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. Despite the high prevalences and the variety of therapeutic options available no national or international evidence-based guideline for the treatment of androgenetic alopecia in men and women exist. That's why 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 as well as general practicioner 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 chronic dermatologic disease, affecting both men and women. It is characterized by progressive hair loss in a usually pattern distribution. The frequency increases with age. In Caucasians, at the age of 70 or beyond 80% of men and up to 42% of women have signs of androgenetic

alopecia. Though the prevalence is high in elderly patients, androgenetic alopecia often already starts at puberty.

Age- and gender-independent, patients afflicted with androgenetic alopecia undergo significant impairment in their 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 is clearly a burden for both sexes, but it is substantially more distressing for women [2].

Patient's therapeutic experiences. Although there is a significant impairment in quality of life in most of the patients, Alfonso et al. revealed that three out of four men afflicted with androgenetic alopecia had never pursued therapy of hair loss [1]. On the other hand lots of patients 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's compliance. There are discrepancies between the wish of hair regrowth and willingness to perform a therapeutic regimen consequently. Limited efficacy, poor tolerance, fear and lack of information on treatment duration and possible adverse events lead to disappointment again.

Therapeutic concepts. The individual therapeutic concepts are still mainly based on physicians' personal experiences without taking into account the current evidence-based knowledge regarding the efficacy of the therapies.

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 concept.

Improved patient care. The use of these evidence-based recommendations in clinical routine will lead to an improved patient care, as the physicians' personal experiences and traditional therapeutic concepts will be added and, if necessary, replaced by evidence-based assessments of the efficacy of the different therapeutic options.

Insure optimal usage of therapeutic regimen. In addition to the efficacy assessment the guideline provide details on administration and safety aspects of systemic, topical or surgical therapy. These instructions for use should remove reservations of physicians and patients and assure that the therapy is provided in an optimal way. Initiation of the right therapy at the right time can prevent or at least slow down severe progression.

Improvement of patient's knowledge and compliance. Patients' compliance is most important in the individual response on a therapeutic concept. Good compliance is not only related with a balance of benefits, costs and adverse effects, but also

requires informed patients. By increasing the level of the patients' knowledge about the optimal use of each therapy and its possible complications patients' compliance, response rates and satisfaction will increase. Information on administration and adverse reactions should serve to eliminate or reduce these and therefore will additionally improve compliance.

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. It should provide support in the development of individual therapeutic concept.

Each chapter summarizes the efficacy resulting from the evidence-based evaluation separately for men and women. Moreover, the experts provide 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 have to consider additionally the manufacturer's product information and check the recommendations concerning completeness and up-to-dateness of dosages, contraindications or 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 underlie changes in-between the actualisation cycles of the guideline. Therefore the usage of the recommendations is at own responsibility and users are requested to keep informed about new knowledge regularly published in parallel to the guidelines. The authors and publishers of the guideline would be pleased, if readers could inform them on any inaccuracies that they notice.

1.4 Methodology

Literature research. A detailed description of methodology reflecting the process of developing the guidelines can be found in the method report of the guidelines. The methodology was defined as first step in development of the guideline. It 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 in the databases Medline, Embase and Cochrane Library was conducted at 25th January 2007 and updated at 07th August 2008. Overall 1245 articles were found. Additionally 51 articles were added by hand search. 125 articles were found by updating the literature research. Overall, after checking for doublets and relevance 396 articles were evaluated using the literature evaluation form (LEF) (*see Attachment 1)*. 85 articles fulfilled the inclusion criteria of the guideline and built consequently the basis of the guideline. *Figure 1* summarizes the process of literature research.

The evidence-based evaluations of these guidelines are restricted on the efficacy of the particular therapeutic options. 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:

A$_1$ Meta-analysis, which includes at least one randomized clinical trial of grade A$_2$ evidence with consistent results of the different studies.

A$_2$ 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 A$_1$ evidence or studies with mainly consistent results grade A$_2$ evidence

2   Studies grade A$_2$ 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 consented in a formal consensus process. The expert group agreed on a 5-point scale. This scale is illustrated by arrows:

⬆⬆   We recommend
⬆   We suggest
➜   Can be considered
⬇   We suggest not
⬇⬇   We do not recommend

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 stimulating regrowth. Knowledge on the efficacy of the different therapeutic options is essential for treating doctors and interest groups in the management of the disease and will lead to enhanced patient satisfaction.

2.1 Epidemiology

Androgenetic alopecia in men and women is present in populations of different ethnicities. Typically, frequency and severity increase with age. The highest prevalence is reported in the Caucasian population. At the age of 70 and beyond around 80% of men and up to 42% of women suffer from androgenetic alopecia[3,4]. Usually, initial signs of the disease already develop in men at teenage[3-6]. Female pattern hair loss shows peaks of incidence at teenage and in postmenopause.
In the Asian population the frequency of androgentic alopecia in male and female patients is lower compared to the European part. Information on prevalences of the disease in African men and women is less to missing.

2.2 Aetiology

Androgenetic alopecia is characterized by a non-scarring progressive miniaturization of the hair follicle in predisposed men and women, usually in a specific pattern distribution. Its aetiology is multifactorial and polygenetic[3].

In men androgenetic alopecia is an androgen-dependent trait. The terminal hair follicle becomes susceptible against dihydrotestosteron, which leads to shortening of anagen phase and miniaturization of terminal to vellus hair. The development of male androgenetic alopecia is predominantly hereditary. In men family analyses showed strong concordance rates in twins and increased risk for sons with bald father[7].

Moreover, variant regions on the androgen receptor gene and at chromosome 20p11 are associated with the development of androgenetic alopecia in men [8,9].

In female patients, less is known on the aetiology of androgenetic alopecia. Regarding inheritance, incidence of 54% respectively 21% are reported for women with male respectively female first degree relatives suffering from androgenetic alopecia [10,11]. Possibly, early and late onset female androgenetic alopecia have different genetic traits. The androgen dependence is likewise uncertain in women, that is to say, other factors seem to be involved.

Nevertheless, it is important to consider, 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 [3].

2.3 Clinical features

Clinically, androgenetic alopecia is characterized 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[3].

Male pattern, Hamilton-Norwood
It 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 centro-parietal region with maintaining 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 androgenetic alopecia is usually made clinically by inspection of hair and scalp showing a non-scarring alopecia in the typical pattern distribution[3].

The clinical examination should also include pull test as well as examination of facial and body hair as well as nails to exclude differential diagnoses; in particular diffuse telogen effluvium, alopecia areata and cicatrical alopecia[3].

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, further diagnostic, measurement of hair density, laboratory 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 guaranties the 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 experts 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's and investigator's perception can be excluded. In the opinion of the experts 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 exclusively on the efficacy, but also on practicability, risks and costs. The assessment of cost effectiveness has to be made by balancing the costs with the benefit attained. Consequently, expensive therapeutic options can also be cost-effective, if they are highly effective.

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 leads also 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 in1988 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.

3.1.2 Mechanism of action
To exert its effect minoxidil needs to be transformed to its active metabolite, minoxidil sulphate by the enzyme sulphotranspherase, 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

34 studies assessing the efficacy of minoxidil in male patients with androgenetic alopecia met the inclusion criteria for the guideline [12-45]. 3 out of them treated male and female patients. 25 studies were placebo controlled. The majority of studies obtained grade A2 and B evidence (A2 = 17, B = 13, C = 3) resulting in **EVIDENCE LEVEL 1**.

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

OUTCOMES

The mean change from baseline *total hair count* ranged between 5.4 hairs/cm^2 and 29.9 hairs/cm^2 (11.0 – 54.8%) at 4 to 6 months and between 15.5 hairs/cm^2 and 83.3 hairs/cm^2 (14.8-248.5%) at 12 months [12,13,17,19,22,23,26,27,29,30,35,38-40,42,43].

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/cm^2 to 37.3 hairs/cm^2 (17.2 – 59.4%) at 6 months, between 9.4 hairs/cm^2 to 41.8 hairs/cm^2 (8.8 – 443.8%) at 12 months [12,13,17-22,24,26,27,29,30,33,35,43,45].

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).

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/cm^2 and 22.4 hairs/cm^2 (9.3 and 48.8%) at 4 to 6 months.

DOSAGE

Concentration. Minoxidil dosages below 2% showed significant reduced mean changes from baseline total hair count in comparison to minoxidil 2% at 6 months [30,45]. 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) [21,25,26,29,31,32,39,40,43]. Only Katz et al. reported a significance of p = 0.0464 at 4 months in mean change of nonvellus hair counts [24].

2 studies comparing minoxidil 2% solution, twice daily and minoxidil 5% solution, twice daily were included in the evidence based analysis [33,37]. 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/cm^2 (12.3%) vs. 12.7 hairs/cm^2 (8.8%) at 12 months, p = 0.025, mean % change from baseline total hair count 30% vs. 25% at 24 months, p = 0.455).

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/cm^2 vs. 44.1 hairs/cm^2 at 33 months, p = 0.015, mean change from baseline nonvellus hair count 4.4 hairs/cm^2 vs. -13.4 hairs/cm^2 at 36 months)[32].

FORMULATION
The standard formulation of minoxidil is a solution containing propylenglycol. Olsen et al. studied a foam formulation containing 5% minoxidil [34]. The mean change from baseline nonvellus hair count was highly significant different from placebo at 16 weeks (20.9 hairs/cm^2 (13.4%) vs. 4.7 hairs/cm^2 (3.4%), p < 0.0001).

Piepkorn et al. examined minoxidil 2% in a gel formulation and as solution [36]. 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
In comparison to finasteride 1 mg daily Arca et al. reported 80% improvement in global photographic assessment for minoxidil 5%, twice daily and 52% for finasteride at 12 months [14]. On the other hand, a study by Saraswat et al. reported superiority of minoxidil 2% solution, applied twice daily, in comparison to finasteride 1 mg/d (mean change from baseline total hair count 36.1 hairs/cm^2 (29.1%) vs. 19.6 (14.8%) at 12 months, p = 0.003)[42].

