Interventions for female pattern hair loss

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Interventions for female pattern hair loss (Review)

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Interventions for female pattern hair loss.
Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD007628.
DOI: 10.1002/14651858.CD007628.pub3.

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[Intervention Review]

Interventions for female pattern hair loss

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Editorial group: Cochrane Skin Group.
Publication status and date: New, published in Issue 5, 2012.

Citation: van Zuuren EJ, Fedorowicz Z, Carter B, Andriolo RB, Schoones J. Interventions for female pattern hair loss. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No.: CD007628. DOI: 10.1002/14651858.CD007628.pub3.

ABSTRACT

Background

Female pattern hair loss, 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 people.

Objectives

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

Search methods

We searched the following databases up to October 2011: the Cochrane Skin Group Specialised Register, CENTRAL in *The Cochrane Library* (2011, Issue 4), MEDLINE (from 1946), EMBASE (from 1974), PsycINFO (from 1806), AMED (from 1985), LILACS (from 1982), PubMed (from 1947), Web of Science (from 1945), and reference lists of articles. We also searched several online trials registries for ongoing trials.

Selection criteria

Randomised controlled trials that assessed the effectiveness of interventions for female pattern hair loss in women.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data.

Main results

Twenty two trials, comprising 2349 participants, were included. A wide range of interventions were evaluated, with 10 studies investigating the different concentrations of minoxidil. Pooled data from 4 studies indicated that a greater proportion of participants (121/488) treated with minoxidil reported a moderate increase in their hair regrowth when compared with placebo (64/476) (risk ratio (RR) = 1.86, 95% confidence interval (CI) 1.42 to 2.43). In 7 studies, there was an important increase of 13.28 in total hair count per cm^2 in the minoxidil group compared to the placebo group (95% CI 10.89 to 15.68). There was no difference in the number of adverse events in the twice daily minoxidil and placebo intervention groups, with the exception of a reported increase of adverse events (additional hair growth on areas other than the scalp) with minoxidil (5%) twice daily. Most of the other comparisons consisted of single studies. These were assessed as high risk of bias: They did not address our prespecified outcomes and provided limited evidence of either the efficacy or safety of these interventions.

Authors' conclusions

Although more than half of the included studies were assessed as being at high risk of bias, and the rest at unclear, there was evidence to support the effectiveness and safety of topical minoxidil in the treatment of female pattern hair loss. Further direct comparison studies of minoxidil 5% applied once a day, which could improve adherence when compared to minoxidil 2% twice daily, are still required. Consideration should also be given to conducting additional well-designed, adequately-powered randomised controlled trials investigating several of the other treatment options.

PLAIN LANGUAGE SUMMARY

Treatments for female pattern hair loss

The most common type of hair loss in women is female pattern hair loss, also known as androgenic alopecia. Unlike men, they 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. Female pattern hair loss can have a significant impact on self-consciousness, and the damage to a woman's self-confidence can affect her quality of life, leading to feelings of unattractiveness, shame, discomfort, emotional stress, and low self-esteem. This review was needed to clarify the best approach to treat this condition and provide reliable decision-making information for women and clinicians.

Twenty two studies, comprising 2349 women, were included. More than half of the studies were assessed as high risk of bias, and the rest, unclear risk of bias. Industry sponsorship represented a potential source of bias in six of the included studies.

This review found that minoxidil is more effective than placebo. In four 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. In seven studies (including the four just mentioned), there was an important increase in total hair count per cm^2 in the minoxidil group compared to the placebo group. Except for an increase in adverse events with minoxidil 5% twice daily, the number was similar for both groups. The adverse events were mostly mild, consisting of itch, skin irritation, dermatitis, and additional hair growth on areas other than the scalp. Minoxidil should not be used in pregnant or lactating women. Most of the other interventions and comparisons were covered in single studies, which were assessed as high risk of bias, did not address our outcomes, or both. Therefore, no firm conclusions can be made about their efficacy or safety.

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, nor on the possible impact of hair regrowth, reflected by a decrease in time spent by the women on hair styling or the use of wigs.

Future research should aim to provide evidence for people to make informed decisions about whether these treatments are effective, and whether the effects are sustainable after discontinuation of treatment.

Summary of findings for the main comparison. Minoxidil compared to placebo for female pattern hair loss

Minoxidil compared to placebo for female pattern hair loss

Participants or population: Participants with female pattern hair loss
Settings: Multicentre hospital setting
Intervention: Minoxidil
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Minoxidil				
The proportion of participants with self-rated clinically significant hair regrowth at the end of the study Assessed on 3- and 5-point scales[1] Follow-up: 24 to 32 weeks	**Study population**		**RR 1.86** (1.42 to 2.43)	964 (4 studies)	⊕⊕⊖⊖ **low**[2]/[3]	-
	134 per 1000	**250 per 1000** (191 to 327)				
	Moderate					
	-	-				
Change in quality of life using any validated and recognised generic or disease-specific instrument[4] Not reported	See comment	See comment	Not estimable[4]	-	See comment	-
Adverse effects: safety and tolerability, and any reported adverse events with 1% minoxidil Laboratory values, blood pressure, participant-reported adverse effects at recall Follow-up: 24 weeks	**Study population**		**RR 1.12** (0.61 to 2.06)	280 (1 study)	⊕⊕⊕⊖ **moderate**[5]	-
	121 per 1000	**136 per 1000** (74 to 250)				
	Moderate					
	-	-				
Adverse effects: safety and tolerability, and any reported adverse events with 2% minoxidil Structured interview, physical examination, and laboratory investigations Follow-up: 32 to 48 weeks	**Study population**		**RR 1.4** (0.6 to 3.27)	604 (3 studies)	⊕⊕⊕⊖ **moderate**[5]	-
	27 per 1000	**38 per 1000** (16 to 88)				

	Moderate					
	-	-				
Adverse effects: safety and tolerability, and any reported adverse events with 5% minoxidil Structured interview, physical examination, and laboratory investigations Follow-up: 48 weeks	**Study population**		**RR 3.55** (1.1 to 11.47)	227 (1 study)	⊕⊕⊕⊖ **moderate**[5]	-
	41 per 1000	**144 per 1000** (45 to 465)				
	Moderate					
	-	-				
Change in total hair count from baseline to the end of the study Hair counts in 1 cm^2 to 1.5 cm^2 area Follow-up: 24 to 48 weeks	The mean change in total hair count from baseline to the end of the study ranged across control groups from **-3.25 to 20.64**	The mean change in total hair count from baseline to the end of the study in the intervention groups was **13.28 higher** (10.89 to 15.68 higher)	-	1166 (7 studies[6])	⊕⊕⊖⊖ **low**[7]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in the footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]3-point scale: none, mild, moderate. 5-point scale: markedly improved, moderately improved, slightly improved, unchanged, worsened
[2]3/4 studies key domains of risk of bias, i.e. sequence generation, allocation concealment, and blinding judged 'unclear'. Tsuboi (2007) 'low risk'
[3]Olsen (1991) - small study no difference between 2 treatment arms, other larger studies show treatment effect
[4]Lucky (2004) - quality of life assessed 6-item questionnaire 100 mm VAS rated 0 = negative to 100 = positive. Unreported if questionnaire piloted tested or validated
[5]Wide confidence interval
[6]Lucky (2004) - comparisons minoxidil 2% versus placebo, minoxidil 5% versus placebo
[7]Price (1990) - outlier, small sample size (8). Possible publication bias, single participant with large treatment effect, result may be due to natural sampling variation

BACKGROUND

Unfamiliar terms are listed in the 'Glossary of terms' in (Table 1).

Description of the condition

Definition and clinical features

Female pattern hair loss is an increasingly common clinical problem in women (Bienová 2005; Gan 2005; Hoffmann 2000), with over 21 million affected in the US 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 are to 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. Female pattern hair loss 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 the 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 2011a; 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).

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), 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 (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 2011a). 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 (Blume-Peytavi 2011a; 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 history taking is suggestive of hyperandrogenism, an examination for cliteromegaly should also be undertaken.

Figure 1. Stage 1 on Ludwig scale

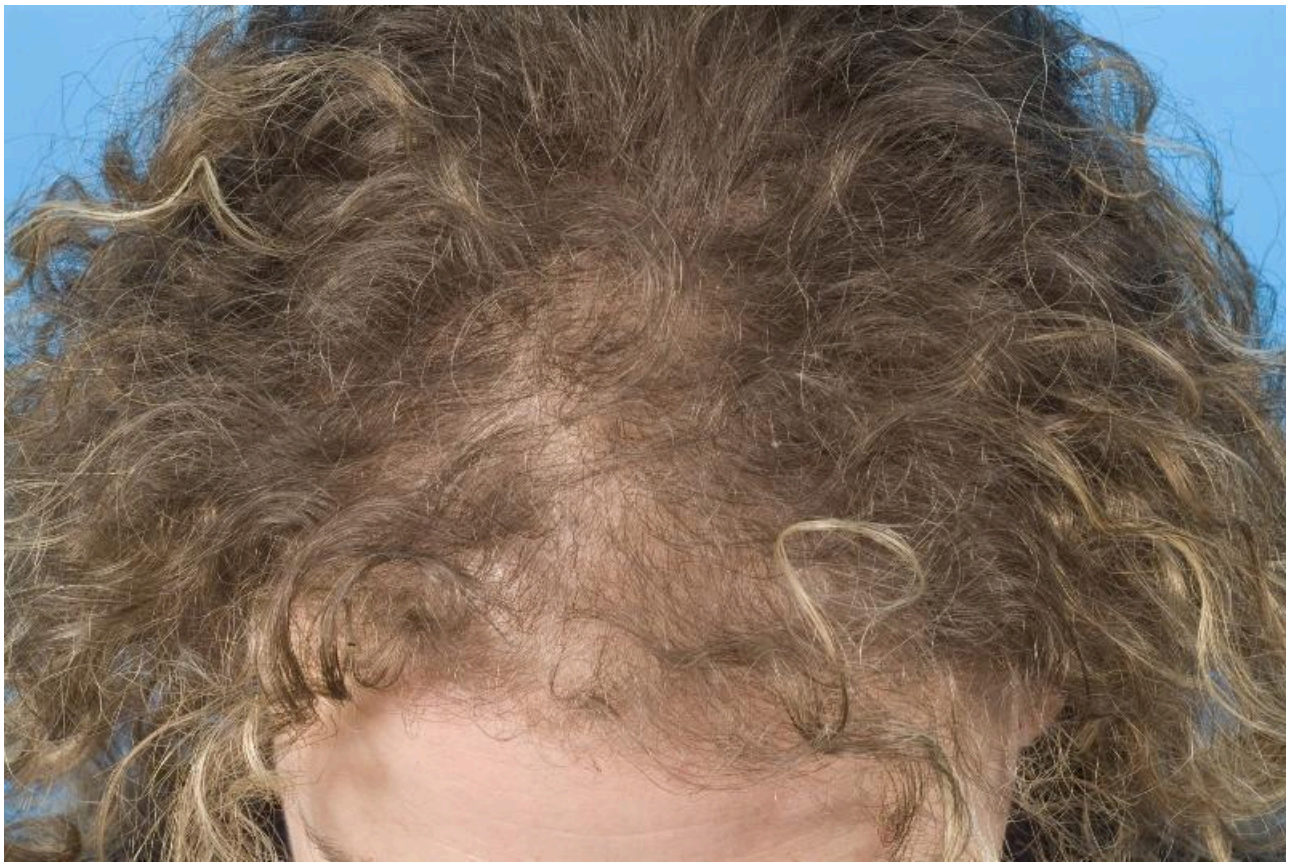
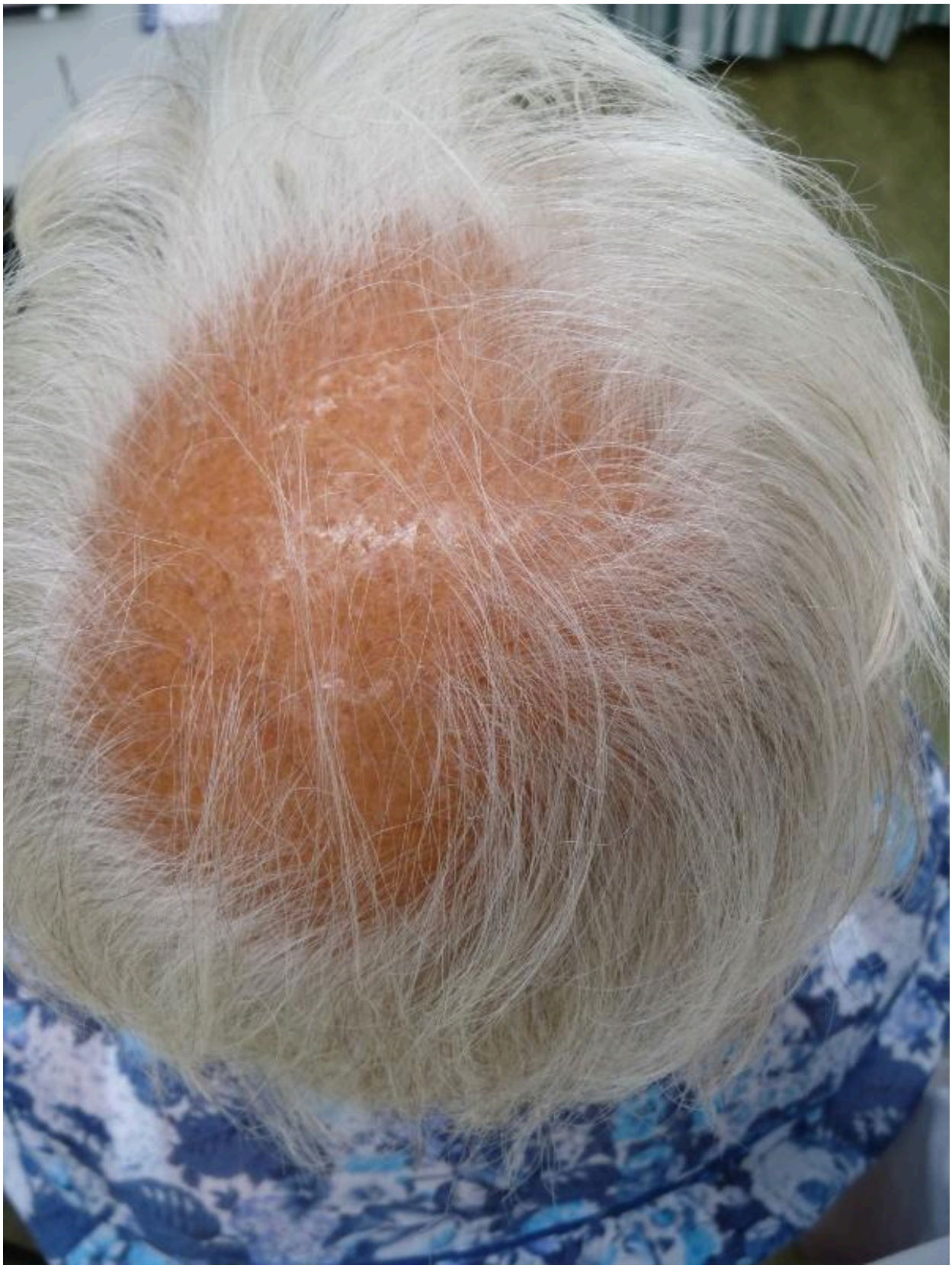


Figure 2. Stage 3 on Ludwig scale (severe FPHL)



Women with menstrual cycle disturbances, or those exhibiting marked acne, hirsutism, or both, should be investigated fully. The tests include the free androgen index test (FAI), and measurement of the levels of sex hormone-binding globulin (SHBG) and prolactin. 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 2011a). Polycystic ovary syndrome (PCOS) 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 2011a; Dinh 2007; Olsen 2005). 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-Martinez 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. It usually affects women over 40 years of age, many of whom are often 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). 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'). For many people, hair is a physical attribute that expresses individuality, and it is central to feelings of attractiveness or unattractiveness. 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, in the presence of both men and women, experience increased levels of self-consciousness, feelings of unattractiveness, shame, discomfort, and emotional stress - some of which can lead to social withdrawal (Cash 2001; van der Donk 1991; Reid 2011). The Women's Androgenetic Alopecia Quality of Life Questionnaire (WAA-QOL) (Dolte 2000) is a validated instrument, which has been used to assess the impact of FPHL on quality of life (QoL) in women. However, recent research has indicated that the severity of a woman's hair loss is not a reliable predictor of quality of life 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 quality of life.

Epidemiology and causes

Although FPHL is the most common type of hair loss in women, estimates of its true prevalence vary widely (Trüeb 2002). This is principally because investigators do not clearly state the diagnostic criteria that have been used in their studies. However, it is generally recognised that the prevalence of FPHL increases with age. 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 oriental women, and, although prevalence is considered to be less in African women, very limited data are available (Blume-Peytavi 2011a).

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 (Blume-Peytavi 2011a; 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 female pattern hair loss (Ali 2008; El-Samahy 2009; Westberg 2001; Yip 2011). A variation of the androgen receptor gene has been identified in postmenopausal women (Ali 2008), leading to increased serum levels of androgens. In premenopausal women, certain variants of the androgen receptor gene and the 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 levels (iron-containing proteins) have been suggested as possible contributory factors in FPHL (Kantor 2003), although this was not supported in a more recent study (Olsen 2010).

The demonstration of thyroid hormone receptor expression in hair follicle cells indicates that thyroid hormone may affect hair growth directly. 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 (Dinh 2007; Olsen 2005).
- Systemic: hormonal contraception, cyproterone acetate, finasteride, spironolactone, and flutamide (Bienová 2005; Dinh 2007; Olsen 2005).

