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Acne Therapies for the Primary Care Physician: What's New and What's Practical

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Acne vulgaris is the most common dermatologic condition worldwide, affecting people across a broad range of ages and skin phototypes. There are a variety of pathophysiological processes involved in the formation of acne lesions, with available anti-acne therapies targeting such pathways. Herein, we provide a review of important acne treatment classes and present novel topical, oral and energy-based interventions.

Introduction

Acne vulgaris (AV) is a chronic inflammatory dermatosis involving the pilosebaceous unit, whereby increased sebum production, follicular hyperkeratinization, *Cutibacterium acnes* (previously *Propionibacterium acnes*) proliferation, and localized, heightened immune responses result in the development of acne lesions.^{1,2} AV is thought to affect more than 80% of adolescents and young adults, forming a substantial proportion of both the dermatologist's and general practitioner's caseload, and is frequently treated in primary care settings by non-dermatologists.^{3,4} Thus, it is of utmost importance that primary care providers stay up to date with acne management strategies and expanding therapeutic options.

Several options are available to treat AV, ranging from conservative measures such as cleansers, moisturizers, and skin care products, to topical mono- and combination therapies including benzoyl peroxide, antibiotics and/or retinoids. Additional treatments include oral therapies, such as antibiotics, hormonal agents and isotretinoin, as well as energy-based devices.⁵ Given the plethora of available and evolving modalities, and the essential role of the primary care provider in the management of patients with acne, a robust therapeutics framework as outlined below offers real-world practical value.

Conservative Measures and Lifestyle Modifications

Given increasing interest in targeted skin care regimens, and growing recognition of the role of a healthy epidermal barrier in the management of various dermatological disorders, the medicalization of skin care is crucial in the overall management of AV.⁶ Recent studies have demonstrated the efficacy of over-the-counter (OTC) acne skin care products, many of which contain Food and Drug Association (FDA)-monographed ingredients. Although these ingredients can be non-prescription, they have been shown to alter both the structure and function of acne-prone skin.⁷ Combining a proper skincare regimen with AV treatments may decrease irritation and support a healthy skin barrier, improving treatment adherence and outcomes.⁸ Moreover, allowing patients to select their own skincare products can provide them with a sense of control in managing their disease, which may reduce the psychological sequelae of acne.⁷

Dermocosmetics are non-medicinal products with both cosmetic and active ingredients that improve cutaneous disorders, and more specifically acneceuticals, which play an important potential role in acne therapy specifically, have been embraced in Europe for decades. However, their use remains limited in North America, despite their ability to target three of the four central pathophysiological processes implicated in acne pathophysiology (keratolytic, antibacterial, and anti-inflammatory) (**Table 1**). Notably, recent data supports the

use of conservative measures including the use of pH-adjusted, gentle cleansers, which act to promote a healthy skin barrier and contribute to the healing or attenuation of inflammatory skin conditions.⁹⁻¹² Importantly, lipid-free cleansers have been found to be most appropriate for use in acne-prone skin as they are less irritating and have a pH similar to that of the stratum corneum.¹¹ The latest guidelines conditionally recommend the use of topical salicylic and azelaic acids in the management of AV, given their ability to target three of the four central pathophysiological processes implicated in acne pathophysiology (keratolysis, antibacterial, and anti-inflammatory).¹³ Other common agents, namely oral or topical niacinamide, topical tea tree oil, topical green tea, topical witch hazel, oral pantothenic acid, oral or topical zinc, topical glycolic acid, sulphur, sodium sulfacetamide, and resorcinol, have insufficient clinical evidence to formulate recommendations at this time.¹³

Multiple studies have explored the relationship between diet and acne, with the notion that acne as an inflammatory pathology is at the centre of it.¹⁴ However, the link between nutrition and acne continues to be extensively debated and remains controversial.¹⁵ Research has found that plant-based foods may improve inflammatory skin diseases by supporting the gut microbiome, exerting anti-inflammatory effects, providing barrier support, and improving glycemic control. Key nutrients contributing to these effects include riboflavin, vitamin B12, vitamin A, omega-3 fatty acids, protein, fibre, antioxidants, and phytonutrients.^{16,17} Studies investigating omega-3 fatty acid levels in acne patients found that many patients had insufficient omega-3 levels, and that normalization of these levels was associated with a significant improvement in acne severity.¹⁸ Additionally, omega-3 indices were increased by means of consuming a Mediterranean diet or through oral supplementation with omega-3 fatty acids.¹⁸ Moreover, daily consumption of omega-3 has been shown to decrease the mucocutaneous side effects of isotretinoin (cheilitis, xerosis, nose dryness), thereby increasing tolerability, compliance, and overall outcomes.^{19,20} Furthermore, use of oral or topical probiotics, symbiotics, or postbiotics has also been shown to restore skin homeostasis, improving acne and other inflammatory skin conditions.¹⁷ However, chocolate consumption was associated with a statistically significant

