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BRIDGING THE GAP IN ACNE MANAGEMENT: A NARRATIVE REVIEW OF CURRENT THERAPIES AND THE EMERGENCE OF CLASCOTERONE

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ABSTRACT

Acne vulgaris is one of the most common dermatological conditions worldwide, estimated to affect up to 85–90% of the population at some point in their lives. While most frequently observed in adolescents and young adults, an increasing number of patients over the age of 25- long after the period of puberty- are presenting with this problem. The pathogenesis of acne is complex, involving sebaceous gland hyperactivity, follicular hyperkeratosis, excessive proliferation of *Cutibacterium acnes*, and inflammation, all of which lead to a disruption of skin homeostasis. The causes of this deregulation are primarily attributed to hormonal imbalances, particularly the influence of androgens, as well as carbohydrate metabolism dysfunction and chronic stress. For decades, several groups of medications have been used interchangeably, including isotretinoin, hormonal contraceptives, antibiotics, spironolactone, and various topical agents. Although these treatments have proven effective in many cases, a significant proportion of patients still face side effects, lack of clinical improvement, or disease recurrence. After many years without the introduction of any innovative medication, a new option has emerged for patients struggling with acne vulgaris: clascoterone. Its mechanism of action consists of blocking androgen receptors in the skin, which suppresses sebaceous gland hyperactivity and reduces inflammation. As a topical preparation, it carries a much lower risk of systemic side effects than oral treatments. In this article, we aim to present this new drug in comparison to currently available therapeutic options, looking forward to a potential breakthrough in the treatment of this common dermatosis.

KEYWORDS

Acne Vulgaris, Clascoterone, Emerging Therapies

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1. Introduction

Acne vulgaris is among the most prevalent dermatological conditions worldwide, affecting individuals across all age groups, with the highest burden among teenagers and young adults and an increasing incidence in later adulthood. (Sutaria i in., 2023) Clinically, acne presents as pustules, papules, comedones, and nodules. (Kutlu i in., 2023) Despite its common occurrence, acne is a chronic, relapsing disorder that remains challenging to manage effectively.

Beyond its cutaneous manifestations, acne imposes a substantial psychosocial burden. It is strongly associated with adverse mental health outcomes, including anxiety and depression, and can significantly impair quality of life and self-esteem, particularly during adolescence- a critical period of psychosocial development. (Samuels i in., 2020) These impacts underscore that acne is not merely a cosmetic concern but a condition with meaningful clinical and societal relevance.

The pathogenesis of acne is multifactorial and involves the interplay of key biological processes, including inflammation, increased sebaceous gland activity, follicular hyperkeratinization, and proliferation of *Cutibacterium acnes*, ultimately disrupting skin homeostasis. (Baldwin & Tan, 2021; Sutaria i in., 2023) In addition, acne may be associated with broader systemic factors, such as hormonal dysregulation, chronic stress, and metabolic disturbances, including abnormalities in carbohydrate metabolism, suggesting a more complex underlying pathophysiology than traditionally recognized. (Barrea i in., 2025; Bungau i in., 2023; Winiarska-Mieczan i in., 2022)

This narrative review aims to provide a comprehensive overview of emerging therapeutic options for acne vulgaris, with a focus on recent advances, underlying mechanisms, and their potential to address current unmet clinical needs.

2. Methods

2.1. Study design

This study was conducted as a narrative review to provide an overview of emerging therapeutic options for acne vulgaris. A narrative approach was selected to allow a broad, clinically oriented synthesis of recent advances, mechanisms of action, and treatment strategies relevant to current practice.

2.2. Search strategy

A literature search was performed to identify relevant studies on emerging treatments for acne vulgaris. The search was conducted in the following electronic databases: PubMed, Google Scholar

The following keywords and/or Medical Subject Headings (MeSH) terms were used: Acne vulgaris, clascoterone, emerging therapies, Boolean operators and database-specific filters were applied as appropriate. Additionally, the reference lists of selected articles were manually screened to identify further relevant publications.

