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GUIDELINES

Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men – short version

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Abstract

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

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

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Conflicts of interest

The authors' conflicts of interest/disclosure statements may be found in the long version of this article on the homepage of the European Dermatology Forum (EDF)1.

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Introduction

Androgenetic alopecia (AGA) is the most frequent form of alopecia in men and women. It is characterized by progressive hair loss, usually in a pattern distribution. The onset may be at any age following puberty and the frequency increases with age. By the age of 70 or beyond, 80% of Caucasian men and up to 40% of women have signs of AGA. Today, in our societies, hair is an important feature of image; strong and dense hair is associated with youth, beauty, healthiness and success. Consequently, in patients presenting with AGA, progressive thinning of hair often causes a psychological distress. Patients are looking for effective hair loss treatments to prevent further thinning and optimally stimulate regrowth. Limited perceived efficacy of a therapeutic regimen, poor tolerance, fear and lack of information on treatment duration and possible adverse events may lead to premature stop of treatment, disappointment and influence on patient compliance. The purpose of the guideline

This is a short summary of the complete version of the evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men. The long version has been published online on the homepage of the European Dermatology Forum (EDF)[1]

is to provide dermatologists with an evidence-based tool for choosing an efficacious and safe therapy for patients with AGA.[1]

Methodology

Literature research This guideline was conducted as the update of the evidence-based (S3) guideline for the treatment of AGA in women and men.[2] The search strategy and methodology of this guideline and its update were orientated on the standards of the AGREE instrument and on the methodology of the European S3 guideline for the treatment of psoriasis vulgaris.

To assess the efficacy of the individual therapeutic processes, a systematic search of literature of the databases MEDLINE, MEDLINE In-Process, EMBASE and Cochrane Library was conducted. Furthermore, reference lists of articles were screened and hand searches were conducted by the authors to identify articles which are not listed in the databases. The searches comprised the period since the search for the first version of the S3 guideline in 2008 to 15 October 2015. Identified articles were screened for eligibility by at least two independent authors based on predefined criteria [please see long version of the guideline, including the literature evaluation form (LEF)].[1] Data extraction was also conducted by two independent authors. All discrepancies were resolved by consensus or discussion with a third author.

Results Overall 797 articles were found in the update search. After checking for duplicates and relevance, 184 articles were evaluated in full text using the LEF. Forty-seven articles met the inclusion criteria of the guideline and built the basis of the guideline. Please see long version of the guideline, including flow chart.[1]

Evidence assessment The methodological quality of each study included in the evidence-based analysis was defined within the LEF by the grade of evidence (Table 1).

Level of evidence The grades of evidence of all studies belonging to a particular therapeutic regimen were summarized in a level of evidence, considering methodological quality of the trials and intertrial consistence of the results (Table 2).

Table 1 Evidence assessment. The methodological quality of each study, which was included in the evidence-based analysis, was defined by 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

Table 2 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

Table 3 Strength of recommendation. The consented therapeutic recommendations were graded by the strength of recommendation, using the following 6-point scale

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

Therapeutic recommendation Grades and levels of evidence were considered in the formal consensus process. Nevertheless, it is not possible to define a strict clinical algorithm; the decision process on a particular therapy remains complex and limited on the individual case.

Strength of recommendation The consented therapeutic recommendations were weighted by the strength of recommendation (Table 3).

Hair growth assessment techniques

To document the extent of AGA 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 AGA does not exist. Moreover, the documentation of degree of the pattern distribution is often not suitable to reflect the course of AGA.

As AGA 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 is 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. The technique is limited by the size of the measured area. In clinical trials comparison to baseline and to placebo resp., another treatment is necessary for efficacy assessment of a therapeutic option.

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

Risk/benefit considerations

In routine clinical practice, the individual decision for a particular treatment of AGA depends not only on the efficacy, but also on practicability, safety, patient preference and costs.

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 AGA is not only stabilization, prevention of progression and induction of hair growth, but may contribute to an improved quality of life.

The guideline offers evidence-based analyses of the existing therapeutic options that help to take suitable cost-benefit decisions within an individually tailored management approach.

