

## Medical treatments for male and female pattern hair loss

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Male and female pattern hair loss affects a large percentage of the population, and patients frequently present for treatment of this to their dermatologist. Here we review the many treatments available for hair loss. We review the evidence for each, and outline the most effective treatment strategies for both men and women.

*Learning objective:* At the conclusion of this article, the reader should be able to describe the most effective treatments for hair loss, understand their mechanism(s) of action, and explain which treatments are the best in different settings. (J Am Acad Dermatol 2008;59:547-66.)

Our hair frames our face. Hair is one of our few physical characteristics we can voluntarily control, through hair length, style, and color. Our hairstyle is often a nonverbal expression of our personality. Male and female pattern hair loss affects 50% of men by 50 years of age and nearly 50% of women. The slow, relentless, involuntary loss of hair creates emotional stress for millions of men and women. Countless Internet sites and late night infomercials purport to have discovered a “miracle” cure for male and female pattern hair loss. Unfortunately, these “cures” are nonexistent and only serve to create cynicism and further stress for patients.

Fortunately, there are safe, effective medications available to treat male and female pattern hair loss. This paper will outline the mechanisms of action, side effects, and expected results from each medication that has been approved by the US Food and Drug Administration (FDA). We will also discuss some other commonly prescribed, non-FDA approved medications.

### MINOXIDIL

The use of minoxidil for hair loss has an interesting history. It was first used during the 1970s as an oral medication for refractory cases of high blood pressure.<sup>1,2</sup> The molecule is a piperidinopyrimidine

derivative, with the chemical structure 2,6-diamino-4-piperidinopyrimidine 1-oxide (Fig 1). It serves as an arteriolar vasodilator, acting specifically to open potassium channels.<sup>3</sup> It also was found to have a side effect of hypertrichosis. Throughout its use in the 1970s, it was found to cause unwanted hair growth in 24%<sup>4</sup> to 100%<sup>5,6</sup> of patients. Hypertrichosis was also noted in 5 out of 6 pediatric patients treated with minoxidil.<sup>7</sup> Interestingly, hypertrichosis is observed in a higher frequency and at lower doses in women than in men (Fig 2).<sup>8</sup> No endocrine abnormalities have been associated, but darkening of the skin and the coarsening of facial features have been reported from long-term oral use.<sup>2</sup>

Hypertrichosis caused by minoxidil was not reported in the dermatology literature until 1979.<sup>9</sup> That same year, the oral tablet form, Loniten (Pharmacia & Upjohn, Bridgewater, NJ), was approved by the FDA for hypertension. Other dermatologists quickly took note in considering it for use in treating different forms of hair loss. Zapacosta<sup>10</sup> noted a reversal of androgenetic alopecia (AGA) in a patient receiving oral minoxidil. However, there were limitations to using the oral formulation, because it could cause an unsafe drop in blood pressure. Patients also experienced side effects of severe water retention and weight gain, often requiring concomitant treatment with a diuretic.

Therefore, several researchers tested its use as a topical formulation for hair loss. Two controlled trials using 1% topical minoxidil for alopecia areata (AA) demonstrated cosmetically acceptable regrowth in approximately half of patients.<sup>11,12</sup> In 1984, topical minoxidil was used for the treatment of AGA. Five patients with AGA and 10 with AA were randomized to 1% or 5% topical minoxidil or placebo.<sup>13</sup> Regrowth was seen in the 3 patients with AGA who were given the 5% solution, suggesting a

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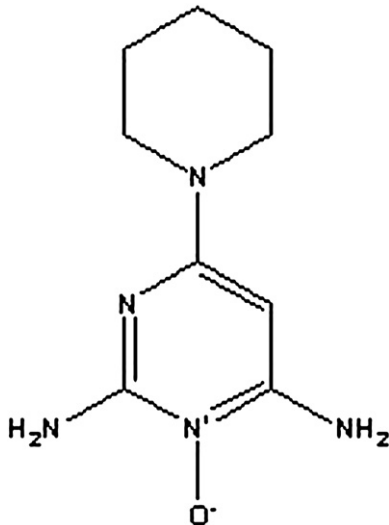
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**Fig 1.** Minoxidil molecule.

clinical dose response. Blood levels of minoxidil were 0.5, 2.0, and 4.5 ng/mL 2 hours after application to the scalp. None of the patients with AA regrew hair, despite comparable blood levels.

### Mechanism of action

Since these initial studies, much research has been done to identify exactly how the topical application of minoxidil can lead to increased hair growth. One important hypothesis is based on its vasodilatory properties. Diazoxide is another antihypertensive potassium channel opener which increases blood flow and is reputed to increase hair growth.<sup>14,15</sup> Laser Doppler velocimetry studies showed an increase in cutaneous blood flow after applying 1%, 3%, and 5% minoxidil solutions to the scalps of 16 balding men.<sup>16</sup> All three groups showed increases compared to a control group, and the 5% group showed the greatest increase. A significant increase in blood flow occurred as soon as 15 minutes after application, and lasted for up to an hour. The role of minoxidil in angiogenesis is further supported by evidence that it upregulates the expression of vascular endothelial growth factor mRNA in human hair dermal papilla cells.<sup>17</sup>

Minoxidil sulfate is the active metabolite that stimulates hair follicles.<sup>18</sup> The conversion of minoxidil to minoxidil sulfate is catalyzed by sulphotransferase enzymes, which exist in the scalp. In scalp skin of the stump-tailed macaque, this enzyme has been localized mainly to the hair follicle, which contains 50% to 85% of the enzyme (versus 10-20% in the epidermis and dermis).<sup>19</sup> Immunolocalization studies of minoxidil sulphotransferase demonstrated that the lower outer root sheath is the most likely site of



**Fig 2.** Hypertrichosis in a young female using topical minoxidil 5%.

conversion of minoxidil to its sulfated form.<sup>20</sup> Just as is the case with dihydrotestosterone (DHT), there are interindividual variations in scalp sulphotransferase levels. Patients with a better response to topical minoxidil were found to have a greater level of enzyme activity.<sup>21</sup>

Cultures of human epidermal cells treated with minoxidil have been shown to survive longer than control cultures.<sup>22</sup> Minoxidil slows the senescence of keratinocytes and reduces the rate at which cells are lost from the germinative pool. This is similar to what has been found with epidermal growth factor. Minoxidil has been shown to increase the proliferation of dermal papilla cells of the human hair follicle.<sup>23</sup> Specifically, minoxidil increased levels of Erk and Akt phosphorylation, with an increased ratio of Bcl-2/Bax, prolonging anagen and preventing cell death with antiapoptotic effects. This same study found that minoxidil elongated individual hair follicles in organ culture.

Minoxidil may also enhance cell proliferation. The uptake of tritiated minoxidil and its conversion to minoxidil sulfate has been found to be relatively higher in the hair follicles than in the epidermis and dermis.<sup>24,25</sup> This group also found that minoxidil caused the enhancement of DNA synthesis in the follicular and perifollicular cells but not in the epidermal keratinocytes. Another study showed a marked dose-dependent second peak of DNA synthesis 8 to 10 days later in epidermal cells cultured with minoxidil.<sup>26</sup> There were two morphologically distinct cell types, suggesting that minoxidil can affect epidermal cells in culture by altering their growth pattern and phenotypic appearance.

