



European Dermatology Forum

S3 - European Dermatology Forum Guideline for the Treatment of Androgenetic Alopecia in Women and in Men

Developed by the Guideline Subcommittee "Androgenetic Alopecia" of the
European Dermatology Forum

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EVIDENCE BASED (S3) GUIDELINES FOR THE TREATMENT OF ANDROGENETIC ALOPECIA IN WOMEN AND IN MEN

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ABSTRACT

Androgenetic alopecia is the most common hair loss disorder, affecting both men and women. Initial signs of androgenetic alopecia usually develop during teenage years leading to progressive hair loss with a pattern distribution. Moreover, its frequency increases with age and affects up to 80% Caucasian men and 42% of women. Patients afflicted with androgenetic alopecia may undergo significant impairment of quality of life. The European Dermatology Forum (EDF) initiated a project to develop evidence-based guidelines for the treatment of androgenetic alopecia. Based on a systematic literature research the efficacy of the currently available therapeutic options was assessed and therapeutic recommendations were passed in a consensus conference.

The purpose of the guideline is to provide dermatologists with an evidence-based tool for choosing an efficacious and safe therapy for patients with androgenetic alopecia.

1 INTRODUCTION TO THE GUIDELINE

1.1 Needs/problems and issues in patient care

Androgenetic alopecia is a common form of scalp hair loss that affects both men and women. It is characterized by progressive hair loss, usually in a pattern distribution. The onset may be at any age following puberty and the frequency increases with age. By the age of 70 or beyond 80% of Caucasian men and up to 40% of women have signs of androgenetic alopecia.

Age- and gender-independent, androgenetic alopecia may be associated with significant impairment in quality of life. Hair is an important feature of image. Hair loss affects self-esteem, personal attractiveness and may lead to depression and

other negative effects of life (1). Androgenetic alopecia can be a burden for both sexes, but it is substantially more distressing for women (2).

Therapeutic experiences. Alfonso *et al* reported that three out of four men with androgenetic alopecia had never pursued therapy for hair loss although over half experienced a significant adverse effect on quality of life (1). On the other hand, some have tried different therapies in vain and are dissatisfied with current therapeutic approaches, before they come to see the specialist. Consequently their compliance is poor. Men who treated their hair loss successfully reported psychosocial benefits with improvements for self-esteem and personal attractiveness (1).

Patient compliance. There are discrepancies between the wish for hair regrowth and consequent willingness to undertake a therapeutic regimen. Limited efficacy, poor tolerance, fear and lack of information on treatment duration and possible adverse events may lead to disappointment.

1.2 Purpose of the guideline

The purpose of the guideline is to provide dermatologists with an evidence-based tool for choosing an efficacious and safe therapy for patients with androgenetic alopecia. The current guideline aims to prevent progressive hair loss and associated dermatological and psychosocial long-term complications by improving the individual therapeutic recommendations and strategy.

Improved patient care. The use of these evidence-based recommendations in clinical routine should improve patient care.

Ensure optimal usage of the therapeutic regimen. In addition to the efficacy assessment, the guideline provides details on administration and safety aspects of systemic, topical or surgical therapy.

Improvement of patient knowledge and compliance. Patient compliance is most important in the individual response to treatment. Good compliance is not only related to balance of benefits, costs and adverse effects, but also requires that the patients are well informed. By increasing the level of patient knowledge about the optimal use of each therapy and its possible complications compliance, response rates and satisfaction will increase.

1.3 Directions for use of the Guideline

The current guideline is meant for dermatologists, general practitioners in clinics as well as in private practice and other specialists who are involved in the treatment of androgenetic alopecia.

Each chapter summarizes the efficacy resulting from the evidence-based evaluation separately for men and women, and provides information on practical aspects important for the different therapeutic regimens. The users of the guideline should be aware that the listed aspects are not intended to be exhaustive. General obligations, which are part of every individual therapeutic decision, like known allergies, potential intolerance reactions or contraindications, are not conclusively individually listed. Consequently, the users of the guideline should also consider the manufacturer's up-to-date product information and check the recommendations concerning dosages, safety, contraindications and drug-interactions.

Although the authors took care that the guidelines correspond to the current state of the art at the time of completion, authors and publishers cannot take responsibility for

dosages and therapeutic choices, as therapy of androgenetic alopecia may change between cycles of the guideline. Therefore the use of this guideline is at the physician's responsibility and users are requested to keep informed about new knowledge published in parallel to the guidelines. The authors and publishers of the guideline would be grateful if readers could inform them of any inaccuracies.

1.4 Methodology

Literature research. This guideline was conducted as the update of the evidence-based (S3) Guideline for the treatment of androgenetic alopecia in women and men (3). A detailed description of methodology used in developing the guidelines can be found in the method report. The search strategy and methodology of this guideline and its update was orientated on the standards of the AGREE instrument and on the methodology of the European S3 guideline for the treatment of psoriasis vulgaris.

To assess the efficacy of the individual therapeutic processes, a systematic search of literature of the databases Medline, Medline in Process, Embase and Cochrane Library was conducted.

To enhance the sensitivity of the search reference lists of articles were screened and hand searches were conducted by the authors to identify articles which are not listed in the databases. The searches comprised the period since the search for the first version of the S3 guideline in 2008 to 15th October 2015. Identified articles were screened for eligibility by at least two independent authors and were retained if they met the predefined criteria (*see Attachment 1, literature evaluation form*). All discrepancies were solved by consensus or involvement of a third author.

Results. Overall 797 articles were found in the update search. After checking for duplicates and relevance 184 articles were evaluated in full text using the literature evaluation form (LEF) (*see Attachment 1*). Forty seven articles met the inclusion criteria of the guideline and built the basis of the guideline. *Figure 1* summarizes the process of literature research.

Data extraction. Data extraction was also conducted by two independent reviewers, resolving discrepancies by discussion with a third author. Extracted data included source, target population, treatment areas, description of treatment and study design, study duration, used outcome assessments and results. Included articles were graded for their degree of evidence

The evidence-based evaluations of these guidelines are based on objective evaluations and standardized criteria using the evidence assessment and the level of evidence scale. All other issues, which are outlined in the guideline, e.g. instructions for use, adverse events, contraindications, are based on opinions and personal experiences of the members of the guideline group.

Evidence assessment. The methodological quality of each study, which was included in the evidence-based analysis, was defined by the **GRADE OF EVIDENCE**. We assessed the grade of evidence according to the following scheme:

- A₁** Meta-analysis, which includes at least one randomized clinical trial of grade A₂ evidence with consistent results of the different studies.
- A₂** Randomized, double-blind, comparative clinical studies of high-quality (e.g. sample size calculation, flow chart of patient inclusion, ITT-analysis, sufficient size).

- B** Randomized, clinical studies of lesser quality or other comparable studies (not-randomized, cohort- or case-control-studies).
- C** Non-comparable studies.
- D** Expert opinion.

The determination of grade of evidence was done within the LEF form by the particular expert group and the staff member. The scheme for grading the evidence was used for assessment of monotherapies as well as combination therapies.

Level of evidence. After determining the grades of evidence of the individual studies, the grades of all studies belonging to a particular therapeutic regimen were summarized in a level of evidence. The **LEVEL OF EVIDENCE** takes into account the methodological quality of the trials (grade of evidence) and the intertrial consistence of the results.

- 1** Studies grade A₁ evidence or studies with mainly consistent results grade A₂ evidence
- 2** Studies grade A₂ evidence or studies with mainly consistent results grade B evidence
- 3** Studies grade B evidence or studies with mainly consistent results grade C evidence
- 4** Little to missing systematic evidence

Therapeutic recommendation. Grades and levels of evidence were considered in the formal consensus process. The guideline group defined particularly relevant sections requiring consensus. These passages were discussed and approved at the consensus conferences. The resulting evidence-based therapeutic recommendations aim to optimize the therapeutic process and to support the practitioner in the individual decision on a suitable therapy. Nevertheless, the decision process on a particular therapy remains complex and limited on the individual case. It is not possible to define a strict clinical algorithm.

Strength of recommendation. This guideline summarizes the characteristics of the available drugs and their evidence-based therapeutic efficacies. The consented therapeutic recommendations were additionally weighted by the **STRENGTH OF RECOMMENDATION**. The strength of recommendation considers efficacy, evidence level, safety and practicability and was agreed in a formal consensus process. The expert group agreed on a 6-point scale. This scale is illustrated by arrows:

- ↑↑ We recommend
- ↑ We suggest
- Can be considered (may be considered if a higher-strength recommendation is not available or appropriate)
- ↓ We suggest not
- ↓↓ We do not recommend
- We cannot make a recommendation for or against treatment X at the present time

2 INTRODUCTION TO ANDROGENETIC ALOPECIA

Androgenetic alopecia is the most frequent form of alopecia in men and women. Today, in our societies, strong and dense hair is associated with youth, beauty, healthiness and success. Consequently, in patients presenting with androgenetic alopecia progressive thinning of hair often causes a psychological distress. Patients are looking for effective hair loss treatments in order to stop and prevent further thinning and optimally stimulate regrowth. Knowledge of the efficacy of the different therapeutic options is essential for those involved in treating AGA.

2.1 Epidemiology

The population frequency and severity of androgenetic alopecia in both sexes increase with age. Almost all Caucasian men develop some recession of the frontal hair line at the temples during their teens. Deep frontal recession and/or vertex balding may also start shortly after puberty although in most men the onset is later. About 50-60% of men are affected by the age of 50 increasing to about 80% by the age of 70 and beyond (4, 5). Hair loss progresses to a bald scalp (Norwood-Hamilton VI/VII) in 50-60% of men by the age of 70 (5). The prevalence of androgenetic alopecia is reportedly lower and its severity less among Asians, Native Americans and African-Americans compared to the European population (6, 7). Two studies in Chinese men found a prevalence rate of 10-20% in men aged 40-49, rising to 40-60% in men aged 70 and over (8, 9).

The frequency and severity of androgenetic alopecia is lower in women than in men but it still affects a sizeable proportion of the population. Two studies in Caucasian women in the UK and USA reported prevalence rates of 3-6% in women aged under 30, increasing to 29-42% in women aged 70 and over (10, 11). As in men, androgenetic alopecia is less common and appears to start later in life in Asian women although nearly 25% of Korean women over 70 years of age show evidence of hair loss (12). The prevalence appears lower in Chinese women with 12-15% of women aged 70 and over reported to show hair loss (8, 9).

2.2 Aetiology

Androgenetic alopecia in both men and women is characterized by progressive shortening of the anagen phase of the hair cycle, prolongation of the post-exogen phase of telogen (latent phase or kenogen) and miniaturization of the hair follicle in predisposed men and women. Its aetiology is multifactorial and polygenic (13).

Men Androgenetic alopecia in men is an androgen-dependent trait (14). Evidence from genetic disorders and from clinical trials of 5 α -reductase inhibitors has shown that dihydrotestosterone (DHT) is the androgen chiefly responsible for the follicular pathology although the molecular and cellular events are only partially understood. DHT probably acts primarily on dermal papilla, the predominant site of androgen receptor and Type II 5 α -reductase expression within the hair follicle. A number of signaling molecules have been implicated in the inhibition of hair growth in AGA including TGF- β 1 and TGF- β 2(14), dickopf 1 (a member of the WNT-signaling family)(15) and IL-6(16). There is also evidence for involvement of prostaglandins in AGA. The enzyme PGD(2)-synthase and its product PGD(2) are elevated in balding scalp skin; PGD(2) has an inhibitory effect on hair growth in animal and in *in vitro* experiments (17).

Twin studies have shown that male AGA is largely determined by genetic factors (18, 19). There is also a strong paternal influence on the risk of balding (and non-balding) (5). Although once thought to be an autosomal dominant trait it is now clear that, like other common human attributes, AGA has a complex polygenic basis. To date, molecular studies have recognised twelve genetic regions that associate with AGA and identified some candidate genes. These include genes for the androgen receptor (*AR*), histone-deacetylases (*HDAC*) 4 and 9, and the WNT molecule *WNT10A* (20).

Women Less is known about the aetiology of androgenetic alopecia in women. There is an increased frequency of balding in first degree male relatives of women with androgenetic alopecia suggesting at least some genetic commonality between female and male AGA (21). On the other hand, the results of a twin study in women, while showing a significant genetic contribution to fronto-temporal recession, suggested that general hair thinning as a non-genetic aetiology (22). However, this study was conducted in older women and does not exclude a genetic component to early onset female AGA. Case control gene association studies have found a weak association between the *AR/EDA2* locus and early onset female AGA but no association with the 11 autosomal loci that associate with male AGA (23-25). There is a weak association with the gene for estrogen receptor 2 (*ESR2*) suggesting involvement of estrogenic pathways in female AGA (26, 27). To date there have been no genome-wide studies in women.

The role of androgens in female AGA is also less certain than in men. Hair loss is undoubtedly a feature of severe hyperandrogenemia, such as occurs with androgen-secreting tumours. Some studies have shown an increased frequency of biochemical hyperandrogenism, mostly minor in degree (28), and of other clinical features of androgen excess such as polycystic ovaries (29). However, many women with AGA show no other clinical or biochemical features of androgen excess. Nevertheless, it is important to bear in mind that there is a subset of women with androgenetic alopecia and associated hormonal dysregulation. Detailed information on the steps in diagnostic procedure can be found in the S1 guideline for diagnostic evaluation in androgenetic alopecia in men, women and adolescents (13).

2.3 Clinical features

Androgenetic alopecia is characterized clinically by a drift from terminal to vellus hairs and progressive thinning, usually in a pattern distribution. The different patterns can occur in men as well as in women, though the frequencies are gender-specific. Moreover, it is not rare, that additionally to the pattern a diffuse thinning of the parietal and occipital areas can be observed (13).

Male pattern, Hamilton-Norwood

This is the most frequent clinical pattern in men with androgenetic alopecia, only occasionally observed in women. Recession of the frontal hair line, mainly in a triangular pattern is the characteristic finding, later followed by a vertex thinning (*Figure 2*).

Female pattern, Ludwig

The so called female pattern is characterized by a diffuse thinning of the centroparietal region with maintenance of the frontal hair line (*Figure 3*). It is the most common type in women, occasionally also observed in men.

Christmas tree pattern

Similar to the Ludwig pattern the Christmas tree pattern shows diffuse centro-parietal thinning, but additionally, the frontal hair line is breached (*Figure 4*). The Christmas tree pattern is another common pattern in women.

2.4 Diagnosis

The diagnosis of androgenetic alopecia is usually made clinically by inspection of the hair and scalp showing a non-scarring alopecia in the typical pattern distribution (13).

The clinical examination should also include a pull test as well as examination of facial and body hair and nails to exclude differential diagnoses; in particular diffuse telogen effluvium, alopecia areata and cicatricial alopecia (13).

Trichoscopy should be used in doubtful cases. The typical trichoscopy features of androgenetic alopecia include; hair shaft thickness heterogeneity of 20% or more, vellus hairs above 10%, increased percentage of follicular units with only one hair shaft, yellow dots, perifollicular discoloration (peripilar sign), empty follicles, circle hair and honey comb pigment pattern and higher prevalence of these abnormalities in the frontal area compared to the occipital area (30).

Due to the high prevalence of androgenetic alopecia its coincident appearance to other hair diseases should be taken into account. If a differential diagnosis cannot be excluded clinically, laboratory tests or histology can be helpful.

2.5 Hair growth assessment techniques

To document the extent of androgenetic alopecia in clinical practice the different classifications of the pattern distribution are subdivided (Hamilton-Norwood I-VII, Ludwig I-III, Christmas tree pattern I-III). However, a generally applicable definition for the extent of androgenetic alopecia does not exist. Moreover, the documentation of degree of the pattern distribution is often not suitable to reflect the course of androgenetic alopecia.

As it is a ***naturally progressive disease***, therapy can have two required ***outcomes***, namely ***stop of hair loss and induction of hair regrowth***. In clinical practice the evaluation and follow-up of hair growth is generally restricted to individual assessment of patient and physician. In clinical studies, the subjective hair growth assessment by patient and investigator are substantiated by objective hair count/density methods and assessment of standardized global photographs.

The global photographic assessment is a semi-objective tool in evaluation of hair growth. Global photographs are assessed by experts blinded to treatment and time.

Automatic digitalized photographic systems are able to quantify hair density, hair thickness, anagen/telogen hair ratio, terminal/vellus hair ratio within an investigational area. To ensure reproducibility in studies a tattoo is generally used to guarantee analysis of the same area. The technique is limited by the size of the measured area. In clinical trials comparison to baseline and to placebo resp. another treatment is necessary for efficacy assessment of a therapeutic option.

Within the development of the S3 guideline the guideline group voted on a ***ranking of the different investigative methods*** and outcome parameters. The global photographic assessment was voted to be most effective in evaluation of hair growth, as the whole scalp hair is evaluated in a standardized way. Patient and investigator perceptions can be excluded. In the opinion of the guideline group global photographs should also be used in routine clinical practice for longterm-follow-up.

2.6 Risk/benefit considerations

In routine clinical practice the individual decision for a particular treatment of androgenetic alopecia depends not only on the efficacy, but also on practicability, risks and costs. The assessment of cost effectiveness is important for counselling patients and may contribute to patients' decisions.

As the patient usually has to bear the full costs of the treatment, consideration of patient-relevant benefit is essential. The benefit attained in the therapy of androgenetic alopecia is not only stabilization, prevention of progression and induction of hair growth, but may contribute to an improved quality of life.

The guideline offers evidence-based analyses of the existing therapeutic options that help to take suitable cost-benefit decisions in the assessment of the specific case.

3 THERAPEUTIC OPTIONS AND THERAPY ASSESSMENT

The following chapters summarize the evidence-based efficacy assessment of the different therapeutic options in the treatment of androgenetic alopecia in men and women. Efficacy was evaluated separately for men and women.

Result tables. All studies that fulfilled the inclusion criteria of the guideline are listed in result tables (*see attachment 2*). The evidence-based results of the trials are outlined in the particular chapter, but can be read in detail in the result tables, if required. Based on the result tables the expert group passed therapeutic recommendations for the different regimens by formal consensus process.

Overview of common therapeutic options. *Table 1* shows a summary of evidence level, efficacy to prevent progression and/or improve androgenetic alopecia, safety aspects and practicability for the most common therapeutic interventions. Its intention is to provide a first rough orientation. Its exclusive use is not sufficient for individual therapeutic choices. Deeper observation of the individual factors of a given patient and its impact on the different therapeutic regimens are necessary.

3.1 MINOXIDIL

3.1.1 Introduction

Minoxidil was originally developed as an oral drug (trade name Loniten®) to treat high blood pressure. Its possible use in androgenetic alopecia was discovered by noticing, that it has a rather interesting side effect: to cause increased hair growth. Chemically, minoxidil is a pyrimidine derivate. It was the first product to be approved for the treatment of AGA in both men and women. The 2% topical solution was first approved by the FDA in 1988 for the treatment of androgenetic alopecia in men and in 1991 in women. The 5% solution was approved in 1997 for the treatment of androgenetic alopecia in men followed by approval of the 5% foam in 2006 also for the treatment of androgenetic alopecia in men and in 2014 for the androgenetic alopecia in women (31).

3.1.2 Mechanism of action

To exert its effect minoxidil needs to be transformed to its active metabolite, minoxidil sulphate by the enzyme sulphotransferase, which is present in the outer root sheath of anagen follicles. The exact mechanism by which minoxidil promotes hair

growth is still unclear. Its active metabolite, minoxidil sulphate opens ATP-sensitive potassium channels in cell membranes, which conveys vasodilatory effect. Vasodilatation however does not appear to be responsible for minoxidil induced hair growth. Studies on skin blood flow after topical minoxidil application produced inconsistent results.

Other possible effects of minoxidil on the hair follicles include:

- a) increased expression of vascular endothelial growth factor (VEGF) mRNA in the dermal papilla. This indicates that the drug induces angiogenesis in the dermal papilla.
- b) activation of cytoprotective prostaglandin synthase-1, a cytoprotective enzyme that stimulates hair growth.
- c) increased expression of hepatocyte growth factor (HGF) m-RNA; HGF is an hair growth promoter.

3.1.3 Efficacy – males

48 studies assessing the efficacy of minoxidil in male patients with androgenetic alopecia met the inclusion criteria for the guideline (6, 32-79). 1 out of them assessed the effect of oral minoxidil (76). 5 out of them treated male and female patients. 30 studies were placebo controlled. The majority of studies obtained grade A2 and B evidence (A2 = 22, B = 18, C = 8) resulting in **EVIDENCE LEVEL 1**.

In general most of the trials assessed the efficacy of topical minoxidil solution or foam 5% and of minoxidil solution 3% or 2% applied twice daily. In most trials that examined the effect of topical minoxidil > 2%, regular topical application resulted in hair regrowth.

OUTCOMES

The mean change from baseline *total hair count* ranged between 5.4 hairs/cm² and 29.9 hairs/cm² (11.0 – 54.8%) at 4 to 6 months and between 15.5 hairs/cm² and 83.3 hairs/cm² (14.8-248.5%) at 12 months (6, 36, 39-43, 47-49, 51, 52, 56, 59-61, 64, 66).

At 4 to 6 months the mean total hair count changes in the majority of studies were statistically significant compared to placebo (p between 0.074 and < 0.0001). At 12 months most of the older trials switched the placebo group also to minoxidil treatment.

Comparable to the results in total hair count the mean changes in *nonvellus hair counts* were also significantly different to placebo (p between < 0.05 and 0.001). There was a mean change in nonvellus hair counts between 4.7 hairs/cm² to 37.3 hairs/cm² (17.2 – 59.4%) at 6 months, between 9.4 hairs/cm² to 41.8 hairs/cm² (8.8 – 443.8%) at 12 months (39-49, 51-54, 56, 57).

The increases from total and nonvellus hair counts at 6 and 12 months did significantly differ from baseline hair counts (p between 0.01 > p < 0.0001).

In a study by Hillmann et al. minoxidil 5% topical foam showed a difference from baseline non-vellus hair count of 27.7 hairs/cm² (14.4%) in the frontotemporal region and of 25.6 hairs/cm² (13.1%) in the vertex region after 16 weeks of application whereas placebo showed a difference from baseline non-vellus hair count of 4.5 hairs/cm² (2.7%) in the frontotemporal region and of 5.9 hairs/cm² (33%) in the vertex region. Comparing the groups a statistically significant increase was found for the minoxidil 5% group compared to placebo (p=0.0001). After 24 weeks of application,

however, minoxidil 5% foam showed a difference from baseline non-vellus hair count of 7.8 hairs/cm² (4.4%) in the frontotemporal region and of 8.7 hairs/cm² (4.9%) in the vertex region whereas placebo showed a difference from baseline non-vellus hair count of -1.5 hairs/cm² (-0.2%) in the frontotemporal region and of 0.4 hairs/cm² (0.9%) in the vertex region. This difference between the groups did not prove to be statistically significant (59).

In an open label 104-week clinical trial by Kanti et al. no significant differences in the growth profile of mean non-vellus hair count or cumulative hair width were found between the frontotemporal and vertex regions in men with androgenetic alopecia treated with minoxidil 5% topical foam (37).

It has to be mentioned, that the reported placebo rate in most of the minoxidil studies is very high. The mean increase from baseline total hair count of the placebo group ranged between 6.1 hairs/cm² and 22.4 hairs/cm² (9.3 and 48.8%) at 4 to 6 months. In the study by Sakr et al, a mean decrease from baseline total hair count of 57 hairs/cm² (-41%) was reported at 24 weeks in the placebo group (72). A study by Hillmann et al. reported a mean change of non-vellus hair count of -1.5 hairs/cm² (-0.2%) in the frontotemporal region in patients with androgenetic alopecia receiving placebo topical foam twice daily for 24 weeks (59).

MINOXIDIL P.O.

Lueangarun et al. investigated the efficacy of oral minoxidil 5 mg once daily per os in men (76). After 24 weeks of treatment, total hair count showed an increase of 35.1 hairs/cm² (19.3%, $p = 0.007$), which is only slightly higher compared to topical administration. Side effects included hypertrichosis (93%), pedal edema (10%) and ECG alteration (10%).

DOSAGE

Concentration. Minoxidil dosages below 2% showed significant reduced mean changes from baseline total hair count in comparison to minoxidil 2% at 6 months (43, 44). The mean changes from nonvellus hair counts were not significantly different for minoxidil 0.1%, 1%, 2% at 6 months.

Minoxidil 3% solution, applied twice daily was not significantly different from minoxidil 2%, twice daily (mean change from total hair count/nonvellus hair count at 4 respectively 12 months) (33, 35, 51, 52, 54-56, 60, 61). Only Katz et al. reported a significance of $p = 0.0464$ at 4 months in mean change of nonvellus hair counts (53). Tanglertsampan reported a statistically non-significant change from baseline in the mean hair count after 24 weeks of twice daily application of minoxidil 3% lotion (70). 2 studies comparing minoxidil 2% solution, twice daily and minoxidil 5% solution, twice daily were included in the evidence based analysis (45, 58). In both studies the outcome of the minoxidil 5% group was superior to minoxidil 2% (mean change from baseline nonvellus hair count 18.6 hairs/cm² (12.3%) vs. 12.7 hairs/cm² (8.8%) at 12 months, $p = 0.025$, mean % change from baseline total hair count 30% vs. 25% at 24 months, $p = 0.455$). Furthermore, in a study by Tsuboi in Japanese males twice daily application of minoxidil solution 5% was found to be superior than 1% after 16 weeks ($p=0.02$). The mean change of non vellus hair count from baseline was 26.4 hairs/cm² (20.4%) for the minoxidil 5% group and 21.2 hairs/cm² (16.2%) for the minoxidil 1% group (6).

Topical minoxidil 5% was reported to lead to a statistically significant increase of mean non-vellus hair count after 3, 4, 6, 12 and 18 months ($p= 0.039$, $p\leq 0.0001$,

p<0.001, 0.014 and 0.030 respectively) (37, 38, 59, 71, 79). After 24 months of treatment with minoxidil 5% topical foam in men with androgenetic alopecia, no significant differences in the growth profile of non-vellus hair count were found between the frontotemporal and vertex regions (37).

Application frequency. Olsen et al. showed, that minoxidil 3% applied twice daily was superior to application once daily (mean change from baseline total hair count 64.4 hairs/cm² vs. 44.1 hairs/cm² at 33 months, p = 0.015, mean change from baseline nonvellus hair count 4.4 hairs/cm² vs. -13.4 hairs/cm² at 36 months) (35).

FORMULATION

Minoxidil is available as a standard thermolabile formulation as a solution containing propylenglycol and as a thermolabile foam formulation. Olsen et al. studied the application of a foam formulation containing 5% minoxidil in the vertex area in male patients (38). The mean change from baseline nonvellus hair count was highly significant different from placebo at 16 weeks (20.9 hairs/cm² (13.4%) vs. 4.7 hairs/cm² (3.4%), p < 0.0001). Hillmann et. al studied the application of minoxidil 5% foam in both the frontotemporal and vertex areas (59). The mean change from baseline nonvellus hair count was highly significant different from placebo at 16 weeks (27.7 hairs/cm² (14.4%) in the frontotemporal region and 25.6 hairs/cm² (13.1%) in the vertex region vs 4.5 hairs/cm² (2.7%) in the frontotemporal region and 5.9 hairs/cm² (33%) in the vertex region, p=0.0001). After 24 weeks of application, no significant changes from baseline were found in either group. Kanti et al. reported stable mean non-vellus hair count between baseline and week 104 in the frontotemporal and vertex regions in men treated with minoxidil 5% topical foam twice daily (37).

Piepkorn et al. examined minoxidil 2% in a gel formulation and as solution (50). Whereas placebo gel and solution reached comparable percentage improvement in subject's assessment (33 vs. 36%), minoxidil 2% gel, twice daily had 26% improvement, minoxidil 2% solution, twice daily 48% improvement after 6 months in subject evaluation.

MINOXIDIL VS. FINASTERIDE

4 studies obtaining grade B evidence where identified comparing the use of oral finasteride 1mg and topical minoxidil, resulting in in **EVIDENCE LEVEL 2**.

Hu et al compared finasteride 1 mg daily per os to minoxidil 5% topical solution twice daily for 12 months in Chinese males with androgenetic alopecia, showing statistically significant increase of hair growth in both groups over time (P<0.01, improvement 80.5% and 59% respectively, based on investigator's assessment) (73). A more pronounced improvement was found in the finasteride group (p<0.01). A study by Saraswat et al. reported superiority of finasteride 1 mg/d per os compared to minoxidil 2% topical solution, applied twice daily, (mean change from baseline total hair count 36.1 hairs/cm² (29.1%) vs. 19.6 (14.8%) at 12 months, p = 0.003) (64). Khandpur et al. reported improvement in 87% of the patients receiving finasteride 1mg daily and 42% in patients receiving minoxidil 2% solution twice daily, as rated by an investigator (67).

On the other hand, Arca et al. reported 80% improvement in global photographic assessment for minoxidil 5%, twice daily and 52% for finasteride 1mg daily at 12 months (63).

MINOXIDIL VS. TOPICAL 5A-REDUCTASE INHIBITOR

In a study by Pumthong et al., males with androgenetic alopecia were randomized to receive a hair tonic including 5% hexane extract of *Curcuma aeruginosa*, a botanically derived 5a-reductase inhibitor, minoxidil 5% topical hair tonic, combination formulation (5% hexane extract of *Curcuma aeruginosa* + 5% minoxidil) or placebo Hair tonic twice daily for 6 months (79). Mean changes from baseline non-vellus hair counts were 30.62 hairs/cm² (20.0%) for the *Curcuma aeruginosa* 5% extract, 31.32 hairs/cm² (18.1%) for minoxidil 5% topical hair tonic, 32.59 hairs/cm² (20.7%) for the combination topical treatment and 20.41 hairs/cm² (11.4%) in the placebo hair tonic group. However, when percent changes between baseline and month 6 of the four groups were compared, these differences did not reach statistically significant levels ($p > 0.05$).

This study obtained grade A2 evidence, resulting in an **EVIDENCE LEVEL 2**.

MINOXIDIL VS. ADENOSINE

Faghihi et al. failed to prove superiority of the application of adenosine 0.75% solution compared to minoxidil 5% topical solution twice daily during 6 months (78). According to the global expert panel assessment, after 3 months of treatment relative recovery was achieved in 1,9% and 2,4% of the patients in the two groups respectively, with no significant between-group difference ($p=0.17$). At the end of 6 months of treatment, complete and relative recovery did not reveal changes between the groups ($p=0.99$), except for the patient satisfaction score, which showed a significant preference for adenosine ($p=0.003$).

MINOXIDIL VS. ROSEMARY OIL

Panahi et al did not find any significant differences in hair growth between therapy with minoxidil 2% topical solution and a formulation containing rosemary oil after 6 months ($p>0.05$) (68).

3.1.4 Efficacy – females

19 studies that investigated the efficacy of topical minoxidil in female patients suffering from androgenetic alopecia could be included in the evidence based evaluation (60, 61, 74, 75, 77, 80-93). 5 studies treated male and female patients. 7 studies obtained grade A2 evidence, 9 studies grade B evidence, 3 studies grade C evidence resulting in an **EVIDENCE LEVEL 1**.

OUTCOMES

Minoxidil 1% solution, applied twice daily led to mean changes from baseline total hair count at 6 months from 15.2 hairs/cm² (8.0%) (94). Minoxidil 2% solution showed mean changes from baseline nonvellus hair count at 6 months between 21.0 hairs/cm² and 50.1 hairs/cm² (12.4 -31.3%) (60, 81-85, 87, 90, 91). Minoxidil 3% solution showed a mean change from baseline hair count of 11.9 hairs/cm² (12.4%) at 6 months (92).