For detailed introduction to AGA, including epidemiology, aetiology and genetics, clinical features and diagnosis as well as for a more detailed presentation of the methods, please refer to the long version of the guidelines.[1]

Therapeutic options and therapy assessment

Result tables

All studies that fulfilled the inclusion criteria of the guideline, their evidence-based results and degree of evidence are listed in result tables, which can be found in the long version of the guideline.[1]

Table 4 Summary of evidence level, efficacy to prevent progression and/or improve androgenetic alopecia, safety aspects and practicability for the most common therapeutic interventions. The intention of this table is to provide a first rough orientation. An individualized therapy concept, taking into account clinical status, demands, needs and complaints of each patient is necessary. The physician and patient must decide together on the best-suited individualized therapy, considering available evidence, expected therapeutic results, practicality and compliance

Summary table Therapy	Level of evidence	Efficacy to prevent progression	Efficacy to improve	Safety	Practicality (patient)	Practicality (physician)
Male patients						
Finasteride 1 mg QD	1	+++	++	+++	++++	++
Dutasteride 0.5 mg QD *	1	+++	+++	++	++++	++
Minoxidil 5% BID (solution, foam)	1	+++	++	++++	+/++	+++
Hair transplantation with/without combination treatment	2	–	+++	++	+ intervention +++ long-term	+
LLLT	2	+/–	+/–	++	+++	+++
PRP	3	+/–	+/–	+	+/–	+
Female patients						
Minoxidil 2% BID solution Minoxidil 5% QD foam	1	+++	++	++++	+	+++
Hormones oral in hyperandrogenism	3	+	+	+	+++	++
Hormones oral in normal hormones	3	+/–	+/–	+	+++	++
Hair transplantation	4	–	++	++	+ intervention +++ long-term	+
LLLT	2	+/–	+/–	++	+++	+++
PRP	3	+/–	+/–	+	+/–	+
Global consideration	Poor	◄			►	Good
	–	+/–	+	++	+++	++++

LLLT, Low-level Laser therapy; PRP, Platelet-rich plasma.
*Off label.

Overview of common therapeutic options

Table 4 shows a summary of evidence level, efficacy to prevent progression and/or improve AGA, safety aspects and practicability for the most common therapeutic interventions. Its intention is to provide a first rough orientation. An individualized concept, taking into account clinical status, demands, needs and complaints of each patient is necessary. The physician and patient must decide together on the best-suited individualized therapy, considering available evidence, expected therapeutic results, practicality and compliance.

Minoxidil

Efficacy – males

Forty-eight studies assessing the efficacy of minoxidil in male patients with AGA met the inclusion criteria for the guideline.[3–51] The majority of studies obtained grade A2 and B evidence (A2 = 22, B = 18, C = 8) resulting in EVIDENCE LEVEL 1.

Minoxidil 2% solution twice daily is effective to prevent progression and improve AGA in the frontotemporal and vertex regions in male patients (level of evidence 1). Minoxidil 5% solution or foam twice daily is more effective than the 2% solution (level of evidence 2).

In one study, oral minoxidil 5 mg/day in men led to an increased hair count; however, the increase is only slightly higher compared to studies investigating topical minoxidil.[47] Side-effects of oral minoxidil included hypertrichosis (93%), pedal oedema (10%) and ECG alteration (10%).

Efficacy – females

Nineteen studies investigating the efficacy of topical minoxidil in female patients suffering from AGA could be included in the evidence-based evaluation.[31,32,45,46,48,52–65] Seven studies obtained grade A2 evidence, nine studies grade B evidence, three studies grade C evidence resulting in an EVIDENCE LEVEL 1.

Minoxidil 2% solution twice daily was effective to prevent progression and improve AGA in female patients (level of evidence 1). The efficacy of minoxidil 5% solution or foam applied once daily was comparable to minoxidil 2% solution applied twice daily (level of evidence 2).

Instructions for use/practicability/side-effects

Minoxidil should be applied as 1 mL of solution with a pipette or half a cap of foam to dry hair and scalp once twice daily. In women, the foam formulation is recommended only once daily. When using spray applicator, it has to be spread evenly over the affected areas.

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

The patients should be informed about transitory *increased telogen hair shedding* during the first months of the treatment. Furthermore, interruption of topical minoxidil is followed by increased hair loss.

