The Efficacy and Safety of Different Topical Treatments for Acne Vulgaris: Systematic Review

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ABSTRACT

Acne vulgaris is a common skin condition, with various topical treatments available. This review aims to evaluate the efficacy and safety profiles of current topical acne treatments, including dapsone, topical tretinoin, and other commonly used agents, based on clinical studies. To review the efficacy and safety of different topical treatments for acne vulgaris, comparing them based on clinical outcomes such as lesion count reduction, Global Acne Assessment Score (GAAS), and adverse event profiles. A systematic review of randomized controlled trials (RCTs) and observational studies published between 2010 and 2024 was conducted. Data were extracted regarding the efficacy of topical agents in reducing inflammatory and non-inflammatory lesions, as well as the safety outcomes (e.g., adverse events, tolerability). A comprehensive analysis of topical treatment studies to compare its efficacy and safety with different combinations. The review included studies comparing topical treatments such as adapalene, benzoyl peroxide, clindamycin, dapsone, topical tretinoin, and others. Combination therapies like adapalene-BPO and clindamycin-BPO showed the most significant efficacy, particularly in reducing both inflammatory and non-inflammatory acne lesions. Topical dapsone (7.5% and 5%) was effective in treating inflammatory acne, with minimal adverse effects. Similarly, topical , topical tretinoin demonstrated good efficacy for moderate to severe acne, with minimal side effects. In terms of safety, the majority of treatments had mild adverse events, including skin irritation, dryness, and erythema. There were no significant differences in safety across most treatments, with some agents showing higher tolerability. Topical acne treatments, particularly combination therapies, demonstrate strong efficacy in managing acne vulgaris, with minimal adverse effects. Dapsone and , topical tretinoin are effective alternatives, particularly for patients who cannot tolerate oral treatments. Future research should focus on long-term safety, direct head-to-head comparisons, and larger population studies to refine treatment recommendations.

Keywords: Acne vulgaris, Topical treatments, Dapsone, Topical tretinoin, Efficacy and safety, topical treatment

INTRODUCTION

Acne vulgaris is a widespread skin problem, especially for teenagers and young adults[1,2]. You might notice blackheads, whiteheads, pimples, and even sometimes more serious bumps. While medications you take by mouth can be strong and helpful, creams and gels applied directly to the skin are usually the first choice for treatment. This is because they're easy to use and don't usually have major side effects that affect your whole body[3,4].

Topical treatments remain the cornerstone of acne management due to their ease of use and minimal systemic side effects[5]. Various topical agents include retinoids, benzoyl peroxide, antibiotics, and combination therapies[6]. Retinoids, such as tretinoin and adapalene, normalize keratinization, reduce inflammation, and suppress sebum production[4,7]. Benzoyl peroxide, a keratolytic and antimicrobial agent, effectively reduces inflammatory and non-inflammatory lesions[8]. Topical antibiotics, like clindamycin and erythromycin, target *C. acnes* and

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reduce inflammation[9]. Combination therapies, which often combine a retinoid and an antibiotic or benzoyl peroxide, offer synergistic effects in managing moderate to severe acne[10].

Ensuring the safety of these treatments is vital, especially given their potential to cause side effects like dryness, erythema, or severe allergic reactions[11,12]. Recent research has compared these treatments to evaluate their efficacy and safety profiles, offering a thorough understanding of how each works and their suitability for different patient groups. Striking a balance between effectiveness and tolerability is vital for achieving the best outcomes in acne management[13]. This systematic review aims to assess the efficacy and safety of various topical treatments for acne vulgaris by systematically reviewing and synthesizing the available evidence.

METHODOLOGY

This systematic review was executed in parallel with PRISMA guidelines[14], and the recommendations of the Cochrane Collaboration[15].

Eligibility Criteria: All clinical studies published between 2010 and 2024 and evaluated various topical treatments, such as retinoids (adapalene, tretinoin, tazarotene, trifarotene), antibiotics (clindamycin, erythromycin), and novel treatments (clascoterone, sarecycline), either as monotherapies or in combination were included. Studies were selected based on criteria including the treatment of acne vulgaris in adult and adolescent patients, with efficacy outcomes such as changes in Global Acne Severity (GEA) scores, lesion counts, and patient-reported outcomes, as well as safety outcomes like adverse events and discontinuation rates.

