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SECTION 5

Emerging Therapies for Hair Loss

16

Emerging Medications

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KEY POINTS

- Topical prostaglandin analogs may increase vellus and terminal hair density and stimulate hair follicle activity.
- Janus kinase inhibitors demonstrate great success in the treatment of alopecia areata, with potential for androgenetic alopecia.
- Therapies targeting growth-factor regulation offer innovative options with success in androgenetic alopecia.
- Antiandrogen therapy has a long history of investigation for therapeutic use androgenetic alopecia, and new topical therapies show promise.
- Topical estrogen therapy is supported by several studies for the treatment of androgenetic alopecia, but conflicting reports exist.

INTRODUCTION

Androgenetic alopecia (AGA) is a common age-dependent hair-loss disorder affecting more than 60% to 70% of men and women worldwide.[1] The exact pathogenesis of AGA is not well understood, but genetic susceptibility and androgens are pivotal in predisposing individuals to pattern hair loss. There are currently only two pharmacologic treatments that the U.S. Food and Drug Administration (FDA) has approved for AGA: oral finasteride and topical minoxidil. Several new medical treatment modalities and pathways are being explored. Remarkable progress has been made in delineating novel signaling targets implicated in hair growth regulation, including pathways that upregulate key growth factors for germ-cell activation (Wnt mediators), reduce pathologic levels of androgenetic hormones (antiandrogen therapy), and reduce the level of inflammatory mediators (prostaglandins, Janus kinase [JAK] inhibitors). The scope of therapeutic options for AGA is rapidly expanding (Fig. 16.1) with emerging treatments that hold promise for improved results.

INFLAMMATORY PATHWAYS

Prostaglandin Analogs

Prostaglandins (PGs), a lipid-derived prostanoid family generated from arachidonic acid by cyclooxygenase (COX) isoenzymes, are known to variably modulate inflammatory responses.[2] PG production typically increases significantly during acute inflammatory processes prior to leukocyte recruitment and immune cell infiltration. The most commonly bioactive prostaglandins implicated in regulation of the hair cycle with distinguishing effects include PGE_2, $PGF_2\alpha$, PGD_2, and prostacyclin (PGI_2) (Fig. 16.2) (level of evidence: 5).[2] PGE_2 and $PGF_{2\alpha}$ can prolong the anagen phase of the hair cycle, with studies showing that patients with AGA have reduced levels of PGE_2.[3,4] PGE_2 acts as a direct vasodilator and suppressor of T-cell signaling and proliferation and can help reduce inflammation present in AGA. PGF_2 and its analogs stimulate follicular melanocytes and murine hair follicles in both the telogen and anagen phases.[5]

In contrast, AGA scalps have increased levels of PGD_2, a lipid synthesized via the COX and PGD_2

1. *Inflammatory pathway*
   - Prostaglandin analogs
   - Janus kinase inhibitors

2. *Growth factor regulation*
   - Wnt pathway mediators
   - Topical growth factors
   - Adenosine
   - Caffeine
   - Botulinum toxin

3. *Hormonal regulalion*
   - Antiandrogen therapy
   - Estrogen therapy
   - Melatonin

4. *Other miscellaneous treatments*
   - Antihistamines

Fig. 16.1 Emerging treatments for androgenetic alopecia. (Image author: Amanda Nguyen)

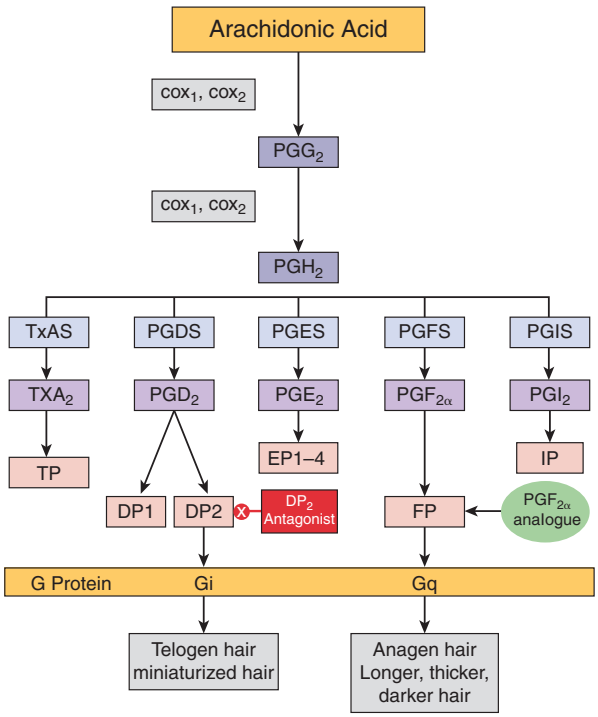

Fig. 16.2 Hair growth mechanistic pathways of prostaglandins and their associated therapies. (Image author: Amanda Nguyen)

synthase pathways (PGDS) (level of evidence: 4).[4,6] PGD_2 acts as a proinflammatory mediator when released from mast cells and T helper (Th2) lymphocytes and has been implicated in the inhibition of hair growth.[7] PGDS activity and PGD_2 levels increase prior to the catagen phase, suggesting their role in the cessation phase of the hair cycle. In murine models, elevated levels of PGD_2 induce follicle miniaturization, sebaceous gland hyperplasia, and alopecia (level of evidence: 5).[4,8] In human balding scalps, there are increased levels of PGD_2, potentially caused by the upregulation of PGDS in comparison to normal scalps.[4] PGD_2 stimulates the expression of androgen-receptor related genes in human dermal papilla cells (DPCs), such as transforming growth factor beta 1 (TGF-β1). New investigational medications targeting prostaglandin pathways are being explored for the treatment of AGA (Table 16.1).

Topical Prostaglandin Analogs

Topical prostaglandin analogs include latanoprost (PGF analog) and bimatoprost (synthetic prostamide F2 analog), which are eyedrops indicated for treatment of open-angle glaucoma.[8] The stimulating effects of PGs on hair growth were first observed as a side effect, prompting further studies and eventual FDA approval of bimatoprost

TABLE 16.1 Inflammatory Pathway Targets Prostaglandin for the Treatment of Androgenetic Alopecia

Medication	Mechanism of Action	Route	Dose	Adverse Effects	Treatment Regimen
Latanoprost	$PGF_{2\alpha}$ analog	Topical	0.1% solution	Eyelash hypertrichosis, malar vellus hair formation, erythema, folliculitis	Once daily
Bimatoprost	Synthetic PGE_2 analog	Topical	0.03% solution	Eyelash hypertrichosis, malar vellus hair formation	Once daily
Setipiprant	Selective PGD_2 receptor antagonist	Oral	500 mg	Gastrointestinal disorders, upper respiratory infection, liver enzyme abnormalities	Twice daily

0.03% solution for eyelash hypotrichosis. PG analogs interact with local receptors to extend the length of the anagen phase while simultaneously stimulating resting telogen-to-anagen hair follicles, with hair bulb and dermal papilla growth. The major reported side effects for both topical PG analogs include eyelash hypertrichosis and malar area vellus hair growth.[9-11]

Bimatoprost (0.03% ophthalmic solution, *Latisse,* Allergan Inc., Irvine, CA) is a synthetic PGE_2 analog that increases the time hair follicles spend in the anagen growth phase.[12-14] The initial excitement for its potential to grow scalp hair has thus far been supported by limited evidence, but clinical trials are still in progress at the time of publication. Studies suggest a concentration-dependent increase in the (a) number of anagen follicles and (b) follicular growth rates.[15] Two large clinical trials evaluated the effect of topical bimatoprost on mean change in hair growth (mm/cm^2) from baseline compared with vehicle-treated groups in men with mild-to-moderate AGA after 24 weeks of treatment. Scalp application of topical bimatoprost 0.03% solution once or twice a day produced a 0.92 mm/cm^2 and 0.76 mm/cm^2 mean change in hair growth, respectively (level of evidence: 1b).[17] However, another large clinical trial reported higher total hair counts with application of minoxidil 2% twice daily compared with once daily application of topical bimatoprost 0.03% among women with AGA after 6 months of treatment (level of evidence: 1b).[18] Common adverse effects included application site pruritis and upper respiratory tract infections.

