NEW MEDICAL TREATMENT FOR AGA

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METHODOLOGY OF THE SCIENTIFIC REVIEW

Inclusion of:

1. Published articles in Pubmed/Medline in 2017/2018
2. Accepted articles in press
3. Lectures in international trichology congresses and meetings
4. Clinical trials at clinicaltrials.gov
5. On-going research projects in the field of hair diseases.
# New Medical Treatment for AGA

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<tr>
<th>Treatment Type</th>
<th>Details</th>
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<td>1. Minoxidil</td>
<td>Oral minoxidil</td>
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<td>2. Topical Agonists of WNT Pathway</td>
<td>Methylvanilate, valproic acid, SM04554</td>
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<td>3. Antiandrogenic Drugs</td>
<td>Safety of 5-Alpha-Reductase-inhibitors</td>
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<td>Effectiveness of oral dutasteride</td>
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<td>Mesotherapy with dutasteride</td>
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<td>4. Prostaglandins</td>
<td>PGF2 analogs / PGD2 – GPR44 inhibitors (setipiprant)</td>
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<td>5. Physical Therapies</td>
<td>Low level light therapy</td>
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<td>Scalp microneedling</td>
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<td>6. Platelet Rich Plasma</td>
<td>More evidence on platelet rich plasma</td>
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<td>7. Stem Cell Therapy</td>
<td>Isolation and injection of stem cells without culture</td>
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<td>Conditioned media of adipose tissue-derived stem cells</td>
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<td>Cultured follicular stem cells</td>
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Dr. Sergio Vañó-Galván. New medical treatment for AGA
1. Minoxidil

Dormant, small miniaturized hair follicle

Larger terminal hair follicle produces fine hair

Size increased, thicker hair produced

Dr. Sergio Vaño-Galván. New medical treatment for AGA
1. ORAL MINOXIDIL

- Some publications about the usefulness of **low doses of oral minoxidil** in the treatment of AGA and telogen effluvium.

- Effective and good safety profile (no changes in blood pressure)

- **MAGA**: 5 mg daily
- **FAGA**: 0.25 - 1 mg daily (+/- spironolactone 25 mg daily)
- **Telogen effluvium**: 0.5-1 mg daily

**IN MY EXPERIENCE:**
ONE OF THE MOST USEFUL NEW THERAPIES FOR AGA IN DAILY PRACTICE

Dr. Sergio Vañó-Galván. New medical treatment for AGA
33-YEAR-OLD FEMALE WITH ANDROGENETIC ALOPECIA.
CLINICAL RESPONSE AFTER 1 YEAR WITH ORAL MINOXIDIL (1 MG DAILY)
2. TOPICAL AGONISTS OF WNT PATHWAY

Dr. Sergio Vaño-Galván. New medical treatment for AGA
New mechanism of action: topical drugs that activate the Wnt/β-catenin pathway

**WNT/β-CATELIN PATHWAY:**
1. Initiation and maintenance of the anagen phase
2. Induction of differentiation of dermal progenitor cells to bulge cells.
3. In AGA, androgens may inhibit Wnt/β-catenin signaling.

**TOPICAL AGONISTS OF WNT PATHWAY:**

<table>
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<tr>
<th>1. Methyl vanillate</th>
<th>3. SM04554</th>
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<td>2. Valproic acid</td>
<td>4. Others</td>
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**ClinicalTrials.gov**

A study of the safety, tolerability, and efficacy of topical SM04554 solution in male subjects with androgenetic alopecia (AGA).

This study has been completed.

A study of the safety, tolerability, and efficacy of topical SM04554 solution in male subjects with androgenetic alopecia (AGA).

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3. ANTIANDROGENIC DRUGS

DHT shrinks hair follicles

DHT may contribute to the shortening of the growth phase of hair follicles, causing them to shrink until there are fewer visible hairs left on the scalp.
SAFETY OF FINASTERIDE / DUTASTERIDE

Concern about the potential adverse effects of finasteride / dutasteride in the treatment of AGA.

**SEXUAL ADVERSE EFFECTS**

**CANCER RISK**

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**Effect of 5α-Reductase Inhibitors on Sexual Function: A Meta-Analysis and Systematic Review of Randomized Controlled Trials.**


PMID: 27475241

**CONCLUSION:** Evidence from the randomized controlled trials suggested that 5αRIs were associated with increased adverse effects on sexual function in men with BPH compared with placebo. However, the association was not statistically significant in men with AGA. Well-designed randomized controlled trials are indicated to study further the mechanism and effects of 5αRIs on sexual function.

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This metanalysis (including 17,494 men) did not find a statistically significant increase of sexual adverse effects with 5αRIs in the treatment of AGA.

