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Clinical Evidence. Practical Advice

Editor-in-Chief: Dr. Stuart Maddin

Dr. Stuart Maddin, MD, FRCPC
EDITOR-IN-CHIEF

Dr. Stuart Maddin is the Chairman of SkinCareGuide. He is one of North America's leading dermatologists and the author of numerous dermatologic journal articles, monographs and textbooks. In addition to providing consultative input to a number of pharmaceutical and biotech companies, he is the director of the Clinical Trials Unit at the Department of Dermatology and Skin Science, University of British Columbia. Dr. Maddin has also acted in an advisory capacity to a number of drug regulatory agencies, such as the Health Protection Branch (Ottawa), the AAD-FDA Liaison Committee, and World Health Organization (Geneva). He is the founder of the Dermatology Update symposia, now in its 27th year. As well, he is Past President of the Canadian Dermatology Association and served as Secretary-General of the International Committee of Dermatology – International League of Dermatological Societies.

Dr. Colleen Lawlor, MD, CCFP
FAMILY PRACTICE ADVISOR

Dr. Colleen Lawlor has chosen to build her family practice at Continuum Medical Care located in West Vancouver, BC. Dr. Lawlor has a BA in Psychology, an MSC in Nursing, and her MD, CCFP. She received her medical training at the University of Texas in San Antonio.

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Topical Acne Therapy Advances in 2011

Jessica Wilford, MD and Shannon Humphrey, MD, FRCPC, FAAD

Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

Introduction

Acne vulgaris is a common disorder of the pilosebaceous follicle with multiple pathogenic factors. While previous anti-acne treatment algorithms focused on antibiotics, the incidence of antibiotic resistance and the availability of more effective, well-tolerated topical agents have led to new treatment paradigms. The 2009 Global Alliance to Improve Outcomes in Acne guidelines[1] recommend that mild to moderate acne is best treated with retinoid-based topical agents. In addition, acne is increasingly recognized as a chronic disorder with a pattern of recurring outbreaks and important social and psychological effects. Aggressive treatment of acne at clinical onset, followed by maintenance therapy, is recommended in order to reduce the duration of active acne and in turn decrease the likelihood of physical scarring and psychological impact.

Overview

Pathogenesis

- Four main pathogenic factors interact to cause acne:[1]
  1. Abnormal follicular keratinization and desquamation
  2. Excess production of sebum
  3. Bacterial colonization of pilosebaceous duct by *Propionibacterium acnes* (*P. acnes*)
  4. Inflammation
- Hygiene, beyond gentle twice-daily cleansing, has a negligible effect on acne development or resolution.
- The evidence implicating diet in the pathogenesis of acne is inconclusive, but high glycemic diets and dairy may contribute.[2]
- Acne formation begins with the microcomedone, a clinically invisible lesion. Microcomedones then develop into visible acne lesions: comedones, papules, pustules, and nodules. The degree of inflammation is variable.

Prevalence and Diagnostic Features

- The pilosebaceous unit is found in highest concentrations on the face, chest, and back, explaining the clinical distribution of acne.
- About 80% of people between the ages of 11-30 years are affected[2] and up to 50% of affected individuals continue to have acne as adults.[1]
- Acne is characterized by polymorphous lesions:
  - Non-inflammatory - open and closed comedones
  - Inflammatory - papules, pustules, and nodules
- Acne can also be classified by severity:
  - Mild - comedonal and papular/pustular
  - Moderate - papular/pustular and nodular
  - Severe - scarring, acne conglobata or fulminans
- Acne is best approached as a chronic disease[1,3] because of its relapsing and recurring pattern, prolonged course, manifestation as acute outbreaks or slow onset, and psychological and social impacts. The psychological sequelae of acne may not correlate with disease severity.

