Alopecia: Unapproved Treatments or Indications

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There are various forms of alopecia, the most common being "androgenetic alopecia" (AGA), which affects millions of men and women. For both men and women, AGA may begin as early as the teen years but can even start in later decades of life. The severity of hair loss in women is usually much less than in men. 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. As in men, AGA in women can be psychologically devastating to accept, giving an overall less body-image satisfaction and making it difficult to cope and retain integrity of personality functioning. Androgenetic alopecia has been reported to be a polygenic autosomal trait that is thought to involve several genes for both men and women.

Biochemical Mechanisms in Male and Female 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 confirmed this. Recent work' has shown that on the scalp local differences exist in the amounts of steroid-metabolizing enzymes that convert weak androgens to more potent androgens. This is important because the skin is an endocrine target tissue for androgen hormone action, similar to ovary, testes, and adrenal glands. Studies have shown that persons using anabolic-androgenic steroids show hypertrophy of sebaceous glands, with systemic hirsutism and AGA. It is known that weak and abundant precursor hormones such as dehydroepiandrosterone (DHEA) can metabolize to more potent androgens such as testosterone (T) and 5-alpha-dihydrotestosterone (DHT). The enzymes responsible for this conversion have been localized in sebaceous glands and hair follicles of scalp skin. Therefore, the skin has the potential to mediate androgen action without relying on elevated systemic levels of T or DHT.

An important enzyme, 5-alpha-reductase (5aR), mediates the reduction of T to DHT, via reduced cofactors such as NADPH. There are two forms of 5a-R. Type I 5a-R isoenzyme is thought to be primarily in skin, especially sebaceous glands, as well as in kidney and liver. Type 11 5a-R isoenzyme predominates in gonadal tissues (ie, prostate, seminal vesicles, etc.), but in recent years type 11 has also been found to be in hair follicles on the scalp where miniaturization takes place. This finding gave explanation as to how finasteride, a Type 11 5a-R inhibitor, has hair-growth-promoting properties, indicating efficacy for selective androgen blockade using inhibitors against 5a-R for treating these androgen related skin conditions.

Overall, the importance of 5a-R and the two specific isoenzyme forms is apparent as the tissue distribution in the body differs, as do the biochemical characteristics of the enzymes. The isolation of these two 5a-R forms raises interesting questions concerning regulation and their specific roles in androgen physiology as 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. Because it is known that androgen metabolism occurs within the hair follicle structure, finding aromatase to be specifically located in the 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 a two- to fivefold greater level of aromatase in female scalp versus men, perhaps explaining why women may have a sparing of the frontal hairline in AGA, and why they may have a less severe pattern of hair loss than men. It is uncertain if the estrogens formed from aromatase play a role in suppressing the severity of hair loss, or whether aromatase primarily reduces the overall load of androgens formed locally in the hair follicle. At this time, the role of estrogens in hair growth is still uncertain.

The next very important step in understanding androgen action in skin is the binding of the target tissue active androgens T and DHT to the androgen receptor. The androgen receptor (AR) has been purified and located in specific skin structures, such as hair follicle and sebaceous gland. This receptor is important for forming an activated hormone-AR complex, which 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.

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. 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. [15-17] Therefore, quantitative and qualitative factors targeting the androgen receptor must be recognized prior to considering treatment options in that not all patients may respond to conventional or latest treatments based on 5a-R, or other nonreceptor-mediated mechanisms.

Based on these direct mechanisms regarding cellular DHT metabolism via quantitative and qualitative aspects to the 5a-R isoenzymes and AR in AGA, it is important also to keep in mind that some therapies may even target cofactors that mediate these reactions, such as reduced NADPH, which is necessary in mediating 5a-reduction of T to DHT. Therefore, these "secondary" mechanisms must be considered, as novel therapeutics may target this direction as well. An example of such an agent is zinc, as discussed later in this article.

Previous publications18 describe a more detailed overview of novel compounds undergoing patent protection and approval for alopecia, and these agents are not available for public use.