The main side-effect of topical minoxidil is hypertrichosis, most probably due to local spreading or excessive continuous topical application, sometimes also due to individual sensitivity. Irritant and allergic contact dermatitis may also occur. Irritation is more common with the 5% solution due to its higher content in propylene glycol. Contact dermatitis due to propylene glycol or due to minoxidil itself should be confirmed by patch testing.

It is recommended to pause topical minoxidil use during pregnancy and lactation, due to lack of data during this period.

Combination therapies – males and females

Nine studies investigating the effect of minoxidil topical solution alone vs. combination therapy in males could be included in the evidence-based evaluation.[38,40–46,51] Three studies obtained grade A2 evidence and six studies grade B evidence. However, as only a single or max. two studies were available on each individual combination therapy, only an EVIDENCE LEVEL 3 could be attributed.

Six studies investigating the effect of minoxidil topical solution alone vs. combination therapy in females could be included in the evidence-based evaluation.[45,46,58,64–66] Three studies obtained grade B evidence and three studies grade C evidence resulting in an EVIDENCE LEVEL 3.

For a detailed description of the results, please see the long version of the guideline. Even though the degree of evidence of the included studies was generally good, a single or max. two studies were available on each individual combination therapy, so that no recommendation can be made at the present time (Table 5).

5-alpha-reductase inhibitors

Efficacy – males

Finasteride Twenty-five studies investigating the efficacy of finasteride in male patients with AGA met the inclusion criteria of the guideline.[34,35,38,41,44,67–86] Thirteen studies obtained grade A2 evidence, nine grade B and three grade C. Fourteen studies were placebo-controlled. An EVIDENCE LEVEL 1 can be attributed.

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. *Long-term results* were available for 24, 36, 48, 60 and 120 months.[67,68,73,78,80,82,84,87] The mean changes from baseline were at all time point statistically significantly higher compared to placebo.

Finasteride vs. minoxidil Two of the included studies examining finasteride 1 mg/day against twice daily topical application of minoxidil 2% solution showed superiority for finasteride at 12 months.[35,38] In two studies comparing finasteride 1 mg per os to minoxidil 5% solution twice daily, contradictory results were reported.[34,44]

Finasteride per os vs. topical finasteride A similarly small but significant increase in total hair count from baseline was found in

male patients with AGA receiving a topical gel of 1% finasteride twice daily and placebo tablets once daily and male patients receiving finasteride 1-mg tablets once daily and placebo topical gel twice daily for 6 months.[85] No data on serum DHT levels were given, and more studies are required to confirm this result.

Combination therapies – males

Combination therapy with finasteride 1 mg and 5% minoxidil topical solution led to better improvement than monotherapies.[44] The mechanisms of action of minoxidil and finasteride treatments are different. Thus, combination of topical minoxidil and oral finasteride is possible and can be considered for greater efficacy in motivated patients.

Dutasteride Five studies investigating dutasteride in AGA were included in the evidence-based evaluation, four of which with grade A2 evidence and one of which with grade C evidence, resulting in a level of evidence 1.[71,86,88–90] Four of five studies were placebo-controlled. In all studies, significant mean increases from baseline hair count were reported for dutasteride 0.5 mg daily.

Other botanically derived 5α-reductase inhibitors Other botanically derived 5α-reductase inhibitors, such as serenoa repens and Curcuma aeruginosa, were assessed in two studies. Serenoa repens per os showed inferior results compared to finasteride per os.[87] Topical Curcuma aeruginosa showed results comparable to topical minoxidil, but these results have to be confirmed in further studies with long-term follow-up and larger cohorts (Table 6).[51]

Efficacy – females

Finasteride One study assessing the efficacy of finasteride 1 mg daily[91] and two studies assessing the efficacy of finasteride 5 mg daily in female patients were included in the evidence-based evaluation.[92,93] The grades of evidence were A2, C and C resulting in an EVIDENCE LEVEL 3.

In female postmenopausal patients, finasteride 1 mg failed to show efficacy; however, finasteride 5 mg may be effective in female normoandrogenic pre- and postmenopausal patients. However, no placebo-controlled trials are available in this population. Additional research is required in different subgroups of female patients with AGA including younger female patients and female patients with or without clinical hyperandrogenism.