Mechanism of Action	Active Ingredients
Keratolytic	- Azelaic acid - Alpha and beta hydroxyacids - Retinol derivatives - Bakuchiol - Silymarin - Sulfur
Antibacterial	- Azelaic acid - Niacinamide - Zinc - Green tea - Resveratrol - Silymarin - Bakuchiol - Soy - Probiotics - Retinaldehyde - Sodium hypochlorite - Tea tree oil
Anti-inflammatory	- Niacinamide - Salicylic acid - Azelaic acid - Bakuchiol - Linoleic acid - Lactobacillus - Aloe vera - Green tea - Cannabidiol - Zinc - Resveratrol - Silymarin - Sodium hypochlorite - Tea tree oil
Sebum reduction	- Niacinamide - Zinc - Green tea - Silymarin - Bakuchiol - Linoleic acid - Clay - Soy - Resveratrol
Barrier repair	- Niacinamide - Hyaluronic acid - Alpha and beta hydroxy acids - Glycerin - Colloidal oatmeal - Panthenol - Ceramides - Shea butter

Table 1. Acneceuticals; adapted from Baldwin et al.⁷

Agent	Mechanism	Administration
Topical Therapies		
Winlevi® Clascoterone 1% cream, available in 30 and 60 g tubes	Topical anti-androgen receptor inhibitor	AM + PM
Cabtreo® Benzoyl peroxide 3.1% + clindamycin phosphate 1.2% + adapalene 0.15% gel, available as a 50 g pump	Topical antibiotic and third-generation retinoid	PM
Arazlo® Tazarotene 0.045% lotion, available in 45 g tubes	Topical third-generation retinoid	PM
Aklief® Trifarotene 0.005% cream, available in 75 g pumps	Topical fourth-generation retinoid	PM
Oral Therapies		
Epuris® Isotretinoin-lidose capsules, available in 10, 20, 30, and 40 mg capsules	Oral systemic retinoid with lipid encapsulation	AM or PM, with food (no need for high-fat content)
Absorica® Isotretinoin-lidose capsules, available in 8, 16, 24, and 32 mg capsules	Oral systemic retinoid with lipid encapsulation in a micronized formulation	AM or PM, food not required

Table 2. Novel Topical and Oral Acne Therapies; courtesy of Santina Conte, MD and Monica K. Li, MD, FRCPC, FAAD.

intensification of acne lesions even in the presence of an anti-inflammatory diet.²¹ Despite this, the current clinical evidence in dietary influences on acne remains insufficient to draw firm conclusions regarding the consumption of a low dairy diet, low whey diet, omega-3 fatty acids, and chocolate. Finally, acne is significantly influenced by glycemic load, with an established association between high glycemic load foods and severe acne secondary to insulin and insulin-like growth factor 1 levels, which stimulate sebum production and androgen hormone release.²²⁻²⁵ Common high glycemic index foods include bread (white, whole wheat), naan (white, whole wheat), white, sticky, or jasmine rice, potatoes, and bananas, amongst others. Importantly, dietary counselling along with the consumption of low glycemic level foods has been shown to improve acne severity and lesions,²² although conflicting evidence continues to exist in the current literature.