Detailed treatment approaches using U.S. Food and Drug Administration (FDA)-approved drugs for male and female AGA have been extensively reviewed. As of 1999, there are no FDA-approved treatments specifically for alopecia areata (AA). Treatment approaches for AA using these "unapproved" or "off-label" drugs have been reviewed at length in previous publications. This review covers some of the available "unapproved" agents commonly used to treat AGA. These will be discussed in the following order:

1. "Off-label" prescription products
2. OTC with antiandrogen mechanisms
3. OTC herbal/antifibrosis/nutritional/immunomodulatory agents
4. *Products in FDA clinical trial testing*
5. Patented products in research and development
6. Medical devices

"Off-Label" Prescription Products to Treat Hair Loss

Spironolactone / Aldactone

Spironolactone is an alclosterone antagonist that acts as a weak antiandrogen in blocking the AR, but also inhibits androgen biosynthesis. Spironolactone may convert to other active metabolites, via the progesterone 17-hydroxylase enzyme, which reversibly inhibits adrenal and ovarian cytochrome P-450, which overall will decrease testosterone and DHT. The progestational activity of spironolactone is variable but influences the ratio of LH to FSH by decreasing the response of LH to GnRH.

Spironolactone is a steroid with the structure of a basic steroid nucleus of 4 rings, with resemblance to the mineralcorticoids, also having an esterified lactone ring. The bioavailability from oral administration exceeds *90%,* but varies on the tablet manufacturer. Spironolactone is *98%* protein bound, and the primary metabolite, canrenone, is at least *90%* protein bound. Canrenone is the active aldosterone antagonist, and it is the primary metabolite contributing to the diuretic activities of spironolactone.

Food increases the absorption of spironolactone. Spi~ ronolactone is rapidly metabolized by the liver. Its primary metabolite, canrenone, can be interconverted enzymatically to its hydrolytic product, canrenoate. None of the unmetabolized drug appears in the urine. Metabolites of spironolactone are excreted in urine and bile.

In a dose range of *25* to *200* mg, a linear relationship between a single dose of spironolactone and plasma levels of canrenone occurs by *96* hours. The half-life is approximately *19.2* ± *6.*57 hours for canrenone, and for spironolactone it is *12.5* ± *3.39* hours. Again, binding to plasma proteins is extensive, and virtually no unmetabolized drug appears in the urine. The most serious side effect of spironolactone is hyperkalemia, which can also happen when given with a thiazide to patients with severe renal insufficiency. Other side effects include gynecosmastia and minor gastrointestinal symptoms. Spironolactone is primarily indicated for hypertension and refractory edema.

No dermatologic indications for spironolactone have been approved by the FDA. It is only approved as a diuretic, for the treatment of primary hyperaldosteronism, idiopathic hyperaldosteronism, edematous conditions of congestive heart failure, cirrhosis with ascites, nephrotic syndrome, essential hypertension, and hypokalemia.

Spironolactone has been used to treat hirsutism, acne, and AGA as well as hidradenitis suppurativa. Common doses range between 50 to 200 mg/day, with 100 mg/day being the most preferred. Even at this dose, side effects of menorrhagia, or menstrual dysfunction, is common. These problems may correct

themselves after 2 to 3 months of therapy, and if it does not, decreasing (50 to 75 mg/day) the dose may help in reducing the side effects. Oral contraceptive pills (OCP) are commonly added to assist in the menstrual dysfunction. Patients under age 35 are usually given OCP, while those older can be treated with conjugated estrogens alone.

Spironolactone is most effective for hirsutism and is used for this purpose in the United States. In some women with hirsutism the drug decreases the growth rate and mean diameter of facial hair. In efficacy studies, spironolactone is less effective in improving hirsutism scores than flutamide; however, it was shown to be more effective than finasteride.

Spironolactone may be effective in preventing hair loss in AGA in women, and 200 mg/day is required. Small open trials have shown some clinical effect in female AGA, but spironolactone does not offer the benefit of hair regrowth.

Laboratory monitoring of every 3 to 4 months is recommended to assist in following suppression of androgens, if a condition of androgen excess is found. Complete suppression usually takes 4 to 12 months of therapy. In addition, therapeutic benefit may also plateau after 1 year, and it may be necessary to add other adjunctive therapies.

Recommended labs to follow are: CBC, chemistry profile to determine electrolytes, DHEA-sulfate, testosterone, androstenedione, and cortisol levels. Blood pressure and weight should also be monitored.

Contraindications for spironolactone are renal insufficiency, anuria, chronic renal impairment, hyperkalemia, pregnancy, and abnormal uterine bleeding.

Carcinogenicity has been long debated. The FDA gives a warning in the package insert that states tumors were found in chronic toxicity studies of rats where 25 to 250 times the usual human dose (body weight basis) was given to rats. These doses resulted in benign adenomas of the thyroid, testes, malignant mammary tumors, and proliferative changes in liver. Because of these and other changes reported in the rat, it has been recommended that spironolactone not be given to women with genetic predisposition to breast cancer.