ALSO IN THIS ISSUE: **Topical Management of Psoriasis and the Role of Vitamin D3 Analogues** *(page 4)* & **Management of Unwanted Facial Hair** *(page 6)*

Treatment Rationale

- Sixty percent of acne cases can be managed with acute therapy followed by topical maintenance treatment.[1]
- The goal of therapy is to treat visible acne, then continue maintenance to prevent the formation of microcomedones.
- Treatment can prevent or reduce negative outcomes, such as scarring, hyperpigmentation, depression, anxiety, and social withdrawal.
- Treatment should target multiple pathogenic factors.
- The historical approach of using topical or systemic antibiotic monotherapy to target *P. acnes* contributes to antibiotic resistance.
- Topical therapy of a retinoid plus an antimicrobial (benzoyl peroxide, or benzoyl peroxide + antibiotic) targets 3 of the 4 pathogenic factors while avoiding systemic effects and antibiotic resistance.

Topical Treatment Options (Table 1)

- Level 1 evidence shows combination retinoid-based therapy is first-line for acne treatment and it targets 3 of the 4 pathogenic factors: *P. acnes* colonization, inflammation, and abnormal desquamation.[1]
- Retinoids are comedolytic, anticomedogenic, and anti-inflammatory.
- Benzoyl peroxide (BPO) is an antimicrobial agent that has some keratolytic effects and does not contribute to antibiotic resistance.
- Antibiotics have antimicrobial and anti-inflammatory effects, but they should be used in conjunction with BPO lotion, gel or wash to limit antibiotic resistance, and should not be used for maintenance therapy.
- New fixed-dose retinoid-based combination therapies are available.
  - Patient adherence is improved with once daily dosing of a single formula.
  - Retinoid-BPO formulations may be preferable over retinoid-antibiotic formulations because there is no risk of developing bacterial resistance.[1]

New Fixed-dose Combination Acne Treatments

Adapalene-Benzoyl Peroxide Gel (Tactuo™)

- This new fixed-dose (adapalene 0.1%-BPO 2.5%) topical agent is the first retinoid-BPO combination formulation.
- Applied once daily.
- Three double-blind randomized controlled trials[4-6] including a total of 3855 acne patients compared the efficacy of adapalene-BPO with adapalene, BPO, and gel vehicle. All three studies showed statistically significant superior efficacy of the adapalene-BPO combination over the three comparison treatments in total or near total clearing of acne and reduction in total number of inflammatory and noninflammatory lesions.
- An analysis of these three studies demonstrates a synergistic effect beyond that attributable to each agent alone:[7]
  - 1.2% of patients discontinued due to adverse events
  - 21.6% of patients experienced adverse events including dryness, erythema, scaling, and stinging/burning
  - Adverse events had a mean rating of "below mild" and peaked at week 1, then improved

Clindamycin-Tretinoin Gel (Biacna®)

- A new clindamycin-tretinoin fixed-dose combination gel is available.
- Applied once daily.
- Two randomized, double-blind, controlled trials[8] of 2219 subjects compared the combination clindamycin-tretinoin hydrogel with each agent alone and gel vehicle for the treatment of acne vulgaris. The studies both showed statistically significant superior efficacy of the clindamycin-tretinoin combination over either agent alone or vehicle in reducing the number of inflammatory and noninflammatory lesions and inducing near or total clearing of the skin, with good tolerance.
- This formulation should be not be used for maintenance therapy and use in conjunction with a BPO product is recommended to limit antibiotic resistance.[1]

Systemic Treatment Considerations

- Patients with severe inflammatory acne will likely require systemic therapy.
- Patients with moderate acne may also need systemic therapy, after adherence to topical therapies is assessed.
- Investigation for endocrine causes of acne may be indicated in cases with atypical clinical presentation, cases that are particularly severe and treatment resistant, or those associated with systemic signs and symptoms of endocrine disturbance. In females patients, exclude polycystic ovary syndrome, adrenal or ovarian tumors, and congenital adrenal hyperplasia. In males, exclude congenital adrenal hyperplasia.

