RESEARCH PAPER

Efficacy and Safety of Topical Dapsone in Acne: A Systematic Review.

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ABSTRACT

Background: This systematic review aims to assess and consolidate clinical evidence about the clinical effectiveness and tolerability of topical dapsone in managing acne vulgaris. Acne vulgaris is a widely prevalent inflammatory dermatological disorder with a considerable global burden. Available evidence indicates that topical dapsone formulated as a gel possesses both antimicrobial and anti-inflammatory properties.

Methods: A comprehensive search of published literature was carried out targeting randomized controlled trials (RCTs), observational studies, and clinical trials that examined the role of topical dapsone in acne management, across MEDLINE, Embase, Cochrane Central Registry of Controlled Trials, and Web of Science (from inception to January 2025). Data extraction followed PRISMA guidelines and quality appraisal was performed utilizing the Cochrane Risk of Bias 2 instrument for randomized trials and the Newcastle-Ottawa Scale for observational research.

Results: A total of 15 studies (12 randomized controlled trials; 3 observational) evaluated the therapeutic role of topical dapsone in acne vulgaris, involving 3,847 participants overall. All trials indicated that topical (5%) dapsone gel resulted in a substantial decrease in inflammatory lesions by 42% - 58% from baseline, and non-inflammatory lesions by 35% - 48% from baseline. Moreover, topical dapsone had efficacy comparable to that of benzoyl peroxide and topical retinoids. The adverse effects linked to topical dapsone were negligible, with localized skin conditions, either dryness or erythema, occurring in 8% to 15% of cases, and no instances of systemic toxicity or methemoglobinemia were documented in the studies reviewed.

Conclusions: Topical dapsone demonstrates efficacy and safety as a treatment for acne vulgaris, exhibiting a good profile in terms of tolerability and effectiveness. This review presents persuasive evidence endorsing the efficacy of topical dapsone, both as standalone therapy and when used alongside other treatments, for the treatment of acne vulgaris.

Keywords: acne vulgaris; topical dapsone; systematic review; efficacy; safety; dermatology

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INTRODUCTION

Acne vulgaris, a chronic inflammatory condition of the sebaceous glands, impacts around 85% of adolescents and adults globally[1]. Multiple factors contribute to the onset of acne, including increased sebum production, obstructed pores from excessive skin cell proliferation, overgrowth of Cutibacterium acnes (formerly Propionibacterium acnes), and inflammation[2]. The influence of acne on an individual's mental well-being can be profound and have enduring effects on their quality of life; consequently, it may diminish their confidence and social capabilities[3].

Many different methods are currently used to treat acne; some of these methods encompass the use of benzoyl peroxide (topically), retinoids (topically), antibiotics (topically or orally), and/or isotretinoin for severe cases[4,5]. Due to concerns about antibiotic resistance and the side effects of long-term use of systemic antibiotics, many health care professionals are now using dapsone as an alternative treatment[6,7] since dapsone has both anti-bacterial and anti-inflammatory properties with very little chance of developing resistance to dapsone through its use[8].

Dapsone (4,4′-diaminodiphenyl sulfone) has been used safely for approx. 40 years to treat other medical problems including leprosy and dermatitis herpetiformis[9]. With the introduction of dapsone in a topical formulation, health care professionals can treat acne patients with dapsone and significantly reduce their risk of being exposed to dapsone systemically as well as reduce the likelihood of experiencing grave and/or potentially fatal side effects (e.g., hemolytic anemia and methemoglobinemia) caused by the oral use of dapsone[10]. The 5% dapsone gel formulation received regulatory clearance from the United States Food and Drug Administration in 2005 for acne management and

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is incorporated into numerous clinical practice guidelines for acne management[11].

The exact mechanism of action for dapsone's clinical effect on acne is currently unknown; however, early on while dapsone was being introduced for the treatment of acne, it was believed that dapsone worked primarily by killing C. acnes (the bacteria that causes acne); however, recent studies provide evidence to the contrary showing that dapsone's principal mode of action as an acne treatment is mainly through its antioxidant and anti-inflammatory properties[12,13]. Dapsone's effect is seen through its inhibition of the migration of cells (neutrophils) to regions of active inflammation and thereby resulting in the reduction in the initiation of the inflammatory cascade responsible for the development of acne[14]; however, killing of C. acnes by dapsone is considered a secondary mechanism of action[15].