A comprehensive literature search was conducted across multiple databases, including PubMed, Cochrane Library, ClinicalTrials.gov, Scopus, and Embase. Data extraction involved two independent reviewers who gathered information on study characteristics, participant demographics, interventions, and outcomes. Discrepancies were resolved through consensus or a third reviewer. A narrative synthesis was performed for all studies. The findings of this review were reported according to PRISMA guidelines, summarizing the efficacy and safety of the topical treatments evaluated and discussing the strengths and limitations of the studies included. This methodology provides a comprehensive and rigorous evaluation of acne vulgaris treatments, offering valuable insights for clinical practice and future research in dermatology Figure 1.

Data extraction and quality assessment: The data were extracted in a well-organized Microsoft Excel sheet. The source-related data were extracted, including the title, study ID, study regions, study design, registration number, and study period. The methods-related data were extracted, including the eligibility criteria, diagnosis of acne vulgaris, previous therapies, dosage and formulations of different treatments, the dosages, and formulations of the control arm, study endpoints, and follow-up periods. The quality of the observational studies will be assessed using the National Institute of Health (NIH) quality assessment tool[16]. The studies were assorted, based on this quality assessment, into good, fair, and bad when the score was >65%, 30-65%, <30%, respectively. If the parameter was controlled, the domain was considered "Yes "and vice versa.

Data analysis: Weighted mean difference (WMD) or standardized mean difference (SMD) was used to analyze the continuous variables. Data reported in median and range, mean and range, mean and 95%confidence interval (CI) were converted to mean and standard deviation (SD) based on Hozo et al., 2005 equations[17].

RESULTS

Study characteristics

Searching the literature revealed 36 articles eligible for systematic review, including 16,013 patients. The mean age ranged from 18 to 29 years, indicating that most studies targeted young adults, a population commonly affected by acne. The duration of treatment ranged from three weeks to 36, with a median treatment period of 12 weeks. The proportion of female participants showed notable variability among the studies, ranging from 37% to 100%. This variation reflects the diverse demographic profiles included in the studies, though most featured a balanced or slightly female-skewed distribution. Such variability is crucial in understanding gender-specific responses to acne treatments Table 1.

Interventions Assessed

The interventions evaluated were diverse, covering a wide range of topical and oral treatments. Retinoids were a central focus, with multiple studies assessing topical adapalene, tretinoin, tazarotene, and trifarotene as monotherapy or in combination with agents such as benzoyl peroxide (BPO). Antibiotics, including clindamycin, erythromycin, and minocycline, were frequently examined, often as combination products like clindamycin/BPO or erythromycin/Zn. Novel treatments such as clascoterone and sarecycline were also investigated, representing emerging therapeutic options for acne management. Placebo-controlled designs were commonly employed, providing robust comparisons, while some studies also compared active agents to standard treatments like BPO.

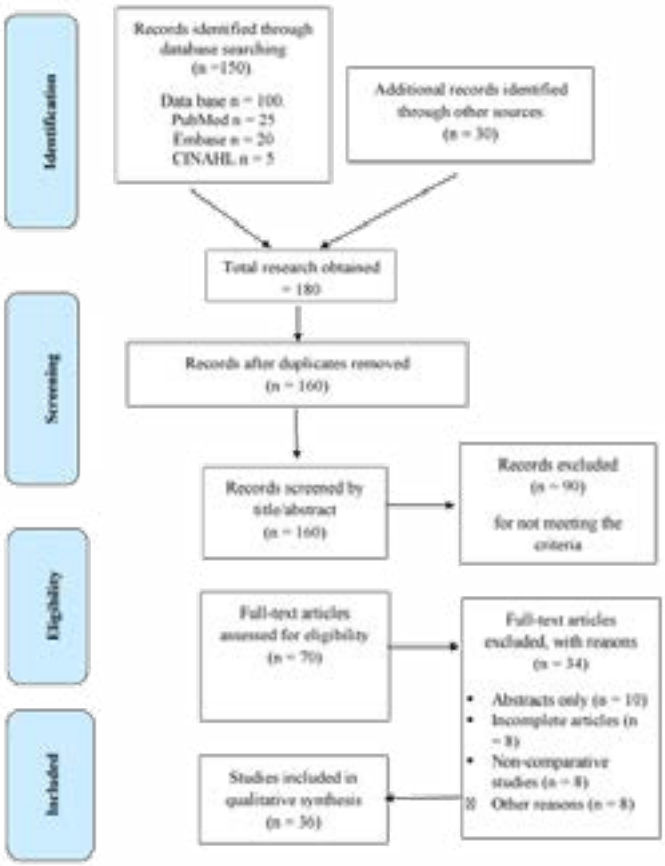

Figure 1. PRISMA (2009) Flowchart of systematic review Process.