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RESULTS AND CONCLUSIONS: Among men with detectable finasteride concentrations, there was no association between finasteride concentrations and prostate cancer risk, low-grade or high-grade, when finasteride concentration was analyzed as a continuous variable or categorized by cutoff points. Since there was no concentration-dependent effect on prostate cancer, any exposure to finasteride intake may reduce prostate cancer risk. Of the twenty-seven SNPs assessed in the enzyme target and metabolism pathway, five SNPs in two genes, CYP3A4 (rs2242480; rs4646437; rs4986910), and

Long-term use of 5alpha-reductase inhibitors and the risk of male breast cancer.
Duijnhoven RG, Straus SM, Souverein PC, de Boer A, Bosch JL, Hoes AW, De Bruin ML.
PMID: 25135615

CONCLUSIONS: In this study, there was no evidence of an association between short- or long-term treatment with 5-ARIs and the risk for breast cancer in older men. (398 cases vs 3930 controls)

There is no evidence that finasteride / dutasteride increase the risk of prostate or male breast cancer

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EFFECTIVENESS OF ORAL DUTASTERIDE

1. Dutasteride 0.5 mg/daily: Effective and safe in MAGA and FAGA.

2. Even more effective than finasteride.

Dr. Sergio Vaño-Galván. New medical treatment for AGA
A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with androgenetic alopecia.


![Image of hair before and after treatment]

**Fig 4.** Median scores for panel global photographic assessment of improvement of hair growth at the vertex and frontal/superior views at week 24. *P < .001 vs placebo; †P = .002 vs finasteride (superiority).
Mesotherapy using dutasteride-containing preparation in treatment of female pattern hair loss: photographic, morphometric and ultrastructural evaluation.
PMID: 22486925

CONCLUSION: We concluded that mesotherapy with dutasteride-containing preparation was effective, tolerable and minimally invasive treatment modality in FPHL with better response for shorter duration of the disease.

- Mesotherapy with dutasteride may be in interesting option in selected patients with MAGA / FAGA.

- Our research group: **PILOT STUDY WITH MESOTHERAPY WITH DUTASTERIDE IN MONOTHERAPY**:
  - 5 males and 1 female
  - Effective in 100% (4/6 slight and 2/6 moderate improvement)
  - No adverse effects
  - No differences between serum hormone levels before and after treatment.

Dr. Sergio Vaño-Galván. New medical treatment for AGA
Mesotherapy with Dutasteride in the Treatment of Androgenetic Alopecia.
Saceda-Corralo D, Rodrigues-Barata AR, Vaño-Galván S, Jaén-Olasolo P.
PMID: 28932074  Free PMC Article

Dr. Sergio Vaño-Galván. New medical treatment for AGA
23-YEAR-OLD MALE WITH ANDROGENETIC ALOPECIA.
CLINICAL RESPONSE AFTER 1 YEAR WITH ORAL DUTASTERIDE (0.5 MG DAILY)
AND MESOTHERAPY WITH DUTASTERIDE 0.05% EACH 3 MONTHS
4. PROSTAGLANDINS
Some prostaglandins play a role in hair growth:

- **PGF2 analogs** (latanoprost, bimatoprost) stimulate hair growth. PGE2 acts in synergy with PGF2.
- An increase in PGE2 levels is possibly one of the mechanisms through which minoxidil induces hair growth.
Prostaglandin D2 has recently been identified as a factor which is elevated in the bald scalp of men with androgenetic alopecia (AGA) and has the capacity to decrease hair lengthening.

PGD2 has two known receptors, GPR44 and PTGDR. GPR44 was found to be necessary for the decrease in hair growth by PGD2.

Drugs that block GPR44 (setipirprant) are currently under clinical trials for asthma and may be a possible future treatment of AGA.
- **SETIPIPRANT**: PGD2-receptor antagonist (GPR44 antagonist)
- First clinical trial for androgenetic alopecia (NCT 02781311).
- Dosage: 1.000 mg twice daily, oral.
- Excellent safety profile in phase-I trials and phase III trials in asthma.
5. PHYSICAL THERAPIES
5. LOW LEVEL LIGHT THERAPY

- Emergent therapy
- It is known that some wavelengths of laser may stimulate hair growth, although the exact mechanism is unknown (anagen induction and activation of Wnt pathway).
- Low level light therapy has demonstrated to be effective in MAGA and FAGA in several trials.

### SCIENTIFIC EVIDENCE OF LLLT IN AGA

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>2007</td>
<td>First scientific articles in Pubmed, describing the potential usefulness of LLLT in AGA.</td>
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<td>2009</td>
<td>First clinical trial showing the effectiveness of the HairMax Laser Comb device in the treatment of AGA</td>
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<td>2012</td>
<td>Review: international experts suggest caution due to the lack of solid scientific evidence</td>
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<tr>
<td>2013</td>
<td>New clinical trial showing the effectiveness of LLLT in AGA, published in Dermatologic Surgery.</td>
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<tr>
<td>2014-2018</td>
<td>Publication of &gt;5 clinical trials demonstrating the effectiveness of LLLT in AGA. Methodology without biases. Sponsored by industry. Publication of a metanalysis demonstrating its effectiveness</td>
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**LLLTT: There is scientific evidence of its effectiveness in AGA.**

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CONCLUSION LLLT / AGA

1. Interesting therapy

2. It may be a good choice for patients with adverse effects to traditional therapy

3. It may be used as a concomitant therapy

4. However, more studies are required to define the best parameters and treatment intervals.
Scalp microneedling may stimulate hair growth

Potential mechanisms:

a) Release of PDGF through platelet activation and skin wound regeneration mechanisms.
b) Activation of follicle stem cells under wound healing conditions
c) Overexpression of hair growth-related genes (VEGF, Wnt3a, b-catenin)

100 patients
2 groups: 5% minoxidil 2/d vs the same + weekly microneedling.
More effectiveness in the group of microneedling at week 12.
PLATELET RICH PLASMA

- Several studies (including a meta-analysis in 2016) addressing the effectiveness of PRP in the treatment of male and female AGA.