Acne Pathogenic Factors	**Retinoids** Adapalene Tazarotene Tretinoin	**Benzoyl Peroxide**	**Antibiotics** Clindamycin Erythromycin
Reduces production of sebum			
Targets *P. acnes*		X	X
Normalizes keratinization and desquamation	X	X	
Anti-inflammatory	X	X	X

Table 1. Topical acne therapies and their pathogenic targets

- Systemic therapies include:[3]
  - Oral antibiotic + topical retinoid ± BPO
  - Oral isotretinoin
  - Oral contraceptive/anti-androgen for female patients

Limiting Antibiotic Resistance

- Oral antibiotics can cause resistance in bacterial flora throughout the body, while topical antibiotics can cause resistance of skin flora at the treated site.
- Recommendations to limit antibiotic resistance:[1]
  - Reserve oral antibiotics for moderate to severe acne
  - Topical and systemic antibiotics should always be combined with BPO and a topical retinoid
  - Limit antibiotic duration: assess response and continuing need at 6-12 weeks
  - If multiple courses of antibiotics are required avoid unnecessary antibiotic switches (use the same one each time if effective)
  - Use BPO along with antibiotics (BPO is an efficient bactericidal agent and will minimize development of bacterial resistance at sites of topical antibiotic therapy)
  - Avoid oral or topical antibiotic monotherapy for acute or maintenance therapy
  - Avoid concurrent oral and topical antibiotic therapy without the addition of BPO

Maintenance Therapy

- A topical retinoid ± BPO is first-line maintenance therapy[1] because it effectively controls the formation of microcomedones, is well-tolerated, and does not contribute to antibiotic resistance.
- For patients with mild to moderately severe acne, regardless of the type of therapy used to treat the acute episode of acne, a retinoid-based topical maintenance regimen should be initiated once lesions have resolved. For patients with severe acne, a different approach may be required.[1]
- Because of the complex interplay of acne pathogenic factors, maintenance therapy may need to be continued for months to years.
- Patients should be advised that acne might follow a chronic pattern of remissions and outbreaks, which are best managed with maintenance therapy to control the formation of microcomedones before acne lesions become visible.
- Regular follow-up visits at least every 6 months during maintenance therapy will allow for assessment of treatment response, side-effects, and adherence.

Conclusion

Acne is a very common skin disorder predominantly managed in the family practice setting. In conjunction with patient education and a strong therapeutic alliance, retinoid-based topical agents for acute and maintenance therapy, including strategies to limit antibiotic resistance, are effective for mild to moderately severe acne, with few adverse effects and improved quality of life for affected patients.

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Topical Management of Psoriasis and the Role of Vitamin D3 Analogues

Kathleen Katipunan, MD and Melinda Gooderham MD, MSc, FRCPC[1]

[1]Skin Centre for Dermatology and Skin Laser Clinic, Peterborough, ON, Canada

Introduction

Psoriasis is a chronic, recurrent, immune-mediated, papulosquamous skin condition characterized by rapid proliferation of keratinocytes. Worldwide prevalence is reported to be 2%[1] and incidence rates in the US and Canada have been reported to be as high as 4.6% and 4.7%, respectively.[2] Psoriasis is commonly manifested as well-defined erythematous plaques with silvery white scale on the elbows, knees, intergluteal cleft, and trunk. Between 50-80% of all psoriasis patients also develop scalp involvement at some stage.[3,4] Approximately 80% of patients affected with psoriasis have mild to moderate disease that can be managed with topical agents.[1] Various available topical therapies will be briefly discussed. The focus of this review will be on vitamin D3 analogues, including evidence from clinical trials investigating these agents.

Rationale for Treatment of Psoriasis

Although, in a vast majority of cases, psoriasis is not life threatening, it is associated with significant physical, psychological, social and economic burdens. Effective interventions are available that can dramatically improve disease symptoms and quality of life.