Whether the minoxidil indeed prolongs anagen or simply shortens telogen is still a matter of debate. It has been shown to shorten the length of telogen phase in the follicular cycle of rats but did not prolong the anagen phase.<sup>27</sup> Rather, there was found to be a premature entry of resting hair follicles back into the anagen stage, with an increased rate of DNA

**Table I.** Minoxidil: proposed mechanisms of action

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Vasodilatory properties <sup>16,38</sup>
Angiogenic properties <sup>17</sup>
Enhanced cell proliferation and DNA synthesis <sup>24,27</sup>
Potassium channel opener <sup>39,40</sup>
Antiandrogen effects <sup>41</sup>
Suppression of collagen synthesis <sup>42,43</sup>
Immunosuppressive effects <sup>32,35,36</sup>

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synthesis during the anagen stage. However, another study in balding stump-tailed macaques found that treatment with minoxidil increased the proportion of hair follicles in anagen, reduced the number of telogen follicles, and increased the follicle size overall.<sup>28</sup> This suggests at least a relative shift chronologically from telogen to anagen. Abell<sup>29</sup> supported the finding of increased anagen/telogen ratios after 12 months of minoxidil treatment in balding men. However, the main finding was an increase in mean hair diameter, which was evident at 4 months. Other histologic studies also demonstrated an increase in the shaft diameter from 0.029 mm at baseline to 0.043 mm at 12 weeks and 0.042 mm at 24 weeks.<sup>30,31</sup>

Lastly, it is possible that minoxidil plays an immunoregulatory role in the hair follicle. In vitro studies demonstrate that minoxidil had a suppressive effect on normal human T-lymphocytes in vitro.<sup>32</sup> This may explain minoxidil's reported efficacy in treating some patients with AA.<sup>33</sup> This is supported by histologic findings of a reduced perifollicular infiltrate.<sup>34</sup> There is also evidence that minoxidil can selectively inhibit prostacyclin production by cells in culture.<sup>35</sup> Somewhat like aspirin, minoxidil has been found to prevent the aggregation of platelets by causing a reduction in the synthesis of prostaglandin E2 and thromboxane B2.<sup>36</sup> This inhibitory effect on the cyclooxygenase enzyme awaits further study.

Regardless of its exact mechanism of action, there is sound histologic and clinical evidence that minoxidil works. A complete list of proposed mechanisms is provided in Table I.<sup>37</sup>

### Studies showing efficacy and safety

There are inherent difficulties in assessing the efficacy of hair growth treatments. We often rely on subjective assessments either by the patient or by the investigators. Referral to a blinded reviewer is helpful, but that assessment may be skewed depending on differences in photographic quality. Some objective measures are hair count and hair weight.<sup>44</sup> Each of these requires careful documentation and standardization of the site being followed. Investigators

**Table II.** Timeline for FDA approval of Rogaine solutions and foam

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#### FDA approvals of Rogaine (minoxidil) solution

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1979—Oral formulation approved by the FDA for severe hypertension
1988—FDA approval for the 2% solution, with prescription, for hair loss in men with AGA
1992—FDA approval for the 2% solution for hair loss in women
1996—FDA approval for the 2% solution for OTC use in men and women with AGA
1997—FDA approval for the 5% solution for OTC use in men, labeled as "extra strength for men"
2006—FDA approval for the 5% foam for OTC use in men

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Rogaine is a trademark of Pfizer, Inc (New York, NY).

AGA, Androgenetic alopecia; FDA, US Food and Drug Administration; OTC, over the counter.

may use stereotactic equipment or tattoos to mark the areas being monitored.

It took several years for researchers to agree on the best concentration of minoxidil solution. Table II describes the timeline of events as different concentrations came to the market. At first, the 2% solution was thought to be the preferred treatment for male pattern baldness, given its increased clinical efficacy over 0.01%, 0.1%, and 1% solutions. There was not a statistical difference between the 1% and 2% solutions.<sup>45</sup>

### Minoxidil for androgenetic alopecia

Early studies testing low (2-3%) strength solutions of minoxidil for the treatment of AGA were promising.<sup>46,47</sup> A 5-year follow-up for 31 men using 2% or 3% for AGA showed that hair regrowth tended to peak at 1 year, with a slow decline in regrowth, but that nonvellus hair, beyond that seen at baseline, was maintained at 4.5 to 5 years later.<sup>48</sup> The topical use of 2% and 5% minoxidil demonstrated statistically significant increases in hair weights compared with placebo.<sup>49</sup> This study was done in four groups of nine men each (5%, 2%, vehicle alone, and placebo). The increase in hair counts was less significant, suggesting that the benefit is mostly maintaining and thickening preexisting hairs.

Most dermatologists agree that greater hair growth can be achieved with the 5% solution. Indeed, a randomized, placebo controlled trial comparing the efficacy of topical 5% solution with topical 2% and placebo in men demonstrated 45% more hair growth at week 48 in the 5% group compared to the 2% group.<sup>50</sup> Another randomized, placebo controlled trial comparing the efficacy of topical 5% solution with topical 2% and placebo in women

demonstrated statistically significant increased hair growth in both the 5% and 2% group over the placebo group, but not necessarily in the 5% over the 2% group.<sup>51</sup> There was an increased occurrence of pruritus, irritation, and hypertrichosis in the 5% versus the 2% group.

Recently, minoxidil was developed into a 5% foam formula. A randomized, placebo controlled trial of 5% foam showed a statistically significant increase in (1) hair counts and (2) subjective assessment over placebo during a 16-week period of twice daily usage.<sup>52</sup> The 1% solution has recently been proven effective in treating Asian women in a randomized, placebo controlled trial, where there was a statistically significant increase in nonvellus hair counts over placebo.<sup>53</sup>

### **Minoxidil for alopecia areata**

Although minoxidil was first tested in the setting of AA, results showing efficacy have not been sufficient to warrant approval by the FDA. Therefore, it remains an off-label indication. An early case report showed vellus hair growth in two cases of alopecia totalis treated with 1% minoxidil.<sup>54</sup> A larger double-blind, placebo controlled crossover trial demonstrated a cosmetically acceptable response in 16 of 30 patients,<sup>11</sup> where patients with AA responded better than those with alopecia totalis or universalis. The best response rate (80%) with 50% cosmetically acceptable hair regrowth was seen in less extensive alopecia among patients experiencing their first episode of alopecia.<sup>55</sup>

Other studies found limited efficacy in the setting of severe AA.<sup>56,57</sup> Results were unsatisfactory because only soft, vellus hair regrew. This hair was then lost as soon as the drug was discontinued. Early histologic studies demonstrated a reduced perifollicular infiltrate in corresponding patients.<sup>34</sup> One study indicated that minoxidil responders had reduced T-cell infiltration compared with nonresponders.<sup>58</sup> Subsequent studies have shown no significant change in peribulbar or perivascular inflammation.<sup>59,60</sup> Therefore, it is unclear exactly whether or not minoxidil has immunosuppressive effects.

### **Minoxidil after hair transplantation**

Topical minoxidil can be a useful adjunct to hair transplant surgery for AGA. Two uncontrolled studies found that the topical use of minoxidil in perioperative periods could prevent the usual shedding that occurs 1 to 2 weeks after transplantation and speed the time for regrowth from 6 to 8 months to 1 to 2 months.<sup>61,62</sup> These results were confirmed in a double-blind trial, wherein 12 males with AGA used

either 2% minoxidil or placebo for 6 weeks before and 17 weeks after surgery. Again, they found that significantly less grafted hair was lost during the shedding period.<sup>63</sup>

A roundtable consensus of 11 international hair transplant surgeons found that most physicians use minoxidil as their primary medical treatment, both in patients who were and were not candidates for hair transplant surgery.<sup>64</sup> They cited advantages such as stabilizing hair loss, increasing the number of hairs in anagen phase, increasing hair weight and density by enlarging miniaturized suboptimal follicles (also making transplanting easier), and decreasing the postsurgical telogen effluvium. Most agreed that minoxidil should be stopped 2 to 3 days before surgery to minimize skin irritation and to reduce the theoretical risk of intraoperative bleeding caused by vasodilation. They then wait 1 to 2 weeks to allow the epithelium time to heal and restart again. Most found better efficacy with 5% than 2%, and few had any side effects.

### **Minoxidil for chemotherapy-induced alopecia**

Early, uncontrolled studies suggested that minoxidil could not prevent the onset of alopecia resulting from chemotherapy<sup>65,66</sup> but the investigators did not keep patients on the drug long enough to study regrowth after shedding. A randomized, double-blind study of breast cancer patients using 2% topical minoxidil for their entire course of adjuvant chemotherapy and for up to 4 months postchemotherapy showed that minoxidil significantly decreased the duration of alopecia caused by chemotherapy by 50 days.<sup>67</sup> It both delayed the time until maximal hair loss by 10 days and shortened the time before maximal regrowth by 40 days.

### **Minoxidil for traction alopecia**

One case report described how two African American patients, 45 and 54 years of age, respectively, found that their frontal hairlines improved after 3 to 9 months of topical 2% minoxidil.<sup>68</sup> Although other treatments such as intralesional steroid injections are considered first-line treatment, we frequently include topical minoxidil in the treatment of this group, especially when hair loss is still in its early stages.