2.3. Study selection

Studies were selected based on their relevance to the scope of this review. The inclusion criteria were:

- studies addressing emerging or novel treatments for acne vulgaris
- clinical trials, observational studies, and relevant reviews
- studies published in English

The selection process was guided by clinical relevance, recency of evidence, and contribution to understanding emerging therapeutic approaches.

2.4. Methodological considerations

As a narrative review, this study did not follow a formal systematic review protocol, and no quantitative meta-analysis was performed. However, efforts were made to ensure a balanced and comprehensive representation of the available evidence by incorporating studies of varying designs and critically appraising their clinical relevance.

3. Results

This narrative review identified and synthesized current evidence on emerging therapeutic approaches for acne vulgaris, with particular emphasis on treatments targeting key pathogenic mechanisms. The findings are organized into two main domains: (i) the underlying pathophysiological role of androgens in acne development, which provides the biological rationale for targeted therapies, and (ii) a critical overview of current treatment modalities and their limitations, highlighting unmet clinical needs.

Understanding the role of androgen signalling in sebaceous gland activity and cutaneous homeostasis is essential for contextualizing newer therapeutic agents, particularly those designed to modulate androgen receptor pathways. The following sections, therefore, first outline the mechanistic basis of androgen involvement in acne, before examining existing treatments and the rationale for emerging alternatives.

3.1. Pathophysiological role of androgens in acne vulgaris

3.1.1 Androgens: synthesis and biological function

Androgens are a class of steroid hormones derived from cholesterol. They are produced mainly by the gonads and the adrenal cortex, but can also be synthesized in peripheral tissues, such as the skin, adipose tissue, or brain, from intermediate steroid products generated through enzymatic conversion of cholesterol. (Alemany, 2022; Karakus i in., 2025; Schiffer i in., 2017) Major androgens include testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione. Testosterone and DHT are considered potent androgens, whereas DHEA, DHEAS, and androstenedione, which exhibit weaker activity. (Buendía-González i in., 2022) Beyond their established roles in sexual differentiation and reproductive function, androgens are also involved in metabolic regulation, neurodevelopment, and maintenance of energy homeostasis. (Alemany, 2022; Cornejo i in., 2016; Morford i in., 2018)

3.1.2. Androgen effects on skin cells

Skin and its appendages are sensitive to androgen activity due to the presence of androgen receptors (AR), which are expressed in epidermal and follicular keratinocytes, dermal papilla cells, dermal fibroblasts, sebocytes, sweat gland cells, endothelial cells, and genital melanocytes. (Zouboulis & Degitz, 2004) Importantly, AR activation is mediated not only by circulating androgens but also by locally synthesized androgens within the skin, making this an example of intracrinology. (Chen i in., 2002; Zouboulis & Degitz,

2004) Furthermore, research has shown that androgen levels in patients with acne are not consistently elevated, suggesting a complex pathology and an important role of local androgen metabolism, particularly within the sebaceous glands. (Del Rosso *et al.*, 2020) Androgens influence hair growth, but can also lead to the miniaturization of hair follicles, depending on their location and androgen-dependence. They can also disrupt cutaneous homeostasis by impairing the skin barrier, which can lead to inflammation and delayed wound healing. (Taieb *et al.*, 2024)

3.1.3. Role of the sebocytes and sebaceous gland activity

Sebaceous glands use holocrine secretion, which means the entire cell breaks down and becomes part of the secretion (sebum). (Kurokawa *et al.*, 2009) Although sebum secretion is a normal physiological process that contributes to the maintenance of the skin barrier, its hypersecretion and increased sebaceous gland activity are known to exacerbate acne. (D. Li *et al.*, 2025) One of the main factors of their hyperactivity is the influence of androgens on sebaceous glands. These steroid hormones stimulate sebocyte proliferation, intracellular lipid synthesis, and hyperkeratinization both by positively influencing mTOR (mammalian target of rapamycin) phosphorylation and by activating SREBP-1 (sterol regulatory-element-binding protein-1). (Kim *et al.*, 2024) These processes lead to comedogenesis and subsequently acne development.