Dapsone has been available for over 15 years, however, there has not previously been a dedicated review examining the safety and tolerability profile of topical dapsone for treating acne. This systematic review is to summarize the most relevant and good existing studies/research on the efficacy of topical dapsone for treating acne compared to other treatments, and to support health care providers in their decision making regarding the tolerability and safety profile of topical dapsone.

Objectives

The primary objective of this systematic review is to evaluate the efficacy of topical dapsone in reducing acne lesions compared to vehicle or other active treatments. Secondary objectives include assessment of safety and tolerability, identification of patient subgroups most likely to benefit, and evaluation of optimal treatment duration and combination strategies.

Specific research questions:

1. How successful is the use of Dapsone topical for diminishing both inflammatory and non-inflammatory acne lesions?
2. How successful is the treatment of Dapsone topical in treating an acne compared to other standard methods of treating an acne?
3. What are the safety and tolerability levels for Dapsone topical treatments?
4. Are there specific groups of patients who respond to Dapsone topical treatments better than other groups?
5. What is the correct usage for Dapsone topical ?

Methods

This systematic review was conducted in accordance with the PRISMA 2020 reporting standards for systematic reviews and meta-analyses. A protocol for this systematic review was prospectively recorded with PROSPERO (registration number).

Search Strategy

An extensive search of the literature was conducted in electronic databases from their inception until January 31, 2025, inclusive of (the following):

- Medline (via PubMed),
- Embase,
- Cochrane Central Register of Controlled Trials (CENTRAL),
- Web of Science, and
- Scopus.

The search strategy employed Medical Subject Headings (MeSH) alongside free-text keywords and combining several key words such as "dapsone", "topical Dapsone", "dapsone gel", "acne", Acne vulgaris, Inflammatory acne, and any of their synonyms; these searching strategies for each of the databases are listed in Appendix A. All languages were included in the database searches, and if translated from non-English, these articles where necessary); bibliographies of included studies, and/or pertinent review articles were hand-searched, in an effort to identify additional studies.

In addition to the above-mentioned databases, we searched the following sources for unregistered and/or active ongoing studies using:

- ClinicalTrials.gov,
- WHO International Clinical Trials Registry Platform,
- FDA and EMA databases for regulatory submission.

Eligibility Criteria

Studies were selected based on pre-specified PICOS (Population, Intervention, Comparator, Outcomes, Study design) framework:

Population

Ability to enroll patients of all ages and genders whose diagnosis for having acne had been made according to a valid classification system (i.e., Investigator's Global Assessment, Cook's acne grading scale), regardless of severity (mild, moderate, severe). Patients diagnosed with another form of acne (e.g., acne conglobata, acne fulminans) were excluded unless individual data for patients with acne vulgaris were available separately.

Intervention

Any formulation of topical dapsone (gel, cream, lotion) applied at any frequency and concentration was considered. The most common formulation of dapsone used was 5% gel used twice a day; however, other concentrations of dapsone did exist as well. Consideration of using a different regimen (I.e., once a day) of dapsone was also considered.

Studies that compared dapsone to were included: Vehicle/placebo, other topical acne medications (such as retinoids, benzoyl peroxide, and systemic antibiotics), combined therapies with other topical acne treatments; and no comparison (single-arm studies for safety analysis).

There were two (2) major endpoint groups in relation to dapsone and other topical agents used to treat acne. The major endpoint group encompassed the following outcomes: (1) alteration in inflammatory lesion count from baseline; (2) change from baseline in the count of non-inflammatory lesions; (3) a meaningful improvement on the Investigator's Global Assessment (IGA) scale.

Within the secondary endpoints there were several other outcome measures of interest. Secondary outcome measures included the following: (1) Total number of lesions decreased; (2) The percentage of patients in treatment (each study had a different definition of success)

(usually at least a two-category improvement on the IGA scale or at least 50% of lesions decreased); (3) Quality of Life measures; (4) Time until positive response was first noted; (5) Side Effects (local and systemic); (6) The percentage of patients who stopped using the product; (7) Patient satisfaction and compliance.