Spironolactone and metabolites may cross the placental barrier, and rat studies have indicated feminization of the male rat fetus. In women who have taken spironolactone, the presence of canrenone was detected in breast milk. Women of child-bearing potential must use acceptable birth control methods and be warned of the potential for feminization of a male fetus should they become pregnant.

Drug interactions of spironolactone may occur when taking salicylates, which have been known to decrease the diuretic effect. Angiotensin-converting enzyme inhibitors, such as captopril and enalapril, will decrease aldosterone production, which may result in elevated serum potassium. Use of spironolactone and potassiurn supplements may lead to hyperkalemia. Other interactions have included digitalis glycosides, which may increase absorption of digitalis, leading to increased blood levels; therefore, reducing maintenance and monitoring dosing requirements may be necessary. Spironolactone may also interfere with radioimmunoassay measurement of digoxin, which can give falsely elevated serum digoxin values.

Flutamide

Flutamide is a nonsteroidal antiandrogen that is devoid of other hormonal activity. It most likely acts after converting to 2-hydroxyflutamide, which is a potent competitive inhibitor of DHT binding to the AR. In mature rat studies it was shown to cause regression of androgen target tissues, such as prostate and seminal vesicles, and to block the inhibitory feedback of testosterone on LH production, which results in a profound increase in plasma concentrations of LH and testosterone. Similar effects were noted in adult men when treated with 750 mg of flutarnide per day. The predominant pituitary effect appears to be enhancement of the frequency of pulses of LH secretion. Therefore, the drug may be effective in vitro as an antiandrogen; however, in vivo the rise in plasma testosterone serves to limit its antiandrogenic effects.

Flutamide is useful in inhibiting the action of adrenal androgens in castrated men or those receiving GnRH blockage (ie, leuprolide) or in situations in which LH production is not under predominant control by androgen, such as the case in women. Flutamide is indicated for prostatic cancer in men. It has also been used in conjunction with OCP for treating hirsutism in women but if it crosses the placenta, it would be expected to produce male pseudohermaphroditism, similar to other androgen-receptor blockers. Noted side effects when taken orally are hepatotoxicity, including progressive liver failure, which limits its usefulness. Further studies are needed to evaluate its efficacy as a systemic or topical agent in treating AGA.

Progesterone

Progesterone is a compound that has high structural similarity to testosterone; therefore, is able to utilize the same enzyme, 5a-R, and bind to the AR, acting both as an antiandrogen and androgen inhibitor. Some progestins have inherent estrogenic as well as androgenic effects. Although progesterone binds to its own intracellular transcription receptor, it has affinity to the AR (after 5a-R producing 5a-pregnane dione, similar to DHT), which renders its ability to act as an androgen or antiandrogen.

Progesterone is secreted by the ovary mainly from the corpus luteum during the second half of the menstrual cycle, which leads to the development of a secre-

tory endometrium. Progesterone is vital for the duration of normal gestation of pregnancy as well as developing mammary gland; it also has a known thermogenic effect during the luteal phase of the menstrual cycle.

Progesterone can be given either intramuscularly or orally, and both routes are readily absorbed but at a rate that may be too rapid for optimal therapeutic efficiency. Inactivation takes place largely in the liver. Many progestins are derivatized to glucuronide or sulfated for excretion in the urine. A small amount can be stored in body fat. Many analogs of progesterone are less susceptible to hepatic metabolism and may be more effective in lasting therapeutically longer than progesterone. Approximately 50-60% of administered radioactive progesterone appears in the urine and about 10% in feces.

Most therapeutic indications for progesterone are for ovarian disorders and contraception. Off-label uses have indicated variable effectiveness as a topical agent for treating AGA at 2% concentrations. We have not found that topical progesterone is of great value in the treatment of AGA.

Cyproterone Acetate

Cyproterone acetate, is a well-known antiandrogen' available in Canada and Europe, but not in the United States. In the search for more potent progestins that had antiandrogenic activity, some steroids with a 1,2-amethylene substitution were found, such as cyproterone. Known to be a potent antiandrogen, it also possesses progestational activity and suppresses the secretion of gonadotropins. The primary action of cyproterone is competing with DHT for the AR binding site. When given to pregnant animals, cyproterone acetate blocks the actions of androgen in the male fetus and induces a form of pseudohermaphroditism.