3.2. Current therapeutic approaches: Advantages and limitations

Despite the availability of multiple treatment modalities, acne management remains challenging due to variable patient responses, adverse effects, and increasing antimicrobial resistance. This underscores the need for novel therapeutic strategies targeting key pathogenic pathways, including androgen signaling.

3.2.1. Oral therapies

Isotretinoin

Isotretinoin remains the most efficient treatment for severe acne vulgaris. It strongly reduces sebum secretion by promoting apoptosis of sebocytes, leading to the involution of sebaceous glands. (Agamia *et al.*, 2023; A. Layton, 2009) In addition, it normalizes keratinization, thereby reducing comedogenesis. (A. Layton, 2009) Despite its efficiency in treating intractable acne, isotretinoin is associated with severe adverse effects, including teratogenic effects on the fetus and mental disorders. (Comprehensive Dermatologic Drug Therapy, *b.d.*) The most frequent adverse effects include skin dryness, which particularly affects the lips and leads to cheilitis. (Abtahi-Naeini *et al.*, 2025) Regular laboratory monitoring of liver function and lipid profile is required due to potential biochemical abnormalities, which typically do not pose risks to patients and are transient, but call for periodic assessment. (Nast *et al.*, 2012) It is imperative to initiate the contraceptive therapy at least one month before starting isotretinoin, and to continue it throughout the treatment and for one month after its completion. (Ganceviciene & Zouboulis, 2010) It should be emphasized that, in spite of complete therapy, relapses are still observed.

Systemic antibiotics

Tetracyclines are the primary class of antibiotics prescribed for acne vulgaris due to their combined antibacterial and anti-inflammatory properties. (Reynolds *et al.*, 2024) Other options include clindamycin and macrolides. Although *C. acnes* is a known trigger for acne flares, it is not considered the fundamental etiological factor for this multifactorial inflammatory disease. *C. acnes* is a microorganism that belongs to the human skin microbiota, and its eradication does not necessarily correlate with sustained clinical improvement. (Dreno *et al.*, 2014) Crucially, the bacterial resistance to antibiotics is rising due to the misuse and overuse of these medications. In addition, long-term antibiotic use is associated with numerous adverse reactions, such as gut dysbiosis and its subsequent clinical consequences. (Issa *et al.*, 2025) Tetracyclines also cause photosensitivity and enamel hypoplasia. Consequently, they are contraindicated for children under 9 years of age and during pregnancy. An unsatisfactory, temporary effect that contributes to the accumulation of resistance and antibiotic inefficiency while posing a high risk of adverse effects forces us to consider other treatment paths.

3.2.2. Topical treatments

Topical agents are commonly used and particularly effective in mild and moderate acne vulgaris. (Nast *et al.*, 2016) Most frequently used involve antibiotics, azelaic acid, retinoids, and benzoyl peroxide. Like oral antibiotics, topical ones have been analyzed for their effectiveness and validity, especially in monotherapy. The key adverse factors include emerging antimicrobial resistance and disruption of the skin microbiome. To increase therapeutic efficacy and reduce the risk of resistance, the topical antibiotic should be used in polytherapy; combining it with topical retinoids or benzoyl peroxide effectively mitigates this phenomenon.

(Thiboutot *et al.*, 2009; Zaenglein *et al.*, 2016) Nevertheless, current guidelines emphasize the need to limit and restrict the use of antibiotics in acne management.

The other most used topical treatments, such as azelaic acid, retinoids, or benzoyl peroxide, can be effective but may also cause skin irritation, photosensitivity, and dryness. Although their effectiveness is impressive, there remains a demand for new therapies that could complement these treatments and help many patients who do not respond sufficiently to current therapies.