Minoxidil 5% topical foam, applied once daily led to mean changes from baseline nonvellus hair count between 13.4 and 31.9 hairs/cm² (16.2%) after 6 months (89-91). A significantly different mean change was shown in comparison to placebo

($p < 0.0001$) (89). Two studies by Blume-Peytavi et al. showed noninferiority of minoxidil 5% foam used once daily compared to minoxidil 2% solution used twice daily for 6 months and 1 year (90, 91). A further study by Sheng et al. showed comparable improvement ratio in female patients applying minoxidil 2% topical solution twice daily and minoxidil 5% topical solution once daily for 6 months ($p = 0.076$) (88).

In the study by Lucky et al., topical minoxidil 5% solution twice daily, topical minoxidil 2% solution twice daily or placebo twice daily was applied for 48 weeks in women with androgenetic alopecia (83). No significant difference was found between the 5% and 2% topical minoxidil groups in the mean change from baseline in non-vellus hair count at week 48. In adverse event reporting, 46% of the patients in the 5% minoxidil group reported increased facial hair growth vs. 22% in the 2% minoxidil group and 16% in the placebo group.

Except the study by Whiting et al. all studies showed significant different mean changes from baseline hair counts in comparison to placebo (p between 0.02 and < 0.00001) (81-84, 89-91, 94).

DOSAGE

Concentration. The mean changes in nonvellus hair counts between minoxidil 5% and 2% in female patients were not statistically significant ($p = 0.129$) (83). At 12 months the mean change from nonvellus hair count was 20.7 hairs/cm² (13.8%) for minoxidil 2%, twice daily, 24.5 hairs/cm² (17.3%) for minoxidil 5%, twice daily and 9.4 hairs/cm² (6.8%) for placebo, twice daily ($p < 0.001$ vs. placebo).

Two studies by Blume-Peytavi et al. showed noninferiority of minoxidil 5% foam once daily compared to minoxidil 2% solution twice daily for 6 months and 1 year (90, 91).

MINOXIDIL VS. ALFATRADIOL

In comparison to topical Alfatradiol 0.025%, once daily, minoxidil 2% solution, twice daily led to increased hair counts after 6 months (80). The mean change from baseline total hair count was -7.8 hairs/cm² (-4.3%) for alfatradiol and 15.3 hairs/cm² (8.7%) for minoxidil 2% ($p < 0.0005$).

3.1.5 Instructions for use / Practicability

Treatment with minoxidil converts partially miniaturized (intermediate) to terminal hair and produces at least a partial normalization of the hair follicle morphology.

Minoxidil should be applied as 1 ml of solution with a pipette or half a cap of foam to dry hair and scalp once in the morning and again in the evening and left in place for at least four hours. In women the foam formulation is recommended only once daily. When using spray applicator it has to be spread evenly over the affected areas. After application the hands should be washed with warm water.

Treatment efficacy should be assessed at least 6 months after initiation of therapy and treatment should be maintained as long as the effect is to be desired by the patient in order to prevent hair loss.

Some patients may experience *increased hair shedding* during the first months of the treatment. This is transitory and only indicates that the drug is stimulating telogen follicles to re-enter anagen. It is important to inform the patient about a possible

telogen shedding, before the treatment is started. If shedding occurs, therapy should be maintained. Usually, increased hair loss and reduced hair density due to telogen shedding normalizes within a few weeks to months. Good patient-practitioner-relationship and detailed patient information are essential for good compliance. Interruption of topical minoxidil is followed by increased hair loss, which usually starts 3 months after stopping the treatment.

Main side effect of topical minoxidil is *hypertrichosis*, which is more common with the 5% concentration and is usually due to incorrect application and rarely to systemic absorption. To avoid contamination of the pillow with subsequent contact with face patients should be advised to apply the drug at least 2 hours before going to bed. *Irritant and allergic contact dermatitis* may also occur. Irritation is more common with the 5% solution due to its higher content in propylenglycole. Contact dermatitis should be confirmed by patch testing. If it is due to propylenglycole, an alternative vehicle can be used, whereas if irritation and contact dermatitis are due to minoxidil itself, drug interruption is unavoidable.

Some women report difficulties in topical foam application in daily use. Evaluation of hair density, practicability for the patient and thorough instructions are needed prior to first prescription.

Minoxidil is contraindicated in pregnancy and lactation.

3.1.6 Combination therapies – males

9 studies investigating the effect of minoxidil topical solution alone vs combination therapy could be included in the evidence based evaluation (67, 69-75, 79). 2 studies treated male and female patients. 3 studies obtained grade A2 evidence and 6 studies grade B evidence resulting in an **EVIDENCE LEVEL 3**.

MINOXIDIL AND FINASTERIDE COMBINATION

In a study by Hu et al., Chinese males with androgenetic alopecia were randomized into three groups, treated with finasteride 1 mg per os once daily, topical minoxidil 5% twice daily and combination treatment with finasteride 1 mg per os once daily and topical minoxidil 5% twice daily for 12 months. According to the investigator's assessment, the efficacy of the combined treatment was the best ($p < 0.01$) with an increase of 94.1% in hair growth after 12 months (73).

Khandpur et al. reported improvement in 100% of the patients receiving combination therapy with finasteride 1mg per os daily and minoxidil 2% topical solution twice daily and 42% in patients receiving minoxidil 2% topical solution twice daily, as rated by an investigator (67).

MINOXIDIL AND TOPICAL 5A-REDUCTASE INHIBITOR COMBINATION

A study by Tanglertsampan did not show any difference in the mean change in hair counts between two groups treated for 24 weeks with minoxidil 3% topical lotion vs combined minoxidil 3% and finasteride 0,1% topical lotion ($p = 0.503$) (70). Another study by Pumthong et al failed to show superiority of a combination hair tonic formulation containing 5% hexane extract of *Curcuma aeruginosa* and 5% minoxidil compared to a hair tonic containing 5% hexane extract of *Curcuma aeruginosa*, 5% minoxidil hair tonic or placebo hair tonic (79).

MINOXIDIL AND PYRITHIONE ZINC SHAMPOO COMBINATION

A study by Berger et al. failed to show, that combination of minoxidil 5% solution and pyrithione zinc shampoo is superior to minoxidil monotherapy (65). Minoxidil 5% solution, twice daily combined with pyrithione zinc shampoo 1x/d vs. minoxidil 5% solution twice daily and placebo shampoo showed mean change from baseline total hair count of 6.2 hairs/cm² and 12.3 hairs/cm² respectively.

MINOXIDIL, DICLOFENAC AND TEA TREE OIL COMBINATION

A pilot study by Sakr et al compared a multimodal oil/water micro emulsion comprising minoxidil 5%, diclofenac 0.5% and tea tree oil 5% (n=11), a formulation containing minoxidil 5% alone (n=11), and placebo (n=10) applied twice daily for 32 weeks (72). Mean changes from baseline total hair count were 84 hairs/cm² (63.2%), 48 hairs/cm² (39.3%) and -57 hairs/cm² (-41%) respectively. Improvement in hair count with the multimodal minoxidil microemulsion was significantly greater than with minoxidil alone or placebo throughout the treatment period (P < 0.01 and P < 0.001, respectively). The study obtained an evidence grade B. However, due to the small number of subjects per group, the results should be confirmed in larger cohorts.

MINOXIDIL, BETAMETHASONE VALERATE AND AZELAIC ACID COMBINATION

Pazoki-Toroudi et al. compared in a study in male and female patients minoxidil 5% topical solution, combination of minoxidil 12.5% with azelaic acid 5.0% and betamethasone valerate 0.025% 1x/d and placebo topical solution 2x/d (75). At 24 weeks, improvement was found according to investigator's assessment in 40%, 61,91% and 37,5% of male patients in the minoxidil, combination and placebo group respectively. Improvement was reportedly statistically significant in the combination group compared to placebo (p<0.001) and topical minoxidil 5% (p<0.05). This study obtained a grade of evidence B.

MINOXIDIL AND TRETINOIN COMBINATION

Bazzano et al. compared in a study of male and female patients minoxidil 0.5% solution, 2x/d, tretinoin 0.025% solution, 2x/d, placebo and the combination of minoxidil 0.5% with tretinoin 0.025% (74). At 12 months, 58% of the patients of the tretinoin group and 66% of the patients with the combined treatment had at least 20% or more increase from baseline total hair count.

Shin et al. failed to prove significance between minoxidil 5% solution, twice daily and a combination of minoxidil 5% and tretinoin 0.01%, once daily in men with androgenetic alopecia (69). The mean change from baseline total hair count at 18 weeks was 15.9 hairs/cm² (12.8%) vs. 18.2 hairs/cm² (14.7%) (p not significant).

MINOXIDIL AND MICRONEEDLING COMBINATION

In a 12-week study by Dhurat et al. (71), combination therapy consisting of weekly microneedling treatment and twice daily 5% minoxidil topical lotion showed a mean change in total hair count from baseline of 91.4 hairs/cm², while 5% minoxidil topical lotion monotherapy showed a mean change in total hair count from baseline of 22.2 hairs/cm² (p=0.039).

3.1.7 Combination therapies – females

5 studies investigating the effect of minoxidil topical solution alone vs combination therapy in females could be included in the evidence based evaluation (74, 75, 86,

92, 93, 95). 2 studies treated male and female patients. 3 studies obtained grade B evidence and 2 studies grade C evidence resulting in an **EVIDENCE LEVEL 3**.

MINOXIDIL AND ORAL SUPPLEMENT COMBINATION

Trüeb et al compared in a study in female patients minoxidil 2% monotherapy with combination therapy with minoxidil 2% and an oral supplement (medicinal yeast 100 mg, thiamine mononitrate 60 mg, calcium pantothenate 60 mg, cyctine 20 mg, paraaminobenzoic acid 20 mg and keratin 20 mg), showing comparable change from baseline percentage of telogen hair count after 9 months of treatment (93).

MINOXIDIL AND KOREAN RED GINSENG COMBINATION

A study by Ryu et al. failed to show that combination of minoxidil 3% topical solution and Korean red ginseng is superior to minoxidil monotherapy in women (92).

MINOXIDIL, BETAMETHASONE VALERATE AND AZELAIC ACID COMBINATION

Pazoki-Toroudi et al. compared in a study in male and female patients minoxidil 5% topical solution, combination of minoxidil 12.5% with azelaic acid 5.0% and betamethasone valerate 0.025%1x/d and placebo topical solution 2x/d. At 24 weeks, improvement was found according to investigator's assessment in 37.5% of the female patients in the minoxidil group and in 14.9% of the female patients in the placebo group. Improvement was only significant compared to placebo ($p < 0.01$) but not compared to minoxidil 5% topical solution (75).

MINOXIDIL AND HORMONAL CONTRACEPTIVE COMBINATION

Topical minoxidil 2% solution, 2x/d in combination with an oral hormonal contraceptive led to a mean change from baseline total hair count of 16.1 hairs/cm² (8.6%) at 6 months, 16.9 hairs/cm² (9.1%) at 12 months, whereas cyproterone acetate 50 mg in combination with oral hormonal contraceptive led to decreased values (-2.8 hairs/cm² (-1.4%) at 6 months, -7.8 hairs/cm² (-3.9%) at 12 months ($p < 0.001$) (86).

3.1.8 Summary

Minoxidil 2% solution twice daily is effective to prevent progression and improve androgenetic alopecia in male and female patients (**LEVEL OF EVIDENCE 1**). Minoxidil 5% solution or foam twice daily is more effective than the 2% solution in male patients (**LEVEL OF EVIDENCE 2**). In female patients, the efficacy of minoxidil 5% solution or foam applied once daily is comparable to minoxidil 2% solution applied twice daily (**LEVEL OF EVIDENCE 2**). Patients should be informed on telogen shedding within the first 8 weeks of therapy. Further studies are required to compare efficacy of minoxidil solution and foam formulation.

3.1.9 Therapeutic recommendation – Male

↑↑ **Topical Minoxidil 2 to 5% solution 1 ml or half a cap of 5% foam twice daily is recommended to improve or to prevent progression of AGA in male patients above 18 years with mild to moderate AGA (Hamilton-Norwood II-V).**

↑ **We suggest using 5% solution or half a cap of 5% foam for greater efficacy.**

○ **We cannot make a recommendation for the 5% minoxidil foam instead of the 5% solution at the present time.**

↑ **The response to treatment should be assessed at 6 months. If successful, treatment needs to be continued to maintain efficacy.**

→ **For greater efficacy the combination of oral finasteride 1 mg, 1x/d and topical Minoxidil 2% to 5% solution, 2x/d can be considered.**

○ **We cannot make a recommendation for combination therapy of topical minoxidil with topical 5 α -reductase or azelaic acid and betamethasone valerate at the present time.**

Further studies are needed to confirm superiority of combination therapies consisting of topical minoxidil, diclofenac and tea tree oil, topical minoxidil, azelaic acid and betamethasone or topical minoxidil and microneedling.

3.1.11 Therapeutic recommendation – Female

↑↑ **Topical Minoxidil 2% solution 1 ml twice daily or half a cap of 5% minoxidil topical foam once daily is recommended to improve or to prevent progression of AGA in female patients above 18 years with AGA.**

○ **We cannot make a recommendation for the 5% minoxidil foam once daily instead of the 2% solution twice daily at the present time.**

↑ **The response to treatment should be assessed at 6 months. If successful, treatment needs to be continued to maintain efficacy.**

○ **We cannot make a recommendation for combination therapy of topical minoxidil with red ginseng, azelaic acid and betamethasone or oral nutritional supplements at the present time**

3.2 5-ALPHA-REDUCTASE-INHIBITORS

3.2.1 Introduction

Androgenetic alopecia (AGA) occurs after puberty in men with an inherent sensitivity to the effects of androgens on androgenetic sensitive scalp hair follicles. AGA does not develop in men who lack nor in men with a genetic deficiency of the enzyme 5 α -reductase type 2 which converts testosterone to dihydrotestosterone (DHT). There are three 5 α -reductase isoenzymes. Type 1 predominates in liver, skin and scalp. Type 2 is found mainly in prostate and genitourinary tract and also in the human hair follicle. Type 3 5 α -reductase is widely distributed including in skin, prostate and brain.

Pharmaceutical 5 α -reductase inhibitors were initially developed for the treatment of benign prostatic hyperplasia. Two drugs inhibiting 5 α -reductase are available on the market: finasteride registered in Europe in 1992, and dutasteride registered in 2003. Finasteride is a type 2 5 α -reductase inhibitor which decreases DHT by about 65% in serum, prostate and scalp. Finasteride also inhibits type 3 5 α -reductase. Dutasteride inhibits both type 1 and type 2 5 α -reductase decreasing serum DHT level by about 90%.

Two years after the registration of finasteride for the treatment of benign prostatic hyperplasia, the first publications appeared concerning the efficacy of finasteride in androgenetic alopecia in male patients. At the same time the drug was registered in the US (1993) and Europe (1994) for treatment of mild to moderate androgenetic alopecia in men.

The first report on the use of dutasteride as a treatment for androgenetic alopecia was published in 2006, but it has not been registered for this indication in Europe, only for treatment of benign prostatic hyperplasia.

3.2.2 Mechanism of action

A single oral dose of finasteride 1 mg decreases serum and scalp DHT up to 70% compared to baseline. Tachyphylaxis is not observed with long-term administration. Finasteride is quickly absorbed after oral intake with peak plasma level occurring 1 to 2 hours after drug intake. The serum half-life of the drug is about 6 hours. 90% of the drug is bound to plasma proteins. Finasteride is metabolised in the liver by hydroxylation and oxidation using P 450 3A4 pathway. There is no interaction with other drugs known to be metabolized by this cytochrome such as warfarin, theophylline, digoxin, propranolol and others.

3.2.3 Efficacy – males

Finasteride

25 studies investigating the efficacy of finasteride in male patients with androgenetic alopecia met the inclusion criteria of the guideline (63, 64, 67, 70, 73, 96-117). 24 out of these 25 studies assessed the efficacy of finasteride monotherapy in male patients with androgenetic alopecia. One included both male and female patients. Thirteen studies obtained grade A2 evidence, 9 grade B and 3 grade C. 14 studies were placebo controlled. Summarizing these results an **EVIDENCE LEVEL 1** can be attributed for finasteride.

OUTCOMES

In all of the included trials, the intake of finasteride 1 mg daily led to a significant increase in *total hair counts* compared to placebo. The mean change from baseline total hair count was 7.0 hairs/cm² (3.3%) in the frontal/centroparietal region (p < 0.0001 vs. placebo) (107) and 13.5 hairs/cm² (7.3%) in the vertex (p < 0.0001 vs. placebo) (103) at 6 months.

The mean increase from baseline total hair counts at 12 months was between 7.2 hairs/cm² (3.6%) and 36.1 hairs/cm² (29.1%) for the vertex (p between < 0.05 and 0.001 vs. placebo) (98, 103, 104, 106-108) and 9.3 hairs/cm² (4.9%) and 9.6 hairs/cm² (4.6%) in the frontal/centroparietal region (p between < 0.01 and 0.001 vs. placebo) (97, 101). The placebo group showed mean changes from baseline total hair count between 2.4 hairs/cm² (1.4%) and -10.1 hairs/cm² (-5.2%).

At *global expert panel assessment* between 37 % and 54 % of the patients were rated as improved at 12 months (p < 0.001 vs. placebo) (98, 99, 103, 104, 107, 109, 111). In addition subjective assessments by investigator and patients yielded significant improvements in the finasteride group (98, 99, 103, 104, 107, 109).

Long-term results were available for 24, 36, 48, 60 and 120 months (96, 97, 102, 107, 109, 111-113, 118). The mean changes from baseline total hair counts were

13.0 hairs/cm² (6.2%) at 24 months (107), 8.5% at 36 months (102), 7.2% at 48 months (102) and 7.5 hairs/cm² (4.3%) at 60 months (111) respectively. In comparison to placebo they were statistically significant different.

Price et al. reported increase in hair weight at 12 to 48 months (20.4% at 12 months, 21.5% at 24 months, 19.5% at 36 months and 21.6% at 48 months versus -5.2%, -14.2%, -14.8% or -24.5% in the placebo group, $p < 0.001$) (101, 102).

In a 3.5-year study by Sato et al. in Japanese man with androgenetic alopecia receiving 1 mg finasteride once daily hair growth improved in 87.1% (greatly in 11.1%, moderately in 36.5% and slightly in 39.5%) according to investigator assessment (112). The response rate improved with increasing duration of treatment. Adverse reactions occurred in 0.7% of men, while no specific safety issues associated with long-term use were observed. In a 5-year open-label study by Yoshitaki et al. in Japanese men with androgenetic alopecia receiving 1 mg finasteride once daily hair growth improved in 99.4% and progression of hair loss was halted in 100% as assessed by global photography. The degree of improvement was highest after 1 year of treatment (96).

In a 10-year study by Rossi et al., at global expert panel assessment, 40.5% of patients between 26-30 years of age showed a remarkable improvement after 1 year of therapy with finasteride 1 mg/day, 16.7% showed a remarkable improvement after 2 years of therapy and 42.8% remained unchanged after 10 years (113). Patients between 31-40 years of age showed 53.6% remarkable improvement after 1 year of therapy, 14.3% after 2 years, 10.7% after 5 years, while 21.4% remained unchanged after 10 years of treatment. Patients older than 40 years showed 47.4% remarkable improvement after 1 year of therapy, 15.8% after 2 years, 5.2% after 5 years, and 31.6% remained unchanged after 10 years of treatment.

DOSAGE

Concentration. Two studies examining different finasteride dosages could be included in the evidence based evaluation (99, 103). Roberts et al. examined finasteride 0.01 mg, 0.2 mg, 1 mg and 5 mg versus placebo (103). The mean change from baseline total hair counts under finasteride therapy (0.2 mg, 1 mg and 5 mg) was significantly different to placebo at 6 and 12 months ($p < 0.001$), whereas dosage of 0.01 mg showed progressing hair loss (difference to placebo not statistically significant). The differences in mean change from baseline total hair count between the finasteride groups (0.2 – 5mg) did not reach significance. Kawashima et al. reported 58% and 54% improvement in global expert panel assessment for finasteride 1 mg and 0.2 mg respectively (99). The efficacy in both groups was comparable and significantly different to placebo ($p < 0.001$).

FINASTERIDE VS. MINOXIDIL

Only few data comparing finasteride 1 mg daily and minoxidil solution are available. Two of the included studies examined finasteride 1 mg against twice daily topical application of minoxidil 2% solution (64, 67). Both studies showed superiority for finasteride. At 12 months the mean change from baseline total hair count was 36.1 hairs/cm² (29.1%) for finasteride 1 mg and 19.6 hairs/cm² (14.8%) for minoxidil 2%, twice daily application ($p = 0.003$) (64). 87% of the patients taking finasteride versus 42% of the minoxidil 2% patients were rated as improved ($p < 0.001$) (67).

Arca et al. reported a better outcome for minoxidil 5% solution applied twice daily against finasteride 1 mg daily at global photographic assessment of the frontal/parietal region at 12 months (80% vs. 52% improvement) (63). In the study by

Hu et al. improvement was found in 80.5%, 59%, and 94.1% of men treated with finasteride 1 mg once daily, 5% minoxidil topical solution twice daily and combination therapy with finasteride 1 mg and 5% minoxidil topical solution respectively (73).

FINASTERIDE PER OS VS. TOPICAL FINASTERIDE

Hajheydari et al. found a similar small but significant increase in total hair count from baseline in male patients with androgenetic alopecia receiving a topical gel of 1%finasteride twice daily and placebo tablets once daily and male patients receiving finasteride 1 mg tablets once daily and placebo topical gel twice daily for 6 months (114). No data on serum DHT levels were given and more studies are required to confirm this result.

Other botanically derived 5 α -reductase inhibitors, such as serenoa repens and Curcuma aeruginosa were assessed in 2 studies and compared to finasteride per os and topical minoxidil respectively:

FINASTERIDE VS. SERENOA REPENS

Serenoa repens is a plant of the Arecaceae's family, acting as a competitive, non-selective inhibitor of 5 α -reductase of types 1 and 2. Rossi et al. compared finasteride 1 mg per os once daily to serenoa repens 320 mg per os once daily for 24 months in male patients with androgenetic alopecia (118). According to global expert panel assessment, 38% of patients treated with Serenoa repens and 68% of patients treated with finasteride showed an increase in hair growth.

CURCUMA AERUGINOSA TOPICAL EXTRACT VS. MINOXIDIL

In a study by Pumthong et al. males with androgenetic alopecia were randomized to receive a hair tonic including 5% hexane extract of Curcuma aeruginosa, a botanically derived 5 α -reductase inhibitor, minoxidil 5% topical hair tonic, combination formulation (5% hexane extract of Curcuma aeruginosa + 5% minoxidil) or placebo hair tonic twice daily for 6 months (79). Mean changes from baseline non-vellus hair counts were 30.62 hairs/cm² (20.0%) for the Curcuma aeruginosa 5% extract, 31.32 hairs/cm² (18.1%) for minoxidil 5% topical hair tonic, 32.59 hairs/cm² (20.7%) for the combination topical treatment and 20.41 hairs/cm² (11.4%) in the placebo hair tonic group (p<0.001). No significant differences were found between the groups (p>0.05).

Dutasteride

5 studies investigating dutasteride in androgenetic alopecia were included in the evidence based evaluation, 4 of which with grade A2 evidence and 1 of which with grade C evidence, resulting in a **LEVEL OF EVIDENCE 1** (100, 117, 119-121).

OUTCOMES

Stough et al. reported a significant mean increase from baseline total hair count of 6.8 hairs/cm² at 6 months and 16.5 hairs/cm² at 12 months for dutasteride 0.5 mg daily (119).

Eun et al. reported a significant mean increase from baseline total hair count of 12.2 hairs/cm² (8.2%) for dutasteride 0.5 mg daily vs 4.7 hairs/cm² (3.3%) for placebo at 6 months (P = 0.03) (121). The improvement ratio of investigator photographic assessment at 6 months was 61.6%in the dutasteride group and 20.0% in the placebo group.

In a study in 35 Korean men with androgenetic alopecia Jung et al. showed a mean change from baseline total hair count of 14 hairs/cm² for dutasteride 0.5 mg daily (120).

DUTASTERIDE VS. FINASTERIDE

In a 24-week study of 416 patients Olsen et al. showed a significant increase from baseline total hair count of 15.4 hairs/cm² (8.7%), 18.6 hairs/cm² (10.2%) and 21.5 hairs/cm² (11.3%) in men treated with dutasteride 0.1mg daily, 0.5mg daily and 2.5mg daily (p=0.009) respectively (100). All dutasteride arms and finasteride 5 mg showed a significant difference of p < 0.001 vs. placebo.

It should be pointed out that the most effective dosage of dutasteride (2.5mg daily) is 5 times higher than the standard dose used in the treatment of benign prostatic hyperplasia (dutasteride 0.5 mg corresponds to finasteride 5 mg).

In a study by Gubelin Harcha et al. 917 male patients with androgenetic alopecia were randomized to receive different dutasteride doses (0.02 mg/d, 0.1 mg/d, 0.5 mg/d), finasteride 1 mg/d, or placebo for 24 weeks (117). A significant increase from baseline in hair counts and hair diameters and improved hair growth at global panel photographic assessment was reported in patients receiving dutasteride 0.1mg and 0.5 mg daily and finasteride 1mg daily. Dutasteride 0.5mg daily was significantly superior to finasteride 1 mg/d (p=0.16). Some aspects of sexual dysfunction were more common in men receiving dutasteride and finasteride (e.g. altered libido: finasteride 6.7%, dutasteride 0.5mg 4.9%, placebo 1.7%) whereas there was no difference between treatment and placebo groups in the frequency of ejaculation disorders.

3.2.4 Efficacy – females

One study assessing the efficacy of finasteride 1mg daily (122) and two studies assessing the efficacy of finasteride 5 mg daily in female patients were included in the evidence based evaluation (115, 116). The grades of evidence were A2, C, C resulting in an **EVIDENCE LEVEL 3**.

OUTCOMES

A 12-month randomised controlled trial of finasteride 1mg daily in postmenopausal women with AGA showed a further progression of hair loss and no significant difference from the placebo-control group. After one year there was a mean change from baseline hair count at -8.7 hairs/cm² in women taking finasteride and -6.6 hairs/cm² in the control group.

On the contrary, both studies assessing the efficacy of finasteride 5 mg daily reported improvement in hair growth. In the study by Yeon et al. in normoandrogenic Asian women with female pattern hair loss, there was a mean increase in hair count from baseline of 18.9 hairs/cm² (21%) and a mean increase from baseline in hair diameter of 9.4 µm (14.7%) after 12 months of treatment (115). Reported adverse events included headache, menstrual irregularity, dizziness and increased body hair growth. Oliveira-Soares et al. found 'major' improvement in 55%, as assessed by global photography, and 'moderate' improvement in 37.5% of normo-androgenic postmenopausal women treated with finasteride 5 mg daily for 18 months (116). However, both studies using finasteride daily 5mg were uncontrolled.

3.2.5 Instructions for use / Practicability

Finasteride can be taken with or without food and there is no known interaction with other drugs.

Finasteride is not licenced in women and is contraindicated in pregnant women and women of childbearing potential, because of the risk of feminisation of a male foetus. Finasteride treated men must therefore avoid donating their blood.

The level of finasteride in the semen of treated man is very low even with regular intake of finasteride 5 mg/day, and there is no risk in case of sexual relation with pregnant women. The use of a condom is not necessary for this reason.

The recommended dosage of finasteride in men is 1 mg a day, but in a dose finding study with a lower dosage of 0.2 mg/day also led to significant improvement compared to placebo. For this reason, if a patient forgets a pill, we do not recommend taking two the next day.

The minimal period of use to assess the efficacy for reducing hair loss is 6 months and 12 months for regrowth of hair. If a patient intends to switch from minoxidil to finasteride we recommend a combination therapy for at least 3, better 6 months before stopping minoxidil in order to avoid significant hair loss before finasteride action can take over.

Finasteride reduces PSA levels and may decrease prostate size. If treatment is started after 45 years of age, a baseline PSA level should be obtained and regular prostate screening by a urologist should be recommended. The PSA levels should be doubled to compensate the reduction due to finasteride for an accurate interpretation of the test.

Additional research is required in different subgroups of female patients with pattern hair loss including younger female patients and female patients with or without clinical hyperandrogenism. However, the use of finasteride in females can be considered only in combination with safe contraceptive methods due to the risk of malformation of genitals in male foetus (feminization).

Adverse effects of finasteride

Sexual dysfunction

Impaired sexual function is the most commonly reported adverse effect of finasteride, including erectile dysfunction, ejaculation dysfunction, reduced ejaculate volume and loss of libido. In controlled clinical trials of finasteride in AGA the frequency of adverse effects on sexual function has been around 2-6% although not all studies have shown this when compared to rates in placebo groups. In a study where sexual function was specifically assessed using the International Index of Erectile Function questionnaire there was no significant difference in sexual or erectile function between 236 men taking finasteride for AGA and 236 controls (123). A review of 12 controlled trials of finasteride in the treatment of AGA concluded there was moderate evidence for an increase in erectile dysfunction in men taking finasteride (RR 2.2, 95% CI 1.03-4.78) and a possible increased risk of any sexual disturbance (124). However, the quality of safety reporting in clinical trials of finasteride has been criticized. In a meta-analysis of 34 trials the authors concluded that none had adequate safety reporting and 19 were only partially adequate (125). They stated that published trials provided insufficient information to establish the safety profile for finasteride in the treatment of AGA.

Depression

Depression as an adverse effect of finasteride has also received much media attention though the evidence is limited. Altomare et al reported 19 cases (14 men, 5 women) of depression that appeared temporally related to finasteride 1mg daily for treatment of AGA(126). Symptoms resolved promptly when the drug was discontinued. In a prospective study in 128 men prescribed finasteride 1mg for AGA there was a significant increase in Beck's Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) scores after 2 months of treatment (127). It has been proposed that an adverse effect of 5 α -reductase inhibitors on mood is caused by inhibition of GABAergic neuroactive steroids (e.g. allopregnanolone, 3 α -androstane-20-one), which are derived from 5 α -reduced steroid metabolites. A study in 12 men found a significant and progressive reduction of plasma neuroactive steroids during one year of treatment with finasteride 1mg daily (128). Low levels of neuroactive steroids have been associated with depression (in the absence of finasteride therapy), post-natal depression and post-traumatic stress disorder (129), providing some support for this idea.

The frequency of depression and alteration of mood in men taking finasteride is unknown. It was not reported in the pivotal clinical trials and is probably uncommon. However, it is possible that finasteride does have a negative impact on those who have a constitutive predisposition to psychological disorders.

Others

Less common or rare adverse effects of finasteride include gynaecomastia, testicular pain and hypersensitivity reactions.

Prostate cancer

In a study published in 2003 of 9060 men aged over 55 years randomised to finasteride 5mg daily or placebo and followed for 7 years the frequency of prostate cancer in the finasteride cohort was 18.4% compared to 24.4% in men receiving placebo but there was a significantly greater frequency of high-grade prostate cancer (Gleason grade 7-10) in the finasteride group (6.4% vs 5.1%) (130). However, a later study of 18,880 men in the same trial followed for up to 18 years found no difference in survival between the finasteride and placebo groups (131). Two other studies, using datasets from the UK and Scandinavia, also found no effect of finasteride on overall or prostate cancer-specific survival (132, 133). Current data suggest that finasteride reduces the overall risk of prostate cancer by about a third and may increase the detection of high-risk prostate cancer (detection bias) but does not affect the outcome in terms of survival.