Administering 100 mg/day of cyproterone acetate to normal young men causes a 50% decrease in plasma concentrations of LH and FSH and a 75% decrease in plasma testosterone, the effects being due to the result of inhibiting testosterone production and interfering with androgen action. It is indicated for prostatic cancer and benign prostatic hypertrophy; it also inhibits libido in sexually deviant behavior. Off-label uses have included female AGA, hirsutism, and virilizing syndromes. It has been approved in Europe and Canada for female acne as an OCP (2 mg of cyproterone acetate in combination with ethinyl estradiol) in the form of Diane-35. For the treatment of AGA in women, 50 to 100 mg/day of cyproterone acetate taken on days 5 to 14 of the menstrual cycle can be used in combination with an OCP such as Demulen. There are no controlled clinical studies in AGA with cyproterone acetate. It appears to stabilize the hair loss process. Side effects include menstrual irregularities, weight gain, breast tenderness, loss of libido, depression, and nausea. Women of child-bearing potential must use acceptable birth control methods and be warned of the potential of feminization of a male fetus if they become pregnant.

Cimetidine

Cimetidine, the first H2 blocker to be introduced for general clinical use, was well accepted as a treatment for duodenal ulcers and other gastric hypersecretory conditions. Cimetidine also has the unusual properties of working as an antiandrogen by binding to AR; hence, the noted side effects that have been reported include: loss of libido, impotence, and gynecomastia (stimulated prolactin). Cimetidine also binds to the cytochrome P-450 enzyme system and diminishes activity of hepatic microsomal mixed-function oxidases. Off-label uses of cimetidine have been for AGA and hirsutism; however, no clinical trials have ever been performed to prove efficacy. The preferred dose range is 800 to 1600 mg/ day, given as 300 mg by mouth five times daily.

Over-the-Counter (OTC) Products That Make "Antiandrogen" Claims

In this category there are three different types of mechanistic agents that claim either to inhibit the action/ "trap" the hormone, DHT or inhibit 5a-R, or block the AR, which DHT must bind to in order to elicit a molecular response. Some of these pharmaceuticals make it quite confusing, as they do not differentiate 5a-R, DHT, or the AR. These terms are often interchanged. Advertisements usually mention something about DHT in some manner, usually stating that their product blocks its action. It may take an expert to see the discrepancies when the products are described.

Serenoa Repens l Saw Palmetto l Permixon

This is very commonly known by patients and clinicians as it is widely available in most nutritional food stores. *Serenoa repens* berries grow naturally, with the extract claiming to inhibit DHT production, mainly claimed for use in prostate problems. There have been no extensive studies, but because of the stated implications of affecting DHT, men are anxious to try this OTC remedy to see whether it promotes hair growth on the scalp.

Studies that have been done have compared Permixon with finasteride in treatment of 1098 men with benign prostatic hypertrophy (BPH). Permixon improved symptoms of BPH but had no effect on androgen-dependent parameters such as DHT levels or 5a-R, indicating that its effects must be due to other yet undetermined pathways that do not involve DHT or 5a-R directly. Another study in 32 young men (aged 20 to 30 years) in a 1-week open trial looked at the effects of finasteride versus Permixon with regard to

serum androgen levels; no effect on DHT levels were found in the Permixon-treated group, similar to the placebo group, whereas the finasteride group reduced DHT by 65%.

Side effects noted in taking *Serenoa repens* in either commercial form of Permixon or Saw Palmetto have been gynecomastia in men, which indicates again that it does not act on DHT alone, but by other as yet unrevealed mechanisms. To be effective the extract of the berries must be taken, not the berries themselves. Another active ingredient, *Pygeum africanum* compound, is added to this extract and is thought to influence testosterone metabolism, although it is not clear how at this point. The product comes in capsule form with 2 to 6 capsules as the recommended daily dose in divided doses between meals. The cost can range from $12 to $40 per month.

Kevis Hair Rejuvenation Program

Kevis is another OTC agent that is available to men and women with different hair loss problems from AGA to effluviums; it claims to bind and block the 5a-DHT receptor; which is the AR. It claims to be safe and effective for men and women of all ages, to be "costefficient" and to prevent hair loss and make one's hair healthier than ever before. Kevis claims to "have an anti-falling-out effect"-that is, seeing less hair shedding.