3.2.3. Anti-androgenic therapeutic options

Contraceptives

Research demonstrates the efficacy of combined oral contraceptive pills (COCs) whose mechanisms reduce free testosterone levels by decreasing androgen synthesis and increasing the sex-hormone binding globulin (SHBG) production via estrogen activity. (Arowojolu *et al.*, 2012) Furthermore, contraceptives inhibit the conversion of testosterone to dihydrotestosterone (DHT). (Arowojolu *et al.*, 2012) The degree of anti-androgenic activity also depends on the specific type of progestogen utilized in the formulation. Among the most widely employed agents with potent anti-androgenic effects are cyproterone acetate, drospirenone, chlormadinone acetate, and dienogest. (Arowojolu *et al.*, 2012) These substances compete with testosterone and dihydrotestosterone (DHT) for binding sites on receptors in the sebaceous glands, thereby inhibiting androgenic activity. (Zouboulis & Degitz, 2004)

Nevertheless, these medications have systemic effects and may carry adverse risks, such as an increased likelihood of venous thromboembolism (VTE), mood swings, or a slightly higher risk of breast cancer. However, it is important to note that they also significantly decrease the incidence of ovarian, endometrial, and colorectal cancers. (Mørch *et al.*, 2017; Skovlund *et al.*, 2016; Vinogradova *et al.*, 2015) There are also reports that, despite its efficacy, long-term treatment with cyproterone acetate may increase the risk of meningiomas. (Weill *et al.*, 2021; Zouboulis & Rabe, 2010)

Spironolactone

Although spironolactone is not FDA-approved for this indication, it remains a frequently utilized off-label intervention in the treatment of acne, primarily among women. (A. M. Layton & Ravenscroft, 2023) Spironolactone is an antagonist of mineralocorticoid and androgen receptors, and while its diuretic effect is well-established, its anti-androgenic properties are the primary focus in dermatological therapy. The research established the efficacy of the therapy in reducing acne symptoms by mitigating sebum secretion. (Charny *et al.*, 2017) Spironolactone has a high safety profile; however, adverse reactions such as increased diuresis, menstrual irregularities, or dizziness may occur. Despite the theoretical risk of hyperkalemia, current research does not demonstrate a clinically significant prevalence of this condition among patients with preserved hepatic, renal, and adrenal function. (Charny *et al.*, 2017; Zaenglein *et al.*, 2016) It must be emphasized that this treatment should not be used for men due to the high risk of gynecomastia, reduced libido, and feminization. Furthermore, its use is prohibited during pregnancy, as it may interfere with the development of the male fetus, posing a significant risk of feminization. (Zaenglein *et al.*, 2016)

While current treatments can be effective, they have limitations such as side effects, incomplete responses, relapse, and antimicrobial resistance. These issues underscore the importance of developing new therapies. Notably, targeting androgen signaling pathways is a promising approach due to their key role in acne development.

3.4. Clascoterone – a new asset in the treatment of acne vulgaris

As of early 2026, clascoterone - or cortexolone 17 α -propionate - awaits its release in the form of a 1% cream in Europe and holds a great promise in the treatment of androgen-induced acne, as well as androgen-related alopecia. (Rosette, Rosette, *et al.*, 2019) Notably, this is the first drug with a novel mechanism of action to have emerged in acne vulgaris treatment since isotretinoin in 1982. (Y. Li *et al.*, 2024)

3.4.1. Clascoterone - General Characteristics

Clascoterone is a novel antiandrogen designed to competitively bind to the androgen receptors, disrupting inflammatory cytokine and lipid synthesis in sebocytes, which play a pivotal role in the development of acne vulgaris. (Rosette, Agan, *et al.*, 2019) Through these mechanisms, clascoterone may impede multiple pathways leading to acne onset, making it highly effective. The newest drug poses no threat of systemic adverse effects due to its form - the topical cream operates only locally. It is quickly metabolized by the enzymes present in skin tissue. (Hebert *et al.*, 2020; Celasco *et al.*, 2004a) Its biochemical antiandrogen activity was measured to be stronger than flutamide or finasteride – hence it can be of potential use in the treatment of alopecia - and as strong as cyproterone acetate. (Celasco *et al.*, 2004b)