- Mechanisms:
  
a) Increase of the expression of b-catenin, inducing differentiation of bulge stem cells.
  
b) Increase of fibroblast growth factor 7 (which prolongs anagen phase)
  
c) Increase of bcl-2 protein (which protects cells from apoptosis)

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**Meta-analysis of efficacy of platelet-rich plasma therapy for androgenetic alopecia.**
Gupta AK, Carviel JL.
PMID: 27152474

**Randomized Placebo-Controlled, Double-Blind, Half-Head Study to Assess the Efficacy of Platelet-Rich Plasma on the Treatment of Androgenetic Alopecia.**
Alves R, Grimalt R.
PMID: 27035501

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PRP showed a positive effect on AGA with no adverse effects and could be regarded as an adjuvant therapy for AGA.

In my experience: safe therapy but with an heterogeneous effectiveness. Some patients respond well but others have almost no benefit of this therapy.

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7. STEM CELL THERAPY

Dr. Sergio Vañó-Galván. New medical treatment for AGA
## STEM CELL THERAPY IN ANDROGENETIC ALOPECIA

<table>
<thead>
<tr>
<th>MODALITY</th>
<th>A) FOLLICULAR STEM CELL ISOLATION AND INJECTION (WITHOUT CULTURE)</th>
<th>B) ADIPOSE TISSUE DERIVED STEM CELLS (ADSC)</th>
<th>C) CULTURED FOLLICULAR STEM CELLS (“FOLLICULAR REGENERATION”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROCEDURE</td>
<td>A biopsy from the scalp is processed in a device that centrifuges and isolates the follicular stem cells without culturing. The solution with follicular stem cells is then injected in the bald area.</td>
<td>Adipose-derived stem cells and Stromal Vascular Fraction obtained from the fat tissue (liposuction) are centrifuged, isolated and then injected in the bald area.</td>
<td>A biopsy from the scalp is obtained. The follicular stem cells are isolated, cultured and expanded in vitro (2 months). The solution enriched with a high amount of follicular stem cells is then injected in the bald area.</td>
</tr>
<tr>
<td>COMPLEXITY</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>POTENTIAL EFFECTIVENESS</td>
<td>+</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>SCIENTIFIC EVIDENCE</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>COUNTING OF STEM CELLS</td>
<td>300-600 per procedure</td>
<td>250.000-500.000 per procedure</td>
<td>$3.6 \times 10^9$ per procedure (“theoretically infinite”)</td>
</tr>
<tr>
<td>REQUIREMENTS</td>
<td>Basic surgery room - Basic surgical material - Patented device (approx. 7.000€)</td>
<td>Totally equipped surgery room - Surgical material - Device for processing the ADSC (10-15.000€).</td>
<td>ETHICAL COMMITTEE APPROVAL!!! - License for Advanced Medical Therapies - Clean Room / laboratory - Basic surgery room - Basic surgical material</td>
</tr>
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</table>

1. Stem cell therapy is a promising field of regenerative medicine.

2. Follicular stem cell isolation and injection without culture is an interesting and easier way of treatment, but further scientific evidence is required.

3. Adipose-derived stem cells therapy seems to be effective, but requires a surgical procedure to obtain the adipose tissue (liposuction).

4. Stem cell “fOLLICULAR REGENERATION” therapy: may be the future but not yet the present. Human trials have shown disappointing results compared with murine trials. Further research is required in this field.
Stem cell therapy will be the future, but it is still far away...

THIS IS JUST THE BEGINNING
CONCLUSIONS

1. Several **new treatments for AGA** have emerged in the last years. **Low-dose oral minoxidil** is one of the most useful, specially in females.

2. New mechanism of actions: **topical agonists of the Wnt pathway and prostaglandins**. Promising, more studies are required.

3. Antiandrogenic drugs: **Dutasteride seems to be more effective than finasteride, with the same safety profile**. New ways of administration of antiandrogens: injected, topical.

4. **Physical therapies (LLLT/microneedling)**: interesting as a potential adjuvant therapy for AGA.

5. Usefulness of **platelet rich plasma** in AGA (evidenced by meta-analysis).

6. **Stem cell therapy**: may be the future but not yet the present. The results of the ongoing studies are eagerly awaited.

Dr. Sergio Vañó-Galván. New medical treatment for AGA
SAVE THE DATE

WCHR
Barcelona
April 24th - 27th, 2019

www.barcelonahair2019.org