Topical Therapies

According to the most recent *Journal of the American Academy of Dermatology* (JAAD) acne guidelines (January 2024), topical benzoyl peroxide (BP) is strongly recommended for the management of AV.¹³ BP is generally regarded as an effective first-line therapy for AV whether used as monotherapy or in combination with a topical antibiotic and/or topical retinoid.²⁶ Available both OTC or by prescription, BP targets three of the four major acne pathophysiological pathways: it exhibits bactericidal activity against *C. acnes*, as well as possessing mild sebostatic and keratolytic properties, which are potentiated when used in combination with other topical therapies.²⁷ There is no current literature to suggest the development of drug resistance with BP use.²⁸

Several innovative novel therapies for AV have come to market in recent years (**Table 2**). Clascoterone 1% cream (Winlevi®) is a first-in-class topical androgen receptor inhibitor approved for the treatment of

acne in patients 12 years and older.²⁹ It has demonstrated efficacy and is well-tolerated regardless of acne severity, age, gender, and ethnicity.²⁹⁻³¹ Expert panels emphasized that clascoterone should be used in conjunction with other acne treatments—such as in conjunction with topical retinoids or systemic therapies such as isotretinoin or spironolactone—to achieve optimal results, as acne is best targeted by multiple mechanisms.²⁹ Reinforcing the importance of multimodal therapy in the management of AV, Cabtreo® is a novel triple combination gel containing 1.2% clindamycin phosphate, 0.15% adapalene and 3.1% BP.³² Studies have demonstrated that this agent offers superior efficacy compared to vehicle or unimodal therapy with BP, adapalene, or clindamycin topicals, with good overall treatment tolerance.^{32,33} Finally, there are two relatively recent topical retinoid additions to the acne armamentarium: tazarotene lotion (Arazlo®) and trifarotene cream (Aklief®). Arazlo® is a third-generation retinoid with polymeric emulsion technology and a honeycomb hydrating base designed to reduce irritation.³⁴ It has demonstrated efficacy and safety in treating of both acne and acne-induced post-inflammatory hyperpigmentation.³⁵⁻³⁸ Aklief®, the sole fourth-generation topical retinoid-based formulation, selectively targets the most common retinoid acid receptor isotype (RAR- γ) in the epidermis. It has also demonstrated notable success in treating mild-to-moderate acne.³⁹⁻⁴² Most importantly, it has demonstrated clinical efficacy in reducing atrophic acne scars and acne-induced post-inflammatory hyperpigmentation, thus treating acute acne lesions and their sequelae, with potent anti-inflammatory effects.^{41,43} Moreover, while both Arazlo® and Aklief® are effective for treating truncal acne, Aklief® holds a specific on-label indication for this use.^{40,44} A systematic review of randomized controlled trials comparing clascoterone, trifarotene, or tazarotene with vehicle concluded that no significant differences in efficacy were observed between the three molecules after 12 weeks of treatment in patients with moderate-to-severe acne, suggesting similar overall efficacy.⁴⁵ Thus, differences in dosing schedule, mechanism of action, accessibility/cost, and tolerability profiles become key factors determining prescription selection.

Oral Therapies

Multiple oral therapies are available for managing AV, such as antibiotics, retinoids, oral contraceptive pills, and aldosterone antagonists. Current guidelines recommend the use of isotretinoin for patients with severe acne, those unresponsive to standard treatment with oral or topical therapies, or those experiencing psychosocial burdens or scarring. Since its initial availability on the market, newer formulations of isotretinoin, namely Epuris® and Absorica® have become available. Historically, Accutane® required administration alongside a high-fat meal to ensure proper absorption, potentially leading to issues with patient adherence.⁴⁶ Epuris®, a lidose-coated form of isotretinoin, uses lipid encapsulation technology to enhance drug absorption, though it still recommends consumption with food, albeit not necessarily of high-fat content.⁴⁶ However, Absorica® and AbsoricaLD®, the latest form of lidose-isotretinoin in a micronized formulation, enhances drug absorption and maintains consistent serum isotretinoin levels regardless of gastrointestinal contents, making it the only on-label form of isotretinoin that can be taken on an empty stomach.⁴⁷ Before initiating isotretinoin therapy, baseline assessments should include liver enzyme tests, lipid panels, and pregnancy status in applicable individuals. Monthly pregnancy tests should be performed throughout treatment for individuals with childbearing potential. If baseline alanine aminotransferase (ALT) and triglyceride levels are normal, tests should only be repeated after the peak dose is reached, with tests typically obtained one month after starting the peak dose, or typically after completion of a total of two months of isotretinoin therapy.⁴⁸ If results remain normal upon reaching the peak dose, further monitoring is not required. However, if abnormalities are detected, or if the patient is known to have dyslipidemia, periodic monitoring should continue. Most importantly, for patients with childbearing potential, pregnancy prevention is mandatory given isotretinoin's teratogenic capacity.