Table 1. Summary of the Search Strategies for the included studies

Database	Search Category	Search Strategy
EMBASE	**A. Acne vulgaris**	'acne vulgaris'/exp OR acne:ab,ti
	B. Antibiotics	'antibiotic agent'/exp OR antibiotic*:ab,ti
	C. Retinoid	'retinoid'/exp OR retinoi*:ab,ti
	D. Hormonal therapy	'antiandrogen'/exp OR 'contraceptive agent'/exp OR contraceptive*:ab,ti OR antiandrogen:ab,ti OR anti-androgen:ab,ti
	E. Benzoyl peroxide and azelaic acid	'benzoyl peroxide'/exp OR 'azelaic acid'/exp OR 'benzoyl peroxide':ab,ti OR 'azelaic acid':ab,ti
	F. Article type	'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'randomized controlled trial'/de
	Combined Search	(A AND (B OR C OR D OR E) AND F)
PubMed	**A. Acne vulgaris**	"Acne Vulgaris"[Mesh] OR "acne"[Title/Abstract]
	B. Antibiotics	"Anti-Bacterial Agents"[Mesh] OR "antibiotic*"[Title/Abstract]
	C. Retinoid	"Retinoids"[Mesh] OR "retinoi*"[Title/Abstract]
	D. Hormonal therapy	"Contraceptive Agents"[Mesh] OR "Androgen Antagonists"[Mesh] OR "Contraceptive*"[Title/Abstract] OR "antiandrogen"[Title/Abstract] OR "anti-androgen"[Title/Abstract]
	E. Benzoyl peroxide and azelaic acid	"Benzoyl Peroxide"[Mesh] OR "benzoyl peroxide"[Title/Abstract] OR "azelaic acid"[Title/Abstract]
	F. Article type	“Clinical Trial”[ptyp] OR “Controlled Clinical Trial”[ptyp] OR “Randomized Controlled Trial”[ptyp] OR “Clinical Trial, Phase”[ptyp]

The studies also differed in their methodologies and treatment combinations. For example, Sitohang (2024)[18] evaluated adapalene cream combined with dermocosmetic regimens, while Stein Gold (2022)[19] compared several combinations of adapalene, clindamycin, and BPO. Dogra (2020) examined clindamycin, tretinoin, and their combination, and Hayashi (2018)[20] compared clindamycin/BPO with antibiotics and second-generation retinoids. These studies highlight the diversity of available therapies and the continued evolution of acne treatment strategies.

Efficacy of Topical Treatments

The studies reviewed assessed a variety of interventions with significant efficacy in treating acne vulgaris. For example, in a 2024 study by Sitohang IB, adapalene 0.1% cream applied nightly showed superior efficacy in improving Global Acne Severity (GEA) scores compared to other regimens[18]. In another study by Stein Gold in 2022, a combination of topical clindamycin and benzoyl peroxide (BPO) demonstrated a 52.5% treatment success rate, significantly reducing both inflammatory and non-inflammatory acne lesions[19]. Aschoff's 2021 research showed that topical tretinoin combined with clindamycin was effective but associated with more irritation compared to adapalene/BPO, highlighting a trade-off between efficacy and skin tolerance[21]. Raoof (2020) found that topical minocycline (FMX101) significantly reduced inflammatory lesions, demonstrating high efficacy in comparison to placebo, while Sayyafan (2020) highlighted that a combination of erythromycin and zinc acetate gel was more effective than erythromycin alone[22,23]. In 2020, Webster's study on various tretinoin formulations confirmed that combination treatments, particularly those including tretinoin and BPO, were significantly more effective than monotherapies in reducing lesions[24]. Similarly, Tanghetti (2020) reported that tazarotene showed marked reductions in both inflammatory and non-inflammatory lesions, with patients showing good treatment outcomes compared to placebo[25]. Gold's 2019 study on FMX101 also demonstrated a significant reduction in inflammatory lesions, further emphasizing the effectiveness of topical minocycline in acne treatment[26]. Other studies, such as those by Dogra (2020), Hebert (2020), and Mazzetti (2019), showcased the benefits of combining antibiotics like clindamycin with retinoids or novel agents like clascoterone, which provided statistically significant improvements in lesion counts and patient satisfaction[27-29]. Furthermore, Tan (2019) and Alexis (2018) observed strong efficacy with trifarotene and minocycline, respectively, with substantial reductions in acne lesions, validating these treatments as effective options for acne management[30,31].