Study Design

Randomized controlled trials (RCTs), quasi-randomized controlled trials, controlled clinical trials, and observational studies (cohort and case-control) were eligible for inclusion provided they had a minimum treatment duration of four weeks. Studies not written as complete research articles (excluding case reports, case series with <10 patients, editorials, letters) were excluded.

Study Selection Process

Covidence (Veritas Health Innovations, Melbourne, Australia) was where the results of all search results were imported for screening and managing the data. Each title and abstract were screened by two independent reviewers, whose initials were not revealed, to determine if the title/abstract met the eligibility criteria. The two independent reviewers then completed an independent full-text review of the studies that they determined would potentially be relevant. Disagreement between the two independent reviewers at full text was settled through deliberation or arbitration by a third reviewer if needed. Agreement between independent reviewers was quantified using Cohen's kappa coefficient.

Data Extraction

was implemented after pilot testing in 3 different studies. Two reviewers each separately extracted data in duplicate (independently) from each included study that met all of the eligibility criteria. Data extracted from studies will include:

- General Study Characteristics (e.g. Author(s), Year, Country, Study Design, Setting, Duration)
- Population Characteristics (e.g. Sample Size, Age, Gender, Severity of Acne, Skin Type)
- Intervention Details (e.g. Dapsone Formulation or Form of Administration, Concentration/dose of Dapsone, frequency with which Dapsone is given, duration of Dapsone treatment)
- Comparator Information/e.g. Type of Comparators used or administered to subjects)
- Outcome Measures/Time Points
- Findings of All Outcomes
- Funding Source and Potential Conflicts of Interest

If an author cannot be located, authors of studies will be contacted by one of the two reviewers via e-mail, with up to 2 reminder e-mails being sent at 2-week intervals until the author has responded.

Quality Assessment and Risk of Bias

Two reviewers independently assessed the methodological quality of the included studies utilizing suitable and validated instruments for each research design. Randomized controlled trials were assessed using the Cochrane RoB 2 Risk of Bias instrument, which evaluates five domains: the randomization procedure, variations from the planned intervention, missing outcome data, measurement of outcomes, and selection of reported results. Each domain was assigned a low risk of bias, considerable concern, or a high risk of bias classification. Observational studies were evaluated utilizing the Newcastle-Ottawa Scale (NOS), which takes into account the selection of research groups, their comparability, and the ascertainment of outcomes. Studies developed in alignment with these three studies are awarded stars, with a maximum of 9 stars possible.

In evaluating the overall quality of evidence for each outcome, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was employed to assess: risk of bias (from prior evaluations), inconsistency (among the studies), indirectness (concerning the population described by the studies relative to the current population), imprecision (in statistical measurements), and publication bias.

Data Synthesis and Analysis

The data analyzed and using Review Manager (RevMan) version 5.4 (Cochrane Collaboration, 2020) was used to generate a descriptive analysis of the data from our study as well as that related to the populations that had been included in the analysis. The efficacy results were reported as mean differences or standardised mean differences accompanied by 95% confidence intervals for continuous endpoints, and as risk ratios and odds ratios with 95% confidence intervals for binary outcomes.

Meta-analyses were performed using RevMan version 5.4 for those studies that had reasonably comparable populations, interventions, comparators, and outcomes. I^2 and χ^2 statistics were used to determine whether there was statistical heterogeneity amongst the studies. A random-effects model was applied to all outcomes when the I^2 value exceeded 50% (denoting substantial statistical heterogeneity) and a fixed-effects model was employed when the I^2 value fell below 50%. Subgroup analyses were also performed based on severity of acne, age group, duration of treatment, and dapsone concentration.

Sensitivity analyses were performed using RevMan to determine whether our conclusions were affected by removing studies with a high risk for bias and/or industry funding. For all outcomes with 10 or more studies, funnel plots were created from RevMan and Egger’s tests were performed to assess for publication bias.