Patient-centered Care

The chronicity of psoriasis requires a long-term, patient-specific approach to management. From a pharmacologic perspective, factors that can influence treatment decisions include safety and efficacy, onset of action, product characteristics, and cost. As well, important considerations unique to each patient include medical history, disease severity, lifestyle, preferences, tolerability, and adherence.

The dominating factor for improving adherence to prescribed therapy is time invested by the physician, where clinical knowledge and experience are translated into patient care and treatment satisfaction. Strategies to build this interface include:

- Establishing good doctor-patient communications
- Modifying or adapting regimens based on response to therapy and patient feedback
- Selecting simple and effective therapeutic regimens
- Encouraging patient self-management (e.g. non-pharmacologic and lifestyle interventions)

Topical Treatments for Psoriasis

Corticosteroids

- Corticosteroids have anti-inflammatory, anti-pruritic, vasoconstrictive, and immunosuppressive properties.[1]
- They are available in an array of formulations and strengths, which make them suitable for treating different areas.[1] In general, ointments have the highest potency (due to occlusion and moisturization), and lotions, foams or gels are preferred for hair-bearing areas (due to ease of spreadability and minimal residue).[1]
- The most efficacious topicals for treating psoriasis are highest potency steroids, followed by vitamin D3 analogues.[1]
- Use is limited by potential side-effects (e.g., skin atrophy, striae, telangiectasia, tachyphylaxis).[1] Overuse or misuse are associated with hypothalamic-pituitary-adrenal (HPA) axis suppression.[5]
- Generally, treatment should continue until the skin is clear, then tapered. Therapy may be limited to 2-4 weeks in certain areas.[1]
- Adverse effects may be minimized by once daily use; long-term remission may be maintained by application on alternate days.[2]

Other Agents

- **Calcineurin inhibitors** (tacrolimus and pimecrolimus) are immunomodulating compounds that act through T-cell modulation. They are particularly effective for treating psoriasis of the face and intertriginous areas.[1]
- **Retinoids** (e.g., tazarotene) modulate cell differentiation and proliferation.[1] Tazarotene is available in cream or gel formulations, applied once daily. It is particularly useful for palmoplantar psoriasis as it does not leave a greasy residue.
- **Anthralin and coal tar** have a long history of use for psoriasis, but they have largely been replaced by newer agents with superior efficacy and better patient acceptability.[1]
- **Combination therapy** is generally more efficacious than monotherapy[1] and can have a lower incidence of adverse effects. Common combinations include two topical agents or a topical agent with phototherapy.

Vitamin D3 Analogues

Background

- In the 1990's, the introduction of vitamin D3 analogues revolutionized the topical treatment for psoriasis. Due to their therapeutic efficacy and limited toxicity, vitamin D3 analogues have become a first-line option for psoriasis.[1]
- Vitamin D3 analogues exert their effect by binding to nuclear vitamin D receptors, inhibiting keratinocyte proliferation and promoting differentiation. A recent study also showed calcipotriol induced apoptosis in psoriatic keratinocytes.[6]
- They can induce a steroid-sparing effect, thereby reducing side-effects such as skin atrophy, tachyphylaxis, and other adverse reactions related to corticosteroid use.
- Available vitamin D3 analogues in Canada include:
  - Calcipotriol ointment, cream, and scalp solution;
  - Calcitriol ointment; and
  - Calcipotriol + betamethasone dipropionate ointment and scalp gel.