3.1.4 Efficacy – females
11 studies that investigated the efficacy of topical minoxidil in female patients suffering from androgenetic alopecia could be included in the evidence based evaluation [15,39,40,46-53]. 3 studies treated male and female patients. 7 studies obtained grade B evidence, 4 studies grade A2 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/cm^2 (8.0%) [54]. Minoxidil 2% solution showed mean changes from baseline nonvellus hair count at 6 months between 21.0 hairs/cm^2 and 50.1 hairs/cm^2 (12.4 -31.3%)[39,47-51,53].
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 <0.001).

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

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 [46]. The mean change from baseline

total hair count was -7.8 hairs/cm^2 (-4.3%) for alfatradiol and 15.3 hairs/cm^2 (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. 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 diminuation of hair density due to telogen shedding normalizes wihtin a few weeks to months. Good patient-practicioner-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.

Minoxidil is contraindicated in pregnancy and lactation.

3.1.6 Combination therapies
A study by Berger et al. failed to show, that combination of minoxidil 5% solution and pyrithione zinc shampoo is superior to minoxidil monotherapy [16]. 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/cm^2 and 12.3 hairs/cm^2 respectively.

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% [15]. 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. The mean change from baseline total hair count at 18 weeks was 15.9 hairs/cm^2 (12.8%) vs. 18.2 hairs/cm^2 (14.7%) (p not significant).

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/cm^2 (8.6%) at 6 months, 16.9 hairs/cm^2 (9.1%) at 12 months, whereas cyproterone acetate 50 mg in combination with oral hormonal contraceptive led to decreased values (-2.8 hairs/cm^2 (-1.4%) at 6 months, -7.8 hairs/cm^2 (-3.9%) at 12 months (p < 0.001) [52].

3.1.7 Summary
Minoxidil 2% solution is effective to prevent progression and improve androgenetic alopecia in male and female patients (evidence level 1). Minoxidil 5% solution is more effective than the 2% solution in male patients (evidence level 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.

3.1.8 Therapeutic recommendation – Male
↑↑ **Topical Minoxidil 2 to 5% solution 1 ml 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 IIv-V).**
↑ **We suggest using 5% solution for greater efficacy.**
→ **There is not enough data to recommend the 5% minoxidil foam instead of the 5% solution.**
↑ **The response to treatment should be assessed at 6 months. If successful, treatment needs to be continued to maintain efficacy.**

3.1.9 Therapeutic recommendation – Female
↑↑ **Topical Minoxidil 2% solution 1 ml twice daily is recommended to improve or to prevent progression of AGA in female patients above 18 years with AGA.**
→ **There is not enough data to recommend the 5% minoxidil solution instead of the 2% solution.**
↑ **The response to treatment should be assessed at 6 months. If successful, treatment needs to be continued to maintain efficacy.**

3.2 5-ALPHA-REDUCTASE-INHIBITORS

3.2.1 Introduction
Androgenetic alopecia (AGA) occurs after puberty in men with an inhered sensitivity to the effects of androgens on androgenetic sensitive scalp hair. AGA does not develop in men without testosterone, and we know since 1974 that AGA does not occur in men with a genetic deficiency of the enzyme 5-alpha-reductase type II which converts testosterone to dihydrotestosterone (DHT) [55]. Two type's of 5-alpha-reductase-inhibitors exist in humans. Type I predominates in liver, skin and scalp. Type II predominates in prostate and genitourinary tract, but also in the human hair follicle.

Initially pharmaceutical 5-alpha-reductase-inhibitors were developed for the treatment of benign prostatic hyperplasia. Two drugs inhibiting the 5-alpha-reductase are

available on the market: finasteride registered in Europe in 1992, and dutasteride registered in 2003. Finasteride is a type II 5-alpha-reductase-inhibitor which decreases DHT of about 65% in serum, prostate and scalp. Dutasteride inhibits both type I and type II 5-alpha-reductase resulting in a decrease of the serum DHT level of about 90%.

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

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

3.2.2 Mechanism of action

A single oral administration of finasteride 1 mg decreases serum DHT as well as 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 but without interaction with other drugs known to be metabolized by this cytochrome also, such as warfarin, theophylline, digoxine, propanolol and others.

3.2.3 Efficacy – males

Finasteride

18 studies looking at the efficacy of finasteride in male patients with androgenetic alopecia met the inclusion criteria of the guideline [14,42,56-71]. 16 out of these 18 studies assessed the efficacy of finasteride monotherapy in male patients with androgenetic alopecia. 12 studies obtained grade A2 evidence, 5 grade B and 1 grade C. 12 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/cm^2 (3.3%) in the frontal/centroparietal region (p < 0.0001 vs. placebo) [60] and 13.5 hairs/cm^2 (7.3%) in the vertex (p < 0.0001 vs. placebo) [64] at 6 months.

The mean increase from baseline total hair counts at 12 months was between 7.2 hairs/cm^2 (3.6%) and 36.1 hairs/cm^2 (29.1%) for the vertex (p between < 0.05 and 0.001 vs. placebo) [57,60,64,65,67,68] and 9.3 hairs/cm^2 (4.9%) and 9.6 hairs/cm^2 (4.6%) in the frontal/centroparietal region (p between < 0.01 and 0.001 vs. placebo) [62,72]. The placebo group showed at the same time mean changes from baseline total hair count between 2.4 hairs/cm^2 (1.4%) and -10.1 hairs/cm^2 (-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) [57,58,60,64,65,71]. In addition

subjective assessments by investigator and patients yielded significant improvements in the finasteride group [57,58,60,64,65,69].

Long-term results were available for 24, 36, 48 and 60 months. The mean changes from baseline total hair counts were 13.0 hairs/cm^2 (6.2%) at 24 months [60], 8.5% at 36 months [63], 7.2% at 48 months [63] and 7.5 hairs/cm^2 (4.3%) at 60 months[71] 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) [62,63].

DOSAGE

Concentration. Two studies examining different finasteride dosages could be included in the evidence based evaluation [58,64]. Roberts et al. examined finasteride 0.01 mg, 0.2 mg, 1 mg and 5 mg versus placebo [64]. 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% respectively 54% improvement in global expert panel assessment for finasteride 1 mg respectively 0.2 mg [58]. The efficacy in both groups were comparable and significant different to placebo (p< 0.001).

FINASTERIDE VS. MINOXIDIL

Only few data comparing finasteride 1 mg daily and minoxidil solution is available. Two of the included studies examined finasteride 1 mg against twice daily topical application of minoxidil 2% solution [42,59]. Both studies showed superiority for finasteride. At 12 months the mean change from baseline total hair count was 36.1 hairs/cm^2 (29.1%) for finasteride 1 mg and 19.6 hairs/cm^2 (14.8%) for minoxidil 2%, twice daily application (p = 0.003) [42]. 87% of the patients taking finasteride versus 42% of the minoxidil 2% patients were rated as improved (p < 0.001) [59].

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) [14].

Dutasteride

2 studies investigating dutasteride in androgenetic alopecia with grade A2 evidence were included in the evidence based evaluation, resulting in a **LEVEL OF EVIDENCE 2** [61,73].

OUTCOMES

Stough et al. reported an significant mean increase from baseline total hair count of 6.8 hairs/cm^2 at 6 months and 16.5 hairs/cm^2 at 12 months for dutasteride 0.5 mg daily [73]. Olsen et al. showed in a study with 416 patients a significant increase from baseline total hair count for the different tested dutasteride dosages (dutasteride 0.1 mg 15.4 hairs/cm^2 (8.7%), dutasteride 0.5 mg 18.6 hairs/cm^2 (10.2%), dutasteride 2.5 mg 21.5 hairs/cm^2 (11.3%)) at 24 weeks) [61]. Dutasteride 2.5 mg daily showed the best increase in hair count. The mean change from total hair count of finasteride 5 mg was significantly different to dutasteride 2.5 mg (14.8 hairs/cm^2 (8.4%) vs. 21.5

hairs/cm^2 (11.3%), p = 0.009). All dutasteride arms and finasteride 5 mg showed a significant difference of p < 0.001 vs. placebo.

Assessing the dutasteride results it is necessary to remark, that the most effective dosage of dutasteride 2.5 mg is 5 times higher than the standard dosage in the treatment of benign prostatic hyperplasia (dutasteride 0.5 mg corresponds to finasteride 5 mg). Trials comparing dutasteride to the standard dosage of finasteride 1 mg daily are required.

3.2.4 Efficacy – females
2 studies assessing the efficacy of finasteride 1mg daily in female patients were included in the evidence based evaluation [68,74]. The grades of evidence were A2 and B, resulting in an EVIDENCE LEVEL 2.

OUTCOMES
Both studies showed a further progression of hair loss. The mean change from baseline hair count at 12 months was -14.6 hairs/cm^2 (- 5.9%) and -8.7 hairs/cm^2 (- 5.8%). Moreover, the mean decrease from baseline hair count in the finasteride group outvalued the placebo group (0 hairs/cm^2 (0%) resp. -6.6 hairs/cm^2 (- 4.0%)). Trials with higher finasteride dosages or subgroup analyses in young female patients were not available.

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 indicated in women and is contraindicated in pregnant women, 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. Use of a condom is not necessary for this reason.

The recommended dosage is 1 mg a day, but in a dose study with lower dosage of 0.2 mg/day led also to significant improvement compared to placebo. For this reason, if a patient forgets a pill, we do not recommend to take two the next day. Furthermore in case of adverse event a dosage of 0.2 mg/ day or a dosage of 0.5 to 1 mg every other day can be discussed, though no clinical studies are available on this question.

Minimal period of use prior to asses the efficacy is 6 months for reducing hair loss 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 while finasteride action can take over.

Finasteride reduces PSA level. If treatment is started after 45 years monitoring of PSA level should be considered. The PSA levels should be double to compensate the reduction due to finasteride, resulting in an interpretation of the test remaining accurate.

Additional research is required on finasteride at higher dosages and different subgroups of female patients with pattern hair loss including younger females patients and including female patients with or without clinical hyperandrogenism. Anyway, use of finasteride in females can be considered only in combination with safe contraceptive method due to the risk of malformation of genitals in male fetus (feminization). Overall, women under systemic finasteride should avoid donating their blood.