Latanoprost (*Xalatan,* Pfizer, Inc.) is a PGF_2 analog currently approved by the FDA for the treatment of open-angle glaucoma and ocular hypertension. It acts as an inducer of the hair anagen phase, making it interesting for use in AGA. Evidence on the efficacy of compounded topical formulations, however, is lacking. A single clinical trial reported 16 men with mild AGA who were treated daily for 24 weeks with topical latanoprost 0.1% had a good clinical response and increased hair density compared with baseline ($p<0.001$) (level of evidence: 1b).[19] Common adverse effects included erythema and folliculitis.

Prostaglandin Antagonists

Setipiprant is a selective PG D2 receptor (PGD2R) antagonist that has been linked to the regulation of inflammatory pathways in asthma and allergies. At the time of publication, a clinical trial was underway to study the efficacy and safety of oral setipiprant 1000 mg twice daily relative to placebo in men with AGA (level of evidence: 1b).[20] Results are eagerly awaited, as setipiprant has been shown to be well-tolerated and with a favorable safety profile for other indications.[21]

Janus Kinase Inhibitors

JAK inhibitors are novel treatment options for alopecia area (AA) with therapeutic potential for other alopecia types. JAK inhibitors are a family of tyrosine kinases that mediate cytokine-receptor signaling through phosphorylation and activation of signal transducer and

activator of transcription (STAT) nuclear proteins, which are critical for leukocyte activation and proliferation and play a major role in immune regulation.[22,23]

Oral JAK inhibitors (e.g., baricitinib, ruxolitinib, and tofacitinib) are emerging as a favorable treatment modality for a variety of inflammatory conditions, with current FDA approval for myelofibrosis, rheumatoid arthritis, polycythemia vera, psoriatic arthritis, ulcerative colitis, and graft-versus-host disease. JAK-STAT inhibitors play a major role in hair regrowth by regulating T-cell mediated responses at the level of the hair follicle, affecting hair follicle growth and promoting anagen progression.[24,25]

Topical JAK inhibitor preparations in AGA have resulted in anagen phase activation and rapid hair regrowth.[26] Investigational topical JAK 1/3 inhibitor (ATI-50002, applied twice daily to scalp) effectively treated both women and men with AGA, with an increase of 8.6 hairs/cm^2 in total nonvellus hair count over 26 weeks and without any serious adverse events (level of evidence: 1b).[27] However, oral JAK inhibitor treatments have not shown to be as effective for AGA thus far, as one study showed that, among men with AA with hair regrowth, the loss in AGA pattern was preserved.[28] Similarly, in a later small observational study, men with severe AA on an oral JAK 1/3 inhibitor for 24 to 50 weeks experienced significant hair regrowth, but the AGA-pattern loss remained (level of evidence: 4).[29]

Future studies are needed to address the conflicting results and determine the specific types of JAK inhibitors of use in AGA. As systemic JAK inhibition can have immunosuppressive properties, there is an inherent risk of increased infections (e.g., herpes zoster),[30-32] laboratory abnormalities (anemia, leukopenia, elevated cholesterol levels), and potential risk for malignancy and thrombosis.[33-35]

GROWTH REGULATORY PATHWAYS

Complex arrays of growth factors are integral paracrine signals that regulate the hair follicle growth cycle.[36] Induction of the anagen phase requires an elevation in Wnt signaling and stabilization of β-catenin within follicular bulge cells, allowing stem-cell differentiation and growth.[36] Also, fibroblast growth factor (FGF) is involved in β-catenin expression and stabilization, while also promoting angiogenesis and improved dermal fibroblast and hair follicle mitogenesis.[37] Maintenance of the anagen phase requires upregulation of three key growth factors: insulin-like growth factor- 1 (IGF-1), hepatocyte growth factor, and vascular endothelial growth factor (VEGF). IGF-1 promotes cellular proliferation and migration, while simultaneously inhibiting the onset of catagen.[38] Hepatocyte growth factor enhances hair follicle elongation and proliferation of follicular epithelial cells,[37] and VEGF is responsible for angiogenesis to support proper vasculature of the growing hair follicle.[38] Several additional paracrine growth factors are believed to play critical roles in the growth cycle, but the entire mechanism remains to be uncovered to further discern new targets in hopes of generating hair growth (Table 16.2).[36]

TABLE 16.2 Growth Regulation Pathways for Treatment of Androgenetic Alopecia

Medication	Mechanism of Action	Route	Formulation / Dose	Adverse Effects	Treatment Regimen
Various Topical Growth Factor Combinations	Paracrine stimulation of hair follicles	Topical or Intradermal	Formulation: FGF (2.5μg/mL), IGF-1 (1 μg/mL), stem cell factor (2.5 μg/mL, VEGF (2.5 μg/mL), keratinocyte growth factor-2 (2.5 μg/mL), superoxide dismutase-1 (5 μg/mL), Noggin (2.5 μg/mL)	NR	Topical and intradermal preparations

(Continued)

TABLE 16.2 Growth Regulation Pathways for Treatment of Androgenetic Alopecia—cont'd

Medication	Mechanism of Action	Route	Formulation / Dose	Adverse Effects	Treatment Regimen
Wnt Pathway Mediators					
Hair Stimulating Complex	Follistatin and Wnt proteins	Intradermal	Proprietary bioengineered Wnt proteins and growth factors, nondisclosed	NR	Single treatment
SM04554	Small molecule that stimulates the Wnt pathway	Topical	0.15% or 0.25% solution	Erythema, site burning or stinging, pruritus, skin exfoliation	Once daily
Adenosine	Upregulated expression of VEGF and FGF-7	Topical	0.75% adenosine lotion	Scaling, seborrhea, folliculitis, pruritus	Twice daily
Botulinum toxin	Stimulation of TGF-β1 in dermal papilla cells	Intradermal	5 to 150 units in at least 30 injection sites	Pain, edema, erythema at the injection site	One to four sessions
Caffeine	Phosphodiesterase inhibitor and IGF-1 stimulator	Topical	0.2 to 1% lotion	NR	Once daily

NR, Not reported.

Wnt Pathway Mediators

Wnt/β-catenin signaling is a well-described pathway that influences the inductive potential of dermal papilla cells and induces the differentiation of bulge stem cells into hair follicles.[39,40] Specifically, Wnt proteins activate the signal transduction pathways for hair germ formation during the next anagen phase and induce the transition from telogen to anagen.[39,41,42]

There are no currently approved alopecia medications targeting Wnt pathways; however, there are promising results from investigational small molecules that activate the Wnt pathway. Topical application of 0.15% SM04554 significantly increases hair follicle counts (average increase of 4.5 hairs/cm^2) and density (average increase of 217.9 μm) after 6 months compared with placebo, while also increasing hair bulb nuclear expression of Ki-67, a marker of cell proliferation (level of evidence: 1b).[43,44] Similarly, an investigational complex consisting of a proprietary concentration of bioengineered Wnt proteins (among other growth factors) increases hair thickness by 6.3%, hair density by 12.8%, and terminal hair density by 20.6% when assessed 52 weeks after a single session of intradermal injections (level of evidence: 1b).[41] The adverse events reported include erythema, site burning or stinging, pruritus, and skin exfoliation.[44]

Topical Growth Factors

Topical growth factors are increasingly popular components of cosmetic hair products, with very little evidence to substantiate their claims of promoting hair growth. Treatment with topical growth factors for hair loss is not FDA approved. Limited studies have examined the efficacy of topical nonautologous growth factor formulations in the treatment of AGA, and the existing preliminary results are positive but may have commercial bias. A topical growth factor solution (2.5 μg/ mL of FGF, IGF-1, VEGF, keratinocyte growth factor [KGF]-2, stem cell factor, Noggin, 5μg/mL superoxide dismutase-1) improved scalp hair-shaft density by greater than 10% when applied weekly with microneedling among 11 female patients (level of evidence: 2b).[45] Similarly, an investigational formulation of topical FGF (with microneedling) improved hair density and hair diameter among 40 men with AGA (level of evidence: 2b).[46] Intradermal injections every 3 weeks of investigational bioengineered, recombinant growth factor formulations (0.01 to 100 mg/L of FGF, VEGF, IGF, and KGF; 0.005 to 100mg/L thymosin β4; and, 0.1 to 500 mg/L copper tripeptide-1) were shown to increase the number of terminal hairs, increase the hair-shaft diameter (3μm), and reduce vellus hair counts after eight sessions of multiple scalp injections in 680 males and 320 females (level of evidence: 2b).[38] More studies are needed in this area to determine the growth factor ingredients and their optimal concentrations to improve AGA outcomes.