### **Pharmacokinetics**

Studies on percutaneous absorption found that twice daily application of 1% to 5% topical minoxidil to the bald scalp corresponded to an average systemic dose of 2.4 to 5.4 mg/day.<sup>69</sup> With topical application, the serum concentration of minoxidil rarely exceeds 5 µg/L, and is frequently even below

detectable levels.<sup>31,34,70</sup> In one study, only 7 of 12 AA patients had detectable levels, ranging from 0.4 to 7.5 ng/mL.<sup>71</sup> Another showed that serum concentration was fairly constant at 2, 4, 6, 15, and 24 hours after a single application (averaging 15 ng/mL with 5% minoxidil).<sup>24</sup> The elimination half-life of minoxidil is 3 to 4 hours,<sup>72</sup> suggesting that the medication is cleared 12 to 20 hours after application.

The oral form of minoxidil is metabolized 90% in the liver, mostly by conjugation with glucuronic acid.<sup>72</sup> It is minimally protein-bound and readily excreted by the kidney. After a topical application of radiolabelled 1% to 5% minoxidil daily for 9 days, mean urinary recovery was less than 5% of the administered dose, with no radioactivity found in fecal samples.<sup>69</sup> Unfortunately, discontinuation of the drug does indeed result in the loss of recruited hairs. Four out of 10 men with male pattern baldness on 2% or 3% minoxidil for 4 months had nonvellus hair counts that even fell below baseline levels after stopping the drug.<sup>73</sup>

### Side effects

Although hair growth is the desired outcome of topical minoxidil in the setting of AGA, it can become a nuisance when it occurs in unwanted areas. Hypertrichosis is the most common side effect seen in patients taking oral minoxidil, but it can also occur in patients using the topical formulation. Sufficient systemic absorption, as noted above, may translate to unwanted hair growth elsewhere on the body. In data from a placebo controlled clinical trial involving 1333 females, 50 patients (4%) noted a dose-related (5% > 2% > placebo) side effects of hypertrichosis.<sup>74</sup> Elsewhere, 5 of 56 (8.9% of women) developed severe hypertrichosis of the face and limbs after using topical 5% minoxidil twice daily for AGA. The hair resolved 1 to 3 months after discontinuing the drug.<sup>75</sup> These findings suggest that the amount of minoxidil absorbed is enough to cause remote pharmacological effects, including hair on the arms, chest, and sacral area.

Hypertrichosis is reported more frequently in women than in men. It is unclear whether this is because it is truly more common or just more noticeable. Some women may have hair follicles that are more sensitive to minoxidil and thus should start with the lower strength (2%).<sup>75</sup> Other women with hyperandrogenism may already have hirsutism that is enhanced by minoxidil. Likewise, some women by ethnicity may have hypertrichosis even before starting minoxidil therapy. It is not fair to tell these women that they cannot use minoxidil, but it is wise to use a lower dose and perhaps take a

baseline photograph of their forearms or other areas.

Minoxidil may also cause local cutaneous complications. Rietschel reported two cases of allergic contact dermatitis and four cases of pruritus out of 149 subjects using 2% or 3% minoxidil solutions.<sup>76</sup> While it is infrequent, patients may suffer scalp irritation or the worsening of seborrheic dermatitis. There are many reports of contact dermatitis.<sup>77-83</sup> These were historically thought to be caused by minoxidil itself, but patch testing recently identified propylene glycol (present in minoxidil solution) as the causative agent in 9 of 11 patients, while only 4 of 11 reacted to minoxidil.<sup>84</sup> The substitution of butylene glycol for propylene glycol was well tolerated.

From a practical perspective, it is reasonable to consider such patch testing in patients who cannot tolerate minoxidil solution. Depending on the reaction, they may simply change to the lower 2% dose of minoxidil. Assuming a threshold sensitivity, 5% minoxidil may contain more propylene glycol than does the 2% concentration, so fewer cases of erythema, itching, and dryness may occur with the lower strength. They may also be able to simply switch to the newer Rogaine 5% foam (Pfizer, Inc, New York, NY), which does not contain propylene glycol. Laboratory studies have shown that the new foam version is safe and effective, even without the propylene glycol vehicle.<sup>85,86</sup> However, patients who are allergic to minoxidil itself will not be able to use any formulation, regardless of the vehicle. Application of a small amount of foam to the antecubital fossa, as a "use test," may help determine the patient's sensitivity.

According to the package insert, minoxidil may be harmful if used when pregnant or breastfeeding. It is pregnancy category C. Although a 1-year, prospective study showed no increase in the cardiovascular events or adverse pregnancy outcomes among patients on topical minoxidil versus controls,<sup>87</sup> there have been scattered reports of fetal malformations. Minoxidil crosses biologic barriers and accumulates into lipids, so that brain and fetal concentrations may be higher than those found in serum.<sup>88</sup> Oral minoxidil has been associated with one case of pronounced hypertrichosis of the back and extremities, dysmorphic facial features, partial clinodactyly, cryptorchidism, and omphalocele was reported in the child of a woman who gave birth while on a four-drug regimen (including minoxidil) for the treatment of malignant hypertension.<sup>89</sup> The child's hypertrichosis resolved postpartum. Another woman treated orally had a baby with great vessel transposition and pulmonary valve stenosis, which ultimately did not survive.<sup>90</sup>

Other reports of mothers using topical minoxidil include a fetus born with hypertrichosis<sup>91</sup> and a fetus born with aplasia of the lower body (caudal regression syndrome).<sup>92</sup> One 28-year-old woman used topical 2% solution twice daily throughout pregnancy. At 22 weeks of gestation, ultrasound showed vascular malformations of the brain, heart, and colon, with enlarged ventricles and many hemorrhages in the brain.<sup>93</sup> Staining showed increased CD34 and CD31 immunoreactivity, suggesting a neoangiogenic process. It is difficult to know whether these events were a result of minoxidil or were isolated events, but it is worthwhile to discuss these potential risks with young women of child-bearing age. If planning to become pregnant, they may want to wait until after they have delivered and finished breastfeeding. They also may benefit from a temporary increase in hair growth during pregnancy.

### **Minoxidil and tretinoin**

There is evidence that tretinoin, when combined with minoxidil, may enhance its efficacy. Tretinoin has been found to increase the percutaneous absorption of minoxidil, leading to a 3-fold increase in absorption versus a 1.3-fold increase using vehicle alone.<sup>94</sup> Tretinoin was found to be effective alone, regrowing hair in 58% of 56 patients, and in combination with minoxidil, regrowing hair in 66% of 56 patients.<sup>95</sup> One randomized, double-blind trial in 31 men with AGA compared twice-daily application of 5% minoxidil with once-daily application of a combined solution of 5% minoxidil and .01% tretinoin.<sup>96</sup> This demonstrated equivalent effects, suggesting that for patients not interested in twice-daily application, they could achieve similar effects using this combination.

Again, it is difficult to know exactly how tretinoin exerts its effect in hair growth. Retinoic acid penetrates the nucleus and binds with the cellular retinoic acid-binding protein. This binding induces protein synthesis and cell turnover. In particular, retinoic acid appears to up- and downregulate certain homeobox genes, which influence hair follicle generation, initiation, differentiation, and inhibition.<sup>97</sup> Histologically, retinoids have also been shown to increase blood flow and promote new blood vessel formation.<sup>98</sup> Studies at the molecular level support the role of tretinoin in enhancing hair growth with minoxidil via dual functions: (1) prolonging cell survival by activating the Erk and Akt signaling pathways, and (2) preventing the apoptosis of dermal papilla cells and epithelial cells by increasing the ratio of Bcl-2/Bax and downregulating the expression of P53 and P21.<sup>99</sup>

### **Minoxidil in everyday practice**

In our experience, we recommend once-daily application of minoxidil 5% foam. This increases compliance and also decreases the risk of contact allergy. In women with evidence of hirsutism, we would recommend the 2% formulation and inquire about their medical history. We find minoxidil helpful in the setting of hair transplantation, and recommend it for use in the frontal two-thirds of the scalp and vertex, even though the package insert recommends only the vertex. Photographs and video microscope images are always helpful in documenting hair growth and encouraging your patients to continue with the medicine. We have observed that the more recent the hair loss, the more success patients will have with the medicine. If they have a large number of partially miniaturized follicles, minoxidil will help thicken these existing hairs. More remote hair loss is difficult to reverse. We encourage patients to use the product for at least 6 months, to allow all catagen and telogen hairs to cycle back into the anagen phase. As with any medication, we advise patients that if they stop using the minoxidil, they will stop growing those hairs. We also mention that if they discontinue minoxidil after being on it for several years, they will only lose those hair follicles that they were genetically programmed to lose. Transplanted hairs would not be affected either way.