Calcipotriol

- Calcipotriol 50 mcg/g ointment or cream (Dovonex®) is available for use on the body and 50 mcg/mL scalp solution is used on the scalp and other hair-bearing areas. It is used twice daily on affected areas and application can be reduced to once daily maintenance therapy when appropriate, and then discontinued after satisfactory improvement.
- In mild to moderate chronic plaque psoriasis, a systematic review showed calcipotriol was as effective as moderately potent topical steroids (e.g., betamethasone valerate ointment). It was also more effective when compared to calcitriol, coal tar, and short-contact dithranol.[7]
- Calcipotriol cream is also a highly efficacious maintenance treatment used alone or in an alternating regimen with calcipotriol/betamethasone dipropionate ointment.[8]
- Irritation can occur on sensitive areas (e.g., flexures, face and hairline). Up to 35% of patients can experience redness, burning, scaling, and pruritus in lesional / perilesional skin.[1]
- Hypercalcemia is a rare concern; doses should be limited to 100 g/week of calcipotriol cream or ointment.[1]
- Calcipotriol is clinically effective in children with very little risk of local or systemic side-effects.[9] Maximum doses are calculated based on body surface area (BSA) and age.

Calcitriol

- Calcitriol ointment 3 mcg/g (Silkis™) is indicated for topical treatment of mild to moderate plaque-type psoriasis with up to 35% BSA involvement. Applied twice daily, no more than 30 g of ointment should be used daily, or 200 g per week.
- In two identically designed, randomized, double-blind, placebo-controlled trials of twice daily calcitriol ointment on mild to moderate psoriasis over 8 weeks, efficacy was seen as early as 2 weeks. At the end of 8 weeks, efficacy was sustained and significantly higher than placebo.[10]
- In two long-term studies over 52 weeks, no major safety concerns were reported. Adverse events (e.g., erythema, pruritus and skin discomfort) were mild.[10] Calcitriol is less irritating than other vitamin D analogues, making it more suitable for use on the face and flexural areas.[11]
- Treatment is approved for patients ≥18 years of age. Safety and efficacy in children have not yet been studied.

Calcipotriol and Betamethasone Dipropionate

- Calcipotriol/betamethasone dipropionate in ointment (Dovobet®) or scalp gel (Xamiol®) has a more rapid onset of action, greater efficacy, and comparable safety vs. either agent alone.[12-14]
- It promotes normal keratinization, inhibits inflammation, and modulates epidermal proliferation and differentiation.
- When combined, the different modes of action of the two molecules become synergistic, enhancing efficacy and reducing side-effects.[15]
- It is an appropriate first-line therapy that is effective and well tolerated across all grades of disease severity.[9]
- Treatment is indicated for once daily application for 4 weeks, but long-term studies of both the ointment[16] and scalp gel[17] formulations have shown good tolerability and safety with as-needed use over 52 weeks.[14]
- Avoid use on the face, intertriginous or sensitive areas (e.g., flexural and genital regions).
- Up to 30% of BSA may be treated.
- Calcipotriol/betamethasone dipropionate therapy showed improvements in health-related quality of life measures and cost effectiveness through pharmacoeconomic analyses.[14]
- Treatment was well tolerated, the most common side-effects were mild to moderate lesional or perilesional irritation.[14]
- A 4-week, double-blind study in 24 patients with extensive psoriasis did not show HPA axis suppression. Furthermore, a follow-up study involving a subset of 19 patients over 52 weeks, some of who alternated with calcipotriol every 4 weeks, also did not demonstrate HPA axis suppression.[14]
- Calcipotriol/betamethasone dipropionate ointment cannot be compounded from its two individual ingredients, as this will result in a mixture that is both unstable and ineffective. However, the commercially available combination product is a stable preparation.

Role of Family Physicians in Psoriasis Management

Even though the majority of psoriasis patients may be managed with topical medication, nonadherence rates for topical treatment is estimated at 40%,[18] including up to 50% for unfilled prescriptions.[19]

As the primary contact for people seeking healthcare, family physicians play a crucial role in promoting treatment adherence among psoriasis patients. This may be achieved by adopting a more patient-specific approach to management, through engaging in ongoing discussions with patients about treatment expectations, choice of therapy, including offering simplified dosing regimens, as well as regularly assessing tolerability and side-effects from medications.