Breast cancer

In 2009 the UK Medicines and Healthcare Regulatory Agency (MHRA) reported there had been 50 cases of breast cancer worldwide in men taking finasteride 5mg daily and 3 cases taking 1mg daily. Breast cancer is a rare tumour in men raising the possibility of a causal relationship. However, two controlled studies using datasets from the UK and the USA found no increase in the incidence of breast cancer in men taking finasteride (134, 135). In the large long-term Prostate Cancer Prevention Trial there were two cases of breast cancer in the finasteride arm and two cases in the placebo arm (136). The Propecia Summary of Product Characteristics (SPC) mentions breast cancer as a possible risk but current data suggest the occurrence of breast cancer in men taking finasteride is coincidental.

Spermatogenesis

In a prospective placebo controlled study finasteride 5mg daily reduced sperm counts by an average of 34% at 24 weeks. Counts recovered to near-baseline levels after 52 weeks treatment and had recovered further at 24 weeks post-treatment follow up (137). A randomised controlled study of finasteride 1mg daily vs placebo in 79 men found no effect on sperm parameters despite a reduction in circulating DHT similar to that in the Amory study (138).

However, there are a small number of case reports of infertility and oligospermia in men taking finasteride 1mg daily (139-142). In a case series of 14 men presenting with infertility who were taking finasteride 1mg daily 9 had oligospermia (143). There was an average 11.6-fold increase in sperm counts after finasteride was discontinued, which was more pronounced in those with initially severe oligospermia. Sperm counts recovered in 4 of the 7 men with severe oligospermia. The authors suggested that finasteride may negatively impact spermatogenesis in those men with pre-existing conditions relating to infertility.

Post-finasteride syndrome

Over the last 5 years several published cases series have reported various symptoms persisting for months or years after discontinuation of finasteride (144-149). The most frequent symptoms are sexual dysfunction, loss of libido and depression. Other symptoms include suicidal ideation, impaired cognition, fatigue and decreased penile sensitivity. This complaint has been termed post-finasteride syndrome (PFS) although a clear causal relationship with finasteride use has not yet been established. Studies reporting PFS have all been retrospective and many cases have been recruited through internet websites targeted at those with persistent symptoms, making selection bias a significant limitation. Assessment of any relationship with finasteride is complicated by the fact that these symptoms also occur in the general population and may be exacerbated psychologically through a nocebo effect (150).

A possible explanation for symptoms occurring for the first time shortly after discontinuation of the drug is a withdrawal effect comparable to a steroid withdrawal. It has been hypothesized that alterations of androgen receptors, androgen resistance or changes of androgen production levels during the time the drug was taken have lead to irreversible androgen-deprivation changes, for example in erectile tissue physiology and function. Another explanation is a sustained change of neuroactive steroids and androgen receptors in the brain tissue (151). One study found significantly lower levels of 5 α -reduced neuroactive steroids (allopregnanolone, 3 α -androstane-2,3-diol) in plasma and CSF of men with neuropsychiatric symptoms post-finasteride compared to otherwise healthy control subjects undergoing spinal surgery(152). However, levels were not measured prior to finasteride treatment.

In a small controlled study, an increased number of androgen receptors (AR) was found in the foreskin stromal and epithelial cells of patients with PFS but not in vessel smooth muscle cells, while the nerve density was not different (153). The ratio of AR to testosterone (T) or free-testosterone (fT) levels was 2-fold higher than in controls. Those patients with more severe sexual side effects had relatively more AR. The reason for these changes and the actual activity of these AR is still unknown. Possible reasons are a regulatory feedback-effect, a direct effect of low androgens or inhibition of the AR by finasteride. However, no pre-treatment data are available and some of the patients were already treated with testosterone or tadalafil. Most affected patients reported low testosterone levels which were detected after symptoms

occurred, but no pre-finasteride levels are known. In the study, the levels of T and fT were not significantly different than in control patients.

The frequency of PFS in men who have taken finasteride is unknown. Many clinicians who frequently prescribe finasteride doubt its existence suggesting that it is uncommon. Nevertheless, despite the uncertainties over the causal relationship it is clear that some men who have taken finasteride for AGA do experience long-term disability and patients should be informed about the matter. It is not clear whether there are risk factors for the development of PFS that can be identified pre-treatment. In a study of 95 men complaining of persistent post-finasteride symptoms 55% gave a history of a psychiatric diagnosis prior to taking finasteride suggesting a pre-morbid component to the development of PFS (154). From a practical standpoint it may be wise to advise caution in men with a history of sexual dysfunction or a personal or family history of psychiatric illness. In patients with active depression or current sexual dysfunction, finasteride is contra-indicated.

Whether PFS is a true consequence of finasteride treatment is controversial. Although there is a body of opinion that strongly believes its existence the case is unproven and further research is needed, ideally prospective in nature. We also need to establish its frequency, how to identify those at particular risk and how best to treat those men who develop persistent symptoms.

Regulatory authorities have changed the package labelling for finasteride to include persistent side effects, which may or may not have a causal relationship to the drug. The UK Patient Information Leaflet lists the following information on side effects:

Frequency unknown:

- Persistent difficulty having an erection after discontinuation of treatment
- Persistent decrease in sex drive after discontinuation of treatment
- Persistent problems with ejaculation after discontinuation of treatment

3.2.6 Combination therapies

Leavitt et al. showed in 79 male patients undergoing hair transplantation, that the combination with finasteride 1 mg daily led to increased hair counts after 12 months, whereas hair transplantation alone resulted in decreased hair count in the frontal area (mean change from total baseline hair count 18.5 hairs/cm² (12.6%) vs. -13.5 hairs/cm² (-8.9%), $p = 0.019$) (110).

Khandpur et al. compared the combination of finasteride 1 mg daily with minoxidil 2% solution twice daily respectively ketoconazole 2% shampoo, 3x weekly to finasteride 1mg daily and minoxidil 2% solution twice daily as monotherapies (67). At 12 months, 100% of the patients of each combined therapy, 87% for finasteride and 42% for minoxidil 2% solution were rated as improved by investigator. The combination of minoxidil 2% and finasteride 1 mg was statistically significant superior to finasteride or minoxidil monotherapies. Furthermore, Diani et al. showed an additive effect of finasteride and minoxidil in stump-tail macaque (155).

Hu et al., showed better efficacy of combination therapy with finasteride 1 mg per os once daily and topical minoxidil 5% twice daily for 12 months (94.1% improvement) compared to finasteride 1 mg per os once daily (80.5% improvement) or topical minoxidil 5% twice daily (59% improvement) as rated by global photographic evaluation (73).

A study by Tanglertsampan failed to show an advantage of therapy with combined minoxidil 3% and finasteride 0,1% topical lotion vs with minoxidil 3% topical lotion after 24 weeks (p=0.503) (70).

The mechanisms of action of minoxidil and finasteride treatments are different. Thus association of topical minoxidil and oral finasteride is possible and can be considered in motivated patients.

3.2.7 Summary

Finasteride 1 mg daily is effective in prevention of progression and induction of hair regrowth in androgenetic alopecia in male patients (evidence level 1).

Evaluation of the efficacy should be assessed 6 months after treatment initiation.

Patients should be aware of reduction of prostate specific antigen, which is important in prostate cancer screening in men < 45 years of age.

Further studies comparing the efficacy of finasteride 1 mg versus minoxidil 5% are needed. If the therapeutic approach is insufficient the combination of finasteride 1 mg and minoxidil 2% or 5% can be considered.

In patients with insufficient efficacy of finasteride 1 mg, the off-label use of Dutasteride 0.5 mg can be considered.

In female postmenopausal patients finasteride 1 mg failed to show efficacy (**LEVEL OF EVIDENCE 2**). Finasteride 5 mg may be effective in female normoandrogenic pre- and postmenopausal patients (**LEVEL OF EVIDENCE 3**). However, there is insufficient data to recommend it, as no placebo-controlled trials are available. Studies in different subgroups of female patients with androgenetic alopecia are required. In women of childbearing age, a safe contraceptive method is essential as finasteride may lead to feminisation of a male foetus.

3.2.8 Therapeutic recommendation – Male

Finasteride

↑↑ Oral Finasteride 1 mg a day is recommended to improve or to prevent progression of AGA in male patients above 18 years with mild to moderate AGA (Hamilton-Norwood IIv-V).

↑ The response to treatment should be assessed at 6 months, although in some men it may not become evident before 12 months. If successful, treatment needs to be continued to maintain efficacy.

○ We cannot make a recommendation for or against treatment with topical finasteride at the present time

→ For greater efficacy the combination of oral finasteride 1 mg, 1x/d and topical Minoxidil 2% to 5% solution or 5% foam 2x/d can be considered.

Dutasteride

→ Oral Dutasteride 0.5 mg a day can be considered in case of ineffective previous treatment with 1 mg finasteride over 12 months as a second line

treatment to improve or to prevent progression of AGA in male patients above 18 years with mild to moderate AGA (Hamilton-Norwood IIIv-V).

Serenoa repens

O We cannot make a recommendation for or against treatment with Serenoa repens per os at the present time

Curcuma Aeruginosa

O We cannot make a recommendation for or against treatment with topical Curcuma aeruginosa at the present time

3.2.9 Therapeutic recommendation – Female

↓ Oral Finasteride 1mg daily is not suggested in the treatment of postmenopausal women with female pattern hair loss.

O We cannot make a recommendation for or against treatment with oral finasteride 5 mg a day at the present time.

3.3 HORMONES

3.3.1 Introduction

The role of androgens in the aetiology of androgenetic alopecia has led to the widespread use of hormonal agents in its treatment. They fall into two broad groups – antiandrogens and oestrogenic (or anti-oestrogenic) drugs, although evidence of efficacy for any of these treatments is limited or absent.

3.3.2 Mechanism of action

Antiandrogens act primarily through blockade of the androgen receptor. Different agents may have other relevant effects on endocrine biology including inhibition of steroid synthesis and progestational activity. Antiandrogens have mainly been delivered systemically and used in women (they are contraindicated in men due to their feminizing action).

Topical oestrogens and anti-oestrogens have been used in both men and women. The rationale for their use is less clear than for antiandrogens as the effect, if any, of oestrogens on human hair growth is unknown. Oestrogens inhibit hair growth in several other mammals lending some support for the potential of antioestrogens to promote hair growth in humans.

3.3.3 Efficacy – males

Oral hormonal treatment

There is no evidence to support the use of oral estrogens or antiandrogens to improve or prevent progression of androgenetic alopecia in male patients (**EVIDENCE LEVEL 4**).

Topical hormonal treatment

There are only two controlled trials of topical hormonal treatment that have employed modern methods of assessment.

OUTCOMES

Sovak et al. studied the change of anagen hair count following daily topical application of the antiandrogen FLURIDIL versus placebo. At 12 months, the response to fluridil was not significantly different from placebo. Therefore there is limited evidence that topical fluridil is ineffective in men (156).

Gassmueller et al. (62) compared topical application of FULVESTRANT (70mg/ml twice daily), an estrogen receptor antagonist, to minoxidil 2 % and placebo. At 16 weeks the mean change from baseline hair counts was not significantly different from placebo in the fulvestrant group whereas there was a significant increase in hair counts in subjects treated with minoxidil. Therefore there is evidence that topical fulvestrant is ineffective in men.

There are three earlier studies on the efficacy of the topical estrogen ALFATRADIOL (=17 alpha-oestradiol) in men. Unfortunately they either had no control group (157, 158) and/or the results were not reported separately for each sex (158, 159). In one study, topical corticosteroid was included (158).

3.3.4 Efficacy – females

Oral hormonal treatment

5 studies met the inclusion criteria, 1 of which was placebo-controlled. 4 of the studies obtained a grade of evidence B and 1 of them obtained a grade of evidence C, resulting in **LEVEL OF EVIDENCE 3**).

OUTCOMES

Peereboom-Wynia et al. compared a group of women treated for one year with 50 µg estradiol +2 mg cyproterone acetate + 20 mg cyproterone acetate (CPA) days 1-14 with an untreated control group (160). Trichogram data showed a mean change in anagen percent from 49.7 at baseline to 74.4 after one year in the treated group compared to a fall from 60.4 to 48.8 in the controls. Subjects appeared not to be randomized to treatment or control groups and hair counts were not performed.

In a 6-month open-label study by Kapadia et al. 26 normoandrogenic women were treated with 35 µg estradiol +2 mg CPA + 50 mg CPA for the first 10 days in combination with 5% topical minoxidil twice daily. According to investigator's assessment, improvement was found in 72.7% of the patients in the frontotemporal region and in 50% of the patients in the vertex region. However, this study was not placebo-controlled (95).

Vexiau et al. reported a mean change baseline total hair count of -2.8 hairs/ cm²(-1,4) at 6 months and -7,8% hairs /cm² (- 3;9%) at 12 months in subjects receiving oral contraceptive + 50 mg cyproterone acetate (86) whereas subjects treated with a combination of minoxidil 2% solution twice daily and oral contraceptive showed a mean increase in hair count of 16.1 hair/cm² (8.6%) at 6 months and 16.9 hair/cm² (9.1%) at 12 months. The differences in total hair count at 12 months were statistically significant between groups (p<0.0001).

In subgroup analysis, patients under treatment with cyproterone acetate with clinical signs of hyperandrogenism tended to show increased hair counts at month 12

compared to those without hyperandrogenism, although the results were not statistically significant. Consequently, there is insufficient evidence that oral hormonal treatment prevents progression or improves androgenetic alopecia in female patients. Nevertheless, subgroup analysis suggests that oral cyproterone acetate may improve androgenetic alopecia in female patients with hyperandrogenism.

In a study by Paradisi et al., 101 female patients with androgenetic alopecia received flutamide in a dose of 250 mg/day during the first year as a loading dose, 125 mg/day during the second year as a continuing dose, and 62.5 mg/day during the third and fourth years as a maintenance dose with or without a monophasic oral contraceptive, comprising of ethinyl estradiol (0.030 mg/day) plus gestodene (0.075 mg/day) for 21 days/month (161). According to the global expert panel assessment, no significant differences were found between the groups: in total, alopecia improved significantly in Ludwig scores after 6 months of treatment ($p < 0.001$) and continued to improve until 2 years of treatment, remaining stable afterwards. The mean improvement of Ludwig score was 15%, 20%, 26%, and 28% at 0.5, 1, 1.5 and 2 years.

Topical hormonal treatment

OUTCOMES

Blume-Peytavi et al. (80) reported a decreased total hair count after 6 months therapy with *ALFATRADIOL* 0.025% solution once daily (mean change from baseline - 7.8 hairs/cm², -4.3%, $p < 0.0005$). Subjects treated with minoxidil 2% solution twice daily showed increased total hair counts at 6 months (15.3 hairs/cm²; 8.7%). Non-vellus hair counts and cumulative hair thickness also showed a decrease in the alfatradiol group and an increase in the minoxidil group at 6 months (-6.0 hairs/cm² versus 14.0 hairs/cm², $p < 0.001$; -0.5mm/cm² versus 1.8mm/cm², $p < 0.0001$).

There are three earlier studies (157, 159, 160) on the efficacy of the *TOPICAL ESTROGEN* alfatradiol in women and one of topical estrogen combined with corticosteroid (158). All assessed responses were obtained using a trichogram. Two studies did not report separately male and female subjects and are not considered further (158, 159). Orfanos and Vogels reported a mean decrease in telogen rate of 24.4% for patients treated with alfatradiol 0.025% solution once daily at 30 weeks (157).

In a study by Georgala et al. the mean change from baseline anagen/telogen ratios at 12 and 24 weeks of treatment with alfatradiol solution once daily was 38.7% and 44.6% respectively (162). The change in anagen /telogen ratio differed significantly from placebo treatment (-3.9% at 24 weeks; $p < 0.01$).

In a current one-arm study, Kim et al. reported an increased hair count after 8 months therapy with 17alpha-estradiol in Korean women with androgenetic alopecia (mean change from baseline 31.57 hairs/cm², 9.8%, $p < 0.0001$). Furthermore an increased cumulative hair thickness was found (mean change from baseline 10.39 μ m, $p < 0.0001$) (163).

As there are contrary results on the efficacy of topical alfatradiol the evidence is insufficient to support its use in female patients with androgenetic alopecia. Further studies are needed to clarify the efficacy of alfatradiol.

Gassmueller et al. (62) compared *FULVESTRANT* (70mg/ml twice daily) to minoxidil 2% and placebo. The mean change in total hair count did not differ from placebo

(14.7hair/cm², 6.9%, versus 15.3 hair/cm², 7.9%). Therefore we suggest that topical fulvestrant is not effective in women with androgenetic alopecia.

There is no evidence to support the use of topical natural estrogens, progestogens or antiandrogens in female androgenetic alopecia.

3.3.5 Instructions for use / Practicability

Oral antiandrogen therapy in women:

Cyproterone acetate (25 - 50mg per day, days 1-10) is generally prescribed together with an oral contraceptive e.g. Dianette.

Side effects of cyproterone acetate include depressive mood changes and liver toxicity. There is an increased risk of venous thromboembolism in patients taking estrogen-containing oral contraceptives, which may be greater in those taking cyproterone acetate than other oral contraceptives.

Spironolactone 100-200mg per day is taken continuously. Concurrent contraception is required in fertile women. Side effects include menstrual disturbance and hyperkalaemia.

3.3.6 Combination therapies

There are no instructive studies of combination therapy (e.g. minoxidil + antiandrogen).

3.3.7 Summary

There is little evidence to support the use of oral or topical hormonal treatment in men and women in androgenetic alopecia (**LEVEL OF EVIDENCE 4**). There is limited proof that oral cyproterone acetate may be helpful in women with AGA and hyperandrogenism.

3.3.8 Therapeutic recommendation – Male

↓↓ We do not recommend the use of oral estrogens or androgen-receptor-antagonists to improve or prevent progression of AGA in male patients.

O We cannot make a recommendation for topical alfatradiol in male patients at the present time

↓ We suggest, that topical fluridil should not be used in male patients with AGA.

↓ We suggest, that topical fulvestrant should not be used in male patients with AGA.

3.3.9 Therapeutic recommendation – Female

O We cannot make a recommendation for the use of oral antiandrogens (chlormadinone acetate, cyproterone acetate (CPA), drospironone, spironolactone, flutamide) to improve or prevent progression of AGA in normoandrogenic female patients at the present time.

→ Oral CPA can be considered to prevent progression of AGA in women with clinical or biochemical evidence of hyperandrogenism.

O We cannot make a recommendation for the use of topical alfatradiol to improve or prevent progression of AGA in female patients at the present time.

O We cannot make a recommendation for the use of topical natural estrogens or progesterones to improve or prevent progression of AGA in female patients at the present time.

O We cannot make a recommendation for the use of topical fluridil to improve or prevent progression of AGA in female patients at the present time.

↓ We suggest that topical fulvestrant should not be used in female patients with AGA.

3.4 SURGERY

3.4.1 Introduction

Hair restoration surgery involves hair transplantation, scalp reduction surgery or a combination of both.

Compared to scalp reduction surgery, hair transplantation is less invasive. In androgenetic alopecia, hairless areas can be permanently covered again cosmetically, albeit with a decreased density. In thinning areas the hair density can be at least temporarily improved, and even in case of progression the coverage will be relatively higher than it would be without the surgery.

Over the last decades, hair transplantation has evolved into a microsurgical procedure. Follicular units of 1 to 4 hairs are transplanted in large numbers and high densities.

3.4.2 Mechanism of action

The efficacy of hair transplantation is based on donor dominance, i.e. non-androgen-sensitive hair follicle keep their properties even when transplanted into scalp areas affected by androgenetic alopecia.

Follicles that are not affected by miniaturization are re-distributed over the scalp under local anaesthesia.

The outcome of hair transplantation-objectively depends on the number of transplanted hairs in relation to the area to be covered or densified, on the quality of hairs such as curl, color and caliber, and on the characteristics of the recipient area.

The technical success of this multi-step procedure is determined by the ability of the surgical team to successfully harvest, prepare and insert the grafts without impairing their viability. Another aspect is a minimal trauma to the recipient and donor areas.

The cosmetic effect greatly depends on the aesthetic skills of the surgeon, as well as patient selection, planning of the procedure considering an optimum life-long result, the creation of an authentic hairline design, the distribution of grafts with different numbers of hair and the natural creation of recipient sites with appropriate size, density and direction.

3.4.3 Efficacy – males

Although there are a lot of publications dealing with hair surgery, there were no randomised controlled studies (RCT) comparing hair transplantation versus no hair transplantation. This is most probably due to high variation in techniques, multiple

steps in the surgical process, problems in measuring hair growth, lack of financial support and difficult patient recruitment for a RCT in hair transplantation. Only 4 studies comparing hair transplantation with or without added combination treatment fulfilled the inclusion criteria of this guideline. 2 of the studies obtained a grade of evidence B, 1 study obtained a grade of evidence A2 and 1 study obtained a grade of evidence C, resulting in a **LEVEL OF EVIDENCE 2** (110, 164-166).

OUTCOMES

Bernstein et al. compared different preparation techniques for follicular unit transplantation (165). The resulting mean harvested hairs were 17% higher for preparation by dissecting microscope compared to preparation by magnifying loupe with transillumination (9.6% more follicular units and 2.28 vs. 2.14 mean hairs per follicular unit).

Uebel et al. (164) showed, that treatment of follicular units (FU) with platelet plasma growth factor before implantation could reduce the number of non-surviving FU grafts after follicular unit transplantation compared to follicular unit transplantation alone (mean change from baseline FU graft number: -25 (-17.6%) vs. -40 (-28.2%), $p < 0.001$).

In a study by Leavitt et al. (110), the combination of FU transplantation and finasteride 1 mg daily in patients with partially still existing hair in the recipient area resulted in an increase of hair density 12 months after transplantation, whereas the patients treated with FU transplantation alone had decreased hair counts. The mean change from baseline total hair count at 12 months was 18.5 hairs/cm² (12.6%) and -13.5 hairs/cm² (-8.9%) respectively ($p = 0.019$).

On frontal-superior global photography, 67% of patients improved and 30% did not improve after hair transplantation alone, versus 94% and 6% after combination therapy, respectively.

This is a considerably higher efficacy than previously reported in other studies with finasteride alone.

The differing results of hair counts and frontal-superior global photography in hair transplantation alone may partly be due to replacement and compensation of miniaturizing hairs by thicker permanent hair from the occipital area. Magnification should be used when making recipient sites in-between pre-existing hairs.

A study by Rinaldi et al. reported that treatment with psittacofulvin topical solution once daily 15 days before to 90 days after FUE transplantation could reduce the number of apoptotic fragments compared to treatment with placebo solution (number of apoptotic fragments 3 months after FUE transplantation 0.07 vs 2.05) (166).

A non-controlled trial by Sethi et al., which did not fulfil the inclusion criteria of the guideline, studied a modified follicular extraction technique called direct hair transplantation (DHT) (167). In this technology the graft was implanted as soon as it was harvested, in order to reduce the risk of desiccation, infection, mechanical trauma and grafts getting heated up and with the intention to improve graft survival. The authors report a good survival of the graft. Practical questions regarding patient comfort and position changes with possible graft dislocation remain, as well as a comparison to a stepwise approach.

3.4.4 Efficacy – females

Only few publications concerning hair surgery studied efficacy in female patients. None of them fulfilled the inclusion criteria.

3.4.5 Instructions for use / Practicability

While scalp reduction and flap surgery in combination with extenders is only successfully performed by a few skilled surgeons, hair transplantation is extensively conducted worldwide with further refined micro-techniques and larger graft numbers.

Hair transplantation in suitable candidates with a good donor hair supply, performed by a skilled team of a surgeon and several assistants, can permanently improve androgenetic alopecia by up to 3 stages on the Norwood-Hamilton scale. In women, hair transplantation can be considered in the male pattern and the frontal accentuation subtypes and Ludwig stage II of stabilized androgenetic alopecia. This only applies if sufficient permanent donor hair is available and no overlying diffuse telogen effluvium is present.

In many cases, more than one surgical session is required and often only critical areas can be improved. Magnification should be used to cautiously insert the grafts in-between pre-existing hair follicles.

The best long-term results can be achieved in medically controlled or spontaneously stabilized androgenetic alopecia. If hair transplantation is performed in early progressive AGA, a sufficient reserve of donor hair should be available for additional surgery, grafts should also be transplanted in-between miniaturizing hairs and the vertex area should not be transplanted initially.

Patients should be extensively counselled regarding the possible outcome and the progressive nature of androgenetic alopecia which may require subsequent surgery and/or medical therapy or even shaving the transplanted hairs.

Body dysmorphic disorder or unrealistic expectations are contraindications for this aesthetic surgery.

Follicular unit transplantation (FUT) has become the standard technique in hair transplantation. Physiologic follicular units are smaller with less interfollicular tissue and can thus be placed denser with less traumatization into finer recipient sites. Larger grafts with multiple FU's should only be used in combination with FUT and in patients with a very good donor hair supply.

The harvesting of FU grafts from the donor area is usually performed by careful excision of a hair-bearing strip. Several techniques are used to minimize follicle transection and scar formation during this step. The use of stereo-microscopes then allows for exact and fast dissection of large numbers of FU's with minimal trauma. The dissected grafts contain follicles with surrounding tissue which may be beneficial for short- and long-term graft survival.

FUT is indicated for patients who do not mind covering the linear scar with longer adjacent hairs, for patients with fine or light hair, for patients who do not want to shave their head, as needed while taking FU grafts, and for maximum donor yield without visible thinning of the donor area. In many patients, FUT provides an option of repeated surgery from the safe permanent mid-occipital donor area.

Individual extraction of FU's from the donor area (FUE) with a manual or motorized punch is also possible but associated with a potentially higher risk of follicle injury and impairment of graft viability. The extracted FU have less surrounding tissue. It

remains unclear if the short- and long-term outcome is equivalent to FUT where more perifollicular tissue is transplanted. The donor and recipient areas have to be trimmed. FUE may be indicated for smaller graft numbers, in patients with thick hair, in cases of tight occipital scalp elasticity, and in patients who do not want a linear scar or who want to wear a short occipital hair cut. Over-harvesting and extraction outside of the safe donor area should be avoided, but this limits the graft yield. In some patients, a combination of FUT and FUE harvesting is possible for maximum yield.

Recipient sites are prepared with different instruments. The creation of slits using micro-blades or needles adapted to graft size enables to achieve high densities. In the frontal area, a transition zone of 1-hair-FU's is created with micro- and macro-irregularities for a more natural appearance.

Patients should be informed, that temporary post-operative telogen effluvium may appear if pre-existing hair is present. This may be minimized by making smaller incisions using magnification.

The final result can be evaluated at 9-12 months.

3.4.6 Combination therapies

As hair surgery has no efficacy to prevent further progression of androgenetic alopecia, a combination of medical and surgical therapy seems to be superior to surgery alone.

In male patients Leavitt et al. (110) reported a better clinical outcome at 12 month after follicular unit transplantation for patients treated with combination of finasteride 1 mg daily and hair surgery versus patients treated with hair surgery alone (see section efficacy males).

Rinaldi et al. reported that treatment with psittacofulvin topical solution reduced the number of apoptotic fragments after FUE transplantation compared to treatment with placebo solution (166).

In female patients there is lack of evidence concerning combination therapies. We suggest that combination therapy may reduce further post-operative progression of androgenetic alopecia.

3.4.7 Summary

4 studies concerning hair surgery fulfilled inclusion criteria of the S3 guideline. Hair transplantation can be considered to improve androgenetic alopecia in suitable patients with sufficient donor hair supply and medically controlled or spontaneously stabilized androgenetic alopecia, especially for the fronto-parietal area. As hair surgery does not influence progression of androgenetic alopecia, long-term results in early stages depend on spontaneous respectively medical stabilization. The result greatly depends on the skills of the surgical team and the adjustment of the surgical plan to individual patient characteristics. Preparation of follicular units using dissecting microscopes and pre-treatment of FU's with platelet growth factor lead to higher graft survival rates.

While follicular unit transplantation (FUT) can be considered a standard, especially when stereo-microscopic dissection is used by a skilled team, other components of the surgical technique require further evaluation. As there are no randomised controlled studies comparing hair surgery versus no hair transplantation, only a **LEVEL**

OF EVIDENCE 2 can be attributed to the included studies comparing hair transplantation versus hair transplantation with supportive therapies (**LEVEL OF EVIDENCE 2**). Combination of finasteride 1 mg and follicular unit transplantation may reduce post-operative progression of androgenetic alopecia.

3.4.8 Therapeutic recommendation – Male

→ **Surgery, especially follicular unit transplantation (FUT) can be considered in male patients with sufficient donor hair.**

↑ **We suggest, follicular unit transplantation (FUT) to be combined with finasteride 1 mg daily to achieve a better clinical outcome.**

3.4.9 Therapeutic recommendation – Female

→ **Surgery especially follicular unit transplantation (FUT) can be considered in female patients with sufficient donor hair.**

3.5 PLATELET-RICH PLASMA (PRP)

3.5.1 Introduction

Platelet-rich plasma (PRP) is defined as an autologous preparation of plasma containing a supraphysiological concentration of platelets. PRP has been studied in several medical fields, mainly because of its known properties to promote wound healing, and is now largely utilized in orthopedics, sport medicine, plastic and aesthetic surgery, and in the treatment of diabetic ulcers. Its possible effects on hair growth were first studied in vitro and in vivo in mice in 2012 (168). Since that time, the clinical usage of PRP has become widespread with the aim to promote hair growth in several hair disorders, alone or in association with hair transplantation.

3.5.2 Mechanism of action

PRP is obtained collecting whole venous blood from the patient and then processing it in order to isolate a solution rich in platelets that is then injected intradermally. Platelet activation induces release of different growth factors, such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor (TGF), insulin-like growth factor (IGF), epidermal growth factor (EGF) and interleukin (IL)-1. The local environment becomes enriched of a natural concentration of autologous growth factors and cytokines that induce tissue regeneration. The presence of leukocytes in PRP is responsible for anti-infectious and immune regulation functions.

The precise mechanisms by which PRP acts on hair follicles are still unclear. In vitro, PRP induces the proliferation of dermal papilla cells and increases their expression of Akt and Bcl-2, which promote cell survival by preventing apoptosis. It also increases the phosphorylation of extracellular signal-regulated kinases known to induce cell growth, increases beta-catenin activity, which plays an important role in hair growth cycle regulation and promotes differentiation of stem cells into hair follicle cells, and upregulates fibroblast growth factor (FGF)-7, which delays hair follicle progression from anagen to catagen phase (168). The backs of rabbits treated with PRP have a higher expression of WNT10a mRNA, which via beta-catenin activity induces follicular stem cell activation that initiates anagen phase, activating anagen reentry of telogen hair follicles (169).

The released VEGF and PDGF have an angiogenic potential and may induce increased follicle vascularization.

Up to now, there is not a standard procedure for treatment with PRP, in regard of:

- a) technical procedures to obtain the platelet preparation, resulting in a variable platelet concentration and growth factors and cytokines in the final substance (including speed of centrifugation)
- b) different modalities to activate platelets, which may cause different concentrations of growth factors;
- b) volume of PRP injected per scalp area (which corresponds to different concentration of platelet-derived factors);
- c) time interval between each injection;
- d) quantity of injections performed in time;
- e) maintenance of results after interruption of treatment.

3.5.3 Efficacy – males

2 studies assessing the efficacy of PRP in male and female patients with androgenetic alopecia met the inclusion criteria for the guideline, both with grade C evidence, resulting in **LEVEL OF EVIDENCE 3** (170, 171).

