24 June 2015

NCT02486848

Trial name or title	Minoxidil Dose Response Study in Females Identified Through IVD Testing as Non-Responders to 5% Topical Minoxidil
Methods	This is a double-blind randomised active-controlled trial
Participants	**Inclusion criteria** • 100 females in overall good health. • Age: 18 to 55. • FPHL (Sinclair 2-4). • Willing to have a mini dot tattoo placed in the target area of the scalp. • Willing to maintain the same hair style, colour, shampoo, and hair products use, and approximate hair length throughout the study. • Able to give informed consent. • Non-responder to 5% minoxidil as determined by the MX-IVD test i.e. low minoxidil metabolizer. • Able to comply with the study requirements for 24 consecutive weeks. • Willing to use an adequate method of birth control (if applicable). • Negative urine pregnancy test. **Exclusion criteria** • Previous adverse event from topical minoxidil treatment. • History of hypotension. • Uncontrolled hypertension. • Use of any hypertensive drugs. • Pregnant, nursing, or planning a pregnancy during the study. • Prior hair transplant. • Uses wigs or hair weaves. • Have used minoxidil (topical or oral) anytime during the past 6 months. • Chronic scalp disorders that require medications.

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NCT02486848 *(Continued)*

	• Uses medication known to cause hair thinning such as Coumadin and anti-depressants/anti-psychotics. • Folliculitis. • Scalp psoriasis • Seborrhoeic dermatitis. • Inflammatory scalp conditions such as lichen planopilaris. • Enrolled in any other medical study or has been enrolled in any medical study in the past 30 days. • Responder to 5% minoxidil as determined by the MX-IVD test.
Interventions	• 5% topical minoxidil solution. • 15% topical minoxidil solution.
Outcomes	**Primary outcomes** • Target area hair count until week 24. **Secondary outcomes** • Target area hair count until week 12. • Expert panel global photography assessment.
Starting date	June 2015. Not yet recruiting
Contact information	Alessandra Palmieri, proricerca@hotmail.it
Notes	We accessed the website on 3 August 2015, which was last updated on 29 June 2015

Abbreviations: AGA: androgenetic alopecia; CPA: cyproterone acetate; CNS: central nervous system; FPHL: female pattern hair loss; RCT: randomized controlled trial

DATA AND ANALYSES

Comparison 1. Minoxidil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with self-rated at least moderate hair regrowth	6	1148	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.51, 2.47]
2 Proportion of participants with adverse events	6	1301	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.98, 1.83]
2.1 Topical minoxidil solution (1%) versus placebo	1	280	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.61, 2.06]
2.2 Topical minoxidil solution (2%) versus placebo	4	727	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.82, 1.87]
2.3 Topical minoxidil solution (5%) versus placebo	2	294	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.96, 4.37]

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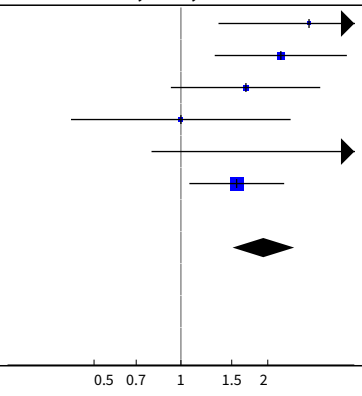
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Proportion of participants with investigator-rated at least moderate hair regrowth	7	1181	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.68, 3.28]
4 Mean increase in total hair count from baseline	8	1242	Mean Difference (IV, Fixed, 95% CI)	13.18 [10.92, 15.44]
4.1 Topical (1% to 2%) minoxidil versus placebo	8	1116	Mean Difference (IV, Fixed, 95% CI)	12.97 [10.58, 15.35]
4.2 Topical (5%) minoxidil versus placebo	1	126	Mean Difference (IV, Fixed, 95% CI)	15.1 [7.96, 22.24]
5 Mean increase in total hair count from baseline (sensitivity analysis)	7	1234	Mean Difference (IV, Fixed, 95% CI)	12.96 [10.69, 15.24]
5.1 Topical (1% to 2%) minoxidil versus placebo	7	1108	Mean Difference (IV, Fixed, 95% CI)	12.72 [10.33, 15.12]
5.2 Topical (5%) minoxidil versus placebo	1	126	Mean Difference (IV, Fixed, 95% CI)	15.1 [7.96, 22.24]

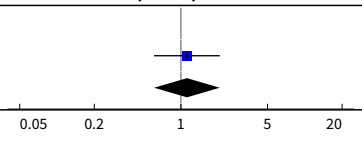
Analysis 1.1. Comparison 1 Minoxidil versus placebo, Outcome 1 Proportion of participants with self-rated at least moderate hair regrowth.

Study or subgroup	Minoxidil n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
DeVillez 1994	26/157	9/151		11.82%	2.78[1.35,5.73]
Jacobs 1993	39/176	17/170		22.28%	2.22[1.31,3.76]
NCT01325350	20/56	13/61		16.03%	1.68[0.92,3.04]
Olsen 1991	6/15	6/15		7.73%	1[0.42,2.4]
Pazoki-Toroudi 2012	16/49	0/18		0.93%	12.54[0.79,198.82]
Tsuboi 2007	50/140	32/140		41.22%	1.56[1.07,2.28]
Total (95% CI)	**593**	**555**		**100%**	**1.93[1.51,2.47]**
Total events: 157 (Minoxidil), 77 (Placebo)					
Heterogeneity: Tau²=0; Chi²=6.57, df=5(P=0.25); I²=23.94%					
Test for overall effect: Z=5.23(P<0.0001)					



Analysis 1.2. Comparison 1 Minoxidil versus placebo, Outcome 2 Proportion of participants with adverse events.

