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Non-surgical treatments for androgenetic alopecia in adult men: indications, adverse effects and efficacy

Systematic Review

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Dissertação para obtenção do Grau de Mestre em
Medicina
(mestrado integrado)

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Dedication

"- Falhamos a vida, menino!
- Creio que sim... Mas todo o mundo mais ou menos a falha. Isto é, falha-se sempre na realidade aquela vida que se planeou com a imaginação. Diz-se: «vou ser assim, porque a beleza está em ser assim». E nunca se é assim, é-se invariavelmente assado, como dizia o pobre marquês. Às vezes melhor, mas sempre diferente."

José Maria Eça de Queirós, Os Maias

Aos falhanços da vida,

que felizmente me trouxeram até aqui

e fizeram de mim aquilo que sou hoje.

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À minha mãe, pela forma como me educou. Com o seu exemplo de vida, valores, e apoio incondicional, que sempre me transmitiu, fez de mim aquilo que sou hoje.

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Resumo

Introdução: A alopécia androgenética é a causa mais comum de queda de cabelo em humanos. Esta é mediada pela dihidrotestosterona [DHT], uma forma de testosterona, geralmente aparece na adolescência e tende a evoluir para queda de cabelo progressiva que segue um padrão de distribuição. A frequência de homens que sofrem de alopécia androgenética aumenta com a idade, afetando até 80% dos homens caucasianos. Nos últimos anos, vários tratamentos cirúrgicos e não cirúrgicos foram desenvolvidos para tratar e prevenir esta condição

Objetivo: Determinar a eficácia e a segurança das terapêuticas não cirúrgicas existentes para a alopécia androgenética. Pretende-se, assim, resumir a evidência terapêutica das mesmas, oferecendo aos médicos uma ferramenta que lhes permita medicar os seus pacientes com base nas evidências demonstradas.

Métodos: Realizou-se uma pesquisa na PubMed, Scopus e Cochrane de ensaios clínicos publicados em inglês, datados entre 2011 e 2021. Utilizou-se como estratégia de pesquisa "(Androgenetic alopecia AND ((therapeutics) OR (therapy) OR (treatment))", tendo adicionado, como filtro, ensaios clínicos envolvendo homens com mais de 18 anos; O principal *outcome* considerado foi a avaliação da eficácia das diferentes terapias e como *outcome* secundário procurou-se analisar o nível de segurança das mesmas.

Resultados: Foram incluídos 14 estudos nesta revisão sistemática, dos quais 11 são ensaios clínicos randomizados e 3 são ensaios clínicos não randomizados. Destes estudos, 4 analisaram a eficácia e a segurança dos inibidores da enzima 5 alpha Reductase, 5 abordaram as terapias com minoxidil e 5 focaram-se na análise da terapêutica com laser de baixa intensidade (LLLT). Estes estudos parecem demonstrar que as 3 terapias mencionadas possuem alguma eficácia no combate à alopécia androgenética.
Os efeitos adversos destas terapêuticas também estão descritos nos estudos incluídos, no entanto, para aferir com maior precisão o nível de segurança dos diferentes tratamentos, sugere-se a realização de mais estudos.

De realçar ainda que 11 dos estudos apresentados apresentam risco de viés moderado, 2 risco de viés elevado e 1 dos estudos risco de viés muito elevado.

Conclusão: As terapêuticas analisadas parecem ser promissoras no tratamento da alopécia androgenética, uma vez que todas as terapias analisadas parecem demonstrar eficácia no tratamento da alopécia androgenética.

Palavras-chave

Alopécia Androgenética; Queda de cabelo; Tratamentos não cirúrgicos;

Resumo Alargado

A alopécia androgenética é a causa mais comum de queda de cabelo no mundo inteiro. A maior parte dos pacientes que são afetados por esta condição têm história familiar da doença.

A alopécia androgenética manifesta-se pela perda de cabelos terminais (espessos e pigmentados) e pelo crescimento de cabelo velino (finos, não pigmentados) ao longo do tempo. Desta forma, os cabelos terminais transformam-se em cabelos velinos, num processo chamado miniaturização. Isto ocorre porque o folículo piloso fica menor, o que consequentemente acaba por se traduzir num menor diâmetro do cabelo. A queda de cabelo resultante desta condição, apesar de não ter um impacto significativo na saúde dos indivíduos que por ela são acometidos, pode ter um impacto psicológico significativo para estes.

Assim sendo, esta revisão sistemática teve como objetivo abordar as terapêuticas existentes e aprovadas pela US FDA (United States Food and Drug Administration), para tratamento e prevenção da alopécia androgenética, focando-se na avaliação da eficácia e efeitos adversos das mesmas.

Ao longo deste trabalho, foi feita uma síntese dos artigos relevantes sobre este tópico que estavam de acordo com os critérios de inclusão definidos pela equipa investigadora.

Foi definido um protocolo de acordo com os critérios PRISMA que posteriormente foi submetido na plataforma Prospero e realizada uma pesquisa inicial nas plataformas de dados Pubmed, Cochrane e Scopus com a seguinte estratégia de pesquisa “(Androgenetic alopecia AND ((therapeutics) OR (therapy) OR (treatment))”, tendo sido adicionado, como filtros, ensaios clínicos envolvendo apenas homens; apenas com participantes maiores de 18 anos; artigos escritos em inglês e publicados entre 2011 e 2021. A equipa de investigadores identificou 789 artigos, dos quais 255 eram duplicados. Dos 534 artigos restantes, após leitura do título e resumo e consequente aplicação dos critérios de inclusão e exclusão, obtiveram-se 37 artigos. Após a leitura completa desses 37 artigos, 23 artigos foram excluídos após a aplicação dos critérios de inclusão e exclusão, restando os 14 artigos finais que foram incluídos nesta revisão sistemática.

Os resultados pareceram demonstrar que todas as terapias analisadas têm algum grau de eficácia no atraso da progressão da alopécia androgenética.

No entanto, nenhum estudo comparou diretamente as 3 terapias e os artigos variam nas escalas que utilizam para medir os *outcomes*, não nos sendo possível identificar qual a terapia mais eficaz ou até qual o efeito da combinação das 3 terapias em simultâneo, (inibidor da enzima 5 alpha reductase+ minoxidil + laser de baixa intensidade).

Quanto à análise dos efeitos adversos das diferentes terapias, os artigos analisados apresentam algumas lacunas, sendo necessários mais estudos para analisar os mesmos.

Abstract

Background: Androgenetic alopecia is the most common cause of hair loss in humans. It is mediated by dihydrotestosterone [DHT], a form of testosterone. It usually appears in adolescence and tends to evolve into progressive hair loss that follows a pattern distribution. The frequency of men suffering from androgenetic alopecia increases with age, affecting up to 80 % of Caucasian men. In recent years, several surgical and non-surgical treatments have been developed to treat and prevent this condition.

Objective: Determine the efficacy and safety of existing non-surgical therapies for androgenetic alopecia. This paper intends to summarize the therapeutic evidence of these therapies, providing doctors with a tool that allows them to medicate their patients based on the evidence shown.

Methods: A search was performed in PubMed, Scopus and Cochrane of clinical trials published in English, dated between 2011 and 2021. The search strategy used was "(Androgenetic alopecia AND ((therapeutics) OR (therapy) OR (treatment))", with the added filter of clinical trials involving only men over 18 years of age. The main outcome was the evaluation of the effectiveness of the different therapies and the secondary outcome was the analysis of the safety of these therapies.

Results: 14 studies were included in this systematic review, of which 11 are randomized controlled trials and 3 are non-randomized clinical trials. Of these studies, 4 analysed the efficacy and safety of 5 alpha Reductase enzyme inhibitors, 5 addressed minoxidil therapies, and 5 focused on the analysis of low-level laser therapy (LLLT).

These studies seem to demonstrate that the 3 therapies mentioned above have some effectiveness in fighting androgenetic alopecia.

The adverse effects of these therapies are also described in the included studies, however, to more precisely assess the safety level of the different treatments, further studies are suggested.

It is also worth noting that 11 of the studies presented have a moderate risk of bias, 2 have a high risk of bias and 1 of the studies has a very high risk of bias.

Conclusion: The analysed therapies seem to be promising in the treatment of androgenetic alopecia, since all seem to demonstrate efficacy in this use.

