



Clinical Efficacy of a Topical Compounded Formulation in Male Androgenetic Alopecia: Minoxidil 10%, Finasteride 0.1%, Biotin 0.2%, and Caffeine Citrate 0.05% Hydroalcoholic Solution

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Abstract

Androgenetic alopecia is the most common form of hair loss. This condition affects both men and women causing significant psychological distress and a decrease in the quality of life. The objective of this study was to investigate the clinical efficacy and patient satisfaction of a topical compounded formulation (minoxidil 10%, finasteride 0.1%, biotin 0.2%, and caffeine citrate 0.05% hydroalcoholic solution) in male androgenetic alopecia patients. A total of five individual, prospective case studies were conducted in the private hair transplant practice of Dr. James C. Marotta. Patients were provided with the topical formulation and instructed to apply a measured 1-mL dose to the entire frontal, parietal, and occipital scalp, twice daily for 6 months. Patients visited the practice periodically (90 days, 120 days, and 180 days post-treatment) for clinical evaluation, photographic assessment, and measurement of their treatment satisfaction by the Men's Hair Growth Questionnaire. By the end of the study, at 180 days, the dermatologist-in-charge concluded that the topical treatment was successful for all five patients. Although moderate, the clinical improvements were visually noticeable as most patients had thicker, more voluminous hair; improved scalp coverage; and improved general hair appearance. These results were consistent with the photographic assessment, which demonstrated a global average increase of +1.05 in the patients' hair density. According to the patients' self-assessment, the topical compounded formulation was effective following 3 months and 6 months of continuous treatment. At 120 days, the patients' satisfaction was neutral or negative, which was likely due to negligible differences in the patients' hair growth and appearance in 90 days compared to 120 days. The results from this study suggest that the new hair-loss topical solution may be considered a safe and effective treatment option in male AGA patients.

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Introduction

Androgenetic alopecia (AGA) is the most common type of progressive hair loss in men,¹ which is estimated to affect 50 million men in the U.S. According to the U.S. National Library of Medicine, more than 50% of men over the age of 50 have some degree of hair loss.² AGA is a genetically predisposed condition that occurs due to the conversion of testosterone to the more potent metabolite dihydrotestosterone (DHT) by the enzyme type II 5 α -reductase (5AR). DHT binds to the androgen receptors of the hair follicle, causing follicular miniaturization and decreased hair density.^{3,4} "Andro" refers to the androgens (testosterone and DHT) necessary for the development of AGA and "genetic" refers to the potential inherited genes. Despite the role of androgens, genes, and age, the pathophysiology of hair loss is still largely unknown.⁵ AGA is physically characterized by a recession of the hairline in the frontal region of the scalp and loss of hair at the vertex, which may worsen with time to a small ring of hair around the scalp.⁶ In AGA, hair is lost in a well-defined pattern and thus this condition is also known as male pattern alopecia/baldness/hair loss; it is usually associated with increasing age

in men.⁷ Although it is neither life threatening nor painful, this benign condition may lead to serious psychosocial consequences such as anxiety and depression.⁸ Hair is an essential component of self-image, and it is a social indicator of gender, age, and status.⁶ Cash stated, “*Hair loss can turn every day into a bad hair day.*”⁶ For many people, men with visible hair loss are perceived as old and unattractive¹ and thus AGA is commonly a distressful condition. As stated by the Roman poet Ovid (Publius Ovidius Naso, 43 BCE–17 CE): “*Ugly is a field without grass, a plant without leaves, or a head without hair.*”⁹

The treatment of AGA consists in the use of topical minoxidil and/or oral finasteride, which are the only two therapeutic drugs currently approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).¹⁰ Although efficacious, these therapeutic drugs alone do not always provide the expected clinical outcomes and patients commonly seek alternative options.³ There are currently new generation therapies, such as hair replacement surgery, that can offer patients excellent results.^{5,11} However, hair transplants are invasive and expensive and pharmacologic therapies may represent the only viable option for some patients.