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/cm^2 (12.6%) vs. -13.5 hairs/cm^2 (-8.9%), p = 0.019) [70].

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 [59]. 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 stumptail macaque [75].
Working mechanism of minoxidil and finasteride treatments are different. Thus association of both drugs 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 therapeutic approach is insufficient the combination of finasteride 1 mg and minoxidil 2% or 5% can be considered.

There is no reason to use dutasteride 0.5 mg instead of finasteride 1mg, as higher dosages are needed to reach comparable efficacy and comparison studies versus finasteride 1 mg daily are missing.

In female postmenopausal patients finasteride 1 mg failed to show efficacy (evidence level 2). Additional research is required at higher dosages and in different subgroups of female patients with androgenetic alopecia. If finasteride 1mg is used off label and on own responsability in particular cases in women of childbearing age a safe contraceptive method is essential as finasteride may lead to feminisation of the 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.**==
==→ **There is insufficient evidence to support the use of topical finasteride.**==
==→ **For greater efficacy the combination of oral finasteride 1 mg, 1x/d and topical Minoxidil 2% to 5% solution, 2x/d can be considered.**==

Dutasteride
==→ **Oral Dutasteride 0.5 mg a day can be considered to improve or to prevent progression of AGA in male patients above 18 years with mild to moderate AGA (Hamilton-Norwood IIv-V).**==
==**High quality controlled clinical trials comparing dutasteride 0.5 mg to finasteride 1 mg are needed.**==

3.2.9 Therapeutic recommendation – Female
==↓ **Oral Finasteride 1mg daily is not suggested in the treatment of postmenopausal women with female pattern hair loss.**==
==**High quality controlled clinical trials with finasteride at different dosages on female patients are required.**==

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 [76] studied the change of anagen hair count following daily topical application of the antiandrogen FLUIRIDIL versus placebo. At 12 months, the response to fluridil was not significantly different from placebo. Therefore it is limited evidence that topical fluridil is ineffective in men [76].

Gassmueller et al. [77] 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 [78,79] and/or the results were not reported separately for each sex [79,80]. In one study, topical corticosteroid was included [79].

3.3.4 Efficacy – females
Oral hormonal treatment
Two studies met the inclusion criteria (grade of evidence B, LEVEL OF EVIDENCE 3).

OUTCOMES
Pereeboom-Wynia compared a group of women treated for one year with Diane® (50 µg estradiol +2 mg cyproterone acetate) + 20 mg cyproterone acetate days 1-14 with an untreated control group. 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 [81].

Vexiau 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 [52] 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/cm^2 (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 statically 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.

Topical hormonal treatment
OUTCOMES

Blume-Peytavi et al. [46] reported a decreased total hair count after 6 months therapy with *ALFATRADIOL* 0.025% solution once daily (mean change from baseline -7.8 hairs/cm^2, -4.3%, p<0,0005). Subjects treated with minoxidil 2% solution twice daily showed increased total hair counts at 6 months (15.3 hairs/cm^2; 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/cm^2, p<0.0001).

There are three earlier studies [78,80,81] on the efficacy of the *TOPICAL ESTROGEN* alfatradiol in women and one of topical estrogen combined with corticosteroid [79]. All assessed response using a trichogram. Two studies did not report separately male and female subjects and are not considered further [79,80]. 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 [78].
In a study by Georgala 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 [82]. The change in anagen /telogen ratio differed significantly from placebo treatment (-3.9% at 24 weeks; p<0.01).

As there are contrary results on the efficacy of topical alfatradiol the evidence is insufficient to support his use in female patients with androgenetic alopecia. Further studies are needed to clarify the efficacy of alfatradiol.
Gassmueller et al. [77] 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 (evidence level 4). There is limited proof that oral cyproterone acetate may be helpful in women with AGA and hyperandrogenism .

3.3.8 Therapeutic recommendation – Male

↓↓ **The use of oral estrogens or androgen-receptor-antagonists is inappropriate to improve or prevent progression of AGA in male patients.**

→ **There is insufficient evidence to support the use of topical alfatradiol to improve or prevent progression of AGA in male patients.**

↓ **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

→ **There is no or insufficient evidence to support the use of oral antiandrogens (chlormadinone acetate, cyproterone acetate (CPA), drosperinone, spironolactone, flutamide) to improve or prevent progression of AGA in female patients.**
→ **Oral CPA can be considered in women with clinical or biochemical evidence of hyperandrogenism.**

→ **There is insufficient evidence to support the use of topical alfatradiol to improve or prevent progression of AGA in female patients.**
→ **There is no evidence to support the use of topical natural estrogens or progesterones to improve or prevent progression of AGA in female patients.**

→ **There is no evidence to support the use of topical fluridil to improve or prevent progression of AGA in female patients.**

→ **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 thin areas the hair density can be at least temporarily improved.

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 result 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 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, only 3 studies out of 77 analyzed publications fulfilled the inclusion criteria, resulting in an **EVIDENCE LEVEL 4**. This may be due to many reasons, such as high variation in techniques, multiple steps in the surgical process, problems in measuring hair growth, lack of financial support and difficult patient recruitment.

OUTCOMES

Bernstein et al. compared different preparation techniques for follicular unit transplantation [83]. 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. [84] 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.[70], 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/cm^2 (12.6%) and -13.5 hairs/cm^2 (-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.

3.4.4 Efficacy – females
Only few of the 77 assessed publications concerning hair surgery studied efficacy in female patients. None of them fulfilled the inclusion criteria, resulting in an **evidence level 4**. This may be due to many reasons, such as high variation in techniques, multiple steps in the surgical process, problems in measuring hair growth, lack of funding and difficult patient recruitment.

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 most 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. In patients with progressive alopecia, hair transplantation should only be performed if additional surgery is possible in terms of donor hair reserve.
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.

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

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.

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 into finer, less traumatic recipient sites. Larger grafts with multipe 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 transsection 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.
Individual extraction of FU's from the donor area is also possible but associated with a potentially higher risk of follicle injury and impairment of graft viability.

Recipient sites are prepared with different instruments. The creation of slits using micro-blades 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. [70] reported at 12 month after follicular unit transplantation better clinical outcome for patients treated with combination of finasteride 1 mg daily and hair surgery versus patients treated with hair surgery alone (see section efficacy males).

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
3 studies concerning hair surgery fulfilled inclusion criteria of the S3 guideline (evidence level 4). 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 pretreatment 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.
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 MISCELLANEOUS

3.5.1 Introduction
Besides the pharmacologic therapeutic options minoxidil, 5-alpha-reductase-inhibitors, hormonal preparations and hair surgery, which were already assessed in the previous chapters, the patient afflicted with androgenetic alopecia is faced to a confusing panel of products claiming to be efficient in androgenetic alopecia.
The range of products is wide and reaches from topical to systemic modalities; it includes cosmetic to pharmaceutical products, natural products, functional food and even electrostatic/-magnetic or laser treatment.
Though scientific investigations are rare in the majority of cases, the patient is attracted by hair growth promoting claims of advertisement or distribution of myths, rumors and assumptions provided in different internet fora.
Within the consultation the practitioner will be confronted with questions concerning the efficacy of some of the following products. So it is important in the development of a stable patient-physician-relationship to know these products and their potentials.

3.5.2 Mechanism of action
The assumed mechanisms of action in androgenetic alopecia are as various as the number of products. Though it remains unclear how these products mediate their effects, most of them claim at least one of the following mechanisms:
  a) Promotion of hair regrowth by activation of the dermal papillae and consequently induction of anagen hair regrowth,
  b) Comparable to minoxidil promoting hair regrowth by improving the perifollicular vascularisation
  c) Hormonal effects, mainly inhibition of 5-alpha-reductase and reducing the activity of dihydrotestosterone (DHT)
  d) Anti-inflammatory activity
  e) Improvement of hair follicle nutrition
In *table 2* we aimed to group the different therapeutic options based on their assumed main mechanism of action.

3.5.3 Efficacy – males and females
Contrary to the previous chapters the efficacy of the miscellaneous therapies is summarized together for males and females, as evidence proving the efficacy of the particular therapies in androgenetic alopecia is less to non-existent.

For almost 50% of the therapeutic agents no literature fulfilling the inclusion criteria of the guideline was found. Furthermore, the evaluation 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. Only 11 of the 20 trials that were included into the guideline examined a single therapeutic agent.
The available evidence is therefore insufficient resulting in EVIDENCE LEVEL 4 for the different therapeutic options.
Hereafter, we will give a short overview on the different therapeutic agents.

Aminoacids, especially cysteine is supposed to lead to increased growth factors involved in hair growth. 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)[85]. 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 sifnificantly different to placebo (p = 0.0225)[86].

Trace elements like *copper* and *zinc* are suggested to improve hair nutrition, though studies examining the link between serum and hair follicle concentration of trace elements, vitamins etc. fail to show correlation. As zinc and copper were only studied in combination with other agents, evidence is missing.

Different beliefs exist concerning the supplementation of *iron* in absence of iron deficiency in patients afflicted with androgenetic alopecia. Various observational studies discussed relation between hair loss and decreased serum ferritin levels with controversy results [87]. There is insufficient evidence for iron supplementation in absence of iron deficiency in patients with androgenetic alopecia.

Vitamines especially *biotin* and *niacin* are also claimed to have hair growth promoting properties and have positive influence on hair nutrition. Draelos et al. studied the effect of topical applied niacin derivates once daily in 60 female patients. After 6 months 69% were rated as improved in global photographic assessment (p = 0.04 vs. placebo)[88]. 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 ß-sitosterol and saw palmetto [89].

Proanthocyanidines like procyanidine B appertain to the group of flavonoids, which are antioxidants. The mechanism of action may be inhibition of transforming growth factor TGF-ß and conversion of telogen follicle to anagen hair follicle. 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) [90].

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 (Priorin®) taken twice the day for 6 months led to increased anagen rates female patients (p = 0.0225 vs. placebo) [86]. Viviscal® is a similar oral supplement composed of marine extracts and a silicea component. Lassus et al. studied this supplement in comparison to fish extract and in combination with topical and oral use [91,92]. Due to lack of placebo respectively standard for comparison the results are deficient.