Keywords

Androgenetic Alopecia; Hair loss; Non-surgical treatments

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List of Abbreviations

AE	Adverse effects
AGA	Androgenetic alopecia
DHT	Dihydrotestosterone
FDA	Food and Drug Administration
LLLT	Low level laser therapy
SDAE	Sexual dysfunction adverse effects
UBI	University of Beira Interior

Introduction

Male and female pattern hair loss, commonly known as androgenetic alopecia, is characterized by the non-scarring progressive shrinking of the hair follicle with a pattern distribution in susceptible men and women. This condition is one of the most prevalent reasons for hair consultation.(1)

Androgenetic alopecia is the most common type of male hair loss and is a physiologic variant. It is most common in white men, with 30%, 40%, and 50% experiencing androgenetic alopecia at 30, 40, and 50 years of age, respectively.(2)

Numerous patients suffering from androgenetic alopecia have a family history of the disorder. Hair thinning manifests in a gender pattern. Men usually present with bitemporal thinning, thinning of the frontal and vertex scalps, or complete hair loss with residual hair at the occiput as well as temporal fringes.(2)

Androgenetic alopecia (AGA) has long been considered to have substantial psychological implications for those suffering from it. One of AGA's most crucial psychological aspects is the perceptions of others, whether true or imagined. Several research findings have also shown that AGA can negatively impact the quality of life of those who are affected.(3)

Balding men have a variety of options. To begin, because the condition is not life-threatening and the morbidity is variable, it is reasonable to abstain from treatment and allow the balding to progress naturally.

The treatments currently approved by the United States Food and Drug Administration for androgenetic alopecia in men are topical minoxidil, oral finasteride, and Low-level laser therapy.

These medications prevent further hair loss but only partially reverse baldness. To maintain the effect, these must be used continuously. Because clinical response can take 6-12 months, these agents should be used for at least one year before deciding whether to continue treatment.(4)

This systematic review intends to verify which of the alternatives approved by the Food and Drug Administration is more effective and safer. It also aims to investigate whether the combination of different therapies has a better result than monotherapy treatment.

Methods

To carry out this systematic review, the PRISMA criteria were adopted(5)

First, we defined the PICO, which consisted of "What is the best therapeutic option for the prevention and treatment of androgenetic alopecia in adult men? Indications, adverse effects, and efficacy of existing therapies".

Subsequently, the inclusion and exclusion criteria were defined as shown in the following table:

Table 1 – Inclusion and exclusion criteria for selection of the articles

Inclusion criteria	Exclusion criteria
Articles written in English	Other types of androgenetic alopecia
Clinical trials	Interventions for women
Adult men (>18 years old diagnosed with androgenetic alopecia)	
Type of intervention must be an FDA-approved treatment	
Clinical trials performed in the last 10 years	

A search was then carried out in PubMed, Cochrane, and Scopus, during the month of December 2021, using the following search strategy "(Androgenetic alopecia AND ((therapeutics) OR (therapy) OR (treatment))", with the following additional filters: clinical trials involving only men; only with participants over 18 years old; articles written in English and published between 2011 and 2021.

As a primary outcome, we considered the evaluation of the effectiveness of the treatments used, as a secondary outcome, we sought to assess the safety (adverse effects) of these therapies.

The team of 3 researchers then identified 789 articles, 255 of which were duplicates.

Of the remaining 534 articles, after reading the title and abstract and consequent application of the inclusion and exclusion criteria, 37 articles were obtained.

After a full reading of these 37 articles, 23 articles were excluded after applying the inclusion and exclusion criteria, leaving the final 14 articles that were included in this review.

The PRISMA flow diagram shown in Figure 1 describes the information selection steps through of the different phases of the systematic review. This diagram comprises the number of articles identified, as well those included and excluded.

We also used the PROSPERO(6) platform to develop a protocol with the strategy endowed to carry out this investigation that was submitted and registered on the PROSPERO website.

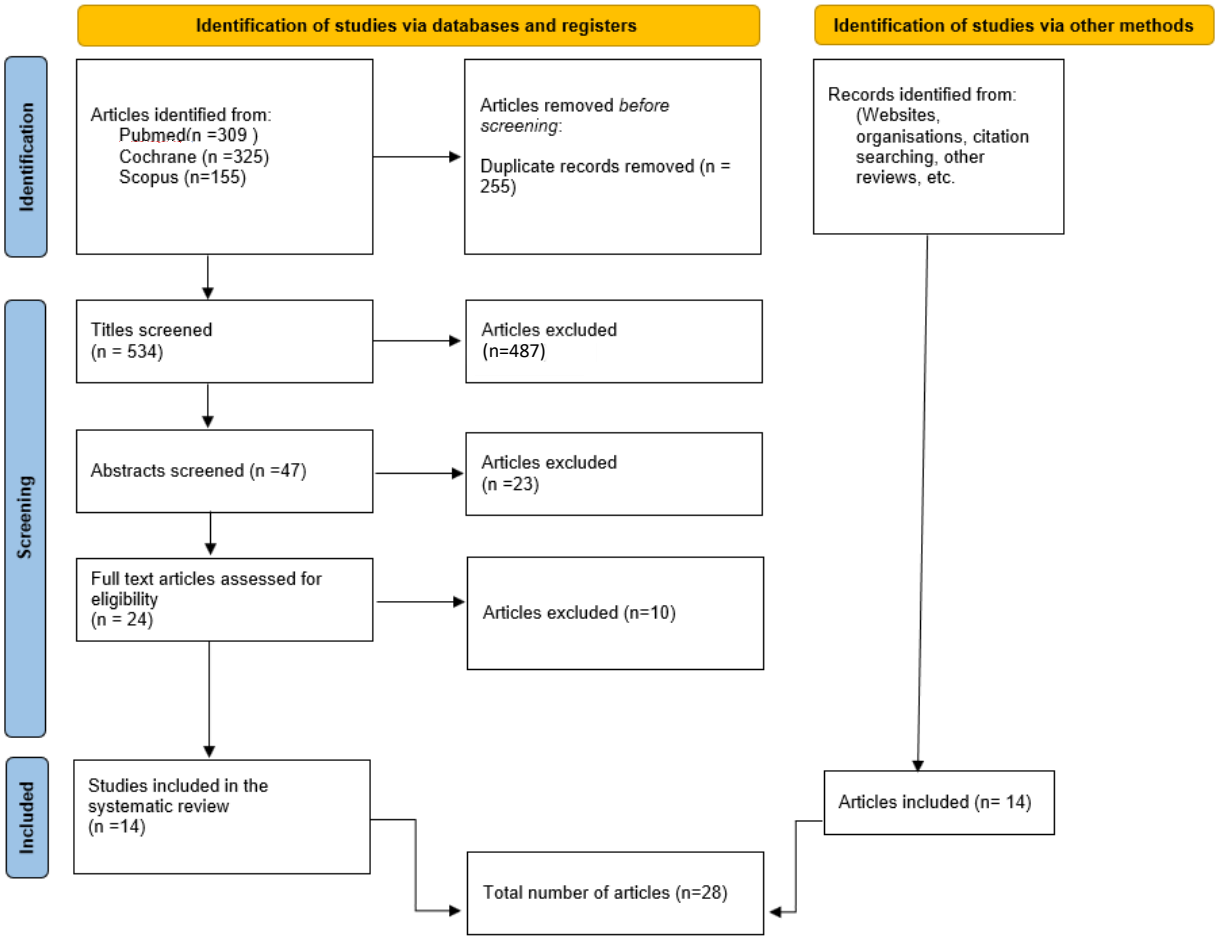

Figure 1: Prisma flow diagram for article selection

Risk of Bias Assessment:

The risk of bias of the studies included in this review was evaluated using the tools: "RoB 2: A revised Cochrane risk-of-bias tool for randomized trials"(7) and "ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions".(8)

Contextualization

Definition:

The most prevalent kind of progressive hair loss is androgenetic alopecia (AGA), commonly known as male pattern baldness. AGA is a polygenetic disorder with varying degrees of severity, onset age, and hair loss location on the scalp. Hair loss in men usually affects the temporal and vertex regions, sparing the occipital region: the so-called "horseshoe" pattern.(9)

Pathophysiology:

Normal hair development happens in a three-phased cycle at the hair follicle level: A hair follicle undergoes anagen, a two- to seven-year active growth phase, during which hair is continuously produced by the division and growth of keratin-producing epidermal cells that encircle a dermal papilla at the hair follicle's base; a second phase, catagen, lasts one to two weeks, and during this time, the hair bulb ascends to the skin's surface, losing its root sheath that anchors it. As soon as the hair follicle is out of the telogen phase, the germinal cells within it begin to proliferate and generate a new hair bulb. At least 90% of hairs on a typical scalp are in anagen, 1% are in catagen, and 9% are in telogen at the same time.