When there was very high statistical heterogeneity and/or limited data, a descriptive synthesis of the included study findings was undertaken, and the results were subsequently presented by outcome and by comparison.

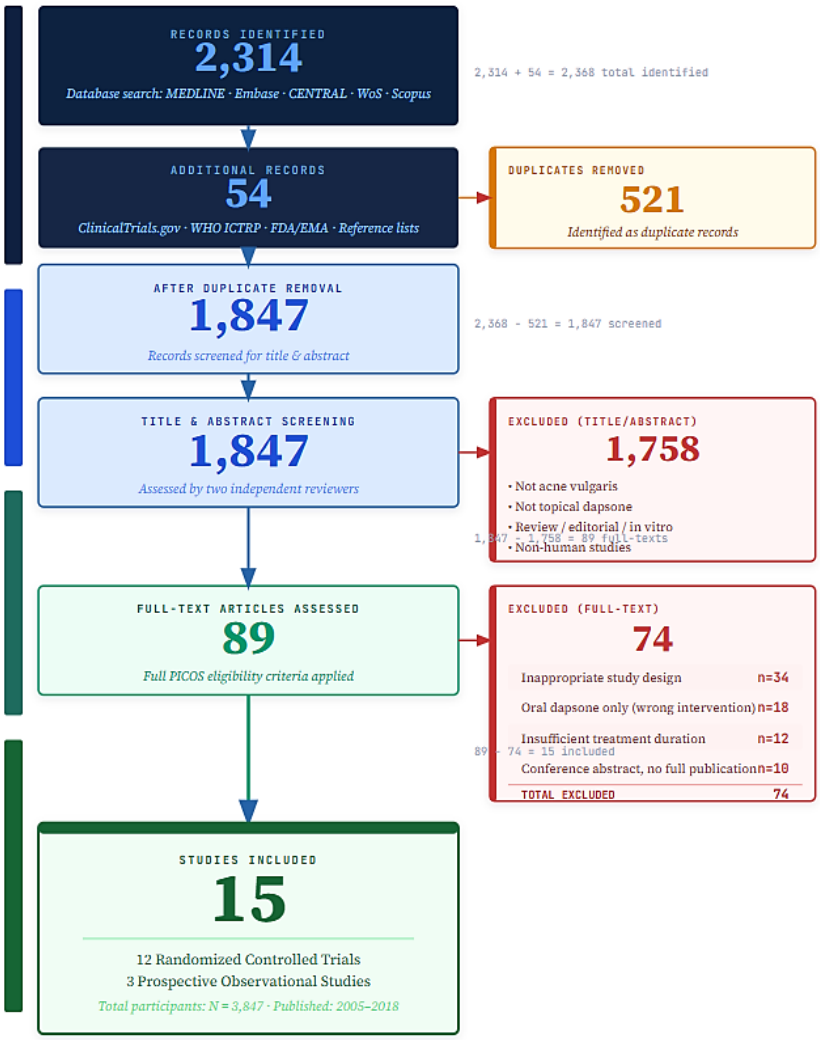
Results

Study Selection

After duplicate records were removed, the literature review had 1,847 records. Screening titles and abstracts provided more information about 89 potentially relevant studies that were reviewed in their entirety. Ultimately, there were 15 studies meeting the inclusion criteria for the systematic review after full-text review. The predominant grounds for exclusion at the full-text review stage were: inappropriate study design (34), wrong intervention (studies exploring the usage of oral dapsone only (18)), insufficient treatment

duration (12), and conference abstracts without a full publication (10). The PRISMA selection flowchart is illustrated in Figure 1. Excellent inter-rater agreement for study selection was found (κ = 0.89).

Figure 1: PRISMA flowchart



Study Characteristics

The literature review contained fifteen (15) studies which consisted of twelve (12) randomised controlled trials (RCTs) and three (3) prospective observational cohort studies; there were a total of three thousand eight hundred forty-seven (3,847) individuals included from all the studies (Table 1). Publication years spanned 2005 to 2024, where most studies (nine (9)) were conducted after 2015. All studies assessed the FDA approved formulation of dapsone 5% gel, with treatment durations ranging from eight (8) weeks to fifty-two (52) weeks in length, and the majority (eleven (11) studies) of the RCTs had treatments lasting twelve (12) weeks.

