Novel Agents for the Treatment of Alopecia

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Recent approval in the United States of two new products, Propecia (Merck Co, Rahway, NJ) and Rogaine Extra Strength 5% (Pharmacia & UpJohn Co, Kalamazoo, MI), indicated In men to promote scalp hair growth, have added a new dimension to treatment options offered by physicians In treating androgenetic alopecia (AGA). The search for new and effective agents to treat many different hair loss problems has been intensified by the increase in hair biology research taking place worldwide, from university-academic institutions to the pharmaceutical companies. All have a desire to profit from marketing such drugs that have been termed, "cosmeceuticals." Millions of men and women of every race suffer from various forms of alopecia, the most common being AGA where the target tissue active androgen, 5 alpha-dihydrotestosterone (DHT) aggravates genetically programmed scalp hair follicles that results in short, fine, miniaturized hairs. Currently available to treat alopecia are drugs indicated for other disease processes because no other agents are accessible; some have severe side-effects and many are minimally effective. These prescription drugs were not originally indicated for alopecia and have not been adequately tested in controlled clinical trials to assess for efficacy, safety, and toxicity. These agents continue to be used clinically to treat patients with various forms of alopecia. As a result, a variety of new agents are emerging in the patient application process to gain protection and approval specifically for various forms of alopecia. This report reviews the most recently approved products, some of the more promising compounds in clinical trial development, as well as those in the over the counter (OTC) "natural" treatments category.

THERE ARE VARIOUS forms of alopecia, the most common being androgenetic alopecia (AGA), which affects millions of men and women. The severity of hair loss in women is usually much less than in men. Hair loss for both men and women may begin as early as the teen years, but can even start in later decades of life. In men with AGA, one of the earliest findings is an increase in the percentage of hairs in a telogen phase of the hair cycle, so that initial hair loss may appear indistinguishable from a telogen effluvium. Similar to that in men, AGA in women can be psychologically devastating to accept, giving less overall body-image satisfaction and making it difficult to cope and retain integrity of personality functioning. AGA has been reported to be an autosomal dominant trait with partial or variable penetrance for both men and women.

BIOCHEMICAL ADVANCES FOR MEN AND WOMEN WITH AGA

Although for many years it had been assumed that the hormonal basis for AGA in women was the same as for men, no studies have confirmed this. Recent work has shown that on the scalp there are local differences in the amounts of steroid metabolizing enzymes that convert weak androgens to more potent androgens (Fig 1). This is important because the skin is an endocrine target tissue for androgen hormone action, similar to ovary, testes, and the adrenal gland. Studies have shown that persons using anabolic-androgenic steroids show hypertrophy of sebaceous glands, with systemic hirsutism, and AGA. In Figure 1, the hormone pathway describes the potential of weak and abundant precursor hormones such as DHEA (dehydroepiandrosterone) to be metabolized to more potent androgens such as testosterone (T) and dihydrotestosterone (DHT). The enzymes have been localized in sebaceous glands and hair follicles of scalp skin. Therefore, the skin has the potential to mediate