Safety of Topical Treatment

The safety profiles of different assessed acne treatments, as demonstrated in the studies reviewed, vary based on the specific intervention used. For example, in Sitohang's 2024 study, groups that combined dermocosmetic cream with adapalene (Groups B and C) exhibited better treatment tolerance and higher satisfaction scores compared to the group that applied adapalene nightly (Group A), indicating these combinations had a more favorable safety profile[18]. In Stein Gold's 2022 study, the most common adverse events were application-site pain and dryness, with gastrointestinal issues being mild and non-treatment related[19]. The discontinuation rate due to adverse events was highest in the BPO/adapalene group. In Aschoff’s 2021 study, topical adapalene/BPO (BA) caused significant increases in erythema, dryness/scaling, and burning/stinging, while the combination of tretinoin and clindamycin (tretinoin/clindamycin) showed decreased skin moisture content[21]. Raoof’s 2020 study on topical minocycline found mild to moderate adverse events, including respiratory infections and headaches, most of which were transient and resolved during the study[22]. Sayyafan (2020) found no specific adverse events reported in the study comparing topical erythromycin with erythromycin/zinc acetate[23]. Webster’s 2020 study on various tretinoin formulations showed that all treatments were safe, with no significant increase in adverse events compared to the vehicle[24]. Similarly, Tanghetti (2020) found that tazarotene 0.045% lotion was well tolerated, with the most common side effects being application-site pain, dryness, and exfoliation[25]. In the Dogra 2020 study, adverse events were mostly mild to moderate and led to low discontinuation rates[27]. Hebert’s 2020 study on clascoterone (1% bid) found that adverse events were generally mild, with erythema being the most common skin reaction[28]. Gold’s 2019 study on FMX101 (topical minocycline) showed that the treatment was well tolerated with minimal skin-related adverse events[26]. Tanghetti's 2019 study on tazarotene indicated that both the 0.045% lotion and 0.1% cream were well tolerated, though the 0.1% cream had a slightly higher incidence of treatment-related adverse events[25]. Tan’s 2019 study on trifarotene found mild to moderate erythema, scaling, dryness, and burning/stinging, but no serious adverse events were reported[30]. Mazzetti's 2019