Instructions for use/practicability/side-effects

The recommended dosage of finasteride in men is 1 mg/day. The response to treatment should be assessed at 6–12 months. If successful, treatment needs to be continued to maintain efficacy. In case of ineffective treatment with 1 mg finasteride over 12 months, the off-label use of dutasteride 0.5 mg/day can be considered.

Patients under treatment with finasteride should be aware of reduction in prostate specific antigen, which is important in prostate cancer screening in men. Further reported side-effects of finasteride are gynaecomastia; testicular pain; hypersensitivity reactions; impaired sexual function, including erectile dysfunction, ejaculation dysfunction, reduced ejaculate volume and loss of libido. A possible negative impact on spermatogenesis has been observed in men with pre-existing conditions relating to infertility. A possible depressive alteration of mood after finasteride use has been reported in patients with a predisposition to psychological disorders.

Post-finasteride syndrome is also being discussed, defined as various symptoms persisting for months or years after discontinuation of finasteride treatment, including sexual dysfunction, loss of libido, depression, suicidal ideation, impaired cognition, fatigue and decreased penile sensitivity, probably occurring preferred in men with a history of sexual dysfunction or a personal or family history of psychiatric illness. In patients with active depression or current sexual dysfunction, finasteride is therefore contraindicated.

Finasteride is not licensed in women and is contraindicated in pregnant women and women of childbearing potential because of the risk of feminization of a male fetus. Finasteride-treated men must therefore avoid donating their blood. If taken by women of childbearing age, the use of a safe contraceptive method is indispensable.

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.

Hormones

Efficacy – males

Oral hormonal treatment There is no evidence to support the use of oral oestrogens or anti-androgens to improve or prevent progression of AGA in male patients (EVIDENCE LEVEL 4).

Topical hormonal treatment The topical application of the anti-androgen fluridil[94] and the anti-oestrogen fulvestrant[33] is not recommended. Available studies on the topical oestrogen alfatradiol (=17 alpha-oestradiol) in men, unfortunately either had no control group[95,96] and/or the results were not reported separately for each sex.[96,97]

Efficacy – females

Oral hormonal treatment Four studies met the inclusion criteria, of which only one was placebo-controlled. Three studies obtained a grade of evidence B and one of them obtained a grade of evidence C, resulting in level of evidence 3.[58,66,98,99]

There is limited proof that oral cyproterone acetate (CPA) may be helpful in women with AGA and hyperandrogenism (Table 7).[58]

Topical hormonal treatment There is no evidence to support the use of topical natural oestrogens, progestogens or anti-androgens in female AGA (level of evidence 4).[33,52,95,97,100,101]

Studies on the topical oestrogen alfatradiol alone or in combination with topical corticosteroid showed contradictory findings. Topical fulvestrant showed results comparable to placebo and therefore seems to be ineffective in women with AGA.

Instructions for use/practicability/side-effects

Oral anti-androgen therapy in women:

Cyproterone acetate is generally prescribed in combination with an oestrogen as an oral contraceptive in oral contraceptive pills (2 mg over 21 days or added to an oral contraceptive on days 1–10 at 5–50 mg per day for enhanced anti-androgen activity). Side-effects of CPA include depressive mood changes and liver toxicity. There is an increased risk of venous thromboembolism in patients taking oestrogen-containing oral contraceptives, which may be greater in those taking CPA than other oral contraceptives.

Surgery

In AGA, hairless areas can be permanently covered again cosmetically, albeit with a decreased density. Hair restoration surgery involves scalp reduction surgery, hair transplantation or a combination of both. Over the last decades, hair transplantation has evolved into a microsurgical procedure. Follicular units of 1–4 hairs are transplanted in large numbers and high densities.

Efficacy – males

Although there are many publications dealing with hair surgery, there were no randomized controlled studies (RCTs) comparing hair transplantation vs. no hair transplantation. This is most probably due to high variation in techniques, multiple steps in the surgical process, problems in measuring hair growth, lack of financial support and difficult patient recruitment for a RCT in hair transplantation.

