
Androgens in women



Hormone-modulating therapies for skin disease

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Learning objectives

After completing this learning activity, participants should be able to list, categorize, and explain the mechanisms of action, safety considerations, and contraindications of these androgen-modulating therapies; identify the hormone-modulating therapies used to treat acne, hirsutism, and androgenetic alopecia; and describe the evidence to support the efficacy of these therapies in the treatment of acne, hirsutism, and androgenetic alopecia.

Disclosures

Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors

The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). Dr Shapiro is a stockholder in Replixel Life Sciences and has been a consultant for Aclaris, Samumed, Incyte, Bioniz, keeps.com, Applied Biology, and Pfizer.

Planners

The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Androgen-mediated cutaneous disorders (AMCDs) in women, including acne, hirsutism, and female pattern hair loss, can be treated with hormone-modulating therapies. In the second article in this Continuing Medical Education series, we discuss the hormone-modulating therapies available to dermatologists for the treatment of AMCDs, including combined oral contraceptives, spironolactone, finasteride, dutasteride, and flutamide. Available hormone-modulating treatments used for each AMCDs are reviewed, along with mechanisms of androgen modulation, safety profile, contraindications, monitoring parameters, and evidence of efficacy. Medications discussed include those that are approved by the US Food and Drug Administration for certain AMCDs and some that are used off-label. Despite the ubiquity of hormone-modulating therapies used for AMCDs, this review highlights the need for more rigorous studies to evaluate these therapies for acne, hirsutism, and female pattern hair loss. (*J Am Acad Dermatol* 2019;80:1509-21.)

Key words: acne; androgenetic alopecia; androgen receptor; androgens; combined oral contraceptive; congenital adrenal hyperplasia; dutasteride; female pattern hair loss; finasteride; flutamide; hirsutism; polycystic ovary syndrome; spironolactone.

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Funding sources: None.

Dr Shapiro is a stockholder in Replixel Life Sciences and has been a consultant for Aclaris, Samumed, Incyte, Bioniz, keeps.com, Applied Biology, and Pfizer.

Accepted for publication August 22, 2018.

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0190-9622

Published by Elsevier on behalf of the American Academy of Dermatology, Inc.

<https://doi.org/10.1016/j.jaad.2018.08.061>

Date of release: June 2019

Expiration date: June 2022



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ANDROGEN-MODULATING THERAPIES USED IN DERMATOLOGY

Combined oral contraceptives

Key points

- **Combined oral contraceptives contain estrogen and progestin, although the progestin component varies**
- **While androgenic potential varies among progestins, the net effect of combined oral contraceptives is antiandrogenic**
- **Combined oral contraceptive use is associated with an increased risk of venous thromboembolism, pulmonary embolism, myocardial infarction, stroke, and some cancers**

Combined oral contraceptive (COC) pills, containing estrogen and progestin, suppress ovulation and prevent pregnancy. The estrogen most commonly used is ethinyl estradiol, while the progestin component varies. There are 2 categories of progestins: testosterone derivatives (ie, norethindrone, levonorgestrel, and norgestimate) and androgen receptor antagonists (ie, cyproterone acetate and drospirenone). Cyproterone acetate, used internationally, is not approved in the United States. Four COCs have received approval by the US Food and Drug Administration (FDA) for the treatment of acne in women who also want contraception, but, in practice, COCs are often prescribed solely for their androgen-modulating effects.

Estrogen's inhibition of ovarian and adrenal androgen production is dose-related.¹ Estrogen also promotes synthesis of sex hormone-binding globulin (SHBG) in a dose-related manner, thereby reducing circulating free testosterone and subsequent activation of androgen receptors.^{2,3} In addition, estrogen inhibits 5 α -reductase, decreasing peripheral conversion of testosterone to the more potent androgen dihydrotestosterone (DHT).⁴