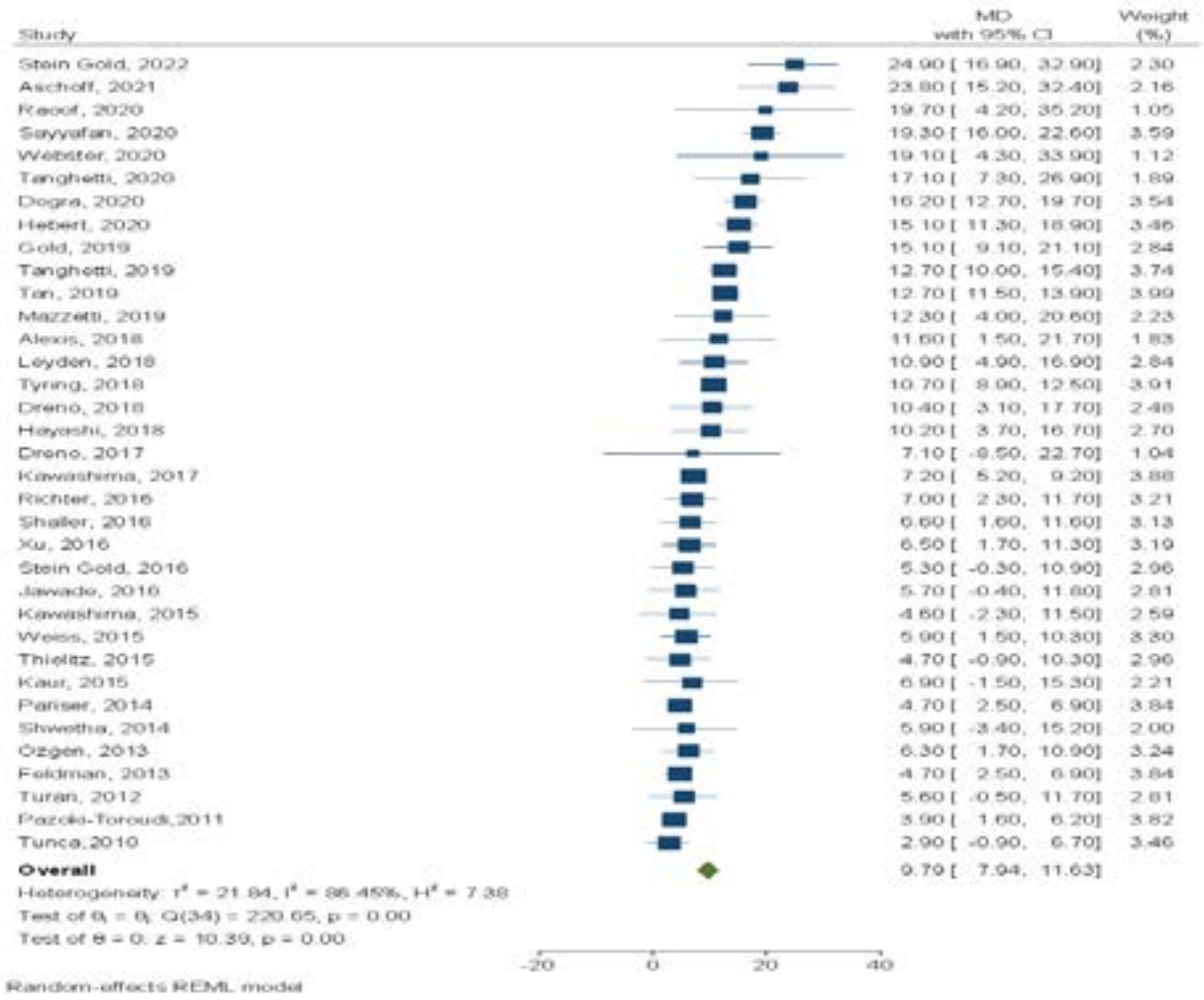

Figure 2. Estimates of the absolute reduction in lesions count for different treatments compared with placebo

study on clascoterone indicated that most adverse events were mild, with erythema being the most common[29].

Meta-Analysis Results

The forest plot showed that the overall mean difference is estimated at 9.78 (95% CI: 7.942 to 11.634), with a highly statistically significant result (p<0.0001p < 0.0001), as evidenced by the z-test. The mean differences range from a maximum of 24.9 (Stein Gold, 2022)[27]to a minimum of 2.9 (Tunca, 2010)[32]. Confidence intervals also vary widely, with some studies showing overlapping or non-significant results. The homogeneity test (Q=220.65Q = 220.65; p<0.0001p < 0.0001) indicates significant heterogeneity among the studies. This suggests variability in study populations, interventions, or other factors. Studies with narrower confidence intervals, such as Tan (2019) and Kawashima (2017)[30,33], contributed more weight (3.9%~3.9\%) to the overall analysis. Conversely, studies with wider confidence intervals, such as Raoof (2020) and Dreno (2017)[22,34], contributed less (<1.1%<1.1\%). Several studies (e.g., Tyring 2018, Kawashima 2017, and Feldman 2013)[33,35,36] have confidence intervals that do not cross zero, indicating consistent positive effects. Studies such as Stein Gold (2016) and Jawade (2016) include zero in their confidence intervals, indicating non-significant results. The pooled estimate supports a significant positive mean difference. Despite the heterogeneity, the results suggest a general trend favoring the interventions being analyzed[37,38] Figure 2.