Minoxidil is an antihypertensive vasodilator. The topical formulation is available in 3 concentrations (1%, 2%, and 5%), with the 2% applied once daily and the 5% either once or twice daily as the most commonly prescribed treatments. Minoxidil as a 1% concentration is less frequently used, and, in the majority of countries, the 5% concentration is only registered for the treatment of AGA in men. Common side-effects include scalp irritation and hypertrichosis on the cheeks and forehead (Rogers 2008). Minoxidil is contraindicated in pregnant and lactating women.

Aminexil is a derivative of minoxidil, which is available as a shampoo and in vials, 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. Alfatradiol is a 5-alpha-reductase inhibitor, but it is not freely available in many countries.

Systemic treatments focusing on antiandrogenic therapy include cyproterone acetate, spironolactone, finasteride, and flutamide. As all of these treatments carry the risk of malformation in male foetuses, effective contraceptive advice should be provided to women of childbearing age.

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 5 to 15 of the menstrual cycle. Important side-effects are depression, weight gain, breast tenderness, and loss of libido.

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).

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 US. Well known side-effects are electrolyte imbalance, cycle disturbances, fatigue, drowsiness, urticaria, breast tenderness, hypotension, and haematological disturbances. 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).

Other treatments that have been considered include food and herbal supplements, hair transplantation, laser comb therapy, and less frequently used medical treatments (e.g. dutasteride, cimetidine, tretinoin, and ketoconazole). However, the efficacy of these interventions is currently unsupported by clinical trials. Cosmetic aids are other important management options and include hairstyling techniques, hair replacements, camouflage products, and hair accessories (Dinh 2007).

As soon as treatment is stopped, shedding of hair may resume within weeks. 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. In essence, it encourages hair to move from the resting stage to the active growth stage. 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.

Cyproterone acetate is a progestin (synthetic hormone) with antiandrogen action. It acts by blocking androgen receptors, which prevents androgens (male hormones) from binding to them and suppresses luteinizing hormone (which in turn reduces testosterone levels). It is often combined with oral contraceptives, especially Diane-35, which contains 2 mg cyproterone acetate. Spironolactone reduces the activity of 5-alpha-reductase, inhibits the biosynthesis of androgens, and has a direct antagonistic effect on androgen receptors. 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.

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 review is needed to clarify the best approach to treating this condition, provide reliable decision-making information to clinicians and people with the condition about the benefits and harms of available treatments, and be the basis for recommendations for future research.

OBJECTIVES

To determine the effectiveness and safety of the available options for the treatment of FPHL 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. Women with increased circulating androgens, whether due to physiological causes, polycystic ovary syndrome, or any other causes, were included. However, women with androgen-producing adrenal or ovary tumours were excluded.

Types of interventions

We considered any intervention for FPHL or AGA.

Types of outcome measures

Primary outcomes

1) The proportion of participants with self-rated clinically significant hair regrowth at the end of the study.

2) Change in quality of life 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).

3) Adverse effects: safety and tolerability and any reported adverse events.

Secondary outcomes

1) Proportion of participants with investigator-rated clinically significant hair regrowth at the end of the study.

2) Mean change in total hair count from baseline to the end of the study.

3) Degree of hair shedding from baseline to the end of the study.

4) Cosmetic appearance of the hair or participant satisfaction.

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

'Clinically significant' outcomes were defined as, for example, a single level change on the Sinclair scale (Messenger 2006; Sinclair 2004). All outcomes measures that used a validated scale were accepted (e.g. Ludwig scale, Sinclair scale).

Search methods for identification of studies

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

Electronic searches

The Cochrane Skin Group searched for relevant studies up to 16 July 2010. Jan Schoones (JS) then updated the searches to 28 October 2011.

- 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) (last search 20 December 2011);
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* using the search strategy in Appendix 1;
- MEDLINE (from 2004) using the strategy in Appendix 2;
- EMBASE (from 2007) using the strategy in Appendix 3;
- PsycInfo (from 1872) using the strategy in Appendix 2;
- AMED (Allied and Complementary Medicine, from 1985) using the strategy in Appendix 2;
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 4;
- PubMed (from 1947) using the strategy in Appendix 5;
- Web of Science (from 1945) using the strategy in Appendix 6.

The UK and US Cochrane Centres have ongoing projects to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE to 2004 and in EMBASE to 2006. Further searching has been undertaken for this review by the Cochrane Skin Group and JS to cover the years that have not been searched by the UK Cochrane Centre.

Ongoing Trials

We searched the following ongoing trials registries on 28 October 2011 (EvZ) using the following search terms: androgenic alopecia, androgenetic alopecia, and female pattern hair loss.

- The metaRegister of Controlled Trials (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 Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials).

Searching other resources

References from published studies

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

Language

No language restrictions were imposed, and any studies not in the English language were translated prior to full assessment for eligibility.

Correspondence

Trial investigators were contacted and asked to provide missing data or clarify study details (see Table 2).

Data collection and analysis

Selection of studies

Three review authors (EvZ, ZF, and RBA) assessed the titles and abstracts identified from the searches. Only RCTs evaluating FPHL in women were included in this review. These authors independently assessed each included study to determine whether the pre-defined selection criteria were met, and they resolved any differences of opinion through discussion within the review team. Excluded studies and the reasons for their exclusion are listed in the 'Characteristics of excluded studies' section of the review.

Data extraction and management

Two authors (EvZ and RBA) extracted data using a previously developed data extraction form, and any disagreements on data extraction were resolved by consensus. Trial authors were contacted and asked to provide missing data where possible. Two review authors (EvZ and ZF) checked and entered the data into Review Manager (RevMan) (Review Manager (RevMan) 2011).

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). The evaluations were

compared, and any inconsistencies between the review authors were discussed and resolved.

The following domains were rated separately for each of the included studies as 'low risk of bias', 'high risk of bias', and 'unclear' if the risk of bias was uncertain or unknown:

(a) the allocation sequence was adequately generated ('sequence generation');
(b) the allocation was adequately concealed ('allocation concealment');
(c) knowledge of the allocated interventions was adequately prevented during the study ('blinding');
(d) incomplete outcome data were adequately addressed;
(e) reports of the study were free of suggestion of selective outcome reporting; and
(f) the study was apparently free of other sources of bias that could put it at high risk of bias, e.g. potential conflicts of interest, pharmaceutical funding/support, or both (Lexchin 2003).

These assessments are reported 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; or
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

These assessments are reported in the 'Risk of bias in included studies' section of this review.

Measures of treatment effect

We presented continuous outcomes on the original scale as reported in each individual study. In future updates, if similar outcomes are reported using different scales, these will be standardised by dividing the estimated coefficient by its standard deviation (SD), thereby allowing comparisons to be made between scales.

Dichotomous outcomes data were presented as risk ratios (RR). All outcomes data were reported with their associated 95% confidence intervals and were analysed in RevMan using the Mantel-Haenszel test, unless stated otherwise.

Unit of analysis issues

Cross-over studies

One cross-over study was included (Blume-Peytavi 2007), but, as no wash-out period was reported, we only included data from the first treatment period.

Multi-armed studies

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

Dealing with missing data

We were able to contact the investigators in several of the trials (see Table 2). Data were re-analysed 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 data were not reported and authors 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.

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, and the interventions. The degree of heterogeneity between the studies was assessed using the I^2 statistic. We reported heterogeneity as important if it was at least moderate to substantial by I^2 statistic > 60% (Higgins 2011). If this could be explained by clinical reasoning and a coherent argument could be made for combining the studies, these were entered into a meta-analysis. In cases where the heterogeneity could not be adequately explained, the data were not pooled.

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

Assessment of reporting biases

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), were performed for primary and secondary outcomes where meta-analysis (at least 3 studies needed) was performed. Funnel plots were only presented where there was some evidence of asymmetry in the plots. Possible sources of asymmetry were explored with an additional sensitivity analysis.

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

The different concentrations of the interventions were analysed as subgroups by comparing the risk ratios (RR) and 95% CI. If differences in effect estimates between the subgroups were observed, these were analysed separately.

In future updates 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 carried out sensitivity analyses to assess the robustness of the results of this review; thus, all fixed-effect meta-analyses were repeated using random-effects models. An additional sensitivity analysis was conducted, which excluded one study with suspected reporting bias.

RESULTS

Description of studies

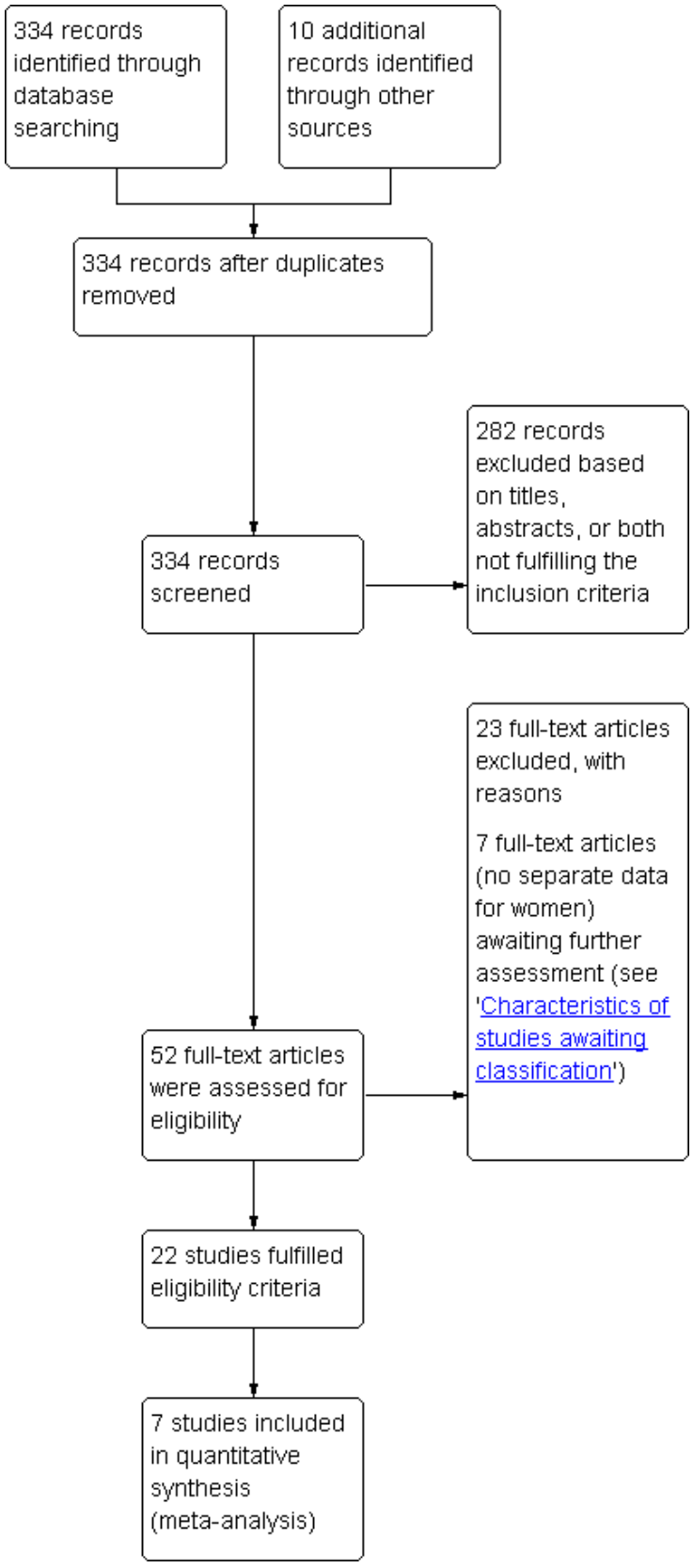
Results of the search

Our searches retrieved 334 references to studies. After the removal of duplicates and examination of the titles and abstracts, 282 of these references were excluded from the review. Full-text copies of the remaining studies were obtained and subjected to further evaluation. Several studies that were not published in the English language - Chinese (1) (Li 1996), Farsi (1) (Enshaieh 2005), Spanish (1) (Guerrero 2009), German (1) (Gehring 2000), and Italian (3) (Farella 1991; Minozzi 1997; Policarpi 1993) - were translated prior to assessment for eligibility.

We excluded 23 studies (see the 'Characteristics of excluded studies' section) and identified 12 ongoing studies (see the 'Characteristics of ongoing studies' section), which, if assessed as eligible, will be included in future updates of this review.

Finally, 22 studies were included, and 7 studies await further assessment (see the 'Characteristics of studies awaiting classification' section). For further details see the 'Study Flow Diagram' (Figure 3).

Figure 3. Study flow diagram



Included studies

Twenty-two studies comprising 2349 participants were included in this review (see the 'Characteristics of included studies' section).

Characteristics of the trial setting and methods

Although all of the studies were randomised controlled trials, 16 had a placebo, and 6, an active control treatment arm. Ten of the studies were conducted prior to the year 2000. The duration of most of the studies was between 6 and 12 months, and 12 of them were conducted in Europe, 8 in the US, and 2 in Japan.

Characteristics of the participants

The number of participants included in the individual studies varied widely, from 6 to 381 women, with between 30 and 70 representing the most common sample size. The age of the participants ranged from 18 to 89 years, with the majority between 18 and 60 years. All of the women had been diagnosed with AGA or FPHL, and two studies included hyperandrogenic women (Carmina 2003; Vexiau 2002).

Characteristics of the interventions

A wide range of interventions were evaluated: minoxidil in 10 studies (Blume-Peytavi 2007; Blume-Peytavi 2011; DeVillez 1994; Jacobs 1993; Lucky 2004; Olsen 1991; Price 1990; Tsuboi 2007; Vexiau 2002; Whiting 1992), and 4 studies examined the effects of finasteride (Carmina 2003; Price 2000; Ukşal 1999; Whiting 1999). Two studies included cyproterone acetate in one treatment arm (Carmina 2003; Vexiau 2002), and flutamide was evaluated in two other studies (Carmina 2003; Ukşal 1999).

A further 10 studies addressed other interventions: alfatradiol (Blume-Peytavi 2007); 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); systemic oestrogens (Minozzi 1997); 0.75% adenosine lotion (Oura 2008); the application of a pulsed electrostatic field (Policarpi 1993); and spironolactone (Ukşal 1999). Several of the trials compared and evaluated a number of these interventions.

Characteristics of the outcome measures

A majority of the studies included participant-assessed, in addition to investigator-assessed, outcomes. However, only 10 studies (Blume-Peytavi 2011; Carmina 2003; DeVillez 1994; Jacobs 1993; Lucky 2004; Olsen 1991; Oura 2008; Policarpi 1993; Price 2000; Tsuboi 2007) evaluated "hair regrowth", which was the primary outcome for this review. Moreover, 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 based on 3-, 4-, or 5-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 (Carmina 2003; Oura 2008; Price 2000) reported that they had applied a "modified version of a validated self-administered hair growth questionnaire" which had been 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 female pattern hair loss is unclear. Only one study (Lucky 2004) utilised a standard 100 mm visual analogue scale (VAS) for participant assessments of hair growth. These assessments were scored as follows: 0 = "much less scalp coverage", 50 = "same scalp coverage", and 100 = "much more scalp coverage". Benefit from treatment was scored similarly: 0 = "no benefit" to 100 = "great benefit". This study was also the only one to assess the effects of two of the interventions on quality of life, a key primary outcome for this review. A six-item VAS-based questionnaire was used for these assessments, but the report did not indicate if the instrument had been previously tested or validated.

A large proportion of the trials 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.

The secondary outcomes for this review were assessed in several of the included studies, 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, i.e. investigator-rated clinically significant hair regrowth and the change in total hair count from baseline to study conclusion.

Nine studies (Blume-Peytavi 2011; Carmina 2003; DeVillez 1994; Draelos 2005; Lucky 2004; Oura 2008; Price 2000; Tsuboi 2007; Whiting 1992) included a number of participant-preferred outcomes, e.g. appearance of the hair, degree of hair-shedding, general satisfaction, benefit of treatment, and cosmetic effectiveness. In three of the studies (Carmina 2003; Oura 2008; Price 2000), these outcomes were measured with a questionnaire (Barber 1998). A VAS instrument was used in two further studies (Lucky 2004; Vexiau 2002). Two questionnaires were used for participant-assessed outcomes in Blume-Peytavi 2011. These also included global photographs of the hair and scalp used for assessment of the change in hair volume and density from baseline, in addition to a nine-item questionnaire, which assessed the "participants perception of product aesthetics and consumer benefits". The responses in both questionnaires were rated on a seven-point Likert-type scale, but the report failed to mention if either questionnaire had been piloted, tested, or validated prior to use.

Several studies (DeVillez 1994; Tsuboi 2007; Whiting 1992) compared the degree of hair shedding before and after the intervention, which was rated on a three-point scale as "decreased, unchanged, [or] increased". Comparisons of photographic images were used to assess "hair fullness" in one study (Draelos 2005), but the methods used by the participants to assess this "fullness" were not adequately reported, highlighting the subjectivity of these assessments as reliable outcome measures.

The other secondary outcomes for this review, i.e. quality and pattern of hair regrowth, were evaluated in six studies (Blume-Peytavi 2007; Blume-Peytavi 2011; Carmina 2003; Gassmueller 2008; Lucky 2004; Oura 2008).

We examined any of the patient-reported outcomes (PRO) that were 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

Twenty-three studies were excluded, and the reasons for their exclusion are reported in the 'Characteristics of excluded studies' tables. All of these studies were excluded only after assessment of the full text of the report. The most frequent reason for their exclusion was that they were non-randomised trials.