An alternative pharmacologic therapy of choice may be achieved by pharmaceutical compounding, the preparation of customized medications to meet the patient’s individual needs. These non-standardized medications may combine different therapeutic drugs, in variable dosage strengths, that target the multifactorial causes of hair loss. According to Garre et al,¹⁰ finding the right combination of therapeutic drugs and taking advantage of their different mechanisms of action can improve penetration and achieve faster results.¹⁰ As such, topical compounded formulations may be key in the pharmacologic management of AGA.

The objective of this study was to evaluate the clinical efficacy and patient satisfaction of a new hair-loss topical solution containing a combination of minoxidil, finasteride, biotin, and caffeine citrate.

Minoxidil has been used topically to stimulate hair growth since the early 1980s, and it is commonly dispensed as 2% or 5% hydroalcoholic solutions, applied to the scalp twice daily. It is the only FDA- and EMA-approved treatment for hair loss in women. Although minoxidil causes direct peripheral vasodilation, its mechanism of action in AGA is still poorly understood. It is believed that minoxidil affects the hair cycle by causing premature termination of the telogen (resting) phase and probably prolonging the anagen (growth) phase of the hair follicles. Topical minoxidil has to be applied continually to be effective and clinical outcomes should only be expected following 3 to 4 months of treatment.^{12,13} Despite being widely used, it is perceived only moderately effective.⁷ For this reason, minoxidil may be fortified with finasteride for better clinical outcomes.⁴

Finasteride is a urologic drug with anti-androgenic properties that works by inhibiting the 5AR and thus inhibits the miniaturization of hair follicles and increases hair density.⁴ In the treat-

ment of AGA, finasteride is commonly given by mouth in a dose of 1 mg daily for at least 3 months. However, response may be delayed and treatment of 6 months or more may be required to achieve clinical outcomes. Oral finasteride, though effective, is associated with erectile dysfunction, decreased libido, ejaculation disorders, and reduced volume of ejaculate.⁷ These side effects are reversible upon discontinuation of treatment, but patients are still apprehensive about using oral finasteride on a long-term basis. In a study by Chandrashekar et al,⁴ patient compliance was good when oral finasteride was replaced for topical finasteride combined with minoxidil. In 6-months (and longer) studies, topical finasteride has shown similar therapeutic efficacy to oral finasteride and better tolerance. However, topical absorption of finasteride may be a limitation and thus minoxidil should be combined for its vasodilation properties.^{4,14,15}

Biotin is a vitamin B substance, also known as vitamin H (from *Haar und Haut*, meaning hair and skin), that is important for the maintenance of healthy hair and skin. Symptoms of biotin deficiency include hair loss, and, as such, biotin is commonly included in healthcare products and nutritional supplements for the treatment of alopecia.¹⁶ The possible mechanism of action is attributed to the role of biotin as a coenzyme for mitochondrial carboxylases in hair roots, although there is no clear evidence in the scientific literature.³

Caffeine is a well-known stimulant substance that promotes cell proliferation by increasing the metabolic activity. In the management of AGA, topically applied caffeine reportedly inhibits the miniaturization of hair follicles and stimulates hair growth. In an *in vitro* study by Fisher et al,¹⁷ low doses of caffeine were shown to counteract the growth suppression of human hair follicles treated with testosterone. Moreover, caffeine alone led to a significant stimulation of hair follicle growth.¹⁷ The role of caffeine in human hair biology was further explored by Fisher et al,¹⁸ who discovered new growth-promoting effects of caffeine on the human hair follicles at different levels: molecular, cellular, and organ. These findings are supportive of the potential clinical impact of caffeine in male AGA patients.¹⁸

Methodology

A new hair-loss topical solution was developed by the VLS Pharmacy (New York, New York), in collaboration with the Marotta Plastic Surgery Specialists (Smithtown, New York), and with the support of Professional Compounding Centers of America (PCCA) (Houston, Texas).