Male alopecia is caused by the loss of terminal (thick and pigmented) hairs and the growth of vellus (fine, non-pigmented) hairs over time.

In this way, terminal hairs are terminated and become vellus hairs. This is because the hair follicle gets smaller, which means the diameter of the hair gets smaller, too. Miniaturization can happen quickly in just one or a few hair cycles.

Miniaturization may happen in 1 or 2 hair cycles. In one piece of research, the ratio of terminal to vellus hairs was 7:1 in nonbalding scalps against 2:1 in balding scalps. In male pattern baldness, the anagen phase shortens while the telogen phase lengthens or stays constant, resulting in decreased hair length. The hair never reaches the skin's surface. The duration between the telogen and anagen stages lengthens, reducing the amount of scalp hairs. Male pattern baldness is recognized to be dependent on androgens, particularly dihydrotestosterone (DHT). 5-alpha reductase type 1 and type 2 are lipophilic enzymes located in intracellular (nuclear) membranes. Type 2 5-alpha reductase seems to be more essential than type 1 in male pattern baldness. Several lines of evidence indicate the function of androgens, particularly DHT, in male pattern

baldness. First, this syndrome is not seen in eunuchs, who lack androgens, or pseudohermaphrodites, who lack 5-alpha reductase. Second, the development of androgenetic alopecia in males is stopped concomitant with castration in post pubertal men. Third, balding scalp has high levels of 5-alpha reductase, DHT, and androgen receptor. It is possible to limit the conversion of testosterone to DHT by specifically blocking the activity of 5-alpha reductase type 2. Androgens and a genetic predisposition are required for androgenetic alopecia in males, although the etiology of this disorder is unknown. A single autosomal dominant gene, a pair of sex-linked components, a dominant gene with higher or varied penetrance in males, and polygenic inheritance are all hypothesized. Nevertheless, a family history of androgenetic alopecia is not required to make the diagnosis. (10)

Clinical picture:

Most men's AGA includes the frontotemporal and vertex, following the Hamilton–Norwood scale (11). However, males may acquire widespread crown thinning with preservation of the frontal hairline, similar to the Ludwig type seen in women.(12)

Indications:

First of all, to know which patients are indicated for treatment, we must make a correct diagnosis of androgenetic alopecia.

The physical examination should focus on the hair and scalp, but physical indications of any concomitant condition revealed by the assessment of systems should also be considered. If only the scalp is affected, the doctor should check for a normal male pattern to rule out androgenetic alopecia.(2)

The pull test can be used to find out if you have hair loss. The examiner uses the thumb, index, and middle fingers to hold about 40 to 60 hairs at their base. Then, the examiner gently pulls the hairs away from the scalp. A positive test is when more than 10% of hairs (four to six) are pulled from the scalp. This means that there is active hair shedding and that the person has telogen effluvium, anagen effluvium, or alopecia areata. However, a negative test result doesn't mean that those conditions are not true. There are two reasons why the pull test is hard to standardize: the pulling force isn't evenly distributed, and it's hard to estimate how many hairs were seized. This can lead to false conclusions.(2)

Figure 2 shows an algorithm for the correct diagnostic of AGA based on Blume-Pevtavi et al, guideline for diagnostic evaluation in androgenetic alopecia in men. (12)

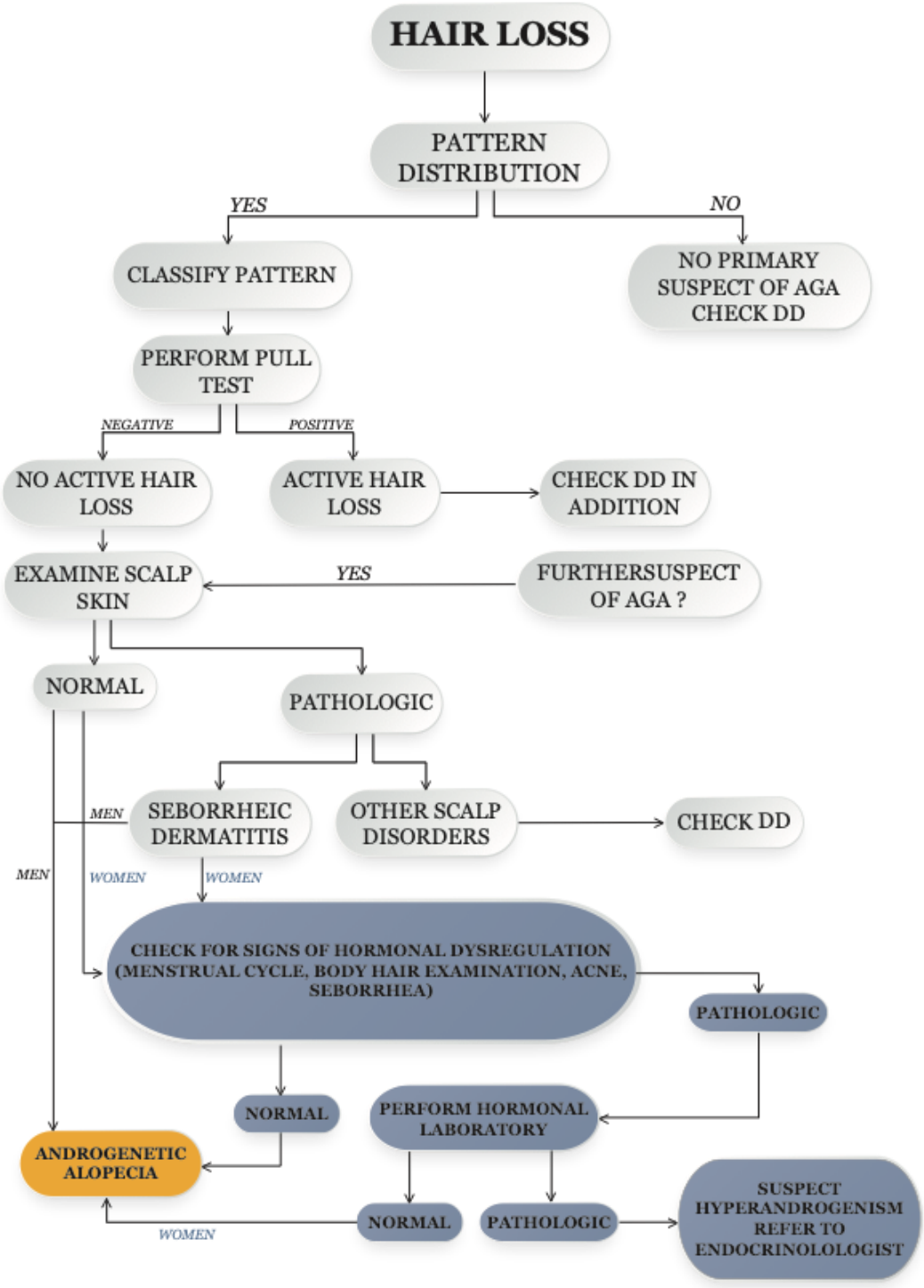

Figure 2: Algorithm for the correct diagnostic of AGA

Approved treatments:

In this systematic review, we only intend to study the treatments for androgenetic alopecia approved by the US FDA, such as first-line therapies (finasteride and minoxidil), as well as the main adjuvant approved therapies (LLLT- Low-level laser therapy).

We also include dutasteride because its use is approved in some countries such as Korea and Mexico.

The treatments addressed in this systematic review are described in table 2(1)

Table 2: Approved treatment options for male androgenetic alopecia (1)

Medication	Treatment approval: US FDA	Mechanism of action	Dosage recommendation	Major adverse effects
Finasteride	Approved	5 alpha-reductase inhibitor	1mg once daily	Sexual adverse effects
Dutasteride	Approved in several countries, e.g., Korea and Mexico	5 alpha-reductase inhibitor	0.5mg once daily	Sexual adverse effects
Minoxidil	Approved	Unknown, possible antiandrogenic, vasodilatory, and inflammatory effects	5% solution: topical application twice daily	Hypertrichosis, contact dermatitis Contraindicated during pregnancy Erythematous reaction
Low-level laser therapy (655nm)	Approved	Possibly activation of dormant hair follicles, increased blood flow, upregulated growth factors and adenosine triphosphate, and stimulation of anagen hair	20 min/day, 3 times a week	----------

Mechanism of action:

5 Alpha Reductase inhibitor:

A hereditary susceptibility of the hair follicles to DHT is one of the etiological factors in AGA. Humans have two 5-alpha-reductases. This occurs in the prostate, genitourinary tract, and hair follicles.