Risk of bias in included studies

We assessed each of the included studies 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

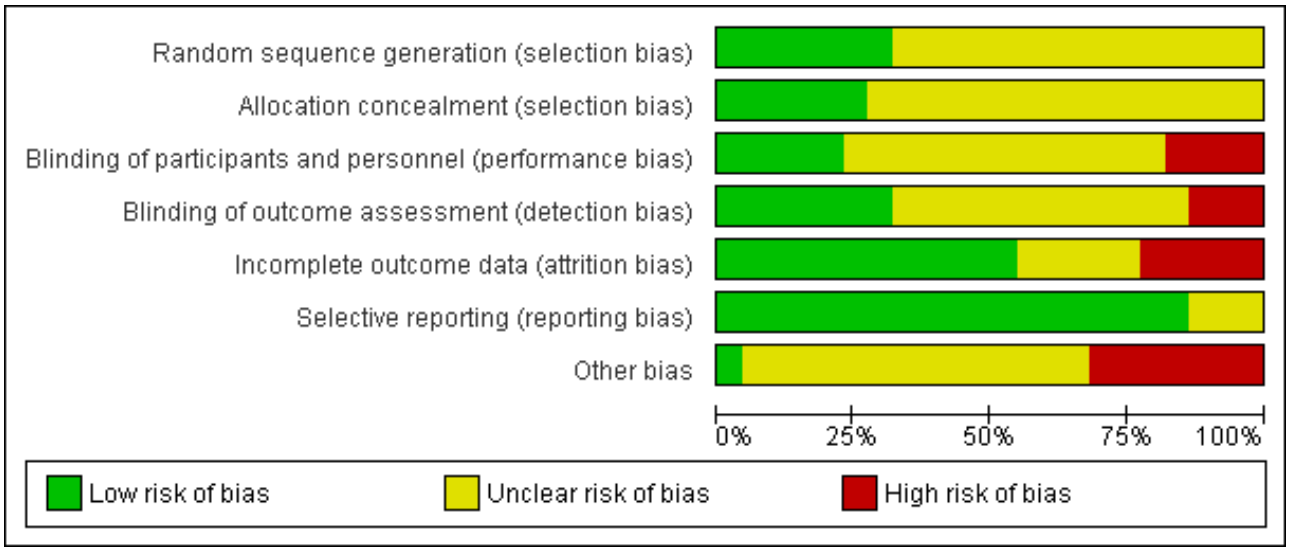


Figure 5. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study

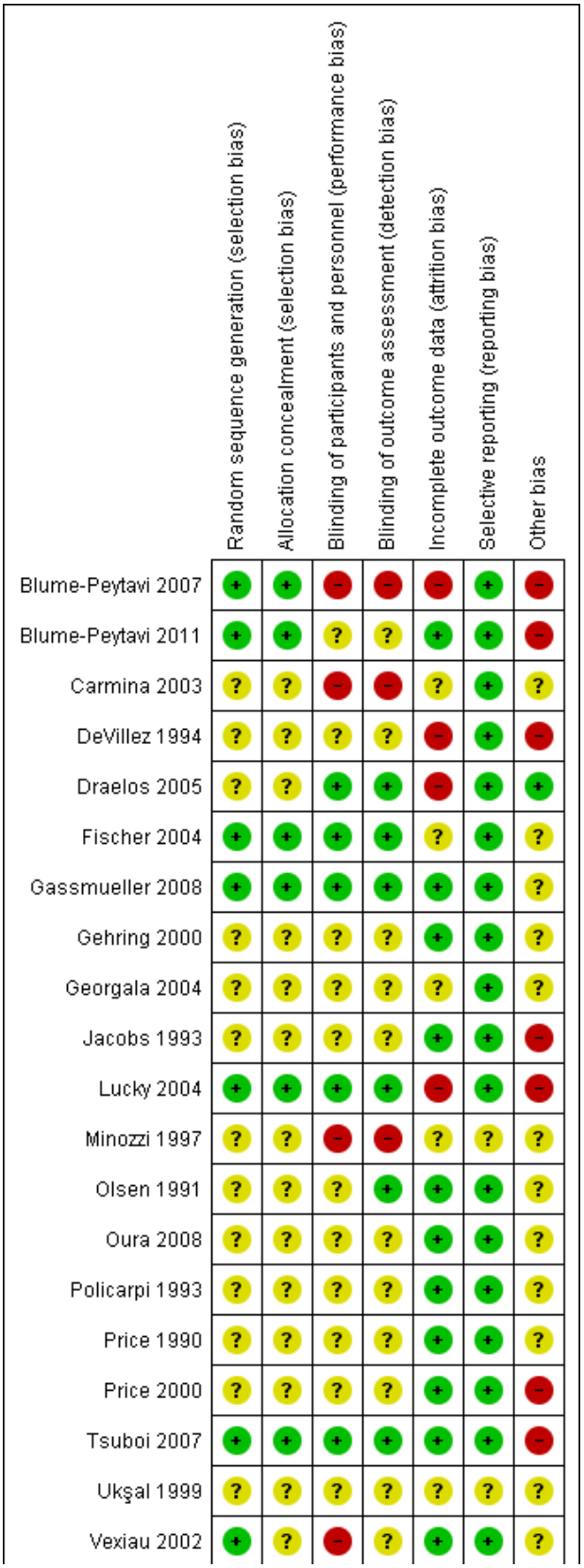
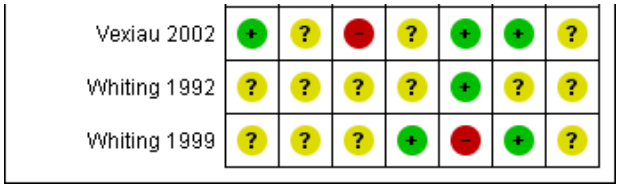


Figure 5. (Continued)



The overall risk of bias was assessed for each study, and 12 (Blume-Peytavi 2007; Blume-Peytavi 2011; Carmina 2003; DeVillez 1994; Draelos 2005; Jacobs 1993; Lucky 2004; Minozzi 1997; Price 2000; Tsuboi 2007; Vexiau 2002; Whiting 1999) were categorised as high risk of bias (plausible bias that seriously weakens confidence in the results) because 1 or more domains received a judgement of high risk. The remaining 10 studies were rated as unclear risk of bias (plausible bias that raises some doubt about the result) because 1 or more criteria were assessed 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 the studies in this review provided insufficient detail to enable accurate judgements to be made. 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 contacting several of the 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

In seven of the studies (Blume-Peytavi 2007; Blume-Peytavi 2011; Fischer 2004; Gassmueller 2008; Lucky 2004; Tsuboi 2007; Vexiau 2002) the method used to generate the allocation sequence was described in sufficient detail; therefore, this domain was judged as low risk of bias for these studies. The remaining 15 studies were judged as unclear risk of bias.

Allocation concealment

Pharmacy-controlled or central allocation ensured that the intervention allocations could not have been foreseen in advance of, or during, enrolment in six studies (Blume-Peytavi 2007; Blume-Peytavi 2011; Fischer 2004; Gassmueller 2008; Lucky 2004; Tsuboi 2007), which were judged low risk of bias for this domain. The method used to conceal the allocation sequence was not reported in the remaining trials; thus, receiving a judgment of unclear risk of bias for this domain.

Blinding

The measures used to blind study participants and personnel from knowledge of which intervention a participant received were described in sufficient detail in Draelos 2005, Fischer 2004, Gassmueller 2008, Lucky 2004, and Tsuboi 2007. Blinding was achieved by identical pre-labelled bottles or packages. As four of the studies (Blume-Peytavi 2007; Carmina 2003; Minozzi 1997; Vexiau 2002) were open label, the outcome or outcome measurement was likely to be influenced by lack of blinding. In these studies, this domain was judged as high risk of bias. One study (Blume-Peytavi 2011) was investigator-blinded and judged unclear. Inadequate reporting did not permit a clear judgement to be made for this domain in the other 12 studies.

Incomplete outcome data

In slightly more than half (12) of the studies, incomplete outcome data appear to have been adequately addressed. They were reasonably well-balanced across intervention groups, with similar reasons for missing data across the groups. However, in Blume-Peytavi 2007, DeVillez 1994, Draelos 2005, Lucky 2004, and Whiting 1999, the high dropout rate and subsequent per-protocol analysis of the data resulted in a judgement of high risk of bias for this domain.

In five studies (Carmina 2003; Fischer 2004; Georgala 2004; Minozzi 1997; Ukşal 1999) insufficient information was reported to permit a clear judgment of the risk of bias for this domain.

Selective reporting

The protocols were not available for any of the included studies. Based on the information in the methods section of the reports, 19 of the 22 studies appear to have reported all prespecified outcomes and were therefore judged to be free of selective reporting. The remaining three studies (Minozzi 1997; Ukşal 1999; Whiting 1992) were judged to be unclear to high risk of bias. 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 the primary outcomes of participant and investigator assessments of hair regrowth were not fully reported in Whiting 1992, this did not appear to be intentional, and, as the impact of this was unclear, this domain was judged as 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, this domain was judged as unclear risk of bias.

Other potential sources of bias

This domain was judged as 'unclear' in most of the studies, e.g. declarations of potential conflicts of interest or funding support were frequently unreported, or the report did not clearly state to what extent any support might have posed a risk of bias (Lexchin 2003). However, industry sponsorship represented a potential source of bias in six of the included studies (Blume-Peytavi 2007; Blume-Peytavi 2011; DeVillez 1994; Jacobs 1993; Price 2000; Tsuboi 2007). Although the impact of study sponsorship in Lucky 2004 was unclear, the "protocol-prohibited concomitant 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 2011, the baseline imbalance between the intervention groups, i.e. a higher proportion of participants with more extensive hair thinning in the minoxidil (5%) group, posed a risk of bias for this domain in this study.

Effects of interventions

See: **Summary of findings for the main comparison** Minoxidil compared to placebo for female pattern hair loss

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

Seven trials provided data for this comparison (DeVillez 1994; Jacobs 1993; Lucky 2004; Olsen 1991; Price 1990; Tsuboi 2007; Whiting 1992). Six of them examined the effects of a 2% strength of minoxidil, whereas Tsuboi 2007 compared a 1% strength with placebo, and one study (Lucky 2004) included an additional 5% arm.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

Four studies reported participant-rated clinically significant hair regrowth (DeVillez 1994; Jacobs 1993; Olsen 1991; Tsuboi 2007). Pooled data from these studies indicated that a greater proportion of participants (121/488) treated with minoxidil reported a statistically significant moderate increase in hair regrowth when compared with placebo (64/476) (RR 1.86, 95% CI 1.42 to 2.43, I^2 statistic = 31%) (see Analysis 1.1). After comparing the effect size and precision of estimates minoxidil (1%) versus placebo and minoxidil (2%) versus placebo, we conclude that, although the difference would appear to favour minoxidil (2%), this was small and provides no evidence of any genuine difference between the 2 concentrations. Although there was little suggestion of heterogeneity, we repeated the analysis using a random-effects model to assess the extent of the between study heterogeneity (Table 4).

Change in quality of life

The impact of hair loss on quality of life in Lucky 2004 was rated on a VAS, and at 48 weeks the mean score in the minoxidil (2%) group was 52.1 and 46.5 in the placebo group (P value = 0.04, Student t-test), where a score of 50 indicates "neutral" impact, ranging up to 100 as "positive" impact. In the minoxidil (5%) group, the mean VAS score was 54.4 (slightly more than no change) compared to 46.5 with placebo (P value = 0.004, Student t-test). Although these scores were reported without standard deviations and as statistically significant by the investigators, the mean differences between intervention groups were marginal and can be considered not clinically important.

Adverse effects, safety, and tolerability

Comparison of the effect size and precision of estimates for minoxidil (1%) versus placebo (RR 1.12, 95% CI 0.61 to 2.06) and minoxidil (2%) versus placebo (RR 1.40, 95% CI 0.60 to 3.27) reveals that, although the difference between the adverse effects favours the minoxidil (1%) concentration, this is small and provides little evidence of any genuine difference between the 2 concentrations (see Analysis 1.2). However, there was a statistically significant increase in the number of adverse events reported with minoxidil (5%) when compared to placebo (RR 3.55, 95% CI 1.10 to 11.47). 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 = 0.23).

In most instances, the adverse events 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). Although the data for adverse events were incomplete in DeVillez 1994, the investigators reported that adverse events were similar in both groups, and in Whiting 1992 it was reported that no serious adverse events had occurred.

The subgroups of the three different concentrations encapsulate clinical diversity, which did not permit pooling of data. The result of this diversity was illustrated by an increased likelihood of adverse events occurring with the higher (5%) concentration of minoxidil.

Secondary outcomes

Proportion of participants with investigator-rated hair regrowth

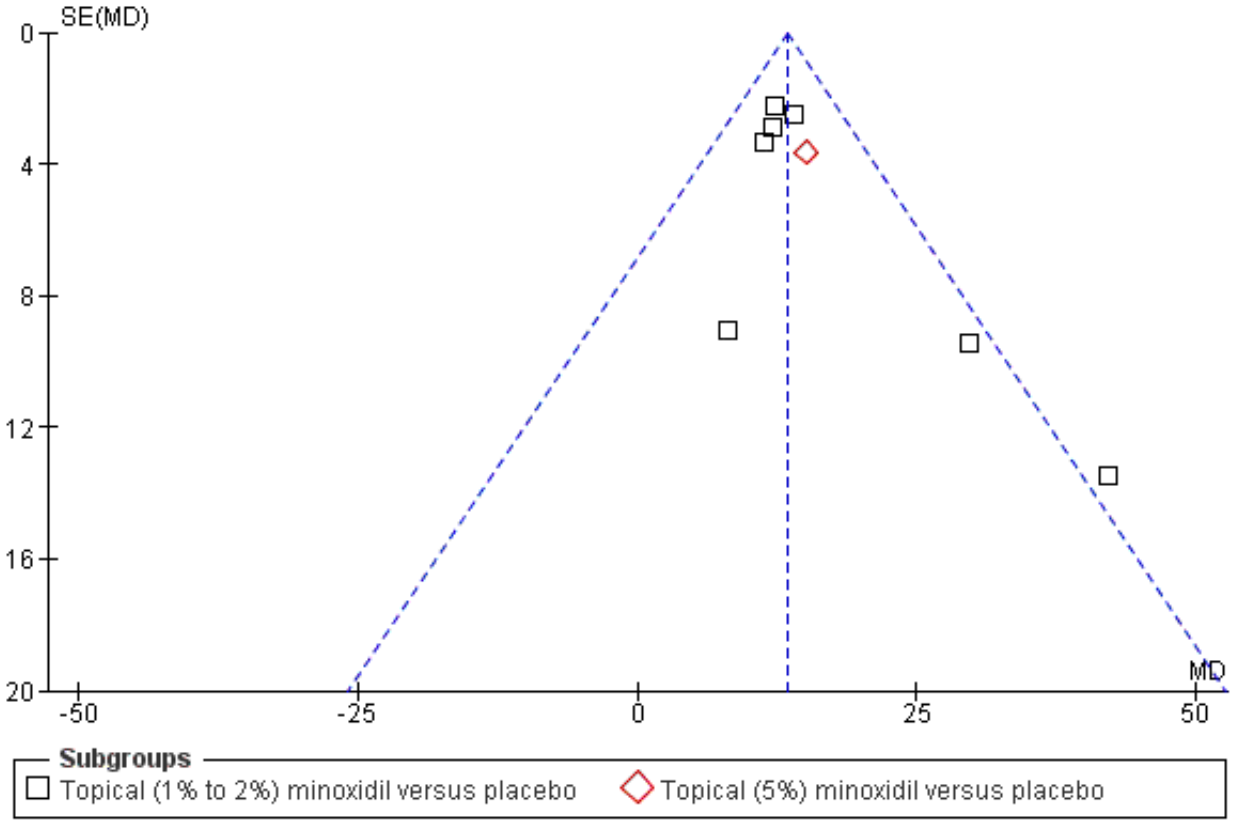
Five of the studies comparing one or more of these interventions provided data for this outcome (DeVillez 1994; Jacobs 1993; Olsen 1991; Tsuboi 2007; Whiting 1992). The investigator-rated assessments were in agreement with the participant self-rated assessments, both of which reported, and confirmed a statistically significant increase in moderate hair regrowth with minoxidil (86/505) compared to placebo (34/492) (RR 2.48, 95% CI 1.71 to 3.60, I^2 statistic = 0%) (see 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 2 minoxidil concentrations for this outcome.

Change from baseline in total hair count

All seven studies reported data for the mean change in total hair count from baseline. The mean difference across the studies favoured minoxidil and ranged from 8 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 13.28 (95% CI 10.89 to 15.68, I^2 statistic = 22%) (see 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 8 participants (Price 1990) (see Figure 6). It remains unclear if this asymmetry was the result of publication bias, small-study effects, or an artefact of natural variability. The impact of removing this study from Analysis 1.4 had a marginal effect on the overall pooled result since RR = 13.04 (95% CI 10.64 to 15.45, I^2 statistic = 0% (see Analysis 1.5); however, it did remove any

suggestion of heterogeneity. In an attempt to assess the between study heterogeneity, both of these analyses were repeated using a random-effects model, and the results are presented in Table 4. 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.



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

A decrease in hair shedding was reported by two thirds (10/17) of the participants in the minoxidil (2%) group compared with less than half (7/16) in placebo 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).

There was no statistically significant difference in the number of participants in Tsuboi 2007 reporting a decreased hair loss, with 98/140 participants in the minoxidil (1%) group compared to 87/140, demonstrating a large placebo effect (RR 1.13, 95% CI 0.95 to 1.33).