OUTCOMES

Schiavone et al. (170) used macrophotographic evaluation to assess, in a non-controlled double-blind study, the effectiveness of 2 injections at 3-month interval, of autologous platelet and leukocyte concentrate at high concentration levels (L-PRP) plus autologous concentrated plasmatic protein solution. Sixty four patients (42 men and 22 women) were enrolled and evaluated by 2 evaluators using a clinical rating. Platelet activation was based on scalp inflammation induced by gentle pressure of a 1.0- mm deep Scalproller before the injections. The platelet concentration injected on the scalp was six fold to sevenfold greater than that of the patient's blood in the first injection and 4 times greater in the second injection. Macrophotographs were taken at baseline and after 3 and 6 months. After 6 months of follow-up, the overall proportion of patients reaching a clinically important difference was 40.6% and 54.7%, according to the 2 evaluators respectively. A "Minimal Clinical Important Difference" in the clinical change score which was defined as a score of at least +4, "moderately better" on a 15-point scale (Jaeschke Rating), was reached by 41.9 to 58.1% of patients, according to the assessment of the 2 evaluators. However, this study was not placebo-controlled, no long-term follow-up was performed and the reported results were pooled for men and women. To evaluate the effectiveness of PRP in AGA, randomized controlled clinical trials over longer follow-up periods are necessary.

Gkini et al. (171) performed 3 treatment sessions of PRP at 3-week interval, with an additional treatment after 6 months (the data include results of 18 men and 2 women). Platelet concentration in PRP was approximately 5.8 times greater than in whole blood. Activation of PRP included adding of calcium gluconate in a 1:9 ratio. At the 1-year follow up the mean hair density (hair/cm²) increased by 7.41% compared to baseline (P<0.001). The highest hair density recorded was at 3 months, after the 3rd treatment session (9.19%), followed by a gradual downward trend. In this study statistical significant results were obtained within a short time of evaluation, however a control group and a long-term follow up are lacking.

3.5.4 Efficacy – females

3 studies assessing the efficacy of PRP in female patients were included in the evidence based evaluation (169-171). Two out of them included male and female patients, the study by Gkini only 2 females (170, 171). The grades of evidence were B, C and C, resulting in a **LEVEL OF EVIDENCE 3**.

OUTCOMES

Schiavone et al. (170) investigated the effect of two L-PRP injections at 3-month interval in 22 women. Pooled results for men and women at 6 months showed an at least moderate response in 41.9 to 58.1% of patients, according to the macro-photographic assessment of 2 evaluators.

The results of Gkini et al (171), with 3 treatment sessions of PRP at 3-week interval with an additional treatment after 6 months refer to 2 female patients with androgenetic alopecia of grade I-III severity, according to the Ludwig scale. Pooled results for men and women showed an increase of the mean hair density (hair/cm²) of 7.41% compared to baseline (P<0.001) at the 1 year follow-up, with the highest hair density recorded after the 3rd treatment session. Due to the small sample size and the non-controlled study setting, this study provides insufficient evidence that PRP therapy is able to induce significant improvement of AGA in females within one year.

Lee et al (169) performed a double blind study in 40 Korean females affected by androgenetic alopecia, treating 1 arm with a single injection of CD34+ cell (Stem cells) -containing PRP preparation, without prior activation, followed by 12 sessions of polydeoxyribonucleotide (PDRN) intra-perifollicular injection performed at weekly intervals. The 2nd arm was treated with 12 sessions of intra-perifollicular PDRN injection alone at weekly intervals. Phototrichogram showed statistically significant improvements of both the mean hair count and the mean hair thickness after 3 months in both groups compared to baseline (p<0.001), with PRP + PDRN treatment being more effective than PDRN alone in improving hair thickness not hair count. Compared to the baseline value the patients treated with both PRP+PDRN and PDRN alone for 12 weeks exhibited statistically significant clinical improvement in mean hair counts and mean hair thickness. However, this study was not placebo controlled and no long-term follow-up was performed.

3.5.5 Instructions for use / Practicability

There is not a standard procedure for treatment of androgenetic alopecia with PRP. There are no standardized techniques for platelet isolation and activation, for dosage and frequency of injections, also more information about the need to combine PRP with other chemical/cells is needed. No standardized procedures for the implementation of PRP in the treatment of AGA have been evaluated. Moreover, as AGA is a genetic trait, the clinical advantage of intermittent PRP treatment needs to be further investigated.

Main side effect of PRP include immediate effects of the procedure, including pain and transient post-treatment edema and tenderness, which are reported by almost all patients, and post treatment sequelae, reported in a smaller number of cases. These include persistent trichodynia, psoriasiform scalp reactions, telogen effluvium, and more rarely, secondary infections and scarring. The impact of PRP treatment on quality of life of the patients should be further questioned.

3.5.6 Summary

3 studies concerning PRP fulfilled inclusion criteria of the S3 guideline. The grades of evidence were C for all studies, resulting in a **LEVEL OF EVIDENCE 3**. Based on these

studies, there is little evidence to support the use of PRP in men and women with androgenetic alopecia.

3.5.7 Therapeutic recommendation for men and women

There is no standardized technique for performing PRP to permit objective evaluation of its effects on AGA.

O We cannot make a recommendation for or against treatment of AGA with platelet-rich plasma at the present time

3.6 LOW LEVEL LASER (LIGHT) THERAPY (LLLT, LASER HAIR COMB)

3.6.1 Introduction

Low Level Laser therapy (LLLT), or Laser phototherapy, consists in the exposure of tissues to low levels of visible or near infrared light. LLLT has shown beneficial effects for a variety of medical conditions such as wound healing, nerve regeneration, joint pain relief, stroke recovery, and the prevention and treatment of mucositis. The idea to apply LLLT to hair disorders came from the observation that some patients treated with for hair removal exhibited paradoxical hair growth at the periphery or at the treated areas. Currently, several LLLT devices are marketed for the treatment of alopecia.

3.6.2 Mechanism of action

The basis of the biostimulatory effect of laser phototherapy during wound healing is not fully understood. LLLT seems to stimulate cell proliferation both directly, through increase of endogenous growth factors, and secondarily, through increased cutaneous microcirculation. Other hypothesized effects include decrease of 5-alpha reductase expression and modulatory effects on inflammation.

3.6.3 Efficacy – males

Two studies assessing the efficacy of LLLT in male patients with androgenetic alopecia with grade of evidence A2 and C were included in the evaluation, resulting in a **LEVEL OF EVIDENCE 2** (172, 173).

OUTCOMES

Leavitt et al. performed a 26-week randomized, double-blind, sham device-controlled, multicentre trial to investigate the effect of LLLT (665 nm) in 123 male patients with AGA Grade 2a to V according to the Norwood Hamilton Classification (172). The study results showed a significant increase in the hair count in the patients treated compared to controls (+19.8 versus -7.6 hairs/cm², $p < 0.0001$). According to the subjects' assessment, patients in the LLLT group perceived significantly greater improvement in hair regrowth than those in the sham device group at the end of the study. The investigator's global assessment, on the other hand, did not detect substantial differences between treatment groups.

Satino et al. examined the effects of LLLT in men and women with androgenetic alopecia (173). They reported a mean change from baseline total hair count of 14.1 hairs/cm². A control group for comparison was missing.

3.6.4 Efficacy – females

Two studies assessing the efficacy of LLLT in female patients with androgenetic alopecia met the inclusion criteria of the guideline, with grade of evidence A2 and C, resulting in a **LEVEL OF EVIDENCE 2** (173, 174).

OUTCOMES

Lanzafame et al. performed a double-blind, sham device-controlled multicenter study on 47 women with AGA Ludwig grade I-II (174). A $48.7 \pm 17.61\%$ increase in hair count was reported after 16 weeks of LLLT (60 treatments) vs an increase of $11.05 \pm 48.30\%$ in the sham device group ($p < 0.001$).

Satino et al. examined the effects of a low level laser comb in men and women with androgenetic alopecia (173). Pooled results showed a mean change from baseline total hair count of 14.1 hairs/cm². A control group for comparison was missing.

3.6.5 Instructions for use / Practicability

Treatment with LLLT is performed at home, using a LaserComb or wearing for a certain amount of time a helmet whose power cord is plugged into a standard outlet. Duration of therapy and frequency varies for the different devices.

LLLT is generally well tolerated and reported adverse events are usually mild, including scalp dryness, itching, tenderness and a warm sensation.

3.6.6 Summary

3 studies concerning LLLT fulfilled the inclusion criteria of the S3 guideline. When used for 16 and 26 weeks under different protocols and with 2 different devices, LLLT showed an increased hair count (**LEVEL OF EVIDENCE 2**). However, no long-term follow-up was performed. Further controlled randomized clinical studies are required to establish the efficacy of these devices for hair growth in comparison to established therapies and to evaluate long-term use.

3.6.7 Therapeutic recommendation for men and women

↑ We suggest using LLLT as ancillary therapy for AGA with devices that use energy levels shown to be effective in randomized controlled clinical trials

○ We cannot make a recommendation for or against treatment for more than 6 months with LLLT for AGA at the present time

3.7 MISCELLANEOUS

3.7.1 Introduction

Besides the pharmacologic therapeutic options, which were already assessed in the previous chapters, the patient afflicted with androgenetic alopecia is faced to a confusing panel of molecules, products and interventions claiming to be efficient in androgenetic alopecia. The range of products is wide and reaches from cosmetic to pharmaceutical agents, natural products, functional food and even electrostatic/-magnetic treatment. The mode of application comprises topical application, oral intake and scalp injections. The majority of these products claim hair promoting properties, even though controlled clinical studies are scarce. The aim of this chapter is to gather available evidence for these miscellaneous products.

3.7.2 Mechanism of action

The herein described miscellaneous products are grouped based on their reported assumed main mechanism of action (Table 2):

- a) DHT inhibitory activity* (hormonal effects, mainly inhibition of 5-alpha-reductase and reduced DHT activity)

- b) Anti-inflammatory activity
- c) Improved perifollicular vascularisation
- d) Improved hair follicle nutrition (anti-apoptotic activity, anti-fibrotic activity)
- e) Not precisely reported or unknown mechanism

*Botanically derived 5 α -reductase inhibitors, which were compared to established therapies for androgenetic alopecia (finasteride per os and topical minoxidil) are cross-referenced in the corresponding chapters and tables.

3.7.3 Efficacy – males and females

Due to the limited number of studies, the efficacy of the miscellaneous therapies is in contrast to all other chapters summarized based on the application mode (oral, topical, interventions) grouped for males and females.

For many miscellaneous products, no clinical studies fulfilling the inclusion criteria of the guideline were found. Evaluation of individual ingredients is limited, as most of the tested products contain multiple different substances, e.g. food supplements with aminoacids and trace elements or different herbal preparations. Furthermore, even though the degree of evidence of the included studies was generally good, a single or max. 2 studies were available on each individual miscellaneous agent or product.

Hereafter, we provide a short overview on the different miscellaneous products.

21 of the included trials examined a single product (66, 68, 78, 175-192), while 5 trials investigated combinations of different products (65, 69, 74, 176, 193).

Oral Supplements

Serenoa repens, β -sitosterol, niacin, biotin: A combination of serenoa repens, β -sitosterol, niacin and biotin in an oral softgel taken twice daily led to improvement significantly different to placebo treatment (investigator assessment 60% improved vs. 11%) (175).

In a study by Rossi et al. 38% of male patients with androgenetic alopecia treated with ***serenoa repens*** 320 mg per os once daily for 24 months showed an increase in hair growth according to global expert panel assessment. However this increase was less than in the group treated with finasteride 1 mg once daily (increase in hair growth in 68% of patients) (118).

Aminoacids: Morganti et al. report a significant mean change from total hair count in male and female patients after a 50-week-treatment with an oral supplement containing cysteine, histidine, copper and zinc taken 4 times daily (29% vs. 11% placebo, $p < 0.005$) (193). A combination of cysteine, calcium pantothenate and millet seed twice a day for 6 months in 40 female patients showed increased anagen rate that was significantly different to placebo ($p = 0.0225$) (187).

Millet seed is a natural product that contains silicic acid, aminoacids, vitamins and minerals. An oral supplement composed of millet seed extract, cysteine and calcium pantothenate taken twice the day for 6 months led to increased anagen rates female patients ($p = 0.0225$ vs. placebo) (187). Another oral supplement composed of marine extracts and a silicea component was studied by Lassus et al. in comparison to fish extract and in combination of topical and oral use (176, 194). However, these studies were not placebo controlled.

Vitamines: Prager et al. reported 60% improvement rated by investigator in 26 male patients after 18-24 weeks treatment with an oral combination containing biotin and niacin, but also β -sitosterol and serenoa repens (175).

Moers-Campi et al. investigated the effect of an oral supplement containing fenugreek and micronutrients (vitamins C, E, nicotinamide, panthotenacid, zinc, vitamins B1, B6, B12, copper, biotin, folic acid, iod, selen) compared to placebo (2 capsules once per day) in 56 male and female patients with androgenetic alopecia (177). After 6 months of treatment, the supplement group showed a mean change of anagen hair count from baseline of 5.9% ($p < 0.0001$). In the placebo group, no significant changes were found in mean anagen hair count after 6 months (0.62%).

Omega 3&6: In a study by Le Floc'h et al. 120 female patients were randomized to receive a nutritional supplement containing omega 3&6 and antioxidants or no treatment for 6 months (190). In the investigator's assessment, increased hair density was reported in 62% of subjects in the supplement group versus 28.2% in the no treatment group after 6 months ($p = 0.001$). There is no report of hair count in this study.

Different opinions exist concerning the supplementation of **iron** in absence of iron deficiency in patients with androgenetic alopecia. Various observational studies discussed relation between hair loss and decreased serum ferritin levels with controversial results (195). There is insufficient evidence for iron supplementation in absence of iron deficiency in patients with androgenetic alopecia.

Trace elements like **copper** and **zinc**: As zinc and copper were only studied in combination with other agents, evidence on their efficacy is inadequate.

Topically applied products

Ketoconazole or zinc pyrithione are effective agents in the treatment of seborrheic dermatitis. As concomitant seborrheic dermatitis is common in androgenetic alopecia and may aggravate hair loss, impact on androgenetic alopecia is difficult to evaluate. Berger et al. showed significant improvement for 1% pyrithione zinc shampoo, minoxidil 5% solution or the combination of both compared to placebo treatment at 26 weeks (65). The mean change from baseline hair count for the 1% pyrithione zinc shampoo group was significantly below the standard therapy with minoxidil. Combination of minoxidil and pyrithione zinc was inferior to minoxidil monotherapy. Baek et al. investigated the application of a commercially available shampoo containing 0.6% zinc pyrithione, 0.5% dexpanthenol, 0.1% nicotinamide, 0.5% triaminodil and 0.17% Thujae occidentalis semen (TOS) extract in male and female subjects in comparison to placebo (189). After 16 weeks, a mean change from baseline total hair count of 3.4 hairs/cm² (3.9%) was found in the 20 patients of the shampoo group, whereas a mean change from baseline hair count of -0.8

hairs/cm² (-0.9%) was found in the 20 patients of the placebo group ($p > 0,05$ between the two groups).

Niacin derivatives: Draelos et al. studied the effect of topical applied niacin derivatives once daily in 60 female patients. After 6 months 69% were rated as improved in global photographic assessment ($p = 0.04$ vs. placebo) (186).

Melatonin: A trial by Fischer et al. in 35 males with androgenetic alopecia (stage I to II of Hamilton/Norwood Scale) reported an increased hair count in 54,8% and 58,1% of participants after respectively 3 and 6 months of topical use of melatonin solution once daily for 6 months, and with no control group (185). In a further open-label, 3-month, multicenter study, which did not fulfil the inclusion criteria of the guideline due to lack of a standardized objective quantification technique, 901 men and 990 women with androgenetic alopecia included in 200 dermatological centers applied a topical melatonin solution once daily for 3 months. Evaluation via hair pull test showed a decrease from 61.6% to 7.8% of the percentage of patients with a 2- to 3-fold positive hair-pull test and an increase from 12.2% to 61.5% in the percentage of patients with a negative hair-pull test ($p < 0.001$) (196): Study outcomes were obtained by hair pull tests, a semi-quantitative method with high investigator dependent variations, performed by doctors from 200 different centers on more than 1800 patients.

Roxithromycin is an antimicrobial macrolide, with anti-inflammatory and antioxidant effects and anti-apoptotic activity on keratinocytes. Ito et al performed a double blind trial with topical 0.5% roxithromycin or placebo applied once a day on the scalp for 6 months, on 24 Japanese males with AGA (13 in the RXM group and 11 in the placebo group) (184). 58% of the patients applying 0.5% RXM solution were improved, compared to 0% with placebo, after 6 months of treatment, according to the global expert panel assessment. The hair shaft thickness measured on 5 cutting hairs was significantly increased compared to baseline only in the treated group (+30.09 μm) but there is no hair count in this study.

Proanthocyanidines like procyanidine B belong to the group of flavonoids, which are antioxidants. Kamimura et al. showed, that the topical application of procyanidine B 1% twice the day leads to significant mean changes from total hair count in male patients after 6 months ($p < 0.0005$ vs. placebo) (178).

Adenosine is an endogenous nucleoside. Oura et al performed a double-blind, randomized, placebo-controlled study with topical 0.75% adenosine or placebo applied on the scalp twice a day on 30 Japanese women affected by androgenetic alopecia (188). After 12 months, 62% (8/13) of the treated patients were rated as improved in global photographic assessment, compared to the 36% (5/14) improved with placebo ($p = 0,0337$). Phototrichogram did not show significant changes in hair density, anagen hair ratio and thin hair ratio in both groups, while it showed a significantly increased anagen growth rate in the adenosine group.

2 trials examining the efficacy of topically applied **herbal preparations** fulfilled the inclusion criteria of the guideline (179, 180). As the ingredients of the particular herbal preparations significantly differ, they have to be evaluated separately. Kessels et al. reported a mean change from baseline nonvellus hair count of 26.6 hairs/cm² vs. 21.8 hairs/cm², $p = 0.02$ vs. placebo in 396 male patients, who applied twice daily

a Chinese herbal preparation for 6 months (179). Greenberg et al. reported a mean change from baseline total hair count of 77.4 % in 24 men after 40 weeks usage of herbal extract containing fennel, polygonum, menthe, chamomile, thuja, hibiscus) ($p = 0.003$) (180).

A lotion containing **Biochanin A** and acetyl tetrapeptide-3 applied once a day by males with androgenetic alopecia induced an 13% increase in the number of anagen hair in 14 patients ($p < 0.1$; NS)) compared to the -2% decreased induced by placebo in 15 patients, after 4 months of treatment (191).

Serenoa repens: The application of a lotion containing serenoa repens extract twice a day showed statistically significant improvement in mean change from baseline total hair count at 50 weeks ($p < 0.005$ vs. placebo) (193).

A trial by Groveman et al. failed to prove efficacy of the non-ionic detergent **polysorbate 60** applied twice daily topical in 174 male patients (182). After 16 weeks global photographic assessment for the polysorbate group was below the placebo group.

Red ginseng: A study by Ryu et al. failed to show that combination of minoxidil 3% topical solution and red ginseng is superior to minoxidil monotherapy in women (92).

Retinoids modulate proliferation, differentiation of keratinocytes and the T-cellular immune response. Their usage as pharmaceutical excipients to improve minoxidil resorption is discussed. Two trials fulfilled the inclusion criteria of the guideline (69, 74). Bazzano et al. reported in 58 % of the male and female patients, who treated their scalp twice daily with tretinoin 0.025% solution, at least 20% increase from baseline hair count at 12 months (74). It is conspicuous that the placebo and the minoxidil 0.5% group reached no improvement at all. The trial was not blinded and not randomized. Shin et al. failed to show superiority of minoxidil 5% solution combined with tretinoin 0.01% once daily versus minoxidil 5% solution applied twice daily in 31 male patients (69). The mean changes from baseline total hair count did not differ significantly at 18 weeks, though the combination of minoxidil and tretinoin led to slightly elevated values (15.9 hairs/cm² vs. 18.2 hairs/cm²).

Ciclosporin: The induction of hypertrichosis is known as adverse event in systemic treatment with ciclosporin. Experimental models could also demonstrate this effect for topical application of ciclosporin. In a small study by Gilhar et al., which did not fulfil the inclusion criteria for the guideline, 2 patients out of 8 had response to topical application of ciclosporin after 12 months (197).

Another group of substances were the prostaglandine analogues like **viprostol orlatanoprost**. The topical application of viprostol for 24 weeks in male patients did not show significant difference compared to placebo or vehicle treatment (181).

Minerals and niacin derivates: Reygagne et al. assessed the efficacy of a topical combination of glycerol oxyesters and silicium (Maxilene®) (66). In comparison to standard minoxidil treatment Maxilene® led to statistically significant hair loss.

Aminexil is a molecule chemically similar to minoxidil. Studies, that provide evidence for its efficacy, are missing. **Stemoxydine** is a molecule which mimics effect of

hypoxia with stabilisation of Hypoxia Inducible Factor HIF 1 alpha. Published studies providing efficacy in androgenetic alopecia are missing.

Cimicifuga racemosa is a natural product with positive influence on the estrogenic level, mainly used for perimenopausal complaints. No evidence was found for its efficacy in androgenetic alopecia.

No trials were found concerning the ***natural products ginkgo biloba, aloe vera, bergamot or sorphora***. Animal models and resp. or in vitro studies suggest hair growth promoting properties. The agents are used in cosmetical hair care products.

There are different hair care products containing ***caffeine*** claiming to be an effective in treating androgenetic alopecia in men and women. Caffeine showed in in vitro studies higher transfollicular penetration rates than in vivo (198); in microdissected male and female human scalp hair follicles caffeine led to an enhanced hair shaft elongation (199). Currently only clinical studies on the efficacy of caffeine shampoo or topical caffeine solution in AGA not meeting the inclusion criteria for the current guideline are available, which reported increased patient satisfaction after caffeine use as well as a positive effect of the combination of caffeine and minoxidil (in one study additionally with azelaic acid) compared to topical minoxidil solution or placebo (200-204). However, these studies present methodological limitations (lack of a standardized evaluation, high publication bias risk, in most cases uncontrolled study design) (205).

Interventions

Besides cosmetic and pharmaceutical agents, ***pulsed electromagnetic/-static field*** is also claiming efficacy in androgenetic alopecia. 4 trials for pulsed electrostatic field could be included into the evidence-based evaluation of the guideline (206-209). Though the trials showed modest increase in total, anagen or nonvellus hair counts, the implementation in clinical routine is doubtful due to unfavourable cost-benefit ratio.

Another therapeutic regimen that claims to improve androgenetic alopecia is ***mesotherapy***. Different agents, e.g. vitamins are intracutaneously injected. Few available studies on the efficacy of these procedures did not meet the inclusion criteria of this guideline.

The injection of ***botulinum toxin*** has been suggested to improve androgenetic alopecia. Freund and Schwartz (183) reported 18% increase in hair count between baseline and week 48 in 40 male subjects with androgenetic alopecia, who underwent 2 cycles of botulinum toxin scalp injections, at baseline and after 24 weeks. Each treatment cycle consisted in injections of 150 units of Botox (5 units per 0,1ml saline) in 30 sites, in the muscles surrounding the scalp. Therefore, there is insufficient evidence for therapy with Botulin toxin injection in patients with androgenetic alopecia.

3.7.4 Instructions for use / Practicability

For instructions for use for the miscellaneous products the reader is asked to consult the information of the particular product information. In case of an intervention, such as botulinum toxin injections or mesotherapy, the treating physician is responsible to provide detailed patient information on the procedure and possible side effects.

3.7.5 Combination therapies

Patients often ask for one of the particular miscellaneous therapies in combination with another treatment. As evidence is insufficient to missing for the therapies mentioned above, the combination of different miscellaneous products cannot be recommended. Additional use depends on the individual case and decision of the patient and the physician.

3.7.6 Summary

Plenty of marketed oral and topical miscellaneous therapies and interventions claim to be effective in the treatment of androgenetic alopecia in men and women. Based on currently available literature data no evidence-based recommendation can be given for these miscellaneous products. Their use as a supportive strategy within an individually tailored management approach remains to the discretion of the treating dermatologist and the decision of the patient. Further controlled studies to prove the relevance of these and other new approaches in the treatment of AGA are needed.

3.7.7 Therapeutic recommendation – Male and Female

O We cannot make a recommendation for or against a treatment with the mentioned molecules, substances and interventions at the present time

References

1. Alfonso M, Richter-Appelt H, Tosti A, Viera MS, García M. The psychosocial impact of hair loss among men: a multinational European study. *Curr Med Res Opin.* 2005;21(11):1829-36.
2. Cash TF, Price VH, Savin RC. Psychological effects of androgenetic alopecia on women: comparisons with balding men and with female control subjects. *Journal of the American Academy of Dermatology.* 1993;29(4):568-75.
3. Blumeyer A, Tosti A, Messenger A, Reygagne P, Del Marmol V, Spuls PI, et al. Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men. *JDDG - Journal of the German Society of Dermatology.* 2011;9(SUPPL. 6):S1-S57.
4. Norwood OT. Male pattern baldness:classification and incidence. *Southern Medical Journal.* 1975;68(11):1359-65.
5. Birch MP, Messenger AG. Genetic factors predispose to balding and non-balding in men. *European Journal of Dermatology.* 2001;11:309-14.
6. Tsuboi R, Arano O, Nishikawa T, Yamada H, Katsuoka K. Randomized clinical trial comparing 5% and 1% topical minoxidil for the treatment of androgenetic alopecia in Japanese men. *Journal of Dermatology.* 2009;36(8):437-46.
7. Hoffmann R, Happle R. Current understanding of androgenetic alopecia. Part II: clinical aspects and treatment. *Eur J Dermatol.* 2000;10(5):410-7.
8. Xu F, Sheng YY, Mu ZL, Lou W, Zhou J, Ren YT, et al. Prevalence and types of androgenetic alopecia in Shanghai, China: a community-based study. *British Journal of Dermatology.* 2009;160(3):629-32.
9. Wang TL, Zhou C, Shen YW, Wang XY, Ding XL, Tian S, et al. Prevalence of androgenetic alopecia in China: a community-based study in six cities. *British Journal of Dermatology.* 2010;162(4):843-7.
10. Birch MP, Messenger JF, Messenger AG. Hair density, hair diameter and the prevalence of female pattern hair loss. *Br J Dermatol.* 2001;144:297-304.
11. Norwood OT. Incidence of female androgenetic alopecia (female pattern alopecia). *Dermatol Surg.* 2001;27(1):53-4.
12. Paik JH, Yoon JB, Sim WY, Kim BS, Kim NI. The prevalence and types of androgenetic alopecia in Korean men and women. *Br J Dermatol.* 2001;145(1):95-9.
13. Blume-Peytavi U, Blumeyer A, Tosti A, Finner A, Marmol V, Trakatelli M, et al. S1 guideline for diagnostic evaluation in androgenetic alopecia in men, women and adolescents. *Br J Dermatol.* 2011;164(1):5-15.
14. Inui S, Itami S. Androgen actions on the human hair follicle: perspectives. *Exp Dermatol.* 2013;22(3):168-71.
15. Kwack MH, Kim MK, Kim JC, Sung YK. Dickkopf 1 promotes regression of hair follicles. *J Invest Dermatol.* 2012;132(6):1554-60.
16. Kwack MH, Ahn JS, Kim MK, Kim JC, Sung YK. Dihydrotestosterone-inducible IL-6 inhibits elongation of human hair shafts by suppressing matrix cell proliferation and promotes regression of hair follicles in mice. *J Invest Dermatol.* 2012;132(1):43-9.
17. Garza LA, Liu Y, Yang Z, Alagesan B, Lawson JA, Norberg SM, et al. Prostaglandin D2 inhibits hair growth and is elevated in bald scalp of men with androgenetic alopecia. *Sci Transl Med.* 2012;4(126):126ra34.

18. Nyholt DR, Gillespie NA, Heath AC, Martin NG. Genetic basis of male pattern baldness. *J Invest Dermatol.* 2003;121(6):1561-4.
19. Rexbye H, Petersen I, Iachina M, Mortensen J, McGue M, Vaupel JW, et al. Hair loss among elderly men: etiology and impact on perceived age. *J Gerontol A Biol Sci Med Sci.* 2005;60(8):1077-82.
20. Heilmann-Heimbach S, Hochfeld LM, Paus R, Nöthen MM. Hunting the genes in male-pattern alopecia: how important are they, how close are we and what will they tell us? *Exp Dermatol.* 2016;25(4):251-7.
21. Smith MA, Wells RS. Male-type alopecia, alopecia areata, and normal hair in women. *Archives of Dermatology.* 1964;89:155-8.
22. Gunn DA, Rexbye H, Griffiths CE, Murray PG, Fereday A, Catt SD, et al. Why some women look young for their age. *PLoS One.* 2009;4(12):e8021.
23. Redler S, Brockschmidt FF, Tazi-Ahnini R, Drichel D, Birch MP, Dobson K, et al. Investigation of the male pattern baldness major genetic susceptibility loci AR/EDA2R and 20p11 in female pattern hair loss. *Br J Dermatol.* 2012;166(6):1314-8.
24. Heilmann S, Kiefer AK, Fricker N, Drichel D, Hillmer AM, Herold C, et al. Androgenetic alopecia: identification of four genetic risk loci and evidence for the contribution of WNT signaling to its etiology. *J Invest Dermatol.* 2013;133(6):1489-96.
25. Redler S, Dobson K, Drichel D, Heilmann S, Wolf S, Brockschmidt FF, et al. Investigation of six novel susceptibility loci for male androgenetic alopecia in women with female pattern hair loss. *J Dermatol Sci.* 2013;72(2):186-8.
26. Yip L, Zaloumis S, Irwin D, Severi G, Hopper J, Giles G, et al. Association analysis of oestrogen receptor beta gene (ESR2) polymorphisms with female pattern hair loss. *Br J Dermatol.* 2012;166(5):1131-4.
27. Redler S, Birch P, Drichel D, Hofmann P, Dobson K, Böhmer AC, et al. The oestrogen receptor 2 (ESR2) gene in female-pattern hair loss: replication of association with rs10137185 in German patients. *Br J Dermatol.* 2014;170(4):982-5.
28. Vexiau P, Chaspoux C, Boudou P, Fiet J, Abramovici Y, Rueda MJ, et al. Role of androgens in female-pattern androgenetic alopecia, either alone or associated with other symptoms of hyperandrogenism. *Arch Dermatol Res.* 2000;292(12):598-604.
29. Cela E, Robertson C, Rush K, Kousta E, White DM, Wilson H, et al. Prevalence of polycystic ovaries in women with androgenic alopecia. *Eur J Endocrinol.* 2003;149(5):439-42.
30. Rakowska A, Slowinska M, Kowalska-Oledzka E, Olszewska M, Rudnicka L. Dermoscopy in female androgenic alopecia: method standardization and diagnostic criteria. *Int J Trichology.* 2009;1(2):123-30.
31. Drugs@FDA: FDA Approved Drug Products. Women's rogain 5% minoxidil topical aerosol, approval history and label. [Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetails>.
32. Roenigk HH, Jr., Pepper E, Kuruvilla S. Topical minoxidil therapy for hereditary male pattern alopecia. *Cutis cutaneous medicine for the practitioner.* 1987;39(4):337-42.
33. Olsen EA, DeLong ER, Weiner MS. Long-term follow-up of men with male pattern baldness treated with topical minoxidil. *Journal of the American Academy of Dermatology.* 1987;16(3 Pt 2):688-95.
34. Montagnani A, Bardazzi F. Open not controlled clinical study on 2% topical minoxidil solution in the treatment of patients with androgenetic alopecia. *Dermatologia Clinica.* 1990;10(1-4):47-9.