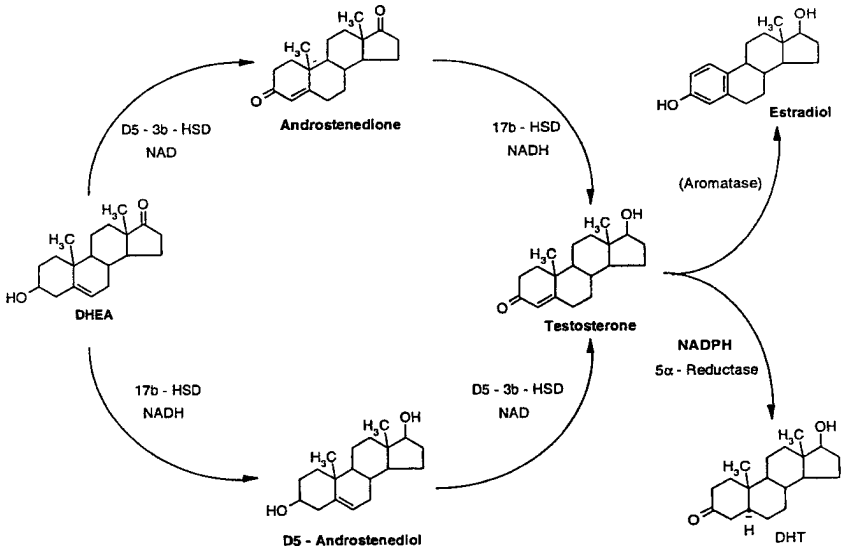


Fig 1. Androgen metabolic pathway in skin, where conversion of the weak circulating precursor, dehydroepiandrosterone (DHEA) to 4-androstenedione and testosterone takes place via 3B and 17B-hydroxysteroid dehydrogenase (HSD) enzymes, respectively. Testosterone is converted to 5 alpha-dihydrotestosterone (DHT) via 5 alpha-reductase (5aR). Estrogens are synthesized from precursors, 4-androstenedione and testosterone to estrone and estradiol, respectively.

androgen action without relying on elevated systemic levels or production of T or DHT.

An important enzyme in the Figure 1 pathway is 5 alpha-reductase (5aR), which mediates reduction of T to DHT, via the reduced pyridine cofactor, nicotinamide adenine dinucleotide phosphate (NADPH). There are two forms of 5aR, type 1, which is thought to be primarily in the skin, especially sebaceous glands, as well as the kidney and liver; type 11 isoenzyme is predominant in gonadal tissues, ie, prostate, seminal vesicles, and others, but in recent years, it was also found in hair follicles on the scalp where miniaturization takes place. This finding explains how finasteride has hair growth-promoting properties, indicating efficacy for these specific androgen inhibitors against the type 1 or 11 isoenzyme form for treating these androgen related skin conditions.

Overall, the importance of 5aR and the two specific isoenzyme forms are apparent because the tissue distribution in the body differs, as well as biochemical characteristics of the enzymes. The isolation of these two 5aR forms raises interesting questions concerning regulation and their specific roles in androgen physiology because new compounds will be designed to target one specific enzyme or both enzyme forms, depending on the condition being treated.

Another important enzyme that has come to recent attention is the cytochrome P-450 aromatase enzyme (Fig 1). Because it is known that androgen metabolism occurs within the hair follicle structure, finding aromatase to be specifically located in outer root sheath of hair follicles adds to the importance of studying the entire hair follicle and not just the dermal papilla cells. Aromatase has been shown to convert androgens such as T, and androstenedione to the estrogens, estradiol and estrone, respectively. It was also found that in women, there may be two- to five-fold greater levels of aromatase in female scalp versus male, perhaps explaining why women may have a sparing of the frontal hairline in AGA and may have a less severe pattern of hair loss than men. It is uncertain if the estrogens formed from aromatase are playing a role in suppressing the severity of hair loss, or whether aromatase is primarily reducing the overall load of androgens formed locally in the hair follicle.

The next very important step to understanding androgen action in skin is the binding of the target tissue active androgens, T and DHT, to the androgen receptor (Fig 2). The androgen receptor (AR) has been purified and located in specific skin structures, such as hair follicles and sebaceous glands. Although the mechanism described in Figure 2 depicts T binding to the AR, we are now realizing that very complex enzyme mechanisms such as phosphorylation and sulfhydryl reduction of this receptor are important in forming an activated hormone-AR complex that has the ability to bind to specific hormone response elements at gene sites in the nucleus to

stimulate or alter cellular processes mediating hair growth.

CLINICAL OBSERVATIONS OF AGA

In genetically predisposed men, the balding process is triggered by exposure to androgens at puberty. In women, the relationship between systemic elevated androgen levels and alopecia is difficult to determine, because approximately 30% to 40% of women who experience AGA have a systemic endocrine problem, leaving the condition in a majority of women to be called idiopathic. We are now finding that many patients who were once called "idiopathic" have qualitative differences in the N-terminal domain of the androgen receptor where the number of polyglutatmine repeats can render androgen sensitivity. Therefore, quantitative and qualitative factors targeting the androgen receptor must be recognized before considering treatment options because not all patients may respond to conventional treatments based on 5aR, or other nonreceptor-mediated mechanisms.

Based on these direct mechanisms regarding cellular DHT metabolism via quantitative and qualitative aspects to the 5aR isoenzymes and AR in AGA, it is important to also keep in mind that some therapies may even target cofactors that mediate these reactions, such as reduced NADPH, which is necessary in mediating 5aR of testosterone to DHT. Therefore, these "secondary" mechanisms must be considered because novel therapeutics may target this direction as well (see Zinc).