Although endogenous progesterone decreases ovarian androgen production, some synthetic progestins have androgenic potential.⁵ First- and second-generation testosterone-derived progestones (estrans and gonanes, respectively) have more androgenic activity^{6,7} than third-generation testosterone-derived progestones (ie, norgestimate, desogestrel, and gestodene).^{4,5,7,8} Drospirenone, an antiandrogenic progesterone derived from 17 α -spironolactone, has a pharmacologic and biochemical profile that is more similar to endogenous progesterones.^{9,10} Cyproterone acetate, derived from 17 α -hydroxyprogesterone, is a potent antiandrogen.¹¹ Despite the greater androgenic potential of early generation testosterone-derived synthetic progestones, evidence suggests that the

net effect of all COCs, regardless of the progesterone component, is antiandrogenic.^{2,12}

There are several safety considerations with COCs, including an increased risk of venous thromboembolism (VTE) and pulmonary embolism. A Cochrane meta-analysis demonstrated that COCs increase the risk of VTE fourfold.¹³ COCs containing >30 μ g of ethinyl estradiol, a third-generation progesterone, or drospirenone conferred a higher increased risk of VTE than COCs containing low-dose ethinyl estradiol or a second-generation progesterone.¹³ Although there is an increased relative risk of VTE with COCs, the baseline risk in nonpregnant women who are not taking COCs is low (1-5 per 10,000 woman-years),² so the overall absolute risk remains negligible. In addition, the risk of VTE with COC use is lower than the risk of VTE in pregnant or 12-week postpartum women.^{2,5} COCs are also associated with an estrogen dose-dependent increased risk of myocardial infarction (MI) and ischemic stroke.¹⁴ The risk, however, is negligible in nonsmoking, normotensive women who are taking COCs.¹⁵ Although age is an independent risk factor for MI and stroke, COCs are still safe in healthy, nonsmoking women >35 years of age according to the American College of Obstetricians and Gynecologists.¹⁶

The association of COCs with malignancy is controversial. Women with a history of COC use have a higher incidence of breast cancer (odds ratio [OR] 1.08; 95% confidence interval [CI] 1.003-1.165), with more recent use conferring a higher risk.¹⁷ In women with human papillomavirus, COC duration is associated with an increased risk of cervical cancer.¹⁷ Conversely, COCs significantly decrease the risks of colorectal (OR 0.86 [95% CI 0.79-0.95]) and endometrial (OR 0.57 [95% CI 0.43-0.77]) cancers.¹⁷ A metaanalysis of 55 studies found that ovarian cancer incidence is also significantly reduced in women who are taking COCs (OR 0.73 [95% CI 0.66-0.81]).¹⁸

Given the possible side effects, COCs are contraindicated in women with a documented history of unexplained or pregnancy-associated VTE, exogenous estrogen use, migraine headaches with focal neurologic signs, smoking over 35 years of age, or a history of coronary artery disease, congestive heart failure, or cerebrovascular disease.¹⁶

Spironolactone

Key points

- **Spironolactone is a synthetic aldosterone receptor antagonist with mineralocorticoid and antiandrogen properties**
- **Potassium monitoring is not necessary in healthy patients \leq 50 years of age who are taking spironolactone and who do not have baseline renal dysfunction**

Spironolactone is a synthetic mineralocorticoid and aldosterone receptor antagonist used primarily as a diuretic for the treatment of hypertension, hyperaldosteronism, and heart failure. Spironolactone is used off-label for its antiandrogenic properties; it competes with testosterone and DHT for androgen receptor binding.^{19,20} Spironolactone also destroys a cofactor of cytochrome p450 necessary for testosterone synthesis, increases SHBG levels, and reduces 5 α -reductase activity.^{21,22}

Spironolactone is generally well-tolerated; its dose-related antiandrogenic side effects include menstrual irregularities, breast tenderness, and decreased libido in women. Spironolactone should not be given to women who are currently or planning to become pregnant because of its potential risk of feminization of a male fetus. Its mineralocorticoid side effects include diuresis, headache, and dizziness. Spironolactone carries a risk of hyperkalemia and hyponatremia because it is a potassium-sparing diuretic. Studies, however, have found that healthy adults ≤ 50 years of age who are taking spironolactone and who do not have preexisting renal disease are not at risk for clinically significant hyperkalemia and do not require monitoring.²³ Although drospirenone is a derivative of spironolactone, a small prospective study of 27 women taking drospirenone-containing COCs and spironolactone found no significant serum potassium elevations.²⁴