Laser and Light Therapies

Lasers and energy-based technologies are other treatment modalities used for acne given their precise and non-invasive nature.⁴⁹ More recently, the efficacy of light- and laser-based devices have demonstrated efficacy in managing AV via reducing inflammatory lesions by

targeting *C. acnes*, suppressing sebaceous gland activity, and modulating inflammation.⁵⁰ Notably, the novel 1726 nm laser, marketed under the name AviClear™, is the first and only FDA-approved laser treatment for mild to severe acne. This laser targets acne by inducing necrosis and thereby suppressing sebaceous gland activity. Clinical use has shown considerable lesion reduction with good tolerability and minimal side effects.^{51,52} However, this treatment has limitations. Patients typically require a series of three treatments, with the total cost averaging CAD \$3000–\$5000. Access to such therapy may vary geographically, given that it is largely offered by dermatologists or aesthetic medicine providers. Of note, some patients have reported the procedure to be painful, with prolonged post-procedure edema and erythema, which may negatively impact the patient experience. Despite these limitations, the AviClear™ laser may be an effective alternative for patients who would prefer to avoid, have not responded to, or cannot tolerate topical or systemic acne therapies.⁵³

Special Clinical Considerations – Adult Female Acne

While acne is typically regarded as a disease of adolescence, it remains prevalent throughout adulthood, especially among women.⁵⁴ Coined “adult female acne” (AFA), it can also result in scarring and dyspigmentation, impacting psychosocial health. AFA is frequently driven by an excess in androgens, which stimulate sebum production and the production of inflammatory cytokines.⁵⁵ Importantly, standard acne treatments typically do not treat AFA, as they do not address the patient’s hormonal profile. In contrast, AFA typically responds very well to systemic anti-androgen therapies. Currently, four major anti-androgen treatments are available to treat AFA. Hormonal contraceptives, most notably the oral contraceptive pill (OCP), provide an anti-androgenic effect through an estrogen-mediated decrease in circulating free testosterone.^{56,57} Progestins exhibit variable androgenic and anti-androgenic effects, potentially resulting in acne exacerbation. Notably, progestin-only pills should be avoided in acne-prone patients given their inherent risk of worsening the patient’s skin. Otherwise, fourth-generation OCPs, namely Diane®-35

Can Treat Acne	Can Worsen Acne
Diane®-35	Lolo®
Yasmin®	Min-Ovral®
Yaz®	Seasonique®
Marvelon®	Indayo®
Mirvala®	Alesse®
Linessa®	Aviane®
Cyclen®	Alysena®
Tri-Cyclen®	Triguilar®
	Depo-Provera®
	Micronor®
	Movisse®

Table 3. Hormonal Management of Acne Vulgaris; courtesy of Santina Conte, MD and Monica K. Li, MD, FRCPC, FAAD.

(cyproterone acetate), Yasmin®, and Yaz® (drospirenone), are the most effective hormonal options managing female acne given their synthetic anti-androgenic formulations.⁵⁴ Third-generation OCPs (Marvelon®, Mirvala®, Linessa®, Cyclen®, Tri-Cyclen®) are considered to be the least intrinsically androgenic, and are also thought to be effective in treating acne.⁵⁴ Importantly, first (Lolo®) and second (Min-Ovral®, Seasonique®, Indayo®, Alesse®, Aviane®, Alysena®, Triguilar®) generation OCPs have marked and varying androgenic effects, potentially worsening, triggering, or improving acne.⁵⁴ Other forms of hormonal contraception, such as Depo-Provera® and progesterone-only pills (Micronor® and Movisse®), which contain first-generation progestins, medroxyprogesterone acetate, and norethindrone, or hormonal intrauterine devices (IUDs) that contain levonorgestrel without estrogen, may cause or exacerbate acne.⁵⁴ While progestin-only contraception is not advised for patients with acne-prone skin, Slynd®, a new and highly effective progesterone-only OCP, has shown promise for patients with acne-prone skin given the pathophysiology of drospirenone.⁵⁴ Importantly, patients should be advised that regardless of the hormonal contraceptive chosen, the effect on their acne may only be observed in 4–6 months. **Table 3** summarizes hormonal contraceptives and their impact on acne.