2 trials examining the efficacy of topical applied *herbal preparations* fulfilled the inclusion criteria of the guideline [93,94]. As the ingredients of the particular herbal preparations significantly differ, they have to be evaluated separately. Kessels et al. proved modest increase in hair regrowth in 396 male patients, who applied twice daily a Chinese herbal preparation for 6 months. The mean change in nonvellus hair counts was 26.6 hairs/cm^2 vs. 21.8 hairs/cm^2, p = 0.02 vs. placebo)[94]. 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)[93].

No trials were found concerning the *natural products gingko biloboa, aloe vera, ginseng, bergamot, hibiscus or sorphora*. Animal models and resp. or in vitro

studies suggest hair growth promoting properties. The agents are used in cosmetically hair care products.

There are different hair care products with **caffeine** claiming to be an effective treatment in androgenetic alopecia in men and women. Caffeine showed in in vitro studies higher transfollicular penetration rates [95]. Caffeine is suggested to prevent progression and induce hair regrowth in androgenetic alopecia. Studies investigating this hypothesis are missing/not available.

Topical application of **melatonin** leads to induction of anagen hair in animal models. A small trial, which did not fulfil the inclusion criteria of the guideline, reported significantly increased anagen hair rates in trichogram in women with androgenetic alopecia or diffuse effluvium after topical use of melatonin 0.1% for 6 months [96].

Retinoids modulate proliferation, differentiation of ceratinocytes and the T-cellulary immune response. Moreover, its usage as pharmaceutical excipient to improve minoxidil resorption is discussed. Two trials fulfilled the inclusion criteria of the guideline [15,44]. 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 [15]. 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 [44]. 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/cm^2 vs. 18.2 hairs/cm^2).
The induction of hypertrichosis is well known as adverse event in systemic treatment with ciclosporin. Experimental models could demonstrate this effect for topical application of ciclosporin, too. In a small study by Gilhar et al. 2 patients out of 8 had response to topical application of ciclosporin for 12 months [97].

Besides cosmetic and pharmaceutic agents **physicalic treatments** like pulsed electromagnetic/-static field and low level laser therapy are also claiming efficacy in androgenetic alopecia.
4 trials for pulsed electrostatic field could be included into the evidence-based evaluation of the guideline [98-101]. Though the trials showed modest increase in total, anagen or nonvellus hair counts, the use in clinical routine is doubtful due to unfavourable cost-benefit ratio.
Satino et al. examined the effects of a low level laser comb in androgenetic alopecia [102]. They reported a mean change from baseline total hair count of 14.1 hairs/cm^2. A control group for comparison was missing.

Cimicifuga racemosa is a natural product with positive influence on the estrogenic level. It is mainly used for perimenopausal complaints. No evidence was found for its efficacy in androgenetic alopecia, though it is conceivable that elevation of estrogen levels in menopause can improve androgenetic alopecia in female patients.

Other therapeutic agents may act by inhibition of the activity of dihydrotestosterone (DHT), namely **saw palmetto, ß-sitosterol, green tea or polysorbate 60**.
The application of a lotion containing saw palmetto extract twice a day showed statistically significant improvement in mean change from baseline total hair count at

50 weeks (p < 0.005 vs. placebo)[85]. A combination of saw palmetto, ß-sitosterol, nicacin and biotin in an oral softgel taken twice daily also led to improvement significantly different to placebo treatment (investigator assessment 60% improved vs. 11%)[89].

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 [103]. After 16 weeks global photographic assessment for the polysorbate group was below the placebo group.

Whereas the previous agents claim to have mechanism of action comparable to 5-alpha-reductase-inhibitors, others may improve perifollicular vascularization similar to minoxidil. **Aminexil** is a vasodilatator chemically similar to minoxidil. Studies, that provide evidence for its efficacy, are missing.

Another promising group of substances were the prostaglandine analogues like **viprostol or latanoprost**. They mediate vasodilatatory effects and latanoprost leads in topical use as eye drops to induction of hair growth of the eye lashes. Unfortunately, the topical application of viprostol for 24 weeks in male patients did not show significant difference compared to placebo or vehicle treatment [104].

Minerals and niacin derivates should have additional to the hair growth promoting property positive effects on perifollicular vascularisation. Reygagne et al. assessed the efficacy of a topical combination of glycerol oxyesters and silicium (Maxilene®)[38]. In comparison to standard minoxidil treatment Maxilene® led to statistically significant hair loss.

Another therapeutic regimen that claims to improve andorgenetic alopecia by improvement of vascularization and hair nutrition is the **mesotherapy**. Different agents, e.g. vitamins are intracutaneously injected. There was no evidence of efficacy found.

The injection of botulinum toxin is also suggested to improve androgenetic alopecia. A traction component by tension of the musculus occipitofrontalis is discussed, but studies are missing.

A further therapeutic approach is to act on the inflammatory component of androgenetic alopecia. **Ketoconazole or zinc pyrithione** are antimicrobial and are effective agents in the treatment of seborrhoic dermatitis. As concomitant seborrhoic 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 [16]. 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.

3.5.4 Instructions for use / Practicability
For instructions for use the reader is asked to consult the information of the particular product information.

3.5.5 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, it cannot be recommended in combination. Additional use depends on the individual case and decision of the patient and the physician.

3.5.6 Summary
A plenty of oral and topical miscellaneous therapies claim to be effective in the treatment of androgenetic alopecia in men and women. There is insufficient to missing evidence for this assumption (evidence level 4).

3.5.7 Therapeutic recommendation – Male and Female
→ **There is no or insufficient evidence that the following molecules, substances and interventions improve or prevent progression of AGA in male and female patients.**

4 Implementation and evaluation
References
Attachment 1: Inclusion criteria for the S3 guideline
Attachment 2: Result tables

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Literature Evaluation Form (LEF)

A. Inclusion/Exclusion of an article:

This serves as a prescreening. If the article is not included, neither the quality nor the results will be assessed. (tick a grey box = exclusion of the article)

1. Author + Year: _____ + ____

2. Language: _____

3. Type of the study: prospective study?   Yes ☐   No ■

4. Number of patients ≥ 20?   Yes ☐   No ■
    Exception in identical twin studies no minimal patient number required.

5. Age: Adults (≥ 18 years)   ☐
    Adolescents (≥ 12 years)   ☐
    (Studies of adolescents will be evaluated separately)
    Children / n.d.   ■

6. Confirmed diagnosis of androgenetic alopecia male versus female pattern, respectively
    (diagnosis either clinically or by further diagnostic evaluations e.g. trichogram, trichoScan,
    biopsy)?   Yes ☐   No/n.d. ■

7. Type of therapy?
    monotherapy ☐   *or*   combination therapy ☐   distinct classification not possible ■

8. Objective outcome measure of efficacy described?   Yes ☐   No ■
    For drug therapy:
    Mean change from baseline hair count in target area OR
    Measurement of hair growth/loss in target area by global photography
    For surgical therapy:
    Mean change from baseline hair count in target area OR
    Measurement of hair growth/loss in target area by global photography OR
    Graft survival and global photography

9. Exception:
    Category of the article: Review ☐   Safety study ☐   Other ☐
    Article should be quoted: Yes ☐   No ■

B. Quality of articles / Methods / will be partly published in table

1. Randomisation?   Yes ☐   No ☐
   A. Adequate - e.g. computerized randomization list,
         table with random numbers   ☐
   B. Unclear - insufficient details provided   ☐
   C. Inadequate - e.g. open list or day of week   ☐
   D. Not used   ☐

2. Concealment of allocation
   A. Adequate - e.g. third party or opaque sealed envelopes   ☐
   B. Unclear - insufficient details provided   ☐
   C. Inadequate - e.g. open list or day of week   ☐
   D. Not used   ☐

3. Blinding of randomisation
   Participant/Patient   Yes ☐   No ☐   Unsure ☐
   Clinician   Yes ☐   No ☐   Unsure ☐
   Outcome assessor   Yes ☐   No ☐   Unsure ☐

4. Intention-to-treat analysis
   Were all randomised participants included within the analysis in the groups they have been
   randomised?   Yes ☐   No ☐   Unsure ☐

5. Definition of the disease stage?
   Hamilton-Norwood ☐   Ludwig ☐   Savin scale ☐   No definition ☐

6. Population's gender   male ☐   female ☐   both ☐

7. Groups comparable at baseline point? Yes ☐   No ☐   Unsure ☐
   Note any differences: _____

8. Interventions described adequately?   Yes ☐   No ☐   Unsure ☐

9. Previous treatments stopped?   Yes ☐   No ☐   Unsure ☐
   Wash-out period reported?   Yes ☐   No ☐
   Duration of the wash-out period: _____

10. Study duration adequate?   Yes ☐   No ☐   Unsure ☐
    (At least 12 weeks. Minimum of 24 weeks are recommended)

11. Concomitant active treatment permitted? Yes ☐   No ☐   Unsure ☐
    Details: _____

12. Assessment of compliance undertaken? Yes ☐   No ☐   Unsure ☐
    Method: _____

13. Sponsorship
    Mentioned: Yes ☐   No ☐
    Name: _____

14. If Sponsorship mentioned: Dependent Sponsor   ☐
                                  Independent Sponsor   ☐
                                  Unsure   ☐

C.   Degree of Evidence

This article belongs to the following classes:

A_1 ☐ Meta-analyses which include at least one randomized clinical trial of A_2 - level with consistent results of the different studies.

A_2 ☐ Randomized, double blind clinical studies of good quality (e.g. sample size calculation, flow chart of patient inclusion, ITT - analysis, sufficient size)

B ☐ Randomized, clinical studies of less good quality or other comparable studies (not - randomized: cohort- or case - control - studies)

C ☐ Non - comparable studies

D.   Results (will be published in table)

Methods / Results:

1. Number of patients: _____

2. Duration of treatment: _____

3. Intervention / dosage scheme / application methods:
    Arm 1: _____
    Arm 2: _____
    Arm 3: _____
    Arm 4: _____
    Arm 5: _____
    N.B. Please indicate the study design in each individual therapy arm concerning the treatment groups and the dosages.