Spironolactone has a black box warning to avoid off-label use because of possible carcinogenic or mutagenic side effects, but these effects have only been demonstrated in animal studies using significantly higher doses than those used in humans.²⁵ Two large, population-based retrospective studies evaluating cancer incidence in 2.3 million women and 1.3 million men have not shown any association between spironolactone and increased risk of breast, uterine, cervical, or ovarian cancers.^{25,26}

Flutamide

Key points

- **Flutamide is a competitive antagonist of the androgen receptor**
- **Flutamide is used off-label for the treatment of acne, hirsutism, and female pattern hair loss in women**
- **Flutamide can be hepatotoxic and monitoring of liver function is recommended**

Flutamide antagonizes the androgen receptor to which testosterone and DHT bind. Flutamide is approved by the US FDA for the treatment of prostate cancer but is used off-label for the treatment of

AMCDs in women. Given its antiandrogenic effects, flutamide should not be administered to women who are currently or planning to become pregnant because of the potential risk of feminization of a male fetus. In addition to decreased libido and hot flashes, more serious side effects of flutamide include hepatotoxicity, for which it has a black box warning.²⁷⁻³¹ Flutamide should not be given to patients with impaired hepatic function at baseline. It is recommended to measure serum transaminases at baseline, monthly for the first 4 months, and periodically thereafter.³² Physicians who are prescribing flutamide should educate patients about the signs and symptoms of liver dysfunction, including jaundice, nausea, vomiting, and abdominal pain.³²

Finasteride and dutasteride

Key points

- **Finasteride competitively inhibits 5 α -reductase isoenzyme type II, and dutasteride irreversibly inhibits 5 α -reductase isoenzymes types I and II**
- **Finasteride and dutasteride are used off-label for the treatment of female pattern hair loss**
- **Flutamide, dutasteride, and finasteride should not be used in women who are pregnant or who might become pregnant**
- **Finasteride is used off-label for hirsutism**

Finasteride and dutasteride are 5 α -reductase inhibitors that prevent the conversion of testosterone to DHT. Finasteride competitively inhibits 5 α -reductase isoenzyme type II, which is found in reproductive tissues. Dutasteride irreversibly inhibits both isoenzymes types I and II of 5 α -reductase,^{33,34} resulting in increased activity in the skin. Finasteride is approved by the US FDA for the treatment of benign prostatic hypertrophy and male androgenetic alopecia (AGA), but it is used off-label to treat hirsutism and female pattern hair loss (FPHL). Dutasteride is only indicated for benign prostatic hypertrophy and is used off-label for male AGA and FPHL.

Finasteride and dutasteride are contraindicated and should not be handled in women who are currently pregnant or trying to conceive.³⁵ Documented side effects of these medications in women also include headaches, depression, nausea, hot flashes, decreased libido, and reduced intensity of orgasm.³⁶⁻³⁸ Finasteride use in women has controversially been associated with estrogen-mediated malignancies such as breast cancer because it generates a relative estrogen excess. However, no studies have investigated this relationship, and only a few case reports have been published.³⁹ Dutasteride carries the same theoretical risk of breast cancer as finasteride,^{40,41} but has not been studied.

Table I. Strength of recommendations for hormone-modulating therapies used for the treatment of acne in women

Medication	Mechanism of action	FDA indicated?	Side effects	Dosing and frequency	Monitoring	Strength of recommendation*	Level of evidence [†]
Combined oral contraceptives (estrogen-progestin)	Suppress LH secretion and stimulate SHBG leading to decreased testosterone	Yes	Bloating, nausea, breast tenderness, abnormal bleeding, and amenorrhea	One of the following, daily: ethinyl estradiol/cyproterone acetate (Diane 35), [‡] ethinyl estradiol/norgestimate (Ortho Tri-Cyclen), ethinyl estradiol/norethindrone acetate/ferrous fumarate (Estrostep Fe), ethinyl estradiol/drospirenone (Yaz), or ethinyl estradiol/drospirenone/levomefolate (Beyaz)	Allow for 6-month trial	A	IA
Spirolactone	Androgen receptor antagonist (steroidal)	No	Menstrual irregularities or changes, decreased libido, polyuria, headaches, and hyperkalemia	50-200 mg/day	No need to monitor potassium in a healthy adult without kidney disease	B	IB
Flutamide	Androgen receptor antagonist (nonsteroidal)	No	Diarrhea, hot flashes, and hepatotoxicity	250 mg/day	Measure serum transaminases at baseline, then monthly for first 4 months, then periodically	C	IIA

LH, Luteinizing hormone; SHBG, sex hormone-binding globulin.