Cosmetic appearance of the hair or participant satisfaction

In one study, participants' satisfaction was measured as a 'benefit of treatment' and rated using a VAS (0 = no benefit, 50 = moderate benefit, and 100 = great benefit) (Lucky 2004). Participant satisfaction in the 2 minoxidil groups compared to placebo was 18.2 for the minoxidil (5%) group (P value < 0.001, Student t-test) and 8.7 for the minoxidil (2%) group (P value = 0.09, Student t-test). The score for the minoxidil (5%) group was 60.0 (27.6), for the (2%) group 50.5 (32.5), and 41.8 (29.9) for the placebo group, 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.

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

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 (P value = 0.012, Student t-test), with a lower score representing 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.

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

These interventions were compared in two studies (Blume-Peytavi 2011; Lucky 2004). In one of the studies (Blume-Peytavi 2011), a 2% concentration was applied twice daily and the 5% once daily, whereas in Lucky 2004, both concentrations were applied twice daily. Neither of the two studies reported any significant difference in efficacy between either of the two concentrations of minoxidil.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

Forty-four per cent (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) (Blume-Peytavi 2011).

Change in quality of life

The investigators in Lucky 2004 reported that at week 48 there was no statistically significant difference in impact of hair loss on quality of life between the 2 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 Blume-Peytavi 2011. These were reported by 51/57 participants in the minoxidil (2%) twice daily group compared to 43/56 in the 5% once daily group (RR 1.17, 95% CI 0.98 to 1.38).

In Lucky 2004, the number of participants reporting 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 5% twice daily group (RR 0.45, 95% CI 0.22 to 0.92). Hypertrichosis (more hair growth on areas other than the scalp), dermatitis, and pruritus were also reported more frequently in the minoxidil (5%) group.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The investigator- and participant-rated assessments were largely in agreement in both of the studies, i.e. that there was no evidence of a difference between the two concentrations of minoxidil for stimulating hair growth. In Blume-Peytavi 2011, 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 5% group (RR 0.84, 95% CI 0.43 to 1.66). These results were confirmed by the investigator-rated VAS scores in Lucky 2004 showing no statistically significant difference in efficacy between either concentration of minoxidil.

Change from baseline to study conclusion in total hair count

Both studies reported 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. In Blume-Peytavi 2011, the mean difference in total hair count from baseline to the end of study between the minoxidil (2%) and (5%) group was -3.50 (95% CI -10.55 to 3.55). These results were in agreement with data presented in Lucky 2004, which reported a mean difference of -3.80 between the minoxidil (2%) and (5%) group (95% CI -9.21 to 11.61).

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

This outcome was not assessed.

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 5% group (Blume-Peytavi 2011). Assessments of 'benefit of treatment' in Lucky 2004 rated on a VAS scored 50.5 (SD 32.5) in the 2% group versus 60.0 (SD 27.6) in the 5% group (P value = 0.29, Student t-test).

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

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 2011, and similarly in Lucky 2004 for hair density, assessed as the mean change from baseline based on the Savin female density scale.

(3) Minoxidil (2%) versus alfatradiol

One study that was assessed as 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

This outcome was not assessed.

Change in quality of life

This outcome was not assessed.

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, it was referred to by the investigators 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, these have not been included in the meta-analysis.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

This outcome was not assessed.

Change from baseline to study conclusion in total hair count

This outcome was not assessed.

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

This outcome was not assessed.

Cosmetic appearance of the hair or participant satisfaction

This outcome was not assessed.

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

The mean change in cumulative hair thickness from baseline to 6 months was 1.8 (SD 2.3) mm/cm^2 in the minoxidil group compared to –0.5 (SD 2.5) mm/cm^2 in the alfatradiol group (P value > 0.05, Wilcoxon signed-rank test). Between both study groups, minoxidil had a significantly better result on hair density (P value < 0.0002, Wilcoxon signed-rank test).

At 6 months the increase in hair density was 15.3 (SD 29.0) hairs/cm^2 (P value = 0.003, Wilcoxon signed-rank test) in the minoxidil group compared to -7.8 (SD 24.6) hairs/cm^2 in the alfatradiol group

(P value > 0.05, Wilcoxon signed-rank test). Treatment of FPHL with minoxidil in the first 6 months showed significantly better results (P value < 0.0005, Wilcoxon signed-rank test) in comparison with alfatradiol. Significant losses to follow up are likely to have had an impact on the precision, although not the direction of the effect estimate.

(4) Octyl nicotinate (0.5%) and myristyl nicotinate (5%) versus placebo

A single study compared the safety and effectiveness of octyl nicotinate (0.5%) and myristyl nicotinate (5%) versus placebo (Draelos 2005).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

This outcome was not assessed.

Change in quality of life

This outcome was not assessed.

Adverse effects, safety, and tolerability

Data for adverse events were not reported separately 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 authors concluded that they were related to the volatile vehicle, not the active constituent.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

At 6 months, 22 of the 40 participants treated with the combination therapy showed an increase in hair fullness compared to 4 of 20 of those treated with placebo (RR 2.75, 95% CI 1.10 to 6.90).

Change from baseline to study conclusion in total hair count

This outcome was not assessed.

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

This outcome was not assessed.

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 (P value = 0.05).

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

This outcome was not assessed.

(5) Topical melatonin-alcohol solution versus placebo

This comparison was evaluated in Fischer 2004; however, none of our primary or secondary outcomes were assessed.

(6) Fulvestrant 70 mg/mL versus placebo

A single study provided limited outcomes data for this comparison (Gassmueller 2008), concluding that fulvestrant was ineffective in the treatment of female pattern hair loss.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

This outcome was not assessed.

Change in quality of life

This outcome was not assessed.

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). Both fulvestrant and the vehicle were reported to have been well-tolerated.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

This outcome was not assessed.

Change from baseline to study conclusion in total hair count

This outcome was not assessed.

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

This outcome was not assessed.

Cosmetic appearance of the hair or participant satisfaction

This outcome was not assessed.

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

No statistically significant differences were reported in terms of percentage change from baseline in cumulative hair thickness, nor in hair density, favouring fulvestrant over placebo.

(7) Oral combination product of millet seed extract, L-cystine, and calcium pantothenate versus placebo

One study evaluated these interventions, but none of our primary or secondary outcomes were assessed (Gehring 2000).

(8) Adenosine versus placebo

The effect of this intervention in the treatment of FPHL was evaluated in only one study (Oura 2008).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

Assessments of improvement in hair growth rated by a dermatologist, the investigator, and the participants were in agreement that adenosine was not effective compared to placebo.

Change in quality of life

This outcome was not assessed.

Adverse effects, safety, and tolerability

There were no adverse events in both groups.

Secondary outcomes

Proportion of participants with investigator-rated clinically significant hair regrowth

The dermatologist-rated assessments indicated that 5 out of 15 participants in the adenosine treatment group were slightly improved or improved versus 3/15 in the placebo group (RR 1.67, 95% CI 0.48 to 5.76), and that these results were reasonably consistent with the investigator-rated assessments.

Change from baseline to study conclusion in total hair count

This outcome was not assessed.

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 with regard to the prevention of hair loss (P value = 0.036, Mann–Whitney U-test). However, no data were provided to support this conclusion.

Cosmetic appearance of the hair or participant satisfaction

Although the "change in appearance" at 12 months appeared to favour adenosine (P value = 0.048, Mann–Whitney U-test), there was no statistically significant difference in satisfaction between the 2 groups at the end of the study.

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

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 (P value = 0.002, Student t-test) with a difference between the 2 groups in favour of adenosine (P value = 0.04, Student t-test). The hair density (per cm^2) did not improve with a statistically significant difference from baseline in both groups, nor between the two groups at the end of treatment.

(9) Pulsed electrostatic field versus sham

One poorly reported trial 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 4 participants in the active treatment group showed a significant improvement at 36 weeks compared to neither of the 2 participants in the sham group.

Change in quality of life

This outcome was not assessed.

Adverse effects, safety, and tolerability

This outcome was not assessed.

Secondary outcomes

Quality and pattern of hair regrowth

This outcome was not assessed.

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 2 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

This outcome was not assessed.

Cosmetic appearance of the hair or participant satisfaction

This outcome was not assessed.

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

This outcome was not assessed.

(10) Finasteride versus placebo

Two studies examined this comparison (Price 2000; Whiting 1999).

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).

Change in quality of life

This outcome was not assessed.

Adverse effects, safety, and tolerability

A similar number of adverse events were reported for both groups in Price 2000: 53/67 in the finasteride group versus 55/70 in the placebo group (RR 1.03, 95% CI 0.45 to 2.34). Several of the adverse events reported in this study are common in postmenopausal women and not necessarily drug-related. More adverse events, such as headache and depression, were reported in the placebo group.

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 1 participant with a greatly increased change in hair growth (RR 0.77, 95% CI 0.31 to 1.90).

Change from baseline to study conclusion in total hair count

At 12 months, both treatment groups in Price 2000 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. In Whiting 1999, there was an increase of 0.2 in change from baseline in total hair count of terminal hairs in the finasteride group versus 1.1 in the placebo group.

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.

Cosmetic appearance of the hair or participant satisfaction

No data were reported, but the investigators indicated that there was no statistically significant difference in the proportion of participants in either intervention group, indicating satisfaction with their hair overall or its appearance at the end of the study (Price 2000).

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

This outcome was not assessed.

(11) Minoxidil and oral contraceptive pill (OCP) versus cyproterone acetate and OCP

One study assessed as high risk of bias (Vexiau 2002) compared the effects of these interventions.

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

This outcome was not assessed.

Change in quality of life

This outcome was not assessed.

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

This outcome was not assessed.

Change from baseline to study conclusion in total hair count

Minoxidil combined with the OCP was more effective than cyproterone acetate. The mean difference in total number of hairs per 0.36 cm^2 between the minoxidil group and the cyproterone acetate group was 7.90 (95% CI 3.70 to 12.10).

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

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

Cosmetic appearance of the hair or participant satisfaction

Hair loss and degree of seborrhoea were used to evaluate cosmetic effectiveness by the participants using VAS. Both groups reported a decrease in seborrhoea, but this was more noticeable in the cyproterone acetate group.

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

This outcome was not assessed.

(12) Cyproterone versus flutamide versus finasteride

One study examined these comparisons (Carmina 2003), but it was assessed as high risk of bias. The investigators reported that flutamide at a dose of 250 mg daily provided a modest improvement in alopecia after 1 year, whereas cyproterone acetate and finasteride 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 quality of life

This outcome was not assessed.

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

This outcome was not assessed.

Change from baseline to study conclusion in total hair count

This outcome was not assessed.

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).

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

Baseline to end of study hair density was investigator-assessed on a 7-point scale (-3 = greatly decreased to 3 = greatly increased). In the

cyproterone group, this scale was rated after 12 months as 0.5 (SD 0.2) in the flutamide group 0.9 (SD 0.2) and in the finasteride group 0.1 (SD 0.2).

(13) 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 provided minimal data for this comparison (Georgala 2004).

Primary outcomes

Proportion of participants with self-rated clinically significant hair regrowth

This outcome was not assessed.

Change in quality of life

This outcome was not assessed.

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, 2 participants experienced postmenopausal uterine bleeding, resulting in their withdrawal from the study.

Secondary outcomes

None of our secondary outcomes were assessed.

(14) Ethinylestradiol and medroxyprogesterone acetate (MPA) versus transdermal estradiol and (MPA) versus ethinylestradiol and cyproterone acetate

One study (Minozzi 1997) compared these interventions, but it was assessed as high risk of bias and did not address any of our outcomes.

(15) Spironolactone versus finasteride versus flutamide

Only one study addressed these interventions (Ukşal 1999), but the investigators provided very limited data, none of which could be reported. Therefore, no conclusions could be drawn regarding the efficacy or safety of these interventions.

DISCUSSION

Summary of main results

Twenty-two studies, which examined 2349 participants, were included in this review. One of our key patient-preferred outcomes, 'quality of life', was assessed in only one of the studies (Lucky 2004). The majority of 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. Female pattern hair loss can be distressing, and it is known to have an impact on quality of life. Thus, the importance of assessing the effectiveness 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.

Based on the findings of this review, the only intervention that appeared to demonstrate a measure of efficacy was minoxidil. The 2% concentration illustrated a good safety profile, and, although more undesirable side-effects, such as hypertrichosis and increased hair growth on other areas than the scalp, were associated with the 5% concentration (Lucky 2004), these were not confirmed by the findings in a further study (Blume-Peytavi 2011). However, it should be noted that different dosing regimens were used in these 2 studies, i.e. the 5% solution twice daily (100 mg) in Lucky 2004 in contrast to once daily in Blume-Peytavi 2011. And there is wide acknowledgement that doses in excess of 60 mg a day may lead to an increase in the number of adverse effects.

For further details see the 'Summary of findings for the main comparison'.

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, which, based on the evidence available, appeared to be safe and effective in the treatment of FPHL.

The majority of interventions were evaluated in a single study, and none of the studies addressed more than a very limited number of our outcomes, illustrating gaps in the overall completeness of the evidence. The quality of data reporting was very variable across the studies, and, in several, it was unclear to what extent the impact of industry sponsorship may have had on the direction and completeness of the results.

Hair regrowth and adverse events were the most commonly addressed outcomes, but 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, with the exception of 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.

Several ongoing studies were identified that may eventually help to fill in some of the gaps in the evidence for the effectiveness or otherwise of some of the other interventions, e.g. spironolactone and the use of laser combs (see the 'Characteristics of ongoing studies' section).

Quality of the evidence

Limitations in study design and implementation

Although 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 have been 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 used to generate the

sequence, to conceal the allocation, and the measures taken to blind investigators and participants. These factors, compounded with unsuccessful attempts to contact many of the investigators for additional information, created difficulties in making accurate assessments of the risk of bias in almost half of the included studies.

In many instances, the key outcomes that were assessed in the included studies provided limited data, much of which could not be pooled except for minoxidil, 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).

Fourteen of the 22 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. To fill the evidence gap, clinicians need to have access to information about the benefits and harms of individual interventions as well as the comparative efficacy of these interventions. Thus, 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 quality of life and which are of direct relevance to patients - appears to have been underestimated by the investigators in the majority of the included studies. A validated disease-specific tool for the assessment of quality of life 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 single study (Lucky 2004) which evaluated the impact of the interventions on quality of life utilised a simple questionnaire, and, as with the majority of the PROs that were 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, 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 this comparison. All of the meta-analyses carried out for the comparison of minoxidil versus placebo illustrated a low degree of unexplained heterogeneity (I^2 statistic < 32%) and allowed us to conclude that the differences in treatment effect seen between the studies may not be important and with no suggestion of inconsistency, as described in section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Imprecision of the results

Of the 22 studies included in this review, one third (7) compared the effects of minoxidil versus placebo; therefore, our results reflect and draw conclusions only on this comparison. Each pooled analysis was carried out with at least 964 participants and provided consistent evidence that all efficacy outcomes were superior in all of the concentrations of minoxidil (1%, 2%, 5%) compared to placebo. In each of the efficacy outcomes, the effect estimate was tightly bound by the confidence interval and demonstrated clear improvement favouring all of the concentrations of minoxidil. More adverse events were reported in the 5% concentration of minoxidil (see Analysis 1.2), but we highlight that both the lowest and highest concentrations of minoxidil were analysed as subgroups that consisted of single studies of 227 and 280 participants. Therefore, we advise caution when interpreting this finding as the results reflect a relatively low number of studies and participants. However, on balance, they provide consistent and reliable evidence that minoxidil in either of the three concentrations is more effective than placebo.

Publication bias

Based on a visual assessment of the funnel plot, 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 investigating 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, a sensitivity analysis was carried out, 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 authors' independent assessments of eligibility of studies for inclusion in this review and the 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, this was explicitly stated in the text of our review. 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 that were not in the English language were translated so that they could be assessed for eligibility.

Agreements and disagreements with other studies or reviews

We identified several literature reviews (Birch 2002; Camacho-Martinez 2009; Dinh 2007; Leavitt 2008; Olsen 2005; Price 2003; Trüeb 2010) and two guidelines (Blumeyer 2011; Drake 1996) which covered aspects of the diagnosis and management of female pattern hair loss in women. Although the reviews were a valuable resource to answer background questions covering the pathogenesis, classification, and epidemiology of the condition, none of them had 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 clearly demonstrate that the supporting evidence was systematically reviewed (Nasser 2011).

The earlier of the two 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, 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 more recently published "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 of the 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 nothing was reported by the guideline developers. 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 not consistent with our judgment that they were all categorised as 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 assessments of risk of bias carried out 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 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 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 assessments of risk of bias 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 evaluating minoxidil (1%) (Tsuboi 2007) provided results that were the third largest treatment effect out of the 7 included studies in Analysis 1.4 and, similarly, in Analysis 1.1 and Analysis 1.3. It should also be highlighted that whilst the guideline provided a narrative synthesis of the data, the conclusions in this review are inferences derived from a systematic and evidence-based approach.

In this 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 this 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 (Grades of Recommendation, 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. This explains our confidence in the effect estimate for minoxidil in particular (this has been reported in the 'Summary of findings for the main comparison').

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 evidence to support the effectiveness of only one of the interventions for female pattern hair loss, 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 (5%) of minoxidil is only registered for therapeutic management of female pattern hair loss in a small number of countries around the world.

Clinical decision-making on the choice of intervention for female pattern hair loss 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 minoxidil (2%) 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 1 study included in this review indicate that minoxidil (1%) does not appear any less effective than minoxidil (2%) and is also associated with a potentially lower number of adverse events. There was also some evidence that minoxidil (5%) once daily was as effective as (2%) minoxidil twice daily, a factor which may be important in improving adherence. In view of these findings, further research is required, in particular, direct comparison studies of minoxidil (5%) applied once a day versus minoxidil (2%) twice daily.