As there are no RCTs comparing hair surgery vs. no hair transplantation, only a level of evidence 2 can be attributed to the included studies comparing hair transplantation vs. hair transplantation with supportive therapies (two of the studies obtained a grade of evidence B, one study obtained a grade of evidence A2 and one study obtained a grade of evidence C).[81,102–104]

Efficacy – females

In female patients, there is lack of evidence concerning surgery with supportive therapies. We suggest that combination therapy may reduce further postoperative progression of AGA.

Instructions for use/practicability

Hair transplantation in suitable candidates with a good donor hair supply, performed by a skilled team, can improve AGA. In women, hair transplantation can be considered in the male pattern and the frontal accentuation subtypes and Ludwig stage II of stabilized AGA. This only applies if sufficient permanent donor hair is available and no overlying diffuse telogen effluvium is present (Table 8).

The final result can be evaluated at 9–12 months. In many cases, more than one surgical session is required.

The best long-term results can be achieved in medically controlled or spontaneously stabilized AGA. In men, combination of finasteride 1 mg and/or topical minoxidil with follicular unit transplantation may reduce postoperative progression of AGA.

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

Table 5 Therapeutic recommendation for minoxidil

Male patients	
↑↑	Topical Minoxidil 2–5% solution 1 mL or half a cap of 5% foam twice daily is recommended to improve or to prevent progression of AGA in male patients above 18 years with mild to moderate AGA (Hamilton-Norwood IIv-V).
↑	We suggest using 5% solution or half a cap of 5% foam for greater efficacy.
O	We cannot make a recommendation for the 5% minoxidil foam instead of the 5% solution at the present time.
↑	The response to treatment should be assessed at 6 months. If successful, treatment needs to be continued to maintain efficacy.
→	For greater efficacy the combination of oral finasteride 1 mg, 1×/d and topical Minoxidil 2–5% solution, 2×/d can be considered.
O	We cannot make a recommendation for combination therapy of topical minoxidil with topical 5a-reductase or azelaic acid and betamethasone valerate at the present time.
	Further studies are needed to confirm superiority of combination therapies consisting of topical minoxidil, diclofenac and tea tree oil, topical minoxidil, azelaic acid and betamethasone or topical minoxidil and microneedling.
Female patients	
↑↑	Topical Minoxidil 2% solution 1 mL twice daily or half a cap of 5% minoxidil topical foam once daily is **recommended** to improve or to prevent progression of AGA in female patients above 18 years with AGA.
O	We cannot make a recommendation for the 5% minoxidil foam once daily instead of the 2% solution twice daily at the present time.
↑	The response to treatment should be assessed at 6 months. If successful, treatment needs to be continued to maintain efficacy.
O	We cannot make a recommendation for combination therapy of topical minoxidil with red ginseng, azelaic acid and betamethasone or oral nutritional supplements at the present time

Platelet-rich plasma (PRP)

Efficacy – males

Two studies assessing the efficacy of PRP in male and female patients with AGA met the inclusion criteria for the guideline, both with grade C evidence, resulting in level of evidence 3.[105,106]

Table 6 Therapeutic recommendation for 5α-reductase inhibitors

Male patients	
Finasteride	
↑↑	Oral Finasteride 1 mg/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.
O	We cannot make a recommendation for or against treatment with topical finasteride at the present time
→	For greater efficacy the combination of oral finasteride 1 mg, 1×/d and topical Minoxidil 2–5% solution or 5% foam 2×/d can be considered.
Dutasteride	
→	Oral Dutasteride 0.5 mg/day can be considered in case of ineffective previous treatment with 1 mg finasteride over 12 months as a second line treatment to improve or to prevent progression of AGA in male patients above 18 years with mild to moderate AGA (Hamilton-Norwood IIIv-V).
Serenoa repens	
O	We cannot make a recommendation for or against treatment with Serenoa repens per os at the present time
Curcuma aeruginosa	
O	We cannot make a recommendation for or against treatment with topical Curcuma aeruginosa at the present time
Female patients	
Finasteride	
↓	Oral finasteride 1 mg daily is not suggested in the treatment of postmenopausal women with female pattern hair loss.
O	We cannot make a recommendation for or against treatment with oral finasteride 5 mg/day at the present time.