*Strength of recommendation taxonomy: A, consistent, good-quality patient-oriented evidence; B, inconsistent or limited-quality patient-oriented evidence; C, consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening.

[†]Levels of evidence: IA, evidence from metaanalysis of randomized controlled trials; IB, evidence from ≥ 1 randomized controlled trial; IIA, evidence from ≥ 1 controlled study without randomization; IIB, evidence from ≥ 1 other type of quasiexperimental study; III, evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and IV, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

[‡]Not available in the United States.

HORMONE-MODULATING TREATMENTS FOR ACNE IN WOMEN

Although acne pathogenesis is multifactorial, androgen mediation of sebum production contributes to acne development. COCs, spironolactone, and flutamide are hormone-modulating therapies that are used for the treatment of acne in women (Table I).

Key points

- **Four COCs are approved by the US FDA for the treatment of acne in women also desiring contraception. Other COCs, spironolactone, and flutamide are used off-label for the treatment of acne**
- **After 6 months of therapy, COCs are as effective as antibiotics for the treatment of acne. Practitioners may use COCs instead of antibiotics, given the concern for microbial resistance**
- **There is a paucity of high-quality evidence demonstrating spironolactone's superiority over placebo. Its use is based on consensus and expert opinion**
- **Given the lack of evidence demonstrating its efficacy, flutamide is not commonly used in the treatment of acne**

COCs: Efficacy and use in acne

Principal factors in acne pathogenesis—increased sebum production and sebocyte proliferation—are influenced by testosterone and DHT. In 1 randomized controlled trial (RCT), COCs decreased sebum production by 25.1%.⁴² Antiandrogen effects of COCs have been used in the treatment of acne, and 4 COCs have been approved by the US FDA for the treatment of acne in women who also want contraception (Tables I and II). A fifth COC, ethinyl estradiol/cyproterone acetate (Diane-35; Berlex Canada, Pointe-Claire, Quebec, Canada), is used worldwide for acne (along with hirsutism and FPHL)⁴³⁻⁴⁵ but is not available in the United States because of its potential hepatotoxicity.^{42,46}

Many clinical trials have demonstrated the efficacy of COCs in the reduction of inflammatory and noninflammatory acne in women.⁴⁷⁻⁵⁴ COCs can even improve acne in normoandrogenic women⁵⁵ and should not be limited to individuals with established endocrine diagnoses. A 2012 Cochrane review compiled 31 studies investigating the efficacy of COCs in acne and concluded that COCs reduced the number of acne lesions in women.⁵⁶ However, there are limited data on the comparative effectiveness of various COC formulations, so the superiority of one type of COC cannot be determined.⁵⁶

As prolonged use of antibiotics for acne has come under scrutiny because of concerns of antimicrobial

Table II. Combined oral contraceptives specifically approved by the US Food and Drug Administration for the indication of acne in women also desiring contraception

Estrogen	Progestin	Trade names
Ethinyl estradiol	Norethindrone acetate	Estrostep Fe
Ethinyl estradiol	Norgestimate	Ortho Tri-Cyclen
Ethinyl estradiol	Drospirenone	Yaz, Beyaz

resistance, COCs are an effective alternative for women with acne who have no contraindications. A metaanalysis of 32 RCTs found that although oral antibiotics appear to reduce lesion count more than COCs after 3 months of use, by 6 months, COCs and oral antibiotics had similar efficacies.⁵⁷ However, this metaanalysis included heterogeneous studies without controls for confounders, including age and underlying endocrine abnormalities. Because of the delayed effect of COCs on acne, patients should be properly counseled to manage expectations. COCs can also be used in combination with other acne treatments, such as spironolactone or oral antibiotics. In addition, with the exception of rifampin, antibiotics do not appear to decrease the efficacy of COCs.⁵⁸