35. Olsen EA, Weiner MS, Amara IA, DeLong ER. Five-year follow-up of men with androgenetic alopecia treated with topical minoxidil. *Journal of the American Academy of Dermatology*. 1990;22(4):643-6.
36. Karam P. Topical minoxidil therapy for androgenic alopecia in the Middle East. The Middle-Eastern Topical Minoxidil Study Group. *International journal of dermatology*. 1993;32(10):763-6.
37. Kanti V, Hillmann K, Kottner J, Stroux A, Canfield D, Blume-Peytavi U. Effect of minoxidil topical foam on frontotemporal and vertex androgenetic alopecia in men: a 104-week open-label clinical trial. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2015.
38. Olsen EA, Whiting D, Bergfeld W, Miller J, Hordinsky M, Wanser R, et al. A multicenter, randomized, placebo-controlled, double-blind clinical trial of a novel formulation of 5% minoxidil topical foam versus placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol*. 2007;57(5):767-74.
39. Califano A, Virgili A, Caputo R, Cavalieri R, Celleno L, Finzi A, et al. 2% Minoxidil topical solution in the treatment of alopecia androgenetica. A controlled clinical study. *Giornale Italiano di Dermatologia e Venereologia*. 1991;126(3):V-X.
40. Anderson CD, Hansted B, Abdallah MA, Oumeish OY, Rushaidat Q, Moerk C, et al. Topical minoxidil in androgenetic alopecia. Scandinavian and Middle East experience. *Int J Dermatol*. 1988;27(6 SUPPL.):447-51.
41. Dutree M, Nieboer C, Koedijk FHJ, Stolz E. Treatment of male pattern alopecia using topical minoxidil in The Netherlands. *Int J Dermatol*. 1988;27(6 SUPPL.):435-40.
42. Petzoldt D, Borelli S, Braun-Falco O, Holzmann H, Laux B, Metz J, et al. The German double-blind placebo-controlled evaluation of topical minoxidil solution in the treatment of early male pattern baldness. *Int J Dermatol*. 1988;27(6 SUPPL.):430-4.
43. Olsen EA, DeLong ER, Weiner MS. Dose-response study of topical minoxidil in male pattern baldness. *Journal of the American Academy of Dermatology*. 1986;15(1):30-7.
44. Shupack JL, Kassimir JJ, Thirumoorthy T, Reed ML, Jondreau L. Dose-response study of topical minoxidil in male pattern alopecia. *Journal of the American Academy of Dermatology*. 1987;16(3 Pt 2):673-6.
45. Olsen EA, Dunlap FE, Funicella T, Koperski JA, Swinehart JM, Tschen EH, et al. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *Journal of the American Academy of Dermatology*. 2002;47(3):377-85.
46. Civatte J, Laux B, Simpson NB, Vickers CF. 2% topical minoxidil solution in male-pattern baldness: preliminary European results. *Dermatologica*. 1987;175:42-9.
47. Lopez-Bran E, Robledo A, Aspiolea F, Moragas JM, Yu A, Quintanilla E, et al. Multicenter comparative study of the efficacy of topical 2% minoxidil (Regaine) versus placebo in the treatment of male baldness. *Advances in Therapy*. 1990;7(3):159-68.
48. Civatte J, Degreef H, Dockx P, Kint A, Lachapelle JM, Amblard P, et al. Topical 2% minoxidil solution in male pattern alopecia: The initial european experience. *Int J Dermatol*. 1988;27(6 SUPPL.):424-9.
49. Alanis A, Barbara F, Meurehg C, Montes d, Ramirez L. Double-blind comparison of 2% topical minoxidil and placebo in early male pattern baldness. *Curr Ther Res Clin Exp*. 1991;49(5):723-30.
50. Piepkorn MW, Weidner M. Comparable efficacy of 2% minoxidil gel and solution formulations in the treatment of male pattern alopecia. *Journal of the American Academy of Dermatology*. 1988;18(5 Pt 1):1059-62.

51. Olsen EA, Weiner MS, DeLong ER, Pinnell SR. Topical minoxidil in early male pattern baldness. *Journal of the American Academy of Dermatology*. 1985;13(2 Pt 1):185-92.
52. Savin RC. Use of topical minoxidil in the treatment of male pattern baldness. *Journal of the American Academy of Dermatology*. 1987;16(3 Pt 2):696-704.
53. Katz HI, Hien NT, Praver SE, Goldman SJ. Long-term efficacy of topical minoxidil in male pattern baldness. *Journal of the American Academy of Dermatology*. 1987;16(3 Pt 2):711-8.
54. De-Villez RL. Androgenetic alopecia treated with topical minoxidil. *Journal of the American Academy of Dermatology*. 1987;16(3 Pt 2):669-72.
55. Koperski JA, Orenberg EK, Wilkinson DI. Topical minoxidil therapy for androgenetic alopecia. A 30-month study. *Archives of dermatology*. 1987;123(11):1483-7.
56. Kreindler TG. Topical minoxidil in early androgenetic alopecia. *Journal of the American Academy of Dermatology*. 1987;16(3 Pt 2):718-24.
57. Connors TJ, Cooke DE, De-Launey WE, Downie M, Knudsen RG, Shumack S, et al. Australian trial of topical minoxidil and placebo in early male pattern baldness. *Australasian journal of dermatology, The*. 1990;31(1):17-25.
58. Price VH, Menefee E, Strauss PC. Changes in hair weight and hair count in men with androgenetic alopecia, after application of 5% and 2% topical minoxidil, placebo, or no treatment. *Journal of the American Academy of Dermatology*. 1999;41(5 Pt 1):717-21.
59. Hillmann K, Garcia Bartels N, Stroux A, Canfield D, Blume-Peytavi U. Investigator-initiated double-blind, two-armed, placebo-controlled, randomized clinical trial with an open-label extension phase, to investigate the efficacy of 5% Minoxidil topical foam twice daily in men with androgenetic alopecia in the fronto-temporal and vertex regions regarding hair volume over 24/52 weeks. *Journal of Investigative Dermatology*. 2013;133 (5):1400.
60. Rietschel RL, Duncan SH. Safety and efficacy of topical minoxidil in the management of androgenetic alopecia. *Journal of the American Academy of Dermatology*. 1987;16(3 Pt 2):677-85.
61. Roberts JL. Androgenetic alopecia: treatment results with topical minoxidil. *Journal of the American Academy of Dermatology*. 1987;16(3 Pt 2):705-10.
62. Gassmueller J, Hoffmann R, Webster A. Topical fulvestrant solution has no effect on male and postmenopausal female androgenetic alopecia: results from two randomized, proof-of-concept studies. *Br J Dermatol*. 2008;158(1):109-15.
63. Arca E, Acikgoz G, Tastan HB, Kose O, Kurumlu Z. An open, randomized, comparative study of oral finasteride and 5% topical minoxidil in male androgenetic alopecia. *Dermatology Basel, Switzerland*. 2004;209(2):117-25.
64. Saraswat A, Kumar B. Minoxidil vs finasteride in the treatment of men with androgenetic alopecia. *Archives of dermatology*. 2003;139(9):1219-21.
65. Berger RS, Fu JL, Smiles KA, Turner CB, Schnell BM, Werchowski KM, et al. The effects of minoxidil, 1% pyrithione zinc and a combination of both on hair density: a randomized controlled trial. *British journal of dermatology, The*. 2003;149(2):354-62.
66. Reygagne P, Assouly P, Catoni I, Jouanique C, Maffi-Berthier N, Moisson YF, et al. Male androgenic alopecia. Randomized trial versus 2% minoxidil. *Nouvelles Dermatologiques*. 1997;16(2):59-63.
67. Khandpur S, Suman M, Reddy BS. Comparative efficacy of various treatment regimens for androgenetic alopecia in men. *Journal of dermatology, The*. 2002;29(8):489-98.

68. Panahi Y, Taghizadeh M, Marzony ET, Sahebkar A. Rosemary oil vs minoxidil 2% for the treatment of androgenetic alopecia: a randomized comparative trial. *Skinmed*. 2015;13(1):15-21.
69. Shin HS, Won CH, Lee SH, Kwon OS, Kim KH, Eun HC. Efficacy of 5% minoxidil versus combined 5% minoxidil and 0.01% tretinoin for male pattern hair loss: a randomized, double-blind, comparative clinical trial. *Am J Clin Dermatol*. 2007;8(5):285-90.
70. Tanglertsampan C. Efficacy and safety of 3% minoxidil versus combined 3% minoxidil / 0.1% finasteride in male pattern hair loss: A randomized, double-blind, comparative study. *Journal of the Medical Association of Thailand*. 2012;95(10):1312-6.
71. Dhurat R, Sukesh M, Avhad G, Dandale A, Pal A, Pund P. A randomized evaluator blinded study of effect of microneedling in androgenetic alopecia: a pilot study. *International Journal of Trichology*. 2013;5(1):6-11.
72. Sakr FM, Gado AM, Mohammed HR, Adam ANI. Preparation and evaluation of a multimodal minoxidil microemulsion versus minoxidil alone in the treatment of androgenic alopecia of mixed etiology: a pilot study. *Drug design, development & therapy*. 2013;7:413-23.
73. Hu R, Xu F, Sheng Y, Qi S, Han Y, Miao Y, et al. Combined treatment with oral finasteride and topical minoxidil in male androgenetic alopecia: a randomized and comparative study in Chinese patients. *Dermatol Ther*. 2015;28(5):303-8.
74. Bazzano GS, Terezakis N, Galen W. Topical tretinoin for hair growth promotion. *Journal of the American Academy of Dermatology*. 1986;15(4 Pt 2):880-3.
75. Pazoki-Toroudi H, Babakoochi S, Nilforoushzadeh MA, Nassiri-Kashani M, Shizarpour M, Ajami M, et al. Therapeutic effects of minoxidil high extra combination therapy in patients with androgenetic alopecia. *Skinmed*. 2012;10(5):276-82.
76. Lueangarun S, Panchaprateep R, Tempark T, Noppakun N. Efficacy and safety of oral minoxidil 5 mg daily during 24-week treatment in male androgenetic alopecia. *Journal of the American Academy of Dermatology*. 2015;72(5):Ab113-Ab.
77. Piraccini B, Starace M, Alessandrini A, Guarrera M, Fiorucci MC, Lorenzi S. [Efficacy and tolerability of 5% minoxidil solution (Carexidil) in male and female androgenetic alopecia: a 6-month open multicentric study]. *Giornale Italiano di Dermatologia e Venereologia*. 2011;146(6 Suppl 1):1-8.
78. Faghihi G, Iraj F, Harandi MR, Nilforoushzadeh MA, Askari G. Comparison of the efficacy of topical minoxidil 5% and adenosine 0.75% solutions on male androgenetic alopecia and measuring patient satisfaction rate. *Acta Dermatovenerologica Croatica*. 2013;21(3):155-9.
79. Pumthong G, Asawanonda P, Varothai S, Jariyasethavong V, Triwongwanat D, Suthipinittharm P, et al. Curcuma aeruginosa, a novel botanically derived 5alpha-reductase inhibitor in the treatment of male-pattern baldness: a multicenter, randomized, double-blind, placebo-controlled study. *Journal of Dermatological Treatment*. 2012;23(5):385-92.
80. Blume-Peytavi U, Kunte C, Krisp A, Bartels NG, Ellwanger U, Hoffmann R. Comparison of the efficacy and safety of topical minoxidil and topical alfatradiol in the treatment of androgenetic alopecia in women. *Journal der Deutschen Dermatologischen Gesellschaft JDDG; Journal of the German Society of Dermatology*. 2007;5(5):391-5.
81. DeVillez RL, Jacobs JP, Szpunar CA, Warner ML. Androgenetic alopecia in the female. Treatment with 2% topical minoxidil solution. *Archives of dermatology*. 1994;130(3):303-7.

82. Jacobs JP, Szpunar CA, Warner ML. Use of topical minoxidil therapy for androgenetic alopecia in women. *International journal of dermatology*. 1993;32(10):758-62.
83. Lucky AW, Piacquadio DJ, Ditre CM, Dunlap F, Kantor I, Pandya AG, et al. A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss. *Journal of the American Academy of Dermatology*. 2004;50(4):541-53.
84. Olsen EA. Topical minoxidil in the treatment of androgenetic alopecia in women. *Cutis*. 1991;48(3):243-8.
85. Tsuboi R, Yamazaki M, Matsuda Y, Uchida K, Ueki R, Ogawa H. Antisense oligonucleotide targeting fibroblast growth factor receptor (FGFR)-1 stimulates cellular activity of hair follicles in an in vitro organ culture system. *International Journal of Dermatology*. 2007;46(3):259-63.
86. Vexiau P, Chaspoux C, Boudou P, Fiet J, Jouanique C, Hardy N, et al. Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *British journal of dermatology*, The. 2002;146(6):992-9.
87. Whiting DA, Jacobson C. Treatment of female androgenetic alopecia with minoxidil 2%. *International journal of dermatology*. 1992;31(11):800-4.
88. Sheng Y, Rui W, Xu F, Qi S, Hu R, Miao Y, et al. A randomized controlled clinical study on 2% and 5% topical minoxidil solution in the treatment of female pattern hair loss. *J Clin Dermatol*. 2014;43(10).
89. Bergfeld W, Washenik K, Callender V, Zhang P, Quiza C, Doshi U, et al. A Phase III, Multicenter, Parallel-Design Clinical Trial to Compare the Efficacy and Safety of 5% Minoxidil Foam Versus Vehicle in Women With Female Pattern Hair Loss. *J Drugs Dermatol*. 2016;15(7):874-81.
90. Blume-Peytavi U, Shapiro J, Messenger AG, Hordinsky MK, Zhang P, Quiza C, et al. Efficacy and Safety of Once-Daily Minoxidil Foam 5% Versus Twice-Daily Minoxidil Solution 2% in Female Pattern Hair Loss: A Phase III, Randomized, Investigator-Blinded Study. *J Drugs Dermatol*. 2016;15(7):883-9.
91. Blume-Peytavi U, Hillmann K, Dietz E, Canfield D, Garcia Bartels N. A randomized, single-blind trial of 5% minoxidil foam once daily versus 2% minoxidil solution twice daily in the treatment of androgenetic alopecia in women. *Journal of the American Academy of Dermatology*. 2011;65(6):1126-34.e1.
92. Ryu HJ, Yoo MG, Son SW. The efficacy of 3% minoxidil vs. combined 3% minoxidil and Korean red ginseng in treating female pattern alopecia. *International Journal of Dermatology*. 2014;53(6):e340-2.
93. Trüeb R, Gadzhigoroeva AG, Kubanov AA, Tsimbalenko TV, Chistiakova T, Kondrakhina IN, et al. Superiority of combination treatment over monotherapy for female alopecia. 8th World Congress for Hair Research; Jeju Island, South Korea 2014.
94. Tsuboi R, Tanaka T, Nishikawa T, Ueki R, Yamada H, Katsuoka K, et al. A randomized, placebo-controlled trial of 1% topical minoxidil solution in the treatment of androgenetic alopecia in Japanese women. *European journal of dermatology EJD*. 2007;17(1):37-44.
95. Kapadia N, Borhany T, Khalid G, Fatima A. Systemic cyproterone acetate and 5% minoxidil topical in the treatment of female pattern hair loss. *Journal of Pakistan Association of Dermatologists*. 2009;19(4):216-9.
96. Yoshitake T, Takeda A, Ohki K, Inoue Y, Yamawaki T, Otsuka S, et al. Five-year efficacy of finasteride in 801 Japanese men with androgenetic alopecia. *J Dermatol*. 2015;42:735-38.

97. Brenner S, Matz H. Improvement in androgenetic alopecia in 53-76-year-old men using oral finasteride. *International journal of dermatology*. 1999;38(12):928-30.
98. Kaufman KD, Olsen EA, Whiting D, Savin R, DeVillez R, Bergfeld W, et al. Finasteride in the treatment of men with androgenetic alopecia. Finasteride Male Pattern Hair Loss Study Group. *Journal of the American Academy of Dermatology*. 1998;39(4 Pt 1):578-89.
99. Kawashima M, Hayashi N, Igarashi A, Kitahara H, Maeguchi M, Mizuno A, et al. Finasteride in the treatment of Japanese men with male pattern hair loss. *European journal of dermatology EJD*. 2004;14(4):247-54.
100. Olsen EA, Hordinsky M, Whiting D, Stough D, Hobbs S, Ellis ML, et al. The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride. *Journal of the American Academy of Dermatology*. 2006;55(6):1014-23.
101. Price VH, Menefee E, Sanchez M, Ruane P, Kaufman KD. Changes in hair weight and hair count in men with androgenetic alopecia after treatment with finasteride, 1 mg, daily. *Journal of the American Academy of Dermatology*. 2002;46(4):517-23.
102. Price VH, Menefee E, Sanchez M, Kaufman KD. Changes in hair weight in men with androgenetic alopecia after treatment with finasteride (1 mg daily): three- and 4-year results. *Journal of the American Academy of Dermatology*. 2006;55(1):71-4.
103. Roberts JL, Fiedler V, Imperato-McGinley J, Whiting D, Olsen E, Shupack J, et al. Clinical dose ranging studies with finasteride, a type 2 5alpha-reductase inhibitor, in men with male pattern hair loss. *Journal of the American Academy of Dermatology*. 1999;41(4):555-63.
104. Stough DB, Rao NA, Kaufman KD, Mitchell C. Finasteride improves male pattern hair loss in a randomized study in identical twins. *European journal of dermatology EJD*. 2002;12(1):32-7.
105. Trueb RM, Itin P. Fotografische Dokumentation der Wirksamkeit von 1 mg oralem Finasterid in der Behandlung der androgenetischen Alopezie des Mannes im Praxisalltag in der Schweiz. *Schweizerische Rundschau fur Medizin Praxis Revue suisse de medecine Praxis*. 2001;90(48):2087-93.
106. Van-Neste D, Fuh V, Sanchez-Pedreno P, Lopez-Bran E, Wolff H, Whiting D, et al. Finasteride increases anagen hair in men with androgenetic alopecia. *British journal of dermatology, The*. 2000;143(4):804-10.
107. Leyden J, Dunlap F, Miller B, Winters P, Lebwohl M, Hecker D, et al. Finasteride in the treatment of men with frontal male pattern hair loss. *Journal of the American Academy of Dermatology*. 1999;40(6 Pt 1):930-7.
108. Whiting DA, Waldstreicher J, Sanchez M, Kaufman KD. Measuring reversal of hair miniaturization in androgenetic alopecia by follicular counts in horizontal sections of serial scalp biopsies: results of finasteride 1 mg treatment of men and postmenopausal women. *Journal of investigative dermatology, The Symposium proceedings the Society for Investigative Dermatology, Inc [and] European Society for Dermatological Research*. 1999;4(3):282-4.
109. Whiting DA, Olsen EA, Savin R, Halper L, Rodgers A, Wang L, et al. Efficacy and tolerability of finasteride 1 mg in men aged 41 to 60 years with male pattern hair loss. *European journal of dermatology EJD*. 2003;13(2):150-60.
110. Leavitt M, Perez-Meza D, Rao NA, Barusco M, Kaufman KD, Ziering C. Effects of finasteride (1 mg) on hair transplant. *Dermatologic surgery official publication for American Society for Dermatologic Surgery [et al]*. 2005;31(10):1268-76.

111. Kaufman KD. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. *European Journal of Dermatology*. 2002;12(1):38-49.
112. Sato A, Takeda A. Evaluation of efficacy and safety of finasteride 1 mg in 3177 Japanese men with androgenetic alopecia. *Journal of Dermatology*. 2012;39(1):27-32.
113. Rossi A, Cantisani C, Scarno M, Trucchia A, Fortuna MC, Calvieri S. Finasteride, 1 mg daily administration on male androgenetic alopecia in different age groups: 10-year follow-up. *Dermatologic Therapy*. 2011;24(4):455-61.
114. Hajheydari Z, Akbari J, Saeedi M, Shokoohi L. Comparing the therapeutic effects of finasteride gel and tablet in treatment of the androgenetic alopecia. *Indian Journal of Dermatology, Venereology and Leprology*. 2009;75(1):47-51.
115. Yeon JH, Jung JY, Choi JW, Kim BJ, Youn SW, Park KC, et al. 5 mg/day finasteride treatment for normoandrogenic Asian women with female pattern hair loss. *Journal of the European Academy of Dermatology and Venereology*. 2011;25(2):211-4.
116. Oliveira-Soares R, E Silva JM, Correia MP, Andre MC. Finasteride 5 mg/day Treatment of Patterned Hair Loss in Normo-androgenetic Postmenopausal Women. *International Journal of Trichology*. 2013;5(1):22-5.
117. Gubelin Harcha W, Barboza Martinez J, Tsai T-F, Katsuoka K, Kawashima M, Tsuboi R, et al. A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with androgenetic alopecia. *Journal of the American Academy of Dermatology*. 2014;70(3):489-98.e3.
118. Rossi A, Mari E, Scarno M, Garelli V, Maxia C, Scali E, et al. Comparative effectiveness of finasteride vs serenoa repens in male androgenetic alopecia: A two-year study. *International Journal of Immunopathology and Pharmacology*. 2012;25(4):1167-73.
119. Stough D. Dutasteride improves male pattern hair loss in a randomized study in identical twins. *Journal of cosmetic dermatology*. 2007;6(1):9-13.
120. Jung JY, Yeon JH, Choi JW, Kwon SH, Kim BJ, Youn SW, et al. Effect of dutasteride 0.5 mg/d in men with androgenetic alopecia recalcitrant to finasteride. *International Journal of Dermatology*. 2014;53(11):1351-7.
121. Eun HC, Kwon OS, Yeon JH, Shin HS, Kim BY, Ro BI, et al. Efficacy, safety, and tolerability of dutasteride 0.5 mg once daily in male patients with male pattern hair loss: A randomized, double-blind, placebo-controlled, phase III study. *Journal of the American Academy of Dermatology*. 2010;63(2):252-8.
122. Price VH, Roberts JL, Hordinsky M, Olsen EA, Savin R, Bergfeld W, et al. Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. *Journal of the American Academy of Dermatology*. 2000;43(5 Pt 1):768-76.
123. Tosti A, Piraccini BM, Soli M. Evaluation of sexual function in subjects taking finasteride for the treatment of androgenetic alopecia. *J Eur Acad Dermatol Venereol*. 2001;15(5):418-21.
124. Mella JM, Perret MC, Manzotti M, Catalano HN, Guyatt G. Efficacy and safety of finasteride therapy for androgenetic alopecia: a systematic review. *Arch Dermatol*. 2010;146(10):1141-50.
125. Belknap SM, Aslam I, Kiguradze T, Temps WH, Yarnold PR, Cashy J, et al. Adverse Event Reporting in Clinical Trials of Finasteride for Androgenic Alopecia: A Meta-analysis. *JAMA Dermatol*. 2015;151(6):600-6.

126. Altomare G, Capella GL. Depression circumstantially related to the administration of finasteride for androgenetic alopecia. *J Dermatol*. 2002;29(10):665-9.
127. Rahimi-Ardabili B, Pourandarjani R, Habibollahi P, Mualeki A. Finasteride induced depression: a prospective study. *BMC Clin Pharmacol*. 2006;6:7.
128. Dušková M, Hill M, Stárka L. The influence of low dose finasteride, a type II 5 α -reductase inhibitor, on circulating neuroactive steroids. *Horm Mol Biol Clin Investig*. 2010;1(2):95-102.
129. Schüle C, Nothdurfter C, Rupprecht R. The role of allopregnanolone in depression and anxiety. *Prog Neurobiol*. 2014;113:79-87.
130. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349(3):215-24.
131. Thompson IM, Goodman PJ, Tangen CM, Parnes HL, Minasian LM, Godley PA, et al. Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med*. 2013;369(7):603-10.
132. Kjellman A, Friis S, Granath F, Gustafsson O, Sørensen HT, Akre O. Treatment with finasteride and prostate cancer survival. *Scand J Urol*. 2013;47(4):265-71.
133. Azoulay L, Eberg M, Benayoun S, Pollak M. 5 α -Reductase Inhibitors and the Risk of Cancer-Related Mortality in Men With Prostate Cancer. *JAMA Oncol*. 2015;1(3):314-20.
134. Bird ST, Brophy JM, Hartzema AG, Delaney JA, Etminan M. Male breast cancer and 5 α -reductase inhibitors finasteride and dutasteride. *J Urol*. 2013;190(5):1811-4.
135. Duijnhoven RG, Straus SM, Souverein PC, de Boer A, Bosch JL, Hoes AW, et al. Long-term use of 5 α -reductase inhibitors and the risk of male breast cancer. *Cancer Causes Control*. 2014;25(11):1577-82.
136. Tangen CM, Goodman PJ, Thompson IM. Survival in the prostate cancer prevention trial. *N Engl J Med*. 2013;369(20):1968.
137. Amory JK, Wang C, Swerdloff RS, Anawalt BD, Matsumoto AM, Bremner WJ, et al. The effect of 5 α -reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men. *J Clin Endocrinol Metab*. 2007;92(5):1659-65.
138. Overstreet JW, Fuh VL, Gould J, Howards SS, Lieber MM, Hellstrom W, et al. Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men. *J Urol*. 1999;162(4):1295-300.
139. Chiba K, Yamaguchi K, Li F, Ando M, Fujisawa M. Finasteride-associated male infertility. *Fertil Steril*. 2011;95(5):1786.e9-11.
140. Tu HY, Zini A. Finasteride-induced secondary infertility associated with sperm DNA damage. *Fertil Steril*. 2011;95(6):2125.e13-4.
141. Collodel G, Scapigliati G, Moretti E. Spermatozoa and chronic treatment with finasteride: a TEM and FISH study. *Arch Androl*. 2007;53(4):229-33.
142. Liu KE, Binsaleh S, Lo KC, Jarvi K. Propecia-induced spermatogenic failure: a report of two cases. *Fertil Steril*. 2008;90(3):849.e17-9.
143. Samplaski MK, Lo K, Grober E, Jarvi K. Finasteride use in the male infertility population: effects on semen and hormone parameters. *Fertil Steril*. 2013;100(6):1542-6.
144. Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. *J Sex Med*. 2011;8(6):1747-53.

145. Irwig MS. Depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects. *J Clin Psychiatry*. 2012;73(9):1220-3.
146. Irwig MS. Persistent sexual side effects of finasteride: could they be permanent? *J Sex Med*. 2012;9(11):2927-32.
147. Ganzer CA, Jacobs AR, Iqbal F. Persistent sexual, emotional, and cognitive impairment post-finasteride: a survey of men reporting symptoms. *Am J Mens Health*. 2015;9(3):222-8.
148. Chiriaco G, Cauci S, Mazzon G, Trombetta C. An observational retrospective evaluation of 79 young men with long-term adverse effects after use of finasteride against androgenetic alopecia. *Andrology*. 2016;4(2):245-50.
149. Traish AM, Hassani J, Guay AT, Zitzmann M, Hansen ML. Adverse side effects of 5 α -reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. *J Sex Med*. 2011;8(3):872-84.
150. Mondaini N, Gontero P, Giubilei G, Lombardi G, Cai T, Gavazzi A, et al. Finasteride 5 mg and sexual side effects: how many of these are related to a placebo phenomenon? *J Sex Med*. 2007;4(6):1708-12.
151. Giatti S, Foglio B, Romano S, Pesaresi M, Panzica G, Garcia-Segura LM, et al. Effects of Subchronic Finasteride Treatment and Withdrawal on Neuroactive Steroid Levels and their Receptors in the Male Rat Brain. *Neuroendocrinology*. 2015.
152. Caruso D, Abbiati F, Giatti S, Romano S, Fusco L, Cavaletti G, et al. Patients treated for male pattern hair with finasteride show, after discontinuation of the drug, altered levels of neuroactive steroids in cerebrospinal fluid and plasma. *J Steroid Biochem Mol Biol*. 2015;146:74-9.
153. Di Loreto C, La Marra F, Mazzon G, Belgrano E, Trombetta C, Cauci S. Immunohistochemical evaluation of androgen receptor and nerve structure density in human prepuce from patients with persistent sexual side effects after finasteride use for androgenetic alopecia. *PLoS One*. 2014;9(6):e100237.
154. Ganzer CA, Jacobs AR. Emotional Consequences of Finasteride: Fool's Gold. *Am J Mens Health*. 2016.
155. Diani AR, Mulholland MJ, Shull KL, Kubicek MF, Johnson GA, Schostarez HJ, et al. Hair growth effects of oral administration of finasteride, a steroid 5 alpha-reductase inhibitor, alone and in combination with topical minoxidil in the balding stump-tail macaque. *The Journal of clinical endocrinology and metabolism*. 1992;74(2):345-50.
156. Sovak M, Seligson AL, Kucerova R, Bienova M, Hajduch M, Bucek M. Fluridil, a rationally designed topical agent for androgenetic alopecia: first clinical experience. *Dermatologic surgery official publication for American Society for Dermatologic Surgery [et al]*. 2002;28(8):678-85.
157. Orfanos CE, Vogels L. Lokalthherapie der Alopecia androgenetica mit 17 alpha-Oestradiol. Eine kontrollierte, randomisierte Doppelblindstudie. *Dermatologica*. 1980;161(2):124-32.
158. Wustner H, Orfanos CE. [Alopecia androgenetica and its local treatment with estrogen- and corticosteroid externa]. *Z Hautkr*. 1974;49(20):879-88.
159. Wozel G, Narayanan S, Jackel A, Lutz GA. Alfatradiol (0.025%) - An effective and safe therapy for the treatment of androgenetic alopecia in women and men. *Aktuelle Dermatologie*. 2005;31(12):553-60.
160. Peereboom-Wynia JD, van-der-Willigen AH, van-Joost T, Stolz E. The effect of cyproterone acetate on hair roots and hair shaft diameter in androgenetic alopecia in females. *Acta dermato venereologica*. 1989;69(5):395-8.

161. Paradisi R, Porcu E, Fabbri R, Seracchioli R, Battaglia C, Venturoli S. Prospective cohort study on the effects and tolerability of flutamide in patients with female pattern hair loss. [Spanish] Un estudio de cohorte prospectivo sobre los efectos y la tolerabilidad de flutamida en pacientes con perdida de pelo de patron femenino. *Annals of Pharmacotherapy*. 2011;45(4):469-75.
162. Georgala S, Katoulis AC, Georgala C, Moussatou V, Bozi E, Stavrianeas NG. Topical estrogen therapy for androgenetic alopecia in menopausal females. *Dermatology Basel, Switzerland*. 2004;208(2):178-9.
163. Kim J-H, Lee SY, Lee H-J, Yoon N-Y, Lee W-S. The Efficacy and Safety of 17alpha-Estradiol (EII-Cranell alpha 0.025%) Solution on Female Pattern Hair Loss: Single Center, Open-Label, Non-Comparative, Phase IV Study. *Annals of Dermatology*. 2012;24(3):295-305.
164. Uebel CO, da-Silva JB, Cantarelli D, Martins P. The role of platelet plasma growth factors in male pattern baldness surgery. *Plastic and reconstructive surgery*. 2006;118(6):1458-66.
165. Bernstein RM, Rassman WR. Dissecting microscope versus magnifying loupes with transillumination in the preparation of follicular unit grafts. A bilateral controlled study. *Dermatologic surgery official publication for American Society for Dermatologic Surgery [et al]*. 1998;24(8):875-80.
166. Rinaldi F, Giuliani G. The anti-apoptotic activity of Psittacofulvin in transplanted hair bulbs. [Italian]. *Journal of Plastic Dermatology*. 2010;6(3):221-4.
167. Sethi P, Bansal A. Direct hair transplantation: a modified follicular unit extraction technique. *Journal of Cutaneous & Aesthetic Surgery*. 2013;6(2):100-5.
168. Li ZJ, Choi HI, Choi DK, Sohn KC, Im M, Seo YJ, et al. Autologous platelet-rich plasma: a potential therapeutic tool for promoting hair growth. *Dermatol Surg*. 2012;38(7 Pt 1):1040-6.
169. Lee SH, Zheng Z, Kang JS, Kim DY, Oh SH, Cho SB. Therapeutic efficacy of autologous platelet-rich plasma and polydeoxyribonucleotide on female pattern hair loss. *Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society*. 2015;23(1):30-6.
170. Schiavone G, Raskovic D, Greco J, Abeni D. Platelet-rich plasma for androgenetic alopecia: a pilot study. *Dermatologic Surgery*. 2014;40(9):1010-9.
171. Gkini MA, Kouskoukis AE, Tripsianis G, Rigopoulos D, Kouskoukis K. Study of platelet-rich plasma injections in the treatment of androgenetic alopecia through an one-year period. *Journal of cutaneous and aesthetic surgery*. 2014;7(4):213-9.
172. Leavitt M, Charles G, Heyman E, Michaels D. HairMax LaserComb laser phototherapy device in the treatment of male androgenetic alopecia: A randomized, double-blind, sham device-controlled, multicentre trial. *Clinical Drug Investigation*. 2009;29(5):283-92.
173. Satino JL, Markou M. Hair regrowth and increased hair tensile strength using the HairMax LaserComb for low-level laser therapy. *International Journal of Cosmetic Surgery and Aesthetic Dermatology*. 2003;5(2):113-7.
174. Lanzafame RJ, Blanche RR, Bodian AB, Chiacchierini RP, Fernandez-Obregon A, Kazmirek ER. The growth of human scalp hair mediated by visible red light laser and LED sources in males. *Lasers in Surgery and Medicine*. 2013;45(8):487-95.
175. Prager N, Bickett K, French N, Marcovici G. A randomized, double-blind, placebo-controlled trial to determine the effectiveness of botanically derived inhibitors of 5-alpha-reductase in the treatment of androgenetic alopecia. *Journal of alternative and complementary medicine New York, N Y*. 2002;8(2):143-52.