Study or subgroup	Minoxidil n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Topical minoxidil solution (1%) versus placebo					
Tsuboi 2007	19/140	17/140		30.02%	1.12[0.61,2.06]
Subtotal (95% CI)	**140**	**140**		**30.02%**	**1.12[0.61,2.06]**



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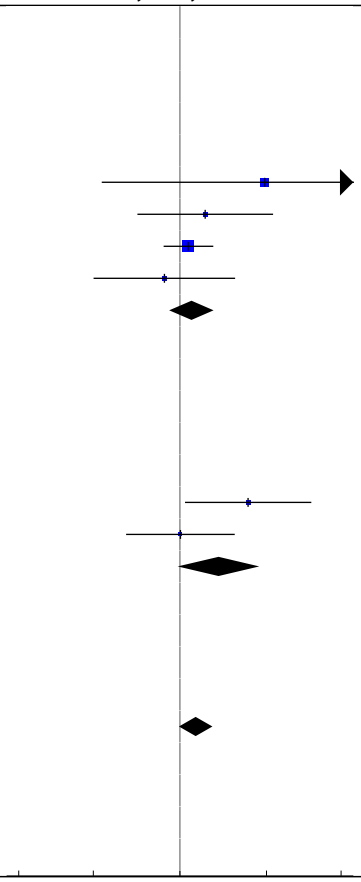
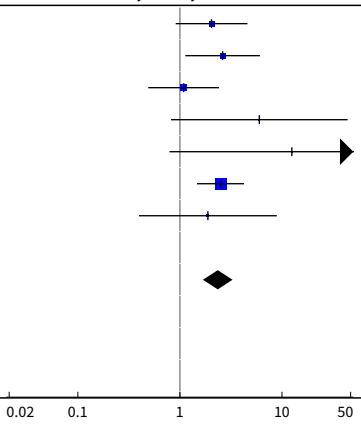
Study or subgroup	Minoxidil n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 19 (Minoxidil), 17 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.36(P=0.72)					
1.2.2 Topical minoxidil solution (2%) versus placebo					
Jacobs 1993	2/176	0/170		0.9%	4.83[0.23,99.89]
Lucky 2004	10/154	3/74		7.16%	1.6[0.45,5.65]
NCT01325350	25/62	21/61		37.39%	1.17[0.74,1.86]
Olsen 1991	3/15	4/15		7.06%	0.75[0.2,2.79]
Subtotal (95% CI)	**407**	**320**		**52.51%**	**1.24[0.82,1.87]**
Total events: 40 (Minoxidil), 28 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.55, df=3(P=0.67); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					
1.2.3 Topical minoxidil solution (5%) versus placebo					
Lucky 2004	22/153	3/74		7.14%	3.55[1.1,11.47]
Pazoki-Toroudi 2012	11/49	4/18		10.33%	1.01[0.37,2.77]
Subtotal (95% CI)	**202**	**92**		**17.47%**	**2.05[0.96,4.37]**
Total events: 33 (Minoxidil), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.72, df=1(P=0.1); I^2=63.3%					
Test for overall effect: Z=1.85(P=0.06)					
Total (95% CI)	**749**	**552**		**100%**	**1.34[0.98,1.83]**
Total events: 92 (Minoxidil), 52 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.13, df=6(P=0.53); I^2=0%					
Test for overall effect: Z=1.84(P=0.07)					
Test for subgroup differences: Chi^2=1.67, df=1 (P=0.43), I^2=0%					



Analysis 1.3. Comparison 1 Minoxidil versus placebo, Outcome 3 Proportion of participants with investigator-rated at least moderate hair regrowth.

Study or subgroup	Minoxidil n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
DeVillez 1994	17/157	8/151		18.27%	2.04[0.91,4.59]
Jacobs 1993	19/176	7/170		15.95%	2.62[1.13,6.08]
NCT01325350	10/56	10/61		21.45%	1.09[0.49,2.42]
Olsen 1991	6/15	1/15		2.24%	6[0.82,44]
Pazoki-Toroudi 2012	16/49	0/18		1.62%	12.54[0.79,198.82]
Tsuboi 2007	40/140	16/140		35.85%	2.5[1.47,4.25]
Whiting 1992	4/17	2/16		4.62%	1.88[0.4,8.9]
Total (95% CI)	**610**	**571**		**100%**	**2.35[1.68,3.28]**
Total events: 112 (Minoxidil), 44 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.13, df=6(P=0.41); I^2=2.11%					
Test for overall effect: Z=5.01(P<0.0001)					



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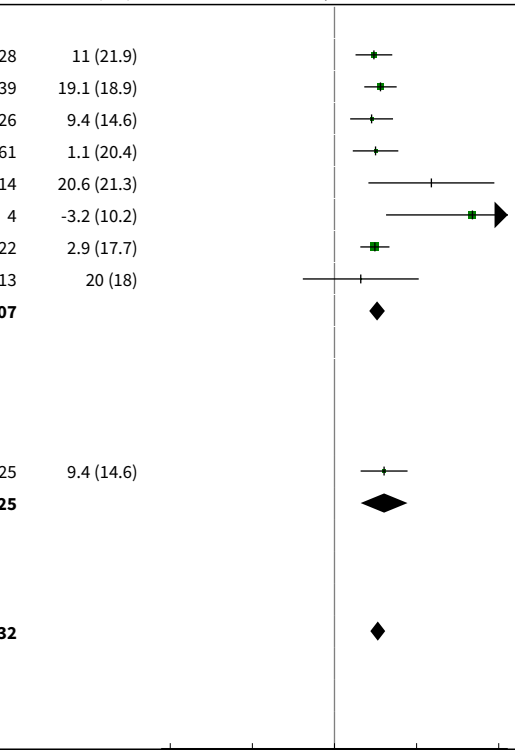
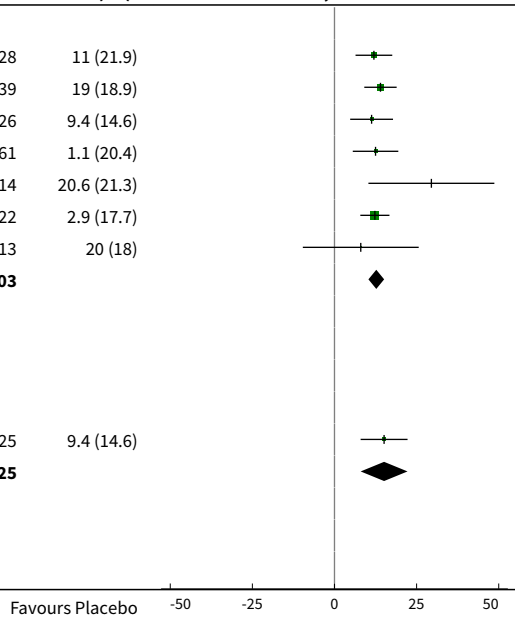
Analysis 1.4. Comparison 1 Minoxidil versus placebo, Outcome 4 Mean increase in total hair count from baseline.