Besides hormonal contraceptives, spironolactone, a potassium-sparing diuretic with anti-androgenic properties, reduces sebum production and hyperkeratinization in acne-prone follicles.⁵⁸ Dermatologists have been prescribing spironolactone off-label for acne in women for over three decades, with doses ranging from 50 to 200 mg per day, with 50 and 100 mg per day being the most commonly used.^{57,58} Treatment can be initiated at 50 mg daily and titrated as tolerated in 25 mg increments. Importantly, patients should be notified that irregular menstruation is observed in 15–30% of patients, which can be managed by the addition of a third- or fourth-generation OCP or a hormonal IUD, as described above. Laboratory monitoring is typically not required for healthy women under the age of 45.⁵⁹ Spironolactone is contraindicated in pregnancy or for those trying to become pregnant due to its anti-androgenic effects, which may affect sex differentiation of the male during embryogenesis.^{60,61} Importantly, once AV control has been attained with spironolactone, the dose can be tapered. The longer-term maintenance goal is to use topical agents only.

Regarding topical therapies, clascoterone can be considered, as described above (see *Topical Therapies* section). Otherwise, dapsone 5% gel (Aczone®) has anti-inflammatory properties that allow it to treat a variety of inflammatory skin conditions, including AV.⁶² Additionally, a randomized study comparing the efficacy of tazarotene monotherapy to combination therapy with tazarotene and dapsone reported that combination therapy was more effective for treating comedonal acne.⁶³

Special Clinical Considerations – Acne in the Pregnant Patient

Treating AV in the pregnant patient adds a layer of complexity, given that several of the above-mentioned medications and topicals are teratogenic and/or have not been extensively studied in a pregnant population. Notably, topical azelaic acid and glycolic acid have been deemed safest to use in pregnancy, as well as topical BP.^{64,65} Topical clindamycin has been deemed compatible with pregnancy outside of the first trimester.⁶⁵ Both topical and oral retinoid formulations are either contraindicated or used with caution due to the teratogenic nature of the class.^{65–67} Regarding topical retinoids, while

the amount of drug absorbed from the skin is very low, there are case reports in the literature describing birth defects consistent with retinoid embryopathy.⁶⁵

Therapeutics in the Horizon

Minocycline 4% foam (Amzeeq®) and the fixed-dose combination of tretinoin 0.1% with BP 3% cream (Twynéo®) are both approved for the management of AV in the United States, and may be available in Canada within the next 1–2 years. Minocycline foam was formulated with the goal of minimizing absorption and toxicity. When applied once daily, it demonstrated significant improvements in both inflammatory and non-inflammatory lesions compared to vehicle.^{68,69} Tretinoin and BP cream, in a microencapsulated formulation, has also been shown to significantly reduce inflammatory and non-inflammatory acne lesions, as well as improve Investigator Global Assessment ratings.⁷⁰

Benzoyl Peroxide Controversy

Since March 2024, there has been a great deal of controversy regarding the use of BP-containing products. The FDA recently tested 95 products and found that six contained elevated levels of benzene.⁷¹ Benzene is classified as carcinogenic to humans, with research proving a causal relationship between benzene and acute myeloid leukemia, amongst other hematologic malignancies.⁷² Valisure, the independent lab who performed the testing, reported that these BP acne treatments can break down and generate high levels of the carcinogen benzene when stored at high temperatures, notably 37°C, 50°C, and 70°C, representing body heat, standard pharmaceutical stability conditions, and extreme environmental heat, respectively.^{71,73} However, the study was not conducted under ambient conditions, as most individuals would not store their acne treatments in such high temperature environments. The American Academy of Dermatology has since released an official statement regarding best practices for storing and handling products with BP. They recommend storing the product at room temperature or cooler conditions (e.g., in the refrigerator, not in or near direct sunlight or heat), and discarding products that are old (over 3–6 months after opening), expired or heat-exposed.^{71,74,75}

Conclusion

AV is the most common dermatological condition worldwide, affecting people across a broad age range. Given its highly variable clinical presentation, management plans should be tailored to each individual patient, taking into account the presence and severity of inflammatory or non-inflammatory lesions, scarring, and/or the extent of hormonal contribution. A growing array of topical and oral treatment modalities reinforces the importance of staying current with the latest, most effective, individualized treatment combinations. Successful treatment of the acne-prone patient involves long-term acne clearance and minimizing the impact of undesirable sequelae, including scarring and dyspigmentation.

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