Previous publications provide a more detailed overview of novel agents for alopecia; however, this review will cover some of the more pertinent agents approaching the marketplace for clinical application.

5aR Inhibitors

In this category there are the structural steroid competitive inhibitors that chemically resemble the substrate, T and bind to the active site of the enzyme so that DHT is not formed.

Table 1 describes 5aR inhibitors along with their structures, trade names (chemical names), and indication(s).

Propecia (finasteride; Merck Co, Rahway, NJ) has recently been approved by the Food and Drug Administration (FDA) in the US for men with AGA. Propecia is a specific 5aR type 11 enzyme inhibitor and does not bind to the AR; therefore, it is not called an antiandrogen, but an androgen inhibitor.

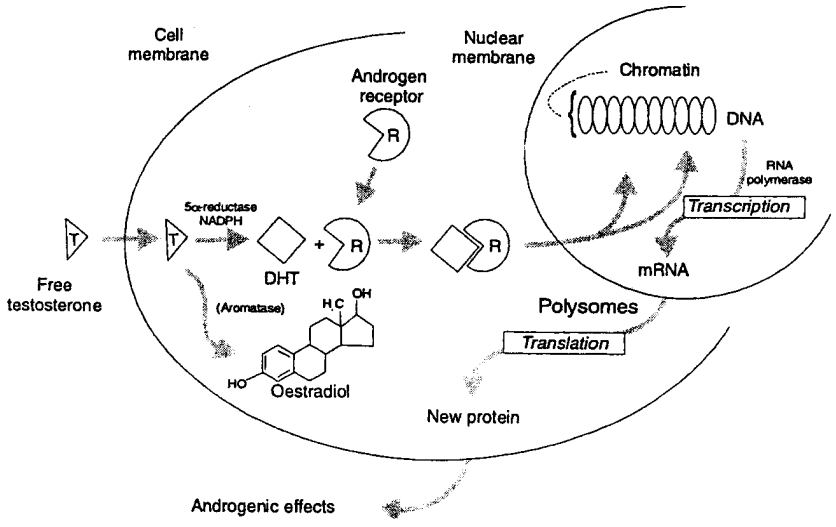
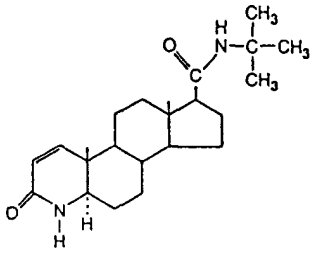
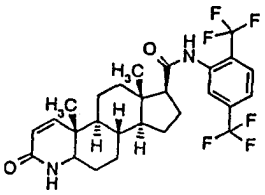
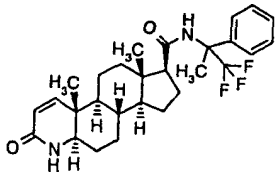


Fig 2. Cellular mechanism for androgens in skin. Steroids can enter the hair follicle cells from systemic sources that circulate via blood vessels. Once steroids passively diffuse through cell membrane, enzyme conversion to DHT can take place via 5aR and cofactor, nicotinamide adenine dinucleofide phosphate (NADPH). DHT has high affinity to the androgen receptor. The DHT-androgen receptor (AR) complex is sulfhydryl reduced and undergoes phosphorylation, enabling it to bind to specific gene sites and alter RNA polymerase activity of cellular factors that affect hair growth.

Table 1. Androgen Inhibitors

Nonproprietary Name/Trade Name	Chemical Structure	Dosage/Indications
Finasteride/PROSCAR, Propecia		5 mg/d of Proscar tablets for benign prostatic hyperplasia Propecia indicated for men with AGA, current trials for women with AGA, 1 mg/d of Propecia tablet Off label indications: for women with AGA, hirsutism, acne
GI 198745/Dutasteride		Not currently available; in clinical trial studies for AGA at GlaxoWellcome (Research Triangle Park, NC); future acne studies being developed
W09704002		Not currently available; undergoing patent review at Pharmacia & Upjohn Co (Kalamazoo, MI), but indicated for AGA as well as other dermatologic indications. Note similarity in structure to above compounds.