Study or subgroup	Minoxidil N	Minoxidil Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.4.1 Topical (1% to 2%) minoxidil versus placebo							
DeVillez 1994	128	23 (23.7)	128	11 (21.9)		16.37%	12[6.41,17.59]
Jacobs 1993	155	33.1 (24.1)	139	19.1 (18.9)		21.09%	14[9.07,18.93]
Lucky 2004	108	20.7 (17.6)	26	9.4 (14.6)		12.04%	11.3[4.78,17.82]
NCT01325350	62	13.6 (18.7)	61	1.1 (20.4)		10.65%	12.5[5.57,19.43]
Olsen 1991	14	50.1 (29.8)	14	20.6 (21.3)		1.39%	29.5[10.33,48.67]
Price 1990	4	38.8 (24.8)	4	-3.2 (10.2)		0.74%	42[15.71,68.29]
Tsuboi 2007	123	15.2 (17.7)	122	2.9 (17.7)		26.04%	12.3[7.87,16.73]
Whiting 1992	15	28 (29)	13	20 (18)		1.64%	8[-9.64,25.64]
Subtotal ***	**609**		**507**			**89.97%**	**12.97[10.58,15.35]**
Heterogeneity: Tau^2=0; Chi^2=8.48, df=7(P=0.29); I^2=17.5%							
Test for overall effect: Z=10.66(P<0.0001)							
1.4.2 Topical (5%) minoxidil versus placebo							
Lucky 2004	101	24.5 (21.9)	25	9.4 (14.6)		10.03%	15.1[7.96,22.24]
Subtotal ***	**101**		**25**			**10.03%**	**15.1[7.96,22.24]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.14(P<0.0001)							
Total ***	**710**		**532**			**100%**	**13.18[10.92,15.44]**
Heterogeneity: Tau^2=0; Chi^2=8.79, df=8(P=0.36); I^2=9.02%							
Test for overall effect: Z=11.42(P<0.0001)							
Test for subgroup differences: Chi^2=0.31, df=1 (P=0.58), I^2=0%							



Analysis 1.5. Comparison 1 Minoxidil versus placebo, Outcome 5 Mean increase in total hair count from baseline (sensitivity analysis).

Study or subgroup	Minoxidil N	Minoxidil Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 Topical (1% to 2%) minoxidil versus placebo							
DeVillez 1994	128	23 (23.7)	128	11 (21.9)		16.5%	12[6.41,17.59]
Jacobs 1993	155	33 (24.1)	139	19 (18.9)		21.24%	14[9.07,18.93]
Lucky 2004	108	20.7 (17.6)	26	9.4 (14.6)		12.13%	11.3[4.78,17.82]
NCT01325350	62	13.6 (18.7)	61	1.1 (20.4)		10.73%	12.5[5.57,19.43]
Olsen 1991	14	50.1 (29.8)	14	20.6 (21.3)		1.4%	29.5[10.33,48.67]
Tsuboi 2007	123	15.2 (17.7)	122	2.9 (17.7)		26.23%	12.3[7.87,16.73]
Whiting 1992	15	28 (29)	13	20 (18)		1.66%	8[-9.64,25.64]
Subtotal ***	**605**		**503**			**89.89%**	**12.72[10.33,15.12]**
Heterogeneity: Tau^2=0; Chi^2=3.76, df=6(P=0.71); I^2=0%							
Test for overall effect: Z=10.41(P<0.0001)							
1.5.2 Topical (5%) minoxidil versus placebo							
Lucky 2004	101	24.5 (21.9)	25	9.4 (14.6)		10.11%	15.1[7.96,22.24]
Subtotal ***	**101**		**25**			**10.11%**	**15.1[7.96,22.24]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.14(P<0.0001)							



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Study or subgroup	Minoxidil N	Minoxidil Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Total ***	**706**		**528**		◆	**100%**	**12.96[10.69,15.24]**
Heterogeneity: Tau²=0; Chi²=4.14, df=7(P=0.76); I²=0%							
Test for overall effect: Z=11.19(P<0.0001)							
Test for subgroup differences: Chi²=0.38, df=1 (P=0.54), I²=0%							

Comparison 2. Minoxidil 2% versus minoxidil 5%

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of adverse events	4	1006	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.91, 1.15]
2 Number of adverse events (sensitivity analysis)	3	699	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.99, 1.23]
3 Mean increase in total hair count from baseline	3	631	Mean Difference (IV, Fixed, 95% CI)	-2.12 [-5.47, 1.23]

Analysis 2.1. Comparison 2 Minoxidil 2% versus minoxidil 5%, Outcome 1 Number of adverse events.