Finasteride, a type II 5-alpha-reductase inhibitor, and dutasteride, a type I and II 5-alpha-reductase inhibitor, are both used in AGA, once they prevent the conversion of testosterone to DHT by blocking the converser enzyme (5-alpha reductase)

Oral finasteride 1 mg/day is suggested for mild to moderate AGA male patients aged 18 and above. The therapy response should be reviewed after 6 months; however, it may take 12 months for some men.

Oral dutasteride 0.5 mg/day is another option. Gynecomastia, decreased libido, and erectile dysfunction are rare side effects. Finasteride also lowers Prostate Specific Antigen (PSA). If therapy begins beyond 45 years of age, PSA monitoring should be considered. The PSA levels should be doubled to compensate for the finasteride drop, allowing for reliable test interpretation.(3)

Minoxidil:

Minoxidil's specific mechanism of action is unknown. The drug's active form, minoxidil sulphate, activates ATP-sensitive potassium channels in cell membranes, causing vasodilation. In addition to vasodilation, minoxidil may also increase the expression of VEGF mRNA in the dermal papillae, cytoprotective prostaglandin synthase 1, an enzyme that promotes hair growth, and hepatocyte growth factor (HGF) mRNA, another hair growth promoter. The following recommendations should be followed: Topical 2 % or 5% minoxidil solution used twice daily (2ml /day) for men over 18 years old prevents progression and improves AGA. The normal formulation (with propylene glycol) is used since alternate preparations including foam preparations or greater concentrations have not been well studied. The therapeutic response should be reviewed after 6 months. Telogen shedding occurs in the first 8 weeks of treatment.

Most often, topical minoxidil causes hypertrichosis. Contact dermatitis may be irritant or allergic. The increased propylene glycol level of the 5% solution causes more irritation.(3)

Low level laser therapy (LLLT):

Low-level laser therapy is becoming more popular as an AGA treatment. These days, several gadgets may be used at home or at a clinic to treat AGA. Inhibitory cells that impede the development of follicular stem cells to progenitor cells may be suppressed by particular light wavelengths, which may function by upregulating PGE2. The therapy

period is usually 6–12 months. The FDA approved Low-level laser therapy to treat AGA in 2007.(13)

Results

5 Alpha Reductase Inhibitors:

Sato et al., 2012, investigated the efficacy and safety of finasteride 1mg in 3177 Japanese men suffering from androgenetic alopecia. 616 patients were excluded because they only made the first visit assessment, among the entire study population.
Efficacy was evaluated in the 2561 patients who remained in the study. The response rate evaluated showed the following: greatly, moderately, or slightly increased hair growth in the efficacy analysis population was 87.1% (2230/2561). 12,5% (320/2561) of the patients had no changes in response rate, and 0.4% (11/2561) of the patients has a slightly decreased response rate.(14)
During the study's full duration, adverse events occurred in 0.7 %of the whole study group (23 /3177). Reduced libido (n = 8), hepatic functioning impairment (n = 3), a unilateral breast enlargement (n = 2), and a bilateral mammary hypertrophy (n = 2).
7 of these 23 patients terminated therapy owing to adverse responses, which included reduced libido (n = 3); hepatic functional disorder, memory impairment, and unilateral mammary enlargement (all n = 1); and palpitations, febricula, and headache (all n = 1). The majority of them were minor, and follow-up statistics are unavailable due to a lack of contact.(14)

Gubelin Harcha et al., 2014 investigated the efficacy and safety of various dosages of dutasteride against placebo in the treatment of males with androgenetic alopecia.
For this, males between the ages of 20 and 50 with androgenetic alopecia were randomly assigned to receive dutasteride (0.02, 0.1, or 0.5 mg/d), finasteride (1 mg/d), or placebo for 24 weeks.
At week 24, dutasteride 0.5 mg substantially enhanced hair count, hair thickness, and hair growth (front view; photographic panel evaluation) compared to finasteride (p=0.003, p=0.004, and p=0.002, respectively) and placebo (p=0.003, p=0.004, and p=0.002, respectively) (all p \ 0.001).(15)
The majority of adverse effects reported were minor or moderate. There was no statistically significant difference between the groups receiving active treatment and the placebo group.
The incidence of adverse effects related to sexual function was similar in the groups receiving active treatment and lower in the placebo group, with the adverse effect of libido reduction contributing the most to this difference.
No evidence of a dose-dependent relationship between the adverse effects of dutasteride was found.

There were no reports of ovarian or mammary cancer, nor adverse cardiovascular effects.(15)

Shanshanwal et al., 2017 compared the efficacy of dutasteride 0.5 mg to finasteride 1 mg in males aged 18 to 40 with androgenetic alopecia. The study population was randomly assigned to receive either 0.5 mg dutasteride or 1 mg finasteride daily for a month.

The change in total hair count after 24 weeks of treatment was significantly greater in the dutasteride group than in the finasteride group ($p<0.001$). In 24 weeks, the dutasteride group had significantly fewer balding hairs than the finasteride group ($p=0.0156$).

The proportion of patients with a significant improvement in their condition was higher in the dutasteride group compared to the control group ($p<0,001$).

The subjective assessment of the study participants revealed that the hair growth scale was significantly better in the dutasteride group compared to the finasteride group ($p<0.05$). However, there was no difference in the size of the vertex size, hair loss, or hair quality between the two groups.(16)

The majority of adverse effects were mild or moderate (8 AE in the dutasteride group and 7 AE in the finasteride group). There was no statistical difference in the incidence of adverse effects, adverse effects related to the drug, adverse effects leading to study termination, or adverse effects related to sexual dysfunction between the two groups.(16)

Tsunemi et al., 2016 performed a multicentre, open-label, prospective outpatient research in which participants took dutasteride 0.5 mg once a day for 52 weeks.

The total AE (adverse effects) rate was 17%. The most prevalent SDAE (sexual dysfunction adverse effect) were erectile dysfunction and reduced libido. At week 52, 3 patients experienced probable suicidality-related AEs: suicidal thoughts in 1 patient and depression in 2 patients. The most common AE was sexual dysfunction, which was recorded in 19 (15.8%) individuals. Except for one incidence of impotence, no other SDAE recorded was severe enough to cause removal from the trial. When the 52-week treatment period came to an end, 6 patients had their SDAEs resolved. The 13 patients with SDAEs which persisted after the treatment period were all resolved within 6 months of stopping treatment. Except for hypertension in one patient, which the investigator attributed to study therapy, no additional cardiovascular AEs were reported. Aside from the 2 SAE recorded (stress fracture and post-traumatic neck syndrome), there were no fatalities in this research. A total of 51 out of 118 patients

(43%) had clinical laboratory results shift from normal to abnormal after baseline. High total bilirubin and alanine aminotransferase were the most often reported abnormalities (change from normal at baseline to abnormal at any time post-baseline). During the trial, 2% or fewer of participants had alterations in vital signs. 1 patient had breast pain at week 52, but no other abnormalities were discovered.

The outcomes varied depending on the patients' Norwood–Hamilton stage at baseline. At week 26, 6 of 53 patients (11%) who were at stage III vertex improved, as did 16 of 46 (35%) who were at stage IV and 14 of 19 (74%) who were at stage V. Week 52 improvements were 21 of 53 (40%) patients, 20 of 46 (43%) patients, and 16 of 19 (84%) patients respetively.(17)

Minoxidil:

Hillmann et al., 2015 designed a clinical study to determine the efficacy and safety of topical minoxidil in males who suffer from androgenetic alopecia in the frontotemporal and coronal regions, the treatment consisting of 5% minoxidil applied twice a day.

At week 16 the frontotemporal and vertex regions showed a significant increase in non-vellus hair count and hair width compared to the placebo group ($p<0.001$).

After 24 weeks of treatment, the non-vellus hair width in the frontotemporal and vertex areas increased significantly in the minoxidil 5% group compared to the placebo group ($p=0.017$) ($p=0.016$) respectively.