The pharmokinetics of finasteride show that after a 1 mg dose, serum concentration of DHT decreases by 65% in 24 hours. Serum concentrations of testosterone and estradiol increase about 15%, but remain within normal limits. Prostate concentrations of testosterone increase about sixfold. Finasteride is well absorbed in the gastrointestinal tract, metabolized in the liver, and excreted in urine and feces, with a half-life of 5 to 6 hours. Small nanogram levels of the drug are detectable in human semen; this is not thought, however, to have any consequence in women who are exposed by sexual contact.

Three double-blind multicenter trials were conducted in men ages 18 to 41 years and the results of these trials have been presented as abstracts. In combined results from two of the trials, 1,553 men with mild to moderate male AGA of the vertex took finasteride 1 mg/day or placebo orally for 1 year. After 3 months of treatment, the men who took finasteride were more satisfied with the appearance of their hair. At the end of 1 year, in a circle on the vertex scalp, a 1 inch diameter-mean baseline hair count was 876; patients who took the drug had an average of 107 more hairs than those who took the placebo. Hair counts were maintained for up to 24 months in the men who continued to take the drug. A third study of 326 men with mild to moderate frontal hair loss found that after 1 year, finasteride treated men had statistically significantly higher hair counts on the frontal scalp. Approximately 50% of treated men and 30% of those who took placebo thought the appearance of their hair had improved. Hair regrowth was not reported in older men taking 5 mg finasteride (Proscar; Merck Co, Rahway, NJ), perhaps because it was not indicated in those trials to make observations on the scalp.

Adverse events described with 5 mg finasteride (Proscar) in a small percent of older men were loss of libido, erection, ejaculatory dysfunction, hypersensitivity reactions, gynecomastia, and severe myopathy. Finasteride causes a 30% to 50% decrease in prostate specific antigen (PSA) in clinical trials with 1 mg tablets in men 18 to 41 years old. A decreased libido, erectile dysfunction, or a decreased volume of ejaculate have been

reported in less than 2% of patients, which in reality is between 0.5% to 1% when compared with placebo. Finasteride had teratogenic effects in animals on high doses, causing genitourinary abnormalities in male offspring. The concentration of the drug in semen of men who took 1 mg/day was much lower than the concentration associated with teratogenic effects in monkeys. The Merck manufacturers warn that women who are or may be pregnant should not have exposure to finasteride orally or handle crushed or broken tablets.

Thirty tablets of Propecia 1 mg/day cost the pharmacist less than $47, according to wholesale price (AV*/P) listings, whereas 30 tablets of Proscar 5 mg/day cost less than $64.

G1198745 (GlaxoWellcome, Research Triangle Park, NC) investigational compound is currently in clinical trial studies around the US for men with AGA. Structurally, as shown in Table 1, it is similar to the parent structure of finasteride, maintaining the 4-aza structure of the steroid nucleus; however, on the 21-carbon position is a tri-fluorophenyl group that renders the molecule to be electronegative and perhaps gives greater affinity for both the type 1 and 11 isoenzyme forms of 5aR. Therefore, this drug is similar to finasteride, in that both competitively inhibit 5aR; however, finasteride is specific for inhibiting type 11, whereas G1198745 inhibits both isoenzymes. This compound is known to inhibit >90% serum DHT levels in 24 hours after oral administration, and because of this greater ability to inhibit DHT, it may be more effective in promoting hair growth on the scalp of men, as well as treating acne, with clinical trials results still pending.

WO9704002 is a new compound undergoing patent review for Pharmacia & Upjohn Co (Kalamazoo, MI). It has great structural similarity to the above two compounds, with activity against 5aR inhibition similar to G1198745. This compound is not available, and it is not known if there are plans for clinical trial development at this time, but has been indicated for AGA and other dermatologic hormone-related conditions.

Vascular/Angiogenic-Related Compounds

Regaine/Rogaine (minoxidil; Pharmacia & Upjohn Co, Kalamazoo, MI) 2% has been used worldwide for over 10 years, and is now over the counter (OTC) in the US. Most recently, Extra Strength 5% Rogaine (Pharmacia & Upjohn Co) has hit the OTC shelves in the US, with approval on November 1997. Pharmacia & Upjohn has sole rights to being the only manufacturer for the next 3 years for this new version of minoxidil, which is indicated only for men.