Study or subgroup	Minoxidil 2% n/N	Minoxidil 5% n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Blume-Peytavi 2011a	51/57	43/56		23.39%	1.17[0.98,1.38]
Lucky 2004	10/154	22/153		11.9%	0.45[0.22,0.92]
NCT01145625	126/161	111/161		59.85%	1.14[0.99,1.3]
Sheng 2014	3/132	9/132		4.85%	0.33[0.09,1.2]
Total (95% CI)	**504**	**502**	◆	**100%**	**1.02[0.91,1.15]**
Total events: 190 (Minoxidil 2%), 185 (Minoxidil 5%)					
Heterogeneity: Tau²=0; Chi²=12.71, df=3(P=0.01); I²=76.39%					
Test for overall effect: Z=0.37(P=0.71)					

Analysis 2.2. Comparison 2 Minoxidil 2% versus minoxidil 5%, Outcome 2 Number of adverse events (sensitivity analysis).

Study or subgroup	Minoxidil 2% n/N	Minoxidil 5% n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Blume-Peytavi 2011a	51/57	43/56		26.55%	1.17[0.98,1.38]
NCT01145625	126/161	111/161		67.94%	1.14[0.99,1.3]
Sheng 2014	3/132	9/132		5.51%	0.33[0.09,1.2]
Total (95% CI)	**350**	**349**	◆	**100%**	**1.1[0.99,1.23]**

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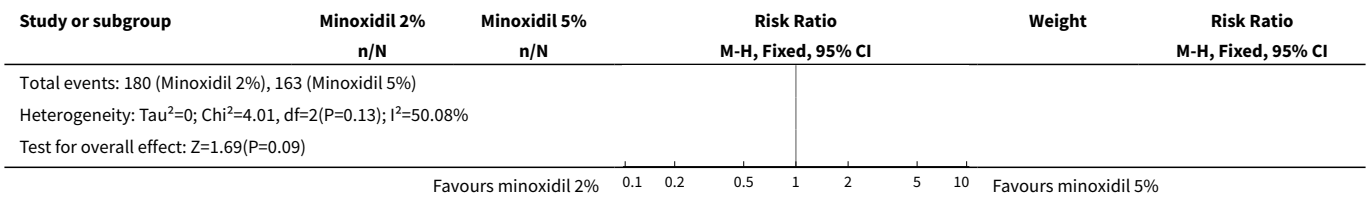
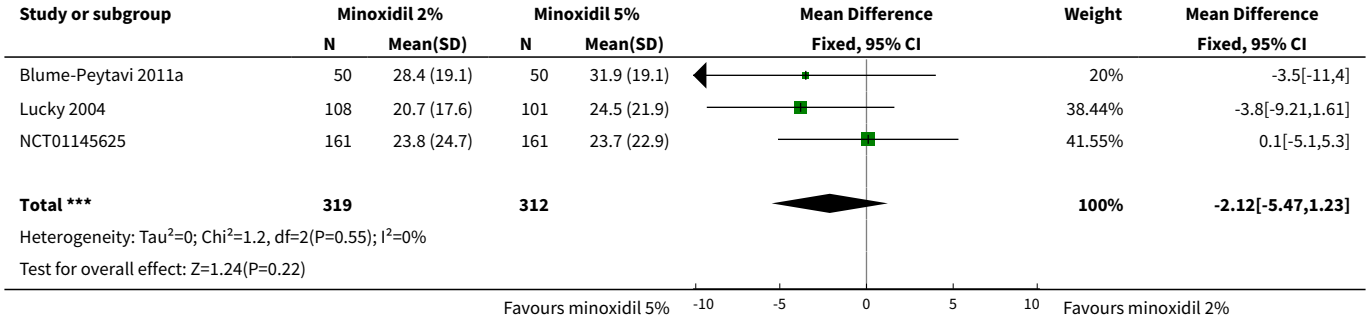


Analysis 2.3. Comparison 2 Minoxidil 2% versus minoxidil 5%, Outcome 3 Mean increase in total hair count from baseline.



ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Definition
Alopecia	Loss of hair from head or body
Anagen hair	Active, growing hair
Anagen phase	Active growth phase of hair follicles (2 to 7 years)
Catagen phase	Involution phase of the hair follicle
Ferritin	Iron-containing proteins that are widely distributed in animals, plants, and micro-organisms. Their major function is to store iron in a non-toxic bioavailable form
Follicular miniaturisation	The follicles produce hair that is thinner and thinner, until they either stop producing hair or produce hair that is so fine it is barely noticeable
Hepatotoxic	Chemical-driven liver damage
Hyperandrogenism	Condition characterised by excessive production/secretion of androgens
Hypertrichosis	Excessive (terminal and vellus) hair in non-androgen dependent body sites; varies in people with different ethnic background without any pathological findings
Hirsutism	Excessive hairiness on women in those parts of the body where terminal hair does not normally occur or is minimal - for example, beard or chest hair

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Table 1. Glossary of terms *(Continued)*

Ludwig scale	Classification of female pattern hair loss (FPHL) stages I to III (minimal, moderate, intense) (Ludwig 1977)
5-alpha-reductase	An enzyme that converts testosterone, the male sex hormone, into the more potent hormone, dihydrotestosterone
Sinclair scale	5-point scale (1 = normal, 5 = advanced hair loss) used to assess FPHL (Dinh 2007)
Telogen hair	Dormant, inactive hair
Telogen phase	Resting phase of the hair follicle (3 months)
Telogen effluvium	Massive hair loss resulting from the early entry of hairs into the telogen phase
Terminal hair	Thicker, longer, and pigmented hair
Tincture[1]	An alcoholic extract of a drug derived from a plant
Vasodilation[1]	Widening of the blood vessels
Vellus hair	Short, fine, light-coloured, and barely noticeable hair that develops on most of a person's body from childhood

Abbreviations: FPHL: female pattern hair loss.
[1]Definition taken from: Martin 1998

Table 2. Contact with investigators

Study ID	Response	Additional	Comment
Bezzola 2009	No	No	There were no separate data for women. The primary outcome was diameter of hair, not one of the outcomes for this review. We excluded this study.
Blume-Peytavi 2007	Yes	Yes	IPD (individual patient data) were unavailable. We included this study.
Blume-Peytavi 2011a	Yes	Yes	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study. We received a response on 16 November 2011: "The allocation concealment was performed using sequentially numbered, sealed, opaque envelopes, and kept by the project manager of the CRC."
Bureau 2003	Yes	No	We could contact one of the investigators, who was unable to provide separate data on women. We included this study.
Carmina 2003	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study.
DeVillez 1994	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study.
Draelos 2005	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study.