Adenosine

Adenosine is an extracellular purine nucleoside that has far-reaching effects across many organ systems, with systemic therapeutic use for cardiovascular regulation.[47] Adenosine regulates several growth factor transduction pathways within dermal papilla cells and is known to upregulate the expression of VEGF.[48,49] When bound to adenosine receptor A2b, production of FGF-7 increases and TGF-β levels decrease.[50] TGF-β is an inhibitory factor in DPCs, which can be induced by androgens.[51]

Several clinical trials show promising results for off-label use of topical adenosine in the treatment of AGA. Topical 0.75% adenosine lotion increases the quantity of thick hair (>60 μm) by 5.5 hairs/cm^2 after 6 months (level of evidence: 4),[52,53] with comparable clinical improvement to patients using topical minoxidil (relative recovery rate of 1.9% vs. 2.4%, respectively, $p = 0.17$) (level of evidence: 2b).[54] After 12 months, topical adenosine is reported to increase the ratio of thick hairs (>80 μm) and increase the anagen growth rate by at least 0.4 mm/day (level of evidence: 1b).[50] Adverse events are minimal, including scaling and seborrhea, folliculitis, and pruritus.[52,54]

Botulinum Toxin

Botulinum toxin (BTX) prevents the release of acetylcholine at the neuromuscular junction and is a treatment modality for various neurologic and dermatologic conditions.[55-57] It has gathered attention as an emerging therapy for AGA after several successful clinical studies. Though the mechanisms are not fully understood, botulinum toxin has potential as another future treatment for patients with AGA.

Its success in AGA has been speculative and attributed to increased oxygen delivery to tissue secondary to musculature relaxation. Higher concentrations of oxygen allow for greater quantities of testosterone to be converted to estradiol rather than dihydrotestosterone (DHT), with potential reduction of hair loss.[58] DHT is known to induce TGF-β1 in DPCs to inhibit follicular epithelial cell growth; therefore botulinum toxin type A (BTX) may indirectly inhibit TGF-β1 secretion within the hair bulb, similar to its action on scar tissue fibroblasts.[59]

Several open-label studies have evaluated the safety and efficacy of BTX injections, with varying dosages (5 to 150 units) injected into the muscles surrounding the scalp with over 30 injection sites and variable numbers of sessions (one to four). One study showed a statistically significant increase of mean hair counts between baseline and week 48 ($p<0.0001$) and visible hair growth in men with AGA after 60 weeks and three treatment cycles (level of evidence: 4).[58] Other studies report 70% of patients with good-to-excellent responses after 24 weeks (Fig. 16.3) (level of evidence: 4)[60] and hair regrowth in 36% of subjects 6 months after receiving one BTX treatment (level of evidence: 4).[61] The latest open-label study showed a superior therapeutic effect demonstrated by higher hair counts with the combination of BTX and oral finasteride compared with BTX alone after a total of four sessions (one BTX injection every 3 months) (level of evidence: 2b).[62] Commonly described transient side effects are pain, edema, or erythema at the injection site.[61,62] As there are also reports

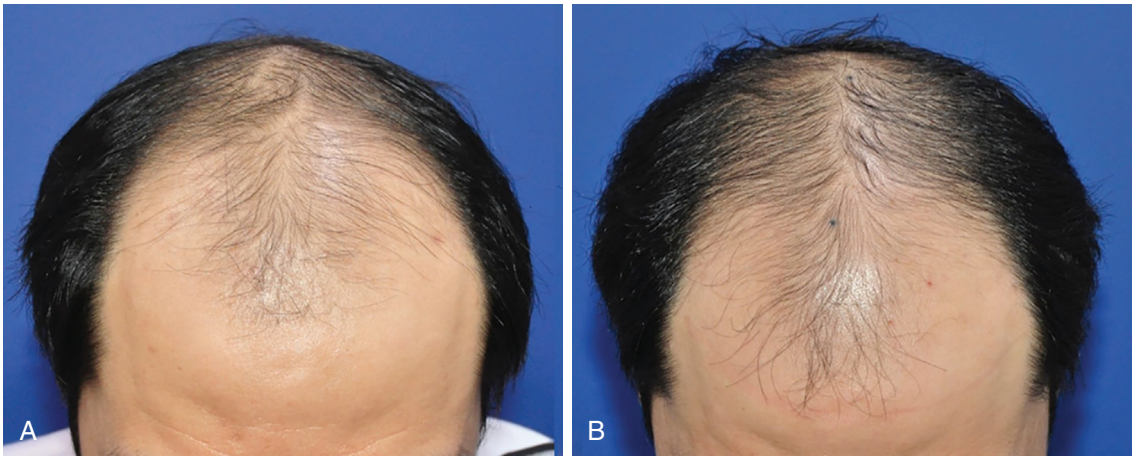

Fig. 16.3 Clinical photographs of a male patient with AGA at baseline (A) and at 6 months after treatment (B) with botulinum toxin. (Source: Shon U, Kim MH, Lee DY, Kim SH, Park BC. The effect of intradermal botulinum toxin on androgenetic alopecia and its possible mechanism. *J Am Acad Dermatol*. 2020;83(6):1838-1839. doi:10.1016/j.jaad.2020.04.082)

of facial and scalp hair loss secondary to botulinum toxin treatment for other indications, it is imperative that the details of its effects and mechanisms are well established and confirmed in larger, randomized trials.

Caffeine

Caffeine is a phosphodiesterase inhibitor that increases cell cyclic adenosine monophosphate levels, thereby promoting cellular proliferation and metabolism.[63] It is consumed in foods and beverages (2 to 200 mg of caffeine per 100 mL) and over-the-counter pain and weight-loss supplements, and it can cross the blood-brain barrier as a central nervous system stimulant.[64]

Although topical caffeine-containing products have not been FDA approved for hair loss, many investigational studies have focused on its use for the treatment of AGA. Topical caffeine easily crosses skin barriers, and *in vivo* studies demonstrated good follicular penetration and absorption (level of evidence: 5).[65] Several *in vitro* studies have noted that caffeine can promote hair growth [63] by (1) reversing the testosterone-inhibiting effect on keratinocyte proliferation[66]; (2) enhancing hair shaft elongation, prolonging anagen duration, and stimulating keratinocyte proliferation of the hair matrix[67]; (3) increasing IGF-1 expression (which promotes hair growth in both males and females)[67]; and (4) downregulating testosterone-induced TGF-β_1 expression (level of evidence: 5).[67]

Daily use of caffeine shampoo (unspecified concentration) results in reduced hair shedding, decreased hair loss intensity, and fewer hairs extracted during hair-pull test in both men and women with AGA (level of evidence: 1b).[68-70] Similarly, caffeine lotion (unspecified concentration) has shown decreases in hairs extracted during the hair-pull test with potential increase in hair tensile strength for men with AGA (level of evidence: 2b).[71] Topical caffeine has also been compared with other standard treatment modalities (topical minoxidil 5%, topical minoxidil 2.5%, azelaic acid 1.5%), with results showing improvements in anagen ratio (level of evidence: 1b),[72] increased patient satisfaction (level of evidence: 1b), [73] and decreased hair shedding (level of evidence: 1b).[74] No serious adverse events were reported.