Despite lack of understanding of the distinct mechanism of action, in women it has been shown to increase the nonvellus hairs when using it for 32 weeks or more. One potential drawback to minoxidil therapy is that spontaneous reversal to the pretreatment state can be expected 1 to 3 months after cessation of therapy, indicating minoxidil has a direct effect on the hair follicle, sensitizing it and making it dependent on the drug for future growth. In the US, various generic brands are now available OTC, which have brought down the price of minoxidil therapy from $50/bottle when it was Rogaine, a prescription product, to now approximately $10 to $15 dollars per generic bottle, which lasts about 1 month. Rogaine Extra Strength costs the pharmacist approximately $28.32 for 60 mL, who can raise the price to the consumer; therefore, good advice to patients would be to shop around before buying the product, at least in the US.

The mechanism of action although still unclear, seems to open potassium channels and increases proliferation and differentiation of epithelial cells in the hair shaft.

Serum concentrations after topical application of 2% minoxidil, used twice a day, (about 5% of those with oral minoxidil), and of the 5% solution (about 10% of those with the oral drug), have been reported in some patients using 2% solution. Minoxidil is metabolized in the liver and excreted in the urine.

As far as effectiveness, four unpublished 32 to 48 week studies presented to the FDA compared the effects of placebo, 2% minoxidil, and 5% minoxidil by counting the net gain in hairs in 1 cm 2 areas of the scalp. As described, two studies in women did not find statistically significant differences between 2% and 5% minoxidil. A 32-week study in men found that the mean increase from baseline in hairs/cm2 was 5 with placebo, 30 with 2% minoxidil, and 39 with 5% minoxidil. A 48-week study in men found a mean increase in hairs/cm2 of 3.9 with placebo, 12.7

with 2% minoxidil, and 18.5 with 5% minoxidil. Previous studies have shown that when the drug is stopped, all of the newly regrown hair falls out. Despite these reports, the new advertisements claim 45% more effective hair growth than regular strength 2%, with regrowth occurring as early as 2 months, with five times more hair regrowth overall than placebo and with no major safety concerns. Most physicians and lay people who have been using minoxidil for many years are not concerned about safety aspects because most feel it to be a very safe product. Concerns are more focused on the effectiveness of the product in promoting and maintaining hair growth. The 5% Extra Strength brings a new glimmer of hope by showing improved hair growth for individuals that may not have seen results with 2% minoxidil.

Adverse effects noted with oral minoxidil include tachycardia, angina pectoris, and fluid retention. When taken orally during pregnancy, minoxidil has been associated with hypertrichosis of the fetus and congenital anomalies. One double-blind study in 35 balding men found that topical use of 2% minoxidil caused small but statistically significant increases in left ventricular end-diastolic volume, cardiac output, and left ventricular mass. Infrequently, dizziness and tachycardia have been reported with 2% solution, and patients are advised to reduce frequency of application, which helps to eliminate these side effects. Local irritation, itching, dryness, and erythema may occur with use of topical minoxidil, most likely caused by the vehicle formulation of alcohol and propylene glycol.

The conclusion on minoxidil 5% and 2% solutions are that they can produce a modest increase in hair growth on scalps of young men with mild to moderate hair loss, with continuous application for years to maintain the effect. Questions as to the use of 5% Extra Strength in women are being posed, with some clinicians already giving this to young women with early hair loss, even though it is only indicated by the manufacturer, Pharmacia & Upjohn Co, for use in men.

Combinations. Many patients may be asking their physicians now and in the future about using both topical Extra Strength 5% Rogaine along with oral Propecia 1 mg/day, which many believe may be beneficial working together synergistically; however, further human clinical trials are needed to verify this because the only previous study was performed in the macaque monkey model, which did show benefit when used together.

Although other vasodilatory/angiogenic related compounds are progressing through the development pipeline, it is difficult to ascertain their effectiveness at this time until human clinical trials are performed. Many compounds that mimic minoxidil in vasodilatory properties fail to show the same results, hence there may still be a unique mode of action about this compound that is yet to be fully uncovered. Unpublished investigations have suggested minoxidil to have oxidative-reductive potential to facilitate cofactor reactions necessary in side chain steps for hair follicle growth, as well as other suggestions of stimulating some of the keratin genes of hair matrix cells for synthesis of hair shaft keratins, producing thin, fine, indeterminate hairs often seen with continued use of minoxidil.