### **FINASTERIDE**

The relationship of baldness with testosterone levels was observed by Hippocrates, who noticed that young male eunuchs did not develop hair loss.<sup>100</sup> Male pattern baldness also does not occur in men with a genetic deficiency of the second isoenzyme of 5- $\alpha$  reductase.<sup>101</sup> Both types I and II of 5- $\alpha$  reductase convert testosterone to dihydrotestosterone (DHT). Type I predominates in the skin, including the scalp, while type II is present in hair follicles and the prostate.<sup>102</sup> The finasteride molecule (Fig 3) works by inhibiting type II 5- $\alpha$  reductase. This lowers serum and scalp levels of DHT while increasing scalp levels of testosterone<sup>103</sup> (Fig 4). Table III summarizes the effect of finasteride on scalp and serum hormone levels.

These effects on scalp and serum DHT and testosterone levels were demonstrated in 17 patients who underwent scalp biopsy before and after a 28-day treatment with either placebo or finasteride 5 mg daily.<sup>104</sup> At baseline, DHT levels were higher in bald areas of the scalp compared to areas of the scalp that had hair, but there was no difference in testosterone levels. In the bald scalp of patients receiving finasteride, the mean DHT concentration decreased from 6.4 pmol/g at baseline to 3.62

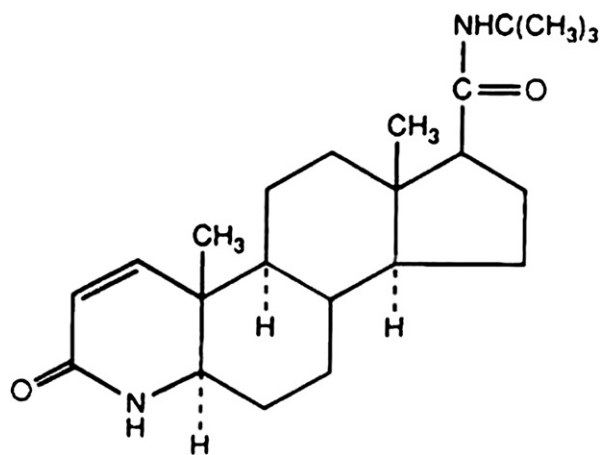


Fig 3. Finasteride molecule.

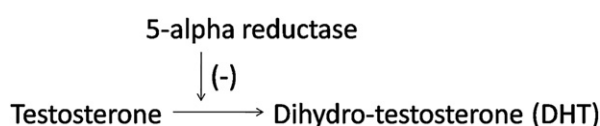


Fig 4. The 5- $\alpha$  reductase enzyme inhibits the conversion of testosterone to dihydrotestosterone.

pmol/g. Scalp testosterone levels increased in 6 of 8 subjects treated with finasteride. Finasteride also decreased the mean serum DHT concentration from 1.36 nmol/L at baseline to 0.46 nmol/L on day 28, but serum testosterone levels were not affected.

In a much larger study, 249 patients were randomized to placebo or finasteride at doses ranging from 0.01 to 5 mg/day, in an effort to understand the lowest possible dose that could affect scalp and serum DHT levels.<sup>105</sup> They found that after 6 weeks, doses as low as 0.2 mg/day could significantly decrease scalp DHT levels by 60% to 75%. The serum testosterone levels were not significantly affected, and in any case have little to do with the balding process. Based on this evidence, investigators next investigated the optimal dosing for AGA, assuming it to be between 0.2 and 1 mg daily.

The optimal dose of finasteride for male AGA has since been identified as 1 mg/day.<sup>106,107</sup> FDA approval for this product was obtained in 1997 under the name Propecia (Merck & Co, Inc, Whitehouse Station, NJ). According to the product information, finasteride is metabolized extensively in the liver, and should be used with caution in patients who have known liver abnormalities. However, no drug interactions of clinical importance have been recognized. It does not appear to affect the cytochrome P450-linked drug metabolizing enzyme. Patients treated with warfarin, digoxin, theophylline,

Table III. Effects of 5- $\alpha$  reductase inhibitors on DHT and testosterone levels<sup>144,105,146,147</sup>

	Finasteride	Dutasteride
Scalp DHT	↓	↓
Scalp testosterone	↑	↑
Serum DHT	↓	↓↓
Serum testosterone	No effect/↑ (dose-dependent)	↑↑

DHT, Dihydrotestosterone.

propranolol, and antipyrine have seen no clinically meaningful interactions.<sup>108,109</sup>

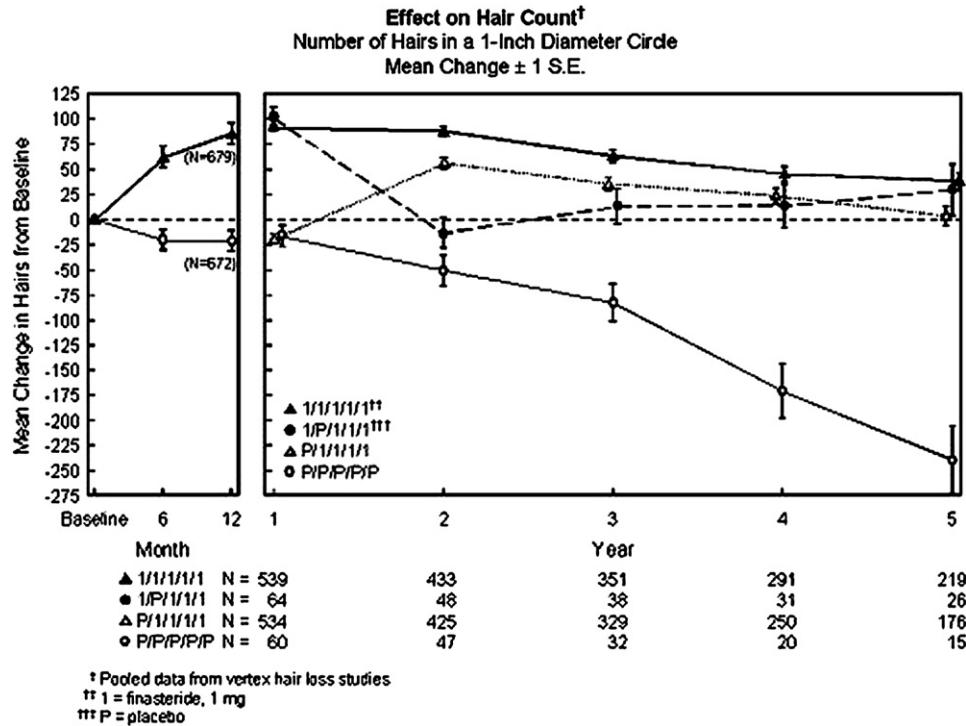
### Efficacy and safety in men

Original studies of oral finasteride focused on measuring hair growth in the vertex area. A randomized trial of 1553 men given either finasteride 1 mg daily or placebo for 1 year with a blinded extension for a second year showed significantly greater hair counts in the balding vertex after 1 year than in patients receiving placebo.<sup>110</sup> Five-year results from this same trial showed that hair growth peaked at 1 to 2 years, but still stayed above baseline for 90% of patients.<sup>108,111</sup> These results are shown in Fig 5. In comparison, the placebo group continued to lose hair.