HORMONAL REGULATION

Novel Antiandrogen Therapy

Classically, it is believed that 5α-reductase converts testosterone to DHT within DPCs and that DHT binds the androgen receptors resulting in the diminution of the number of terminal hairs.[75] Finasteride, a 5α-reductase inhibitor, is the only FDA approved antiandrogen treatment for AGA, but several additional antiandrogen medications are currently under review (Table 16.3).[76]

TABLE 16.3 Emerging Hormonal Targets for Treatment of Androgenetic Alopecia

Medication	Mechanism of Action	Route	Dose	Adverse Effects	Treatment Regimen
Anti-Androgen Therapies					
Clascoterone	Direct androgen receptor inhibitor	Topical	2.5%, 5%, or 7.5% solution	NR	Once daily
Pyrilutamide	Androgen receptor antagonist	Oral	2.5-5 mg	NR	Once to twice daily
Fluridil	Competitive androgen receptor antagonist	Topical	2% solution	Scalp yellowing, reactivation of seborrheic dermatitis, allergic reaction	Once daily
Flutamide	Selective nonsteroidal androgen receptor antagonist	Oral	62.5-250 mg	Liver toxicity, depressed plasma androgen levels, headaches, respiratory tract disorders, nausea and/or vomiting, diarrhea, dry skin, reduced libido	Once daily, increasing the dose as tolerated
Estrogen Therapies					
17α-estradiol	Inhibition of 5α-reductase	Topical	0.025% solution	Irritation, mild pruritus, erythema, scaling	Once daily
Estradiol valerate	Inhibition of 5α-reductase	Topical	0.03% lotion	Irritation, mild pruritus, erythema, scaling, postmenopausal uterine bleeding	Once daily
Melatonin Therapy					
Melatonin	Antioxidant and prolactin stimulator	Topical	0.0033% solution	Headache, gastrointestinal distress, pruritus, erythema	Once daily

NR, Not reported.

Topical Anti-Androgens

Clascoterone is an ester derivative of cortexolone and is a potent direct androgen receptor inhibitor.[77] When applied topically, the drug penetrates the skin and binds to androgen receptors within sebaceous glands and hair follicles and inhibits DHT-stimulated signaling. At the time of publication, clascoterone was approved for acne vulgaris treatment and under investigation for treatment of AGA. A clinical trial with 400 men with AGA reported increased hair counts (growth of additional 10 to 14 hairs per 1-cm^2 area, on average) with use of a 2.5%, 5%, or 7.5% clascoterone solution for 12 months, without any reported adverse events (level of evidence: 1b).[77]

Fluridil is an investigational topical nonsteroidal antiandrogen that competitively binds to androgen receptors in the dermal papilla. A clinical trial of 43 men with AGA receiving topical fluridil 2% reported increases in anagen counts and decreases in telogen counts

compared with placebo (level of evidence: 1b).[78] Minimal adverse reactions were reported, including yellowing of the scalp, reactivation of seborrheic dermatitis by sun exposure, and allergic reaction after concurrent application of topical deodorant.

Oral Anti-Androgens

Flutamide is a pure selective nonsteroidal antiandrogen and acts peripherally to competitively block the binding of androgens to cytoplasmic and/or nuclear androgen receptors, and is currently approved for oral administration (250 mg thrice daily) solely for the treatment of metastatic prostate cancer.[79,80] Few studies have examined the efficacy of off label use of flutamide for AGA, but preliminary results note improvements in Ludwig scores with daily oral 62.5 to 250 mg flutamide (level of evidence: 2b).[79,81] Reported adverse reactions include depressed plasma androgen levels, elevated transaminase levels, headaches, respiratory tract disorders, nausea and vomiting, diarrhea, dry skin, and reduced libido.[79]

Pyrilutamide is an oral androgen receptor antagonist currently investigated for AGA. A randomized, double-blind, placebo-controlled clinical trial is in progress, using oral pyrilutamide 2.5 to 5 mg daily in 120 men with AGA (level of evidence: 1b).[82] There are no known serious side effects.

Estrogen Therapies

The mechanism delineating how estrogen may benefit AGA-affected hair follicles remains unclear despite prolific scientific efforts. At the level of the hair follicle, 17 α-estradiol can suppress the function of 5α-reductase and diminish the quantity of DHT formed.[83] Moreover, by stimulating P-450 aromatase, it may upregulate the conversion of testosterone to 17β-estradiol and the conversion of androstenedione to estrone, further decreasing pathologic levels of DHT.[83,84]

Topical estrogen therapy is currently FDA approved for treatment of postmenopausal symptoms and for hormone replacement therapy.[85] In terms of AGA, evidence for estradiol off label use has predominantly shown promising results. Postmenopausal women (ages 48 to 71 years) applying estradiol valerate 0.03% lotion to the scalp for 12 weeks experienced an anagen-to-telogen ratio increase from 1.57 to 2.27, indicating a decreased telogen rate and/or increased anagen rate (level of evidence: 1b).[84] Female patients applying topical 0.025% 17 α-estradiol solution experienced increases in total hair counts by an average of 60.08 hairs/cm^2 and hair caliber from 0.058±0.016 μm to 0.073±0.015 μm ($p < 0.05$) after 12 months of therapy (level of evidence: 2b).[86] Another study concurred that topical 0.025% 17 α-estradiol increases total hair counts by an average of 31.57 hairs/cm^2 and hair diameter by an average of 10.39 μm after 8 months of therapy (level of evidence: 2b).[83] However, one clinical trial using topical 0.025% alfatradiol therapy among 51 women for 6 months demonstrated no significant difference in hair thickness or absolute hair density from baseline (level of evidence: 1b).[87] Similarly, oral cyproterone acetate therapy was found to be inferior to topical minoxidil therapy among 66 women after 12 months of treatment (level of evidence: 1b).[88] Reported adverse events include irritation, mild pruritus, erythema, and/or scaling from the topical formulations. A case of breast adenocarcinoma was reported in a patient who used estradiol valerate topical therapy, but no direct causation was established.[84]

Fulvestrant

Fulvestrant is an estrogen receptor antagonist without any known agonist properties, originally formulated for intramuscular administration (250 mg/mL) in the treatment of breast cancer.[89,90] When bound to the estrogen receptor, the complex is destabilized and internalized within the cell for degradation.[91] Interestingly, topical formulations have demonstrated preclinical murine success in the treatment of hair loss by causing hair follicles to transition from the telogen to anagen phase (level of evidence: 5).[92] Despite this preclinical success, to date, clinical trials using topical 30 μL/cm^2 of fulvestrant 70 mg/mL solution reported no improvement in men and women over the age of 18 with Hamilton-Norwood grades III to Va or Ludwig I to II after 16 weeks of use (level of evidence: 1b).[92]

Melatonin

Melatonin (5-methoxy-N-acetyltryptamine) is a lipophilic hormone synthesized and secreted by the pineal gland from a pathway that includes both tryptophan and serotonin.[93] The well-established function of melatonin is its involvement in circadian rhythm and sleep cycle control and its strong antioxidant properties.[93,94] Human skin is known to have its own melatoninergic antioxidative system, which includes melatonin receptors within hair follicle keratinocytes and dermal papilla

fibroblasts.[95] Keratinocytes, fibroblasts, and melanocytes have functional melatonin receptors located in the hair root sheath, which are thought to assist in hair growth regulation and hair shaft stabilization.[96] *In vitro* studies demonstrated that low doses of melatonin enhance human follicle proliferation, while melatonin antagonists suppress follicular stimulation. Thus, it is theorized that melatonin has a specific receptor-mediated effect on follicular oxidative stress and growth, making it a possible candidate to counteract the oxidative stress associated with AGA.[97]