176. Lassus A, Santalahti J, Sellmann M. Combined topical external and oral administration of marine polysaccharide derivatives in the treatment of hereditary androgenetic alopecia in adults. *Nouvelles Dermatologiques*. 1994;13(5):254-5.
177. Moers-Carpi M. Influence of nutritive factors on hair growth. [German] Nutritive Beeinflussung des Haarwachstums. *Aktuelle Dermatologie*. 2011;37(5):171-5.
178. Kamimura A, Takahashi T, Watanabe Y. Investigation of topical application of procyanidin B-2 from apple to identify its potential use as a hair growing agent. *Phytomedicine : international journal of phytotherapy and phytopharmacology*. 2000;7(6):529-36.
179. Kessels AG, Cardynaals RL, Borger RL, Go MJ, Lambers JC, Knottnerus JA, et al. The effectiveness of the hair-restorer "Dabao" in males with alopecia androgenetica. A clinical experiment. *Journal of clinical epidemiology*. 1991;44(4-5):439-47.
180. Greenberg JH, Katz M. Treatment of androgenetic alopecia with a 7.5% herbal preparation. *Journal of Dermatological Treatment*. 1996;7(3):159-62.
181. Olsen EA, DeLong E. Transdermal viprostol in the treatment of male pattern baldness. *Journal of the American Academy of Dermatology*. 1990;23(3 Pt 1):470-2.
182. Groveman HD, Ganiats T, Klauber MR. Lack of efficacy of polysorbate 60 in the treatment of male pattern baldness. *Archives of internal medicine*. 1985;145(8):1454-8.
183. Freund BJ, Schwartz M. Treatment of male pattern baldness with botulinum toxin: a pilot study. *Plastic and reconstructive surgery*. 2010;126(5):246e-8e.
184. Ito T, Fukamizu H, Ito N, Seo N, Yagi H, Takigawa M, et al. Roxithromycin antagonizes catagen induction in murine and human hair follicles: Implication of topical roxithromycin as hair restoration reagent. *Archives of Dermatological Research*. 2009;301(5):347-55.
185. Fischer TW, Trueb RM, Hanggi G, Innocenti M, Elsner P. Topical melatonin for treatment of androgenetic alopecia. *International Journal of Trichology*. 2012;4(4):236-45.
186. Draelos ZD, Jacobson EL, Kim H, Kim M, Jacobson MK. A pilot study evaluating the efficacy of topically applied niacin derivatives for treatment of female pattern alopecia. *Journal of cosmetic dermatology*. 2005;4(4):258-61.
187. Gehring W, Gloor M. Use of the phototrichogram to assess the stimulation of hair growth - An in vitro study of women with androgenetic alopecia. *H+G Zeitschrift fur Hautkrankheiten*. 2000;75(7-8):419-23.
188. Oura H, Iino M, Nakazawa Y, Tajima M, Ideta R, Nakaya Y, et al. Adenosine increases anagen hair growth and thick hairs in Japanese women with female pattern hair loss: a pilot, double-blind, randomized, placebo-controlled trial. *Journal of Dermatology*. 2008;35(12):763-7.
189. Baek JH, Lee SY, Yoo M, Park WS, Lee SJ, Boo YC, et al. Effects of a new mild shampoo for preventing hair loss in Asian by a simple hand-held phototrichogram technique. *International Journal of Cosmetic Science*. 2011;33(6):491-6.
190. Le Floch C, Cheniti A, Connétable S, Piccardi N, Vincenzi C, Tosti A. Effect of a nutritional supplement on hair loss in women. *J Cosmet Dermatol*. 2015;14:76-82.
191. Loing E, Lachance R, Ollier V, Hocquaux M. A new strategy to modulate alopecia using a combination of two specific and unique ingredients. *Journal of cosmetic science*. 2013;64(1):45-58.
192. Jo SJ, Shin HS, Park YW, Paik SH, Park WS, Jeong YS, et al. Topical valproic acid increases the hair count in male patients with androgenetic alopecia: A

- randomized, comparative, clinical feasibility study using phototrichogram analysis. *J Dermatol.* 2014;41:285-91.
193. Morganti P, Fabrizi G, James B, Bruno C. Effect of gelatin-cystine and serenoa repens extract on free radicals level and hair growth. *Journal of Applied Cosmetology.* 1998;16(3):57-64.
194. Lassus A, Eskelinen E. A comparative study of a new food supplement, ViviScal, with fish extract for the treatment of hereditary androgenic alopecia in young males. *Journal of international medical research, The.* 1992;20(6):445-53.
195. Trost LB, Bergfeld WF, Calogeras E. The diagnosis and treatment of iron deficiency and its potential relationship to hair loss. *J Am Acad Dermatol.* 2006;54(5):824-44.
196. Fischer TW, Trueb RM, Hanggi G, Innocenti M, Elsner P. Topical melatonin for treatment of androgenetic alopecia. *Int J Trichology.* 2012;4(4):236-45.
197. Gilhar A, Pillar T, Etzioni A. Topical cyclosporine in male pattern alopecia. *Journal of the American Academy of Dermatology.* 1990;22(2 Pt 1):251-3.
198. Otberg N, Patzelt A, Rasulev U, Hagemester T, Linscheid M, Sinkgraven R, et al. The role of hair follicles in the percutaneous absorption of caffeine. *Br J Clin Pharmacol.* 2008;65(4):488-92.
199. Fischer TW, Herczeg-Lisztes E, Funk W, Zillikens D, Biro T, Paus R. Differential effects of caffeine on hair shaft elongation, matrix and outer root sheath keratinocyte proliferation, and transforming growth factor-beta2/insulin-like growth factor-1-mediated regulation of the hair cycle in male and female human hair follicles in vitro. *Br J Dermatol.* 2014;171(5):1031-43.
200. Bussoletti C, Mastropietro F, Tolaini MV, Celleno L. Use of a cosmetic caffeine lotion in the treatment of male androgenetic alopecia. *Journal of Applied Cosmetology.* 2011;29:167-80.
201. Bussoletti C, Mastropietro F, Tolaini MV, Celleno L. Use of a caffeine shampoo for the treatment of male androgenetic alopecia. *Journal of Applied Cosmetology.* 2010;28:153-62.
202. Sisto T, Bussoletti C, Celleno L. Efficacy of a cosmetic caffeine shampoo in androgenetic alopecia management. *Il Note. Journal of Applied Cosmetology.* 2013;31(1):57-66.
203. Pazoki-Toroudi H, Mobasher Moghadam R, Ajami M, Nassiri-Kashani M, Ehsani A, Tabatabaie H, et al. The efficacy and safety of minoxidil 5% combination with azelaic acid 1/5% and caffeine 1% solution on male pattern hair loss. *Journal of Investigative Dermatology.* 2013;133:S84.
204. Golpour M, Rabbani H, Farzin D, Azizi F. Comparing the effectiveness of local solution of minoxidil and caffeine 2.5% with local solution of minoxidil 2.5% in treatment of androgenetic alopecia. [Persian]. *Journal of Mazandaran University of Medical Sciences.* 2013;23(106):29-36.
205. Dressler C, Blumeyer A, Rosumeck S, Arayeh A, Nast A. Wirksamkeit von topischem Koffein bei androgenetischer Alopezie des Mannes. *JDDG - Journal of the German Society of Dermatology.* 2017.
206. Bureau JP, Ginouves P, Guilbaud J, Roux ME. Essential oils and low-intensity electromagnetic pulses in the treatment of androgen-dependent alopecia. *Advances in therapy.* 2003;20(4):220-9.
207. Maddin WS, Bell PW, James JH. The biological effects of a pulsed electrostatic field with specific reference to hair. *Electrotrichogenesis. International journal of dermatology.* 1990;29(6):446-50.

208. Maddin WS, Amara I, Sollecito WA. Electrotrichogenesis: further evidence of efficacy and safety on extended use. *International journal of dermatology*. 1992;31(12):878-80.
209. Policarpi F, Giorgini S, Farella V, Melli MC, Campolmi P, Panconesi E. Effects of application of a pulsed electrostatic field in male and female androgenic alopecia. *Annali Italiani di Dermatologia Clinica e Sperimentale*. 1993;47(3):227-32.

Figure 1. Flow Diagram of the search and selection process

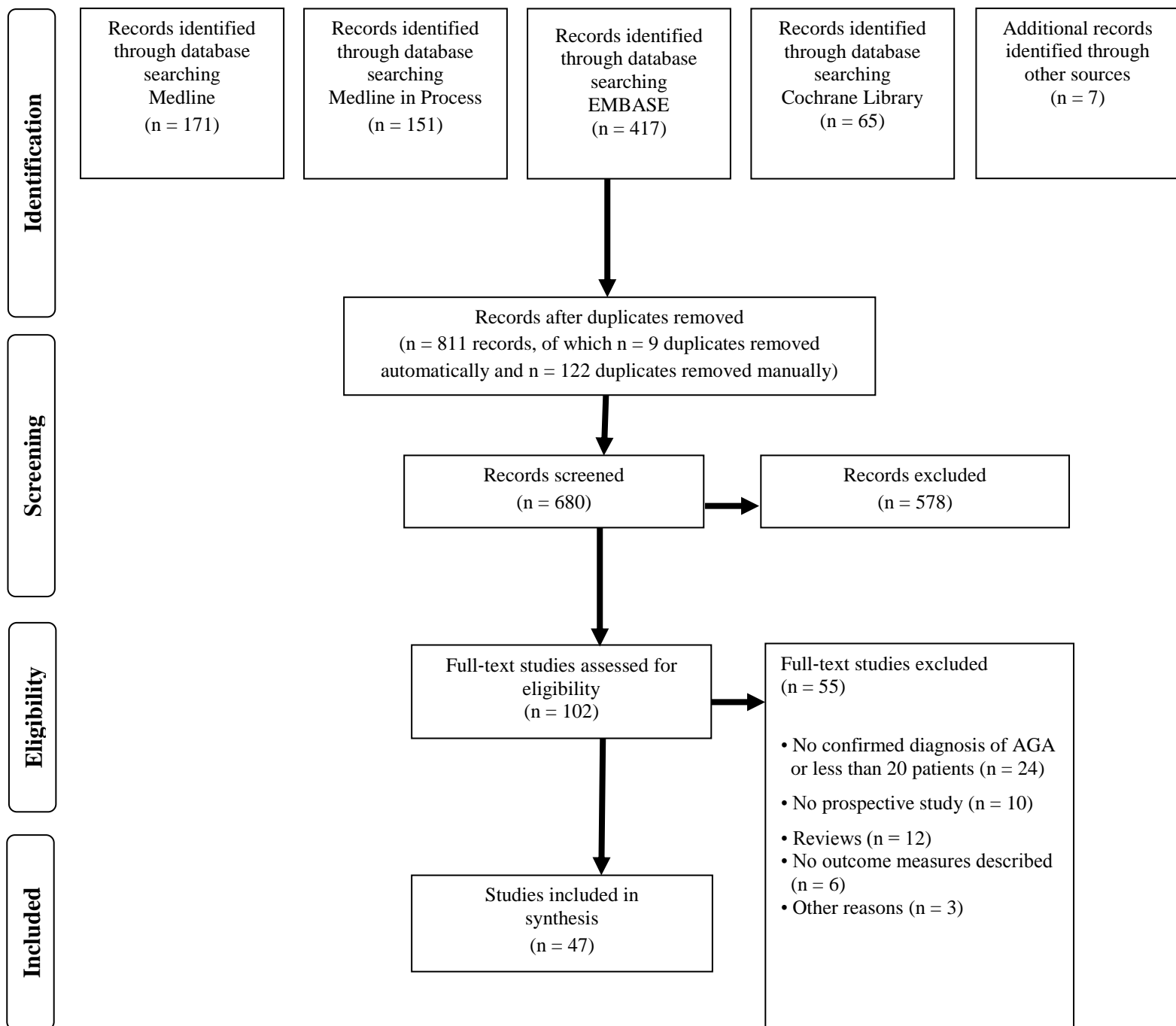


Table 1: Summary Table

Therapy	Level of evidence	Efficacy to prevent progression	Efficacy to improve	Safety	Practicality (patient)	Practicality (physician)
Male patients						
Finasteride 1 mg QD	1	+++	++	+++	++++	++
Dutasteride 0,5 mg QD	1	+++	+++	++	++++	++
Minoxidil 5 % BID (solution, foam)	1	+++	++	++++	+ / ++	+++
Hair transplantation with/without combination treatment	2	-	+++	++	+ intervention +++ long-term	+
LLLT	2	+ / -	+ / -	++	+++	+++
PRP	3	+ / -	+ / -	+	+ / -	+
Female patients						
Minoxidil 2 % BID solution Minoxidil 5% QD foam	1	+++	++	++++	+	+++
Hormones oral in hyperandrogenism	3	+	+	+	+++	++
Hormones oral in normal hormones	3	+ / -	+ / -	+	+++	++
Hair transplantation	4	-	++	++	+ intervention +++ long-term	+
LLLT	2	+ / -	+ / -	++	+++	+++
PRP	3	+ / -	+ / -	+	+ / -	+

Global consideration: **poor** ← —————→ **good**
 - +/- + ++ +++ ++++

LLLT: Low Level Laser therapy
 PRP: Platelet-rich plasma

Table 2 Miscellaneous agents, products and interventions, grouped according to their assumed main mechanism of action

	Claimed mechanism of action	Active	Level of evidence	Studies included (n)	Grade of evidence	Mode of application	Part of combination product
1	DHT-inhibitory activity	β -sitosterol	3	1	B	oral	yes
		biochanin A	3	1	B	topical	no
		polysorbate 60	2	1	A2	topical	no
			3	1	B, B	oral	yes, no
		serenoa repens	3	1	B	topical	yes
		curcuma aeruginosa	2	1	A2	topical	yes, no
		biochanin A	3	1	B	topical	no
2	Anti-inflammatory activity	ketoconazol	3	1	B	topical	yes
		roxithromycin	3	1	B	topical	no
		zinc pyrithione	2	2	B, A2	topical	yes, no
3	Improved perifollicular vascularisation	glyceroloxiesters and silicium	3	1	B	topical	yes
		niacin derivates	2	2	A2	topical	yes
		prostaglandines (viprostol, latanoprost)	2	1	A2	topical	no
4	Improved hair folliclenutrition	aminoacids (cysteine, histidine)	3	1	B	topical	yes
			3	1	B	topical	yes
		vitamins (biotin, niacin)	3	2	B	oral	yes
		trace elements (zinc, copper)	3	1	B	oral	yes
5	Not precicely reported or unknown mechanism of action	adenosine	3	1	B	topical	no
			3	1	B	oral	yes
		biotin	2	1	A2	topical	
		hibiscus	3	1	B	topical	Yes
		marine extract and silicea component	2	1	A2	oral	no
		melatonin	4	1	C	topical	no
		millet seed	3	1	B	oral	yes
		niacin derivates	2	2	A2	topical	yes
		proanthocyanidines	3	1	B	topical	no
		red ginseng	4	1	C	topical	yes
		tretinoin	2	2	B, A2	topical	yes, no
		red ginseng	4	1	C	topical	yes
		valproic acid	2	1	A2	topical	no
Interventions							
	Not precicely reported or unknown mechanism of action	botulinum toxin	4	1	C	scalp injections	no
		electromagnetic/-static field	1	4	A2, A2, B, B	device	yes, no

Additional reported actives without clinical studies included in the guideline comprise: aloe, aminexil, bergamot, caffeine, ciclosporin, cimicifuga racemosa, ginkgo, mesotherapy, sophora.

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count (µg/cm ² , anagen/totalogen ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence	
Minoxidil male patients																
32	Roenigk	1987	777	male	6m	Arm1: minoxidil 2.8%, 2x/d, topical						46.6%		unclear	C	
33	Olsen	1987	127	male	132w	Arm1: minoxidil 3% solution, 2x/d, topical	64.4	65.7						vertex	B	
						Arm2: 24m minoxidil 3% solution, 2x/d, topical, 25-33m minoxidil 3% solution, 1x/d, topical	44.1	46.1								
34	Montagnani	1990	33	male	24w	Arm1: Minoxidil 2% solution, 2x/d, topical						37.5%		unclear	C	
35	Olsen	1990	31	male	3y	Arm1: minoxidil 3% solution, 2x/d, topical		4.4						vertex	B	
						Arm2: 1 st y minoxidil 3% solution, 2x/d, topical, 2 nd -3 rd y, 1x/d, 4 th -5 th y 2x/d		-13.4								
36	Karam	1993	195	male	48w	Arm1: minoxidil 2% solution, 2x/d, topical	44.7 (82.1%) p < 0.001 vs. Baseline	47.8 (119.7%) p < 0.0001 vs. Baseline						vertex	C	
6	Tsuboi	2009	300	male	24w	Arm1: minoxidil 1% solution, 2x/d, topical	16w: 17.2 (7.5%) p<0.001 vs. Baseline	16w: 21.2 (16.2%) p<0.001 vs. Baseline					16w: improved 77.4%	16w: improved 61.6%	vertex	A2
						Arm2: minoxidil 5% solution, 2x/d, topical	16w: 22.3 (9.8%) p<0.001 vs. Baseline	16w: 26.4 (20.4%) p<0.001 vs. Baseline					16w: improved 81.1%	16w: improved 67.1%		
37	Kanti	2015	45	male	104w	Arm1: 104w: Minoxidil 5% foam, 2x/d, topical		w104 frontal: 10.8 (5.5%), vertex: 7.1 (3.5%)		w104 frontal: 0.30 (2.5%), vertex: 0.24 (1.9%)			w104: frontal: 35% vertex: 29%	w104: 47%	frontal and vertex	C
						Arm2: 24 w: Placebo foam 2x/d, topical, w25-104: Minoxidil 5% foam, 2x/d, topical		w104 frontal: -13.1 (-6.3%), vertex: -5.8 (-2.8%)		w104 frontal: -0.58 (-4.4%), vertex: -0.37 (-2.8%)			w104: frontal: 8% vertex: 33%	w104: 63%		
Minoxidil female patients																
38	Yang	2014	264	female	26w	Arm1: minoxidil 2% solution, 2x/d, topical							w26: 53.44% improvement ratio	midline	D	

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total hairs/cm ²) (%)	mean change from baseline hair count (non-vertex)	mean change from baseline hair count (vertex, vertex, andagenitolepigen ratio)	mean change from baseline hair weight/thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
	Shi				Arm2: Minoxidil 5% solution, 1x/d, topical	global photograph						w26: 64.46% improvement ratio			
Minoxidil female and male patients															
	Pracchini	2011	75	male and female	6m	1Arm: minoxidil 5% solution, 2x/d, topical	global photograph	females m6: 45.2 (21.4%) males m6: 18.9 (9.4%)				females m6: 78.13% improved 21.87% unchanged males m6: 72.7% improved 27.3% unchanged	females and males m6: 100% at least mild improvement	frontal and vertex	C
Minoxidil vs. Placebo male patients															
	Olsen	2007	352	male	16w	Arm1: minoxidil 5% foam, 2x/d, topical Arm2: placebo foam, 2x/d, topical	phototrichogram		20.9 (13.4%) p < 0.0001 vs. Baseline			improved: 38.3% unchanged: 52.2% p < 0.0001 vs. Placebo		vertex	A2
	Callifano	1991	132	male	24w	Arm1: minoxidil 2% solution, 2x/d, topical Arm2: placebo solution, 2x/d, topical	manual hair count	18.8 (47.6%)	17.3 (59.4%)					vertex	A2
	Anderson	1988	154	male	24w	Arm1: minoxidil 2% solution, 2x/d, topical Arm2: placebo, 2x/d, topical	manual hair count	25.4 (40.0%) p = 0.0001 vs. Placebo	25.4 (69.9%) p = 0.002 vs. Placebo					vertex	A2
	Dutree-Maulenberg	1988	151	male	24w	Arm1: minoxidil 2% solution, 2x/d, topical Arm2: placebo, 2x/d, topical	manual hair count	29.9 (35.3%) p = 0.02 vs. Placebo	17.5 (38.0%) p = 0.0003 vs. Placebo					vertex	A2
	Peizold	1988	201	male	24w	Arm1: Minoxidil 2% solution, 2x/d, topical Arm2: placebo, 2x/d, topical	manual hair count	16.1 (39.2%) p = 0.0076 vs. Placebo	10.8 (33.1%) p = 0.0104 vs. Placebo					vertex	A2

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hairs/cm ² (%)	mean change from baseline hair count hairs/cm ² (%)	mean change from baseline hair count (range, number, and genotype/allele ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
Olsen	1986	100	male	6m	Arm1: minoxidil 0.01% solution, 2x/d, topical	manual hair count	16.5 (15.3%)	9.4 (14.2%)						vertex	A2
					Arm2: minoxidil 0.1% solution, 2x/d, topical		18.0 (18.9%)	15.9 (27.1%)							
					Arm3: minoxidil 1% solution, 2x/d, topical		29.2 (27.8%)	35.3 (53.3%)							
					Arm4: minoxidil 2% solution, 2x/d, topical		34.3 (33.1%) significant vs. Arm1-3, 5	37.3 (52.1%)							
					Arm5: placebo, 2x/d, topical		17.6 (17.1%)	15.9 (23.1%)							
Shupack	1987	58	male	6m	Arm1: placebo, 2x/d, topical	phototrichogram		2.9 (14.4%)						vertex	B
					Arm2: minoxidil 0.01% solution, 2x/d, topical			0.3 (1.2%) p > 0.2 vs. Placebo							
					Arm3: minoxidil 0.1% solution, 2x/d, topical			5.1 (16.3%) p < 0.01 vs. Placebo p > 0.1 vs. Arm4/5							
					Arm4: minoxidil 1% solution, 2x/d, topical			7.8 (39.6%) p < 0.01 vs. Placebo p > 0.1 vs. Arm3/5							
					Arm5: minoxidil 2% solution, 2x/d, topical			10.6 (58.2%) p < 0.01 vs. Placebo p > 0.1 vs. Arm3/4							
Olsen	2002	393	male	48w	Arm1: minoxidil 5% solution, 2x/d, topical	phototrichogram		18.6 (12.3%) p < 0.01 vs. Placebo p = 0.025 vs. Arm2			Improved: 57.9%			vertex	A2
					Arm2: minoxidil 2% solution, 2x/d, topical			12.7 (8.8%) p < 0.013 vs. Placebo			unchanged: 30.3%				
					Arm3: placebo, 2x/d, topical			3.9 (2.6%)			improved: 40.8%	unchanged: 48.6%			
Chattle	1987	247	male	24w, 48w	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count		24w: 13.3 (47.2%) p < 0.01 vs. Baseline 48w: 32.0 (78.2%) p = 0.02 vs. Baseline					vertex	A2	
					Arm2: 24w placebo, 2x/d, topical, 25-48w minoxidil 2% solution, 2x/d, topical			24w: 13.3 (42.0%) p < 0.01 vs. Baseline 48w: 31.4 (99.0%)							
Iran					Arm1: minoxidil 2% solution, 2x/d, topical	count	24w: 5.4 (12.1%) 48w: 15.5 (34.6%)	24w: 4.7 (17.2%) 48w: 14.2 (52.4%)							

AN Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hair/c ² cm (%)	mean change from baseline hair count hair/cm (%)	mean change from baseline hair count (anagen, catagen, anagen/catagen ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
47	López	1990	114	male	24w, 48w	Arm2: 24w placebo, 2x/d, topical, 25-48w minoxidil 2% solution, 2x/d, topical	manual hair	24w: 4.7 (10.4%) 48w: 12.2 (27.1%)	24w: 2.9 (10.8%) 48w: 10.5 (39.4%)						vertex	A2

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total hairs/cm ²) (%)	mean change from baseline hair count (nonvulvas) hairs/cm ² (%)	mean change from baseline hair count (ginger, eyelashes, and genitofemoral ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
48	Chavite	1988	428	male	24w, 48w	Arm1: minoxidil 2% solution, 2x/d, topical	24w: 23.8 (54.8%) p = 0.0611 vs. Arm2 48w: 36.1 (83.0%)	24w: 13.3 (48.6%) p = 0.0187 vs. Arm2 48w: 25.0 (91.3%)						vertex	A2
						Arm2: 24w placebo, 2x/d, topical, 25-48w minoxidil 2%, 2x/d, topical	24w: 19.9 (47.5%) 48w: 34.6 (82.7%)	24w: 9.7 (39.6%) 48w: 22.6 (91.8%)							
49	Alarits	1991	240	male	24w, 48w	Arm1: minoxidil 2% solution, 2x/d, topical	24w: 13.7 (25.6%) 48w: 25.5 (47.8%) p = 0.000 (24w, 48w) vs. Baseline							vertex	A2
						Arm2: 24w placebo, 2x/d, topical, 25-48w minoxidil 2% solution, 2x/d, topical	24w: 5.1 (9.3%) 48w: 16.9 (31.0%) p = 0.000 (24w, 48w) vs. Baseline								
50	Pheptkom	1988	72	male	6m	Arm1: minoxidil 2% gel, 2x/d, topical						26% p < 0.05 vs. Arm2		vertex	B
						Arm2: placebo gel, 2x/d, topical					33%				
						Arm3: minoxidil 2% solution, 2x/d, topical					48% p < 0.05 vs. Arm4				
						Arm4: placebo solution, 2x/d, topical					36%				
51	Olisen	1985	153	male	4m, 12m	Arm1: minoxidil 2% solution, 2x/d, topical	4m: 29.6 (53.6%) 12m: 63.5 (114.9%) n.s. vs. Arm3 (4m), n.s. vs. Arm2 (4m, 12m)	4m: 24.7 (100.0%) 12m: 42.8 (173.0%)						vertex	A2
						Arm2: minoxidil 3% solution, 2x/d, topical	4m: 32.6 (52.0%) p = 0.04 vs. Arm3 12m: 66.3 (106.0%)	4m: 27.5 (95.2%) 12m: 53.5 (185.7%)							
						Arm3: 4m placebo, 2x/d, topical, 5-12m minoxidil 3% solution, 2x/d, topical	4m: 22.4 (39.3%) 12m: 61.4 (108.0%)	4m: 11.6 (44.7%) 12m: 42.9 (165.9%)							

AN Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total hairs/cm ²) (%)	mean change from baseline hair count (nonvulvar hairs/cm ²) (%)	mean change from baseline hair count (gingiva, eyelashes, and genital/leg hair ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
52	Savith	1987	96	male	4m, 12m	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	4m: 14.9 p = 0.0076 vs. Baseline p = 0.013 vs. Arm3 12m: 16.4 p < 0.001 vs. Baseline	4m: 11.4 12m: 22.0						vertex	A2
						Arm2: minoxidil 3% solution, 2x/d, topical		4m: 11.9 12m: 28.3 p < 0.001 vs. Baseline	4m: 9.6 12m: 30.9							
						Arm3: 4m placebo, 2x/d, topical, 5-12m minoxidil 3% solution, 2x/d, topical		4m: 9.3 12m: 24.7 p < 0.001 vs. Baseline	4m: 0.8 12m: 33.2							
53	Katz	1987	153	male	4m, 12m	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	4m: 20.4 (216.7%) p = 0.0002 vs. Arm3, p = 0.0464 vs. Arm2 12m: 41.8 (443.8%)							vertex	A2
						Arm2: minoxidil 3% solution, 2x/d, topical		4m: 14.5 (168.2%) p = 0.0833 vs. Arm3 12m: 39.6 (459.1%)								
						Arm3: 4m placebo, 2x/d, topical, 5-24m minoxidil 3% solution, 2x/d, topical		4m: 9.8 (116.3%) 12m: 33.1 (393.0%)								
54	De Villez	1987	64	male	4m, 12m	Arm1: minoxidil 3% solution, 2x/d, topical	phototrichogram	4m: 1.2 p < 0.05 vs. Arm3, n.s. vs. Arm2 12m: 9.4	4m: 1.2 p < 0.05 vs. Arm3 12m: 8.6						vertex	B
						Arm2: minoxidil 2% solution, 2x/d, topical		4m: 1.2 p < 0.05 vs. Arm3 12m: 8.6								
						Arm3: 4m placebo, 2x/d, topical, 5-12m minoxidil 3% solution, 2x/d, topical		4m: -0.2 12m: 4.9								
55	Wang	1988	240	male	24w, 48w	Arm1: minoxidil 2% solution, 2x/d, topical	hair count	24w: 9.9 (27.7%) 48w: 18.2 (50.9%)								

AN Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total hairs/cm ²) (%)	mean change from baseline hair count (non-ovipos) hairs/cm ² (%)	mean change from baseline hair count (anagen, catagen, andagenitrogen ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
		Alc				Arm2: 24w placebo, 2x/d, topical, 25-48w minoxidil 2% solution, 2x/d, topical	manual			24w: 4.8 (12.6%) 48w: 12.3 (32.4%)						
						Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	12m: 46.9 (191.7%) 30m: 22.5 (91.7%) p < 0.001 (4m, 12m) vs. Baseline n.s. vs. Arm2							vertex	A2
	55	Köperski	1987	72	male	12m, 30m		Arm2: minoxidil 3% solution, 2x/d, topical	12m: 36.7 (163.6%) 30m: 26.5 (118.2%) p < 0.001 (4m, 12m) vs. Baseline							
						Arm3: 4m placebo, 2x/d, topical, 5m-30m minoxidil 3% solution, 2x/d, topical		12m: 44.9 (200.0%) 30m: 36.7 (163.6%) p < 0.01 (4m), p < 0.001 (12m) vs. Baseline								