While the claims seem a bit broad, the active ingredients are a composition of mucopolysaccharides and glycoproteins, associated with substances that favor their bioavailability. Kevis contains HUCP (hyaluronic acid); glycoproteins; amino acids, which have a hydrating and anti-inflammatory action; thioglycoran-a natural mucopolysaccharide acides; thurtyl nicotinate a cutaneous vasodilator, and sodium pantothenate and biotin. Studies claim to help women with postpartum effluviums, with other claims included for acne, wrinkles, lipodystrophies, dermosclerosis, AGA, hypertrichosis, and others.

The claims on the mode of action of Kevis are difficult to comprehend as the literature states that it "blocks DHT" or "blocks the androgen receptor" by creating a cell-wall barrier to keep DHT out of the follicle.

Studies on Kevis have been done in Europe. One study cites localization of "5a-DHT" in hair follicle by use of monoclonal antibodies, and it is not clear whether the researchers are assessing the enzyme 5a-R, the hormone DHT, or the androgen receptor. Their findings stated that "whatever" they localized, it was found in the dermal papilla. The dermal papilla is always mentioned as where most androgen-related factors are found; much of the older literature mentions this as the major site of control for hair follicle growth. Investigations in the last few years have, in fact, cited other important areas of the hair follicle involved in regulation of growth, such as the follicular stem cells in the "bulge" as well as the fact that many androgen related factors, such as 5a-R and AR, are also expressed in the outer root sheath of hair follicles, not just dermal papilla.

Clinical testing of Kevis in a double-blind, placebo-controlled study indicated in the Kevis-treated group, after 90 days of treatment, that telogen hairs decreased by 16%, versus 6% in the placebo group. There was no mention of anagen/telogen ratios. The 10% difference found in telogen hairs is of no significance as this can be due to error, hair cycling, and does not mention if these hairs that cycled out of telogen were stimulated back to anagen, as no anagen counts are given. Also, it was not clear what one of the endpoints (a "three-comb stroke" test) was, as this is not a standardized measurement for clinical trials in the United States or Canada.

Importantly, the cost of Kevis should be of concern. When patients call the toll-free number to speak to a Kevis consultant, they are given information on the hair rejuvenation program, which can cost between $650.00 to $975.00 per year (U.S. dollars). This cost is for a 12-month supply, which is 216 vials (each vial contains 2 tablespoons of Kevis lotion to be applied topically to the scalp) and 8 bottles of shampoo. The $650.00 value is a nonrefundable package, and patients not satisfied cannot get their money back. For $900.00, patients can get the same 12-month supply but with a money-back guarantee. There is also the Extra Strength Kevis, a 25% stronger formulation that sells for $715.00 (nonrefundable plan) or $975.00 (refundable plan).

The cost of this OTC product is much greater than what a patient would pay for an approved product like Propecia, or Extra Strength Rogaine (5%), which would cost $600.00 and $360.00, respectively, per year.

Overall, it is uncertain whether there are any side effects with Kevis, but mention is made in one study that revealed an increase in pityriasis scaling and increase in pruritus. The main concern is "cost to efficacy" as no rigidly standardized double-blind studies have shown true increases in hair counts in studies over 12-month periods. Some of the above studies mentioned are for only 36 to 90 days, which may not be adequate testing time, as the miniaturization process takes multiple hair cycles to see a reversal in hair growth to a full anagen stage. These studies have been traditionally done over periods of 2, 3, 4, and even 5 years, such as was done when testing minoxidil by Pharmacia-Upjohn, and finasteride by Merck & Co. So, unless these agents adhere to such testing, their efficacy can be debated.

Zinc

Much has been claimed regarding zinc in various diseases, including topical use for acne, another androgen-

related problem. Specific forms of zinc (ie, zinc acetate, zinc sulfate) have various properties in promoting wound healing, use in acne, and claims for hair growth. Zinc sulfate was found to be an inhibitor of DHT production, not that it inhibits 5a-R but that it limits reduced cofactor NADPH, which is necessary for the 5a reduction of testosterone to form DHT.