There is also an urgent need for high-quality, well-designed, and rigorously-reported studies of other widely-used treatments, such as spironolactone, finasteride, cyproterone acetate, and laser comb therapy. Conceivably, some of the 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 not only the conduct but also in the quality of reporting of many of the 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 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 quality of life 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 5.

ACKNOWLEDGEMENTS

The Cochrane Skin Group editorial base wishes to thank Hywel Williams who was the Key Editor for this review; Jo Leonardi-Bee and Philippa Middleton who were the Statistical and Methods Editors, respectively; the clinical referee, Abby Macbeth; another clinical referee who wishes to remain anonymous; and the consumer referees Shirley Manknell, Jack Tweed, and Amy Zelmer.

The review authors would like to thank former authors of this review for their contribution to an earlier version: Carlos Cesar Cusmanich, Virginia Fernandes Moça Trevisani, C Whitney Hannon, Hermenio C Lima, and Rod Sinclair. We are indebted to the following colleagues for their help with translating studies: Raphael Freitas De Souza, Ribeirão Preto Dental School, University of São Paulo Ribeirão Preto, Brazil (Spanish into English); Mona Nasser, Clinical lecturer in Evidence-based dentistry, Peninsula Dental School, Plymouth, UK (Farsi into English); Edwin Chan Shih-Yen, Duke-NUS Graduate Medical School, Singapore Director, Singapore Branch, Australasian Cochrane Centre (Chinese into English). ZF would also like to thank Armin van Buuren for providing the creative atmosphere that was so essential to the writing up phase of this review.

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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

Blume-Peytavi 2007 *(Continued)*

	Multicentre (4), Germany Date of study Unspecified (but 12-month duration)
Participants	103 women Mean age = 50.7 years in group I, 45.6 years in group II **Inclusion criteria of the trial** • FPHL grade I or II (Ludwig 1977) **Exclusion criteria of the trial** Nothing was reported. Randomised 103 participants were randomised (group I = 52, group II = 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 (12 months). **Comparator** • 0.025% alfatradiol solution 3 mL once daily (months 1 to 6); cross-over (months 7 to 12) to minoxidil 2%. No wash-out period was specified.
Outcomes	Assessment was of the central parietal region of the scalp, defined and marked with a semipermanent tattoo. The area was shaved (baseline 3-, 6-, 12-month recall) and assessed by TrichoScan ® (Hoffmann 2002), epiluminescence microscopy and digital image analysis. **Outcomes of the trial** (as reported) 1. Cumulative hair thickness (mm/cm^2)# 2. Hair density (number of hairs/cm^2)# 3. Terminal hair density 4. Vellus hair density 5. "Tolerability of treatment" by participant and investigator on a scale of 1 (excellent) to 5 (unsatisfactory) 6. "Unwanted event or side effect" Denotes outcomes prespecified for this review.
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.

Blume-Peytavi 2007 *(Continued)*

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.

The Principal Investigator, Ulrike Blume-Peytavi, was an advisor for Pfizer and Golderma R&D. The authors Christian Kunte, Natalie Garcia Bartels, and Rolf Hoffmann were advisors for Pfizer.

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 or outcome measurement 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 or 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)..." 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 post randomisation losses of participants, nor the potential carry-over and period effects due to the cross-over design in 1 treatment arm. Given the high attrition rate, the per-protocol analysis of these data is likely to inflate the effect estimate, and, consequently, it may raise concerns about the reliability of the data as reported.
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. Comment: We judged this as at a low risk of bias.
Other bias	High risk	The principal and several of the investigators declared their conflicts of interest as 'advisors' for Pfizer and Golderma R&D. Although they did not confirm

Blume-Peytavi 2007 *(Continued)*

	what, if any, support was provided, the intervention under investigation was Regaine ® Frauen (Pfizer Consumer Healthcare); thus, a potential risk of bias cannot be excluded.

Blume-Peytavi 2011

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 of the trial** • > 18 years • Savin grade D3 to D6 female pattern AGA • Hair density ≤ 220 hairs/cm^2 as measured by TrichoScan **Exclusion criteria of the trial** • 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 Randomised 113 participants were randomised (minoxidil 5% group = 56, minoxidil 2% group = 57). Withdrawals/losses to follow up There were 13 withdrawals/losses to follow up: 6 in the minoxidil 5% group, and 7 in the minoxidil 2% group. • Minoxidil 5% group: 1 subject preference, 1 lost to follow up, 3 to adverse events, 1 serious adverse event • Minoxidil 2% group: 4 subject 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%.

Blume-Peytavi 2011 *(Continued)*

	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 (24 weeks) **Control** • minoxidil 2% topical solution (MTS) twice daily (24 weeks)
Outcomes	Assessment was at weeks 1,12, and 24. **Primary outcomes of the trial** (as reported) 1. Change from baseline in non-vellus target area hair count at week 24# **Secondary outcomes of the trial** (as reported) 1. Change in non-vellus target area hair width 2. Overall efficacy by global photographic review as assessed by treatment-blinded evaluators and the subject herself 3. Adverse events# 4. Participants' assessment of product aesthetics Denotes outcomes prespecified for this review.
Notes	Quote (page 1126): "Supported by a medical grant application, Johnson & Johnson Consumer Co Inc. Dr Blume-Peytavi is a consultant for Johnson & Johnson Consumer Co Inc. Dr Garcia Bartels was a consultant for Pfizer GmbH Germany until 2008."

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." After e-mail communication with investigators: The allocation was performed using block randomisation (27 blocks, sequences 4 and 6). Comment: This was judged 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: This was judged 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 provid-

Blume-Peytavi 2011 *(Continued)*

		ing 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." Comment: 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 not available, 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	High risk	There was baseline imbalance, with a higher proportion of participants with more extensive hair thinning in the minoxidil (5%) group. The Principal Investigator declared a conflict of interest as a consultant of Johnson & Johnson Services, Inc., who provided a medical grant, and another investigator was a consultant for Pfizer GmbH Germany. Thus, a potential risk of bias cannot be excluded.

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 (duration 12 months)
Participants	48 hyperandrogenic women with alopecia Mean age = 25 ± 2 years **Inclusion criteria of the trial**

Carmina 2003 *(Continued)*

- FPHL Ludwig scale grade I to III (Ludwig 1977)
- Premenopausal with increased serum androgens

Exclusion criteria of the trial

Nothing was reported.

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

- group I = cyproterone acetate (CPA) 50 mg/day with 25 µg of ethinylestradiol in a reverse sequential regimen (CPA from day 5 to 15 of the cycle, and ethinylestradiol from day 5 to 25 of the cycle)
- group II = flutamide (250 mg/day)
- group III = finasteride (5 mg/day)
- control group = no treatment (observational, not randomised)

The duration of treatment for groups I, II, and III was 1 year.

Outcomes

There was inadequate and unclear information on the frequency and timing of the following assessments.

Primary outcomes of the trial (as reported)

1. Hair thinning (frontal) on Ludwig scale (Ludwig 1977)
2. 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)
3. Hair density: investigator-assessed (frontal–parietal region) before and after treatment rated on 7-point scale: greatly decreased (-3) to greatly increased (+3)#

Secondary outcomes of the trial (as reported)

1. Possible side-effects and liver function tests assessed at 3-month intervals

Denotes outcomes prespecified for this review.

Notes

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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."

Carmina 2003 *(Continued)*

		Comment: Insufficient detail was reported about the method used to generate the allocation sequence 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	Quote (page 91): "...unmasked trial of three treatments." Comment: The outcome or outcome measurement 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 or 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. Comment: We judged this as at a low risk of bias.
Other bias	Unclear risk	There were no declaration of potential conflicts of interest or funding support. Comment: There was insufficient information to permit a clear judgement of the potential risk of bias.

DeVillez 1994

Methods	This was a randomised, double-blind, placebo-controlled trial. Setting Multicentre (11), US, but no further details reported Date of study Unspecified (duration of 32 weeks)
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 of the trial** • 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

DeVillez 1994 *(Continued)*

Exclusion criteria of the trial

- 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 in the minoxidil group (16.6%), and 25 in the placebo group (14.8%).

- 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

Interventions	**Intervention** • 2% topical minoxidil 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	**Primary outcomes of the trial** (as reported) 1. Hair counts (combination photography and computer-assisted image counting) **Secondary outcomes of the trial** (as reported) 1. Investigator- and participant-assessed new hair growth, rated as none/minimal or moderate/dense compared to baseline 2. Participant-assessed hair shedding (degree), rated as increased/decreased/unchanged 3. Adverse events# Denotes outcomes prespecified for this review.
Notes	3 of the 4 investigators were from the Dermatology Division of Upjohn Laboratories.

Risk of bias

Bias	Authors' judgement	Support for judgement

DeVillez 1994 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote (page 304): "...randomized to receive either..." Comment: There was insufficient detail reported about the method used to generate the allocation sequence 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 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." 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	High risk	52/308 participants "discontinued"; the majority were voluntary withdrawals and were balanced across both groups. The data analysis was per-protocol. Comment: The large number of dropouts (17%), incomplete outcome data, and inappropriate analysis were potential sources 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. Comment: We judged this as at a low risk of bias.
Other bias	High risk	3 of the 4 investigators were from the Dermatology Division of Upjohn Laboratories, the manufacturer of the intervention under investigation, and, although the report was unclear about the extent and level of any funding or support, a potential risk of bias cannot be excluded. Comment: We judged this as at a high risk of bias.

Draelos 2005

Methods	This was a randomised, double-blind, placebo-controlled trial. Setting A "research center" in the US Date of study Unreported (6-month duration)
Participants	60 women **Inclusion criteria of the trial**

Draelos 2005 *(Continued)*

- Age 20 to 80 years
- FPHL Ludwig scale grade I to III (Ludwig 1977)

Exclusion criteria of the trial

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** • 0.5% octyl nicotinate and 5.0% myristyl nicotinate in vehicle. 6 drops/night to the scalp (right anterior/right-middle top/left-middle top/right posterior/left posterior) for 6 months **Control** • vehicle only. 6 drops/night to the scalp (right anterior/right-middle top/left-middle top/right posterior/left posterior) for 6 months
Outcomes	**Outcomes of the trial** (as reported) 1. Investigator-assessed hair growth by standardised photographic techniques (baseline and end points), rated as follows: -1 = decrease/no change, +1 = increased 2. Appearance of hair (participant-assessed) 3. Adverse events# Denotes outcomes prespecified for this review.
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: There was insufficient detail reported about the method used to generate the allocation sequence 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)	Low risk	Quote (page 259): "Dispensed products were packaged in identical containers."

Draelos 2005 *(Continued)*

All outcomes		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	Incomplete outcome data were not adequately addressed; timing of, and reasons for, withdrawal were unreported; and there were substantial differences between the 2 groups. 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	The study was supported in part by an NIH grant and Niadyne, Inc. and conformed to the University of Arizona's 'conflict of interest' policies. Comment: The sponsorship/support as declared by the investigators did not appear to indicate a potential source of 'other 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 of the trial** • AGA Ludwig scale (Ludwig 1977) • Diagnosis of diffuse alopecia; hair thinning all over the scalp **Exclusion criteria of the trial** • Thyroid disease or iron deficiency Randomised 40 participants were randomised (melatonin group = 20, placebo group = 20). Withdrawals/losses to follow up None were reported.

Fischer 2004 *(Continued)*

	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** • 0.1% topical melatonin-alcohol solution. 1mL as a spray once daily in the evening for 6 months **Control** • alcohol solution alone. 1mL as a spray once daily in the evening for 6 months
Outcomes	**Outcomes of the trial** (as reported) 1. Hair counts by frontal and occipital Trichograms (baseline, 3, and 6 months)
Notes	There was separate analysis for AGA and diffuse alopecia. The investigators acknowledged the "support of ASAT Applied Science & Technology, Zug, Switzerland and Biomedical Software Tübingen Germany for the "statistical analysis".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (pg 342): "...double-blind randomized..." Comment: There was insufficient detail reported about the method used to generate the allocation sequence 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 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: "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."

Fischer 2004 *(Continued)*

		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.
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	Unclear risk	There were no declarations of potential conflicts of interest. The investigators acknowledge the "support of ASAT Applied Science & Technology, Zug, Switzerland and Biomedical Software Tübingen Germany for the "statistical analysis" (page 344). Comment: There was insufficient information to permit a clear judgement of the risk 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 of the trial** • Postmenopausal • AGA Ludwig scale grade I or II (Ludwig 1977) **Exclusion criteria of the trial** • 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

Gassmueller 2008 *(Continued)*

- 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

- (2) for personal reasons (on days 15 & 17), and (1) for protocol deviation (use of prohibited concomitant medication). It was unclear from which of the groups the losses were

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)

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** • 30 µL per cm^2 fulvestrant, 70 mg per mL (0.115 mol per L) solution. Applied topically twice daily for 16 weeks **Control** • vehicle (40% propylene glycol, 40% isopropanol, 20% water). Applied topically twice daily for 16 weeks
Outcomes	**Outcomes of the trial** (as reported) 1. Hair density, TrichoScan analysis of digital images of test area (baseline and days 29, 57, 85, and 113)# 2. Hair thickness and hair growth rate by TrichoScan analysis 3. Level of systemic exposure to fulvestrant and tolerability of topical fulvestrant Denotes outcomes prespecified for this review.
Notes	Of 2 phase II RCTs of men and women with AGA, only the trial including women was considered in this review. 1 of the investigators was associated with AstraZeneca, and the study was supported financially by AstraZeneca.

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 as-

Gassmueller 2008 *(Continued)*

		signment 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 sequence was generated by the sponsor, 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. 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 not available, 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	Unclear risk	Quote: Although one of the investigators was associated with AstraZeneca and "this study was supported financially by AstraZeneca", the report did not include a declaration of conflicts of interest. Comment: There was insufficient information to permit a clear judgement of the extent to which the financial support may have had any impact on the conduct of the study.

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

Gehring 2000 *(Continued)*

	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 of the trial** • Female 18 to 65 years • Anagen hair ratio < 80% **Exclusion criteria of the trial** • 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. AIDS, cancer) • Malnutrition (iron deficiency, anorexia nervosa) • 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 **Placebo** • vehicle. 2 capsules 3 times a day for 6 months
Outcomes	**Outcomes of the trial** (as reported) 1. Anagen hair rate, change from baseline, 3, and 6 months by phototrichogram
Notes	Quote (page 420): "Medication provided by Company Roche Nicholas, Germany."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 419): "...randomized, double-blind..." Comment: There was insufficient detail reported about the method used to generate the allocation sequence 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.

Gehring 2000 *(Continued)*

		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 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	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 not available, 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	Unclear risk	There were no declarations of potential conflicts of interest or funding support. Medication was provided by Roche Nicholas, Germany. Comment: There was insufficient information to permit a clear judgement of the risk 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 of the trial** • Postmenopausal female with clinical diagnosis AGA • AGA telogen rate > 20% • Good general health, absence of other causes of alopecia **Exclusion criteria of the trial** • 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

Georgala 2004 *(Continued)*

	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
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 • 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 **Control** • 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	**Outcomes of the trial** (as reported) Trichograms were taken at baseline and the completion of the study. 1. Ratio of anagen/telogen compared to baseline 2. Adverse events and side-effects Denotes outcomes prespecified for this review.
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: There was insufficient detail reported about the method used to generate the allocation sequence 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	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.

Georgala 2004 *(Continued)*

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. 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 not available, 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	Unclear risk	There were no declarations of potential conflicts of interest or indication of funding or support. Comment: There was insufficient information to permit a clear judgement of the risk 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 of the trial** • 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 of the trial** • 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 in the minoxidil group (11.9%), and 31 in the placebo group (18.2%).

Jacobs 1993 *(Continued)*

	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** • 2% topical minoxidil solution (minoxidil powder, propylene glycol, alcohol, and water). Applied 1 mL twice daily at 12-hour intervals to the scalp for 32 weeks **Control** • placebo (propylene glycol, alcohol, and water). Applied 1 mL twice daily at 12-hour intervals to the scalp for 32 weeks
Outcomes	**Primary outcomes of the trial** (as reported) 1. Hair counts (non-vellus) by standardised photographic techniques and computer-assisted image counting (4-week intervals) **Secondary outcomes of the trial** (as reported) 1. New hair growth (investigator- and participant-assessed) from baseline, rated minimal/moderate/dense# 2. Safety evaluation (electrocardiogram (ECG)/serum chemical tests/blood count/platelet count/serum ferritin level/urinalysis) Denotes outcomes prespecified for this review.
Notes	Although adverse events are not mentioned as an outcome by the investigators, 2 adverse events were reported regarding withdrawals in the minoxidil group. The 3 Principal Investigators were from the Dermatology Division of Upjohn Laboratories, Kalamazoo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 759): "...randomized to receive either..." Comment: There was insufficient detail reported about the method used to generate the allocation sequence 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.

Jacobs 1993 *(Continued)*

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	Low 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. Reasons for withdrawal were reported, and the numbers were reasonably balanced across the groups. 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 not available, 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	High risk	The 3 Principal Investigators were from the Dermatology Division of Upjohn Laboratories, Kalamazoo; no declarations of conflicts of interest or sources of support were declared. Although, it remains unclear to what extent these may pose a potential high risk of bias. Comment: We judged this as at a high risk of bias.

Lucky 2004

Methods	This was a randomised, double-blind, placebo-controlled trial. Setting Multicentre (9), US Date of study May 1992 to 1993 (48-week duration)
Participants	381 women Age = 18 to 49 years **Inclusion criteria of the trial** • 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 of the trial** • 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)

Lucky 2004 *(Continued)*

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 in the minoxidil 5% group (33.9%), 46/108 in the minoxidil 2% group (29.8%), and 23/74 in the placebo group (31.1%).