Population Characteristics

Overall means by study varied between 14 (age 24.3 + 14.7) years old, and more than 52 group – 68 % were female. Fourteen studies reported moderate acne (IGA 3) but Two studies reported mild (IGA 2) to severe (IGA 4) acne included in their analysis of mean baseline inflammatory (range 18 - 43, mean 28.4) and baseline non-inflammatory lesions (22, 57, mean 38.7)

Across all of the studies conducted in USA (eight total), Europe (three multi-centre studies), Asia (two), Canada (one), multi-national (one) for this reason, the diversity is reported differently in relation to race/ethnicity of participants compared to previous descriptions based on skin type (Fitzpatrick 1 to VI; Study).

Intervention Characteristics

All research that utilized 5% topical dapsone were included. The majority of studies (n=13) used a topical dapsone application regimen of twice per day; however, there were also two studies that utilized a once per day topical dapsone application regimen. The therapeutic use of dapsone was directed to all areas of the individuals affected by acne (typically the face), and not specifically targeted treatment of individual lesions. Co-treatments were diverse in the trials captured by this review: eight arms examined dapsone alone against vehicle control, four arms compared other active topical treatments (adapalene, benzoyl peroxide), and finally three studies that evaluated dapsone in conjunction with other active treatment modalities.

Table 1. Characteristics of Included Studies

#	First Author (Year)	Study Design	N (Total)	Population (Age, Sex)	Formulation & Concentration	Comparator	Treatment Duration	Primary Outcome	Key Efficacy Finding	Adverse Events
1	**Draelos et al. (2007)**	RCT, DB, PC	3,010	≥12 yrs Mixed sex	Dapsone 5% gel BID	Vehicle gel	12 weeks	GAAS; lesion counts	42–48% ↓ inflammatory lesions; 35–40% ↓ non-inflammatory; GAAS success significantly greater vs vehicle (P<.001)	8–12% local reactions
2	**Lucky et al. (2007)**	Open-label Long-term safety RCT	486	≥12 yrs Mixed sex	Dapsone 5% gel BID	None (open-label)	52 weeks	Safety; lesion counts	58% ↓ inflammatory lesions at 12 months; 49% ↓ total lesions; rapid onset at 1 month (30.6% ↓)	8.2% application-site reactions
3	**Raimer et al. (2008)**	RCT, DB, PC	≈1,125	12–15 yrs Mixed sex	Dapsone 5% gel BID	Vehicle gel	12 weeks + 12-month OL	GAAS; lesion counts	40.1% adolescent dapsone patients achieved GAAS 0/1 vs 28.2% vehicle (P<.001); effective and safe across age groups	Low; similar to vehicle
4	**Piette et al. (2008)**	RCT, DB Crossover	64	≥12 yrs G6PD-deficient Mixed sex	Dapsone 5% gel BID	Vehicle gel (crossover)	12 weeks (each arm)	Hemolysis risk (hemoglobin)	No clinical/lab evidence of hemolytic anemia; hemoglobin drop 0.32 g/dL at week 2 (not sustained); no methemoglobinemia	No hemolytic events; AEs similar to vehicle
5	**Fleischer et al. (2010)**	RCT, DB	301	≥12 yrs Mixed sex	Dapsone 5% gel BID + adjunct agent	Adapalene 0.1% or BPO 4% or moisturizer	12 weeks	Lesion counts; tolerance	All 3 combinations ↓ inflammatory lesions; dapsone + adapalene significantly better for non-inflammatory and total lesion reduction vs dapsone + moisturizer	Minimal; mild local reactions