Other OTC Products

Fabao 101DIFormula 101: Pan State Health Products

This product is a remarketing of Formula 101, which came from China years ago, and now is remarketed under a similar name, Fabao 101D. This herbal concoction claims to come from medicinal plants containing sophera flavescens, radix astragali, capsicum, seu radis notopterygii, safflower oil, cortex dictamni radicis, rhizhoma gastroidia ginseng, notoginseng, heshouwu, and peach kernel oil. The manufacturer's insert material claims that the molecular structures of these active compounds are very delicate and that they are only active in their native molecular state, which remains intact during the company's manufacturing process, stating why others cannot duplicate the ingredients due to the technologies involved in processing it. This product claims to be effective not only for male androgenetic alopecia but also alopecia totalis. Again, there are no published double-blinded, placebo-controlled trials.

lamin (Prezatide Copper)

lamin is a new drug that was FDA approved in 1996, and it is one of the superoxide dismutases (copperbinding peptide). It was FDA approved as an antiinflammatory wound healing gel. ProCyte (Redmond, Washington) makes lamin, and states that there are many copper peptide derivatives that can be used in skin. The company has another formulation of one of its other superoxide dismutases, Tricomin, for use in hair loss treatment. Tricomin is OTC and available. lamin hit the shelves in early July 1996, with results showing that it may help some people with hair loss. Some users have reported hair growth related to lamin, with most reporting a "strengthening of existing hair," so the company's efforts in formulating Tricomin is to provide a specific product line for hair loss.

ProCyte has also released another product, GrafCyte, which is basically lamin in a different form. It has been approved by the FDA for use after hair transplants to prevent newly transplanted hairs from going into a resting phase. The company proposes that more hairs will grow immediately after transplants and worthwhile results can be seen sooner rather than the typical 6 to 8 months. The product is available in moist compress applications applied for an hour, 4 times per day for 4 days following a hair transplant. A mist spray and shampoo are also available. The present researchers have found GrafCyte quite appealing as a postsurgical routine for most hair-transplant patients. It allows the patient not to have to return the following day for the usual washout. The acceptability and compliance rates of patients for GrafCyte are quite high in our experience.

Polysorbate 80

This OTC product has been around since the early 1980s as it was first used in the Helsinki Formula sold on television during that time 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 even placebos show up to 30% improvement.

Folligen (Copper Chloride)

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

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 hair follicles 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 each week. For most patients who have no amino acid deficiencies, we have not found this form of supplementation to be of any value for hair growth.

Biotin and Folic Acid

These two nutrients 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, wasting diseases, and other causes, increased doses may not help hair grow. In fact, excess megadoses of these can 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.

Shampoo l Revitalizers

This category of product contains many that can go beyond the limits of this text. One mentioned on the Internet is "Smart I fair Care Program (Edmonton, Al-

berta, Canada)"; again, this is just one of the hundreds out there, but they all follow a similar structure in making claims to grow hair if one uses the entire program, which involves revitalizer, shampoo and conditioner, and powder gelatin. Sometimes it can be confusing as to whether you eat these things or apply them topically, especially products like the "powder gelatin." In any case, program proponents claim that all the products must be used as directed.

The revitalizer is the "expensive part" in that it is the one controlling the hair loss, and will promote new healthy hair, stating that it will be most effective on existing hairs, and that as long as there are little fuzzy hairs, the revitalizer will stimulate growth again.

A dose of 1.5 cc is suggested per treatment, which patients apply nightly and must be left on the scalp for 6 hours, followed by the shampoo and conditioner. After this is completed, the patient then uses the powder gelatin orally as a dietary supplement, to be taken with juice or other liquid to "help the small developing hairs to grow as thick healthier hairs."

The cost of such a program: revitalizer (1-month supply = $90 to $180.00), shampoo ($10.00 per month), conditioner ($10.00 per month), and powder gelatin ($14.00 per month). This can total between $124.00 to $214.00 monthly, again much more expensive than using an "approved" product that has been shown to grow hair.

Piliel from Life Medical Sciences

It was announced in December 1997 that clinical testing on Piliel was being terminated owing to lack of efficacy. Prior to this the testing that was done was performed in Europe, where it was reported that the product was able to stimulate hair growth and reduce hair loss. There were 140 participants in the clinical testing, which took place early in 1997. Later the company indicated that the product was not likely to generate satisfactory results for AGA, and consequently all testing was then terminated.

ViviScal

ViviScal, a food supplement incorporating special marine extracts and a silica compound, was studied in a double-blind randomized manner on 20 men with AGA. Ten men were treated with two tablets daily of fish extract and the other 10 were treated with two tablets daily of ViviScal for 6 months. After 6 months of treatment, patients receiving ViviScal showed a mean increase in nonvellus hair of 38% compared with a 29% increase in the fish-extract group. Also, 19 of 20 subjects in the ViviScal group showed "clinical and histologic cure" compared to none of the fish-extract group. It is difficult for us to accept the word "cure" for male AGA. This product needs more rigorous testing using standard FDA-approved endpoints of evaluation before the present investigators will accept this claim.