Spironolactone: Efficacy and use in acne

Spironolactone is used off-label for the treatment of acne (Table I). Spironolactone competitively inhibits testosterone and DHT binding in the sebaceous gland, thereby decreasing sebum production and sebocyte proliferation.^{19,20} Although only 2 RCTs have studied spironolactone compared with placebo for acne, many observational studies indicate that spironolactone is effective. The 2 RCTs found statistically significant decreases in sebum production as well as improvement in acne in patients receiving spironolactone 50 to 200 mg daily compared with placebo.^{59,60} Many observational studies also indicate that spironolactone is effective for acne.^{24,61-64} Nevertheless, a 2009 Cochrane review found insufficient evidence demonstrating the efficacy of spironolactone for acne.⁶⁵ A recent hybrid systematic review concurred that although there is a paucity of high-quality trials investigating the efficacy of spironolactone use in acne, the lack of evidence is not proof of inefficacy.⁶⁶ The American Academy of Dermatology work group for the treatment of acne² and the Global Alliance to Improve Outcomes in Acne⁸ support the use of spironolactone for the management of acne based on available evidence and expert opinion.²

For the treatment of acne, spironolactone may be used as a single agent or adjunctive therapy to

COCs.^{24,63} The dosing of spironolactone studied in the literature varies from 50 to 200 mg per day and can be dosed once or twice daily.^{55,67} The optimal dose is unknown, but side effects are dose-related. Given spironolactone's antiandrogenic effects and the subsequent potential of feminization of male fetuses, some groups recommend concomitant use of COCs when prescribing spironolactone.²

Flutamide: Efficacy and use in acne

Flutamide, a competitive inhibitor of the androgen receptor, is used off-label and rarely for the treatment of acne (Table D). In several small, prospective studies, flutamide decreased total acne score and lesion count.⁶⁸⁻⁷² Reported doses range from 6.25 to 250 mg per day, but optimal dosing has not been established. Because of the paucity of data, flutamide has a low-strength recommendation from the American Academy of Dermatology for acne.²

HORMONE-MODULATING TREATMENTS FOR HIRSUTISM IN WOMEN

Hirsutism is the growth of terminal hairs in a male-patterned distribution—specifically on the chin, upper cutaneous lip, chest, back, and abdomen. Androgens play a critical role in hirsutism, and 4 hormone-modulating medications are currently used in the treatment of hirsutism: COCs, spironolactone, finasteride, and flutamide (Table III). The Ferriman-Gallwey (F-G) scale is used to assess hirsutism.

Key points

- **COCs are first-line therapy for the treatment of hirsutism in women with and without hyperandrogenemia**
- **Spironolactone, finasteride, and flutamide are used off-label to treat hirsutism**
- **When treating women of child-bearing potential, birth control (such as COCs) must be used in combination with spironolactone, finasteride, or flutamide in order to prevent pregnancy**
- **Studies suggest that flutamide may be more effective than COCs for hirsutism, but it is not recommended as first-line therapy because of the risk of hepatotoxicity**

COCs

COCs modulate hirsutism by reducing local testosterone levels and are considered first-line treatment for hirsutism, despite the lack of strong evidence or RCTs (Table III).⁷³⁻⁷⁶ A combined analysis of 2 low-quality trials comparing COCs with placebo or no

treatment in women with hirsutism showed a greater reduction in hirsutism scores in patients treated with COCs (OR -8.0 [95% CI -11.0 to -4.5]).^{44,77,78} Improvements in hirsutism with COCs are not limited to those with abnormal serum androgen levels; studies comparing the effects of COCs in normoandrogenic and hyperandrogenic women have shown similar improvement in hirsutism scores regardless of androgen status.^{43,79,80}

Some evidence suggests that COCs containing drospirenone (or cyproterone acetate outside the United States),^{44,78} which have minimal androgenic activity, are most effective for hirsutism. A metaanalysis found that drospirenone-containing COCs were associated with greater improvement in F-G scores (OR 0.49 [95% CI -0.96 to -0.03])⁸¹ than levonorgestrel-containing COCs, which performed similarly to all other COCs (OR 0.49 [95% CI -0.22 - 1.20]). In addition to choosing a COC with the least androgenic activity,⁸² studies have suggested that treatment is more effective when COCs are augmented with spironolactone or finasteride,^{82,83} particularly for patients with treatment-resistant hirsutism.