- 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)
- 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

- 5% topical minoxidil solution. 1 mL of assigned solution twice daily at approximately 12-hour intervals (total daily dose of 2 mL) for 48 weeks

Comparator

- 2% topical minoxidil 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

Primary outcomes of the trial (as reported)

1. Hair count (non-vellus) at 48 weeks (change from baseline)
2. Hair growth/scalp coverage (participant-assessed) at 48 weeks#
3. Hair growth/scalp coverage (investigator-assessed) at 48 weeks#

Secondary outcomes of the trial (as reported)

1. Participant-assessed by 12-item questionnaire: quality of life (6), global benefit (6), i.e. hair growth, and hair styling measures⁎
2. Safety evaluation

Denotes outcomes prespecified for this review.

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.

Lucky 2004 *(Continued)*

Quote (page 541): "Supported by Pfizer Inc (formerly Pharmacia Corporation, formerly The Upjohn Company."

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.
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. Quote (page 541): "Supported by Pfizer Inc (formerly Pharmacia Corporation, formerly The Upjohn Company)..." Comment: The impact of study sponsorship was unclear. As there was a potential source of bias from other sources, we judged this as at a high risk 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 I, Rome, Italy Date of study Unspecified (12-month duration)
Participants	63 women Age = 52 to 63 years **Inclusion criteria of the trial** • Postmenopausal women with excessive hair loss as a predominant symptom **Exclusion criteria of the trial** • 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	• group I = ethinylestradiol (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. • 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. • group III = ethinylestradiol (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	**Outcomes of the trial** (as reported) 1. Hormonal assays 2. Trichogram (with microscope) The measurements were repeated 1 year after the end of administration of the intervention.
Notes	Diagnosis of FPHL was not clearly defined/stated. We sent e-mails to the PI on 3rd April and 15th April, but received no response.

Minozzi 1997 *(Continued)*

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." Comment: There was insufficient detail reported about the method used to generate the allocation sequence 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 or outcome measurement 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 or 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 not clear 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	Unclear risk	There were no declarations of potential conflicts of interest or indication of funding or support. Comment: There was insufficient information to permit a clear judgement of the risk of bias.

Olsen 1991

Methods	This was a randomised, double-blind, placebo-controlled trial. Setting Duke University Medical Center, Durham, US Date of study Not reported (32-week duration)
Participants	30 women

Olsen 1991 *(Continued)*

	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 of the trial** • 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 of the trial** • 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 (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 **Placebo** • placebo (vehicle: propylene glycol, alcohol, water) solution. 1 mL of assigned solution applied to involved scalp twice daily for 32 weeks
Outcomes	**Primary outcomes of the trial** (as reported every 4 weeks) 1. Hair counts at target area (frontoparietal tattooed), macro-photography assessed 2. Regrowth: subjective assessment (investigator/participant), rated none/minimal/moderate/dense regrowth **Secondary outcomes of the trial** (as reported) 1. Adverse events: investigator-assessed by clinical exam and questionnaire Denotes outcomes prespecified for this review.
Notes	"...supported in part by a grant from the Upjohn Company."

Olsen 1991 *(Continued)*

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: There was insufficient detail reported about the method used to generate the allocation sequence 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 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 not available, 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	Unclear risk	The work was "supported in part by a grant from the Upjohn Company", but the report was unclear to what extent this grant may pose a potential source or risk of bias. Comment: There was insufficient information to assess whether important risk of bias existed.

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)

Oura 2008 *(Continued)*

Participants	30 women Mean age (range) = 38.9 years (22 to 53) **Inclusion criteria of the trial** • Clinical diagnosis of FPHL • No systemic disease **Exclusion criteria of the trial** Nothing was reported. Randomised 30 women participants were randomised into 2 equal groups. Withdrawals/losses to follow up There were 2/15 withdrawals/losses to follow up in the adenosine group, and 1/15 in the placebo group: 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 **Placebo** • vehicle solution. 3 mL of assigned lotion applied twice daily over 12 months
Outcomes	Assessment was at 6 and 12 months. **Outcomes of the trial** (as reported) 1. Hair loss (dermatologist-assessed) via standardised photographic techniques (6-point scale: 1 = no hair loss, 6 = detectable hair loss) (Tajima 2007)# 2. Improvement in hair loss (investigator-assessed) via standard photography (6-point scale: 1 = no hair loss, 6 = detectable hair loss)# 3. Phototrichograms (counting hair numbers, anagen hair growth, hair thickness, hair density) 4. Self-assessments by 7-item questionnaire (Barber 1998)# Denotes outcomes prespecified for this review.
Notes	Quote (page 767): "Shiseido Research Centre were cooperative investigators."

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: There was insufficient detail reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.

Oura 2008 *(Continued)*

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 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: 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 not available, 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	Unclear risk	The trialists acknowledged "Shiseido Research Centre as cooperative investigators" (page 767). They are cosmetic manufacturers, but the report was unclear to what extent their support may pose a potential source or risk of bias. Comment: There was insufficient information reported to assess whether there were other sources of important risk of bias.

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 of the trial** • Female: Ludwig scale grade II or III (Ludwig 1977) [Male: II to IV alopecia; Hamilton-Norwood scale] **Exclusion criteria of the trial** • Cardiac pacemakers or with cardiac problems in which the intervention may have a negative effect

Policarpi 1993 *(Continued)*

	• 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 withdrawals/losses to follow up: 5 in the active intervention group, and 1 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 **Control** • sham treatment for 36 weeks Very limited information was reported.
Outcomes	Assessment was at 18 and 16 weeks. **Outcomes of the trial** (as reported) 1. Hair count (anagen) using standardised photographic technique 2. Self-assessment with clinical condition (4-point scale: 0 = worse, 1= unchanged, 2 = slightly improved, 3 = significantly improved) 3. Investigator-assessed satisfaction with clinical condition (4-point scale)# # Denotes outcomes prespecified for this review.
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: There was insufficient detail reported about the method used to generate the allocation sequence 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 risk of bias.

Policarpi 1993 *(Continued)*

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 not available, 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	Unclear risk	There were no declarations of potential conflicts of interest or indication of funding or support. Comment: There was insufficient information to permit a clear judgement of the risk 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, US Date of study Unreported (40-week duration)
Participants	9 women Age = 22 to 41 years **Inclusion criteria of the trial** • Female 18 to 45 years • Ludwig scale grade I and II (Ludwig 1977) • Good health • Regular menses • Dark undyed hair **Exclusion criteria of the trial** • Pregnancy • < 12 months postpartum or breastfeeding • Previous use of topical minoxidil

Price 1990 *(Continued)*

- < 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. **Placebo** • 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	Assessment was at 8-week intervals. **Outcomes of the trial** (as reported) 1. Hair weight of clipped sample 2. Hair count of clipped sample 3. Hair width/length of clipped sample Denotes outcomes prespecified for this review.
Notes	Individual patient data were reported, but there were small sample sizes. Quote (page 683): "The Upjohn Company provided support and encouragement of this research."

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: There was insufficient detail reported about the method used to generate the allocation sequence 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 risk of bias.

Price 1990 *(Continued)*

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 not available, 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	Unclear risk	Quote (page 683): "The Upjohn Company provided support and encouragement of this research." Comment: It was unclear to what extent the level of support provided may pose a potential risk of bias. There was insufficient information to assess whether important risk of bias existed.

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) **Inclusion criteria of the trial** • < 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 of the trial** Nothing was reported. Randomised

Price 2000 *(Continued)*

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 in the finasteride group (7.5%), and 7/70 in the placebo group (10%).

- 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. **Placebo** • placebo during 12 months.
Outcomes	Assessment was at 1, 3, 6, 9, and 12 months. **Primary outcomes of the trial** (as reported) 1. 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# **Secondary outcomes of the trial** (as reported) 1. 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)# 2. Investigator-assessed hair growth, a standardised 7-point rating scale (-3 = greatly decreased to +3 = greatly increased) 3. Scalp biopsies; terminal hair bulbs; terminal anagen, catagen, and telogen hairs; and vellus and vellus-like (miniaturised) hair counts 4. Laboratory tests; haematology, urinalysis, serum chemistry, hormone analysis, and bone marker analyses

Price 2000 *(Continued)*

Denotes outcomes prespecified for this review.

Notes	Quote (page 768): "...supported by Merck Research Laboratories." Almost half of the investigators indicated an affiliation with Merck Research Laboratories.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 769): "...randomized to receive either..." Comment: There was insufficient detail reported about the method used to generate the allocation sequence 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 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; the reasons were reported. Intention-to-treat analysis (ITT) analysis was done. Comment: We judged this as at a low 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. Comment: We judged this as at a low risk of bias.
Other bias	High risk	Quote (page 768): "...supported by Merck Research Laboratories." Comment: Almost half of the investigators indicated an affiliation with Merck Research Laboratories, Rahway. It remains unclear to what extent the level of support poses a potential risk of bias. Comment: We judged this as at a high risk 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 of the trial** • > 20 years • Ludwig scale grade I or II (Ludwig 1977) **Exclusion criteria of the trial** • 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)

Tsuboi 2007 *(Continued)*

	• 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 **Placebo** • vehicle only. 1 mL twice daily for 24 weeks
Outcomes	Assessment was every 4 weeks. **Outcomes of the trial** (as reported) 1. Hair counts assessed with photography/microscopy 2. Investigator-assessed hair growth, photographic comparison (5-point scale: 1= markedly improved, 5 = worsened) 3. Participant-assessed hair growth (5-point scale) compared to baseline every 4 weeks# 4. Participant-assessed hair loss (3-point scale: 1 = good, i.e. decreased hair loss; 2 = unchanged; 3 = worsened, i.e. increased hair loss)# 5. Adverse events as reported and investigator-assessed dermatological and abnormal changes in laboratory values Denotes outcomes prespecified for this review.
Notes	The investigators declared the following: "[We] received financial support from: Taisho Pharmaceutical Co, Ltd. Conflict of interest: None." (page 43).

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: This was judged 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.

Tsuboi 2007 *(Continued)*

		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.
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 protocol for the study was not available, 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	High risk	Quote (page 43): The investigators declared the following, "[We] received financial support from: Taisho Pharmaceutical Co, Ltd. Conflict of interest: None." Comment: Taisho Pharmaceuticals Co, Ltd markets the study drug minoxidil; thus, a potential risk of bias cannot be excluded.

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 of the trial** • Androgenetic alopecia Ludwig scale grade II or III (Ludwig 1977)

Ukşal 1999 *(Continued)*

	Exclusion criteria of the trial 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	• group I = oral spironolactone 100 mg/day during 3 months • group II = oral flutamide 125 mg/day during 3 months • group III = oral finasteride 2.5 mg/day during 3 months
Outcomes	These were not stated.
Notes	The poster abstract had minimal reported trial details. We sent 3 e-mails to the Principle Investigator, but we received no response.

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: There was insufficient detail reported about the method used to generate the allocation sequence 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	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 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 of the trial** • Age 18 to 35 years • Female pattern AGA **Exclusion criteria of the trial** • 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 in the minoxidil group (18%), and 8/33 in the CPA group (24.2%). • 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

Vexiau 2002 *(Continued)*

- Minoxidil group = 70%, CPA group = 61%

Menstrual cycle irregularities

- Minoxidil group = 61%, CPA group = 58%

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	**Primary outcomes of the trial** (as reported) 1. Number of hairs > 40 µm in diameter measured with phototrichogram at baseline, 6, and 12 months# **Secondary outcomes of the trial** (as reported) 1. Total number of hairs# 2. Number of hairs in the anagen and telogen phases 3. Participant assessment (VAS) of cosmetic effectiveness of treatment (hair loss and degree of seborrhoea at the beginning and end of the study)# Denotes outcomes prespecified for this review.
Notes	Baseline data were not provided for all randomised participants. women with hyperandrogenic profile included. Intergroup data were provided as well as intra group (women with versus women without hyperandrogenism), although this was not specified in the methods section. The study was sponsored by Schering Laboratories.

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 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 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."

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 protocol for the study was not available, 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	Unclear risk	There were no declarations of potential conflicts of interest or indication of funding or support. After e-mail contact, the PI declared only that the study was sponsored by Schering Laboratories. Comment: We judged this as at an unclear risk 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, US Date of study Unspecified (32-week duration)
Participants	33 women Mean age (range) = 34 years (20 to 44) **Inclusion criteria of the trial** • Good general health; no evidence of cardiac, scalp, systemic, or psychiatric disease • No previous treatment with topical minoxidil solution **Exclusion criteria of the trial** • Pregnancy or risk of pregnancy • A postpartum period < 12 months • Breast-feeding

Whiting 1992 *(Continued)*

- 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).

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 **Placebo** • vehicle. 1 mL twice daily to the scalp for 32 weeks
Outcomes	Assessment was every 4 weeks. **Outcomes of the trial** (as reported) 1. Hair counts: macro-photograph pre-defined tattooed area and count with Quantimet 920 Image Analyzer Cambridge Instrument, Cambridge, MA# 2. Overall growth: a global photograph of the affected area# 3. Regrowth: investigator- and participant-assessed (subjective) 4. Participant-assessed hair shedding between visits Denotes outcomes prespecified for this review.
Notes	Adverse events were not an outcome, but it was reported that local side-effects were not severe, and no patients 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: There was insufficient detail reported about the method used to generate the allocation sequence 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.

Whiting 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 801): "...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	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 protocol for the study was not available. 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." As primary outcomes for this review they were under-reported, so judged as unclear risk of bias.
Other bias	Unclear risk	There were no declarations of potential conflicts of interest or funding support. The 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, US Data of study Unspecified (12-month duration)
Participants	137 women Age = 41 to 60 years **Inclusion criteria of the trial** • Postmenopausal women with AGA **Exclusion criteria of the trial** Nothing was reported. Randomised

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 **Placebo** • placebo. Duration of 12 months
Outcomes	**Outcomes of the trial** (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 (baseline and 12 months)
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 282): "...137 patients randomized..." Comment: There was insufficient detail reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.

Whiting 1999 *(Continued)*

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	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 protocol for the study was not available, 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	Unclear risk	There were no declarations of potential conflicts of interest or indication of funding or support. Comment: There was insufficient information to permit a clear judgement of the risk of bias.

FPHL = Female pattern hair loss

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

Study	Reason for exclusion
Ahn 2006	This was a non-RCT.
Bazzano 1986	This was a CCT.
Bezzola 2009	There were no separate data for women.
Califano 1991	This was published in Italian; the language abstract was in English, and the study only included male participants.
DDI 2008	This was a non-RCT. All women received the same treatment.
Enshaieh 2005	This was translated from Farsi into English by Mona Nasser (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 29th March 2011. Only male participants were included.

Study	Reason for exclusion
Farella 1991	This was translated and assessed by the Italian Cochrane Centre, but it was a CCT, so it was excluded
Greenberg 1996	Only male participants were included.
Inui 2007	Only male participants were included.
Kohler 2007	This was a non-RCT (retrospective study).
Li 1996	This study written in Chinese was translated into English by Edwin Chan Shih-Yen. (see Acknowledgements). This was a quasi-randomised (CCT) study into 2 treatment groups by odd-even visit number.
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 31 years old, so it was unlikely that we would receive individual patient data.
Peereboom-Wynia 1989	This was a non-RCT.
Piérard-Franchimont 1996	This was a non-RCT.
Piérard-Franchimont 1998	Only male participants were included in this study.
Prager 2002	Only male participants were included in this study.
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, 60 participants were randomised, but only 1 woman (with male pattern baldness) was included in the study.
Satino 2003	This was a CCT.
Sinclair 2002	Allocation was according to month of birth, so the study was a CCT (quasi-randomised). An inadequate method of sequence generation was used.
Sinclair 2005	This used the same data set as Sinclair 2002. It was a non-RCT.
Yang 2002	Only male participants were included.

RCT = Randomised controlled trial
CCT = Controlled clinical trial (quasi-randomised)

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

Bureau 2003

Methods	This was a randomised, double-blind, placebo-controlled trial. Setting Multicentre (4), France

Bureau 2003 *(Continued)*

	Date of study Unspecified (6-month duration)
Participants	3 men/women enrolled Mean age = 38.6 ± 8.14 years (SD) in group I, 40.6 ± 9.32 years (SD) in group II **Inclusion criteria of the trial** • Female: stage I and II alopecia Ludwig scale (Ludwig 1977). [Male: I to VII alopecia; Hamilton-Norwood scale] **Exclusion criteria of the trial** Nothing was reported. Randomised 69 participants were randomised (group I = 31 men/9 women, group II = 21 men/8 women). Withdrawals/losses to follow up There were 24/69 (35%) 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 electromagnetic pulses (12.5 V/m at 1 cm,10 MHz) delivered by a synthetic resin helmet for 30 min [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*]. **Control** • 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 minutes
Outcomes	Assessments were monthly (6). **Primary outcomes of the trial** (as reported) 1. Mean hair counts# 2. Hair density via macro-photography 3. Biopsy/histo-chemical examination of hairs **Secondary outcomes of the trial** (as reported) 1. Tolerability (side-effects) 2. Acceptability of treatment and hair quality evaluation: participant-assessed VAS (monthly) and investigator-assessed clinically Denotes outcomes prespecified for this review.

Bureau 2003 *(Continued)*

Notes	Data were not stratified for gender. E-mails were sent to the PI, but we received no response.

Guerrero 2009

Methods	This was a randomised, active-controlled trial. Setting 3 centres in Chile Date of study Unspecified (12-week duration)
Participants	40 with FPHL (22 men, 18 women) Mean age = 43.7 years (range 20 to 69)
Interventions	• Minoxidil 2% • 17-alfa-estradiol al 0.025%
Outcomes	**Outcomes of the trial** 1. % hair in telogen and anagen phase, adverse events, hair loss, and hair growth
Notes	This study written in Spanish was translated into English and assessed by Prof Raphael Freitas De Souza (see Acknowledgements). 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.