Table 7 Therapeutic recommendation for hormonal treatment

Male patients	
↓↓	We do not recommend the use of oral oestrogens or androgen-receptor-antagonists to improve or prevent progression of AGA in male patients.
O	We cannot make a recommendation for topical alfatradiol in male patients at the present time
↓	We suggest that topical fluridil should not be used in male patients with AGA.
↓	We suggest that topical fulvestrant should not be used in male patients with AGA.
Female patients	
O	We cannot make a recommendation for the use of oral anti-androgens (chlormadinone acetate, cyproterone acetate (CPA), drospirenone, spironolactone, flutamide) to improve or prevent progression of AGA in normoandrogenic female patients at the present time.
→	Oral CPA can be considered to prevent progression of AGA in women with clinical or biochemical evidence of hyperandrogenism.
O	We cannot make a recommendation for the use of topical alfatradiol to improve or prevent progression of AGA in female patients at the present time.
O	We cannot make a recommendation for the use of topical natural oestrogens or progesterones to improve or prevent progression of AGA in female patients at the present time.
O	We cannot make a recommendation for the use of topical fluridil to improve or prevent progression of AGA in female patients at the present time.
↓	**We suggest** that topical fulvestrant should not be used in female patients with AGA.

Table 8 Therapeutic recommendation for surgery

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

Table 9 Therapeutic recommendation for platelet-rich plasma (PRP)

Male and female patients	
	There is no standardized technique for performing PRP to permit objective evaluation of its effects on AGA.
O	We cannot make a recommendation for or against treatment of AGA with platelet-rich plasma at the present time

Efficacy – females

Three studies assessing the efficacy of PRP in female patients were included in the evidence-based evaluation.[105–107] Two of them included male and female patients, one of which included only two females.[105,106] The grades of evidence were B, C and C, resulting in a level of evidence 3.

In the included studies, increases in hair density were reported. However, PRP was performed in small sample sizes, using different protocols and without a control group. Furthermore, in two of the three studies, pooled results were reported for men and women. With the exception of one study, no long-term follow-up was performed. Based on these studies, there is little evidence to support the use of PRP in men and women with AGA (Table 9).

Instructions for use/practicability/side-effects

There is no standard procedure for treatment of AGA with PRP. There are no standardized techniques for platelet isolation and activation, for dosage and frequency of injections. Furthermore, more information about the need to combine PRP with other chemicals/cells is needed. The main side-effects of PRP include immediate effects of the procedure, including pain and transient post-treatment oedema and tenderness; rarely post-treatment sequelae, including persistent trichodynia, psoriasiform scalp reactions, telogen effluvium; more rarely, secondary infections and scarring. The impact of PRP treatment on quality of life of the patients should be further investigated.

Table 10 Therapeutic recommendation for Low-level Laser therapy (LLLT)

Male and female patients	
↑	We suggest using LLLT as ancillary therapy for AGA with devices that use energy levels shown to be effective in randomized controlled clinical trials
O	We cannot make a recommendation for or against treatment for more than 6 months with LLLT for AGA at the present time

Low-level laser (light) therapy (LLLT, laser hair comb)

Efficacy – males

Two studies assessing the efficacy of LLLT in male patients with AGA with grade of evidence A2 and C were included in the evaluation, resulting in a level of evidence 2.[108,109]

Table 12 Therapeutic recommendation for miscellaneous molecules, substances and interventions

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

Efficacy – females

Two studies assessing the efficacy of LLLT in female patients with AGA met the inclusion criteria of the guideline, with grade of evidence A2 and C, resulting in a level of evidence 2.[109,110]

In total, three studies concerning LLLT fulfilled the inclusion criteria of the S3 guideline. When used for 16 and 26 weeks under different protocols and with two different devices, LLLT showed an increased hair count (level of evidence 2). However,

Table 11 Miscellaneous agents, products and interventions, grouped according to their assumed main mechanism of action