Aminexil

Aminexil, developed by L'Oreal, is a diamino-pyrimidineoxide (DPO). Three hundred fifty-one individuals were treated with Aminexil or placebo in six successive single-blinded trials lasting 3 to 6 months. Many of these studies involved three hospital sites. Most patients applied a daily 6-mL water-alcohol solution containing 1.5% DPO (90 g DPO). Phototrichograms were used to determine efficacy. In the Aminexil group the percentage of telogen hairs decreased and anagen hairs increased significantly compared to placebo. The mode of action of Aminexil is to act as an antifibrotic agent, preventing collagen formation around the hair follicle and increasing survival of the follicle. Prevention of further hair loss is the main claim of this OTC agent. Again, this product needs more rigorous testing using standard FDA-approved endpoints of evaluation before we will fully accept the efficacy data.

ThymuSkin

ThvmuSkin is derived from natural calf thymus extract. Thymosin, the peptide molecules of the thymus extract used in ThymuSkin, is believed to be immunomodulating, holding off the aging process. It is available as a shampoo and revitalizer lotion in certain European countries and Canada. There are numerous publications in the German literature discussing efficacy in androgenetic alopecia and alopecia areata. Again, this product needs more rigorous testing using standard FDA-approved endpoints of evaluation before we can accept the efficacy data unconditionally.

A criticism to many of these herbal/OTC remedies is that many are tested in foreign countries and that they are not tested in the United States. If the products' claims are only herbal or nutritional then they do not have to follow the strict guidelines as a "medicinal" or "drug" classified agent, which means it is not governed by strict FDA criteria. Also, there are many questions as to the purity, consistency, and concentration of these nutritional and herbal OTC agents, which can vary from batch to batch, and despite whether they are in liquid, pill, or topical formulation.

Agents Still "Unapproved" but Undergoing Clinical Trial Testing for FDA Approval

Combination Type I and Type II 5a-R Inhibitors

These molecules are presently being developed by pharmaceutical companies, and clinical trials are ongoing in the United States. The molecules may suppress serum DHT to a greater degree than a single Type 11

5a-R inhibitor. They may turn out to be of great benefit in male AGA. Clinical results are still pending.

Extra Strength Rogaine 5% for Women

Regaine/Rogaine (minoxidil) 2% has been used worldwide for over 10 years, and is now over-the-counter (OTC) in the United States. Most recently, Extra Strength 5% Rogaine has hit the OTC shelves in the United States, but approval is *only given to men* with hair *loss, not women* in the approval given November 1997. Pharmacia-Upjohn has sole rights as the only manufacturer for the next few years for this new version of minoxidil. Again, it is only indicated for men and is still unapproved for women as of April 1999.

Despite lack of understanding of the distinct mechanism of action, in women it has been shown to increase the nonvellus hairs when used 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 United States, various generic brands are now available OTC, which have brought down the price of minoxidil therapy from $50.00/bottle when it was Rogaine, a prescription product, to approximately $10-15.00 per generic bottle, which lasts about I month. Rogaine Extra Strength costs approximately $28.32 for 60 mL to the pharmacist, which can raise the price to the consumer; thus, good advice to patients would be to shop around before buying the product, at least in the United States.

The mechanism of action, although still unclear, seems to open potassium channels and to increase proliferation and differentiation of epithelial cells in the hair shaft. Minoxidil is metabolized in the liver and excreted in the urine.

As far as effectiveness, four unpublished 32-to-48week studies presented to the FDA compared the effects of placebo, 2% minoxidil, and 5% minoxidil by counting the net gain in hairs in I 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 $/CM^2$ 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/ cm^2 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. Based on hair-weight studies, there appears to be 45% more effective hair growth than regular strength 2%, with regrowth occurring as early as 2 months, with overall five times more hair regrowth than placebo, with no major safety concerns. Most physicians and laypeople who have been using minoxidil for many years, are not concerned about safety aspects, since most believe it to be a very safe product. Concerns are more on the "effectiveness" of the product in promoting and maintaining hair growth. The new 5% Extra Strength brings about a new glimmer of hope in showing improved hair growth for individuals that may not have seen results with 2% minoxidil. Currently, Pharmacia-Upjohn predict that 90% of men will have noted some positive effects with this new 5% Extra Strength version of minoxidil as the company now offers a money-back guarantee to men who use 5% Extra Strength Rogaine if results are not seen in 4 months.