A randomized, placebo controlled trial using finasteride 1 mg/day in men showed that it also had efficacy in treating anterior and midscalp hair loss.<sup>112</sup> These were supported by previous laboratory studies of finasteride 5 mg given to male and female stump-tailed macaques that showed an increase in hair weights and increase in mean follicle length along the frontal scalp, as shown histologically.<sup>103</sup>

Interestingly, one randomized, double-blind, placebo controlled trial of 9 sets of male twins with AGA demonstrated that the twins receiving oral finasteride 1 mg/day had significantly greater hair growth after 1 year than their perfectly matched controls<sup>113</sup> (Fig 6). Finasteride also is helpful in the setting of hair transplantation. Another randomized, double-blind trial of 79 men with AGA were treated with finasteride 1 mg daily or placebo for 4 weeks before and 48 weeks after hair transplantation demonstrated that the treatment group had significant improvement from baseline, in comparison with placebo.<sup>114</sup>

We understand finasteride's mechanism of action, but it is worthwhile to discuss its actual effect on hair follicles. One study on 212 men with AGA who were randomized to either finasteride 1 mg/day or placebo for 48 weeks demonstrated an increase in the



**Fig 5.** Graph showing the long-term efficacy of finasteride in treating hair loss. (Reproduced from the Propecia package insert<sup>108</sup> with the permission of Merck & Co, Inc).



**Fig 6.** Study of twins. One took finasteride, the other did not. (Reprinted from Stough et al<sup>113</sup> with permission from Editions John Libbey Eurotext, Paris.)

ratio of anagen to telogen hairs.<sup>115</sup> Long-term studies of men with AGA who were given either finasteride 1 mg daily or placebo showed a sustained increase in hair weight, even after 3 to 4 years.<sup>116,117</sup> In both studies, the hair weight increased more than the hair count, suggesting that finasteride was better at increasing the growth rate (length) and thickness of hair. At 192 weeks, finasteride showed a 21.6% increase from baseline, whereas the placebo group had a 24.5% decrease from baseline. Also at 192 weeks, the finasteride group had a 7.2% increase in hair count from baseline compared to a 13.0% decrease from baseline among the placebo group.

### Efficacy and safety in women

Finasteride is pregnancy category X. It is contraindicated for use in females of childbearing age unless they are using strict birth control measures. This is because if they became pregnant, the finasteride might cause the feminization of a male fetus. Women are instructed to not even handle crushed or broken pills given this potential risk. Finasteride has not been studied for use in children. However, men may continue to use the medication even if their wife becomes pregnant.

Besides this risk of birth defects, studies have not shown that it is effective in treating female pattern hair loss. In a 1-year, double-blind, placebo controlled trial, 137 postmenopausal women received either finasteride 1 mg/day or placebo.<sup>118</sup> Patient, investigator, and histologic analyses all failed to show any improvement in slowing hair thinning, increasing growth, or improving the appearance of hair in the finasteride-treated group.

Finasteride was found to benefit four women with hyperandrogenism.<sup>119</sup> These results remind us that not all types of female hair loss have the same underlying cause. Hair specialists agree that there is a need to do larger, more well controlled trials investigating the use of finasteride in this subset of women.<sup>120</sup> They suggested using three study groups: finasteride plus oral contraceptive pills (OCPs; to

protect against development of genital anomalies in male fetuses), OCP alone (to control for the inherent antiandrogen effects of OCP), and placebo. No such study has yet been performed.

One group in Italy did demonstrate increased hair growth in 23 of 27 premenopausal women who were given finasteride 2.5 mg in combination with an OCP containing both drospirenone and ethinyl estradiol.<sup>121</sup> The patients were normoandrogenic. These results are promising, but are confounded by the antiandrogenic effects of the birth control and the increased dosage of finasteride (2.5 vs 1 mg). Other normoandrogenic women have also benefited from increased doses of oral finasteride (5 mg).<sup>122</sup> One interesting theory is that some women may have excessive activity of the 5- $\alpha$  reductase enzyme. This explains why they would not benefit from systemic antiandrogen treatments but would benefit from finasteride.

### Effects on prostate-specific antigen levels

Patients taking finasteride will see their prostate-specific antigen (PSA) score decrease by approximately 50%.<sup>123</sup> This was discovered in a study of 355 men between the ages of 40 and 60 years who were stratified by age group and randomized in a ratio of 4:1 to finasteride 1 mg/day or placebo. Patients 40 to 49 years of age had a median decrease in serum PSA of 40%, and patients 50 to 60 years of age had a median decrease of 50%. This is consistent with the existing recommendation for adjustment of PSA in men taking finasteride 5 mg/day (Proscar; Merck & Co, Inc), who are instructed to double their PSA to gauge the correct value.

Being on finasteride also increases the sensitivity of PSA as a screening tool. In one large study, the area under the curve of PSA was greater in the finasteride group than for the placebo group.<sup>124</sup> This should contribute to better detection of all grades of prostate cancer in patients taking finasteride.

### Risks of prostate cancer

Much work has been done to investigate whether finasteride affects the rate and grade of prostate cancer. The Prostate Cancer Prevention Trial (PCPT), which followed 18,882 men 55 years of age and older for 7 years demonstrated that patients taking finasteride 5 mg/day had a 24.8% relative reduction in the prevalence of prostate cancer compared with those taking placebo.<sup>125</sup> However, tumors with higher Gleason scores (7-10) were more frequent in the finasteride-treated group (37% vs 22% of tumors;  $P < .01$ ). Although this trial was done in patients much older than the men who usually take finasteride, the results are noteworthy. The worrisome finding of increased

Gleason score has limited its use as a chemopreventive agent.<sup>126</sup>

Recent work has shown that finasteride does not induce histomorphologic changes in prostatic carcinoma.<sup>127</sup> Blinded pathologists could not distinguish histopathologic differences between carcinoma in the finasteride and placebo arms. Similar histologic findings have been seen in tissue following androgen deprivation therapy.<sup>128</sup> There may be a loss of luminal glandular spaces (luminal collapse) and the creation of single-cell infiltrates, which simulate high-grade cancer.<sup>129</sup>

Mathematical models have examined the role of detection bias as an explanation for the increased number of high-grade cancers.<sup>130</sup> Because finasteride reduces prostate volume, the relative size of a core biopsy increases. This can increase the sensitivity of the biopsy and increase the likelihood of finding high-grade disease. Serfling et al<sup>131</sup> showed that a decrease of 25% in prostate volume (as occurs after finasteride treatment) can increase cancer detection by 23%.

Indeed, Kulkarni et al<sup>132</sup> found a greater occurrence of high-grade cancer on biopsy among men with smaller prostates, but an equivalent occurrence of high-grade disease in radical prostatectomy specimens. Taken together, these studies provide reassurance that we are not placing our patients in danger by prescribing finasteride.<sup>133</sup> We believe that it is neither a promoter nor preventer of prostate cancer.

### Effects on sperm

At present, there is little evidence that finasteride has a negative effect on sperm count or morphology. The longest double-blind, placebo controlled study of 181 men with AGA, randomized to receive either finasteride 1 mg or placebo for 48 weeks, found no significant effects on sperm concentration, total sperm per ejaculate, sperm motility, or sperm morphology.<sup>134</sup> The authors conclude that testosterone—and not DHT—is the primary androgen regulating spermatogenesis, sperm maturation, and seminal fluid production in the testis, epididymis, and seminal vesicle. One recent study did find a significant drop in sperm count by 34% after 26 weeks of once-daily finasteride 5 mg, but the change became smaller and then was insignificant by week 52 and again on the 24-week follow-up. There were no effects on sperm morphology.<sup>135</sup>

One very small study recruited three men who had been on finasteride 1 mg/day for 5 years for sperm analysis. Using a transmission electron microscope, researchers found altered sperm morphology consistent with necrosis.<sup>136</sup> One of these patients

was azoospermic, and two showed normal sperm concentration but with severely reduced motility. After 1 year off of medication, the tests were repeated and found a recovery of the spermatogenic process.

There have also been two case reports of severe azoospermia resulting in impaired fertility.<sup>137</sup> Such reports remind us to inquire whether the man and his partner are having difficulty getting pregnant. Stopping finasteride in these situations may improve semen parameters and help the couple avoid more invasive fertility treatments.

### Side effects

Besides the above-mentioned risk of feminization of a male fetus, there have been scattered reports of sexual side effects. Approximately 1 in 50 males (2%) reported one or more sexual side effects during finasteride (decreased libido, erectile dysfunction, or ejaculation disorder), compared with 1% in the placebo group.<sup>108,138</sup> Gynecomastia and other breast disorders, such as mastalgia, were reported in 0.4% of patients, and did not occur until later in the treatment period. More unusual side effects were exfoliative dermatitis, perioral numbness, and swollen glands, all of which resolved with drug cessation and returned with rechallenge.