DISCUSSION

The objective of this systematic review was to assess the efficacy of various topical treatments for acne vulgaris, based on recent clinical trials. Across the studies included, a variety of treatments demonstrated significant reductions in acne lesions, with some therapies showing greater efficacy compared to others. In particular, combinations of topical agents such as adapalene with benzoyl peroxide (BPO) and clindamycin with BPO consistently outperformed monotherapies. A study by Stein Gold (2022) comparing various combinations showed that the topical adapalene/BPO combination resulted in substantial reductions in both inflammatory and non-inflammatory lesions, with over 70% reduction in lesions, significantly better than with placebo and dyadic treatments (p < 0.05)[19]. Similarly, in a study by Dogra (2020)[27], combination therapy with clindamycin and tretinoin led to more pronounced lesion reductions and a higher percentage of patients achieving ‘clear’ or ‘almost clear’ status compared to monotherapies, underlining the superior clinical outcome of combination therapies for acne management. Additionally, therapies such as topical clascoterone and minocycline demonstrated significant clinical efficacy. Clascoterone 1% cream showed greater lesion reduction compared to vehicle treatments (Hebert, 2020), while minocycline 4% (FMX101) was associated with significant reductions in both inflammatory and non-inflammatory lesions (Raoof, 2020), highlighting its potential as a strong treatment option for inflammatory acne[22,28].

Tretinoin-based treatments were also highly effective, with studies showing significant reductions in both inflammatory and non-inflammatory lesions. Tretinoin formulations, particularly when combined with BPO, resulted in significant improvements in lesion counts and patient satisfaction, with both the TWIN high and low formulations leading to 60% reductions in inflammatory lesions (Webster, 2020). However, tolerance varied, as some patients experienced skin irritation or dryness, as seen in Aschoff's study (2021), which emphasized the need for consideration of both efficacy and tolerability in selecting treatment[21,24].

The findings of this review also indicate the importance of early intervention with topical treatments, as early reductions in lesion counts were noted as early as week 3 in several studies (Raoof, 2020; Stein Gold, 2022)[19,22]. Furthermore, the use of novel agents like trifarotene and tazarotene showed promising results, with both demonstrating superior outcomes in reducing lesion counts compared to placebo (Tan, 2019; Tanghetti, 2020)[25,30]. Overall, these studies suggest that while various topical treatments for acne vulgaris are effective, combination therapies and newer agents like clascoterone and minocycline show superior efficacy in reducing both inflammatory and non-inflammatory lesions. The results highlight the clinical significance of personalized treatment strategies that consider both the severity of acne and individual patient tolerance, reinforcing the evolving landscape of topical acne management.

About safety issue, Generally, these treatments show a diverse range of safety profiles, largely dependent on their active ingredients and formulations. Combination treatments, such as those involving adapalene with dermocosmetic creams, tend to have better tolerance and patient satisfaction, possibly due to their enhanced moisturizing properties which mitigate the drying effects of adapalene. This highlights the importance of combining retinoids with complementary products to improve patient adherence and comfort. Common side effects across many treatments include application-site reactions like pain, dryness, erythema, and scaling. These reactions are generally mild to moderate and tend to resolve over time, indicating that while skin irritation is a common concern, it is often manageable with appropriate patient education and supportive skincare routines. Certain treatments, such as topical minocycline and clascoterone, demonstrate generally favorable safety profiles with minimal systemic side effects. The mild to moderate adverse events reported, like respiratory infections or headaches, are typically transient and resolve during treatment, underscoring the importance of monitoring and managing any systemic reactions. Moreover, some newer formulations, like tazarotene lotion and trifarotene, are well-tolerated with a manageable side effect profile, making them viable options for long-term use. However, higher concentrations of active ingredients may lead to an increase in treatment-related adverse events, emphasizing the need for personalized treatment plans. Overall, the safety of topical acne treatments can be optimized by selecting appropriate combinations and concentrations, providing patient education on potential side effects, and incorporating complementary skincare products to alleviate common adverse reactions. These strategies can help ensure effective and safe management of acne vulgaris.