Also at 24 weeks, 5% minoxidil topical foam users rated a significant improvement in scalp coverage for the frontotemporal ($p=0.016$) and vertex areas ($p=0.027$)

On the other hand, the non-vellus hair count did not increase significantly in any of the regions at week 24.(18)

During the study, there were 3 adverse effects related to the product in the experimental group and 1 in the control group.

There were 16 cases of local intolerance in the experimental group and 11 in the placebo group.

As a result:

The occurrence of local intolerances in both groups reflected the potential irritating effect of penetrating potentiators (for example, glycerine for 5% Minoxidil and placebo).

Erythema, papules, folliculitis, and a sense of tension in the skin were only reported in the Minoxidil group.(18)

Hasanzadeh et al., 2016 compared the efficacy, safety, and patient satisfaction with minoxidil 5% topical foam in males with androgenetic alopecia.

The patients had an increase in hair counts evaluating with the naked eye (O) and using the camera (C) at week 16 ((C) p=0.015; (O) p=0.003) and 24 weeks ((C) p=0.019; (O) p=0.002).

The effectiveness of the product was also evaluated (reduction in hair loss, growth of new hair, or increase in hair size), with the results showing that at the weeks 16 and 24, 50% and 75% of participants respectively, were very satisfied with the product's efficacy. In terms of the product's application method, dose, and ease of application throughout the 16th and 24th weeks, 85,7% and 91,6% of participants, respectively, were very satisfied.(19)

No skin burning, itching, erythema, oedema, or scaling occurred after administering minoxidil 5% topical foam. 7% of patients experienced itching, dryness, or redness after applying minoxidil 2% topical solution to their scalp. (19)

Ghonemy et al. 2021. evaluated the effectiveness and safety of 10% minoxidil against 5% minoxidil and placebo.

Ratio changes in the mean number of total hairs in the crown region revealed that minoxidil 5% increased total hair count in a non-statistically significant manner compared to the other groups. (p=0.749).

However, when the frontal region is analysed, we discover that the overall hair count is considerably greater in the group that took 5% minoxidil than in the other two groups ($p<0.0001$).

There was a substantial increase in hair thickness in favour of minoxidil 5% in both the crown and frontal regions ($p<0.0001$). The greatest difference was between the minoxidil 5% and placebo groups ($p<0.0001$), and between 5% and 10% of the group in the vertex region (p=0.039), but not in the frontal (p=1).(20)

There is a very significant difference in irritation across the three groups, with the greatest difference between the 5% and 10% groups (all patients using Minoxidil 10% experienced irritation, whereas 22% of patients using Minoxidil 5% had irritation).

In the 10% minoxidil group, more patients had adverse symptoms such as erosion, hypertrichosis, and headache, which were not seen in the 5% minoxidil group.(20)

Hu et al., 2015 developed a 12-month study to examine the effectiveness of finasteride (1mg daily), minoxidil 5% (1ml twice daily), and combined treatment (1mg finasteride + 1ml minoxidil 5% twice daily) in 428 males.

At 3 months, the growth rate of the finasteride group was comparable to that of the minoxidil group (finasteride: 39.0% vs. minoxidil: 38.5%, $p>0.05$), but much lower than that of the combination group (54.6 %, $p<0.01$).

At 6, 9, and 12 months, patients receiving finasteride improved much more than those receiving minoxidil ($p<0.01$); the combined therapy remained the most effective ($p<0.01$). (21)

Among those on finasteride (including those with combination treatment) 6 individuals (1.8%) had side effects. Adverse effects included decreased libido (n=3, 0.9%), erectile dysfunction (n=1, 0.3%), testicular pain (n=1, 0.3%), and abnormal liver function (n=1, 0.3%). Patients returned to normal after a few weeks of stopping the drug.

Between the individuals taking 5% minoxidil, contact dermatitis (n = 16, 5.5%) was the most common side event recorded. The majority of side effects were mild and manageable; just six individuals (2.1%) dropped out.

Additionally, headache (n=1, 0.3%) and increased body hair (n=1, 0.3%) were also recorded as adverse effects. When the drug was stopped, all side effects went away.(21)

Sakr et al. 2013 performed a pilot trial to compare minoxidil 5% alone with a minoxidil microemulsion (containing 0.5% diclofenac, 5% tea tree oil, 5% minoxidil, 5% lauryl alcohol, and 35% water in combination with 55% Labrasol [(surfactant)/ (propylene glycolethanol mixture at 1:1 as cosurfactant) at (1:1)]. One group received the microemulsion, another received minoxidil alone, and the third received a placebo.

In terms of mean hair count, the formulation comprising the minoxidil microemulsion was significantly superior to the formulations containing minoxidil alone and placebo in terms of mean hair count ($p=0.009$ and $p< 0.001$, respectively). Hair weight on average ($p<0.001$) and hair thickness on average ($p<0.05$).

The results also indicate that the multimodal minoxidil formulation was significantly better ($p<0,001$) in terms of patient satisfaction and had a more rapid onset of action when compared to minoxidil alone and placebo formulations.

Patients treated with a multimodal minoxidil formulation reported an increase in hair growth, a decrease in sebum production, and a significant decrease in hair loss during the first week of treatment, in comparison to patients treated solely with minoxidil, who reported a delayed effect beginning after 4–5 weeks. The placebo-controlled treatment resulted in a significant decrease in hair growth.(22)

There were more people who had contact dermatitis in the group that used the 5% minoxidil solution than in the group that used the placebo solution (7 of 11 patients, about 64%) in 5% minoxidil group and (4 of 10 patients, about 40 % in placebo group).

In comparison, symptoms were less common in the group treated with the multimodal minoxidil formulation (1 out of 11 patients, or about 9%).(22)

Low level laser therapy:

Lanzafame et al.2013 conducted a clinical investigation to determine the safety and physiological effects of low-level laser treatment (LLLT) on males with androgenetic alopecia.

Each of the patients had a part of their scalp chosen. The hairs in this area were shaved to a height of 3 mm, and a tattoo was used to mark the area.

It took the experimental group 60 treatments over 16 weeks with the duration of 25 minutes each.

The data suggest that 16 weeks of LLLT therapy raised the average hair count by around 39%. A multivariate analysis was conducted to account for variations in the quantity of local hair on the study scalp prior to treatment. This suggested that the augmentation was adjusted for the treated scalp area, which had a statistically significant impact ($p < 0.0001$).(23)

There were no studies on harmful effects with any participants.(23)

Fan et al. 2018 conducted a 24-week study to determine the efficacy and safety of LLLT in the treatment of androgenetic alopecia.

All patients received LLLT on one side of the head and a treatment with simulated light on the other side, three times a week for a total of 24 weeks.

After 24 weeks of treatment, the side exposed to LLLT had a significant increase in the coverage of the scalp in comparison to the side exposed to artificial light. (14.2% vs. 11.8%, $p<0.001$). Additionally, a significant increase in hair thickness, count of hair, and significant improvements in the investigator's global assessment were seen when comparing the LLLT-treated side to the non-exposed side ($p<0.001$).(24)

29 patients (29.3%) experienced adverse events, which were assessed to be possible or probably related to therapy. These adverse events included dermatitis (4.0%), pruritus (3.0%), and acne (1.0%). None of the individuals suffered an adverse event that necessitated the discontinuation of study device usage or the study's suspension. The majority of adverse effects were resolved within two weeks.(24)

Kim et al. 2013 developed a clinical trial to evaluate the efficacy and safety of low-intensity laser therapy for androgenetic alopecia.

The experimental group used a LLLT helmet for 18 minutes every day.