Mondaini et al<sup>139</sup> describes a “nocebo” phenomenon as when an adverse side effect is not a direct result of the pharmacologic action of the drug but rather of the patient knowing that it is a side effect. They tested this hypothesis in 120 patients on finasteride for benign prostatic hypertrophy (BPH) who were randomly assigned to groups that were informed or not informed of the side effects. After 6 and 12 months, the informed group reported a significantly higher incidence (43%) of sexual side effects than did the uninformed group (15%).<sup>139</sup> While these results do not mean that we can intentionally withhold information from our patients, they do suggest that the sexual side effects can sometimes have a psychological, rather than a pharmacologic, cause.

Isolated reports of depression have also occurred in patients taking finasteride.<sup>140,141</sup> This adverse effect still needs further investigation, but it is something to consider in patients with a known history of severe depression.

### Finasteride every day

Finasteride is an excellent option for male patients experiencing AGA, either alone or as an adjunct to topical minoxidil. It successfully halts hair loss or regrows hair in 9 out of 10 patients. In our experience, it may also benefit women who are postmenopausal or have signs of hyperandrogenism. It can

be taken any time of day, with or without food. There are no known drug interactions or allergies that have been reported. Although the package insert cautions use in patients with liver abnormalities, we do not routinely perform liver function tests. A conservative approach might be to ask about history of hepatitis or other liver abnormalities.

The Propecia package insert<sup>108</sup> instructs patients to allow 3 months to see results, but we instruct them to wait at least 6 to 9 months. It comes as a “Propak,” including 90 tablets, and we provide patients with three refills to last an entire year. There is some debate about using the 5-mg dose (Proscar), which is indicated for BPH. Although we do not advocate its use, some patients find it a less expensive option, and break the tablets into quarters, taking one quarter of one pill daily.

### DUTASTERIDE

Dutasteride (Fig 7) shares important characteristics with finasteride. While finasteride inhibits type II 5- $\alpha$  reductase, dutasteride inhibits both types I and II 5- $\alpha$  reductase isoenzymes.<sup>142</sup> There is no isolated genetic deficiency of type I 5- $\alpha$  reductase to assess its role in male pattern hair loss. However, there is evidence that dutasteride is three times as potent as finasteride at inhibiting type II 5- $\alpha$  reductase and more than 100 times as potent at inhibiting the type I enzyme.<sup>143</sup> This suggests enhanced efficacy over the existing finasteride.

Because of these increased effects on the 5- $\alpha$  reductase enzymes, scalp and serum levels of DHT are more affected. Dutasteride can decrease serum DHT by more than 90%,<sup>143,144</sup> while finasteride decreases serum DHT by 70%.<sup>104</sup> One 4-year study of men on dutasteride 0.5 mg continuously for BPH showed a near complete suppression of serum DHT, decreasing by a mean of 93% from baseline.<sup>145</sup> In comparison with dutasteride, finasteride reportedly reduces scalp DHT by only 34%<sup>104</sup> to 41%.<sup>146</sup>

As with finasteride, inhibition of the 5- $\alpha$  reductase enzyme can increase levels of testosterone locally in the scalp. However, the increased efficacy means that it can also increase testosterone levels in the serum. The 4-year study above noted that serum testosterone rose by 25% from 3951.9 pg/mL to 4767.0 pg/mL.<sup>145</sup> Minimal dose-dependent effects on serum testosterone have been described for finasteride. An overview of these effects is provided earlier in Table III.

### Efficacy

Dutasteride was approved by the FDA in October 2002 for the treatment of symptomatic BPH at dosage of 0.5 mg daily. It is manufactured by GlaxoSmithKline

(New York, NY), and comes in soft gelatin capsules under the trade name Avodart. So far, few studies have been done to assess its efficacy in the setting of hair growth. Phase II trials in 416 men showed that dutasteride increased scalp hair growth in a dose-dependent fashion ( $0.05 < 0.1 < 0.5 < 2.5$ ), and that the dutasteride 2.5 mg group was superior to the finasteride 5 mg group at both 12 and 24 weeks in increasing target hair growths.<sup>146</sup>

One very interesting case report describes a 46-year-old woman who had only limited improvement from finasteride who was placed on dutasteride and an OCP. After 6 months of 0.5 mg daily, she had significant thickening of hair shafts, as noted on dermatoscopy. By 9 months, the clinical diagnosis of AGA could no longer be made.<sup>147</sup>

Another study in 17 sets of male twins with AGA showed that after 1 year of dutasteride 0.5 mg daily, the treatment group had significantly more hair regrowth than did the placebo group.<sup>148</sup> Nonetheless, phase III FDA trials appear to be on hold for using dutasteride to treat male pattern hair loss. It is unclear exactly why, but we hypothesize it is because of concerns about side effects (see below).

### Effects on the prostate

As with finasteride, PSA levels should be approximately doubled in order to gauge the true value.<sup>144</sup>

Type I 5- $\alpha$  reductase enzyme is present in benignly hypertrophied prostate tissues in lower quantities, but it predominates in prostate cancer cell lines and seems to be overexpressed in some prostate cancers.<sup>149,150</sup> Given that finasteride has been shown to lower the risk of prostate cancer, there was proof of principle that hormonal agents like 5- $\alpha$  reductase inhibitors could have a chemopreventive effect. Given this increased expression of the type I isoenzyme, researchers hypothesized that dutasteride may have even greater chemopreventive effects than finasteride in the setting of prostate cancer.<sup>151</sup>

Thus far, the results are promising. In one pilot study, dutasteride 0.5 mg versus placebo was given to 46 men for 6 to 10 weeks before radical prostatectomy and showed increased apoptosis compared to placebo.<sup>152</sup> Patients from three placebo controlled trials (ARIA 3001, ARIA 3002, and ARIA 3003) were secondarily analyzed for prostate cancer development.<sup>153</sup> The cumulative incidence of prostate cancer was significantly lower in the dutasteride group than in the placebo group at 24 months.

Two other studies are ongoing. The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial has enrolled 8000 men in a 4-year, international multicenter study randomizing patients to dutasteride

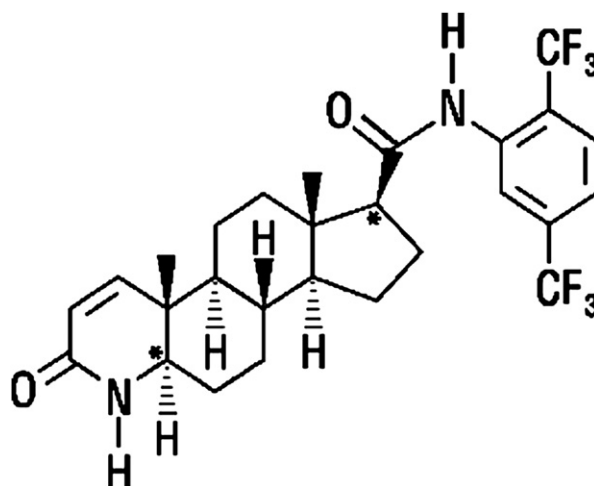


Fig 7. Dutasteride molecule.

0.5 mg or placebo. The primary endpoint will be biopsy-detectable prostate cancer at 2 and 4 years of treatment, including Gleason score analysis.<sup>154,155</sup> Another large study, called the Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial, is enrolling 300 men with low-grade prostate cancer to undergo treatment with dutasteride 0.5 mg/day or placebo for 3 years, to assess whether dutasteride can decrease the time to prostate cancer progression.<sup>156</sup> Patients will be assessed by serial biopsies and PSA scores, and the results will be available in 2010.

### Side effects

As with finasteride, women who are pregnant or thinking of becoming pregnant should not consume or handle this medication because of the potential feminizing effects on a male fetus. One study noted a decreased libido in two of 70 patients for both the 0.05- and 0.1-mg dutasteride groups, and nine of 71 patients treated with dutasteride 2.5 mg for 24 weeks. This compared with three out of 70 patients treated with finasteride subjects and two of 64 placebo patients.<sup>146</sup> Impotence occurred in only two patients taking dutasteride 0.05 mg, one patient taking finasteride 5 mg, and three members of the placebo group. Gynecomastia developed in only one patient in the placebo group.