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Table 2. Contact with investigators *(Continued)*

Farella 1991	No	No	The Italian Cochrane Centre translated and assessed this study, but it was a controlled clinical trial (CCT), so we excluded it.
Fischer 2004	Yes	Yes	We received information that allowed a change in the assessment for several domains from unclear to low risk of bias. We included this study.
Gassmueller 2008	Yes	Yes	We received information that allowed a change in assessment for several domains from unclear to low risk of bias. We included this study.
Georgala 2004	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study.
Gehring 2000	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study.
Golpour 2013	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. One review author, ZF, translated this study, which only included males, so we excluded this study.
Guerrero 2009	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. The data was mixed in terms of gender. We included this study.
Hong 2007	Yes	Yes	The trial conduct was confirmed, i.e. sequence allocation/concealment and blinding. The data was mixed in terms of gender. We included this study. hongck@cau.ac.kr; dermahan@gmail.com
Jacobs 1993	No	No	We were unable to contact the study investigators. We included this study.
Jimenez 2014a; Jimenez 2014b	Yes	Yes	The trial conduct was confirmed, i.e. sequence allocation/concealment and blinding. We included this study. dm@hairmax.com; Leonard Stillman.
Keene 2011	Yes	Yes	The trial conduct was confirmed, i.e. sequence allocation/concealment and blinding. We included this study. drkeene@hairrestore.com; andyg@appliedbiology.com
Kim 2009	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. skin4u@korea.ac.kr. We included this study.
Kim 2013	Yes	Yes	The trial conduct was confirmed, i.e. sequence allocation, but not for concealment and blinding. We did not receive separate data for women. We included this study. chhuh@snu.ac.kr; seokjong@knu.ac.kr
Lanzafame 2014	Yes	Yes	The trial conduct was confirmed, i.e. sequence allocation, as well as losses to follow-up. raymond.lanzafame@gmail.com. We included this study.

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Table 2. Contact with investigators *(Continued)*

Le Floc'h 2015	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study. npiccardi@rd.loreal.com
Li 1996	Yes	Yes	We excluded this study as it was a CCT.
Mazzarella 1997	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. The data was mixed in terms of gender. We included this study.
Minozzi 1997	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study.
Oura 2008	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study.
Pazoki-Toroudi 2012	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study. hpazooki@farabi.tums.ac.ir
Price 1990	Yes	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We received no response from the investigator. We included this study.
Price 2000	Yes	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We received no response from the investigator. We included this study.
Sheng 2014	Yes	Yes	The trial conduct was confirmed, i.e. sequence allocation/concealment and blinding. We included this study. dxq93216@medmail.com.cn; felix_sheng@medmail.com.cn
Shin 2007	Yes	Yes	The trial conduct was confirmed, i.e. sequence allocation/concealment. We included this study. hceun@snu.ac.kr; reslab@naver.com (Dr Shin Hyoseung); oskwon@snu.ac.kr
Sinclair 2002	Yes	Yes	Information provided to us enabled a change from unclear to high risk of bias. We excluded this study.
Thom 2001/Thom 2006	No	No	The data was mixed in terms of gender. We received no response from the investigator. We included this study. erling.thom@parexel.com; info@pharmamedico.com.
Tsuboi 2007	Yes	Yes	The information we received allowed us to change the assessment for several domains from unclear to low risk of bias. We included this study.
Ukşal 1999	Yes	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We included this study, but there were missing data. We received no response from the investigator.
Vexiau 2002	Yes	Yes	We received information regarding the hyperandrogenic profile of the women. We included this study.

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Table 2. Contact with investigators *(Continued)*

AC-TRN12607000027415	No	No	No further information regarding publication date. yazdaa27@gmail.com; Rod.SINCLAIR@svhm.org.au
EUC-TR2013-002740-85-ES	No	No	No further information regarding publication date nor if these are the same studies. eduardoanitua@eduardoanitua.com; virginia.cuadrado@bti-implant.es; alopecia.ccdermatologico@gmail.com. Are EUCTR2013-002740-85-ES and NCT01885676 the same studies, as everything is the same, except contact persons (same inclusion, same number of patients, same treatments, same sponsor)
NCT00175617	No	No	No further information regarding publication date. andreas.finner@vch.ca
NCT00197379	No	No	No further information regarding publication date. itoutai@hama-med.ac.jp
NCT00418249	No	No	No further information regarding publication date. rlurie@bezeqint.net
NCT01145625	Yes	No	The trial conduct was confirmed, i.e. sequence allocation/concealment. LinkedIn Professor Kendall, and U Doshi and website Johnson & Johnson. Received from both Johnson & Johnson international as NL reply they forwarded it to responsible party, however, no response
NCT01189279	No	No	No further information regarding publication date. clinicaltrials@allergan.com, international and Dutch website
NCT01226459	No	No	No further information regarding publication date.
NCT01325350	No	No	Allergan through website twice, no reply.
NCT01655108	Yes	Yes	The trial conduct was confirmed, i.e. sequence allocation/concealment and blinding and received all possible data of the submitted paper. izelda@unb.br, Barbara Uzel: barbara.uzel@gmail.com
NCT01662089	No	No	No further information regarding publication date. rattapongthuangtong@yahoo.com
NCT01686295	No	No	No further information regarding publication date. candresen@tklresearch.com
NCT01885676	No	No	No further information regarding publication date. eduardoanitua@eduardoanitua.com
NCT01900041	Yes	Yes	The trial conduct was confirmed, i.e. sequence allocation and flow chart. We included this study. Larissa.Cheredeeva@merz.ru
NCT01967277	Yes	Yes	The trial conduct was confirmed, i.e. concealment and blinding (but not sequence generation). We included this study. pschnoor@capillus.com, info@capillus.com
NCT02074943	Yes	No	There was no further information regarding publication date, and the study is not yet finished. Jerry.Shapiro@vch.ca

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Abbreviations: CCT: controlled clinical trial (quasi-randomised).