4. Results / Definition of treatment success / Measurements of effect

    N.B. Please define the used outcome measurements. Look for results at month 6, 12 or long time results. If metric baseline points are provided, please indicate unit, baseline points and study end in table A.
    For outcome the measurements without metric baseline points e.g. global photographic assessment, please indicate in percentage in table B the changes from the baseline point to the study end. Please indicate if assessments e.g. baseline photograph are provided.

    Definition of treatment success (outcome): _____

Table A1	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Baseline point Unit: _____	_____	_____	_____	_____	_____
Value at _____ Unit: _____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

Definition of treatment success (outcome): _____

Table A2	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Baseline point Unit: _____	_____	_____	_____	_____	_____
Value at _____ Unit: _____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

Definition of treatment success (outcome): _____
Comparison: _____

Table B1	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
% improvement Time: _____	_____	_____	_____	_____	_____
% unchanged Time: _____	_____	_____	_____	_____	_____
% worsening Time: _____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

Definition of treatment success (outcome): _____
Comparison: _____

Table B2	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
% improvement Time: _____	_____	_____	_____	_____	_____
% unchanged Time: _____	_____	_____	_____	_____	_____
% worsening Time: _____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

Definition of treatment success (outcome): _____
Comparison: _____

Table B3	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
% improvement Time: _____	_____	_____	_____	_____	_____
% unchanged Time:_____	_____	_____	_____	_____	_____
% worsening Time: _____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

5. If other effects than hair loss reduction, stop of hair loss or hair regrowth are described, please indicate the results.
   Definition of alternative outcome measure scores / effects: _____
   Point of time: _____
   Arm 1: _____
   Arm 2: _____
   Arm 3: _____
   Arm 4: _____
   Arm 5: _____

6. Hair loss restart/ Follow up   Yes ☐   No ☐

   Duration of the follow up: _____
   Ending effect after therapy stop:
   Arm 1: _____
   Arm 2: _____
   Arm 3: _____
   Arm 4: _____
   Arm 5: _____

7. ADRs specified

   What are the most important side effects (most frequent and most severe)?
   Listing if not defined in detail: _____
   Arm 1: _____
   Arm 2: _____
   Arm 3: _____
   Arm 4: _____
   Arm 5: _____

8. Losses to follow up

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
n at randomisation	_____	_____	_____	_____	_____
n at follow-up	_____	_____	_____	_____	_____
Drop-outs	_____	_____	_____	_____	_____
%	_____	_____	_____	_____	_____

9. Drop-outs caused by ADRs
   Did the patients drop out predominantly because of adverse effects?   Yes ☐   No ☐
   If yes, please specify:

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
All dropouts (n)	_____	_____	_____	_____	_____
AE related drop-outs (n)	_____	_____	_____	_____	_____
AE related / All dropouts (%)	_____	_____	_____	_____	_____
AE related drop-outs / n at ran-domisation (%)	_____	_____	_____	_____	_____

Minoxidil

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (non vellus) hairs/cm² (%)	mean change from baseline hair count (anagen, telogen.h. anagen/telogen ratio)	mean change from baseline hair weight / thickness	global expert panel assessment	investigator assessment	patient assessment	investigational area	Degree of evidence
41	Roenigk	1987	777	male	6m	Arm1: minoxidil 2.8%, 2x/d, topical							46.6%			C
28	Montagnani	1990	33	male	24w	Arm1: Minoxidil 2% solution, 2x/d, topical							37.5%			C
23	Karam	1993	195	male	48w	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	44.7 (82.1%) p < 0.001 vs. Baseline	47.8 (119.7%) p < 0.0001 vs. Baseline						vertex	C

Minoxidil vs. Placebo
male

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (non vellus) hairs/cm² (%)	mean change from baseline hair count (anagen, telogen.h. anagen/telogen ratio)	mean change from baseline hair weight / thickness	global expert panel assessment	investigator assessment	patient assessment	investigational area	Degree of evidence
34	Olsen	2007	352	male	16w	Arm1: minoxidil 5% 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
						Arm2: placebo foam, 2x/d, topical			4.7 (3.4%)					5.2% unchanged: 77.9%		
17	Califano	1991	132	male	24w	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	18.8 (47.6%)	17.3 (59.4%)						vertex	A2
						Arm2: placebo solution, 2x/d, topical		17.9 (48.8%)	12.3 (46.2%)							
13	Anderson	1988	154	male	24w	Arm1: minoxidil 2% solution, 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
						Arm2: placebo, 2x/d, topical		10.3 (15.5 %)	12.1 (31.8%)							
22	Dutree-Meulenberg	1988	151	male	24w	Arm1: minoxidil 2% solution, 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
						Arm2: placebo, 2x/d, topical		18.4 (20.4%)	5.9 (10.7%)							
35	Petzold	1988	201	male	24w	Arm1: Minoxidil 2% solution, 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
						Arm2: placebo, 2x/d, topical		6.1 (14.9%)	2.5 (7.3%)							
30	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%)							
45	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							
33	Olsen	2002	393	male	48w	Arm1: minoxidil 5% solution, 2x/d, topical	phototrichogram		18.6 (12.3%) p < 0.001 vs. Placebo, p = 0.025 vs. Arm2					improved: 57.9% unchanged: 30.3%	vertex	A2
						Arm2: minoxidil 2% solution, 2x/d, topical			12.7 (8.8%) p < 0.013 vs. Placebo					improved: 40.8% unchanged: 48.6%		
						Arm3: placebo, 2x/d, topical			3.9 (2.6%)					improved: 23.2% unchanged: 60.6%		

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (nonvellus) hairs/cm² (%)	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
18	Civatte	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%)							
27	Lopez-Bran	1990	114	male	24w, 48w	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	**24w:** 5.4 (12.1%) **48w:** 15.5 (34.6%)	**24w:** 4.7 (17.2%) **48w:** 14.2 (52.4%)						vertex	A2
						Arm2: 24w placebo, 2x/d, topical, 25-48w minoxidil 2% solution, 2x/d, topical		**24w:** 4.7 (10.4%) **48w:** 12.2 (27.1%)	**24w:** 2.9 (10.8%) **48w:** 10.5 (39.4%)							
19	Civatte	1988	428	male	24w, 48w	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	**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%)							
12	Atanis	1991	240	male	24w, 48w	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	**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								
36	Piepkorn	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%**		
29	Olsen	1985	153	male	4m, 12m	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	**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%)							
43	Savin	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							
24	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%)							

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (nonvellus) hairs/cm² (%)	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
						Arm3: 4m placebo, 2x/d, topical, 5-24m minoxidil 3% solution, 2x/d, topical			4m: 9.8 (116.3%) 12m: 33.1 (393.0%)							
21	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						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							
31	Olsen	1987	127	male	132w	Arm1: minoxidol 3% solution, 2x/d, topical	phototrichogram	64,4	65.7						vertex	B
						Arm2: 24m minoxidol 3% solution, 2x/d, topical, 25-33m minoxidil 3% solution, 1x/d, topical		44,1	46.1							
12	Alanis	1991	240	male	24w, 48w	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count		24w: 9.9 (27.7%) 48w: 18.2 (50.9%)						vertex	B
						Arm2: 24w placebo, 2x/d, topical, 25-48w minoxidil 2% solution, 2x/d, topical			24w: 4.8 (12.6%) 48w: 12.3 (32.4%)							
25	Koperski	1987	72	male	12m, 30m	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
						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								
32	Olsen	1990	31	male	3y	Arm1: minoxidil 3% solution, 2x/d, topical	phototrichogram		4.4 p = 0.015 vs. Arm2						vertex	B
						Arm2: 1st y minoxidil 3% solution, 2x/d, topical, 2nd-3rdy, 1x/d, 4th-5thy 2x/d			-13.4							
26	Kreindler	1987	150	male	4m, 12m	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	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%)							
20	Connors	1990	169	male	24w, 48w	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count		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)							

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (non-vellus) hairs/cm² (%)	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
37	Price	1999	36	male	96w	Arm1: minoxidil 2% solution, 2x/d, topical	manual hair count	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%					

male and female

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (non-vellus) hairs/cm² (%)	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
39	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	manual hair count	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%)							
40	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								

female

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (non-vellus) hairs/cm² (%)	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
51	Tsuboi	2007	280	female	24w	Arm1: minoxidil 1% solution, 2x/d, topical	phototrichogram	15.2 (8.0%) p < 0.001 vs. Placebo	8.2 (6.1%) p < 0.001 vs. Placebo						bald area	A2
						Arm2: placebo, 2x/d, topical	phototrichogram	2.9 (1.5%)	2.0 (1.5%)							
48	Jacobs	1993	346	female	32w	Arm1: minoxidil 2% solution, 2x/d, topical	phototrichogram		33.1 (24.2%) p = 0.0148 vs. Placebo						bald area	A2
						Arm2: placebo, 2x/d, topical	phototrichogram		19.1 (13.7%)							
47	De Villez	1994	308	female	24w, 32w	Arm1: minoxidil 2% solution, 2x/d, topical	phototrichogram		24w: 21.8 (15.5%) 32w: 22.7 (16.2%) p = 0.02 vs. Placebo						bald area	A2
						Arm2: placebo, 2x/d, topical			24w: 9.9 (7.1%) 32w: 10.1 (7.3%)							
53	Whiting	1992	33	female	24w, 32w	Arm1: minoxidil 2% solution, 2x/d, topical	phototrichogram		21 (12.4%) n.s. vs. Placebo						bald area	B
						Arm2: placebo, 2x/d, topical	phototrichogram		17 (10.6%)							
50	Olsen	1991	30	female	32w	Arm1: minoxidil 2% solution, 2x/d, topical	phototrichogram		50.1 (31.3%) p = 0.006 vs. Placebo						frontoparietal	B
						Arm2: placebo, 2x/d, topical			20.6 (13.4%)							
49	Lucky	2004	381	female	48w	Arm1: minoxidil 5% solution, 2x/d, topical	phototrichogram		24.5 (17.3%) p < 0.001 vs. Placebo, p = 0.129 vs. Arm2						fronto-/occipitoparietal	A2
						Arm2: minoxidil 2% solution, 2x/d, topical			20.7 (13.8%) p < 0.001 vs. Placebo							
						Arm3: placebo, 2x/d, topical			9.4 (6.8%)							