There have been no effects demonstrated on bone density or lipid profiles in patients randomized to dutasteride 0.5 mg, finasteride 5 mg, or placebo for 52 weeks.<sup>157</sup> This same trial, which lasted for 1 year, showed no significant differences in the incidences of the most common adverse effects. The only side effects that occurred in more than 2% of patients were impotence, occurring in 8% (69/817 on

finasteride 5 mg, vs 7% or 55/813 on dutasteride) and decreased libido (6% or 46/817 on finasteride and 5% or 39/813 on dutasteride).

No adjustment is needed for renal or hepatic impairment. However, there is evidence that dutasteride is processed by the CYP3A4 enzymes. It may affect the clearance of other potent CYP3A4 inhibitors, such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, ciprofloxacin, and troleandomycin. Other medications, such as warfarin, diazepam, and phenytoin, do not create any drug interactions with dutasteride. Men being treated with dutasteride should not donate blood until they have been off of the medication for at least 6 months. This prevents administration of the medicine to a pregnant female transfusion recipient.<sup>158</sup>

### Effects on spermatogenesis

The half-life of dutasteride is 5 weeks, compared with 6 to 8 hours for finasteride. This suggests that the effects are longer lasting (several months) and more difficult to reverse. In a double-blind, placebo controlled trial of men given dutasteride 0.5 mg daily or placebo, there were significant decreases from baseline in sperm count: by 28.6% at 26 weeks, by 24.9% at 52 weeks, and by 23.3% 24 weeks after the trial ended.<sup>135</sup> Semen volume was decreased by a corresponding amount. There was also significant reduction in sperm motility during treatment with dutasteride and at the 24-week follow-up. However, no significant changes were observed in sperm morphology.

### Dutasteride every day?

As noted above, most of the work so far has been aimed at using it for benign prostatic hypertrophy or prostate cancer prevention. It has not yet been approved by the FDA for the treatment of hair loss, and phase III trials for the indication of hair loss were put on hold. For these reason, we are hesitant to use it freely in our practice. The increased half-life over finasteride means that while not permanent, the effects on sexual function or spermatogenesis are potentially more severe and long-lasting (ie, weeks not days). In the meantime, some physicians simply use the drug off-label at doses of 0.5 mg daily for 2 weeks (loading) then 0.5 mg twice weekly thereafter.

### Other antiandrogen therapies

Some women with hair loss have a spectrum of other symptoms, including hirsutism, irregular periods, and acne. It is important to look for these signs. Patients who are of normal weight and pluck, shave, or bleach any unwanted hair will be harder to

recognize. Such patients may also suffer from polycystic ovary syndrome. They may also suffer from androgen-producing tumors of the ovaries or adrenal glands or congenital adrenal hyperplasia. It is important to first ask patients whether they have had laboratory tests for changes in their hormone levels. If not, one may consider referral to an endocrinologist to understand the subtle changes. Many other laboratory studies may be performed, such as a thyroid panel and iron studies, but they are beyond the scope of this discussion.

Sinclair<sup>159</sup> investigated the treatment of female pattern hair loss with oral antiandrogens. In an open-label study, spironolactone 200 mg/day was administered to 40 women and cyproterone acetate to another 40 women. The results showed no significant difference between the two groups, so the results were combined. Overall, 44% of women (35/80) had hair regrowth, 44% (35/80) had no clear change, and 10 women (12%) had continuing hair loss. Logistic regression found no predictors of response among such factors as patient age, menopause status, serum ferritin, serum hormone levels, severity of hair loss, or histologic parameters.

In another study, cyproterone acetate was compared to minoxidil to assess its efficacy in the treatment of female pattern hair loss. A trial of 66 women were randomized to take cyproterone acetate 52 mg daily plus an ethinyl estradiol contraceptive or to apply minoxidil 2% twice daily plus a combined OCP.<sup>160</sup> The results showed a mean increase in hair growth for minoxidil group and mean decrease for the cyproterone group. However, they believed that the minoxidil worked better in patients without signs of hyperandrogenism, and that cyproterone worked better in patients who did have those signs.

These results are promising, but must be further investigated in larger, controlled studies.

It is unlikely that either spironolactone or cyproterone acetate will ever show more efficacy than minoxidil, which is the current standard of treatment for hair loss in women. In the event that spironolactone is used, recall that it is pregnancy category D. Patients should ideally be on birth control, and they should be reminded that the drug may elevate potassium levels. Flutamide is another medication that has been used to treat hirsutism, but so far there is little evidence to show its effect in regrowing hair.

### KETOCONAZOLE

Ketoconazole is an imidazole antifungal which has been found to be effective in the treatment of seborrheic dermatitis. One open-label study of

**Table IV.** Supplements and over the counter products for hair growth

Product	Mechanism of action	Reported efficacy
Saw palmetto ( <i>Serenoa repens</i> )	Inhibits 5- $\alpha$ reductase conversion of testosterone to DHT in the prostate <sup>179</sup> ; helpful in mild to moderate BPH symptoms <sup>180</sup> but not helpful in moderate to severe BPH <sup>181</sup>	One randomized, double-blind, placebo controlled trial demonstrated increased hair growth in 6/10 men with mild to moderate AGA <sup>182</sup>
Biotin (vitamin H or B7)	Can help treat onychoschizia, increasing thickness of nails by 25% <sup>183</sup>	No clinical trials showing efficacy treating hair loss; in vitro studies show no influence of biotin on cultured human follicular keratinocytes <sup>184</sup>
Nioxin scalp therapy and treatments	Claims to "actively remove" excess sebum containing DHT, the most frequent cause of hair loss <sup>185</sup> ; does not claim to block DHT	Not approved by the FDA, no clinical trials
Procerin tablets and topical serum	Proprietary blend of herbal, vitamin, and mineral components which "naturally block" DHT levels <sup>186</sup>	Not approved by the FDA, no clinical trials
Tricomin shampoos and treatments (triamino copper nutritional complex)	Targets delivery of copper to the base of the hair follicle <sup>187</sup>	Ex vivo studies support the use of tripeptide-copper complexes to promote the growth of human hair follicles <sup>188,189</sup> ; no clinical trials to date
Toppik (camouflage)	Keratin-based fibers which adhere to scalp and existing hairs; helps thicken the appearance of existing hairs and camouflage balding areas on the scalp; no claims to increase hair growth <sup>190</sup>	Well-liked by patients for its easy application while awaiting new hair growth
Wigs and hairpieces	Can cover the entire area of hair loss, with no chemical side effects	Useful when patients desire greater density than can be achieved with medications and/or surgery alone

Nioxin is a trademark of Nioxin Research Laboratories (Lithia Springs, GA).

Procerin is a trademark of Speedwinds Nutrition, Inc (Portland, OR).

Tricomin is a trademark of PhotoMedex, Inc (Montgomeryville, PA).

Toppik is a trademark of Spencer Forrest, Inc (Westport, CT).

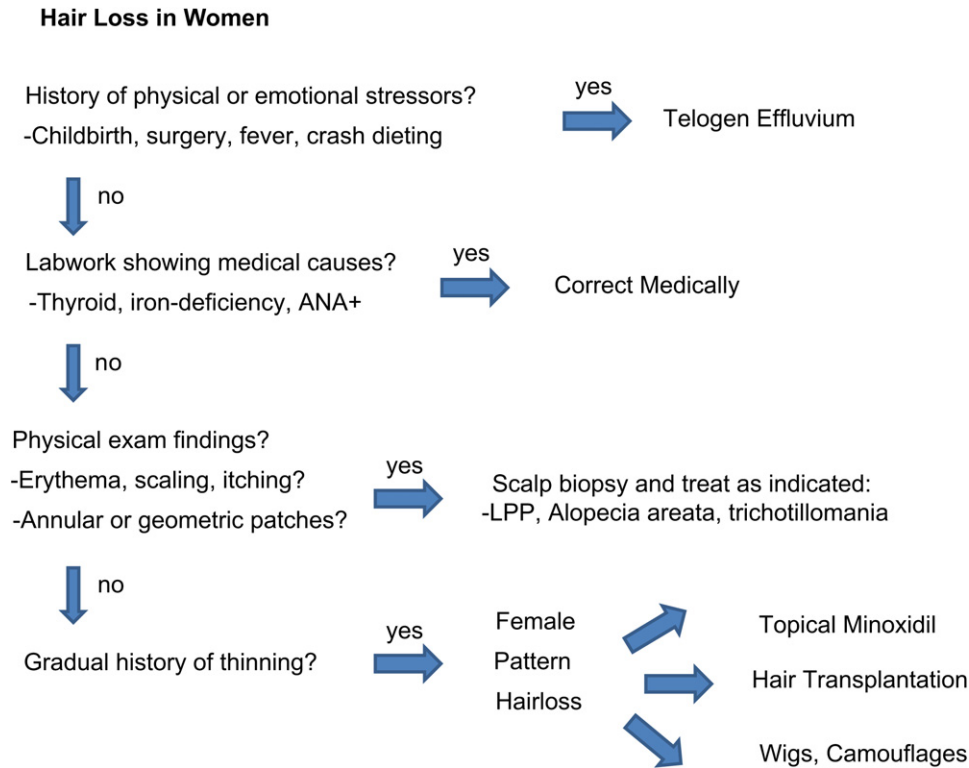
AGA, Androgenetic alopecia; BPH, benign prostatic hypertrophy; DHT, dihydrotestosterone; FDA, US Food and Drug Administration.