Spironolactone

Spironolactone is used off-label for hirsutism (Table III). In an RCT, spironolactone 100 mg daily resulted in a significantly greater decrease in F-G scores compared with placebo (OR -7.69 [95% CI -10.12 to -5.26]).⁸⁴ Because of the small sample size in this study, however, a Cochrane systematic review concluded that the quality of evidence for spironolactone use for hirsutism is low.⁸⁵ However, a systematic review of 26 RCTs comparing the efficacy of various hirsutism treatments including spironolactone in normoandrogenic and hyperandrogenic females concluded that women treated with spironolactone at a dose of 100 mg per day had an average of 38.4% improvement in F-G score, superior to both COCs and finasteride 5 mg daily.⁷⁵ As is the case with COCs, spironolactone used in combination with other antiandrogens is superior to spironolactone alone.⁸⁶

The recommended dose of spironolactone for hirsutism in women ranges from 50 to 200 mg daily.⁷⁷ A study comparing the efficacy of spironolactone 100 mg to 200 mg daily in 30 women found no difference in serum androgens and anagen hair diameters.⁸⁷ Although no rigorous dose-ranging trials have been completed, several studies support the use of spironolactone 100 mg daily for hirsutism because side effects are dose-related.^{77,84,85,88,89}

Finasteride

Hirsutism is associated with increased activity of 5α -reductase in hair follicles,⁸⁴ and finasteride, a

Table III. Strength of recommendations for hormone-modulating therapies used for the treatment of hirsutism in women

Medication	Mechanism of action	FDA indicated?	Side effects	Dosing and frequency	Monitoring	Strength of recommendation*	Level of evidence [†]
Combined oral contraceptives (estrogen-progestin)	Suppress LH secretion and stimulate SHBG leading to decreased testosterone	No	Bloating, nausea, breast tenderness, abnormal bleeding, and amenorrhea	Variable formulations with estrogen and progestin daily	Not needed	A	IA
Spirolactone	Androgen receptor antagonist (steroidal)	No	Menstrual irregularities or changes, decreased libido, polyuria, headaches, and hyperkalemia	100 mg/day, divided into 2 doses	No need to monitor potassium in a healthy adult without kidney disease	A	IB
Finasteride	5 α -reductase inhibitor	No	Decreased libido and teratogenicity	5 mg/day	Not needed for women	B	IA
Flutamide	Androgen receptor antagonist (nonsteroidal)	No	Diarrhea, hot flashes, and hepatotoxicity	250 mg/day	Measure serum transaminases at baseline, then monthly for first 4 months, then periodically	B	IA

LH, Luteinizing hormone; SHBG, sex hormone-binding globulin.

*Strength of recommendation taxonomy: A, consistent, good-quality patient-oriented evidence; B, inconsistent or limited-quality patient-oriented evidence; C, consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening.

[†]Levels of evidence: IA, evidence from metaanalysis of randomized controlled trials; IB, evidence from ≥ 1 randomized controlled trial; IIA, evidence from ≥ 1 controlled study without randomization; IIB, evidence from ≥ 1 other type of quasiexperimental study; III, evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and IV, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

5 α -reductase inhibitor, has demonstrated efficacy in treating hirsutism (Table III).⁹⁰ An abridged Cochrane systemic review pooled data from 3 RCTs^{71,72,84} comparing finasteride 5-7.5 mg daily with placebo and found significantly greater decreases in F-G scores with finasteride (OR -5.73 [95% CI -6.87 to -4.58]).⁸⁵ However, the degree of reduction in F-G scores in these trials was variable, from minimal to clinically significant improvement. Two studies comparing the efficacy of finasteride with COCs and spironolactone found no statistically significant difference between treatments in reduction in F-G scores,^{79,91} whereas 1 study found finasteride to be inferior to spironolactone 100 mg daily.⁹² A 2008 systematic review concluded that finasteride was inferior to COCs, spironolactone, and flutamide for the treatment of hirsutism.⁷⁵