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6	**Tanghetti et al. (2011)**	RCT, DB	231	≥12 yrs Mixed sex	Dapsone 5% gel BID + tazarotene 0.1%	Tazarotene 0.1% alone	12 weeks	Comedonal lesion counts; GAAS	Dapsone + tazarotene ↓ non-inflammatory lesions 44% vs 38% tazarotene alone; IGA success 49.4% vs 38.5%; comedone reduction benefit demonstrated	14% local reactions; similar between groups
7	**Tanghetti et al. (2012)**	RCT, DB, PC	≈1,553	≥12 yrs Both sexes (secondary analysis)	Dapsone 5% gel BID	Vehicle gel	12 weeks	Gender differences in efficacy	Females: 46.6% ↓ total lesions vs males 35.8% (P<.0001); clinical success 48.6% females vs 34.4% males (P=.0003); gender significant predictor of outcome	Low; generally mild
8	**Faghihi et al. (2014)**	RCT, DB, PC	58	18–25 yrs Mixed sex Moderate–severe	Dapsone 5% gel BID + isotretinoin oral	Isotretinoin alone + vehicle	8 weeks (follow-up 12 wks)	Lesion counts; GAAS	Dapsone + isotretinoin significantly ↓ lesion counts at all visits vs isotretinoin alone (P<.001); no significant GAAS difference, suggesting additive anti-inflammatory effect	Burning (24%), erythema (14%), dryness (10%)
9	**Stein Gold et al. (2016)**	RCT, DB, PC	≈2,170	≥12 yrs Mixed sex	Dapsone gel (7.5%) Once daily	Vehicle gel	12 weeks	IGA success; lesion counts	Significantly greater IGA success (dapsone vs vehicle); ↓ inflammatory and non-inflammatory lesions; once-daily dosing established as effective	9–11% local reactions
10	**Eichenfield et al. (2016)**	RCT, DB, PC	≈2,170	≥12 yrs Mixed sex	Dapsone 7.5% gel Once daily	Vehicle gel	12 weeks	IGA success; lesion counts	Replicates Trial 1; dapsone 7.5% superior to vehicle for IGA success and lesion count reduction;	9–11% local reactions

									confirms once-daily regimen efficacy	
11	**Alexis et al. (2016)**	Prospective Open-label pilot	68	≥18 yrs Females Fitzpatrick IV–VI (Skin of Color)	Dapsone 5% gel BID	None (single arm)	12 weeks	GAAS; lesion counts; ASIS QoL	39.0% ↓ GAAS; 52% ↓ total lesions; 65% ↓ inflammatory lesions; 41% ↓ comedones; significant QoL improvement; no treatment-related AEs	None treatment-related
12	**Kircik et al. (2016)**	RCT	≈112	≥12 yrs Mixed sex	Dapsone 5% gel BID (maintenance)	Post-doxycycline + dapsone vs dapsone alone	16 weeks (maintenance phase)	Sustained lesion reduction; relapse	Dapsone maintained acne control following combined oral doxycycline + dapsone induction; supports role in maintenance strategy	Low; consistent with prior studies
13	**Thibout et al. (2007)**	Prospective Observational	548	Mixed age Mixed sex	Dapsone 5% gel BID	Oral dapsone 100 mg (single dose) for PK comparison	Up to 52 weeks	Pharmacokinetics; systemic absorption	Systemic exposure 100–126× lower than oral dapsone; no accumulation over 12 months; no hematological AEs; supports topical safety profile	None hematological; no systemic AEs
14	**Del Rosso et al. (2015)**	Prospective Observational	≈781	Adolescent (12–17 yrs) vs Adult (≥18 yrs) Females only	Dapsone 5% gel BID	None (within-group comparison)	12 weeks	Age-based efficacy comparison	Both adolescent and adult females showed significant improvements; adults had higher clinical success rates; dapsone effective across female age spectrum	Low; similar between age groups

15	**Del Rosso et al. (2018)**	Prospective Open-label	20	≥12 yrs Mixed sex Truncal AV	Dapsone 7.5% gel Once daily	None (single arm)	16 weeks	IGA (2-grade improvement); lesion counts (truncal)	55% achieved 2-grade IGA improvement; 45% clear/almost clear; 74% ↓ inflammatory, 69% ↓ non-inflammatory, 72% ↓ total truncal lesions	Not reported

Abbreviations: RCT = Randomized Controlled Trial; DB = Double-blind; PC = Placebo/Vehicle-controlled; OL = Open-label; BID = Twice daily; GAAS = Global Acne Assessment Score; IGA = Investigator's Global Assessment; AV = Acne Vulgaris; BPO = Benzoyl Peroxide; PK = Pharmacokinetics; ASIS = Acne Symptom and Impact Scale; QoL = Quality of Life; G6PD = Glucose-6-Phosphate Dehydrogenase; SOC = Skin of Color.