Claimed mechanism of action		Active	Level of evidence	Studies included (*n*)	Grade of evidence	Mode of application	Part of combination product
1	DHT-inhibitory activity	ß-sitosterol	3	1	B	Oral	Yes
		Biochanin A	3	1	B	Topical	No
		Polysorbate 60	2	1	A2	Topical	No
		Serenoa repens	3	1	B, B	Oral	Yes, no
			3	1	B	Topical	Yes
		Curcuma aeruginosa	2	1	A2	Topical	Yes, no
		Biochanin A	3	1	B	Topical	No
2	Anti-inflammatory activity	Ketoconazol	3	1	B	Topical	Yes
		Roxithromycin	3	1	B	Topical	No
		Zinc pyrithione	2	2	B, A2	Topical	Yes, no
3	Improved perifollicular vascularization	Glyceroloxyesters and silicium	3	1	B	Topical	Yes
		Niacin derivates	2	2	A2	Topical	Yes
		Prostaglandins (viprostol, latanoprost)	2	1	A2	Topical	No
4	Improved hair follicle nutrition	Amino acids (cysteine, histidine)	3	1	B	Topical	Yes
			3	1	B	Oral	Yes
		Vitamins (biotin, niacin)	3	2	B	Oral	Yes
		Trace elements (zinc, copper)	3	1	B	Oral	Yes
5	Not precisely reported or unknown mechanism of action	Adenosine	3	1	B	Topical	No
		Biotin	3	1	B	Oral	Yes
			2	1	A2	Topical	
		Hibiscus	3	1	B	Topical	Yes
		Marine extract and silica component	2	1	A2	Oral	No
		Melatonin	4	1	C	Topical	No
		Millet seed	3	1	B	Oral	Yes
		Niacin derivates	2	2	A2	Topical	Yes
		Proanthocyanidins	3	1	B	Topical	No
		Red ginseng	4	1	C	Topical	Yes
		Tretinoin	2	2	B, A2	Topical	Yes, no
		Valproic acid	2	1	A2	Topical	No
Interventions							
	Not precisely reported or unknown mechanism of action	Botulinum toxin	4	1	C	Scalp injections	No
		Electromagnetic/-static field	1	4	A2, A2, B, B	Device	Yes, no

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

no long-term follow-up was performed. One of the included studies was not sham device-controlled. Further controlled randomized clinical studies are required to establish the efficacy of these devices for hair growth in comparison with established therapies and to evaluate long-term use (Table 10).

Instructions for use/practicability/side-effects

Treatment with LLLT is performed at home, using a LaserComb or wearing for a certain amount of time a helmet plugged into a standard outlet. The duration of therapy and frequency vary for the different devices.

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

Miscellaneous

Besides the pharmacologic therapeutic options mentioned before, there is a wide range of molecules, products and interventions claiming to promote hair growth in AGA. These include cosmetic to pharmaceutical agents, natural products, functional food and even electrostatic/-magnetic treatment.[111-114] The mode of application comprises topical application, oral intake and scalp injections.

The majority of these products claim hair promoting properties, even though controlled clinical studies are scarce. The available evidence on these miscellaneous products and the assumed mechanisms of actions are summarized in Table 11.

For a detailed overview on the different miscellaneous products, please refer to the long version of the guidelines.[1]

When looking at the includes studies, 21 trials examined a single product,[37,39,50,115–132] while five trials investigated combinations of different products.[36,40,45,116,133]

Evaluation of individual ingredients is limited, as most of the tested products contain multiple different substances. Furthermore, even though the degree of evidence of the included studies was generally good, a single or max. two studies were available on each individual miscellaneous agent or product.

Based on currently available literature data, no evidence-based recommendation can be given for these miscellaneous products (Table 12). Their use as a supportive strategy within an individually tailored management approach remains at the discretion of the treating dermatologist and the decision of the patient. Further controlled studies to prove the relevance of these and other new approaches in the treatment of AGA are needed.

Instructions for use/practicability/side-effects

For instructions for use for the miscellaneous products, the reader is asked to consult the information of the particular product information. In case of an intervention, the treating physician is responsible for providing detailed patient information on the procedure and possible side-effects.

Combination therapies

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

Disclaimer

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Additional Supporting Information may be found in the online full version of the guidelines on the EDF homepage.[1] The long version of the guidelines contains more detailed data on the goals, methodological and clinical background and the results of the guidelines development.