After 24 weeks, the median hair length and density of the hair showed statistically significant improvements in the LLLT group compared to the control group. (P=0.01 and P=0.003, respectively)
Similarly, the investigator's overall assessment revealed a significant difference between the two groups, with the LLLT group obtaining better results (p=0.002), however the subject's perception was not statistically significant.(25)
No severe adverse reactions were detected.(25)

Faghihi et al. 2018 investigated the efficacy of combining low-intensity laser therapy with 5% minoxidil in the treatment of patients with androgenetic alopecia.
The patients were randomly assigned to an experimental and a control group.
The experimental group received topical minoxidil solution at a concentration of 5% twice daily (2ml/d), in addition to low-dose phototherapy twice to three times per week. The control group received the same solution as the treatment group and a laser pen system that was turned off to act as a placebo. The study lasted 12 months.
The average increase in hair count was significantly greater in the experimental group than in the control group (78,3 % vs. 51,3 %; p<0,001). The average increase in hair diameter was also significantly greater in the experimental group compared to the control group (45,4 % vs. 32,3 %; p=0,002).
In comparison to the control group, the percentage of patients who recovered from androgenetic alopecia in the experimental group showed a significant increase at 6, 9, and 12 months after intervention (p< 0,001).
Additionally, a significant difference in satisfaction with the treatment was observed between the two groups (p<0,001).(26)
No significant differences in terms of collateral effects such as headache (p=0,35), pruritis (p=0,44), or burning sensation (p=0,81) were observed between the two groups, even though the probability of developing erythema was significantly greater in the control group than in the case group (5 vs. 1 case; p=0,04).(26)

Ferrara et al.2021 evaluated the efficacy of a combined therapy of 5% minoxidil and photobiomodulation in the treatment of androgenetic alopecia. All participants received 12 minutes of low intensity laser and then a topical application of minoxidil (1 ml of 5% solution) twice daily for 6 months. The photobiomodulation devices were adjusted so that half of them emitted light and half did not. Blind analyses of clinical photographs and automated phototrichograms collected previous to and then after 3 and 6 months of therapy were used to determine efficacy.
At 3 and 6 months, all patients demonstrated improvement in scalp covering on both sides. On the combined treatment side, the total number of hairs grew considerably

after 3 ($p<0.001$) and 6 months ($p=0.001$). On the minoxidil-only side, a comparable rise was seen at both 3 ($p<0.001$) and 6 months ($p<0.001$). There were no statistically significant differences between the two groups ($p>0.05$).(27)

No severe adverse reactions were detected.(27)

Risk of bias in non-randomized clinical trials:

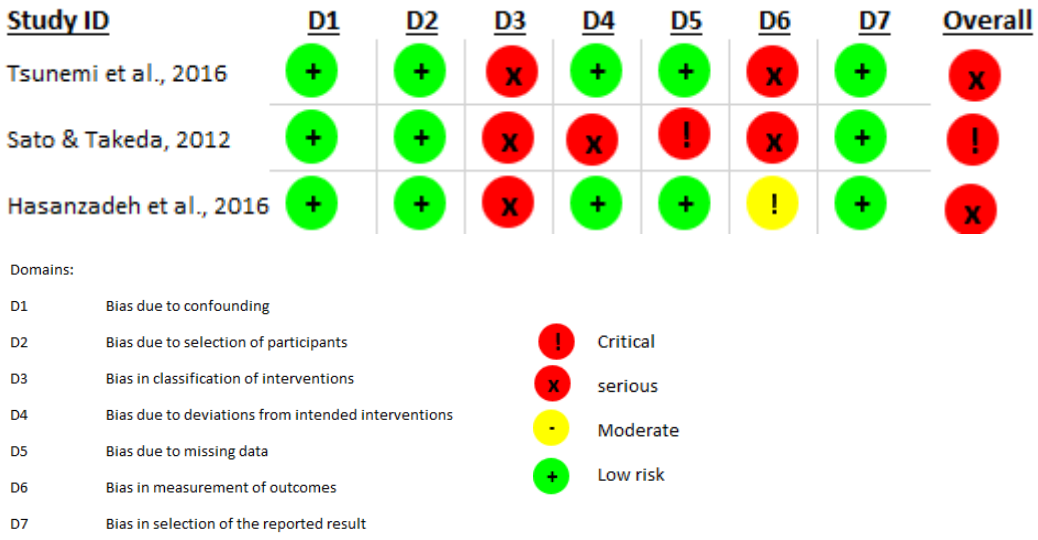

Figure 3: Assessment of individual domains at risk of bias for each non-randomized study included.

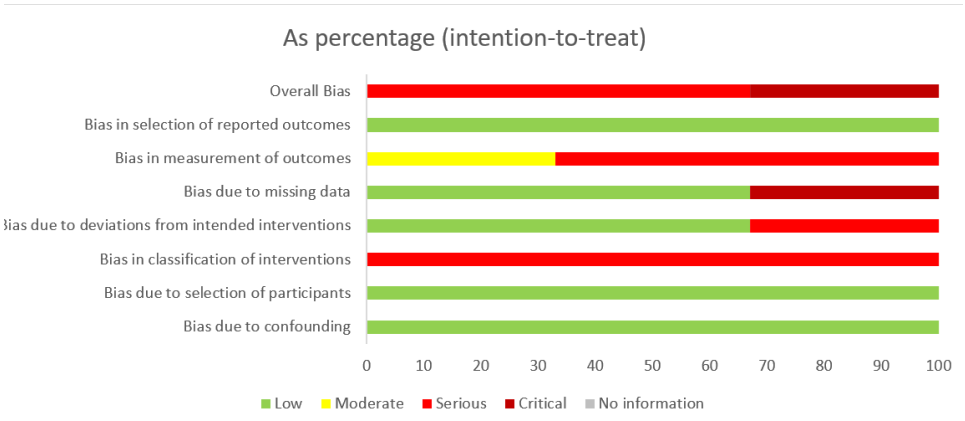

Figure 4: Proportion of risk of bias of non-randomized studies included

Risk of bias in randomized clinical trials:

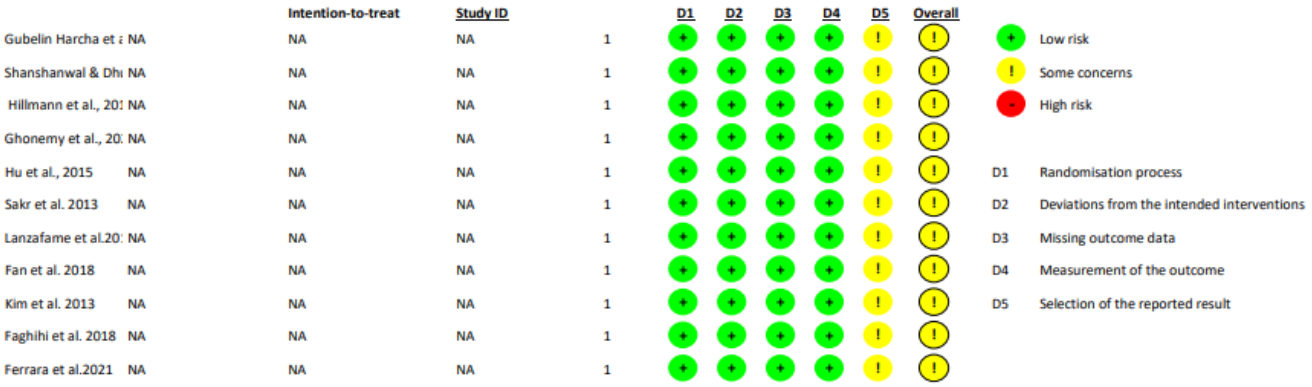

Figure 5: Assessment of individual domains at risk of bias for each randomized study.

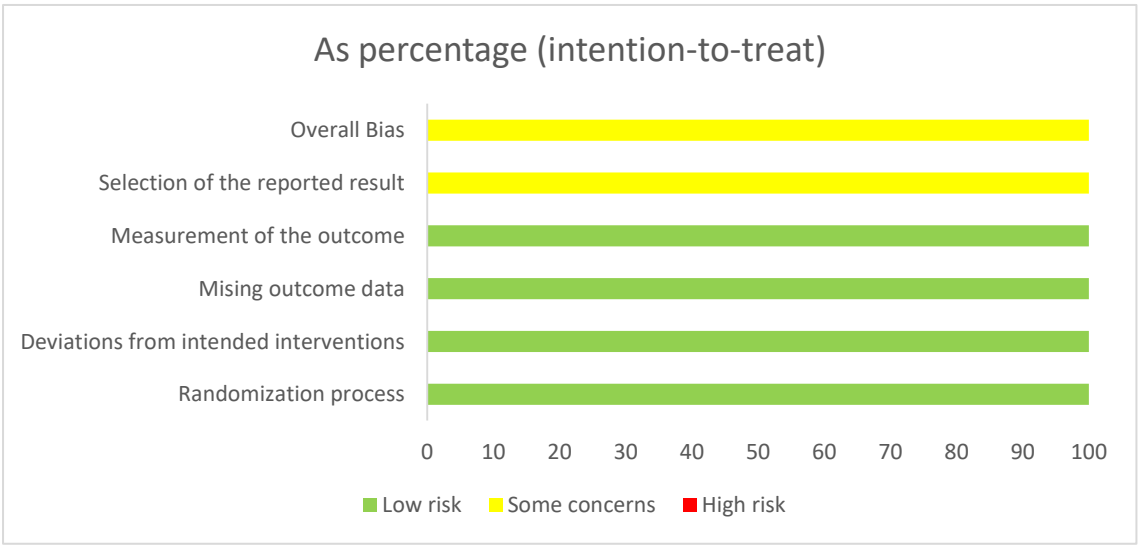

Figure 6: Proportion of risk of bias for randomized studies included

Discussion

In this systematic review, 14 studies were included. 4 of the studies focused on 5 alpha Reductase inhibitors, 5 studies on minoxidil and another 5 on Low level laser therapy.