Table 3. Checklist for describing and assessing patient-reported outcomes (PROs) in clinical trials

1. What were PROs measuring? a. What concepts were the PROs used in the study measuring? b. What rationale (if any) for selection of concepts or constructs did the authors provide? c. Were patients involved in the selection of outcomes measured by the PROs?
2. Omissions a. Were there any important aspects of health (e.g. symptoms, function, perceptions) or quality of life (e.g. overall evaluation, satisfaction with life) that were omitted in this study from the perspectives of the patient, clinician, significant others, payers, or other administrators and decision-makers?
3. If randomised trials and other studies measured PROs, what were the instruments' measurement strategies? a. Did investigators use instruments that yield a single indicator or index number, a profile, or a battery of instruments? b. If investigators measure PROs, did they use specific or generic measures, or both? c. Who exactly completed the instruments?
4. Did the instruments work in the way they were supposed to work - validity? a. Had the instruments used been validated previously (provide reference)? Was evidence of prior validation for use in this population presented? b. Were the instruments re-validated in this study?
5. Did the instruments work in the way they were supposed to work - ability to measure change? a. Are the PROs able to detect change in patient status, even if those changes are small?
6. Can you make the magnitude of effect (if any) understandable to readers? a. Can you provide an estimate of the difference in patients achieving a threshold of function or improvement, and the associated number needed to treat (NNT)?
Table 17.6.a Patrick D, Guyatt GH, Acquadro C. Chapter 17: Patient-reported outcomes. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.

Abbreviations: PRO: patient-reported outcome.

Table 4. Included studies with no usable or irretrievable data

Study ID	Interventions and comparisons	N	Comments
Bureau 2003	Essential oil solution (E2F7) and electromagnetic pulses versus placebo solution and electromagnetic pulses	93	No separate data for men and women Investigators unable to provide these
Fischer 2004	Melatonin–alcohol solution versus alcohol solution	40	None of our outcomes were addressed
Guerrero 2009	Minoxidil 2% versus 17α-estradiol	40	No separate data for men and women No response from principal investigator
Hong 2007	Cytopurine, pentadecanoic glyceride, 95% ethanol topical solution versus vehicle solution	95	No separate data for men and women
Kim 2009	Korean red ginseng versus placebo	40	No separate data for men and women

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Table 4. Included studies with no usable or irretrievable data *(Continued)*

			No response from principal investigator
Kim 2013	Low level light therapy versus sham device	40	No separate data for men and women No response from principal investigator
Mazzarella 1997	Finasteride 0.005% lotion versus vehicle	56	No separate data for men and women No response from principal investigator
Minozzi 1997	Ethinyl estradiol (0.02 mg/day) versus transdermal estradiol (0.05 mg/day) with medroxyprogesterone acetate (MPA) versus ethinyl estradiol (0.02 mg/day) with cyproterone acetate	63	Diagnosis of female pattern hair loss (FPHL) was not clearly defined/stated. No response from principal investigator None of our outcomes were assessed
Morganti 1998	Active lotion (gelatine-cystine and *Serenoa repens*) versus placebo lotion versus active diet supplement (gelatine-cystine) versus placebo supplement versus active lotion and active supplement (n = 12)	60	No separate data for men and women No response from principal investigator
NCT01189279	Bimatoprost A versus bimatoprost B versus bimatoprost C	42	None of our outcomes were addressed, no separate data for men and women. No response from Allergan
NCT01226459	Minoxidil 5% versus vehicle	404	Too many inconsistencies regarding numbers that dropped out and number of participants analysed, as well as in calculations made for mean changes from baseline. No response from principal investigators
Rietschel 1987	Minoxidil 2% versus minoxidil 3% versus placebo	149	No separate data for men and women No response from principal investigator
Thom 2001	Dietary supplement versus placebo	60	No separate data for men and women No response from principal investigator
Thom 2006	Dietary supplement versus placebo	60	No separate data for men and women No response from principal investigator
Ukşal 1999	Spironolactone versus flutamide versus finasteride	?	Poster, limited data, unclear how many participants in each group. No response from principal investigator

Abbreviations: FPHL: female pattern hair loss, N: Number randomised

Table 5. Table of random-effects sensitivity analyses

Analysis	Concentration/subgroups	Risk ratio	95% confidence interval	P value	I^2 statistic	Chi^2 test (P value)
Analysis 1.1	Pooled	1.82	1.34 to 2.46	< 0.00001	24%	0.25

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Table 5. Table of random-effects sensitivity analyses *(Continued)*

Self-rated hair regrowth						
Analysis 1.2	Minoxidil (1%)	1.12	0.61 to 2.06	0.72	—	—
Adverse events	Minoxidil (2%)	1.19	0.79 to 1.79	0.40	0%	0.67
	Minoxidil (5%)	1.83	0.51 to 6.55	0.35	63%	0.10
Analysis 1.3	Pooled	2.17	1.53 to 3.06	< 0.00001	2%	0.41
Investigator-rated hair regrowth						
Analysis 1.4	Pooled	13.24	10.80 to 15.65	< 0.00001	9%	0.36
Increase in total hair count						
Analysis 1.5	Pooled	12.96	10.69 to 15.24	< 0.00001	0%	0.76
Increase in total hair count (sensitivity analysis)						
Analysis 2.1	Pooled	0.96	0.70 to 1.30	0.77	76%	0.005
Analysis 2.2	Pooled	1.12	0.93 to 1.35	0.22	50%	0.13
Analysis 2.3	Pooled	−2.12	−5.47 to 1.23	0.22	0%	0.55