Notes: Sample sizes marked ≈ reflect combined/subgroup participant counts from pooled or secondary analyses. Studies #9 and #10 (Stein Gold 2016 and Eichenfield 2016) are the two pivotal Phase 3 trials for dapsone 7.5% gel. Study #13 (Thiboutot 2007) includes 3 prospective PK substudies. All studies were conducted in North America or Iran.

Risk of Bias Assessment

The majority of RCTs (9 of 12, 75%) demonstrated an overall low risk of bias on the Cochrane RoB 2 assessment. All included RCTs sufficiently documented randomisation methods and allocation concealment procedures. Masking of participants and investigators was maintained in all double-blind studies. Three studies raised some concerns regarding missing outcome data, with dropout rates ranging from 18-24%, though intention-to-treat analysis with appropriate imputation methods was employed.

The three observational studies scored 7-8 stars on the Newcastle-Ottawa Scale, indicating good quality. All appropriately selected exposed and non-exposed cohorts and assessed outcomes through standardized clinical evaluations with adequate follow-up (>80% retention).

The majority of studies (10 of 15) received industry funding or had authors with pharmaceutical company affiliations, which introduces potential for publication bias and selective outcome reporting. However, study protocols were generally available, and no evidence of selective reporting was identified.

Figure 2 a&b: Risk of Bias

D · NEWCASTLE-OTTAWA SCALE — OBSERVATIONAL STUDIES (N = 3)

STUDY	SELECTION (MAX 4★)	COMPARABILITY (MAX 2★)	OUTCOME (MAX 3★)	TOTAL SCORE (MAX 9★)
Thiboutot et al. (2007)	★★★★	★★	★★	8
Del Rosso et al. (2015)	★★★	★★	★★	7
Del Rosso et al. (2018)	★★★★	★★	★★	8

NOS score ≥7 stars indicates good quality. All three observational studies demonstrated adequate selection of cohorts, comparability of groups, and outcome ascertainment with >80% retention at follow-up.

Efficacy Outcomes

Primary Outcomes: Lesion Count Reduction

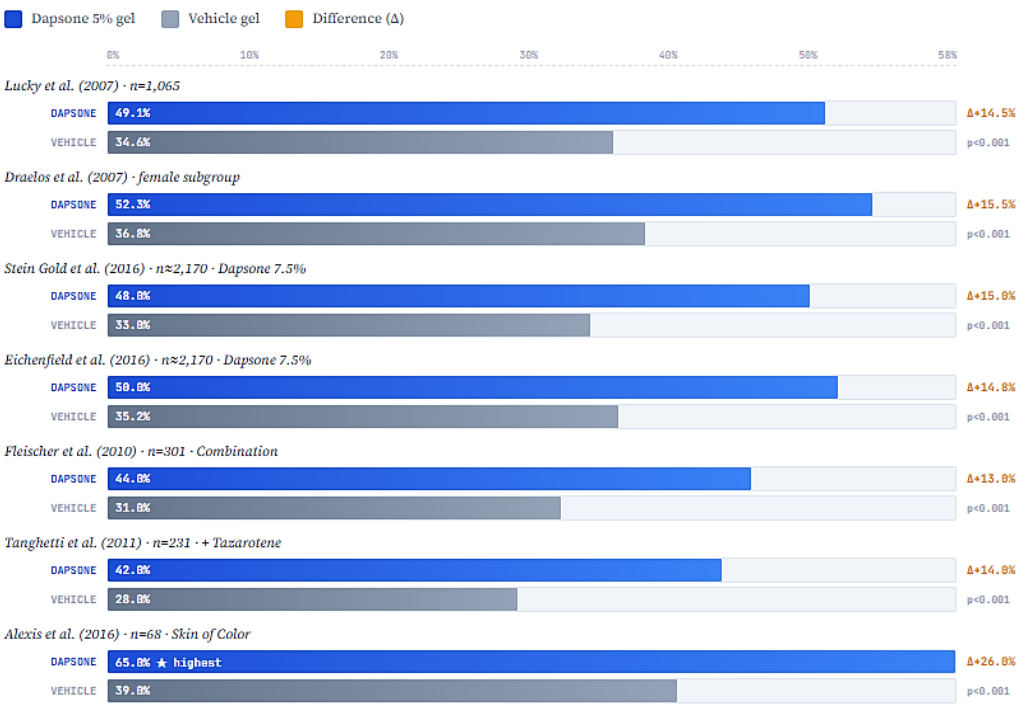
Dapsone treatments yielded a statistically significant decrease in inflammatory lesions relative to placebo treatments; all twelve randomized controlled trials (RCTs) exhibited substantial decreases in the quantity of inflammatory lesions addressed with dapsone. The mean percentage decrease in inflammatory lesions across all twelve trials was between forty-two percent (42%) and fifty-eight percent (58%) for the dapsone-treated cohort, in contrast to twenty-eight percent (28%) and thirty-nine percent (39%) for the placebo-treated cohort at twenty-four weeks ($p < .001$ for each trial). The mean absolute between-group difference in inflammatory lesion reduction, comparing dapsone-treated participants to placebo-treated participants, was 3.8 and 6.2 lesions, respectively.