VLS Pharmacy is a compounding pharmacy that specializes in sterile and nonsterile compounded medications, and PCCA is an international organization that provides products, education, and support to independent compounding pharmacies. Dr. Marotta is a dual board-certified facial plastic surgeon and has a division entitled “Marotta Hair Restoration” which offers advanced hair restoration and transplantation techniques.

FORMULA DEVELOPMENT

The therapeutic drugs in the formulation used for this study were purchased from PCCA. The new hair-loss topical solution was developed to include minoxidil 10% (Lot C1744726), finasteride 0.1% (Lot C172944), biotin 0.2% (Lots C171120 and C179984), and caffeine citrate 0.05% (Lot C174268) in a hydroalcoholic vehicle with propylene glycol. This formula is intended for long-term use since minoxidil and finasteride must be applied continuously to maintain effectiveness.⁷ As such, it is important that the formula presents extended stability and optimized organoleptic characteristics to ensure patient compliance. Propylene glycol and ethyl alcohol are commonly used to solubilize the drugs, but a balanced ratio must be achieved to obtain a formula that improves skin penetration and, at the same time, is not sticky/oily on application.¹² The formula developed has an adjusted ratio of purified water, ethyl alcohol, and propylene glycol, and the beyond-use

FORMULATION FOR HAIR-LOSS TOPICAL SOLUTION USED IN THE STUDY

Rx

MINOXIDIL 10%, FINASTERIDE 0.1%, BIOTIN 0.2%, AND CAFFEINE CITRATE 0.05% HAIR-LOSS TOPICAL SOLUTION

Ingredients

Minoxidil	10%
Finasteride	0.1%
Biotin	0.2%
Caffeine citrate	0.05%
Propylene Glycol USP	10%
Purified water	30%
Sulfuric acid 20% (w/v) aqueous solution	adjust pH to 4.5 to 5.0
Ethyl alcohol 95%	qs to 100%

Note: The pH of this formulation should be approximately 4.5 to 5.0.

METHOD OF PREPARATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Mix the propylene glycol, ethyl alcohol, and purified water in an appropriate size beaker.
4. Add the Minoxidil to step 3 with mixing.
5. Add the sulfuric acid 20% (w/v) aqueous solution dropwise to step 4 to obtain a pH between 4.5 and 5.0.
6. Add the biotin, finasteride, and caffeine citrate to step 5.
7. Bring step 6 to final volume with ethyl alcohol 95% and mix well.

date attributed is 6 months. The formula and the corresponding method of preparation are provided. Two batches of the topical compounded formulation were prepared by the VLS Pharmacy on April 18, 2017 and July 3, 2017.

STUDY DESIGN AND PARTICIPANTS

The AGA patients who presented at the private hair transplant practice of Dr. Marotta and were prescribed the new hair-loss topical solution were invited to participate in an individual, prospective case study to evaluate the efficacy of the topical treatment. Patients were instructed to apply a measured 1 mL of the topical compounded formulation to the entire frontal, parietal, and occipital scalp twice daily and for a minimum period of 6 months. At each visit to the clinic, patients were asked to complete a patient satisfaction questionnaire and to allow standardized photographs to be taken of their scalp. The level of evidence assigned to this case series is VI since the research methodology is descriptive and qualitative.¹⁹

A total of five Caucasian patients participated, and the individual, prospective case studies were initiated between March 2017 and April 2017. The patients, aged between 41 and 71 years old, reported having AGA for a long period, as follows: about 5 years (1 patient), 10 years (3 patients), and over 10 years (1 patient). All patients used topical minoxidil in the past, with the exception of 1 patient; other treatments reported included oral finasteride, microneedling, and hair transplants. The patients were periodically assessed by Dr. Marotta, and the standardized photographs were taken by a nurse or medical assistant, according to an internal protocol.