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (nonvellus) hairs/cm² (%)	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
Other																
14	Arca	2004	65	male	12m (52w)	Arm1: minoxidil 5% solution, 2x/d, topical	7-point-rating scale					80%			frontal/parietal	B
						Arm2: finasteride 1mg, 1x/d, oral						52%				
42	Saraswat	2003	99	male	12m	Arm1: 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
						Arm2: minoxidil 2% solution, 2x/d, topical		19.6 (14.8%)				56%				
16	Berger	2003	200	male	26w	Arm1: minoxidil 5% solution, 2x/d, topical + pyrithione zinc 1% shampoo, 1x/d, topical	photographichogram	6,2							vertex	A2
						Arm2: minoxidil 5% solution, 2x/d, topical + placebo shampoo, 1x/d, topical		12,3								
						Arm3: pyrithione zinc 1% shampoo, 1x/d, topical		5,7								
						Arm4: placebo shampoo, 1x/d, topical		-0.6								
38	Reygagne	1997	72	male	6m	Arm1: minoxidil 2% solution, 2x/d, topical	photographichogram	6.8 (11.0%) p < 0.001 vs. Arm2		anagen: 4.5 (9.8%) p = 0.06 vs. Arm2					vertex	B
						Arm2: maxilene lotion (glycerol oxyesters and organic silicium), 1x/d, topical		-3.0 (-4.8%)		-1.8 (-3.7%)						
44	Shin	2007	31	male	18w	Arm1: minoxidil 5% solution, 2x/d, topical	photographichogram	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, evening		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					
15	Bazzano	1986	56	female and male	12m	Arm1: placebo, 2x/d, topical	manual hair count	0%							bald area	B
						Arm2: minoxidil 0.5%, 2x/d, topical		0%								
						Arm3: tretinoin 0.025% solution 2x/d, topical		58%								
						Arm4: minoxidil 0.5% + Tretinoin 0.025% solution, 2x/d, topical		66%								
46	Blume-Peytavi	2007	103	female	6m, 12m	Arm1: minoxidil 2% solution, 2x/d, topical	TrichoScan	6m: 15.3 (8.7%) p = 0.0025 vs. Baseline, p < 0.0005 vs. Arm2 12m: 17.3 (9.9%) n.s. vs. 6m			hair thickness (mm/cm²) 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					
52	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	photographichogram	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/cm²) 25 p < 0.001 vs. Arm2					frontoparietal	B
						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		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						

Finasteride

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (non vellus) hairs/cm² (%)	mean change from baseline hair count (anagen, telogen.n. anagen/telogen ratio)	mean change from baseline hair weight / thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
66	Trüeb	2001	265	male	6m	Arm1: finasteride 1 mg, 1x/d, oral	n.a.					39.9%				C

Finasteride vs. Placebo

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (non vellus) hairs/cm² (%)	mean change from baseline hair count (anagen, telogen.n. anagen/telogen ratio)	mean change from baseline hair weight / thickness	global expert panel assessment	investigator assessment	patient assessment	Investigational area	Degree of evidence
65	Stough	2002	18	male	1y	Arm1: finasteride 1mg, 1x/d, oral	phototrichogram	16 (9.8%) $p < 0.05$ vs. placebo				44% $p < 0.01$ vs. placebo			vertex	A2
						Arm2: placebo, 1x/d, oral		-4 (-2.5%)				11%				
67	van Neste	2000	212	male	48w	Arm1: finasteride 1 mg, daily, oral	phototrichogram	7.2 (3.6%) $p < 0.001$ vs. placebo		anagen, hairs/cm² (%): 18 (14.5%) $p < 0.001$ vs. placebo					vertex	A2
						Arm2: placebo, daily, oral		-10.1 (-5.2%)		anagen, hairs/cm² (%): -9.0 (-7.6%)						
58	Kawashima	2004	414	male	48w	Arm1: finasteride 1 mg, 1x/d, oral						improved: 58% $p < 0.001$ vs. placebo unchanged: 40%			vertex	A2
						Arm2: finasteride 0.2 mg, 1x/d, oral						improved: 54% $p < 0.001$ vs. placebo unchanged: 41%				
						Arm3: placebo, 1x/d, oral						improved: 6% unchanged: 72%				
57	Kaufman	1998	1553	male	12m	Arm1: finasteride 1 mg, 1x/d, oral	phototrichogram	16.9 (11.0%) $p < 0.001$ vs. placebo				48% (12m) 66% (24m) $p < 0.001$ (12m) vs. placebo			vertex	A2
						Arm2: placebo 1x/d, oral		-4.1 (-2.7%)				7% (12m) 7% (24m)				
						Arm3: 1sty finasteride 1mg, 1x/d, oral, 2ndy placebo, 1x/d, oral										
						Arm4: 1st y placebo, 1x/d, oral, 2nd y finasteride 1 mg, 1x/d, oral										
64	Roberts	1999	693	male	6m, 12m	Arm1: finasteride 5mg, 1x/d, oral	phototrichogram	6m: 12.9 (7.7%) 12m: 18.2 (10.8%) $p < 0.001$ (6,12m) vs. baseline and placebo				51% (6m) 48% (12m) $p < 0.001$ vs. placebo			vertex	A2
						Arm2: placebo, 1x/d, oral		6m: -3.9 (-2.1%) 12m: -3.9 (-2.1)				10% (6m) 3% (12m)				
						Arm3: finasteride 1 mg, 1x/d, oral		6m: 13.5 (7.3%) 12m: 16.7 (9.0%) $p < 0.001$ (6,12m) vs. baseline and placebo				52% (6m) 54% (12m) $p < 0.001$ vs. placebo				
						Arm4: finasteride 0.2 mg, 1x/d, oral		6m: 10.8 (6.1%) 12m: 12.7 (7.2%) $p < 0.001$ (6,12m) vs. baseline and placebo				38% (6m) 38% (12m) $p < 0.001$ vs. placebo				
						Arm5: finasteride 0.01 mg, 1x/d, oral		6m: -1.8 (-1.0%) 12m: -3.5 (-2.0 %)				12% (6m) 10% (12m)				
69	Whiting	2003	424	male	2y	Arm1: finasteride 1 mg, 1x/d, oral						improved: 39% $p < 0.001$ vs. placebo unchanged: 55%			vertex	A2
						Arm2: placebo, 1x/d, oral						improved: 4% unchanged: 73%				
71	The Finasteride Male Pattern Hair Loss Study Group	2002	1553	male	24m, 60m	Arm1: finasteride 1mg, 1x/d, oral	phototrichogram	7.5 (4.3%) $p < 0.001$ vs. baseline and placebo				improved: 48% $p < 0.001$ vs. placebo unchanged: 42% $p < 0.001$ vs. placebo			vertex	A2
						Arm2: placebo, 1x/d, oral		-46.9 (-26.5%) $p < 0.001$ vs. baseline				improved: 6% unchanged: 19%				
						Arm3: 1sty finasteride 1mg, 1x/d, oral, 2ndy placebo, 1x/d, oral, 3rdy-5thy finasteride 1 mg, 1x/d, oral										
						Arm4: 1st y placebo, 1x/d oral, 2nd y-5th y finasteride 1 mg,1x/d, oral										
62	Price	2002	66	male	48w, 96w	Arm1: finasteride 1 mg, 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			hair weight: 48w: 20.4% 96w: 21.5% $p < 0.001$ (48w, 96w) vs. placebo				frontoparietal	A2
						Arm2: placebo, 1x/d, oral		48w: 3.2% 96w: -6.3% $p = 0.11$ (48w) $p < 0.05$ (96w)			hair weight: 48w: -5.2% 96w: -14.2%					

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (nonvellus) hairs/cm² (%)	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
60	Leyden	1999	326	male	6m, 12m, 24m	Arm1: finasteride 1 mg, 1x/d, oral	phototrichogram	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
						Arm2: placebo, 1x/d, oral, 2nd y finasteride 1 mg, 1x/d, oral		6m: -4.0 (-1.8%) 12m: -2.0 (-0.9%) 24m: 8.0 (3.7%)				improved: 7% unchanged: 86%				
72	Brenner	1999	28	male	6m, 12m, 24m	Arm1: 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 p < 0.01 (12,24m) vs. placebo							bald area	B
						Arm2: placebo, 1x/d, oral		6m: -2.6 12m: -1.3 24m: -14.1								
63	Price	2006	28	male	36m (144w), 48m (192w)	Arm1: 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
						Arm2: placebo, 1x/d, oral		36m: -1.6% 48m: -13.0%			weight (%) 36m: -14.8% 48m: -24.5%					

Finasteride vs. other therapies

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change total	nonvellus	anagen/telogen	weight/thickness	global expert panel	investigator assessment	patient assessment	Investigational area	Degree of evidence
14	Arca	2004	65	male	12m (52w)	Arm1: minoxidil 5% solution, 2x/d, topical							80%		frontal/parietal	B
						Arm2: finasteride 1mg, 1x/d, oral							52%			
42	Saraswat	2003	99	male	12m	Arm1: 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
						Arm2: minoxidil 2% solution, 2x/d, topical		19.6 (14.8%)					56%			
59	Khandpur	2002	100	male	12m	Arm1: finasteride 1 mg, 1x/d, oral							87% p < 0.03 vs. Arm2 p < 0.001 vs. Arm3 p = 0.3 vs. Arm4			B
						Arm2: finasteride 1 mg, 1x/d, oral + minoxidil 2% solution, 2x/d, topical							100% p < 0.001 vs. Arm3 p = 1 vs. Arm4			
						Arm3: minoxidil 2% solution, 2x/d, topical							42% p < 0.0014 vs. Arm4			
						Arm4: finasteride 1 mg, 1x/d, oral + ketoconazole 2% shampoo, 3x/w, topical							100%			