Although finasteride 5 mg daily is the most common dose for hirsutism, the data on the impact of dosing are inconsistent. An RCT of 56 hirsute women found that 2.5 mg daily was as effective as 5 mg daily,⁹³ while another study found 7.5 mg daily to be more effective than 5 mg.⁹⁴ Regardless, a longer duration of therapy is associated with greater improvements in F-G scores.^{85,95} Given that most data come from trials of finasteride 5 mg daily, it is the current recommended dose for hirsute women.^{84,96}

Flutamide

Flutamide, an antiandrogen, is used for hirsutism (Table III). Two RCTs found clinically important differences in F-G scores in the flutamide groups compared with placebo groups.^{84,97} However, an abridged Cochrane review rated these studies as low to very low quality. Four clinical trials compared flutamide with finasteride, 2 of which found statistically significant greater reductions with flutamide,^{98,99} while the others found no difference in efficacy.^{79,84} One study comparing flutamide with spironolactone found no significant difference in efficacy for hirsutism.⁹² Nevertheless, a systematic review concluded that flutamide is the most effective antiandrogen treatment for hirsutism.⁷⁵

While trials have studied flutamide doses of 62.5 to 750 mg, the Androgen Excess and Polycystic Ovary Syndrome Society recommends flutamide 250 mg daily for hirsutism.^{100,101} Data from randomized studies support the use of flutamide 250 mg, which is considered low-dose, for the treatment of hirsutism.^{83,84,102} Higher doses are not recommended because of the risk of dose-related hepatotoxicity.¹⁰¹

While there are data supporting the use of flutamide for hirsutism, it is not considered first-line treatment based on the risk of hepatotoxicity. Of note, bicalutamide, an antiandrogen similar to flutamide, was demonstrated to have efficacy in the

treatment of hirsutism in a single study.¹⁰³ Bicalutamide does not have the risk of hepatotoxicity seen with flutamide, but has not been studied extensively for hirsutism.^{104,105}

HORMONE-MODULATING TREATMENTS FOR FPHL

The pathogenesis of FPHL is complicated and the use of antiandrogen drugs as treatment is contested. Minoxidil is the only treatment for FPHL that is approved by the US FDA.¹⁰⁶ Four hormone-modulating therapies are used off-label in the treatment of FPHL: spironolactone, finasteride, dutasteride, and flutamide (Table IV).

Key points

- **Spironolactone, finasteride, dutasteride, and flutamide are antiandrogens that are used off-label for FPHL**
- **When treating women of child-bearing potential, birth control (such as COCs) must be used in combination with these medications to prevent pregnancy**
- **Finasteride is used commonly for FPHL, but there is limited evidence supporting its efficacy**
- **RCTs evaluating spironolactone, flutamide, and dutasteride for FPHL are lacking**

Spironolactone

Spironolactone is commonly used off-label for FPHL; however, evidence supporting its use is limited and there is a dearth of controlled studies evaluating its efficacy (Table IV).⁴⁰ One retrospective review found that 75% of patients with FPHL who were taking spironolactone experienced an improvement in or no worsening of hair loss.¹⁰⁷ Similar results were found in an open intervention study, in which 88% of patients experienced an improvement or stagnation of hair loss.¹⁰⁸ Studies have not documented hair growth as a result of spironolactone therapy.¹⁰⁹ If used, spironolactone should be dosed at 100 to 200 mg daily.^{85,108,110,111} Although spironolactone is often used in conjunction with COCs, there is no evidence that adding a COC is superior to spironolactone alone for FPHL.¹¹²

Finasteride

DHT suppresses terminal hair growth and promotes miniaturization of follicles on the scalp (Table IV). Finasteride lowers scalp and serum DHT levels.¹¹³ Finasteride 1 mg daily is effectively used (and approved by the US FDA) for the treatment of male AGA^{102,114,115} but is used off-label for FPHL with mixed efficacy. Although several uncontrolled studies found improvement in hair density in normoandrogenic

Table IV. Strength of recommendations for hormone-modulating therapies used for the treatment of female pattern hair loss