Other New Compounds in Development

lamin (prezatide copper). lamin (Procyte Co, Seattle, WA) is a new drug that was just FDA approved in 1996, which is one of the superoxide dismutases (copper binding peptide). It was FDA approved as an antimflammatory wound healing gel. Procyte, the company that makes lamin, is working on getting approval for one of its other superoxide dismutases, Tricomin, for use in hair loss treatment. lamin hit the shelves in early July 1996, with results thus far indicating that it may help some people with hair loss. Some people have reported hair growth related to lamin, with most reporting a "strengthening of **existing hair.**"

ProCyte have also announced release of another product, GrafCyte, which is basically lamin in a few different forms. It has been approved by the FDA for use after transplants to prevent newly transplanted hairs from going into a resting phase. They propose that more hairs will grow immediately after transplants and results may be seen sooner than the typical 6 to 8 months. The product will be released in moist press applications to be applied for an hour, 4 times per day for 4 days after a hair transplant. A mist spray and shampoo have also been announced, with hopes that it will be used by those suffering from hair

loss in general; however the moist presses will only be available to the transplant surgeons.

Polysorbate 80. Polysorbate 80, an OTC product, has been around since the early 1980s as it was first used in the Helsinki Formula sold on television until the FDA banned such advertisements. There were claims that it grew hair in some people, but it was not effective in most individuals who used it. Perhaps those who did see a hair growth response were noting hair that was growing through successive miniaturization cycles, which often happens in double-blind studies where placebos have up to 30% improvement.

Folligen (copper chloride). Folligen is a new treatment similar to lamin Gel, but in cream form contains not only a copper complex, but Saw Palmetto (see later) for use as an androgen inhibitor of 5aR. Again, another product that has not been thoroughly tested for positive results in double-blind clinical trials.

Saw Palmetto (serenoa repens). Serenoa repens berries grow naturally, with the extract claiming to be an androgen inhibitor of 5aR to inhibit DHT production, mainly claimed for use in prostate problems. There have not been extensive studies performed, but implications in promoting hair growth on the scalp have been indicated. Side effects noted have been breast growth in men, which may indicate that it does not act on DHT alone. To be effective, the extract of the berries must be taken, not the berries themselves. Another active ingredient, pygeurn. africanum compound, is added to this extract and is thought to influence testosterone metabolism, although it is not clear on how at this point. The product comes in capsule form (60 capsules for $11.80) with two to four capsules as the recommended dose per day in divided doses between meals.

Amino acids. Arginine/L-arginine and/or cysteine/L-cysteine have been proposed as playing a strong role in hair growth and offered in nutrition health food stores to "make nails stronger and help the hair follicle to make more hair." These amino acids can be taken alone or together in oral liquid form with doses recommended at 500 to 1000 mg a few times a week.

Biotin and folic acid. These too have been around for a long time with claims to help hair grow. Nutritionally speaking, biotin and folic acid are required for hair growth and are usually supplied in a normal diet; therefore, unless there is a deficiency in these because of poor nutrition or wasting diseases, increased doses may not help hair grow. In fact, excess megadoses of these may cause hair loss, so if an adequate balanced diet is being maintained, a general vitamin supplement should do as well in providing nutritional needs for hair growth requirements.

Zinc. A lot has been claimed about zinc for use in various diseases, including topical use for acne, another androgen related problem. Specific forms of zinc, ie, zinc acetate, zinc sulfate, and others, have various properties that promote wound healing, help treat acne, and promote hair growth. The last few years spouted a new formulation of zinc in a skin cap to treat scalp psoriasis, and scaley, erythematous conditions of the skin, with findings that the main ingredient was actually clobetasol, a corticosteroid that was found to be the active ingredient that caused the great improvement when used for various conditions. In any case, it is cautioned that zinc may be an important factor topically or for oral use depending on the formulation of the zinc. Zinc sulfate was found to be an inhibitor of DHT production, not that it inhibits 5aR, but that it limits reduced cofactor, NADPH, which is necessary for the 5aR of testosterone to form DHT.

A criticism to many of these herbal or OTC remedies is that they are not governed by strict FDA criteria, and that the purity, consistency, and concentration of these agents can vary from batch to batch, whether they are in liquid, pill, or topical formulation.

In conclusion, there are various new novel treatments for use in alopecia. Some of these have gone through rigorous double-blind clinical trial testing with FDA approval as to their proven claims, whereas others have yet to do so. Although many new products described here may be approaching the marketplace, it is wise to guide patients and advise them of how these agents work and if they have been adequately tested before spending their money and raising their hopes. Realistic expectations should continue to be the main guideline when offering any treatment for alopecia.