CLINICAL EVALUATION

The clinical evaluation was performed by Dr. Marotta at baseline, 3 months, 4 months, and 6 months post-treatment. The efficacy and safety of the new hair-loss topical solution was assessed visually using the Norwood scale. This is a standard of classification for AGA that is widely acceptable, accurate, and reproducible. It is a detailed scale that comprises 7 hair-loss stages (types I through VII) and 4 additional "A" subtypes (II A, III A, IV A, and V A). Type I corresponds to very minimal or no recession of the hairline, whereas type VII corresponds to the most severe form of AGA in which only a narrow band of hair remains on the scalp. The type A variant is expected to affect only a minority of patients.²⁰ The side effects reported, if any, were noted during the visual assessment.

PHOTOGRAPHIC ASSESSMENT

Standardized color photographs were taken of each patient's scalp with a Nikon D-70 digital camera at standard magnification, using the same lighting and position of the camera for comparative purposes. Four standard views of the scalp were taken for each patient (vertex, frontal, and bi-temporal hairline)

at baseline, 3 months, 4 months, and 6 months post-treatment. For one patient, photographs were also taken 18 months post-treatment; for this patient, a total of twelve photographs are presented (FIGURES 1A through 1L), which correspond to the four scalp views at baseline, 6 months, and 18 months post-treatment with the topical compounded formulation. FIGURES 2A through 2D correspond only to two scalp views of another patient at baseline and 6 months post-treatment. Signed informed consents were obtained to publish the photographs of these two patients; their identity was covered for confidentially purposes.

Paired baseline and post-treatment photographs were reviewed by the lead physician in the study, Dr. Marotta, as well as a blinded assessment by a physician at the hair restoration clinic for the purpose of assessing changes in hair density. A 7-point bipolar rating scale was used in the photographic assessment, as described by Kaufman et al²¹:

- -3 = greatly decreased
- -2 = moderately decreased
- -1 = slightly decreased
- 0 = no change
- +1 = slightly increased
- +2 = moderately increased
- +3 = greatly increased

In this study, a negative rating corresponds to decreased hair density (worsened hair loss), whereas a positive rating corresponds to increased hair density (improved hair loss).

PATIENT SATISFACTION

The patient satisfaction with the topical compounded formulation was evaluated using the Men's Hair Growth Questionnaire (MHGQ) (U.S. English version), a brief questionnaire developed for use in clinical trials of experimental medications for the treatment of AGA. This validated, self-administered questionnaire consists of seven global questions which address the patient-perceived changes in hair growth (Q1 through Q4) and the patient satisfaction with hair appearance (Q5a through Q5c), in comparison to baseline (start of the study). Questions are rated according to variable Likert scales of 4, 5, or 7 points. For instance, responses to questions Q5a through Q5c are defined according to a 5-point scale, as follows:

- Very Satisfied (1) / Satisfied (2) (positive response) versus Neutral (3), Dissatisfied (4) / Very Dissatisfied (5) (negative response).

The MHGQ questions should be considered separately and not as part of a total score. As such, no summary score is obtained in the MHGQ.²¹⁻²³ Although patient-reported questionnaires are a subjective measure of treatment efficacy, these are increasingly important since clinical outcomes depend on the patient's satisfaction with

treatment. As such, it is recommended that clinical evaluations be complemented with patient-based assessments.²⁴ The MHGQ is a particularly important self-administered questionnaire considering the relevance of self-perception in hair loss.²²

Results and Discussion

All five patients who participated in the study applied the topical compounded formulation to their scalp twice daily for a minimum period of 6 months. There were no reports of any local or systemic adverse effects that would require discontinuation of the treatment. At each visit to the hair transplant clinic, all five patients completed the MHGQ and allowed standardized photographs to be taken to their scalp.

CLINICAL EVALUATION

At the baseline visit to the clinic, the hair transplant surgeon in charge, Dr. Marotta, collected the medical history for each patient, including the duration of alopecia, past alopecia treatments, relevant allergies, and relevant current medications. An expert clinical evaluation was also performed by visually assessing each patient's scalp hair in detail, and classifying the hair loss condition using the Norwood scale. The most severe form of AGA identified in this study was type IV and IV A for two patients, respectively, followed by type III Vertex for two additional patients. The hair-loss condition of the remainder of the patients was classified as type II, the least severe form of AGA identified in this study. Expert clinical evaluations were repeated by Dr. Marotta for all patients at each follow-up visit to the clinic. By the end of the study, at 180 days of treatment with the topical compounded formulation, Dr. Marotta concluded that the treatment was successful for all five patients. Although moderate, the clinical improvements were visually noticeable as most patients had thicker, more voluminous hair; improved scalp coverage; and improved general hair appearance.