Several trials have evaluated the safety and efficacy of topical melatonin 0.0033% application in women and men with AGA, but it is currently not FDA approved. Various open-label and observational studies indicate topical melatonin 0.0033% cosmetic hair solution is highly tolerable with positive effects on hair growth. Specifically, daily application of 0.003% topical melatonin therapy did not increase serum melatonin levels (level of evidence: 1b),[98] but showed significantly reduced hair loss severity (level of evidence: 2b)[99] and increased hair density and hair count (level of evidence: 2b).[100] One large clinical trial evaluating men with stage I or II AGA (Hamilton scale) and women with stage I or II AGA (Ludwig scale) reported fewer patients with a positive hair-pull test and significant new hair growth ($p<0.001$) after 6 months of daily 0.0033% topical melatonin application (level of evidence: 1a).[101] Interestingly, one study noted only women with AGA experienced hair-loss reduction in comparison to men after a 6 month treatment period of daily topical melatonin 0.0033% solution (level of evidence: 2b).[102] Common side effects include headache,[100] pruritis,[101] burning, itching, erythema, and sensitivity.[102]

OTHER MISCELLANEOUS TREATMENTS

Antihistamines

There has been an increased interest in the role of histamine in various types of alopecias, as it is involved in modulating both innate and adaptive immune responses.[103,104] Two antihistamines, cimetidine and cetirizine, are theorized to help treat AGA based on limited evidence of inherent antiinflammatory properties independent of their blockade of histamine receptors.[105]

Cimetidine is a selective histamine receptor 2 (H2) antagonist, originally FDA approved to reduce gastric acid secretion. Evidence from a small study in the 1980s in women with AGA (n = 10) recorded clinical improvement at a dose of 300 mg five times daily for up to 9 months of therapy.[103,106] However, no further relevant studies have been conducted, and interest surrounding its use for AGA has faded, mostly as a result of its side effect profile (dizziness, somnolence).[103]

Cetirizine, a second-generation selective histamine receptor 1 (H1) antagonist, functions by blocking eosinophil activation and mast cell degranulation. Cetirizine is approved for the treatment of allergic rhinitis and chronic urticaria, administered in oral doses between 5 mg and 10 mg, and is generally well tolerated with minimal side effects such somnolence, fatigue, and dry mouth.[107] Interestingly, cetirizine has antiinflammatory and PGD2 suppressive properties.[104] These newly uncovered PGD2 suppressive properties sparked interest in using cetirizine in hair loss, as PGD2 production is implicated in the pathogenesis of AGA.[4] Investigational topical cetirizine 1% increased new hair growth (based on dermatoscopic exam) in 43.3% of patients after 6 months of daily scalp application (level of evidence: 3b).[108] Similarly, it increases total hair density by 11% and terminal hair density by 18% while reducing vellus hair density by 15% after 6 months (level of evidence: 2b).[105] There have been no reports of adverse reactions to topical cetirizine therapy.

EVIDENCE SUMMARY

- Prostaglandin analog topical therapies show significant evidence of efficacy in the treatment of androgenetic alopecia (strength of recommendation: C).
- Janus kinase inhibitors are greatly beneficial in the treatment of alopecia areata (strength of recommendation: A). Comparable results in the treatment of AGA remain to be seen.
- Growth factor therapy stimulates hair follicle growth at the cellular level, and both topical and intradermal preparations have shown success (strength of recommendation: D).
- Wnt pathway mediators are therapeutic options that may emerge as efficacious in the treatment of androgenetic alopecia, based on preliminary results (strength of recommendation: D).
- Topical adenosine, caffeine, and melatonin may improve hair regrowth by reducing hair loss severity and increasing hair density and hair count in

patients with androgenetic alopecia (strength of recommendation: D).

- Botulinum toxin injections have unclear effects on hair growth in patients with androgenetic alopecia and thus are last-line therapies in refractory cases (strength of recommendation: D).
- Novel antiandrogen therapy encompasses several drugs that have shown moderate success in increasing terminal hair growth (strength of recommendation: D).
- Estrogen therapy has shown inconsistent efficacy in the treatment of androgenetic alopecia and is associated with serious adverse reactions that require careful deliberation of treatment options before use (strength of recommendation: D).

REFERENCES

1. Jain R, De-Eknamkul W. Potential targets in the discovery of new hair growth promoters for androgenic alopecia. *Expert Opin Ther Targets.* 2014;18(7):787-806. doi:10.1517/14728222.2014.922956.
2. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol.* 2011;31(5):986-1000. doi:10.1161/ATVBAHA.110.207449.
3. Johnstone MA, Albert DM. Prostaglandin-induced hair growth. *Surv Ophthalmol.* 2002;47(suppl 1):S185-S202. doi:10.1016/s0039-6257(02)00307-7.
4. Garza LA, Liu Y, Yang Z, et al. Prostaglandin D2 inhibits hair growth and is elevated in bald scalp of men with androgenetic alopecia. *Sci Transl Med.* 2012;4(126):126ra34. doi:10.1126/scitranslmed.3003122.
5. Sasaki S, Hozumi Y, Kondo S. Influence of prostaglandin F2alpha and its analogues on hair regrowth and follicular melanogenesis in a murine model. *Exp Dermatol.* 2005;14(5):323-328. doi:10.1111/j.0906-6705.2005.00270.x.
6. Urade Y, Watanabe K, Hayaishi O. Prostaglandin D, E, and F synthases. *J Lipid Mediat Cell Signal.* 1995;12(2-3):257-273. doi:10.1016/0929-7855(95)00032-l.
7. Tanaka K, Ogawa K, Sugamura K, Nakamura M, Takano S, Nagata K. Cutting edge: differential production of prostaglandin D2 by human helper T cell subsets. *J Immunol.* 2000;164(5):2277-2280. doi:10.4049/jimmunol.164.5.2277.
8. Alkhalifah A. Topical and intralesional therapies for alopecia areata. *Dermatol Ther.* 2011;24(3):355-363. doi:10.1111/j.1529-8019.2011.01419.x.
9. Hart J, Shafranov G. Hypertrichosis of vellus hairs of the malar region after unilateral treatment with bimatoprost. *Am J Ophthalmol.* 2004;137(4):756-757. doi:10.1016/j.ajo.2003.09.002.
10. Tosti A, Pazzaglia M, Voudouris S, Tosti G. Hypertrichosis of the eyelashes caused by bimatoprost. *J Am Acad Dermatol.* 2004;51(suppl 5):S149-S150. doi:10.1016/j.jaad.2004.05.002.
11. Herane MI, Urbina F. Acquired trichomegaly of the eyelashes and hypertrichosis induced by bimatoprost. *J Eur Acad Dermatol Venereol.* 2004;18(5):644-645. doi:10.1111/j.1468-3083.2004.01020.x.
12. Cohen JL. Enhancing the growth of natural eyelashes: the mechanism of bimatoprost-induced eyelash growth. *Dermatol Surg.* 2010;36(9):1361-1371. doi:10.1111/j.1524-4725.2010.01522.x.
13. Barrón-Hernández YL, Tosti A. Bimatoprost for the treatment of eyelash, eyebrow and scalp alopecia. *Expert Opin Investig Drugs.* 2017;26(4):515-522. doi:10.1080/13543784.2017.1303480.
14. Emer JJ, Stevenson ML, Markowitz O. Novel treatment of female-pattern androgenetic alopecia with injected bimatoprost 0.03% solution. *J Drugs Dermatol.* 2011;10(7):795-798.
15. Khidhir KG, Woodward DF, Farjo NP, et al. The prostamide-related glaucoma therapy, bimatoprost, offers a novel approach for treating scalp alopecias. *FASEB J.* 013;27(2):557-567. doi:10.1096/fj.12-218156.
16. A Safety and Efficacy Study of Bimatoprost in Men with Androgenic Alopecia (AGA). Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01904721. Accessed July 22, 2013.
17. Safety and Efficacy Study of Bimatoprost in the Treatment of Men with Androgenic Alopecia. Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01325337. Accessed March 29, 2011.
18. Safety and Efficacy Study of Bimatoprost in the Treatment of Women with Female Pattern Hair Loss. Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01325350. Accessed March 29, 2011.
19. Blume-Peytavi U, Lönnfors S, Hillmann K, Garcia Bartels N. A randomized double-blind placebo-controlled pilot study to assess the efficacy of a 24-week topical treatment by latanoprost 0.1% on hair growth and pigmentation in healthy volunteers with androgenetic alopecia. *J Am Acad Dermatol.* 2012;66(5):794-800. doi:10.1016/j.jaad.2011.05.026.
20. Allergan. *Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2A Study of Setipiprant Tablets in Androgenetic Alopecia in Males.* clinicaltrials.gov; 2019. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02781311. Accessed April 12, 2021.
21. Ratner P, Andrews CP, Hampel FC, et al. Efficacy and safety of setipiprant in seasonal allergic rhinitis: results from Phase 2 and Phase 3 randomized, double-blind, placebo- and active-referenced studies. *Allergy Asthma*