One of the studies was carried out in two continents, South America and Asia (including a total of 9 countries belonging to these continents), two studies were carried out in Japan and another two in Iran. The shelves were performed in India, Germany, Egypt, Saudi Arabia, China, USA, Taiwan, Brazil and South Korea.

The results obtained in this review seem to be promising, as all studies show that either 5 alpha reductase inhibitors, minoxidil and LLLT show improvements in the treatment of androgenetic alopecia.

5 alpha-reductase inhibitors:

Analysing the efficacy of 5 alpha-reductase inhibitors we verified that in one study(14) finasteride 1mg taken once a day seems to be effective in combating androgenetic alopecia, since of the 2561 patients in which it was possible to evaluate the efficacy, 2230, that is 87.1%, reported improvements in terms of hair growth.

However, two studies (15,16) seem to demonstrate that dutasteride 0.5 mg/d may be more effective than finasteride 1mg/d, since in one of these studies (16), we are told that the group that received dutasteride showed significantly fewer balding hairs compared to the finasteride group, and the subjective assessment of the study participants revealed that the hair growth scale was significantly better in the dutasteride group compared to the finasteride group. In the other study (15) it was also suggested that dutasteride 0.5 mg substantially enhanced hair count, hair thickness, and hair growth compared to finasteride.

In terms of safety the studies presented, decreased libido seems to be the most common adverse effect (14,15,17) and there did not seem to be any relevant difference in adverse effects between the groups that took finasteride and dutasteride (15,16)

In one study, we can see that only a small percentage of individuals to whom finasteride was administered had adverse effects (0.7%), although it should be noted that reduced libido was the most frequent adverse effect of this trial.(14)

In the article elaborated by Tsunemi et al, 2016 whose main outcome was the evaluation of adverse effects of individuals who received 0.5mg of dutasteride for 52 weeks, the most frequent adverse effect was the reduction in libido, which occurred in 15.9% of individuals. However, we understand that in all cases the adverse effects resolved after 6 months of discontinuation of treatment. We also highlight the fact that about 43% of patients had clinical laboratory results shifted from normal to abnormal after baseline. High total bilirubin and alanine aminotransferase were the most commonly reported abnormalities(17)

However, in Gubelin Harcha et al 2014 trial(15), it was found that the group which received a placebo had fewer adverse effects than the groups that received finasteride and dutasteride, and the reduction in libido as an adverse effect was what contributed most to this difference.

Minoxidil:

Looking at articles that analyse the efficacy of minoxidil, two of the studies (18,19) showed that minoxidil 5% appears to be effective in mitigating the effects of androgenetic alopecia, and patients who have used it for 24 weeks showed improvements in their hair loss.

In the study conducted by Ghonemy et al (20), where minoxidil 5% was compared with minoxidil 10%, it seems to us that the former presented more favourable results in terms of efficacy than the latter.

As for the combination minoxidil5% (1ml/d) + finasteride (1mg id), it seems to be more effective than the use of minoxidil alone (21). And finasteride alone therapy seems more effective than 5% minoxidil alone therapy (21)

When comparing the use of a minoxidil microemulsion with 5% minoxidil alone (22), the microemulsion appeared to be more effective than minoxidil alone.

In relation to safety of minoxidil in the investigation conducted by Hillmann et al, the occurrence of local intolerances was verified in the experimental and control group (18), which suggests that these adverse effects may be related to the potential irritating effect of penetrating potentiators (for example, glycerine for 5% Minoxidil and placebo).

However, no skin burning, itching, erythema, oedema, or scaling occurred after administering minoxidil 5% topical foam (19). This is probably because the concentration of propylene glycol in minoxidil 5% topical solution increases the sensitivity of irritated skin and is known to induce allergic contact dermatitis. Because the foam has no propylene glycol, it has fewer negative effects than the solution

The comparison between minoxidil 5% and minoxidil 10% (20) also suggests that adverse effects seem to be more intense and frequent in patients who used minoxidil 10% compared to minoxidil 5% group.

When the minoxidil microemulsion was compared with 5% minoxidil alone (22), the microemulsion appeared to be safer and more tolerable as it had fewer adverse effects, which can be explained by the fact that the microemulsion has diclofenac which reduces inflammation and consequently inflammation. production of sebum, which is an environment that facilitates the proliferation of bacteria and fungi. The addition of tea tree oil can also help in this fight against bacteria and fungi.

Low level laser therapy:

There seems to be strong evidence that low level laser therapy (LLLT) is a viable option for the treatment of androgenetic alopecia, since in all the studies that analyse the efficacy of LLLT (23–27) the patients showed improvements in their hair loss condition.

Highlighting the studies which compared the effect of LLT and the addition of 5% minoxidil to the LLLT treatment (26,27), Faghihi et al. suggest that the addition of minoxidil to the LLLT treatment is beneficial since the population that received the combined treatment had more satisfactory results than the population that received only LLT. (26)

On the other hand, the study conducted by Ferrara et al. where participants had half of the scalp treated with minoxidil and LLLT and the other half of the scalp only with minoxidil, apparently resulted in both sides of the scalp showing improvement compared to pre-treatment, however without significant differences between either side.(27)

Analysing the adverse effects of LLLT, two of the studies did not have this evaluation as an outcome (23,25), and one of the studies did not report any adverse effect. (27)

In the study performed by Faghihi et al, we are told that the adverse effects of the population that received LLLT are the same as the control population(26) and in the study conducted by Fan et al. adverse effects were reported in 29.3% of patients, among which we highlight the occurrence of dermatitis, pruritus, and acne, however, none of these adverse effects led to discontinuation of the study and all were resolved within 2 weeks.(24)

Bias analysis:

The risk of bias analysis of the articles included was performed using the "Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)",(7) and "ROBINS-I: a tool for assessing the risk of bias in non-randomized studies of interventions".(8)

We found that the 11 randomized clinical trials (15,16,18,20–27) are classified with the level "some concerns" in terms of risk of bias, essentially because of the domain that evaluates the "selection of reported results", since in all of them there are "multiple measures of eligible outcomes (for example, scales, definitions, time points).

As for non-randomized clinical trials, two of them(17,19) were classified with serious risk of bias and another with the critical risk of bias.(14)

Limitations of the systematic review:

There were some limitations in this work regarding the research strategy. It was limited to 3 databases and only articles written in English and published in the last 10 years were considered. Thus, publication bias and selection of articles must be considered.

Access to some of the available Cochrane studies was also not gained and furthermore, some of the mentioned studies were prospective studies without a control group.

It should also be noted that all the studies mentioned had different scales for assessing the outcome, which leads to a lack of uniformity between them in terms of the comparison of outcomes.

In addition, no study has directly compared the 3 therapies, to assess which one is the most effective, and no study has studied the effect of combining the 3 therapies simultaneously, to evaluate the effectiveness of the triple therapy (5 alpha reductase inhibitor + minoxidil +LLLT)

Conclusion

Androgenetic alopecia is a problem that affects millions of men around the world.

There are some approved treatments for treating and preventing the progression of this condition. In this systematic review, we tried to analyse some of them (finasteride, dutasteride, minoxidil, and Low-level laser therapy) in terms of their efficacy and safety.

On the one hand, regarding the evaluation of efficacy, improvements were reported with all the therapies mentioned.

On the other hand, no study has directly compared the 3 therapies to assess which one is the most effective, and no study has looked at the effect of combining the 3 therapies simultaneously to assess the effectiveness of the triple therapy (5 alpha-reductase inhibitor + minoxidil +LLLT). Therefore, it is not possible to define which treatment is most effective.

It should also be noted that in terms of the analysis of the adverse effects of the different therapies, the analysed articles have some gaps, and more studies are needed to achieve conclusions on this outcome.