PHOTOGRAPHIC ASSESSMENT

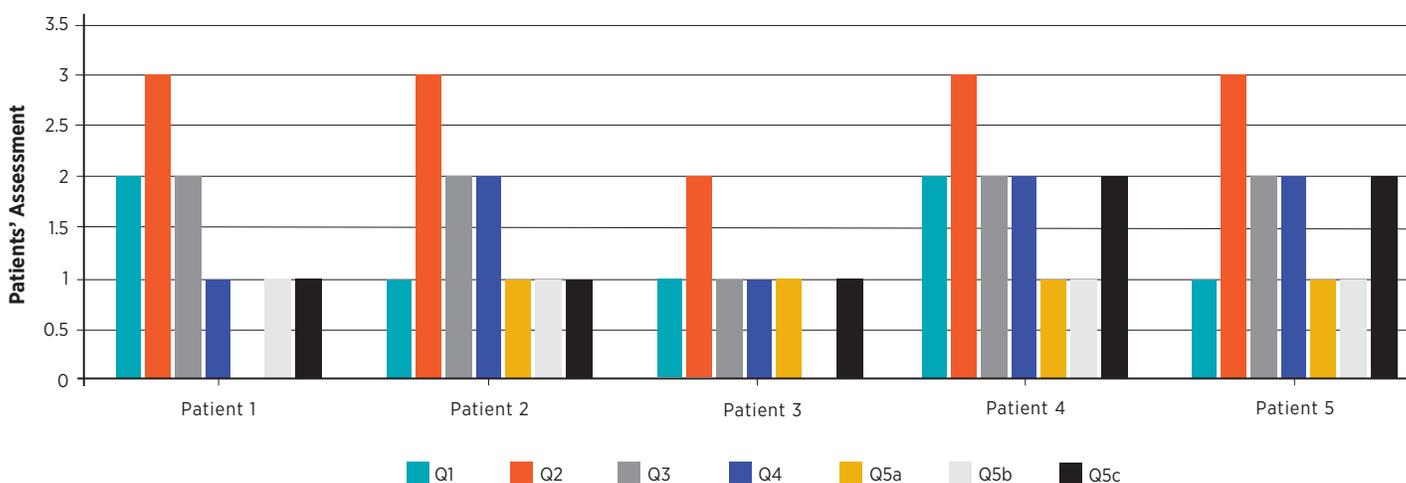
The photographic assessment by Dr. Marotta and a blinded assessment by a physician at the hair transplant clinic was performed for all five patients by comparing the scalp photographs at baseline and 6 months post-treatment, using a 7-point bipolar rating scale. The assessment of paired scalp photographs is a common practice in hair-loss studies, and it is deemed more precise than subjective evaluations, such as comparing current hair loss with a memory of hair loss by the investigators and/or patients. A physician was invited to contribute by way of a blinded assessment of the photographs to balance a potential bias by the lead physician in the study. The assessment per scalp view (vertex, frontal, and bi-temporal hairline) for all five patients varied from "no change" (0) to "moderately increased" (+2) according to both physicians. The average rates obtained per patient were as follows: +1 (Patients 1 and 4); +1.25 (Patients 2 and 5); and +0.75 (Patient 3).

FIGURES 1A THROUGH 1L.**DIGITAL PHOTOGRAPHS OF MALE PATIENT A.**

Digital photographs of male patient A's scalp hair (4 views), before treatment (left column), 6-months post-treatment (middle column), and 18-months post-treatment (right column) with the topical compounded formulation.