Clin Immunol. 2017;13:18. doi:10.1186/s13223-017-0183-z.
22. Murray PJ. The JAK-STAT signaling pathway: input and output integration. *J Immunol.* 2007;178(5):2623-2629. doi:10.4049/jimmunol.178.5.2623.
23. Clark JD, Flanagan ME, Telliez JB. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. *J Med Chem.* 2014;57(12):5023-5038. doi:10.1021/jm401490p.
24. Ito T, Tokura Y. The role of cytokines and chemokines in the T-cell-mediated autoimmune process in alopecia areata. *Exp Dermatol.* 2014;23(11):787-791. doi:10.1111/exd.12489.
25. Strazzulla LC, Wang EHC, Avila L, et al. Alopecia areata: An appraisal of new treatment approaches and overview of current therapies. *J Am Acad Dermatol.* 2018;78(1):15-24. doi:10.1016/j.jaad.2017.04.1142.
26. Harel S, Higgins CA, Cerise JE, et al. Pharmacologic inhibition of JAK-STAT signaling promotes hair growth. *Sci Adv.* 2015;1(9):e1500973. doi:10.1126/sciadv.1500973.
27. *Aclaris Therapeutics Announces Positive 6-Month Results from a Phase 2 Open-Label Clinical Trial of ATI-502 Topical in Patients with Androgenetic Alopecia (Male/Female Pattern-Baldness)*. BioSpace. Available at: https://www.biospace.com/article/aclaris-therapeutics-announces-positive-6-month-results-from-a-phase-2-open-label-clinical-trial-of-ati-502-topical-in-patients-with-androgenetic-alopecia-male-female-pattern-baldness-/. Accessed June 17, 2019.
28. Liu LY, Craiglow BG, Dai F, King BA. Tofacitinib for the treatment of severe alopecia areata and variants: a study of 90 patients. *J Am Acad Dermatol.* 2017;76(1):22-28. doi:10.1016/j.jaad.2016.09.007.
29. Yale K, Pourang A, Plikus MV, Mesinkovska NA. At the crossroads of 2 alopecias: androgenetic alopecia pattern of hair regrowth in patients with alopecia areata treated with oral Janus kinase inhibitors. *JAAD Case Rep.* 2020;6(5):444-446. doi:10.1016/j.jdcr.2020.02.026.
30. Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. *Haematologica.* 2015;100(4):479-488. doi:10.3324/haematol.2014.115840.
31. O'Sullivan JM, McLornan DP, Harrison CN. Safety considerations when treating myelofibrosis. *Expert Opin Drug Saf.* 2016;15(9):1185-1192. doi:10.1080/14740338.2016.1185414.
32. Arana Yi C, Tam CS, Verstovsek S. Efficacy and safety of ruxolitinib in the treatment of patients with myelofibrosis. *Future Oncol.* 2015;11(5):719-733. doi:10.2217/fon.14.272.
33. Verden A, Dimbil M, Kyle R, Overstreet B, Hoffman KB. Analysis of spontaneous postmarket case reports submitted to the FDA regarding thromboembolic adverse events and JAK inhibitors. *Drug Saf.* 2018;41(4):357-361. doi:10.1007/s40264-017-0622-2.
34. Wollenhaupt J, Silverfield J, Lee EB, et al. Safety and efficacy of tofacitinib, an oral janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, long-term extension studies. *J Rheumatol.* 2014;41(5):837-852. doi:10.3899/jrheum.130683.
35. Papp KA, Krueger JG, Feldman SR, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: long-term efficacy and safety results from 2 randomized phase-III studies and 1 open-label long-term extension study. *J Am Acad Dermatol.* 2016;74(5):841-850. doi:10.1016/j.jaad.2016.01.013.
36. Houschyar KS, Borrelli MR, Tapking C, et al. Molecular mechanisms of hair growth and regeneration: current understanding and novel paradigms. *Dermatology.* 2020;236(4):271-280. doi:10.1159/000506155.
37. Gentile P, Garcovich S. Systematic review of platelet-rich plasma use in androgenetic alopecia compared with Minoxidil, Finasteride, and adult stem cell-based therapy. *Int J Mol Sci.* 2020;21(8):2702. doi: 10.3390/ijms21082702.
38. Kapoor R, Shome D. Intradermal injections of a hair growth factor formulation for enhancement of human hair regrowth - safety and efficacy evaluation in a first-in-man pilot clinical study. *J Cosmet Laser Ther.* 2018;20(6):369-379. doi:10.1080/14764172.2018.1439965.
39. Shimizu H, Morgan BA. Wnt signaling through the beta-catenin pathway is sufficient to maintain, but not restore, anagen-phase characteristics of dermal papilla cells. *J Invest Dermatol.* 2004;122(2):239-245. doi:10.1046/j.0022-202X.2004.22224.x.
40. Millar SE. Molecular mechanisms regulating hair follicle development. *J Invest Dermatol.* 2002;118(2):216-225. doi:10.1046/j.0022-202x.2001.01670.x.
41. Zimber MP, Ziering C, Zeigler F, et al. Hair regrowth following a Wnt- and follistatin containing treatment: safety and efficacy in a first-in-man phase 1 clinical trial. *J Drugs Dermatol.* 2011;10(11):1308-1312.
42. Gentile P, Garcovich S. Advances in regenerative stem cell therapy in androgenic alopecia and hair loss: Wnt pathway, growth-factor, and mesenchymal stem cell signaling impact analysis on cell growth and hair follicle development. *Cells.* 2019;8(5):466. doi:10.3390/cells8050466.
43. Yazici Y, Swearingen C, Simsek I, et al. *Safety, tolerability and efficacy of a topical treatment (sm04554) for androgenic alopecia (AGA): results from a phase 2 trial*. Poster Session presented at the: American Academy of Dermatology (AAD); March 4, 2016; Washington, DC.
44. Seykora J, Simsek I, DiFrancesco A, et al. *Safety and biopsy outcomes of a topical treatment (sm04554) for male*

androgenic alopecia (AGA): results from a phase 2, multicenter, randomized, double-blind, vehicle-controlled trial. Poster Session presented at the: American Academy of Dermatology (AAD); March 3, 2017; Orlando, FL.