minoxidil 2% with ketoconazole 2% shampoo for AGA in men showed comparable growth in both groups, with both achieving better growth than unmedicated shampoo alone.<sup>161</sup> These results were also shown in mouse models, showing macroscopically noticeable effects in the group treated with topical ketoconazole 2% versus the placebo group.<sup>162</sup> Large, controlled studies are needed to further investigate and confirm these reports.

It is unclear exactly how this antifungal shampoo helps with hair growth. Its antiinflammatory properties have been well documented.<sup>163,164</sup> This may have to do with a reduction in *Malassezia* colonization of the skin. Some hypothesize that ketoconazole plays a role in local disruption of the DHT pathway. They suggest that when used in conjunction with finasteride, it may help achieve more complete

reduction of DHT.<sup>165,166</sup> This androgen-inhibiting mechanism may explain the side effect of gynecomastia seen in some patients taking oral ketoconazole.<sup>167</sup>

The oral administration of ketoconazole for AGA is limited by its inhibition of the biosynthesis of adrenal glucocorticoids. The drug inhibits cytochrome P-450 enzymes involved in steroid hormone biosynthesis, ultimately reducing the production of both glucocorticoids and androgenic steroids.<sup>168</sup> It also has been used for hirsutism with some success. In one study, 16 hirsute women were treated with 400 mg/day for 3 months, resulting in significant decreases in dehydroepiandrosterone sulfate, androstenedione, and testosterone. Eleven of 16 patients had improvement in their hirsutism on the Ferriman-Gallway score.<sup>169</sup>



**Fig 8.** Flow chart for the diagnosis and treatment of female pattern hair loss.

Although ketoconazole may not be the most effective tool for hair loss, it is an important addition to our toolkit. We find it helpful in patients who have coexistent evidence of seborrheic dermatitis, lichen planopilaris, or sebopsoriasis. By first addressing the flaking and inflammation, it may also address a secondary hair thinning or loss. Likewise, hyperandrogenic women with thinning hair may benefit from ketoconazole's antiandrogenic effects.

### LOW-LEVEL LIGHT THERAPY

A number of products using low-energy laser light beams have been marketed for hair growth. They are available without a prescription and are usually sold directly over the Internet or through late-night infomercials. Most are packaged like a hairbrush or comb which shines red light directly on the scalp while it is used to comb through the hair. Only one such device, called the HairMax LaserComb (Lexington International, LLC, Boca Raton, FL), has obtained 510K FDA approval for use as a medical device. We explain to patients that the 510K status simply demonstrates safety rather than actual efficacy.

The earliest evidence that low-level light therapy (LLLT) could help with hair growth was provided by Hungarian researcher Mester in 1967.<sup>170</sup> He found

that by shining a low-powered ruby red laser (694 nm) on the backs of shaved mice, he could increase their hair growth. This was the origin of biostimulation, using "cold laser" or "soft laser" therapy administered at lower powers of 1 to 500 milliwatts. Since then, basic research has demonstrated that LLLT can improve wound healing, reduce inflammation, and reduce the symptoms of stroke.<sup>171-173</sup> Nonetheless, its mechanism of action is not yet known. Some have proposed that LLLT can enhance the local production of adenosine triphosphate by mitochondria. Indeed, there is evidence that it increases the activity of complexes II and IV in the mitochondrial respiratory transport chain.<sup>174-176</sup> We are not sure exactly how this translates to thickening or promoting hair growth.

There is a paucity of research demonstrating whether these devices are actually effective in treating hair loss. It would seem that the manufacturers have, in their eagerness to make the products available, forgotten to first convince the scientific community. Only one study has been published, in a nonindexed journal, showing its efficacy in treating and maintaining transplanted hair.<sup>177</sup> We frequently discuss LLLT as a safe option for patients unable to use any of the medications described above, either alone or as an adjunct to hair transplant surgery. We make sure to stress the lack of independent,

large-scale clinical trials documenting its efficacy. Many physicians specializing in hair agree that more studies are needed to examine its role in treating hair loss.<sup>178</sup>

### Other vitamins, supplements, and products

In addition to LLLT, many other products are marketed directly to consumers with claims of regrowing or thickening hair. Your patients may already be using them, and they may ask you about their efficacy. Several of these products are listed in Table IV, with their reported effect on the scalp and/or hair follicle. We do not routinely recommend any of them. Although they may not hurt, we remind our patients that the best evidence lies in treatments described above. Moderation of any product is best, especially given the lack of regulation in the vitamin and supplement industry.

### HAIR TRANSPLANTATION

Not all treatments work for all people. Hair transplant surgery remains an important option for patients who do not have success with—or interest in—the aforementioned medical therapies. The present authors specialize in this area. This technique takes advantage of the fact that hair in the posterior scalp grows for much longer than other areas of the scalp. Under local anesthesia, in an outpatient procedure, we harvest an elliptical strip from this donor region, and divide the strip into individual hair follicles. Then, we numb the area to be transplanted and create hundreds of nicks where the transplanted hairs will be placed. With a team of two to four assistants, we move the hair efficiently into the new sites. The grafts heal in overnight, and over the next 6 to 8 months these new hairs will grow and help reframe the patient's face and renew their self-confidence.

### WIGS, HAIRPIECES, AND CAMOUFLAGES

Finally, some patients may choose to use wigs or hairpieces to achieve ideal coverage. These are useful for patients who cannot achieve sufficient density with either medications and/or surgery alone. There are no medical side effects and patients can freely change their style as they wish. Various hair salons and businesses can help patients achieve very natural-looking results using either synthetic or natural hair fibers. Patients may also use various topical sprays or powders to camouflage the areas of thinning scalp.

### CONCLUSION

With all of the options for treating hair loss, it is not surprising that patients frequently feel

overwhelmed and confused. As dermatologists, we can help them sort out the data and decide which options are best for them. Personal preferences may play an important role in determining the best treatment option. Minoxidil and finasteride remain our best agents in handling hair loss. If patients are willing, we encourage them to use both. We find this to be the most effective clinical practice, and it is supported by the literature.<sup>191,192</sup> However, depending on the patient's lifestyle or budget, it may be difficult to use both for an extended period of time. We recommend at least a 6-month overlap when transitioning from one to the other, so that the hairs that are thickened or regrown with one treatment are not abruptly lost. Even then, there is no guarantee that patients will not experience a telogen effluvium when switching from one treatment to another.<sup>193</sup>

It is also important to consider and allow for the differences in the treatment of male and female pattern hair loss. Most men are aware of their diagnosis and may have a notable family history. Their examination is often straightforward. However, many women have no family history, and require a considerable history and physical examination in order to diagnose female pattern hair loss. Fig 8 provides a simple flow chart to help identify and treat women with this condition.

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Many Academy members were dismayed by the decision by the AMA to limit to 1 the number of Category 1 credits associated with journal CME articles. The Academy's Department of Education has disagreed with this mandate and has lobbied vigorously, albeit unsuccessfully, to overturn it. However, we now have a potential solution. This solution would involve posting the journal CME article and exam online as an enduring material. The amount of CME credit would be commensurate with the time necessary to read the article and complete the exam. Although the CME article would still appear in the journal, no exam would appear with it and thus no credit would be offered for those not accessing the online version.

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