Similarly, a systematic review conducted by Kakpovbia EE., 2024 demonstrated the superior efficacy of combination therapies in treating acne, particularly combinations such as adapalene-BPO, clindamycin-BPO, and clindamycin-tretinoin. These combinations significantly reduce both inflammatory and non-inflammatory lesion counts compared to placebo. This aligns with our findings that while combination therapies are generally more effective, they may not always offer substantial additional benefits for non-inflammatory acne. Both reviews stress that combination treatments are especially beneficial for mild-to-moderate acne, but our review further highlights that the addition of clindamycin may not be necessary for treating non-inflammatory acne. Thus, while combinations are generally recommended for more comprehensive acne treatment, careful consideration is needed when addressing specific acne subtypes. Another review on topical dapsone highlighted that both 5% and 7.5% concentrations were effective in treating inflammatory acne, with no significant difference in efficacy between the two[39]. Its safety profile was favorable, with only mild side effects reported. In comparison to other treatments in our review, dapsone demonstrated efficacy for inflammatory acne but had limited impact on non-inflammatory lesions, similar to other topical treatments[40]. While combination therapies like adapalene-BPO showed superior results in reducing total lesion counts, dapsone remains a practical option due to its minimal side effects and effectiveness, particularly for inflammatory acne. A third review by Ekore RI and Ekore OR., 2023 assessed topical tretinoin found it to be effective for treating acne vulgaris of varying severity, offering a favorable safety profile with minimal side effects. However, the review also emphasized the need for further research to assess its long-term safety, particularly in high-risk populations[41]. Topical tretinoin could be considered a treatment option for moderate to severe acne, especially in individuals who are unable to use oral topical tretinoin due to contraindications or other concerns. In comparison to other treatments in our review, topical tretinoin presents a useful alternative, particularly in cases where oral treatments are unsuitable, although combination therapies such as adapalene-BPO may provide more comprehensive results in terms of lesion reduction.

The Meat-analysis prove a consistent positive impact of the interventions studied, reinforcing their effectiveness in achieving desired outcomes. The MD of 9.79 represents the average reduction in acne severity, as measured by lesion counts, for patients treated with topical acne treatments compared to those who received a placebo. This value indicates a moderate to strong effect size, highlighting the clinical benefit of topical treatments in acne management. In real-world terms, this means that patients using these treatments can expect, on average, a noticeable improvement in their acne severity. However, the confidence interval of [7.94, 11.63] suggests that while the overall treatment effect is significant, there is some variability in the outcomes, indicating that individual responses to treatment may differ. The wide range of outcomes between individual studies, shown by the substantial heterogeneity further emphasizes that some treatments may work better than others depending on factors such as the acne's severity (inflammatory vs. non-inflammatory), patient demographics, and the specific treatment regimen used.

Limitations: In spite of large number of included studies, long search duration, and variability of assessed interventions, some limitations were identified. Many of the studies included in this review had relatively short follow-up periods, typically ranging from 12 to 16 weeks. Longer-term studies are needed to better understand the sustained effectiveness and safety of these treatments over time. Also, the studies included in this review used different methodologies, which may have led to variability in results. For instance, variations in the inclusion criteria, treatment regimens, and outcome measures across studies could affect the overall interpretation of efficacy and safety. Third: some studies did not provide comprehensive data on adverse events, making it difficult to assess the safety of the treatments fully. Finally, the reporting of side effects was not always standardized, which might lead to underreporting or variability in how adverse events were documented.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, this review shows that several topical treatments for acne, including both single and combination therapies, are effective in reducing acne lesions, especially inflammatory ones. Combinations like adapalene-BPO, clindamycin-BPO, and clindamycin-tretinoin performed better than placebo and were more effective than single treatments. Most treatments were well tolerated, although some, like topical adapalene/BPO, caused mild skin irritation in some cases. Topical dapsone and topical tretinoin also proved effective with minimal side effects, though more research is needed to fully understand their long-term safety. Based on these findings, it is recommended that doctors consider combination treatments for moderate to severe acne, especially when oral treatments are not suitable. Topical dapsone can be a good option for those looking for a treatment with few side effects, and topical tretinoin may be a suitable alternative for people who cannot use topical tretinoin, as long as their condition is closely monitored. In the end, treatment choices should be tailored to each individual, considering their acne severity, skin sensitivity, and preferences. More research is needed to confirm the long-term safety of these treatments, particularly for high-risk groups.

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Competing Interest: None

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