45. Lee YB, Eun YS, Lee JH, et al. Effects of topical application of growth factors followed by microneedle therapy in women with female pattern hair loss: a pilot study. *J Dermatol.* 2013;40(1):81-83. doi:10.1111/j.1346-8138.2012.01680.x.
46. Yu CQ, Zhang H, Guo ME, et al. Combination therapy with topical minoxidil and nano-microneedle-assisted fibroblast growth factor for male androgenetic alopecia: a randomized controlled trial in Chinese patients. *Chin Med J (Engl).* 2020;134(7):851-853. doi:10.1097/CM9.0000000000001195.
47. Layland J, Carrick D, Lee M, Oldroyd K, Berry C. Adenosine: physiology, pharmacology, and clinical applications. *JACC Cardiovasc Interv.* 2014;7(6):581-591. doi:10.1016/j.jcin.2014.02.009.
48. Iino M, Ehama R, Nakazawa Y, et al. Adenosine stimulates fibroblast growth factor-7 gene expression via adenosine A2b receptor signaling in dermal papilla cells. *J Invest Dermatol.* 2007;127(6):1318-1325. doi:10.1038/sj.jid.5700728.
49. Li M, Marubayashi A, Nakaya Y, Fukui K, Arase S. Minoxidil-induced hair growth is mediated by adenosine in cultured dermal papilla cells: possible involvement of sulfonylurea receptor 2B as a target of minoxidil. *J Invest Dermatol.* 2001;117(6):1594-1600. doi:10.1046/j.0022-202x.2001.01570.x.
50. Oura H, Iino M, Nakazawa Y, et al. Adenosine increases anagen hair growth and thick hairs in Japanese women with female pattern hair loss: a pilot, double-blind, randomized, placebo-controlled trial. *J Dermatol.* 2008;35(12):763-767. doi:10.1111/j.1346-8138.2008.00564.x.
51. Inui S, Fukuzato Y, Nakajima T, Yoshikawa K, Itami S. Androgen-inducible TGF-beta1 from balding dermal papilla cells inhibits epithelial cell growth: a clue to understand paradoxical effects of androgen on human hair growth. *FASEB J.* 2002;16(14):1967-1969. doi:10.1096/fj.02-0043fje.
52. Watanabe Y, Nagashima T, Hanzawa N, et al. Topical adenosine increases thick hair ratio in Japanese men with androgenetic alopecia. *Int J Cosmet Sci.* 2015;37(6):579-587. doi:10.1111/ics.12235.
53. Iwabuchi T, Ideta R, Ehama R, et al. Topical adenosine increases the proportion of thick hair in Caucasian men with androgenetic alopecia. *J Dermatol.* 2016;43(5):567-570. doi:10.1111/1346-8138.13159.
54. Faghihi G, Iraji F, Rajaee Harandi M, Nilforoushzadeh M-A, Askari G. Comparison of the efficacy of topical minoxidil 5% and adenosine 0.75% solutions on male androgenetic alopecia and measuring patient satisfaction rate. *Acta Dermatovenerol Croat.* 2013;21(3):155-159.
55. Başar E, Arıcı C. Use of botulinum neurotoxin in ophthalmology. *Turk J Ophthalmol.* 2016;46(6):282-290. doi:10.4274/tjo.57701.
56. Scott AB, Rosenbaum A, Collins CC. Pharmacologic weakening of extraocular muscles. *Invest Ophthalmol.* 1973;12(12):924-927.
57. Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with C. botulinum-A exotoxin. *J Dermatol Surg Oncol.* 1992;18(1):17-21. doi:10.1111/j.1524-4725.1992.tb03295.x.
58. Freund BJ, Schwartz M. Treatment of male pattern baldness with botulinum toxin: a pilot study. *Plast Reconstr Surg.* 2010;126(5):246e-248e. doi:10.1097/PRS.0b013e3181ef816d.
59. Shon U, Kim MH, Lee DY, Kim SH, Park BC. The effect of intradermal botulinum toxin on androgenetic alopecia and its possible mechanism. *J Am Acad Dermatol.* 2020;83(6):1838-1839. doi:10.1016/j.jaad.2020.04.082.
60. Singh S, Neema S, Vasudevan B. A pilot study to evaluate effectiveness of botulinum toxin in treatment of androgenetic alopecia in males. *J Cutan Aesthet Surg.* 2017;10(3):163-167. doi:10.4103/JCAS.JCAS_77_17.
61. Zhang L, Yu Q, Wang Y, Ma Y, Shi Y, Li X. A small dose of botulinum toxin A is effective for treating androgenetic alopecia in Chinese patients. *Dermatol Ther.* 2019;32(4):e12785. doi:10.1111/dth.12785.
62. Zhou Y, Yu S, Zhao J, Feng X, Zhang M, Zhao Z. Effectiveness and safety of botulinum toxin type A in the treatment of androgenetic alopecia. *Biomed Res Int.* 2020;2020:1501893. doi:10.1155/2020/1501893.
63. Fischer TW, Hipler UC, Elsner P. Effect of caffeine and testosterone on the proliferation of human hair follicles in vitro. *Int J Dermatol.* 2007;46(1):27-35. doi:10.1111/j.1365-4632.2007.03119.x.
64. Völker JM, Koch N, Becker M, Klenk A. Caffeine and its pharmacological benefits in the management of androgenetic alopecia: a review. *Skin Pharmacol Physiol.* 2020;33(3):93-109. doi:10.1159/000508228.
65. Trauer S, Lademann J, Knorr F, et al. Development of an in vitro modified skin absorption test for the investigation of the follicular penetration pathway of caffeine. *Skin Pharmacol Physiol.* 2010;23(6):320-327. doi:10.1159/000313514.
66. Tsianakas A, Hüsing B, Moll I. An ex vivo model of male skin - caffeine counteracts testosterone effects. *Arch Dermatol Res.* 2005;296:450.
67. Fischer TW, Herczeg-Lisztes E, Funk W, Zillikens D, Bíró T, Paus R. Differential effects of caffeine on hair shaft elongation, matrix and outer root sheath keratinocyte proliferation, and transforming growth factor-β2/