Medication	Mechanism of action	FDA indicated?	Side effects	Dosing and frequency	Monitoring	Strength of recommendation*	Level of evidence†
Spirolactone	Androgen receptor antagonist (steroidal)	No	Menstrual irregularities or changes, decreased libido, polyuria, headaches, and hyperkalemia	100-200 mg/day, divided into 2 doses	No need to monitor potassium in a healthy adult without kidney disease	B	IIB
Finasteride	5 α -reductase inhibitor	No	Decreased libido and teratogenicity	2.5-5 mg/day	Not needed for women	B	IB
Dutasteride	5 α -reductase inhibitor	No	Decreased libido and teratogenicity	0.15 mg/day	Not needed for women	C	III
Flutamide	Androgen receptor antagonist (nonsteroidal)	No	Diarrhea, hot flashes, and hepatotoxicity	250 mg/day	Measure serum transaminases at baseline, then monthly for first 4 months, then periodically	B	IB

*Strength of recommendation taxonomy: A, consistent, good-quality patient-oriented evidence; B, inconsistent or limited-quality patient-oriented evidence; C, consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening.

†Levels of evidence: IA, evidence from metaanalysis of randomized controlled trials; IB, evidence from ≥ 1 randomized controlled trial; IIA, evidence from ≥ 1 controlled study without randomization; IIB, evidence from ≥ 1 other type of quasiexperimental study; III, evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and IV, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

women with FPHL who were treated with finasteride 2.5-5 mg daily,^{116,117} 2 RCTs of normoandrogenic women comparing finasteride 1 mg daily with placebo found no significant change in hair density.^{118,119} There is no consensus for finasteride dosing for FPHL, with dosage ranging from 2.5 to 5 mg daily.

Dutasteride

Dutasteride is used off-label for the treatment of FPHL (Table IV). Although similar in mechanism of action to finasteride, studies in men have found that dutasteride (0.5 mg/day) was superior to finasteride (1 mg/day) for AGA, likely because of 5 α -reductase isotype expression.^{120,121} There have been no RCTs or prospective studies evaluating dutasteride's efficacy or safety for FPHL. Although 1 retrospective study of FPHL found both finasteride and dutasteride improved hair thickness at 3 years, dutasteride performed statistically significantly better than finasteride in women <50 years of age.¹²² There are insufficient studies assessing dutasteride's efficacy or dosing for FPHL.

Flutamide

Flutamide is infrequently used for FPHL, despite several studies supporting its use (Table IV).^{123,124} A prospective study of 101 normoandrogenic and hyperandrogenic women with FPHL treated with flutamide found statistically significant improvement in hair density at 6 months, with continued improvement at 2 years.¹²³ In a randomized, uncontrolled trial comparing flutamide with finasteride and cyproterone acetate, only patients who were receiving flutamide experienced a significant reduction in FPHL score.¹²⁴ Although flutamide has demonstrated efficacy in the treatment of FPHL, the risk of hepatotoxicity prevents it from being used as first-line therapy.⁸⁵

CONCLUSION

In conclusion, AMCDs in women include acne, hirsutism, and FPHL. The pathophysiology of these diseases is complicated and incompletely understood. Many women with these cutaneous conditions have no detectable endocrinologic abnormalities but may have variability in local androgen sensitivity. Endocrinologic testing should be considered in patients with symptoms suggesting androgen excess, especially menstrual irregularities and hirsutism, the latter of which is more closely tied to serum androgen abnormalities than other AMCDs.

Regardless of a patient's hormone status, women with AMCDs may benefit from hormone-modulating therapies, including COCs, spironolactone, dutasteride, finasteride, and flutamide. These therapies are used off-label for AMCDs, with the exception of 4

COCs that have been approved by the US FDA to treat acne in women who are also desiring contraception. Notably, spironolactone, flutamide, finasteride, and dutasteride should not be used in women who are planning to become or currently pregnant because of the risk of feminization of the male fetus; thus, concurrent use of contraception, such as COCs, is advised for women of child-bearing age.

Dermatologists are often the first, and frequently only, providers to see women with AMCDs. It is important to be knowledgeable about the pathophysiology, appropriate endocrinologic evaluation, and hormone-modulating treatments available for these conditions.

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Answers to CME examination

Identification No. JD0619

June 2019 issue of the Journal of the American Academy of Dermatology.

Azarchi S, Bienenfeld A, Lo Sicco K, Marchbein S, Shapiro J, Nagler AR. *J Am Acad Dermatol* 2019;80:1509-21.

1. b
2. d

3. b
4. c