Combination therapies

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change total	nonvellus	anagen/telogen	weight/thickness	global expert panel	investigator assessment	patient assessment	Investigational area	Degree of evidence
70	Leavitt	2005	79	male	12m	Arm1: hairtransplantation + finasteride 1mg, 1x/d, oral	macrophotograph	18.5 (12.6%) p = 0.019 (Arm1 vs. Arm2)							frontal	A2
						Arm2: hairtransplantation + placebo, 1x/d, oral		-13.5 (-8.9%)								

Finasteride - female patients

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change total	nonvellus	anagen/telogen	weight/thickness	global expert panel	investigator assessment	patient assessment	Investigational area	Degree of evidence
68	Whiting	1999	163	female and male	12m	Arm1: finasteride 1mg, 1x/d, oral, male	biopsy	17.7 (5.5%)	41.5 (34.8%)						vertex men, frontal/parietal women	B
						Arm2: placebo, 1x/d, oral, male		-0.8 (-0.3%)	7.7 (5.8%)							
						Arm3: finasteride 1mg, 1x/d, oral, female		-14.6 (-5.9%)	1.5 (1.0%)							
						Arm4: placebo, 1x/d, oral, female		0.0 (0.0%)	8.5 (5.3%)							
74	Price	2000	137	female	1y	Arm1: finasteride 1 mg, 1x/d, oral	phototrichogram	-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
						Arm2: placebo, 1x/d, oral		-6.6 (-4.0%) p < 0.05 vs. baseline		A/T ratio 1.7 (29.8%)		improved: 16% unchanged: 77%				

Dutasteride

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change total	nonvellus	anagen/telogen	weight/thickness	global expert panel	investigator assessment	patient assessment	Investigational area	Degree of evidence
73	Stough	2007	34	male	6m, 12m	Arm1: dutasteride 0.5 mg, 1x/d, oral	phototrichogram	6m: 6.8 12m: 16.5 significant (6m) vs. placebo p = 0.14 (12m) vs. placebo							vertex	A2
						Arm2: placebo, 1x/d, oral		6m: -11.0 12m: -3.8								
61	Olsen	2006	416	male	24w	Arm1: dutasteride 0.1 mg, 1x/d, oral	phototrichogram	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%			

ArtNumber / Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (nonvellus) hairs/cm² (%)	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
81 Peereboom-Wynia	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%)						
52 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	phototrichogram	6m: 16.1 (8.6%) 12m: 16.9 (9.1%) p < 0.001 (12m) vs. Baseline and Arm2		anagen (hairs/cm²) 25 p < 0.001 vs. Arm2					frontoparietal	B
					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		6m: -2.8 (-1.4%) 12m: -7.8 (-3.9%) p 0 0.85 (12m) vs. Baseline		-5.6						
77 Gassmueller	2008	172	male and female	16w	Arm1: Fulvestrant 70 mg/ml, 2x/d, topical, men	TrichoScan	8.2 (4.4%) p 0 0.815 vs. Placebo p < 0.001 vs. Minoxidil			hair thickness mm/cm² 0.84 (5.4%) p = 0.968 vs. Placebo p < 0.001 vs. Minoxidil				vertex	A2
					Arm2: placebo, 2x/d, topical, men		8.0 (4.4%)			0.7 (4.4%)					
					Arm3: minoxidil 2% solution, 2x/d, topical, men		25.4 (13.3%)			2.9 (17.3%)					
					Arm4: fulvestrant 70 mg/ml, 2x/d, topical, women		14.7 (6.9%) p 0 0.340 vs. Placebo			1.54 (7.2%) p = 0.227					
					Arm5: placebo, 2x/d, topical, women		15.3 (7.9%)			1.58 (8.1%)					
46 Blume-Peytavi	2007	103	female	6m, 12m	Arm1: 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 (9.9%)	6m: 14.0 p = 0.003 vs. Baseline 12m: 14.9 p < 0.001 vs. Arm2		hair thickness mm/cm² 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: -6.0 12m: 5.9		6m: -0.5 n.s. vs. Baseline 12m: 0.4					
82 Georgala	2004	75	female	12 - 24w	Arm1: Alfatradiol lotion 0.03%, 1x/d, topical, 12w	trichogram			A/T ratio 0.65 (38.7%) p < 0.01 vs. Placebo, n.s. vs. Arm2					bald area	B
					Arm2: Alfatradiol lotion 0.03%, 1x/d, topical, 24w				0.7 (44.6%) p < 0.01 vs. Placebo						
					Arm3: placebo lotion, 1x/d, topical, 24w				-0.06 (-3.9%)						
80 Wozel	2005	233	female and male	30w	Arm1: alfatradiol 0.025% solution, 1x/d, topical, men	trichogram			telogen rate -6.7 (-21.1%)					frontal	C
					Arm2: alfatradiol 0.025% solution, 1x/d, topical, women				-5.8 (-24.4%)						
78 Orfanos	1980	69	female and male	6m	Arm1: Alfatradiol 0.025% solution, 1x/d, topical	trichogram			%improvement from baseline telogen rate**** 63%					triangular	B
					Arm2: placebo, 1x/d, topical				37%						
79 Wüstner	1974	50	female and male	6m	estrogen and corticoid, 1x/d, topical	trichogram	52%		%improvement from baseline telogen rate**** 52%					triangular/parietal	C
76 Sovak	2002	43	male	3m, 9m	Arm1: fluridil, 1x/d, topical	phototrichogram			anagen hairs/cm² 3m: 9.3 (13.5%) 9m: 10.6 (15.5%)						B
					Arm2: placebo, 1x/d, topical				3m: 6.5 (10.1%) 9m:13.1 (20.5%)						

Art.Number	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (nonvellus) hairs/cm² (%)	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
Surgery																
84	Uebel	2006	20	male	7m	Arm1: follicular unit transplantation	manual hair count	**follicular units (%)** ¹-40 (-28.2%) p < 0.001 (Arm1 vs. Arm2)							parietal	C
						Arm2: follicular unit transplantation + platelet plasma growth factor added before implantation		**follicular units (%)** ¹-25 (-17.6%)								
70	Leavitt	2005	79	male	12m	Arm1: hairtransplantation + finasteride 1mg, 1x/d, oral	macrophotograph	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%				
83	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**								
Miscellaneous, oral																
89	Prager	2002	26	male	18-24w	Arm1: active oral softgel supplement (ß-sitosterol 50 mg + saw palmetto extract 200 mg, lecithin 50 mg, inisotol 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%		
91	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%)							
Miscellaneous, topical																
90	Kamimura	2000	30	male	6m	Arm1: procyanidin 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							
88	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%				
94	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							
93	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%							
104	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%)							
38	Reygagne	1997	72	male	6m	Arm1: minoxidil 2% solution, 2x/d, topical	phototrichogram	6.8 (11.0%) p < 0.001 vs. Arm2		**anagen (hairs/cm²)** 4.5 (9.8%) p = 0.06 vs. Arm2					vertex	B
						Arm2: maxilene lotion (glycerol oxyesters and organic silicium), 1x/d, topical		-3.0 (-4.8%)		-1.8 (-3.7%)						
103	Groveman	1985	174	male	16w	Arm1: polysorbate 60 25% lotion, 2x/d, topical						2,6%**			full view	A2
						Arm2: placebo, 2x/d, topical						4,7%**				

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86	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%)						

combination therapies

ArtNumber	Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (nonvellus) hairs/cm² (%)	mean change from baseline hair count (anagen, telogen.h, anagen/telogen ratio)	mean change from baseline hair weight / thickness	global expert panel assessment	investigator assessment	patient assessment	investigational area	Degree of evidence
92	Lassus	1994	30	male	8m	Arm1: viviscal (polysaccharides and salt), 2x/d 80 kg, 3x/d > 80 kg, oral + viviscal shampoo 2-3x/w								93.3%		C
16	Berger	2003	200	male	26w	Arm1: minoxidil 5% solution, 2x/d, topical + pyrithione zinc 1% shampoo, 1x/d, topical	phototrichogram	6,2							vertex	A2
						Arm2: minoxidil 5% solution, 2x/d, topical + placebo shampoo, 1x/d, topical		12,3								
						Arm3: pyrithione zinc 1% shampoo, 1x/d, topical		5,7								
						Arm4: placebo shampoo, 1x/d, topical		-0.6								
15	Bazzano	1986	56	female and male	12m	Arm1: placebo, 2x/d, topical	manual hair count	% > 20% increase from baseline 0%							bald area	B
						Arm2: minoxidil 0.5%, 2x/d, topical		0%								
						Arm3: tretinoin 0.025% solution 2x/d, topical		58%								
						Arm4: minoxidil 0.5% + Tretinoin 0.025% solution, 2x/d, topical		66%								
85	Morganti	1998	60	female and male	50w	Arm1: lotion containing saw palmetto extract, 2x/d, topical	manual hair count	27% p < 0.005 vs. Baseline			hair weight 32%				frontal/parietal	B
						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 saw palmetto extract, 2x/d, topical + diet supplement containing l-cistin, l-methionin, Cu, Zn, 4x/d, oral		38% p < 0.005 vs. Arm1/3			60%					

pulsed electromagnetic field

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101	Policarpi	1993	30	female and male	18w, 36w	Arm1: pulsed electrostatic field, 1-2 sessions per week	phototrichogram			anagen: 18w: 4.5 % 36w: 6.2%					bald area	B
						Arm2: placebo sessions, 1-2x/week				18w: 0.9% 36w: 1.0%						
99	Maddin	1990	73	male	36w	Arm1: pulsed electrostatic field, 1x/w, week 1, 17, 33 2x/w	manual hair count		11.8 (66.1%) p = 0.0298 vs. Arm2						vertex	A2
						Arm2: sham treatment, 1x/w, week 1, 17, 33 2x/w			5.6 (25.6%)							
100	Maddin	1992	34	male	12w, 34w	Arm1: pulsed electrostatic field, 1x/w, pretreatment 36w pulsed electrostatic field	manual hair count	12w: 5.9 (20.0%) 34w: 24.7 (84.0%)							vertex	B
					16w, 30w	Arm2: pulsed electrostatic field, 1x/w, pretreatment 36w sham electrostatic field		16w: -0.8 (-2.5%) 30w: 17.5 (55.6%)								