FIGURES 2A THROUGH 2D.**DIGITAL PHOTOGRAPHS OF MALE PATIENT B.**

Digital photographs of male patient B's scalp hair (2 views), before treatment (left column), and 6-months post-treatment (right column) with the topical compounded formulation.

FIGURE 3.**MEN'S HAIR GROWTH QUESTIONNAIRE PATIENTS' SELF-ASSESSMENT FOLLOWING 6 MONTHS OF TREATMENT WITH THE TOPICAL COMPOUNDED FORMULATION.**

The new hair-loss topical solution has demonstrated to slightly increase the hair density of all patients, with a global average of +1.05, which is consistent with the visual improvements in **FIGURES 1A** through **1L** AND **2A** THROUGH **2D**. As a result, according to both physicians, the new topical treatment has improved the patients' long-established hair-loss conditions.

PATIENT SATISFACTION

The MHGQ was completed by all five patients at the follow-up visits to the clinic on days 90, 120, and 180. As a result, each patient completed three questionnaires over the 6-month study. All questions were scored and thus considered in the data analysis. Interestingly, when comparing the three questionnaires per patient, the satisfaction profile was identical for all five patients. At 90 days, all patients showed satisfaction with their hair growth and appearance, although some were more positive than others. However, at 120 days, the majority of the responses were either neutral or negative, which shows that the treatment was no longer meeting the patient's expectations. By the end of the study, at 180 days, all patients showed satisfaction again with their hair growth and appearance. It is concluded that the topical compounded formulation was effective following 3 months and 6 months of continuous treatment, according to the patients' self-assessment. The neutral/negative responses at 4 months were likely due to negligible differences in the patients' hair growth and appearance from the third to fourth month. Perhaps patients were hoping to see as much improvement in 1 month as in the previous 3 months, which contributed to their disappointment with the treatment at this stage of the study.

For comparison purposes, the MHGQ responses (Q1 through Q5c) at 180 days were put together for all five patients in **FIGURE 3**. All responses were positive with the exception of two neutral responses, namely Q5a and Q5b for patients 1 and 3, respectively. The highest satisfaction was obtained for Q2 as 80% of the patients (4 out of 5) stated that the appearance of their hair was "A lot better." Also, 80% of the patients stated that the growth of their hair (Q3) had "Moderately increased." Regarding the bald spot (Q1), 40% of the patients "Strongly agreed," whereas 60% of the patients only "Agreed" that their bald spot was getting smaller. When asked about the treatment efficacy (Q4), 60% of the patients classified it as "Very effective," whereas 40% of the patients classified it as "Somewhat effective." Considering the questions 5a through 5c, which addressed the patients' satisfaction with hair appearance, 40% of the patients were "Very satisfied" with their hair overall (Q5c). As mentioned previously, two patients were neutral (neither satisfied nor dissatisfied) with the hairline at the front of their head (Q5a) and the hair on top of their hair (Q5b), respectively. All other patients were "Satisfied" with the three hair growth parameters.

Overall, the patients' self-assessments demonstrated that the topical compounded formulation slowed hair loss, increased hair growth, and improved the appearance of hair when applied for at least 6 consecutive months. These improvements were consistent with the clinical evaluation and photographic assessment.

Conclusion

The development of a new hair-loss topical solution resulted from the collaboration of a healthcare team centered on the needs

of the male AGA patients (triad relationship). Because the two hair-loss standard therapeutic drugs (topical minoxidil and oral finasteride) do not always provide the expected clinical outcomes, a topical compounded formulation was developed to combine multiple drugs in one formulation and thus target the multifactorial causes of hair loss at each topical application. The clinical efficacy of the new hair-loss topical solution was tested by five patients who reported having AGA for a long period.

Following 6 months of topical treatment, all patients showed improved hair loss, as demonstrated by the expert clinical evaluation, photographic assessment, and patient satisfaction. It is concluded that the new hair-loss topical solution may be considered a safe and effective treatment option in male AGA patients.

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Disclosure

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