Mazzarella 1997

Methods	This was a randomised, placebo-controlled study. Date of study Unspecified (16-month duration)
Participants	52 FPHL (28 male and 24 women) Age (mean) = 18 to 38 years (28) No participants had received therapy for alopecia or other cutaneous or non-cutaneous diseases for at least 1 month prior to beginning the protocol. Moreover, no female participant had been taking oral contraceptives during the previous year.
Interventions	*1.0 mL medication using a graduated dropper twice daily to the balding area(s) of the scalp.* • 0.005% solution of finasteride • vehicle only (50% ethyl alcohol, 25% propylene glycol, and 25% distilled water)
Outcomes	**Outcomes of the trial**

Mazzarella 1997 *(Continued)*

	1. Photographs at monthly intervals 2. 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
Notes	There were no separate data for women. There were 16 dropouts (31.8%) in the placebo group only. We e-mailed the PI, but received no response.

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 with androgenetic alopecia (at least 24 men and 24 women; for 12, the gender was not reported). Type III or IV on Hamilton scale Age = 21 to 38 years
Interventions	• group I = active lotion (gelatine-cystine and *Serenoa repens*) (n = 12) • group II = placebo lotion (n = 12) • group III = active diet supplement (gelatine-cystine) (n = 12) • group IV = placebo supplement (n =12) • 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	**Outcomes of the trial** 1. Efficacy of oral and lotion based on gelatine cystine and *Serenoa repens* on hair growth promotion and retarding of hair loss 2. Quantify the radical oxygen species (ROS) before, during, and after the diet supplementation
Notes	There were no separate data for women. Dropouts were not reported. We were not able to contact the investigators.

Rietschel 1987

Methods	This was a randomised, double-blind, controlled study. Setting 2 centres in the US Date of study Unspecified (2-year duration)

Rietschel 1987 *(Continued)*

Participants	149 with FPHL (142 men and 7 women) Age (range) = 34.1 years (18 to 49) **Inclusion criteria of the trial** • Subjects were required to have a distinct pattern of balding consistent with androgenetic alopecia and a lack of other scalp pathologic processes. 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	• 2% minoxidil solution • 3% minoxidil solution • a placebo (vehicle) solution 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 subjects continuing past 12 months were using the 3% solution. 1 mL of solution was applied to the balding area of the scalp in the morning and in the evening.
Outcomes	**Outcomes of the trial** • Hair counts according to 3 classifications: (1) terminal, (2) intermediate, and (3) vellus. Total hair counts were the sum of the 3 categories • Examinations were performed at baseline and 2 weeks, at 1-month intervals for 1 year, and at 3-month intervals thereafter • 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 All examinations were performed at Emory University School of Medicine, Atlanta, GA.
Notes	There were no separate data for women. Of the initial group, 102 subjects completed the first year of study and were fully evaluable. Of these, 89 subjects continued to use minoxidil into the second year, and 54 continued into the third year. We were not able to contact the investigators.

Thom 2001

Methods	This was a randomised, placebo-controlled, double-blind study. Setting Norway Date of study Unspecified (6-month duration) A block-randomisation procedure (blocks of 6) was used. Hairgain® and placebo capsules had the same appearance and were packed in similar plastic bottles (page 3).
Participants	60 (55 men and 5 women) > 18 year, hair-loss for > 1 year: androgenic alopecia (56), alopecia totalis (4). Hair loss was graded according to internationally-accepted rating scales

Thom 2001 *(Continued)*

Interventions	• Hairgain® (dietary supplement of marine protein extract, vitamins, and minerals), 2 capsules/day (< 80 kg in body weight) or 3 capsules/day (> 80 kg) • placebo
Outcomes	**Outcomes of the trial** • Hair growth by hair counts assessed by standardised photographic techniques at baseline and completion of study. Blinded (not involved in the study) assessment • Participant-assessed satisfaction VAS (0 to 10) • Tolerability, i.e. adverse effects • Compliance verified
Notes	There were no separate data for women. We e-mailed the PI (Dr E Thom, Postbox 210 2001, Lillestrøm, Norway - e-mail: erling.thom@parexel.com and info@pharmamedico.com), but we received no response.

Thom 2006

Methods	This was a randomised, placebo-controlled, double-blind study. Setting Norway Date of study Unspecified (6-month duration) Nourkrin® and placebo capsules had the same appearance and were packed in similar plastic bottles.
Participants	60 enrolled, but 55 completed the trial (51 men and 4 women). 5 (3 active treatment, 2 control) were lost to follow up and excluded from the analysis. There were no withdrawals because of side-effects.
Interventions	• 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) • placebo
Outcomes	**Outcomes of the trial** • Hair count by magnifying glass of pre-defined areas of scalp • Participant-assessed satisfaction VAS (0 to 10) • Tolerability, i.e. adverse effects/side-effects
Notes	There were no separate data for women. We e-mailed the PI (Dr E Thom, Postbox 210 2001, Lillestrøm, Norway - e-mail: erling.thom@parexel.com and info@pharmamedico.com), but we received no response.

RCT = Randomised controlled trial

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.
Participants	**Inclusion criteria of the trial** • Women from 18 to 40 years with diagnosis of female pattern hair loss, 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 of the trial** 1. Hair counts (measured at baseline and at 6-month intervals) **Secondary outcomes of the trial** 1. Midscalp clinical grading system 2. Participant self-evaluation of hair density
Starting date	1st February 2007
Contact information	Dr. A Yazdabadi (yazdaa27@gmail.com) Department of Dermatology St Vincent's Hospital Fitzroy Australia Telephone: (03) 9288 2211
Notes	At 28-10-2011, the trial was "not yet recruiting". Contact: Rod.SINCLAIR@svhm.org.au

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 randomised controlled trial.
Participants	**Inclusion criteria of the trial** • Women aged 18 to 75 years with a diagnosis of female pattern hair loss
Interventions	• group I = oral spironolactone • group II = topical minoxidil
Outcomes	**Primary outcomes of the trial**

NCT00175617 *(Continued)*

	1. Hair density (measured at baseline, and after 3, 6, and 9 months) **Secondary outcomes of the trial** 1. Percentage of subjects who experience side-effects 2. Subject 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 Telephone: 604 875 4747
Notes	This study is currently recruiting participants (website assessed 28th October 2011).

NCT00197379

Trial name or title	The Study for New Effect of Roxithromycin on Androgenetic Alopecia
Methods	This is a cross-over, randomised controlled trial.
Participants	**Inclusion criteria of the trial** • Women and men older than 20 years with androgenetic alopecia
Interventions	• 0.5% topical roxithromycin lotion • placebo
Outcomes	**Primary outcomes of the trial** 1. No primary outcomes were reported **Secondary outcomes of the trial** 1. Pathological study taken from lesional scalp skin
Starting date	May 2005
Contact information	Department of Dermatology Hammatsu University School of Medicine Hamamatsu Japan 431-3192

NCT00197379 *(Continued)*

Notes	The recruitment status of this study is unknown because the information has not been verified recently; it was last updated July 2010 (website assessed 28th October 2011).

NCT00418249

Trial name or title	Phase 2 Study of Topical AS101 for the Treatment of FAGA (Female Androgenetic Alopecia) in Menopause Women
Methods	This is a randomised controlled trial.
Participants	**Inclusion criteria of the trial** • Women aged 50 years or older in menopause, clinically diagnosed for AGA according to Ludwig scale I to II
Interventions	• Experimental group = topical AS101 • control group = a placebo
Outcomes	**Primary outcomes of the trial** 1. Hair density **Secondary outcomes of the trial** 1. Hair diameter 2. Anagen/telogen ratio 3. Hair growth rate 4. Global photographic assessment according to female Ludwig scale 5. Self-administered satisfaction questionnaire
Starting date	2007
Contact information	Danny Ben-Amital, MD Rabin Medical Center Telephone: 972-3-9253770
Notes	The recruitment status of this study is unknown because the information has not been verified recently; it was last updated July 2010 (website assessed 28th October 2011).

NCT00981461

Trial name or title	A Randomized, Double-Blind Clinical Trial to Evaluate the Safety and Efficacy of the HairMax LaserComb 2009, 9 Beam Model: For the Treatment of Androgenetic Alopecia in Females
Methods	This is a randomised controlled trial.
Participants	**Inclusion criteria of the trial** • 60 women who have been diagnosed with androgenetic alopecia, who are between 25 and 60 years of age, have Fitzpatrick Skin Types I to IV, with classifications of Ludwig I-4, II-1, II-2, or frontal, have active hair loss within the last 12 months

NCT00981461 *(Continued)*

Interventions	• hairMax LaserComb • control device
Outcomes	**Outcomes of the trial** • Evaluating changes in terminal hair count in the evaluation zone having evidence of androgenetic alopecia (miniaturised hair)
Starting date	October 2009 (completed October 2010)
Contact information	David Michaels, Managing Director Lexington International, LLC
Notes	There are no published results (website assessed 28th October 2011).

NCT01016964

Trial name or title	A Randomized, Double-Blind Clinical Trial to Evaluate the Safety and Efficacy of the HairMax LaserComb 2009, 12 Beam Model For The Treatment of Androgenetic Alopecia in Females
Methods	This is a randomised controlled trial.
Participants	**Inclusion criteria of the trial** • 60 women with androgenetic alopecia
Interventions	• hairMax LaserComb 2009 model 12 beam • sham device
Outcomes	**Outcomes of the trial** • Evaluating changes in terminal hair count in the evaluation zone having evidence of androgenetic alopecia (miniaturised hair)
Starting date	January 2010 (study has been completed)
Contact information	David Michaels, Managing Director Lexington International, LLC
Notes	There are no published results (website assessed 28th October 2011).

NCT01042756

Trial name or title	Hairmax Lasercomb For The Treatment Of Androgenetic Alopecia In Females
Methods	This is a randomised controlled trial.
Participants	**Inclusion criteria of the trial** • 15 women with androgenetic alopecia
Interventions	• HairMax LaserComb

NCT01042756 *(Continued)*

	• sham treatment
Outcomes	**Primary outcomes of the trial** 1. Results of week 16 terminal hair count compared to baseline for each user will be analysed between the treatment and sham control arm 2. Terminal hair count, which is non-vellus/non-miniaturised hair counts, will be assessed in the target region **Secondary outcomes of the trial** 1. Subjects' static self global assessment of hair regrowth based on subject questionnaire at each follow-up visit 2. Investigator global assessment (comparing global digital images from baseline and end point) of hair growth
Starting date	December 2009 (completed April 2011)
Contact information	Wilma Bergfeld, MD Cleveland Clinic Foundation
Notes	There are no published results (website assessed 28th October 2011).

NCT01052870

Trial name or title	Study Evaluating the Association of CAG Repeat Polymorphisms and Finasteride Response in Women With Androgenetic Alopecia
Methods	This is a randomised controlled trial.
Participants	**Inclusion criteria of the trial** • 12 women with androgenetic alopecia
Interventions	• finasteride 1 mg • placebo
Outcomes	**Outcomes of the trial** 1. Global photographs and 2 tattooed areas of 1 cm^2 each were measured monthly to assess global appearance and hair counts for medication impact
Starting date	December 2008 (completed December 2009)
Contact information	Hair Dx, Sharon A Keene, MD
Notes	There are no published results (website assessed 28th October 2011).

NCT01145625

Trial name or title	A Phase 3 Multi-Center Parallel Design Clinical Trial to Compare the Efficacy and Safety of 5 % Minoxidil Foam vs. 2 % Minoxidil Solution in Females for the Treatment of Female Pattern Hair Loss - Androgenetic Alopecia (MINALO3004, NCT01145625)

NCT01145625 *(Continued)*

Methods	This is a randomised controlled trial.
Participants	**Inclusion criteria of the trial** • Minimum of 300 women with FPHL will be enrolled
Interventions	52-week duration • 5% minoxidil foam (MTF) • 2% minoxidil solution (MTS)
Outcomes	This clinical trial is designed to compare the risk/benefit profile of the 5% MTF formulation applied once a day versus the 2% MTS applied twice a day (twice daily), using objective efficacy measures and safety assessments. **Primary outcomes of the trial** 1. 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) **Secondary outcomes of the trial** 1. 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)
Starting date	June 2010. This study is ongoing, but not recruiting participants (last updated September 2011).
Contact information	Johnson & Johnson Consumer Co, Inc., and Personal Products Worldwide
Notes	The website was assessed 28th October 2011.

NCT01189279

Trial name or title	Safety and pharmacokinetics study of new formulation of Bimatoprost in patients with alopecia
Methods	This is a randomised controlled trial.
Participants	**Inclusion criteria of the trial** • 42 men and women with alopecia (including androgenetic alopecia), aged 18 to 64 years
Interventions	• bimatoprost (formulation A) 1 mL/day for 14 days followed by multiple doses a day • bimatoprost (formulation B) 1 mL/day for 14 days followed by multiple doses a day • bimatoprost (formulation C) 1 mL/day for 14 days followed by multiple doses a day
Outcomes	**Primary outcomes of the trial** 1. Pharmacokinetics following single dose of bimatoprost 2. Pharmacokinetics following multiple doses of bimatoprost **Secondary outcomes of the trial** 1. 12-lead electrocardiogram (ECG) 2. Local scalp tolerability assessment
Starting date	October 2010. This study is ongoing, but not recruiting participants.

NCT01189279 *(Continued)*

Contact information	Allergan, Inc. Therapeutic Area Head
Notes	It is unclear if the study will be eligible for this review; it is not clear if there was stratification by gender or condition. The website was assessed 28th October 2011.

NCT01226459

Trial name or title	A Phase 3 Multi-Center Parallel Design Clinical Trial to Compare the Efficacy and Safety of 5% Minoxidil Foam vs. Vehicle in Females for the Treatment of Female Pattern Hair Loss (Androgenetic Alopecia)
Methods	This is a randomised controlled trial.
Participants	**Inclusion criteria of the trial** • 300 women with female pattern hair loss
Interventions	• 5% minoxidil topical foam once daily • vehicle topical foam once daily
Outcomes	**Primary outcomes of the trial** 1. Change in target area hair count from baseline to week 24 **Secondary outcomes of the trial** 1. Change in target area hair count from baseline to week 12
Starting date	September 2010 (completed August 2011)
Contact information	Joyce Hauze/Senior Specialist Clinical Research Operations Johnson & Johnson Consumer Co, Inc., and Personal Products Worldwide
Notes	There are no published results (website assessed 28th October 2011).

NCT01292746

Trial name or title	A Double-blind, Placebo-controlled Randomized Evaluation of the Effect of the Erchonia ML Scanner (MLS) on the Treatment of Androgenic Alopecia in Females
Methods	This is a randomised controlled trial.
Participants	**Inclusion criteria of the trial** • 70 women with androgenetic alopecia (18 to 60 years)
Interventions	• Erchonia® ML Scanner (MLS) (low level laser scanner) device • placebo device
Outcomes	**Primary outcomes of the trial**

NCT01292746 *(Continued)*	1. Per cent change in non-vellus terminal hair count across a 3 cm diameter scalp area **Secondary outcomes of the trial** 1. Stage on the Ludwig-Savin hair loss classification scale for female androgenic alopecia 2. Subject global assessment of new hair growth 3. Investigator global assessment of new hair growth 4. Subject satisfaction with procedure outcomes ratings
Starting date	February 2011
Contact information	Paul M Thaxton, MD, FACOG (pthaxton@paulthaxtonmd.com) (Telephone: 706-922-4545)
Notes	The website was assessed 28th October 2011.