ArtNumber Author	Year	Number of patients	Gender	Time of evaluation	Dosage	Method	mean change from baseline hair count (total) hairs/cm² (%)	mean change from baseline hair count (non-vellus) hairs/cm² (%)	mean change from baseline hair count (anagen, telogen h. anagen/telogen ratio)	mean change from baseline hair weight / thickness	global expert panel assessment	investigator assessment	patient assessment	investigational area	Degree of evidence
98 Bureau	2003	93	female and male	6m	Arm1: herbal solution (pimenta racemosa, myrtus communis, cedrus atlantica, laurus nobilis, pogostemon patchouli, rosmarinus officinalis, salvia sclarae, thymus satureioides, 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								
102 Satino	2003	35	female and male	6m	Arm1: HairMax Laser Comb (low level laser therapy), comb hair 1x/d 5-10 minutes	manual hair count	14.1 (76.2%) n.s. vs. Baseline	12.3 (60.0%)						vertex/temporal	C

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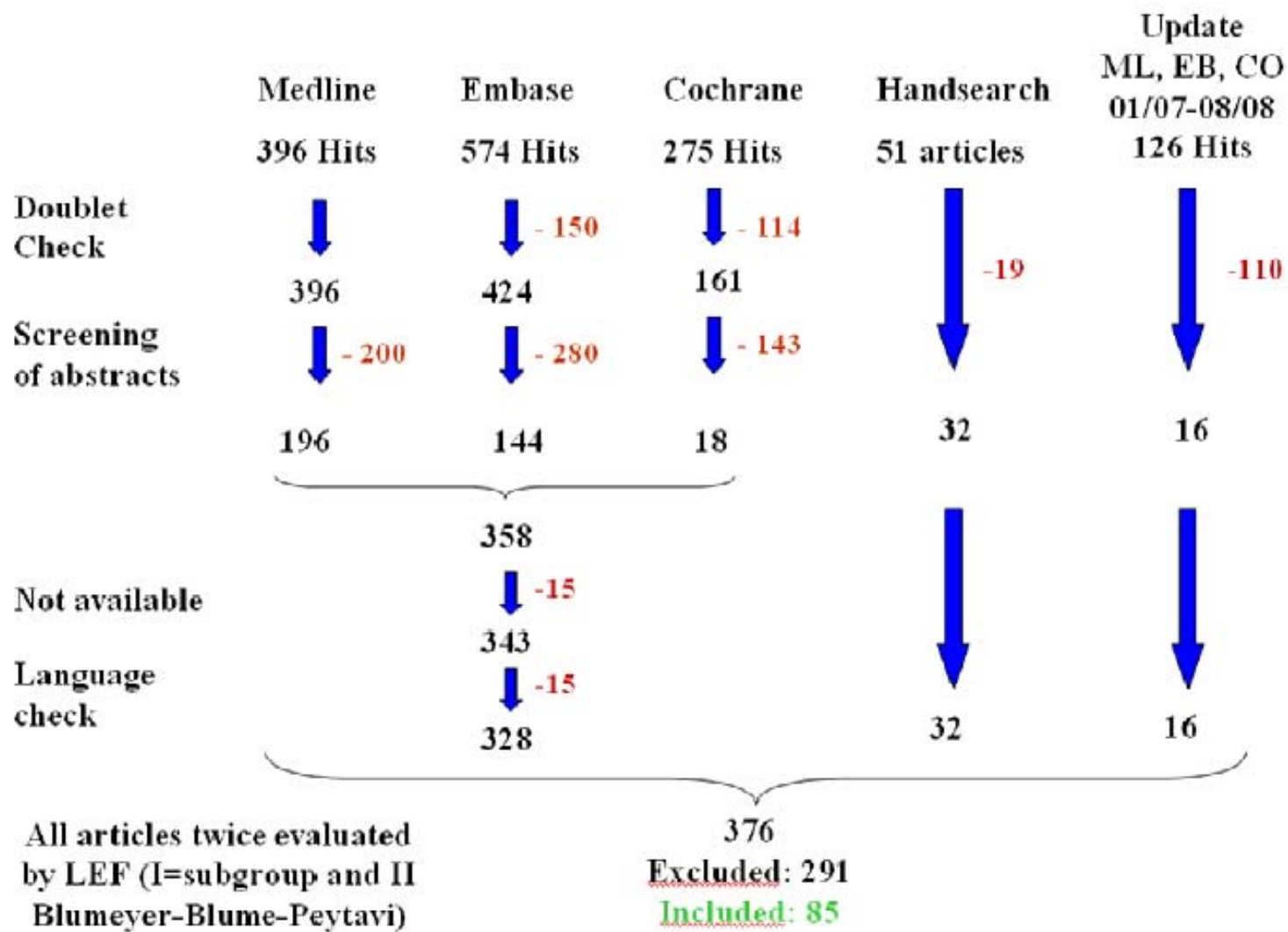***_investigator = outcome assessor

Figure 1

	Medline	Embase	Cochrane	Handsearch	Update ML, EB, CO 01/07-08/08
	396 Hits	574 Hits	275 Hits	51 articles	126 Hits

Doublet Check

396   424 (-150)   161 (-114)   -19   -110

Screening of abstracts

196 (-200)   144 (-280)   18 (-143)   32   16

358

Not available   -15

343

Language check   -15

328   32   16

All articles twice evaluated by LEF (I=subgroup and II Blumeyer-Blume-Peytavi)

376
Excluded: 291
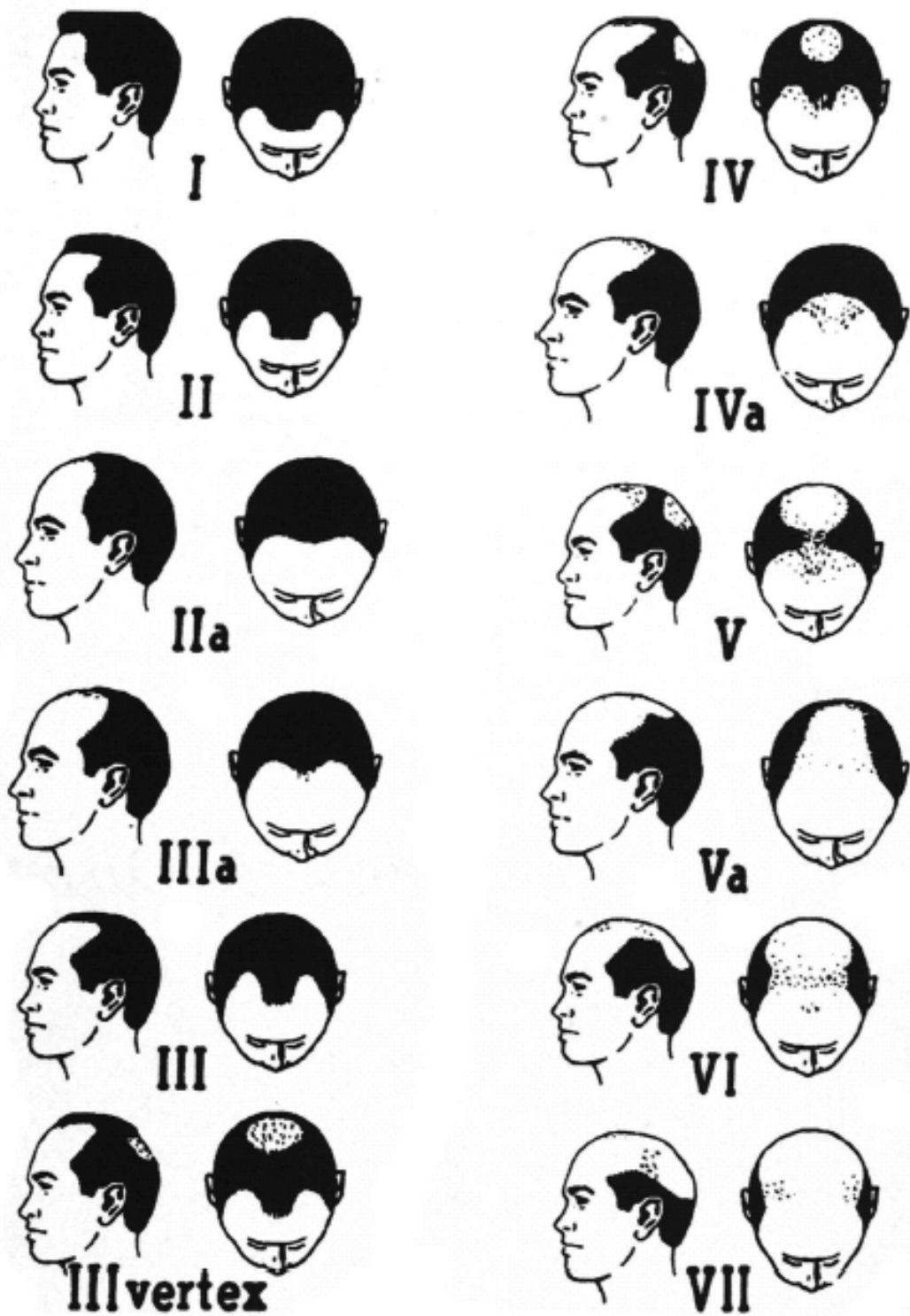Included: 85

Figure 2

Figure 3

Figure 4

Male Pattern
(Hamilton)

Diffuse
(Ludwig)

Frontal Accentuation
(Olsen)

Table 1

Therapy	Level of evidence	Efficacy to prevent progression	Efficacy to improve	Safety	Practicality (patient)	Practicality (physician)
Male patients						
Finasteride	1	+++	++	+++	++++	+++ / ++++
Minoxidil 5%	1	+++	++	++++	+ / ++	+++
Surgery	4	-	+++	++	+ intervention +++ long-term	+
Female patients						
Minoxidil 2%	1	+++	++	++++	+	+++
Hormones oral Hyperandrogenism normal hormones	3	+ + / -	+ + / -	+ +	+++ +++	++ ++
Surgery	4	-	++	++	+ intervention +++ long-term	+