Furthermore, clascoterone has been shown to be more effective at inhibiting the production of inflammatory cytokines by sebocytes than spironolactone. (Rosette, Agan, i in., 2019; Elsaie, 2016) The comparison with spironolactone and other anti-androgens is especially significant, as the new agent may in many cases prove to be a good alternative for the well-known anti-androgen drugs, which are known to produce many adverse effects. It must also be emphasized that clascoterone is the first androgen receptor-blocking pharmacotherapy approved for the treatment of males with acne. („Clinical Review”, 2025) The rationale behind this specific indication stems from a documented low risk of feminization, gynecomastia, and decreased libido among males treated with clascoterone cream, as opposed to other systemic anti-androgenic medications. (Santhosh & George, 2021)

3.4.2. Indications and safety

Clascoterone has been approved by the FDA in the form of a 1% cream applied topically in the treatment of acne in adults and children - both males and females – as a safe and efficient option for all patients aged 12 or older. (Dhillon, 2020) It is said to possibly enter the European market as early as 2026.

Clascoterone, despite influencing many biochemical pathways, causes no significant interactions and thus can be used in polytherapy with other established acne medications, such as retinoids and benzoyl peroxide. (Peterson i in., 2023) It can therefore be added to ongoing therapy without jeopardizing the treatment process.

Recent years have provided valuable data on the efficiency and safety of the newest anti-acne agent in real clinical studies. In phase 2 and 3 trials, clascoterone was proven to be prominently more effective than placebo, posing none or very minor side effects among adult and adolescent females and males – such as pruritus. (Trifu i in., 2011; Mazzetti i in., 2019) Although the drug poses significantly lower risk of side effects than older agents, it still requires caution, as the hypothalamic-pituitary-adrenal axis suppression was reported among a few patients in a phase 2 clinical trial. (Mazzetti i in., 2019; Manjaly i in., 2023)

The available clinical data do not provide sufficient information to assess the safety of the newest agent during pregnancy or breastfeeding periods. (Harris, 2021) It should therefore be emphasized that clascoterone should be administered with extreme caution during these times, and only if deemed necessary. If so, caution is advised for the drug not to come into physical contact with the newborn’s skin. („Clascoterone”, 2006) There is no evidence of a significant skin-related or systemic carcinogenic effect of clascoterone in both male and female patients. (Hebert i in., 2020) The drug is not registered for use among children 12 or younger, due to a significantly higher risk of side effects in this group. (Clascoterone (Winlevi), b.d.)

4. Discussion

Despite numerous existing options for the treatment of acne vulgaris, therapies with novel mechanisms of action offer significant promise for dermatological patients. Clascoterone is a substance that can be utilized not only in resistant cases but also as a first-line treatment in patients aged 12 and older. It is important to highlight its non-systemic profile, which reduces the risk of adverse effects and improves patient well-being. Unlike antibiotics, clascoterone does not disrupt the physiological skin and gut microbiota. Reducing unnecessary antibiotic use is crucial to preventing resistance, and clascoterone represents a promising alternative in these cases. Furthermore, current research indicates that clascoterone is not associated with significant cutaneous irritation, and the irritation appears minimal, comparable to placebo. This is particularly noteworthy when compared to topical and systemic retinoids, which are frequently associated with dose-limiting local skin reactions. A crucial advantage is its suitability for male patients, in contrast to systemic anti-androgen medications. Nevertheless, clascoterone should not be used during pregnancy due to its potential risk of feminization of the male fetus. Another potentially dangerous side effect is suppression of the hypothalamic-pituitary-adrenal (HPA) axis, but this phenomenon is rarely observed and not clinically significant. Thus, the recently and currently tested clascoterone could be both equally effective and significantly safer.

5. Conclusions

After many years of a standstill, the upcoming innovative cure can be a new hope for patients with acne vulgaris, which is resistant to current treatment methods. Foregoing research shows that clascoterone can be not only effective, but also safe, which makes it a good alternative to oral, systemic antiandrogenic medication. Above all, years of real experience in treating various patients are essential for proper evaluation.

Conflict of Interest Statement: The authors declare no conflict of interest.

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