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total hairs/cm ²) (%)	mean change from baseline hair count (nonvulvas) hairs/cm ² (%)	mean change from baseline hair count (ginger, eyelashes, anagen/telegen ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
56	Kreindler	1987	150	male	4m, 12m	Arm1: minoxidil 2% solution, 2x/d, topical	4m: 15.9 (47.4%) 12m: 83.3 (248.5%) p < 0.0001 vs. Baseline	4m: 12.6 (91.4%) p = 0.0018 vs. Placebo 12m: 40.4 (294.3%)						bald area	A2
						Arm2: minoxidil 3% solution, 2x/d, topical	4m: 16.1 (50.9%) 12m: 72.9 (231.1%) p < 0.0001 vs. Baseline	4m: 10.2 (85.3%) p = 0.0167 vs. Placebo 12m: 34.9 (291.8%)							
						Arm3: 4m placebo 2x/d, topical, 5-12m minoxidil 3% solution, 2x/d, topical	4m: 11.0 (37.1%) 12m: 80.4 (271.5%) p < 0.0001 vs. Baseline	4m: 3.1 (23.2%) 12m: 33.1 (244.9%)							
57	Cannars	1990	169	male	24w, 48w	Arm1: minoxidil 2% solution, 2x/d, topical		24w: 7.7 (30.6%) p < 0.05 vs. Placebo 48w: 3.3 (13.1%) p = 0.07 (24-48w)					bald area	A2	
						Arm2: 24w placebo, 2x/d, topical, 25-48w minoxidil 2% solution, 2x/d, topical		24w: 0.4 (1.6%) 48w: 7.8 (34.1%) p < 0.01 (24-48w)							
58	Price	1999	36	male	96w	Arm1: minoxidil 2% solution, 2x/d, topical	25% p = 0.074 vs. Placebo, p = 0.455 vs. Arm2			hair weight 15% p < 0.005 vs. Placebo, p = 0.437 vs. Arm2				frontal/parietal	B
						Arm2: minoxidil 5% solution, 2x/d, topical	30% p = 0.010 vs. Placebo			22% p = 0.000 vs. Placebo					
						Arm3: placebo, 2x/d, topical	9%			-15%					
						Arm4: no treatment	10%			-10%					
59	Hillmann	2014	70	male	24w	Arm1: Minoxidil 5% foam, 2x/d, topical		24w: 7.8 (4.4%) frontal 8.7 (4.9%) vertex		0.90 (8.0%)			frontal and vertex	A2	
						Arm2: Placebo foam, 2x/d, topical		24w: (-1.5) (- 0.2%) frontal 0.4 (0.9%) vertex		0.07 (1.4%)					

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total hairs/cm ²)	mean change from baseline hair count (nonvulvae hairs/cm ²)	mean change from baseline hair count (agenesis hairs/cm ²)	mean change from baseline hair weight/thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
Minoxidil vs. Placebo female patients															
94	Tsuboi	2007	280	female	24w	Arm1: minoxidil 1% solution, 2x/d, topical Arm2: placebo, 2x/d, topical	15.2 (8.0%) p < 0.001 vs. Placebo	8.2 (6.1%) p < 0.001 vs. Placebo						bald area	A2
82	Jacobs	1993	346	female	32w	Arm1: minoxidil 2% solution, 2x/d, topical Arm2: placebo, 2x/d, topical		33.1 (24.2%) p = 0.0148 vs. Placebo						bald area	A2
81	De Villez	1994	308	female	24w, 32w	Arm1: minoxidil 2% solution, 2x/d, topical Arm2: placebo, 2x/d, topical		24w: 21.8 (15.5%) 32w: 22.7 (16.2%) p = 0.02 vs. Placebo						bald area	A2
87	Whiting	1992	33	female	24w, 32w	Arm1: minoxidil 2% solution, 2x/d, topical Arm2: placebo, 2x/d, topical		24w: 9.9 (7.1%) 32w: 10.1 (7.3%)						bald area	B
84	Olsen	1991	30	female	32w	Arm1: minoxidil 2% solution, 2x/d, topical Arm2: placebo, 2x/d, topical		21 (12.4%) n.s. vs. Placebo						frontoparietal	B
83	Lucky	2004	381	female	48w	Arm1: minoxidil 5% solution, 2x/d, topical Arm2: minoxidil 2% solution, 2x/d, topical Arm3: placebo, 2x/d, topical		50.1 (31.3%) p = 0.006 vs. Placebo						fronto-occipitoparietal	A2
91	Blume-Peytavi	2011	114	female	24w	Arm1: minoxidil 5% foam, 1x/d, topical Arm2: minoxidil 2% solution, 2x/d, topical		24.5 (17.3%) p < 0.001 vs. Placebo, p = 0.129 vs. Arm2						centroparietal	A2
								20.7 (13.8%) p < 0.001 vs. Placebo							
								9.4 (6.8%)							
								24w: 31.9 (16.2%) n.s. vs. Arm2		24w: 2.49 (19.6%) n.s. vs. Arm2		24w: improved: 67.7% worsened: 5.4%		24w: improved: 73.2%	
								24w: 28.4 (13.8%)		24w: 2.33 (17.8%)		24w: improved: 56.1% worsened: 10.5%		24w: improved: 80.7%	
								w24: 23.9				49.3% increase for both groups together			

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total hairs/cm ²)	mean change from baseline hair count (nonvulvas)	mean change from baseline hair count (ginger, eyelashes, and genitolepigen ratio)	mean change from baseline hair weight/thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
Blume	2016	322	female	24w	Arm2: 2% minoxidil solution 2x/d, topical	photogram		w24: 24,2				49,3% increase for both groups together			
Bergfeld	2016	404	female	24w	Arm1: 5% minoxidil foam 1x/d, topical	photogram		w24: 13,4		657,5 um more, than Arm2		0,47 points improvement	0,75 points improvement	midline	A2
					Arm2: placebo foam, 1x/d, topical			w24: 4,3				0,11 points improvement	0,06 points improvement		
Minoxidil vs. Placebo female and male															
Rietschel	1987	149	female and male	4m, 12m	Arm1: 1sty minoxidil 2% solution, 2x/d, topical, 2ndy minoxidil 3% solution, 2x/d, topical	manual hair count	4m: 4.8 (38.7%) n.s. vs. Baseline 12m: 23.0 (184.4%) p < 0.001 vs. Baseline, n.s. vs. Arm2+3	4m: 1.5 (16.8%) 12m: 16.0 (175.9%)						vertex	B
					Arm2: minoxidil 3% solution, 2x/d, topical		4m: 5.9 (49.3%) n.s. vs. Baseline 12m: 23.3 (194.9%) p < 0.001 vs. Baseline, n.s. vs. Arm3	4m: 1.7 (19.5%) 12m: 16.9 (195.2%)							
					Arm3: 4m placebo, 2x/d, topical, 5m-24m minoxidil 3% solution 2x/d, topical		4m: 4.7 (36.5%) n.s. vs. Baseline 12m: 24.7 (194.0%) p < 0.001 vs. Baseline	4m: 1.3 (13.9%) 12m: 17.7 (193.4%)							
Roberts	1987	60	female and male	4m, 12m	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	4m: 22.0 (70.8%) n.s. vs. Arm2+3 12m: 50.5 (162.7%) p = 0.0001 vs. Baseline							vertex	B
					Arm2: minoxidil 3% solution, 2x/d, topical		4m: 25.6 (83.3%) n.s. vs. Arm3 12m: 57.2 (186.4%) p = 0.0001 vs. Baseline								
					Arm3: 4m placebo, 2x/d, topical, 5-12m minoxidil 3% solution, 2x/d, topical		4m: 16.5 (51.8%) 12m: 60.5 (189.7%) p = 0.0001 vs. Baseline								
Minoxidil	eller		male		Arm1: Fulvestrant 70 mg/ml, 2x/d, topical, men Arm2: placebo, 2x/d, topical, men	can	8.2 (4.4%) p 0.815 vs. Placebo p < 0.001 vs. Minoxidil	8.0 (4.4%)		hair thickness mm/cm ² 0.84 (5.4%) p = 0.968 vs. Placebo p < 0.001 vs. Minoxidil	0.7 (4.4%)	10/16			

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hair/c ² cm ² (%)	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count (anagen, catagen, anagen/catagen ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
Bz cr Gassini	2008	172	and female	16w	Arm3: minoxidil 2% solution, 2x/d, topical, men Arm4: fulvestrant 70 mg/ml, 2x/d, topical, women Arm5: placebo, 2x/d, topical, women	TrichoS	25.4 (13.3%)			2.9 (17.3%)				vertex	A2
							14.7 (6.9%) p 0.340 vs. Placebo			1.54 (7.2%) p = 0.227					
							15.3 (7.9%)			1.58 (8.1%)					

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total hairs/cm ²) (%)	mean change from baseline hair count (anagen, catagen, anagen/catagen ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
Minoxidil vs. other male patients														
63	Arca	2004	65	male	12m (52w)	Arm1: minoxidil 5% solution, 2x/d, topical Arm2: finasteride 1mg, 1x/d, oral	7-point-rating scale				80%		frontal/parietal	B
64	Saraswat	2003	99	male	12m	Arm1: finasteride 1 mg, 1x/d, oral Arm2: minoxidil 2% solution, 2x/d, topical	manual hair count	36.1 (29.1%) p = 0.003 vs. Minoxidil			62% p = 0.19 vs. Arm2		bald area	B
65	Berger	2003	200	male	26w	Arm1: minoxidil 5% solution, 2x/d, topical + pyrithione zinc 1% shampoo, 1x/d, topical Arm2: minoxidil 5% solution, 2x/d, topical + placebo shampoo, 1x/d, topical Arm3: pyrithione zinc 1% shampoo, 1x/d, topical Arm4: placebo shampoo, 1x/d, topical	phototrichogram	6.2					vertex	A2
66	Rey-Begne	1997	72	male	6m	Arm1: minoxidil 2% solution, 2x/d, topical Arm2: maxilene lotion (glycerol oxyesters and organic silicium), 1x/d, topical	phototrichogram	6.8 (11.0%) p < 0.001 vs. Arm2	anagen: 4.5 (9.8%) p = 0.05 vs. Arm2				vertex	B
67	Khandpur	2002	100	male	12m	Arm1: finasteride 1 mg, 1x/d, oral Arm2: finasteride 1 mg, 1x/d, oral + minoxidil 2% solution, 2x/d, topical Arm3: minoxidil 2% solution, 2x/d, topical Arm4: finasteride 1 mg, 1x/d, oral + ketoconazole 2% shampoo, 3x/w, topical	improvement score				87% p < 0.03 vs. Arm2 p < 0.001 vs. Arm3 p = 0.3 vs. Arm4		not reported	B
78	Faghih	2013	110	male	6m	Arm1: 5% minoxidil solution, 1x/d, topical Arm2: adenosine solution, 1x/d, topical	improvement score based on phototrichogram				3m: 2.4%		rontotemporal and	C
											3m: 1.9%			

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (folly)	mean change from baseline hair count (involley)	mean change from baseline hair count (aragen, vellagen, anagen/totalogen ratio)	mean change from baseline hair weight/thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
Panahi	2015	100	male	6m	Arm 1: 2% Minoxidil topical solution, 2x/d, topical	phototrichogram	6m: 2.3 (1.66%)						24%, 100%	unclear	C
					Arm 2: Rosemary oil 2x/d, topical		6m: 6.8 (5.54%)					38%, 100%			
Minoxidil vs. other female patients															
Blume-Peytavi	2007	103	female	6m, 12m	Arm 1: minoxidil 2% solution, 2x/d, topical	TrichoScan	6m: 15.3 (8.7%) p = 0.0025 vs. Baseline, p < 0.0005 vs. Arm 2 12m: 17.3 (9.9%) n.s. vs. 6m			hair thickness (mm/cm ²) 6m: 1.8 p < 0.0001 vs. Baseline 12m: 2.1				centroparietal	B
					Arm 2: 0-6m: alfatradiol 0.025% solution, 1x/d, topical. 7-12m: minoxidil 2% solution, 2x/d, topical		6m: -7.8 (-4.3%) n.s. vs. Baseline 12m: 9.8 (5.4%) p < 0.0001 vs. 6m			6m: -0.5 n.s. vs. Baseline 12m: 0.4					
Minoxidil vs. other female and male patients															
Gassmuller	2008	172	male and female	16w	Arm 1: Fulvestrant 70 mg/ml, 2x/d, topical, men	TrichoScan	8.2 (4.4%) p 0.0815 vs. Placebo p < 0.001 vs. Minoxidil			hair thickness mm/cm ² 0.84 (5.4%) p = 0.988 vs. Placebo p < 0.001 vs. Minoxidil				vertex	A2
					Arm 2: placebo, 2x/d, topical, men		8.0 (4.4%)			0.7 (4.4%)					
					Arm 3: minoxidil 2% solution, 2x/d, topical, men		25.4 (13.3%)			2.9 (17.3%)					
					Arm 4: fulvestrant 70 mg/ml, 2x/d, topical, women		14.7 (6.9%) p 0.340 vs. Placebo			1.54 (7.2%) p = 0.227					
					Arm 5: placebo, 2x/d, topical, women		15.3 (7.9%)			1.58 (8.1%)					
Minoxidil combination therapies male patients															
Khandpur	2002	100	male	12m	Arm 1: finasteride 1 mg, 1x/d, oral	improvement score							87% p < 0.03 vs. Arm 2 p < 0.001 vs. Arm 3 p = 0.3 vs. Arm 4	not reported	B
					Arm 2: finasteride 1 mg, 1x/d, oral + minoxidil 2% solution, 2x/d, topical						100% p < 0.001 vs. Arm 3 p = 1 vs. Arm 4				
					Arm 3: minoxidil 2% solution, 2x/d, topical						42% p < 0.0014 vs. Arm 4				
					Arm 4: finasteride 1 mg, 1x/d, oral + ketoconazole 2% shampoo, 2x/d, topical						100%				

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total hairs/cm ²) (%)	mean change from baseline hair count (no vellus hairs/cm ²) (%)	mean change from baseline hair count (anagen, catagen, and telogen ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
69 cr Shin	2007	31	male	18w	Arm1: minoxidil 5% solution, 2x/d, topical	phototrichogram	15.9 (12.8%) p < 0.05 vs. Baseline	14.0 (41.9%) p < 0.05 vs. Baseline	anagen ratio -0.014 (-2.5%) n.s. vs. Baseline	hair diameter: µm 2.6 (7.5%) p < 0.05 vs. Baseline				transitional zone to balding area	A2
					Arm2: minoxidil 5% + tretinoin 0.01% solution, 1x/d, topical, morning placebo solution, 1x/d, topical		18.2 (14.7%) p < 0.05 vs. Baseline, n.s. vs. Arm1	6.1 (14.3%) p < 0.05 vs. Baseline, n.s. vs. Arm1	-0.033 (-6.0%) n.s. vs. Baseline	1.9 (5.3%) n.s. vs. Baseline					
70 cr Tanglitsampian	2012	40	male	24w	Arm1: minoxidil 3% lotion, 2x/d, topical	phototrichogram	24w: 2.9 (4.7%) n.s. vs. Baseline n.s. vs. Arm 2							vertex	B
					Arm2: minoxidil 3% + finasteride 0.1% lotion, 2x/d, topical		24w: 4.8 (8.3%) n.s. vs. Baseline								
79 cr Pumitking	2012	89	male	6m	Arm1: 5% curcuma aeruginosa, hair tonic, 2x/d, topical	manual hair count		6m: 30.62 (20.0%) p<0.001 vs. Baseline		6m: improved 43% unchanged 38%		6m: improved 62% unchanged 38%		vertex	A2
					Arm2: 5% minoxidil, hair tonic, 2x/d, topical		6m: 31.32 (18.1%) p<0.001 vs. Baseline	6m: improved 41% unchanged 54%	6m: improved 82% unchanged 18%						
					Arm3: 5% curcuma aeruginosa, 5% minoxidil, hair tonic, 2x/d, topical		6m: 32.59 (20.7%) p<0.001 vs. Baseline	6m: improved 77% unchanged 23%	6m: improved 90% unchanged 9%						
					Arm4: placebo, hair tonic, 2x/d, topical		6m: 20.41 (11.4%) p<0.001 vs. Baseline	6m: improved 14% unchanged 54%	6m: improved 50% unchanged 32%						
71 Dhurat	2013	100	male	12w	Arm1: 5% minoxidil lotion, 2x/d, topical and weekly microneedling	phototrichogram	12w: 91.4 (40.3%)					12 w: improved 100% unchanged 0%	12 w: improved 100% unchanged 0%	vertex	B
					Arm2: 5% minoxidil lotion, 2x/d, topical		12w: 22.2 (5.5%) p = 0.039				12 w: improved 64% unchanged 36%	12 w: improved 66% unchanged 34%			
72 Sakr	2013	32	male	32w	Arm1: minoxidil 5%, diclofenac 0.5% and tea tree oil 5% emulsion, 2x/d, topical	haircount	84 (63.2%)			4.24 (54.6%)		32 w: improved 75%		frontal and vertex scalp	B
					Arm2: minoxidil 5% emulsion, 2x/d, topical		48 (39.3%)			2.52 (32.3%)	32 w: improved 37%				
					Arm3: placebo emulsion, 2x/d, topical		(-57) (-41%)			(-2.03) (-27.5)	32 w: improved 13%				
Minoxidil					Arm1: minoxidil 5% solution, 2x/d, topical						12m: 59%				

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hairs/cm ² (%)	mean change from baseline hair count (involvement)	mean change from baseline hair count (anagen, catagen, anagen/catagen ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
73 cr	Hu	2015	428	male	12m	Arm2: finasteride 1 mg, 1x/d, oral						12m: 80,5%		scalp regions, frontoparietal	B
						Arm3: minoxidil 5% solution, 2x/d and finasteride 1 mg, 1x/d oral						12m: 94,1%			
Minoxidil combination therapies female patients															
86 cr	Vexiau	2002	66	female	6m, 12m	Arm1: minoxidil 2% solution, 2x/d, topical + oral contraceptive (ethinyl oestradiol 30 µg and gestodene 75 µg), 1x/d, 21 of 28 days, oral Arm2: cyproterone acetate 50 mg, 1x/d, 20 of 28 days, oral + oral contraceptive (ethinyl estradiol 35 µg and cyproterone acetate 2 mg), 1x/d, 21 of 28 days, oral	phototrichogram	6m: 16.1 (8.6%) 12m: 16.9 (9.1%) p < 0.001 vs. Baseline and Arm2	6m: 14.0 p = 0.003 vs. Baseline, p < 0.001 vs. Arm2 12m: 14.9	anagen: (hairs/cm ²) 25 p < 0.001 vs. Arm2				frontoparietal	B
								6m: -2.8 (-1.4%) 12m: -7.8 (-3.9%) p = 0.85 vs. Baseline	6m: -6.0 n.s. vs. Baseline 12m: 5.9	-5.6					
95 cr	Kapadia	2009	26	female	6m	Arm1: ethinyl estradiol 35 µg + CPA 2 mg, 1x/d, oral, day 5-27 of menstrual cycle + CPA 50 mg, 1x/d, oral first 10 days + 5% minoxidil solution, 2x/d, topical						6m: improved frontal 72.7% vertex 50%	6m: improved 100%	frontal/ vertex	C
92 cr	Ryu	2014	41	female	24w	Arm1: minoxidil 3% solution, 1x/d, topical Arm2: minoxidil 3% solution, 1x/d, topical and Korean Red Ginseng extract, 1x/d, oral	Hairdensity	11.9 (12.4%)			0.01 (16.7%)			unclear	C
								13.4 (13.2%)			0.02 (33.3%)				
93	Trush	2014	61	female	9m	Arm1: minoxidil 2% solution, topical and Panto(vi)gar 3x/d, oral Arm2: minoxidil 2% solution, 2x/d, topical	n.a.			(-12.9) (-66.7%)				unclear	C
										(-10.9) (-50.7%)					
Minoxidil combination therapies female and male patients															
Minoxidil						Arm1: placebo, 2x/d, topical		0%							

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (follicles/cm ²)	mean change from baseline hair count (involucres)	mean change from baseline hair count (anagen, catagen, and telogen/total ratio)	mean change from baseline hair weight/thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
74 cr Bezzano	1986	56	female and male	12m	Arm2: minoxidil 0.5%, 2x/d, topical	manual hair count	0%							bald area	B
					Arm3: tretinoin 0.025% solution, 2x/d, topical		58%								
					Arm4: minoxidil 0.5% + Tretinoin 0.025% solution, 2x/d, topical		66%								
75 Pazoki Toroudi	2012	124	male and female	24w	minoxidil 12.5%, azelaic acid 5.0%, betamethasone valerate 0.025% lotion, 1x/d, topical, men	wash test				mean change from baseline hair shed: 24 w -67.7 (-43.3%)		improved 24w 66.67%	improved 24w 61.69%	entire scalp	B
					minoxidil 5% solution, 2x/d, topical, men				24w -53.3 (-34.1%)		improved 24w 40%	improved 24w 35%			
					placebo solution, 2x/d, topical, men				24w -14.1 (-8.4%)		improved 24w 37.5%	improved 24w 37.5%			
					minoxidil 12.5%, azelaic acid 5.0%, betamethasone valerate 0.025% lotion, 1x/d, topical, women				24w -42.0 (-26.0%)		missing data	missing data			
					minoxidil 5% solution, 2x/d, topical, women				24w -38.3 (-23.9%)		improved 24w 37.5%	improved 24w 37.5%			
					placebo solution, 2x/d, topical, wo men				24w -0.5 (-0.3%)		improved 24w 14.9%	improved 24w 28.57%			
Minoxidil oral															
76 Luisaigarani	2015	30	male	24w	1Arm: 5mg Minoxidil 1x/d oral	phototrichogram	24w: 35,1 (19,23%)				24w: 100%			vertex	C
* blinding till 12m, afterwards open study design															
** mean of 3 reviewers															
*** investigator = outcome assessor															
cr = cross reference, see also cited in the section of the comparator															

Article number	Author	Year	Number of patients	Gender	Time of evaluation	Disease	Method	mean change from baseline hair count (nagen, anagen, anagen/telogen ratio)	mean change from baseline hair count (nagen, anagen, anagen/telogen ratio)	mean change from baseline hair count (nagen, anagen, anagen/telogen ratio)	global expert panel assessment - improvement	investigator assessment	patient assessment	investigational area	Degree of evidence
Finasteride male patients															
105	Trüb	2001	265	male	6m	Arm1: finasteride 1 mg, 1x/d, oral	n.a.				39.9%				C
112	Sato	2012	3177	male	3.5y	Arm1: finasteride 1 mg, 1x/d, oral	n.a.						time point unclear improved 87.4% unchanged 12.5% worsened 0.4%	bald areas	C
113	Rossi	2011	118	male	10y	Arm1: finasteride 1 mg, 1x/d, oral age 26-30y	n.a.						first remarkable improvement 1y: 40.5% 2y: 16.7% 5y: 0.0% unchanged 10y: 42.8%	frontal and vertex	B
						Arm2: finasteride 1 mg, 1x/d, oral age 31-40y							first remarkable improvement 1y: 53.6% 2y: 14.3% 5y: 10.7% unchanged 10y: 21.4%		
						Arm3: finasteride 1 mg, 1x/d, oral age >40y							first remarkable improvement 1y: 47.4% 2y: 15.8% 5y: 5.2% unchanged 10y: 31.6%		
96	Yoshitake	2015	801	male	5y	1Arm: finasteride 1mg, 1x/d, oral	global photo				5y: 99.4%			frontal and vertex	C
114	Hajhondari	2009	45	male	6m	Arm1: finasteride 1mg, 1x/d, oral + placebo gel, 2x/d, topical	manual hair count	6m: 15.67 (11.4%) p = 0.0000 vs. Baseline n.s. vs. Arm2	6m: 13.03 (12.3%) p = 0.0000 vs. Baseline n.s. vs. Arm2					bald area	B
						Arm2: placebo tablet, 1x/d, oral + finasteride 1% gel, 2x/d, topical		6m: 8.06 (5.8%) p = 0.0000 vs. Baseline	6m: 4.85 (4.5%) p = 0.001 vs. Baseline						
Finasteride female patients															
115	Yoon	2011	87	female	12m	Arm1: finasteride 5mg, 1x/d, oral	phototrichogram	12m: 18.9 (21%)			hair thickness (µm) 12m: 9.4 (14.7%)	12m: improved 81.4% unchanged 15.1% worsened 3.5%		mid scalp	C
116	Olivera	2013	40	female	18m	1 Arm: finasteride 5mg, 1x/d, oral	global photo					18m: major improvement 55% moderate improvement 37.5%	18m: major improvement: 57.5%, moderate improvement: 30.0%	not reported	C
Finasteride vs. Placebo male patients															
104	Stough	2002	18	male	1y	Arm1: finasteride 1 mg, 1x/d, oral Arm2: placebo, 1x/d, oral	phototrichogram	16 (9.8%) p < 0.05 vs. placebo				44% p < 0.01 vs. placebo		vertex	A2
106	van Nestle	2000	212	male	48w	Arm1: finasteride 1 mg, daily, oral	phototrichogram	7.2 (3.6%) p < 0.001 vs. placebo		anagen, hairs/cm ² (%): 18 (14.5%) p < 0.001 vs. placebo				vertex	A2
						Arm2: placebo, daily, oral		-10.1 (-5.2%)		anagen, hairs/cm ² (%): -9.0 (-7.6%)					

Article number	Author	Year	Number of patients	Gender	Time of evaluation	Disease	Method	mean change from baseline hair count (range) (%)	mean change from baseline hair count (range) (%)	mean change from baseline hair count (range) (%)	mean change from baseline hair weight (range) (%)	global expert panel assessment	investigator assessment	patient assessment	investigational area	Degree of evidence
99	Kawahima	2004	414	male	48w	Arm1: finasteride 1 mg, 1x/d, oral Arm2: finasteride 0.2 mg, 1x/d, oral Arm3: placebo, 1x/d, oral	clinical scoring					improved: 58% p < 0.001 vs. placebo unchanged: 40% improved: 54% p < 0.001 vs. placebo unchanged: 41% improved: 6% unchanged: 72%			vertex	A2
98	Kaufman	1998	1553	male	12m	Arm1: finasteride 1 mg, 1x/d, oral Arm2: placebo 1x/d, oral Arm3: 1st ^y finasteride 1mg, 1x/d, oral, 2nd ^y placebo, 1x/d, oral Arm4: 1 st placebo, 1x/d, oral, 2 nd finasteride 1 mg, 1x/d, oral	phototrichogram	16.9 (11.0%) p < 0.001 vs. placebo -4.1 (-2.7%)				48% (12m) 66% (24m) p < 0.001 (12m) vs. placebo 7% (12m) 7% (24m)			vertex	A2
103	Roberts	1999	693	male	6m, 12m	Arm1: finasteride 5mg, 1x/d, oral Arm2: placebo, 1x/d, oral Arm3: finasteride 1 mg, 1x/d, oral Arm4: finasteride 0.2 mg, 1x/d, oral Arm5: finasteride 0.01 mg, 1x/d, oral	phototrichogram	6m: 12.9 (7.7%) 12m: 18.2 (10.8%) p < 0.001 (6,12m) vs. baseline and placebo 6m: -3.9 (-2.1%) 12m: -3.9 (-2.1) 6m: 13.5 (7.3%) 12m: 16.7 (9.0%) p < 0.001 (6,12m) vs. baseline and placebo 6m: 10.8 (6.1%) 12m: 12.7 (7.2%) p < 0.001 (6,12m) vs. baseline and placebo 6m: -1.8 (-1.0%) 12m: -3.5 (-2.0 %)			51% (6m) 48% (12m) p < 0.001 vs. placebo 10% (6m) 3% (12m) 52% (6m) 54% (12m) p < 0.001 vs. placebo 38% (6m) 38% (12m) p < 0.001 vs. placebo 12% (6m) 10% (12m)			vertex	A2	
109	Whiting	2003	424	male	2y	Arm1: finasteride 1 mg, 1x/d, oral Arm2: placebo, 1x/d, oral	clinical scoring					improved: 39% p < 0.001 vs. placebo unchanged: 55% improved: 4% unchanged: 73%			vertex	A2
111	finasteride Male Pattern Hair Loss Study Group	2002	1553	male	24m, 60m	Arm1: finasteride 1mg, 1x/d, oral Arm2: placebo, 1x/d, oral Arm3: 1st ^y finasteride 1mg, 1x/d, oral, 2nd ^y placebo, 1x/d, oral, 3rd ^y -5th ^y finasteride 1 mg, 1x/d, oral	phototrichogram	7.5 (4.3%) p < 0.001 vs. baseline and placebo -46.9 (-26.5%) p < 0.001 vs. baseline				improved: 48% p < 0.001 vs. placebo unchanged: 42% p < 0.001 vs. placebo improved: 6% unchanged: 19%			vertex	A2

Article number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hair count (%)	mean change from baseline hair count hair count (%)	mean change from baseline hair count (margin, anagen, anagen/total, anagen/total ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment improvement	investigator assessment	patient assessment	investigational area	Degree of evidence	
122	Price	2002	66	male	48w, 96w	Arm4: 1 st y placebo, 1x/d oral, 2 nd y-5 th y finasteride 1 mg, 1x/d, oral	Arm1: finasteride 1 mg, 1x/d, oral	Arm2: placebo, 1x/d, oral	manual hair count	48w: 12.4% 96w: 9.1% p < 0.001 (48, 96w) vs. baseline p < 0.01 (48w), p < 0.001 (96w) vs. placebo	48w: 3.2% 96w: -6.3% p = 0.11 (48w) p < 0.05 (96w)	hair weight: 48w: 20.4% 96w: 21.5% p < 0.001 (48w, 96w) vs. placebo	hair weight: 48w: -5.2% 96w: -14.2%			frontoparietal	A2

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Article number	Author	Year	Number of patients	Gender	Time of evaluation	Disease	Method	mean change from baseline hair count (range) (%)	mean change from baseline hair count (range) (%)	mean change from baseline hair count (range) (%)	mean change from baseline hair weight (range) (%)	global expert panel assessment	investigator assessment	patient assessment	investigational area	Degree of evidence
107	Leyden	1999	326	male	6m, 12m, 24m	finasteride 1 mg, 1x/d, oral	phototriogram	6m: 7.0 (3.3%) 12m: 9.6 (4.6%) 24m: 13.0 (6.2%) p < 0.001 vs. placebo				improved: 37% p < 0.001 vs. placebo unchanged: 62%			frontal/centroparietal	A2
								6m: -4.0 (-1.8%) 12m: -2.0 (-0.9%) 24m: 8.0 (3.7%)				improved: 7% unchanged: 96%				
97	Biemer	1999	28	male	6m, 12m, 24m	finasteride 5 mg, 1x/d, oral	manual hair count	6m: 6.4 12m: 16.7 24m: 34.6 p < 0.05 (6, 12, 24m) vs. baseline							bald area	B
								6m: -2.6 12m: -1.3 24m: -14.1 p < 0.01 (12, 24m) vs. placebo								
102	Price	2006	28	male	36m (144w), 48m (192w)	finasteride 1 mg, 1x/d, oral	manual hair count	36m: 8.5% 48m: 7.2% p = 0.119 (36m) vs. placebo p < 0.05 (48m) vs. placebo		weight (%) 36m: 19.5% 48m: 21.6% p < 0.001 (36m, 48m) vs. placebo					frontoparietal	A2
								36m: -1.6% 48m: -13.0%		weight (%) 36m: -14.8% 48m: -24.5%						

Finasteride vs. Placebo female patients

101	Price	2000	137	female	1y	finasteride 1 mg, 1x/d, oral	phototriogram	-8.7 (-5.8%) p < 0.01 vs. baseline n.s. vs. placebo		A/T ratio 1.8 (29.5%)		improved: 11% unchanged: 77%			frontal/parietal	A2
								-6.6 (-4.0%) p < 0.05 vs. baseline		A/T ratio 1.7 (29.8%)		improved: 16% unchanged: 77%				