Table 6. Research recommendations based on a gap in the evidence of the effects of interventions for female pattern hair loss (FPHL)

Core elements	Issues to consider	Status of research for this review
Evidence (E)	What is the current state of the evidence?	This systematic review included 47 RCTs. There is mainly moderate to low quality evidence for the efficacy and safety of topical minoxidil 2% and 5% in the treatment of FPHL. Minoxidil (2%) topical solution twice daily appears to be effective and safe, and minoxidil (5%) used once daily may be as effective as minoxidil (2%) used twice daily, which may result in improved adherence. However, the higher concentration (5%) of minoxidil is only registered for the therapeutic management of FPHL in a small number of countries around the world.
Population (P)	Diagnosis, disease stage, comorbidity, risk factors, gender, age, ethnic group, specific inclusion or exclusion criteria, clinical setting	The participants should be aged 18 to 89 years. A distinction between women with and without a hyperandrogenic profile should be made, and between ethnic groups as well as pre- and post-menopausal women. **Inclusion criteria** • Women with FPHL Ludwig (3-point) classification (Ludwig 1977) or the Sinclair (5-point) scale (Sinclair 2004). **Exclusion criteria** • Local scalp treatments in prior 4 weeks. • Systemic treatment three months prior to study that could interfere with the study medications.

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Table 6. Research recommendations based on a gap in the evidence of the effects of interventions for female pattern hair loss (FPHL) *(Continued)*

		• Chemotherapy, radiation therapy, or laser therapy (on the scalp) within the last 6 months. • Concomitant medication for treatment of hair loss. • Pregnant or lactating women. • Hyper- or hypothyroidism. • Malnutrition. • Liver, renal, or metabolic disease. • Wearing a wig or having had a hair transplant.
Intervention (I)	Type, frequency, dose, duration, prognostic factor	The study duration should be at least 6 months. High-quality, well-designed, and rigorously-reported studies of other widely used treatments, e.g. spironolactone, finasteride (at different dosages), dutasteride, cyproterone acetate, and laser-based therapy should be included. Information on direct and indirect costs of the interventions should be addressed.
Comparison (C)	Type, frequency, dose, duration, prognostic factor	Direct comparison studies of the widely used treatments are warranted.
Outcome (O)	Which clinical or patient-related outcomes will the researcher need to measure, improve, influence, or accomplish? Which methods of measurement should be used?	Participant's assessment of the treatment efficacy and changes in quality of life using standardised questionnaires, e.g. the Women's Androgenetic Alopecia Quality of Life Questionnaire (WAA-QOL) (Biondo 2010; Dolte 2000). Standardised and uniform scales should be developed and used for physicians' assessments, and these should reliably reflect proportion of participants with investigator-rated clinically significant hair regrowth and mean change in total hair count from baseline to the end of the study. Studies should address the sustainability of hair regrowth after discontinuation of treatment. An important patient-reported outcome should be the impact of the hair regrowth reflected by the time spent by women with FPHL on hair styling, including the use of wigs.
Time stamp (T)	Date of literature search or recommendation	7 July 2015
Study type	What is the most appropriate study design to address the proposed question?	• Randomised controlled trial (adequately powered/multicentred). • Methods: concealment of allocation sequence. • Blinding: participants, trialists, outcomes assessors, data analysts. • Setting: hospital/university or general practice with adequate follow-up.

Abbreviations: FPHL: female pattern hair loss.

APPENDICES

Appendix 1. CENTRAL (the Cochrane Library) search strategy

#1 (androgenic alopecia) or (androgenetic alopecia) or (female pattern hair loss) or (female baldness)
#2 MeSH descriptor Alopecia explode all trees
#3 (androgen*)
#4 (#2 AND #3)
#5 (#1 OR #4)
#6 SR-SKIN
#7 (#5 AND NOT #6)

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Appendix 2. MEDLINE (Ovid) search strategy

This strategy also used for AMED and PsycINFO

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animals not (human and animals)).sh.
10. 8 not 9
11. androgenic alopecia.mp.
12. androgenetic alopecia.mp.
13. (female pattern hair loss or female baldness).mp.
14. exp Alopecia/
15. androgen$.mp. or exp Androgens/
16. 14 and 15
17. 11 or 12 or 13 or 16
18. 10 and 17

Appendix 3. EMBASE (Ovid) search strategy

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (assign$ or allocat$).mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. androgenic alopecia.mp.
15. androgenetic alopecia.mp.
16. (female adj pattern adj hair adj loss).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
17. female baldness.mp.
18. alopecia.mp. or exp Alopecia/
19. androgens.mp. or exp Androgen/
20. 18 and 19
21. 16 or 17 or 20 or 15 or 14
22. 21 and 13

Appendix 4. PubMed search strategy

("androgenic alopecia" OR "androgenetic alopecia" OR "alopecia androgenetica" OR ((hair loss OR baldness OR alopecia) AND (androgen OR androgens)) OR "female pattern hair loss" OR "female baldness" OR ("female pattern" AND hairloss)) AND ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trial"[Publication Type] OR "Controlled Clinical Trials as Topic"[Mesh] OR randomized OR random* OR "Random Allocation"[mesh] OR placebo OR placebo* OR "Clinical Trials as Topic"[Mesh] OR RCT OR randomly OR factorial OR factorial* OR crossover OR crossover* OR cross-over OR cross-over* OR "double blind" OR "double blinded" OR "Double-Blind Method"[mesh] OR "Single-Blind Method"[mesh] OR "single blind" OR "single blinded" OR assign* OR allocat* OR volunteer OR volunteer* OR "Clinical Trial"[Publication Type] OR trial OR trials) NOT (animals NOT (human AND animals))