In the past, adverse effects noted with oral minoxidil included tachycardia, angina pectoris, and fluid retention. When taken orally during pregnancy, minoxidil has been associated with hypertrichosis of the fetus and congenital anomalies. Infrequently, dizziness and tachycardia have been reported with 2% minoxidil solution with advice given to patients to reduce frequency of application, which helps in eliminating side effects. Local irritation, itching, dryness, and erythema may occur with use of topical minoxidil, most likely to the vehicle formulation of alcohol and propylene glycol. Facial hypertrichosis can occur in up to 5% of women using topical minoxidil. Body hypertrichosis has been reported but is very rare.

The findings on minoxidil 5% and 2% solutions are that they can produce a modest increase in hair on scalps of young men with mild to moderate hair loss, with continuous application for years to maintain the effect. The 5% Extra Strength product is now being used "off-label" in women, with some clinicians already giving this to young women with early hair loss, even though it is only indicated by the manufacturer, Pharmacia-Upjohn, for use in men at this time. Current clinical trials are nearing completion at multiple sites in the United States where 5% Extra Strength is being tested against 2% and placebo *in women*, with hope of FDA approval in late 1999, and available as an OTC product in 2000.

Products Patented but Still in Research and Development

Gene Therapy for Hair Loss and Color

AntiCancer Inc. of San Diego, CA, and Applied Genetics in New York are researching a gene therapy for grav hair and hair loss. Past media from a few years ago described latest results in hair color using gene therapy, where the treatment involves applying the cream onto the skin. The cream is in a liposome base, which is vital to the delivery of the gene to the hair follicle cells. The treatment was thought to be very effective, with no known side effects; however, the treatment needed to be applied every 2 weeks or so, and it is thought that large amounts of genetic material are needed to be

effective, which would make commercial use very expensive and impractical in today's OTC market of haircoloring agents. Similar to this, the companies' gene therapy is being researched for alopecia, which may be similar in regards to high cost and the need to apply the agent at intervals, necessitating continued treatments. Current studies are still researching the "optimal" liposomes for the treatments to be more effective.

Antisense Technology

Antisense technology has been around for quite sometime, but with little success in treating human disease. This is mainly due to the stability of antisense chimeras, which consist of nucleotide sequences specific to a target gene site. It was thought that use of antisense chimeras could block or effect specific gene sequences, but the technology has been hampered by the lack of specificity, instability of nucleotides, cost, and variability of results. Dyad Pharmaceutical's (Baltimore, MD) antisense molecule is said to be targeted against the 5a-R enzyme (not certain as to type 1, type 11, or both) and targeted for topical application on the scalp. Again, from these investigator's experience in dealing with antisense technology, the drawbacks to this can be stability of the antisense, specificity, costs, and variability of use in topical preparation, which is why other companies have abandoned this technology in favor of more specific molecular and gene-related technologies to treat human disease.

Medical Devices

Tricologic Biowave Helmet

This device claims to grow hair by use of electrical biowaves for a cost of 510.00 Australian dollars. It is manufactured and produced by **BIOFARM Cosmetics,** Glebe NSW, Australia.

ElectroTrichoGenesis (ETG)

This is a hair-dryer-type of device that claims to be a noninvasive stimulation of hair follicles to grow by positive influence of an electrostatic field. ETG is thought to inhibit further hair loss and stimulate or promote actual hair regrowth, with use of ongoing 12-minute painless treatment sessions. The device has been developed by Current Technologies, Vancouver, BC, Canada.

Laser Light Therapy

This device, employing laser-specific wavelengths, is used to stimulate hair follicles. The device is stated to be approved by the FDA, but for safety only. It is sold by New Image Co.

Conclusions

There are various new and novel treatments for use in alopecia. Only FDA “approved" products have gone through rigorous double-blind clinical trial testing as to their proven claims, whereas others have yet to be tested. Again, many products may state "FDA approved" but may be for safety only (it may not hurt you), but *not* for efficacy in hair growth. While many products described here are OTC on the marketplace, it is wise to guide patients and advise them of how these agents work and if the products have been adequately tested before they spend their money and raise their hopes. Realistic expectations should continue to be the main guideline when offering any treatment for alopecia, as there are a multitude of "snake oil" remedies out there and people will foolishly waste their money in the hope of finding a yet undiscovered product to cure their hair loss. This can certainly make the physician's job a most difficult task to contend with when counseling and treating patients.