Finasteride vs. Placebo female and male patients

108	Whiting	1999	163	female and male	12m	finasteride 1mg, 1x/d, oral, male	bospy	17.7 (5.5%)	41.5 (34.8%)						vertex men, frontal/parietal women	B
								-0.8 (-0.3%)	7.7 (5.8%)							
								-14.6 (-5.9%)	1.5 (1.0%)							
								0.0 (0.0%)	8.5 (5.3%)							

Finasteride vs. other therapies male patients

63 cr	Atca	2004	65	male	12m (52w)	minoxidil 5% solution, 2x/d, topical	clinical scoring					80%			frontal/parietal	B
								finasteride 1mg, 1x/d, oral				52%				
64 cr	Saraswat	2003	99	male	12m	finasteride 1 mg, 1x/d, oral	manual hair count	36.1 (29.1%) p = 0.003 vs. minoxidil				62% p = 0.19 vs. Arm2			bald area	B
								minoxidil 2% solution, 2x/d, topical	19.6 (14.8%)			56%				
Ipur						finasteride 1 mg, 1x/d, oral	nt score					87% p < 0.03 vs. Arm2 p < 0.001 vs. Arm3 p = 0.3 vs. Arm4				
								finasteride 1 mg, 1x/d, oral + minoxidil 2% solution, 2x/d, topical				100% p < 0.001 vs. Arm3 p = 1 vs. Arm4				

Article number	Author	Year	Number of patients	Gender	Time of evaluation	Disease	Method	mean change from baseline hair count (hair/cm ²) (%)	mean change from baseline hair count (hair/cm ²) (%)	mean change from baseline hair count (hair/cm ²) (%) (Magnin, Untch, Wenzel, Wenzel, Wenzel)	mean change from baseline hair weight/thickness	global expert panel assessment for improvement	investigator assessment	patient assessment	Investigational area	Degree of evidence
67 cr	Khand	2002	100	male	12m	Arm3: minoxidil 2% solution, 2x/d, topical Arm4: finasteride 1 mg, 1x/d, oral + ketoconazole 2% shampoo, 3x/w, topical	improvement						42% p < 0.0014 vs. Arm4	100%	not reported	B

Combination therapies male patients																
110 cr	Leavitt	2005	79	male	12m	Arm1: hairtransplantation + finasteride 1mg, 1x/d, oral Arm2: hairtransplantation + placebo, 1x/d, oral	macrophotograph	18.5 (12.6%) p = 0.019 (Arm1 vs. Arm2)							frontal	A2
70 cr	Tunggitsampun	2012	40	male	24w	Arm1: minoxidil 3% lotion, 2x/d, topical Arm2: minoxidil 3% + finasteride 0.1% lotion, 2x/d, topical	phototrichogram	24w: 2.9 (4.7%) n.s. vs. Baseline n.s. vs. Arm 2 24w: 4.8 (8.3%) n.s. vs. Baseline						vertex	B	
73 cr	Hij	2015	428	male	12m	Arm1: minoxidil 5% solution, 2x/d, topical Arm2: finasteride 1 mg, 1x/d, oral Arm3: minoxidil 5% solution, 2x/d and finasteride 1 mg, 1x/d oral	clinical scoring					12m: 59%	12m: 80.5%	12m: 94.1%	scalp regions, front	B

Dutasteride male patients																
120	Jung	2014	35	male	6m	1Arm: dutasteride 0.5mg 1x/d, oral	phototrichogram	6m: 14 (40%)				6m: 11 (31.4%)			frontal and vertex	C

Dutasteride vs. Placebo male patients																	
119	Stough	2007	34	male	6m, 12m	Arm1: dutasteride 0.5 mg, 1x/d, oral Arm2: placebo, 1x/d, oral	phototrichogram	6m: 6.8 12m: 16.5 significant (6m) vs. placebo n.s. (12m) 6m: -11.0 12m: -3.8							vertex	A2	
121	Ein	2010	153	male	6m	Arm1: dutasteride 0.5 mg, 1x/d, oral Arm2: placebo, 1x/d, oral	phototrichogram	6m: 12.2 (8.2%) p = 0.0319 vs. Arm2 6m: 4.7 (3.3%)				6m: improved 61.6%	6m: improved 71.2%	6m: improved 20.0%	6m: improved 36.0%	vertex	A2

Article number	Author	Year	Number of patients	Gender	Time of evaluation	Disease	Method	mean change from baseline hair count (hair/cm ²) (%)	mean change from baseline hair count (hair/cm ²) (%)	mean change from baseline hair count (mean length, anagen, anagen/telogen ratio)	mean change from baseline hair weight/thickness	global expert panel assessment % improvement	investigator assessment	patient assessment	investigational area	Degree of evidence
Dutasteride vs. Other male patients																
100	Olsen	2006	416	male	24w		phototrichogram	Arm1: dutasteride 0.1 mg, 1x/d, oral 15.4 (8.7%) p < 0.001 vs. placebo				39%			vertex	A2
								Arm2: dutasteride 0.5 mg, 1x/d, oral 18.6 (10.2%) p < 0.001 vs. placebo				63% p = 0.026 vs. Arm 4				
								Arm3: dutasteride 2.5 mg, 1x/d, oral 21.5 (11.3%) p < 0.001 vs. placebo				78% p < 0.001 vs. Arm4				
								Arm4: finasteride 5 mg, 1x/d, oral 14.8 (8.4%) p < 0.001 vs. placebo p = 0.009 vs. Arm3				57%				
								Arm5: placebo, 1x/d, oral -6.3 (-3.5%)				2%				
117	Gubelin-Hartha	2014	917	male	24w		phototrichogram	Arm1: Placebo 1x/d, oral mean change from baseline:12w: -4.0 (2.54cm), -0.4 (1.13 cm) 24w: -4.9 (2.54 cm), -0.3 (1.13 cm)		hairwidth w24: -0.9		median improvement: -0.15 (vertex), -0.14 (frontal)				
								Arm2: Dutasteride 0.02 mg, 1x/d, oral mean change from baseline:12w: 22.9 (2.54cm), 5.1 (1.13 cm) 24w: 17.1 (2.54 cm), 4.2 (1.13 cm)		hairwidth w24: 0.0		median improvement: -0.09 (vertex), -0.10 (frontal)				
								Arm3: Dutasteride 0.1 mg, 1x/d, oral mean change from baseline:12w: 59.6 (2.54cm), 12.8 (1.13 cm) 24w: 63.0 (2.54 cm), 12.4 (1.13 cm)		hairwidth w24: 3.9		median improvement: 0.42 (vertex), 0.36 (frontal)			frontal and vertex	A2
								Arm4: Dutasteride 0.5 mg, 1x/d, oral mean change from baseline:12w: 82.3 (2.54cm), 17.1 (1.13 cm) 24w: 89.6 (2.54 cm), 18.1 (1.13 cm)		hairwidth w24: 5.8		median improvement: 0.63 (vertex), 0.58 (frontal)				
								Arm5: Finasteride 1 mg, 1x/d, oral mean change from baseline:12w: 50.9 (2.54cm), 10.8 (1.13 cm) 24w: 56.5 (2.54 cm), 12.1 (1.13 cm)		hairwidth w24: 4.0		median improvement: 0.49 (vertex), 0.34 (frontal)				
Other 5-alpha-reductases male patients																
79 or	Purnihong	2012	89	male	6m		manual hair count	Arm1: 5% curcuma aeruginosa, hair tonic, 2x/d, topical 6m: 30.62 (20.0%) p<0.001 vs. Baseline				6m: improved 43% unchanged 38%		6m: improved 62% unchanged 38%	vertex	A2
								Arm2: 5% minoxidil, hair tonic, 2x/d, topical 6m: 31.32 (18.1%) p<0.001 vs. Baseline				6m: improved 41% unchanged 54%		6m: improved 82% unchanged 18%		
								Arm3: 5% curcuma aeruginosa, 5% minoxidil, hair tonic, 2x/d, topical 6m: 32.59 (20.7%) p<0.001 vs. Baseline				6m: improved 77% unchanged 23%		6m: improved 90% unchanged 9%		
								Arm4: placebo, hair tonic, 2x/d, topical 6m: 20.41 (11.4%) p<0.001 vs. Baseline				6m: improved 14% unchanged 54%		6m: improved 50% unchanged 32%		

Article number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hairs/cm ² (%)	mean change from baseline hair count hairs/cm ² (%)	mean change from baseline hair count (magnitude, direction, significance/odds ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment % improvement	investigator assessment	patient assessment	investigational area	Degree of evidence
118 cr	Rossel	2012	100	male	24m	Arm1: finasteride 1mg, 1x/d, oral Arm2: seronoa repens 320 mg, 1x/d, oral	n.a.					24m: improved 68% unchanged 22% worsened 10%			vertex and anterior region	B

*. blinding till 12m, afterwards open study design
 ** mean of 3 reviewers
 *** investigator = outcome assessor
 cr = cross reference, see also cited in the section of the comparator

Article Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (anagen/telogen, anagen/telogen ratio) (hairs/cm ²) (%)	mean change from baseline hair count (hairs/cm ²) (%)	mean change from baseline hair count (anagen/telogen, anagen/telogen ratio)	mean change from baseline hair weight / thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
Hormones oral female patients																
160	Pernebom-Wyria	1989	30	female	12m	Arm1: ethinyl oestradiol 50 µm + CPA 2 mg 1x/d, oral, day 5-27 of menstrual cycle, CPA 20 mg, 1x/d, oral day 5-20 of menstrual cycle	trichogram			anagen / telogen ratio 2.8 (164.7%)					centroparietal	B
						Arm2: no treatment				-1.2 (-50%)						
86 cr	Voxiau	2002	66	female	6m, 12m	Arm1: minoxidil 2% solution, 2x/d, topical + oral contraceptive (ethinyl oestradiol 30 µg and gestodene 75 µg), 1x/d, 21 of 28 days, oral	phototrichogram	6m: 16.1 (8.6%) 12m: 16.9 (9.1%) p < 0.001 (12m) vs. Baseline and Arm2		anagen (hairs/cm ²) 25 p < 0.001 vs. Arm2					frontoparietal	B
						Arm2: cyproterone acetate 50 mg, 1x/d, 20 of 28 days, oral + oral contraceptive (ethinyl oestradiol 35 µg and cyproterone acetate 2 mg), 1x/d, 21 of 28 days, oral		6m: -2.8 (-1.4%) 12m: -7.8 (-3.9%) p 0.085 (12m) vs. Baseline		-5.6						
95 cr	Kapadia	2009	26	female	6m	Arm1: ethinyl estradiol 35 µg + CPA 2 mg, 1x/d, oral, day 5-27 of menstrual cycle + CPA 50 mg, 1x/d, oral first 10 days + 5% minoxidil solution, 2x/d, topical						6m: improved frontal 72.7% vertex 50%	6m: improved 100%		frontal/ vertex	C
161	Paradisi	2011	101	female	4y	Arm1: flutamide, 1x/d, oral 1st y 250 mg 2nd y 125 mg 3rd/4th y 62.5 mg						improvement of Ludwig score 6m: 15% 1y: 20% 2y: 28%	improved 1y: 72.4% 2y: 76.9% 3y: 82.6% 4y: 85.7%		centroparietal	B
						Arm2: flutamide, 1x/d, oral 1st y 250 mg 2nd y 125 mg 3rd/4th y 62.5 mg + ethinyl estradiol 0.030 mg + gestodene 0.075 mg, 1x/d, oral 21 days of menstrual cycle										
Hormones topical male patients																
156	Sovak	2002	43	male	3m, 9m	Arm1: fluridil, 1x/d, topical	phototrichogram			anagen hairs/cm ² 3m: 9.3 (13.5%) 9m: 10.6 (15.5%)					not reported	B
						Arm2: placebo, 1x/d, topical				3m: 6.5 (10.1%) 9m: 13.1 (20.5%)						

Article Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (mm ² /cm ²) (%)	mean change from baseline hair count (mm ² /cm ²) (%)	mean change from baseline hair count (mm ² /cm ²) (percentage telogen, anagen/telogen ratio)	mean change from baseline hair count (mm ² /cm ²) thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
Hormones topical female patients																
80 cr	Blume-Peytavi	2007	103	female	6m, 12m	Arm 1: minoxidil 2% solution, 2x/d, topical Arm 2: 0-6m: alfatradiol 0.025% solution, 1x/d, topical, 7-12m: minoxidil 2% solution, 2x/d, topical	TrichoScan	6m: 1 5.3 (8.7%) p = 0.0025 vs. Baseline p < 0.0005 vs. Arm2 12m: 17.3 (9.3%)	6m: 14.0 p = 0.003 vs. Baseline 12m: 14.9 p < 0.001 vs. Arm2	hair thickness mm ² /cm ² 6m: 1.8 p < 0.0001 vs. Baseline 12m: 2.1				centroparietal	B	
162	Georgala	2004	75	female	12 resp. 24w	Arm1: Alfatradiol lotion 0.03%, 1x/d, topical, 12w Arm2: Alfatradiol lotion 0.03%, 1x/d, topical, 24w Arm3: placebo lotion, 1x/d, topical, 24w	trichogram		A/T ratio 0.65 (38.7%) p < 0.01 vs. Placebo, n.s. vs. Arm2	0.7 (44.6%) p < 0.01 vs. Placebo				bald area	B	
163	Kim	2012	53	female	8m	Arm 1: 17alpha-estradiol (Eli-Cranell) 0.025% solution, 1x/d, topical	phototrichogram	4m: 17.80 (5.5%) p<0.0001 vs. Baseline 8m: 31.57 (9.8%) p<0.0001 vs. Baseline		cumulative hair shaft thickness (µm): 4m: 6.39 (8.2%) p<0.0001 vs. Baseline 8m: 10.39 (13.2%) p<0.0001 vs. Baseline	8m: impr	8m: hair loss was reduced 54% did hair grow again 32%	area of most severe hair loss	C		
Hormones topical female and male patients																
159	Wozel	2005	233	female and male	30w	Arm1: alfatradiol 0.025% solution, 1x/d, topical, men Arm2: alfatradiol 0.025% solution, 1x/d, topical, women	trichogram		telogen rate -6.7 (-21.1%)					frontal	C	
157	Odfanoc	1980	69	female and male	6m	Arm1: Alfatradiol 0.025% solution, 1x/d, topical Arm2: placebo, 1x/d, topical	trichogram		%improvement from baseline telogen rate**** 63%					triangular	B	
158	Wüthner	1974	50	female and male	6m	estrogen and corticoid, 1x/d, topical	trichogram	52%	%improvement from baseline telogen rate**** 52%					triangular/parietal	C	
62 cr	Gassemüller	2008	172	male and female	16w	Arm1: Fulvestrant 70 mg/ml, 2x/d, topical, men Arm2: placebo, 2x/d, topical, men Arm3: minoxidil 2% solution, 2x/d, topical, men Arm4: fulvestrant 70 mg/ml, 2x/d, topical, women	TrichoScan	8.2 (4.4%) p 0.0815 vs. Placebo p < 0.001 vs. Minoxidil		hair thickness mm ² /cm ² 0.84 (5.4%) p = 0.968 vs. Placebo p < 0.001 vs. Minoxidil				vertex	A2	
								8.0 (4.4%)		0.7 (4.4%)						
								25.4 (13.3%)		2.9 (17.3%)						
								14.7 (6.9%) p 0.0340 vs. Placebo		1.54 (7.2%) p = 0.227						

Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hairs/cm ² (%)	mean change from baseline hair count hairs/cm ² (%)	mean change from baseline hair count (margin, telogen, anagen/telogen ratio)	mean change from baseline hair weight/ thickness	global expert panel assessment	investigator assessment	patient assessment	investigational area	Degree of evidence
Surgery															
164	Uebel	2006	20	male	7m	Arm1: follicular unit transplantation	follicular units (%) *40 (-28.2%) p < 0.001 (Arm1 vs. Arm2)							parietal	C
						Arm2: follicular unit transplantation + platelet plasma growth factor added before implantation	follicular units (%) *25 (-17.6%)								
110 cr	Leavitt	2005	79	male	12m	Arm1: hairtransplantation + finasteride 1mg, 1x/d, oral	18.5 (12.6%) p = 0.019 (Arm1 vs. Arm2)				improved: 94% unchanged: 6%			frontal	A2
						Arm2: hairtransplantation + placebo, 1x/d, oral	-13.5 (-8.9%)				improved: 67% unchanged: 30%				
165	Bernstein	1998	41	male		Arm1: follicular unit transplantation, preparation by dissecting microscope	mean hairs/follicular unit 2,28							parietal	B
						Arm2: follicular unit transplantation, preparation by magnifying loupe with transillumination	mean hairs/follicular unit 2,14								
166	Rusdidi	2010	50	male	3m	Arm1: follicular unit transplantation (FUT) + psittacofulvin solution, 1x/d, topical 15 days before till 90 days after FUT	number of apoptotic fragments 3m: 0.07							frontoparietal	B
						Arm2: follicular unit transplantation (FUT) + placebo solution, 1x/d, topical 15 days before till 90 days after FUT	number of apoptotic fragments 3m: 2.05								

Art Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count (aragen to arogen, aragen/telegen ratio)	mean change from baseline hair count thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence	
Miscellaneous, oral																	
175	Prigder	2002	26	male	18-24w	Arm1: active oral softgel supplement (β-sitosterol 50 mg + serenoa repens extract 200 mg, lecithin 50 mg, inositol 100 mg, phosphatidyl choline 25 mg, niacin 15 mg, biotin 100 µg), 2x/d, oral	7-point-rating scale							60%			B
						Arm2: softgel placebo, 2x/d, oral								11%			
118 cr	Rossi	2012	100	male	24m	Arm1: finasteride 1mg, 1x/d, oral	n.a.							24m: improved 68% unchanged 22% worsened 10%		vertex and anterior region	B
						Arm2: serenoa repens 320 mg, 1x/d, oral								24m: improved 38% unchanged 52% worsened 10%			
194	Lassus	1992	40	male	6m	Arm1: viviscal (marine extracts and silicea component), 2x/d, oral	manual hair count	4.8 (38.1%) p < 0.001 vs. Arm2								bald area	A2
						Arm2: fish extract, 2x/d, oral		0.3 (2.1%)									

Art Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count (anagen to anagen, anagen:telogen ratio)	mean change from baseline hair count thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
190	Le Floch	2015	120	female	6m	Arm1: nutritional supplement with omega 3 & 6 and antioxidants (460 mg fish oil, 460 mg blackcurrant seed oil, 5 mg Vitamin E, 30 mg Vitamin C, and 1 mg Lycopene) 1x/d, oral	trichogram, global photography	6m: 11%			6m: 78,01%		62%	6m: 88,6%	and combed away,	A2
						Arm2: no treatment		6m: 18%			6m: 75,88%		28.25	6m: 51,3%		
177	Moers-Carpi	2011	62	female and male	24w	Arm1: 2 capsules containing Fenugreek and micronutrients (vitamines C, E, nicotinamide, panthotenic acid, zinc, vitamins B1, B6, B12, copper, biotin, folic acid, iod, selen), 1x/d, oral	phototrichogram	24w: 6.5 n.s. vs. Arm2		anagen: 24w 5.9% p<0.0001 vs. Arm2				improved hair growth: 24w 56.4%	frontal and vertex	B
						Arm2: 2 placebo capsules, 1x/d, oral		24w: -7.1		anagen: 24w 0.62%				improved hair growth: 24w 23.5		

Art Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count (anagen to telogen, anagen/telogen ratio)	mean change from baseline hair count thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
Miscellaneous, topical																
178	Kaminura	2000	30	male	6m	Arm1: procyranidin 1% solution, 2x/d, topical	phototrichogram	26,7 p < 0.005 vs. Placebo	8,0 p < 0.02 vs. Placebo						vertex	B
						Arm2: placebo, 2x/d, topical		0,3	-3,3							
179	Kessels	1991	396	male	6m	Arm1: herbal preparation, 2x/d, topical	manual hair count		26,6 p = 0.02 vs. Placebo						bald area	A2
						Arm2: placebo, 2x/d, topical			21,8							
180	Greenberg	1996	24	male	40w	Arm1: herbal extract cream (7.5% extract of fennel, polygonum, mentha, chamomile, thuja, hibiscus), 1x/d, topical	manual hair count	77,4% p = 0.003 vs. Placebo	169,4% p = 0.01 vs. Placebo						triangular	B
						Arm2: placebo cream 1x/d, topical		3%	33,9%							
181	Olsen	1990	72	male	6m	Arm1: viprostol solution 120 µg, 2x/d, topical	phototrichogram		-3,9 (-4,0%) n.s. vs. Arm2/3						vertex	A2
						Arm2: vehicle, 2x/d, topical			-9,1 (-9,5%) n.s. vs. Arm1/3							
						Arm3: placebo, 2x/d, topical			-3,1 (-3,3%)							

Art Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (hairs/cm ²) (%)	mean change from baseline hair count (hairs/cm ²) (%)	mean change from baseline hair count (anagen: telogen, anagen:telogen ratio)	mean change from baseline hair count (hairs/cm ²) thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
66 cr	Reygnagne	1997	72	male	6m	Arm1: minoxidil 2% solution, 2x/d, topical Arm2: maxilene lotion (glycerol oxysters and organic silicium), 1x/d, topical	phototrichogram	6.8 (11.0%) p < 0.001 vs. Arm2	-3.0 (-4.8%)	anagen (hairs/cm ²) 4.5 (9.8%) p = 0.06 vs. Arm2	-1.8 (-3.7%)				vertex	B
182	Glovesman	1985	174	male	16w	Arm1: polysorbate 60 25% lotion, 2x/d, topical Arm2: placebo, 2x/d, topical							2,6%**	4,7%**	full view	A2
183	Freund	2010	50	male	48w	botulinum toxin scalp injections 150 units at 30 sites at baseline and 24w	phototrichogram	24w: 19 (8.1%) 48w: 41 (18.0%)							evaluation area	C
184	Ito	2009	24	male	6m	Arm1: Roxithromycin 0.5% solution, 1x/d, topical Arm2: placebo solution, 1x/d, topical	microscope (3 hair studies)				hair thickness (µm): 6m: 30.9 (55,3%) 6m: -0.4 (-0.7%)		6m: improved 58% 6m: improved 0%		evaluation area	B
191	Loing	2013	30	male	4m	Arm1: 5% lotion containing clover extract (15 ppm Biochanin A) + acetyl tetrapeptide-3 300 ppm, 1x/d, topical Arm2: placebo lotion, 1x/d, topical	phototrichogram			4m: anagen 13% telogen -29% A/T ratio 46% 4m: anagen -2% telogen 23% A/T ratio -33%					evaluation area	B
78 cr	Faghi	2013	110	male	6m	Arm1: 5% minoxidil solution, 1x/d, topical Arm2: adenosine solution, 1x/d, topical	improvement score based on						3m: 2,4% 3m: 1,9%		frontotemporal and	C
185	Fischer	2012	35	male	6m	1 Arm: Melatonin topical solution 1x/d	phototrichogram	6m: 36,6 (42,6%)	6m: 50,41 (40,93%)						frontal and vertex	C

Art Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count (no vellus) hair/cm ² (%)	mean change from baseline hair count (anagen to telogen; anagen:telogen ratio)	mean change from baseline hair count (no vellus) thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
192	Jo	2014	40	male	24w	Arm1: 8,3% valproic acid topical solution	phototrichogram	24w: 192 (6,08%)							frontal and vertex	A2
						Arm2: Placebo	phototrichogram	24w: 197 (1,54%)								
68 cr	Panahi	2015	100	male	6m	Arm1: 2% Minoxidil topical solution, 2x/d, topical	phototrichogram	6m: 140,7 (1,66%)						24%, 100%	unclear	C
						Arm2: Rosemary oil 2x/d, topical	phototrichogram	6m: 129,6 (5,54%)						38%, 100%		
186	Draelos	2005	60	female	6m	Arm1: Niacin derivates (octyl nicotinate 0.5% and myristyl nicotinate 5.0%), 1x/d, topical	7-point-rating scale						69% p = 0,04 vs. Placebo		vertex	A2
						Arm2: placebo, 6 drops, 1x/d, topical							33%			
187	Gehring	2000	40	female	6m	Arm1: millet seed extract, L-cysteine and calcium pantothenate, 2x/d, oral	phototrichogram			anagen rate 12.1 (16.0%) p = 0.0225 vs. Placebo					centroparietal	B
						Arm2: placebo, 2x/d, oral			8.4 (11.3%)							
188	Oura	2008	30	female	12m	Arm1: adenosine 0.75% lotion, 2x/d, topical	phototrichogram						6m: improved 23% unchanged 62% 12m: improved 62%		centroparietal	B
						Arm2: placebo lotion, 2x/d, topical							6m: improved 28% unchanged 36% 12m: improved 21% unchanged 79% 12m: improved 36%			
189	Baek	2011	44	female and male	16w	Arm1: shampoo containing zinc pyrithione 0.6%, dexpanthenol 0.5%, nicotinamide 0.1%, triaminolol 0.5%, TOS extract 0.17%, 2x/d, topical	phototrichogram	16w: 3.4 (3.9%)	16w: 3.6 (4.7%)	anagen: 16w: 3.7 (5.4%)	hair thickness (mm): 16w: -0.002 (-1.9%)				evaluation area	B
						Arm2: placebo, 2x/d, topical		16w: -0.8 (-0.9%)	16w: 0.7 (1.3%)	16w: -0.4 (-0.0%)	16w: -0.004 (-4.9%)					

Art Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (10x2) hair/cm ² (%)	mean change from baseline hair count (10x10) hair/cm ² (%)	mean change from baseline hair count (anagen to telogen, anagen:telogen ratio)	mean change from baseline hair count (trichoscopy) thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
combination therapies																
176	Lassus	1994	30	male	8m	Arm1: viviscal (polysaccharides and sate), 2x/d 80 kg, 3x/d > 80 kg, oral + viviscal shampoo 2-3x/w									93.3%	C
65 cr	Berger	2003	200	male	26w	Arm1: minoxidil 5% solution, 2x/d, topical + pyrithione zinc 1% shampoo, 1x/d, topical Arm2: minoxidil 5% solution, 2x/d, topical + placebo shampoo, 1x/d, topical Arm3: pyrithione zinc 1% shampoo, 1x/d, topical Arm4: placebo shampoo, 1x/d, topical	phototrichogram	6,2	12,3	5,7	-0,6				vertex	A2
69 cr	Shin	2007	31	male	18w	Arm1: minoxidil 5% solution, 2x/d, topical Arm2: minoxidil 5% + tretinoin 0.01% solution, 1x/d, topical, morning placebo solution, 1x/d, topical	phototrichogram	15.9 (12.8%) p < 0.05 vs. Baseline	14.0 (41.9%) p < 0.05 vs. Baseline	anagen ratio -0.014 (-2.5%) n.s. vs. Baseline	hair diameter: um 2.6 (7.5%) p < 0.05 vs. Baseline				transitional zone to balding area	A2
92 cr	Ryu	2014	41	female	24w	Arm1: minoxidil 3% solution, 1x/d, topical Arm2: minoxidil 3% solution, 1x/d, topical and Korean Red Ginseng extract, 1x/d, oral	Hairdensity	11.9 (12.4%)	13.4 (13.2%)	-0.033 (-6.0%) n.s. vs. Baseline	0.01 (16.7%) 0.02 (33.3%)				unclear	C

Art Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count (aragen, telogen, anagen/telogen ratio)	mean change from baseline hair weight / thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
						Arm1: placebo, 2x/d, topical	hair count	% > 20% increase from baseline 0%								
						Arm2: minoxidil 0.5%, 2x/d, topical		0%								
74	cr	zaino	1986	56	female and	12m									bald area	B

Art Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count hair/cm ² (%)	mean change from baseline hair count (aragen telogen, aragen/total ratio)	mean change from baseline hair count thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
	Baz			male		Arm3: tretinoin 0.025% solution, 2x/d, topical	manual	58%								
						Arm4: minoxidil 0.5% + Tretinoin 0.025% solution, 2x/d, topical		66%								
	193	Merganti	1998	60	female and male	50w	manual hair count								frontal/parietal	B
						Arm1: lotion containing serenoa repens extract, 2x/d, topical		27% p < 0.005 vs. Baseline			hair weight 32%					
						Arm2: placebo lotion, 2x/d, topical		13%			7%					
						Arm3: diet supplement containing l-cistin, l- methionin, Cu, Zn, 4x/d, oral		29% p < 0.005 vs. Baseline			42%					
						Arm4: placebo supplement, 4x/d, oral		11%			-8%					
						Arm5: lotion containing serenoa repens extract, 2x/d, topical + diet supplement containing l-cistin, l- methionin, Cu, Zn, 4x/d, oral		38% p < 0.005 vs. Arm1/3			60%					
	79 cr	Pumthong	2012	89	male	6m	manual hair count								vertex	A2
						Arm1: 5% curcuma aeruginosa, hair tonic, 2x/d, topical		6m: 30.62 (20.0%) p<0.001 vs. Baseline				6m: improved 43% unchanged 38%		6m: improved 62%, unchange d 38%		
						Arm2: 5% minoxidil, hair tonic, 2x/d, topical		6m: 31.32 (18.1%) p<0.001 vs. Baseline				6m: improved 41% unchanged 54%		6m: improved 82%, unchange d 18%		
						Arm3: 5% curcuma aeruginosa, 5% minoxidil, hair tonic, 2x/d, topical		6m: 32.59 (20.7%) p<0.001 vs. Baseline				6m: improved 77% unchanged 23%		6m: improved 90%, unchange d 9%		
						Arm4: placebo, hair tonic, 2x/d, topical		6m: 20.41 (11.4%) p<0.001 vs. Baseline				6m: improved 14% unchanged 54%		6m: improved 50%, unchange d 38%		

Art Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (cor 2)	mean change from baseline hair count (cor 2)	mean change from baseline hair count (anagen to anagen, anagen to anagen ratio)	mean change from baseline hair count (trichocyte thickness)	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
pulsed electromagnetic field																
207	Maddin	1990	73	male	36w	Arm1: pulsed electrostatic field, 1x/w, week 1, 17, 33 2x/w Arm2: sham treatment, 1x/w, week 1, 17, 33 2x/w	manual hair count		11.8 (66.1%) p = 0.0298 vs. Arm2						vertex	A2
208	Maddin	1992	34	male	12w, 34w 16w, 30w	Arm1: pulsed electrostatic field, 1x/w, pretreatment 36w pulsed electrostatic field Arm2: pulsed electrostatic field, 1x/w, pretreatment 36w sham electrostatic field	manual hair count	12w: 5.9 (20.0%) 34w: 24.7 (84.0%)							vertex	B
209	Policarpi	1993	30	female and male	18w, 36w	Arm1: pulsed electrostatic field, 1-2 sessions per week Arm2: placebo sessions, 1-2x/week	phototrichogram		anagen: 18w: 4.5 % 36w: 6.2%						bald area	B
									18w: 0.9% 36w: 1.0%							

Art Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (fox 2) hair/cm ² (%)	mean change from baseline hair count (fox 2) hair/cm ² (%)	mean change from baseline hair count (aragen, aragen, aragen ratio)	mean change from baseline hair weight I thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence	
	206	Bureau	2003	93	female and male	6m	Arm1: herbal solution (pimenta racemosa, myrtus communis, cedrus atlantica, laurus nobilis, pogostemon patchouli, rosmarinus officinalis, salvia sclariae, thymus saturoioides, cananga odorata), 3x/w, topical + pulsed electromagnetic field 3x/w, topical phototrichogram	34 (22.4%) p = 0.003 vs. Baseline, p = 0.01 vs. Arm2								bald area	A2
							Arm2: placebo, 3x/w, topical + pulsed electromagnetic field 3x/w, topical	9 (5.5%) n.s. vs. Baseline									

* blinding till 12m, afterwards open study design
** mean of 3 reviewers
*** investigator = outcome assessor