RCT = Randomized controlled trial

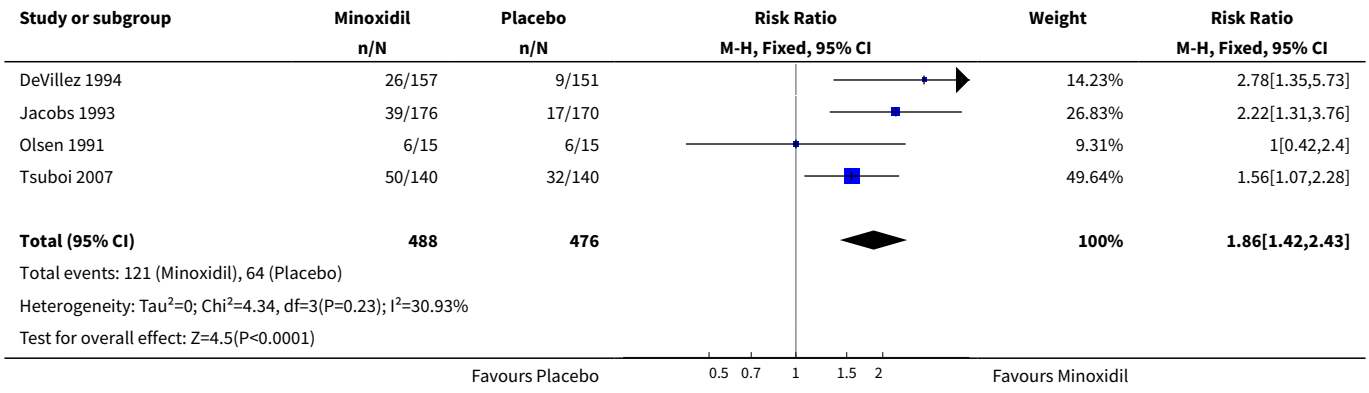
DATA AND ANALYSES

Comparison 1. Minoxidil versus placebo

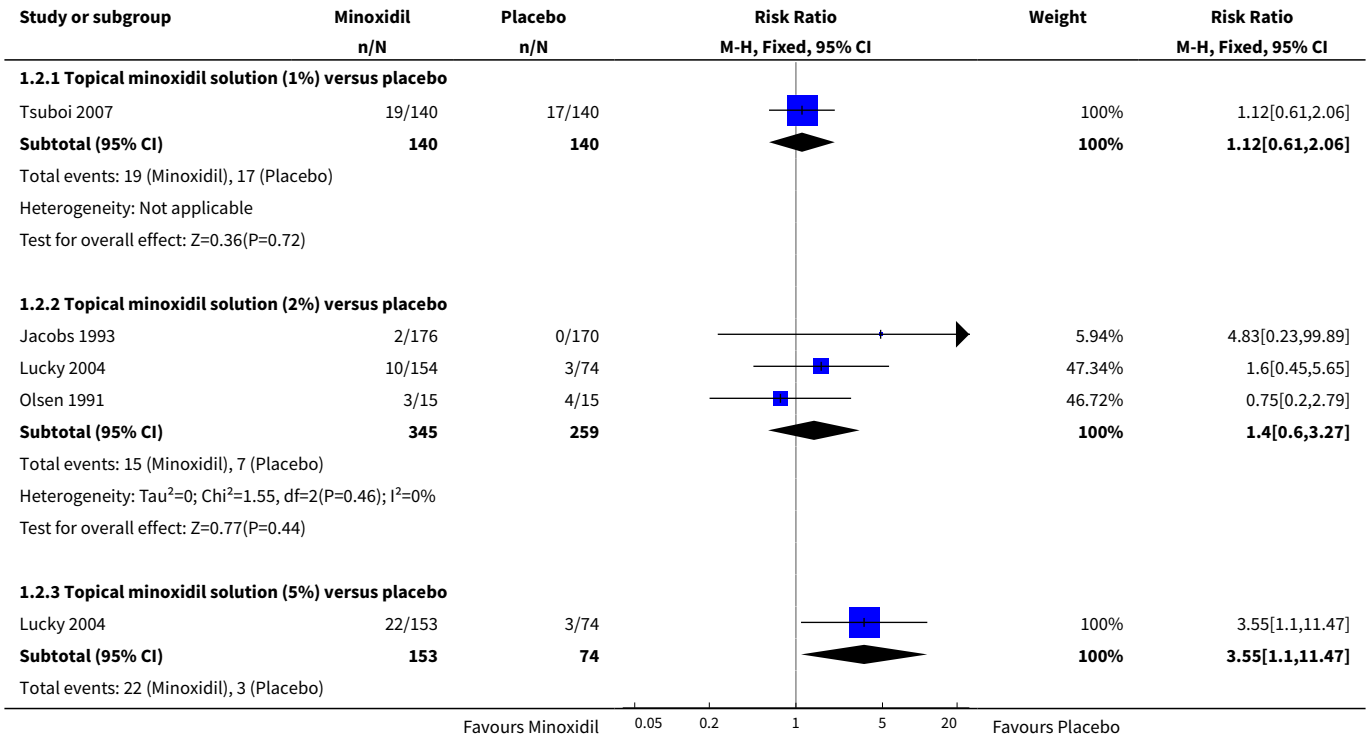
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with self-rated moderate hair regrowth	4	964	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [1.42, 2.43]
2 Proportion of participants with adverse events	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
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	3	604	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.60, 3.27]
2.3 Topical minoxidil solution (5%) versus placebo	1	227	Risk Ratio (M-H, Fixed, 95% CI)	3.55 [1.10, 11.47]
3 Proportion of participants with investigator-rated moderate hair regrowth	5	997	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.71, 3.60]
4 Mean increase in total hair count from baseline	7	1115	Mean Difference (IV, Fixed, 95% CI)	13.28 [10.89, 15.68]
4.1 Topical (1% to 2%) minoxidil versus placebo	7	989	Mean Difference (IV, Fixed, 95% CI)	13.05 [10.51, 15.60]
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)	6	1107	Mean Difference (IV, Fixed, 95% CI)	13.04 [10.64, 15.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Topical (1% to 2%) minoxidil versus placebo	6	981	Mean Difference (IV, Fixed, 95% CI)	12.78 [10.22, 15.34]
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 moderate hair regrowth.



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
Heterogeneity: Not applicable					
Test for overall effect: Z=2.11(P=0.03)					
Test for subgroup differences: Chi²=2.93, df=1 (P=0.23), I²=31.68%					

Favours Minoxidil 0.05 0.2 1 5 20 Favours Placebo

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

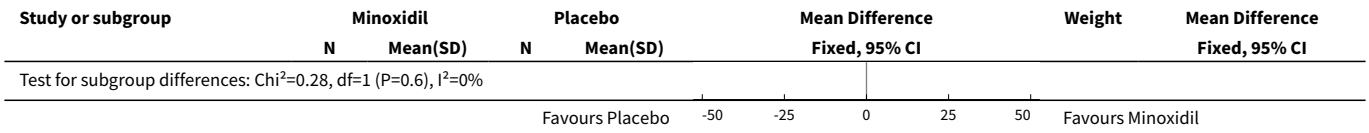
Study or subgroup	Minoxidil n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
DeVillez 1994	17/157	8/151		23.75%	2.04[0.91,4.59]
Jacobs 1993	19/176	7/170		20.74%	2.62[1.13,6.08]
Olsen 1991	6/15	1/15		2.91%	6[0.82,44]
Tsuboi 2007	40/140	16/140		46.6%	2.5[1.47,4.25]
Whiting 1992	4/17	2/16		6%	1.88[0.4,8.9]
Total (95% CI)	**505**	**492**		**100%**	**2.48[1.71,3.6]**
Total events: 86 (Minoxidil), 34 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.11, df=4(P=0.89); I²=0%					
Test for overall effect: Z=4.78(P<0.0001)					

Favours Placebo 0.02 0.1 1 10 50 Favours Minoxidil

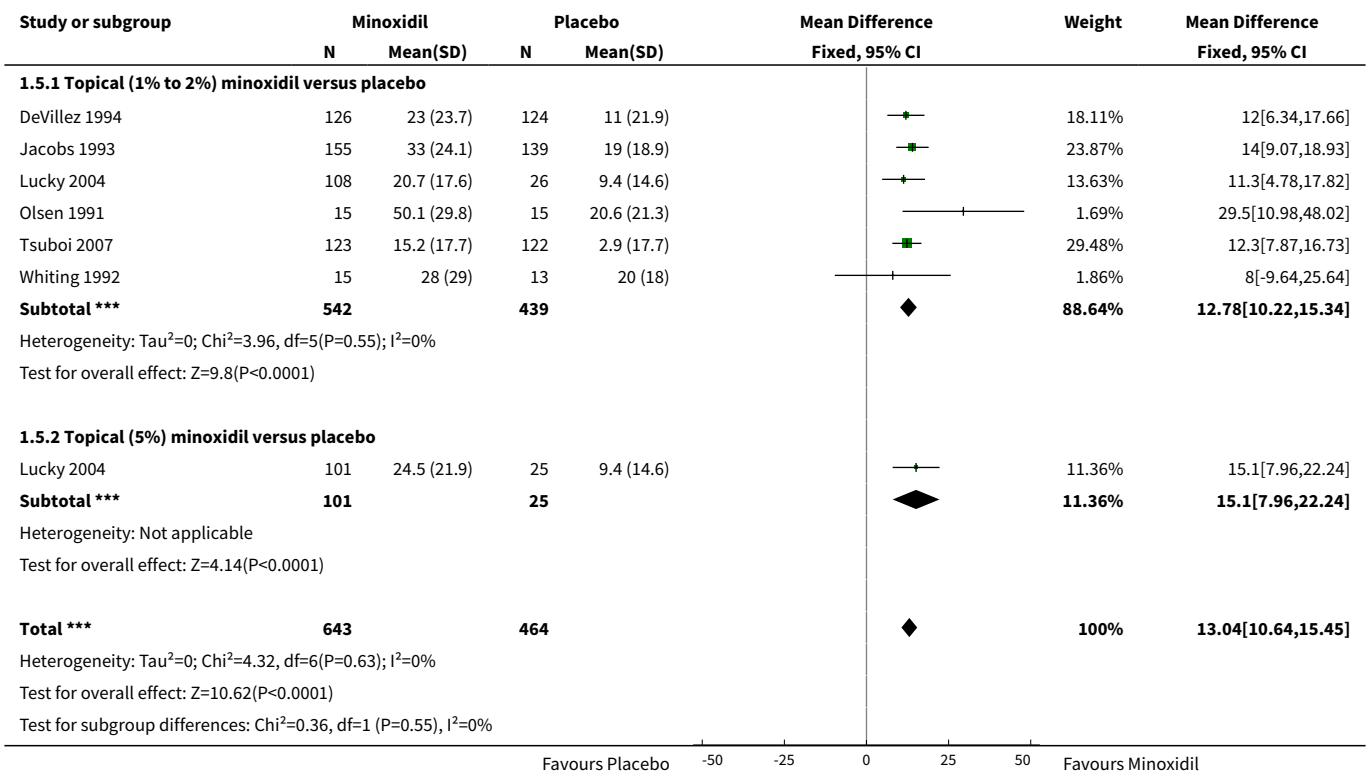
Analysis 1.4. Comparison 1 Minoxidil versus placebo, Outcome 4 Mean increase in total hair count from baseline.

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	126	23 (23.7)	124	11 (21.9)		17.96%	12[6.34,17.66]
Jacobs 1993	155	33 (24.1)	139	19 (18.9)		23.67%	14[9.07,18.93]
Lucky 2004	108	20.7 (17.6)	26	9.4 (14.6)		13.51%	11.3[4.78,17.82]
Olsen 1991	15	50.1 (29.8)	15	20.6 (21.3)		1.67%	29.5[10.98,48.02]
Price 1990	4	38.8 (24.8)	4	-3.2 (10.2)		0.83%	42[15.71,68.29]
Tsuboi 2007	123	15.2 (17.7)	122	2.9 (17.7)		29.24%	12.3[7.87,16.73]
Whiting 1992	15	28 (29)	13	20 (18)		1.85%	8[-9.64,25.64]
Subtotal ***	**546**		**443**			**88.74%**	**13.05[10.51,15.6]**
Heterogeneity: Tau²=0; Chi²=8.66, df=6(P=0.19); I²=30.75%							
Test for overall effect: Z=10.06(P<0.0001)							
1.4.2 Topical (5%) minoxidil versus placebo							
Lucky 2004	101	24.5 (21.9)	25	9.4 (14.6)		11.26%	15.1[7.96,22.24]
Subtotal ***	**101**		**25**			**11.26%**	**15.1[7.96,22.24]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.14(P<0.0001)							
Total ***	**647**		**468**			**100%**	**13.28[10.89,15.68]**
Heterogeneity: Tau²=0; Chi²=8.94, df=7(P=0.26); I²=21.74%							
Test for overall effect: Z=10.86(P<0.0001)							

Favours Placebo -50 -25 0 25 50 Favours Minoxidil



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



ADDITIONAL TABLES

Table 1. Glossary of Terms

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 nontoxic bioavailable form

Table 1. Glossary of Terms *(Continued)*

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
Ludwig scale	Classification of 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

[1] Definition taken from 'Martin A (editor). Concise Colour Medical Dictionary. 2nd edition. Oxford: Oxford University Press, 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. This was excluded.
Blume-Peytavi 2007	Yes	Yes	IPD were unavailable. This was included.
Blume-Peytavi 2011	Yes	Yes	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. This was included.

Table 2. Contact with investigators *(Continued)*

			Response received 16th November: "The allocation concealment was performed using sequentially numbered, sealed, opaque envelopes, and kept by the project manager of the CRC."
Bureau 2003	No	No	None of the investigators could be contacted. This was included.
Carmina 2003	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. This was included.
DeVillez 1994	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. This was included.
Draelos 2005	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. This was included.
Farella 1991	No	No	This was translated and assessed by the Italian Cochrane Centre, but it was a CCT, so it was excluded.
Fischer 2004	Yes	Yes	We received information that allowed a change in the assessment for several domains from unclear to low risk of bias. This was included.
Gassmueller 2008	Yes	Yes	We received information that allowed a change in assessment for several domains from unclear to low risk of bias. This was included.
Georgala 2004	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. This was included.
Gehring 2000	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. This was included.
Guerrero 2009	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. The data was mixed, in terms of gender. This is awaiting assessment.
Jacobs 1993	No	No	Investigators were not able to be contacted. This was included.
Li 1996	Yes	Yes	CCT after translation. This was excluded.
Mazzarella 1997	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. The data was mixed, in terms of gender.

Table 2. Contact with investigators *(Continued)*

			This is awaiting assessment.
Minozzi 1997	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. This was included.
Oura 2008	No	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. This was included.
Price 1990	Yes	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We received no response from the investigator. This was included.
Price 2000	Yes	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. We received no response from the investigator. This was included.
Sinclair 2002	Yes	Yes	Information provided to us enabled a change from unclear to high risk of bias. This was excluded.
Thom 2001/2006	No	No	The data was mixed, in terms of gender. We received no response from the investigator. This is awaiting assessment.
Tsuboi 2007	Yes	Yes	Information received allowed change in assessment for several domains from unclear to low risk of bias.
Ukşal 1999	Yes	No	The trial conduct was unconfirmed, i.e. sequence allocation/concealment and blinding. This was included, but there were missing data. We received no response from the investigator. This was included.
Vexiau 2002	Yes	Yes	Information was received regarding the hyperandrogenic profile of the women.

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

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

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.

Table 4. Table of random-effects sensitivity analyses

Analysis	Concentration / subgroups	RR	95% Confidence Interval	P value	I^2	I^2 (P value)
Analysis 1.1 Self-rated hair regrowth	Pooled	1.80	(1.27 to 2.55)	< 0.001	31%	0.31
Analysis 1.2 Adverse events	Minoxidil (1%)	1.12	(0.61 to 2.06)	0.72	-	-
	Minoxidil (2%)	1.26	(0.53 to 3.01)	0.61	0%	0.46
	Minoxidil (5%)	3.55	(1.10 to 11.47)	0.03	-	-
Analysis 1.3 Investigator-rated hair regrowth	Pooled	2.45	(1.69 to 3.56)	< 0.001	0%	0.89
Analysis 1.4 Increase in total hair count	Pooled	13.49	(10.58 to 16.40)	< 0.001	22%	0.26
Analysis 1.5 Increase in total hair count (sensitivity analysis)	Pooled	13.04	(10.64 to 15.45)	< 0.001	0%	0.63

Table 5. Research recommendations based on a gap in the evidence of the effects of interventions for female pattern hair loss

Core elements	Issues to consider	Status of research for this review
Evidence (E)	What is the current state of the evidence?	This systematic review identified 22 RCTs. 18 addressed at least 1 of our outcomes. There is evidence for the efficacy and safety of topical minoxidil 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 female pattern hair loss 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 postmenopausal 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 3 months prior to study that could interfere with the study medications • 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, assessing minoxidil of all concentrations and formulations. High-quality, well-designed, and rigorously-reported studies of other widely used treatments, e.g. spironolactone, finasteride, cyproterone acetate, and laser comb 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: minoxidil 2% twice daily versus minoxidil 5% once a day.
Outcome (O)	Which clinical or patient-related outcomes will the researcher need to measure, improve, influence, or accomplish? Which methods of	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

Table 5. Research recommendations based on a gap in the evidence of the effects of interventions for female pattern hair loss *(Continued)*

	measurement should be used?	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	28 October 2011
Study Type	What is the most appropriate study design to address the proposed question?	• Randomised controlled trial (adequately powered/multi centred) • Methods: concealment of allocation sequence • Blinding: participants, trialists, outcomes assessors, data analysts • Setting: hospital/university or general practice with adequate follow-up

APPENDICES

Appendix 1. CENTRAL (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)

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. LILACS search strategy

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control$ or tw aleat$ or tw random$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Words] and alopecia [Words]

Appendix 5. 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))

Appendix 6. 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*))

CONTRIBUTIONS OF AUTHORS

Run search - Cochrane Skin Group and JS
Identify relevant titles and abstracts from searches - EvZ and ZF
Obtain copies of trials - EvZ and ZF
Selection of trials - EvZ and ZF
Translation of two Italian studies and one German study - EvZ
Extract data from trials - EvZ, ZF, and RBA
Enter data into RevMan - EvZ, ZF, and BC
Carry out analysis - EvZ, ZF, and BC
Interpret data - EvZ, ZF, and BC
Draft final review - EvZ, ZF, and BC
Update review - EvZ, ZF, and BC

DECLARATIONS OF INTEREST

There are no financial conflicts of interest; the authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Not specified.

External sources

- New Source of support, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After consultation and with the direct agreement of the Cochrane Skin Group editorial base, substantial changes were made to the published protocol. These included rewriting the background, the methods section, clarification of the types of participants, and the inclusion of a broader spread of interventions to be considered in this review.

To ensure that the outcomes sought in this review were clinically relevant, we had extensive discussions with a peer reviewer of the protocol and content expert (Rod Sinclair). The following changes were recorded and carried out prior to data extraction to exclude any possibility of selection bias: age, hormonal status and ferritin were prespecified as subgroups in the protocol, but the only subgroup investigated in the review was dose. However, the objectives, which were 'to determine the effectiveness and safety of the available options for the treatment of FPHL in women', remain largely unchanged.

The degree of homogeneity between the studies permitted the use of a fixed-effect model to pool the data into a meta-analysis, and a random-effects model was only fitted as part of a sensitivity analysis to assess the degree of heterogeneity.

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