Clinical implications:

Androgenetic alopecia is a condition that affects millions of men around the world and, despite not having a big clinical impact on the physical health of individuals who suffer from it, it can have a negative effect on their self-esteem and mental health. Thus, the objective of this systematic review was to create a tool that could serve as a basis for physicians who are not linked to the specialty of dermatology so that they could medicate patients with androgenetic alopecia using the most effective and safe treatments, delaying its progression. This way if the management of alopecia is successful with simple non-invasive therapies, there is a reduction in the number of

medical resource consumption for this problem, channeling these resources to more urgent pathologies.

We must still consider the more effective the non-invasive measures, the less need for patient exposure to surgery for something that is not a disease, but a condition.

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Supplementary data

Supplementary Appendix 1- Hamilton Nordood classification and Ludwig pattern of hair loss

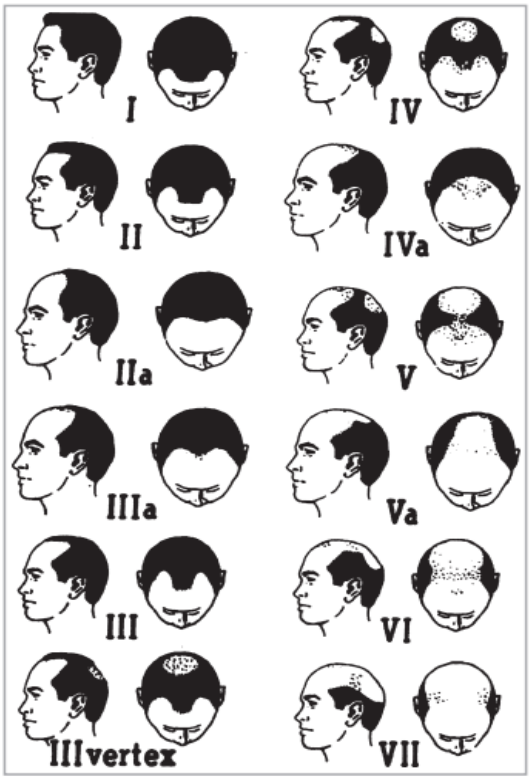

Figure7: Hamilton–Norwood classification of male balding(11)

Figure 8: Ludwig pattern of hair loss (28)

Supplementary Appendix 2 - Summary of the individual characteristics of each included study

Table 3: Summary of the individual characteristics of each included study

Study	Type of study	Sample		Type of intervention	Type of control	Assessments
		EG	**CG**			
Gubelin Harcha et al. 2014	RCT	736	181	dutasteride (0.02, 0.1, or 0.5 mg/d), finasteride (1 mg/d),	Placebo pill	**HG; HR; GPE; IA**
Shanshanwal et al 2017	RCT	45	45	0.5mg /d dutasteride or 1mg/d finasteride	-	**GPE; PA; SA**
Tsunemi et al 2016	open-label, prospective, single-arm outpatient study	**120**	-	0.5 mg/d dutasteride	-	**SA; HG; HR;**
Sato et al 2012	**NRCT**	**3177**	-	1mg/d finasteride	-	**MGPA**
Hillmann et al 2015	RCT	35	35	Half capful of minoxidil 5% topical foam twice a day	Half capful of placebo topical foam twice a day	**TAHC**, Frontotemporal, and Vertex; **TAHW** Frontotemporal and vertex; **PE**
Hasanzadeh et al 2016	phase 2 before-and-after trial	17	0	1 ml of minoxidil 5% TF on the scalp daily for 6 months	-	**TAHC; PE; GPR; SA**
Ghonemy et al 2021	RCT	Group1: 33; group 2: 33	33	G.1: minoxidil 5% 1ml twice daily G.2: minoxidil 10% 1 ml twice daily	Placebo solution 1ml twice daily	**HC; HT; FC**

Sakr et al 2013	RCT	G1: 11 G2: 11	G3: 10	G.1: Multimodal formulation (minoxidil5%; diclofenac 5mg/ml; tea tree oil 50mg/ml lauryl 50mg/ml; propylene glycol 0.1375mg/ml; ethanol 0.3mg/ml; labrasol 27.5%) G.2: minoxidil 5% alone (minoxidil5%; lauryl 50mg/ml; propylene glycol 0.1375mg/ml; ethanol 0.3mg/ml; labrasol 27.5%)	G.3. placebo (lauryl 50mg/ml; propylene glycol 0.1375mg/ml; ethanol 0.3mg/ml; labrasol 27.5%)	**PA; HC; HWGH; HT; PE; GPE**
Hu et al 2015	RCT	G1: 160 G2: 130 G3: 160	-	G1: finasteride 1mg/day G2: minoxidil 5% (1ml twice a day) G3: Minoxidil5% (1ml twice a day) + finasteride 1mg/day	-	**GPE**
Lanzafame et al 2013	RCT	22	19	Helmet containing 20, 5 mW lasers, and 31 LEDS both operating at 655 nm (655 +/-5 nm and 655 +/-20 nm, respectively) Each subject self-treated at home for 25 minutes/treatment every other day for 16 weeks (60 treatments, 67.3 J/cm2 delivered irradiance per treatment session).	Unit that was identical in appearance and function to the laser group devices, with the exception that the light sources were incandescent wheat lights that were painted red to mimic the appearance and configuration of the functioning device. Each subject in the sham group self-treated at home for 25 minutes/treatment, every other day for 16 weeks (60 treatments)	**HC**

Fan et al 2018	NRCT	74	-	All participants were randomly assigned to receive the investigational LLLT*on one side of the head and sham light treatment on the contralateral side, 3 times weekly for 30 minutes each, over a 24- week period * LLLT device with a light source consisting of LEDs array emitting wavelengths of 660 6+/- 5 nm 22 mW/cm2, 27 LED and a laser diode array emitting 650 6 +/-10 nm (4.6 mW, 27 pieces) The system used as the light source for this study was modified such that a 650/660 nm light was emitted to half of the head and the contralateral side was exposed to non LLLT sham light from LED bulbs, which were coated with red paint to resemble the appearance and configuration of the functioning device.	-	**GSP; PA; IA; SA**
Kim et al 2013	RCT	20	20	Helmet with a light source consisting of LEDs emitting wavelengths of 630 nm (3.5 mW, 24 units,) and 660 nm (2.5 mW, 18 units) and laser diodes (emitting 650 nm (4 mW, 27 units)	Identical helmet but that does not emit light	**HD; PA; GPAHR; SS**
Faghihi et al 2018	RCT	23	22	20 drops of topical minoxidil 5% solution twice per day to use on their bald areas for 6 months plus 2–3 20-minute sessions of low-level light therapy with a 10-50 mw power and a 785-nm wavelength per week for 24 weeks	Only topical minoxidil 5% solution in the same manner as in the case group and were given a laser comb system that was switched off to act as a placebo. T	**HC; HD**

Ferrara et al 2021	RCT	19	-	Combined therapy of 5% minoxidil and photobiomodulation with LLLT (with 99 light-emitting LED delivering 5 mW of 660 nm light, which generated a total of 5.5 J/cm2 /day to the irradiated side when used for 24 minutes per day) All participants received 12 minutes of low intensity laser and then a topical application of minoxidil (1 ml of 5% solution) twice daily for 6 months. The photo biomodulation devices were adjusted so that half of them emitted light and half did not.	-	**CP; PA**

RCT: Randomized Clinical Trial; **NRCT**: Non Randomized Clinical Trial; **HW:** Hair Width; **HR:** Hair Restoration; **GPE**: Global Photographic Evaluation; **IA**: Investigator Assessments; **PA**: Phototrichogram Assessments; **SA**: Safety Assessment; **HG:** Hair Growth; **TAHC:** Target Area non-vellus Hair Count; **TAHW:** Target Area non-vellus Hair Width; **PE**: Participant Evaluation; **TF:** Topical Foam; **GPR:** Global Photographic Review; **SA:** Subject Assessment; **TS:** Topical solution; **HC:** Change in Hair count; **HT:** change in Hair Thickness; **FC:** change in Follicular Count; **MGPA**: Modified Global Photographic Assessment; **HD**: Change in Hair Density; **GPAHR:** Global photographic Assessment of Hair Regrowth; **SS**: Subjective Satisfaction; **GSP:** Global Scalp Photography; **CP:** Clinical Photographs;