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Appendix 5. Web of Science search strategy

TS=((androgenic alopecia OR androgenetic alopecia OR alopecia androgenetica OR ((hair loss OR baldness OR alopecia) AND androgen*) OR female pattern hair loss OR female baldness OR female pattern hairloss) AND (Random* OR Controlled OR Trial* OR placebo* OR RCT OR factorial* OR crossover* OR "cross-over*" OR "double blind*" OR "Single Blind*" OR assign* OR allocat*))

Appendix 6. AMED (Ovid) search strategy

1. alopecia/
2. exp Androgens/
3. alopecia.mp.
4. androgen$.mp.
5. 1 or 3
6. 2 or 4
7. 5 and 6
8. (female and pattern and hair and loss).mp.
9. (female and baldness).mp.
10. (female and pattern and alopecia).mp.
11. or/7-10
12. randomized controlled trial$/
13. random allocation/
14. double blind method/
15. single blind method.mp.
16. exp Clinical trials/
17. (clin$ adj25 trial$).mp.
18. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$ or dummy)).mp.
19. (placebo$ or random$).mp.
20. research design/ or clinical trials/ or comparative study/ or double blind method/ or random allocation/
21. prospective studies.mp.
22. cross over studies.mp.
23. Follow up studies/
24. control$.mp.
25. (multicent$ or multi-cent$).mp.
26. ((stud or design$) adj25 (factorial or prospective or intervention or crossover or cross-over or quasi-experiment$)).mp.
27. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 11 and 27

Appendix 7. LILACS search strategy

((hair loss OR baldness or alopecia) AND (androgen$)) OR (female and pattern and hair and loss) OR (female and baldness) or (female and pattern and alopecia)
These terms were combined with the Controlled clinical trials topic-specific query filter.

F E E D B A C K

Studies that examined finasteride, 22 July 2016

Summary

A comment was received from Erik von Elm, Co-director Cochrane Switzerland, that two additional studies that examined finasteride, Keene 2011 and Mazzarella 1997, were not mentioned in the results section (Description of studies: Characteristics of the interventions). The authors agree that this was an omission but stress that the data was nevertheless reported on in the review.

Reply

Both studies should have been listed under Characteristics of the interventions, this is an omission. Thank you for picking this up. They are added now.

However, the study of Mazzarella did not have separate data for women and 61.5% drop-out in placebo group and is therefore listed in Table 4 (table with no usable or irretrievable data). We e-mailed principal investigators several times but received no answer. Under effects of interventions first paragraph it is reported that 15 studies did not provide usable data, as well as being listed in Notes section of COI table. So it is clear why we did not report on data of Mazzarella.

Keene is reported in comparison 17 so data are included.

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In conclusion, we did not fail to report data on studies where we should have reported data, but it was incorrect not to mention those two studies under characteristics of interventions.

Contributors

Our Co-ordinating Editor Hywel Williams, our Feedback Editor Urbà González and the lead author Esther van Zuuren.

WHAT'S NEW

Date	Event	Description
10 October 2016	Feedback has been incorporated	In response to feedback, minor correction in results section; please refer to Feedback section for details.

HISTORY

Protocol first published: Issue 1, 2009
Review first published: Issue 5, 2012

Date	Event	Description
24 May 2016	New search has been performed	We updated the review; we have added 25 randomised controlled trials
24 May 2016	New citation required but conclusions have not changed	There has been no significant alteration to the conclusions of the original review

CONTRIBUTIONS OF AUTHORS

JS and the Cochrane Skin Group performed the literature searches.
EvZ and ZF identified the relevant titles and abstracts from searches.
EvZ obtain the full-text articles of trials.
EvZ and ZF selected trials for inclusion.
EvZ translated two Italian studies, one Spanish study, and one German study.
ZF translated one Farsi study.
EvZ and ZF extracted data from trials, entered data into RevMan (Review Manager (RevMan) 2014), performed data analyses, interpreted the data, drafted the final review, and updated the review.

Disclaimer

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DECLARATIONS OF INTEREST

Evz has no know conflicts of interest. ZF has no known conflict of interest, JS has no known conflict of interest. There are no financial conflicts of interest; the review authors declare that they do not have any associations with any parties who may have vested interests in the results of this Cochrane review.

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Internal sources

- No sources of support supplied

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External sources

- The National Institute for Health Research (NIHR), UK.

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After consultation and with the direct agreement of the Cochrane Skin Group editorial base, we made substantial changes to the published protocol during the preparation of the 2012 published version of this review (van Zuuren 2012). This was partly due to almost the whole review author team on the protocol being replaced for the review, and due to changes in advice from Cochrane including the introduction of Cochrane's Methodological Expections of Cochrane Intervention Reviews (MECIR) standards. Changes to the 2012 review which remain the same for this review update include rewriting the Background and Methods sections, clarification of the types of participants, and inclusion of a broader spread of interventions to be considered in this review. In this review update we revised search strategies in line with current practices.

Subgroup analysis and investigation of heterogeneity: the only subgroup we investigated in this update was dose, which was not planned in the protocol or review.

Incomplete outcome data (attrition bias): regarding attrition bias, we are now consistent in all our reviews that we consider the following: up to 10% attrition (low risk); 10% to 20% (unclear risk); and greater than 20% (high risk).

INDEX TERMS

Medical Subject Headings (MeSH)

Alopecia [*therapy]; Drug Administration Schedule; Finasteride [*therapeutic use]; Hair [*drug effects] [growth & development]; Low-Level Light Therapy; Minoxidil [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans

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