insulin-like growth factor-1-mediated regulation of the hair cycle in male and female human hair follicles in vitro. *Br J Dermatol.* 2014;171(5):1031-1043. doi:10.1111/bjd.13114.
68. Sisto T, Bussoletti C, Celleno L. Efficacy of a cosmetic caffeine shampoo in androgenetic alopecia management. *J Appl Cosmetol.* 2012;31:57-66.
69. Bussoletti C, Mastropietro F, Tolani M. Use of a caffeine shampoo for the treatment of male androgenetic alopecia. *J Appl Cosmetol.* 2011;29:167-180.
70. Bussoletti C, Tolaini MV, Celleno L. Efficacy of a cosmetic phyto-caffeine shampoo in female androgenetic alopecia. *G Ital Dermatol Venereol.* 2020;155(4):492-499. doi:10.23736/S0392-0488.18.05499-8.
71. Bussoletti C, Mastropietro F, Tolaini M, Celleno L. Use of a cosmetic caffeine lotion in the treatment of male androgenetic alopecia. *J Appl Cosmetol.* 2011;29:167-180.
72. Dhurat R, Chitallia J, May TW, et al. An open-label randomized multicenter study assessing the noninferiority of a caffeine-based topical liquid 0.2% versus Minoxidil 5% solution in male androgenetic alopecia. *Skin Pharmacol Physiol.* 2017;30(6):298-305. doi:10.1159/000481141.
73. Golpour M, Rabbani H, Farzin D, Azizi F. Comparing the effectiveness of local solution of minoxidil and caffeine 2.5% with local solution of Minoxidil 2.5% in treatment of androgenetic alopecia. *J Mazandaran Univ Med Sci.* 2013;23(106):30-36.
74. Pazoki-Toroudi H, Moghadam R, Ajami M, Nassiri-Kashani M, Ehsani A, Tabatabaie H. The efficacy and safety of minoxidil 5% combination with azelaic acid 1/5% and caffeine 1% solution on male pattern hair loss. *J Invest Dermatol.* 2013;133:S84.
75. Sun HY, Sebaratnam DF. Clascoterone as a novel treatment for androgenetic alopecia. *Clin Exp Dermatol.* 2020;45(7):913-914. Available at: https://doi.org/10.1111/ced.14292.
76. Zito PM, Bistas KG, Syed K. Finasteride. In: *StatPearls.* StatPearls Publishing; 2021. Available at: http://www.ncbi.nlm.nih.gov/books/NBK513329/. Accessed May 4, 2021.
77. *Cassiopea Announces Very Positive Phase II Twelve Months Results for Breezula (Clascoterone) in Treating Androgenetic Alopecia*. Cassiopea. Published April 16, 2019. Available at: https://www.bloomberg.com/press-releases/2019-04-16/cassiopea-announces-very-positive-phase-ii-twelve-monthsresults- for-breezula-clascoterone-in-treating-androgenetic. Accessed March 28, 2021.
78. Sovak M, Seligson AL, Kucerova R, Bienova M, Hajduch M, Bucek M. Fluridil, a rationally designed topical agent for androgenetic alopecia: first clinical experience. *Dermatol Surg.* 2002;28(8):678-685. doi:10.1046/j.1524-4725.2002.02017.x.
79. Paradisi R, Porcu E, Fabbri R, Seracchioli R, Battaglia C, Venturoli S. Prospective cohort study on the effects and tolerability of flutamide in patients with female pattern hair loss. *Ann Pharmacother.* 2011;45(4):469-475. doi:10.1345/aph.1P600.
80. Johnson DB, Sonthalia S. Flutamide. In: *StatPearls.* Florida: StatPearls Publishing; 2021. Available at: http://www.ncbi.nlm.nih.gov/books/NBK482215/. Accessed May 4, 2021.
81. Carmina E, Lobo RA. Treatment of hyperandrogenic alopecia in women. *Fertil Steril.* 2003;79(1):91-95. doi:10.1016/s0015-0282(02)04551-x.
82. *Kintor Pharmaceutical's Completion of Patients Enrolment for Pyrilutamide's Phase II Clinical Trial for Treatment of Androgenetic Alopecia*. Kintor Pharmaceutical Limited. Available at: https://en.kintor.com.cn/news/155.html. Accessed Dec. 30, 2020.
83. Kim JH, Lee SY, Lee HJ, Yoon NY, Lee WS. The efficacy and safety of 17α-estradiol (Ell-Cranell alpha 0.025%) solution on female pattern hair loss: single center, open-label, non-comparative, phase IV study. *Ann Dermatol.* 2012;24(3):295-305. doi:10.5021/ad.2012.24.3.295.
84. Georgala S, Katoulis AC, Georgala C, Moussatou V, Bozi E, Stavrianeas NG. Topical estrogen therapy for androgenetic alopecia in menopausal females. *Dermatology.* 2004;208(2):178-179. doi:10.1159/000076497.
85. Hariri L, Rehman A. Estradiol. In: *StatPearls.* StatPearls Publishing; 2021. Available at: http://www.ncbi.nlm.nih.gov/books/NBK549797/. Accessed May 4, 2021.
86. Choe SJ, Lee S, Choi J, Lee WS. Therapeutic efficacy of a combination therapy of topical 17α-estradiol and topical minoxidil on female pattern hair loss: a noncomparative, retrospective evaluation. *Ann Dermatol.* 2017;29(3):276-282. doi:10.5021/ad.2017.29.3.276.
87. Blume-Peytavi U, Kunte C, Krisp A, Garcia Bartels N, Ellwanger U, Hoffmann R. Comparison of the efficacy and safety of topical minoxidil and topical alfatradiol in the treatment of androgenetic alopecia in women. *J Dtsch Dermatol Ges.* 2007;5(5):391-395. doi:10.1111/j.1610-0387.2007.06295.x.
88. Vexiau P, Chaspoux C, Boudou P, et al. Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol.* 2002;146(6):992-999. doi:10.1046/j.1365-2133.2002.04798.x.
89. Frank LA. OEstrogen receptor antagonist and hair regrowth in dogs with hair cycle arrest (alopecia X). *Vet Dermatol.* 2007;18(1):63-66. Available at: https://doi.org/10.1111/j.1365-3164.2007.00559.x.
90. Farooq M, Patel SP. Fulvestrant. In: StatPearls. *StatPearls* Publishing; 2021. Available at: http://www.ncbi.nlm.nih.gov/books/NBK560854/. Accessed May 4, 2021.

91. Lai AC, Crews CM. Induced protein degradation: an emerging drug discovery paradigm. *Nat Rev Drug Discov.* 2017;16(2):101-114. doi:10.1038/nrd.2016.211.
92. Gassmueller J, Hoffmann R, Webster A. Topical fulvestrant solution has no effect on male and postmenopausal female androgenetic alopecia: results from two randomized, proof-of-concept studies. *Br J Dermatol.* 2008;158(1):109-115. doi:10.1111/j.1365-2133.2007.08276.x.
93. Ekmekcioglu C. Melatonin receptors in humans: biological role and clinical relevance. *Biomed Pharmacother.* 2006;60(3):97-108. doi:10.1016/j.biopha.2006.01.002.
94. Tan D, Chen L, Poeggeler B, Manchester L, Reiter R. Melatonin: a potent, endogenous hydroxyl radical scavenger. *Endocr J.* 1993;1:57-60.
95. Fischer TW, Sweatman TW, Semak I, Sayre RM, Wortsman J, Slominski A. Constitutive and UV-induced metabolism of melatonin in keratinocytes and cell-free systems. *FASEB J.* 2006;20(9):1564-1566. doi:10.1096/fj.05-5227fje.
96. Fischer TW, Slominski A, Tobin DJ, Paus R. Melatonin and the hair follicle. *J Pineal Res.* 2008;44(1):1-15. doi:10.1111/j.1600-079X.2007.00512.x.
97. Fischer TW, Trüeb RM, Hänggi G, Innocenti M, Elsner P. Topical melatonin for treatment of androgenetic alopecia. *Int J Trichology.* 2012;4(4):236-245. doi:10.4103/0974-7753.111199.
98. Macher JP. Pharmacokinetics and clinical and biological tolerability of repeated topical application of a melatonin-containing cosmetic hair solution in healthy female volunteers. A double-blind, placebo-controlled, crossover design study. Clinical Study Report. MEL-COS-1. Data on file. Asatona AG, Switzerland.
99. Lorenzi S, Caputo R. Melatonin cosmetic hair solution: Open study of the efficacy and the safety on hair loss (telogen) control and hair growth (anagen) stimulation. MEL-COS-AS01. Data on file. Asatona AG, Switzerland.
100. Lorenzi S, Barbareschi M, Caputo R. Efficacy and safety of a melatonin-containing cosmetic hair solution in the treatment of early stages of male androgenic alopecia. Open study with Trichoscan evaluation. Report/Protocol. MEL-COS-AS03. Data on file. Asatona AG, Switzerland.
101. Innocenti M, Barbareschi M. Open-label, non comparative, multicenter clinical study on efficacy and safety of a melatonin-containing cosmetic hair solution in the treatment of hair loss (telogen) and in the stimulation of hair re-growth (anagen) Report. MEL-COS-AS05. Data on file. Asatona AG, Switzerland.
102. Schmid HW. Use Test with of a melatonin-containing cosmetic hair solution to determine the change of the appearance and texture of thinning and fine hair following the application. Statistical Report. MEL-COS-AS04. Data on file. Asatona AG, Switzerland.
103. Jafarzadeh A, Nemati M, Khorramdelazad H, Hassan ZM. Immunomodulatory properties of cimetidine: its therapeutic potentials for treatment of immune-related diseases. *Int Immunopharmacol.* 2019;70:156-166. doi:10.1016/j.intimp.2019.02.026.
104. Charlesworth EN, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Effect of cetirizine on mast cell-mediator release and cellular traffic during the cutaneous late-phase reaction. *J Allergy Clin Immunol.* 1989;83(5):905-912. doi:10.1016/0091-6749(89)90104-8.
105. Rossi A, Campo D, Fortuna MC, et al. A preliminary study on topical cetirizine in the therapeutic management of androgenetic alopecia. *J Dermatolog Treat.* 2018;29(2):149-151. doi:10.1080/09546634.2017.1341610.
106. Aram H. Treatment of female androgenetic alopecia with cimetidine. *Int J Dermatol.* 1987;26(2):128-130. doi:10.1111/j.1365-4362.1987.tb00546.x.
107. Naqvi A, Gerriets V. Cetirizine. In: *StatPearls.* StatPearls Publishing; 2021. Available at: http://www.ncbi.nlm.nih.gov/books/NBK549776/. Accessed May 4, 2021.
108. Zaky MS, Abo Khodeir H, Ahmed HA, Elsaie ML. Therapeutic implications of topical cetirizine 1% in treatment of male androgenetic alopecia: a case-controlled study. *J Cosmet Dermatol.* 2021;20(4):1154-1159. doi:10.1111/jocd.13940.