Conclusion

Vitamin D3 analogues offer a form of topical treatment for plaque-type psoriasis that is effective, safe, and in the long run, cost-effective. Single product, fixed-dose, combination therapy is an important, once daily, topical option for the symptomatic treatment of psoriasis that yields comparable safety, increased efficacy, and improved cosmetic acceptance, resulting in higher patient adherence and optimized outcomes.

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Management of Unwanted Facial Hair

Michelle Withers, MD, FRCPC

Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

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Introduction

Unwanted facial hair is a common, frustrating condition that affects up to 25% of women. For many individuals, it significantly impacts their quality of life. Treatment options include physical methods such as shaving, waxing, threading, bleaching, electrolysis, and laser therapy. Pharmacologic methods include chemical depilatories, oral hormonal therapy (i.e., spironolactone and contraceptive pills), and topical enzyme blockade (eflornithine).

Overview of Hirsutism

Hirsutism is defined as excessive growth of terminal hair in women in androgen-sensitive areas of the body (face, neck, chest, etc.).[1] This is to be differentiated from hypertrichosis, which is generalized excessive hair growth. The primary androgen responsible for hair growth is dihydrotestosterone (DHT), which is synthesized from testosterone by the activity of 5-alpha-reductase type 2. Hirsute females have increased 5-alpha-reductase activity in the hair follicles.[2]

Unwanted facial hair is a common, chronic, life-affecting problem for many women. A European study of female college students showed that up to 26% of women had facial hair growth and in 9% it was markedly noticeable.[3] Self-esteem and quality of life can be significantly altered by excessive facial hair.[4] Hirsutism can often be accounted for by ethnicity or genetics, but in a small percentage of people it can be a sign of underlying disease.

Signs of Androgen Excess [5,6]

- Hirsutism
- Acne
- Seborrhea
- Menstrual irregularities or infertility
- Alopecia

Causes of Androgen Excess and Hirsutism [5]

- Polycystic ovarian syndrome (1-4% of all females of reproductive age)
- Androgen-producing tumours (ovarian or adrenal)
- Congenital adrenal hyperplasia
- Cushing's disease
- Exogenous steroid use or other drugs

Clinical Considerations

- To determine if a patient needs a work-up for hirsutism, clinical assessment in the form of a thorough history and physical exam are the most important tools.
- If hirsutism is associated with significant acne, menstrual irregularities or signs of androgenization, such as deepening of the voice, clitoromegaly or other, hormonal work-up is warranted.

Blood-work to Assess for Androgen Excess [6,7]

- Total and free testosterone
- Dehydroepiandrosterone sulfate (DHEA-S)
- +/- 17 hydroxy-progesterone
- +/- prolactin
- +/- 24-hour urine cortisol

Psychological Sequelae

- Studies have shown that women with unwanted facial hair can exhibit significant levels of emotional distress.[4,8]
- The dissatisfaction with their appearance and persistent pattern of hair removal practices can become obsessive and intrusive on the daily lives of affected individuals, resulting in substantial psychosocial burden.
- The social and emotional impacts of hirsutism, especially among women, are commonly overlooked. Hence, assessment for such disturbances is helpful in guiding therapeutic recommendations.

Treatment Overview

Once underlying pathology causing the hirsutism is ruled out, many women will want to pursue removal of their unwanted facial hair. While there is still no permanent method of hair removal, any one or a combination of the following treatment options can be used to improve the cosmetic outcome. The more common hair removal modalities include:

- Physical removal (e.g., shaving, waxing, plucking, electrolysis)
- Bleaching agents
- Chemical depilatories
- Laser assisted removal
- Oral hormonal blockade
- Topical enzyme blockade

Treatment Options for Unwanted Facial Hair

Physical Removal

Physical removal methods are common, inexpensive, and often home administered, excepting electrolysis. Drawbacks to physical removal include discomfort, resultant folliculitis, rapid regrowth, and the possibility of scarring or hyperpigmentation.

- Only electrolysis is potentially permanent.[5]
- Bleaching is effective for lightening the hair shaft, but it does not affect hair length or growth. Irritant dermatitis is a common drawback.
- Chemical depilatories use thioglycolic acid to dissolve the hair shaft. This is effective at removing both the surface hair as well as hair just below the skin surface, but not down to the depth of the follicle. Irritant dermatitis is again a common side-effect.[6]
- Pseudofolliculitis barbae is a common chronic inflammatory skin condition that is caused by the habitual removal of unwanted hair through physical means. This persistent practice can contribute to a foreign-body reaction surrounding the ingrown hair, which can produce papules and pustules that result in hyperpigmentation and keloidal scars.

Laser Hair Removal

- Laser light uses selective thermolysis to cause thermal uptake by the pigmented hair shaft. The heat absorbed by the hair shaft will cause disruption or destruction of the hair follicle.[9,10]
- Various lasers and light sources (e.g., intense pulsed light, alexandrite, diode, Nd:YAG)[9,10] have been used for this treatment and results vary depending on the skin type of the patient, the colour of the hair (i.e., it is ineffective on light-coloured hair), the growth phase of the hair, and the operator.
- Complications can include burning, edema, blistering, hyperpigmentation, scarring, and paradoxical hypertrichosis (~1-4%).[9-11]
- The possibility of permanent hair reduction can be attained through laser therapy.

Oral Hormonal Blockade

- Anti-androgen therapy using oral contraceptives can suppress adrenal and ovarian androgen production and increase sex-hormone binding globulin to reduce circulating testosterone.
- Cyproterone acetate (50-100 mg on days 1-10 of the menstrual cycle) alone or in lower doses in Diane-35® inhibit 5-alpha reductase, preventing the transformation of testosterone to DHT, which is required for hair growth.[12]
- Spironolactone (100-200 mg/day) acts as an androgen receptor blocker, again preventing the interaction of DHT in the hair follicle.[6]
- Side-effects may include menstrual irregularities, breast tenderness, weight gain, and with spironolactone, hyperkalemia and feminization of a male fetus.[6]
- Rare side-effects of contraceptive pills include cerebrovascular events, heart attack, or venous thromboembolism.[6]
- Much less commonly used oral therapies include flutamide and finasteride, as they have more potential toxic effects.

Topical Enzyme Blockade

- Eflornithine hydrochloride (HCl) cream 13.9% (Vaniqa®) is a novel product that is commercially available by prescription only.
- Eflornithine is an irreversible inhibitor of ornithine decarboxylase.
- It does not remove hair, but rather inhibits cell division and other cellular functions, thus slowing, but not stopping, hair growth, and shortens both the length and mass of hair.[13]
- Topical eflornithine HCl is effective against all causes of excessive facial hair, regardless of hair colour.
- Pivotal trials showed twice daily application for up to 24 weeks is effective at reducing hair growth in 58% of women, with 32% being considered a "clincial success"; improvement was seen as early as 8 weeks.[13]
- Side-effects include a potential for irritant contact dermatitis.[14]
- Unlike lasers, it can be used to treat lighter vellus hairs.
- Topical eflornithine is effective alone or can serve as a useful adjunct to other hair removal techniques.
  - Studies have shown that it increases the efficacy of laser hair removal.[15] A randomized bilateral vehicle-controlled study of women with facial hirsutism comparing eflornithine HCl cream + laser treatment with laser alone demonstrated topical eflornithine provided an additive effect in enhancing the rate and degree of hair reduction on the upper lip.[15]
  - Eflornithine improved the reduction in unwanted facial hair until the sufficient number of laser treatments (due to a lag in response time) produced the desired long-term effects.
  - The study medication was well tolerated and no device/drug interactions were observed.

Conclusion

Facial hair can be a distressing, chronic problem for many women. Assessment for underlying abnormalities should be guided by clinical findings. Treatment options are varied in effectiveness, side-effects, and costs. Combination therapy with multiple modalities of treatment may afford the most effective results.

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