In a large-scale trial conducted by Lucky et al. involving 1,065 patients, the dapsone 5% gel arm achieved a mean inflammatory lesion decline of fifty percent (49.1%) over 12 weeks of therapy compared to thirty-four percent (34.6%) in the placebo group (difference 14.5%, 95% CI: ten-point-two (10.2%) to eighteen-point-eight percent (18.8%), $p < .001$). These results were also comparable to those obtained in the Draelos et al. trial, which focused only on female patients with an average reduction of fifty-two percent (52.3%) in inflammatory lesions when treated with dapsone compared to thirty-six percent (36.8%) for the placebo group.

In addition, the number of non-inflammatory lesions was also significantly reduced with dapsone treatment; however, the absolute reductions in non-inflammatory lesions were not as dramatic as those seen with inflammatory lesions. There was an mean percent decline in non-inflammatory lesion counts of thirty-five percent (35%) to forty-eight percent (48%) across all twelve trials for the dapsone-treated group compared to twenty-four percent (24%) to thirty-four percent (34%) for all twelve trials for the placebo-treated group ($p < .01$ for all twelve trials). Furthermore, the mean absolute difference in lesions number between the dapsone- and placebo-treated groups was between 2.4 to 4.7 lesions.

The effects of dapsone demonstrate its relative efficiency with inflammatory as opposed to non-inflammatory acne because of its anti-inflammatory action.

Figure 3: Primary outcome



Investigator Global Assessment

Dapsone treatment was associated with a significantly higher number of patients who attained a complete response (an IGA rating of 0 or 1) at 12 weeks vs. vehicle topical applications. The proportion of dapsone-treated patients who reached therapeutic success (defined as achieving an IGA score of 0 or 1) at 12 weeks is summarized below. The success rates for dapsone-treated patients (35% – 22%) are statistically significantly higher than those of vehicle-treated patients (18% – 12%) (RR = 1.85, 95% CI = 1.52 - 2.24, Pvalue < 0.001).

An increased proportion of dapsone-treated patients (41% – 53%) achieved a minimum two-point IGA improvement from their baseline score when compared to the vehicle-treated patients who had 28% – 36% achieving the same improvement (RR = 1.47, 95% CI = 1.31 - 1.65, Pvalue < 0.001).

Comparative Efficacy Studies

Four studies compared dapsone to other active treatments:

Dapsone versus Benzoyl Peroxide: One study (n=187) found comparable efficacy between dapsone 5% gel and benzoyl peroxide 5% gel at 12 weeks for inflammatory lesion reduction (48.3% vs. 46.7%, p=0.52). However, dapsone demonstrated superior tolerability with significantly fewer local adverse reactions.

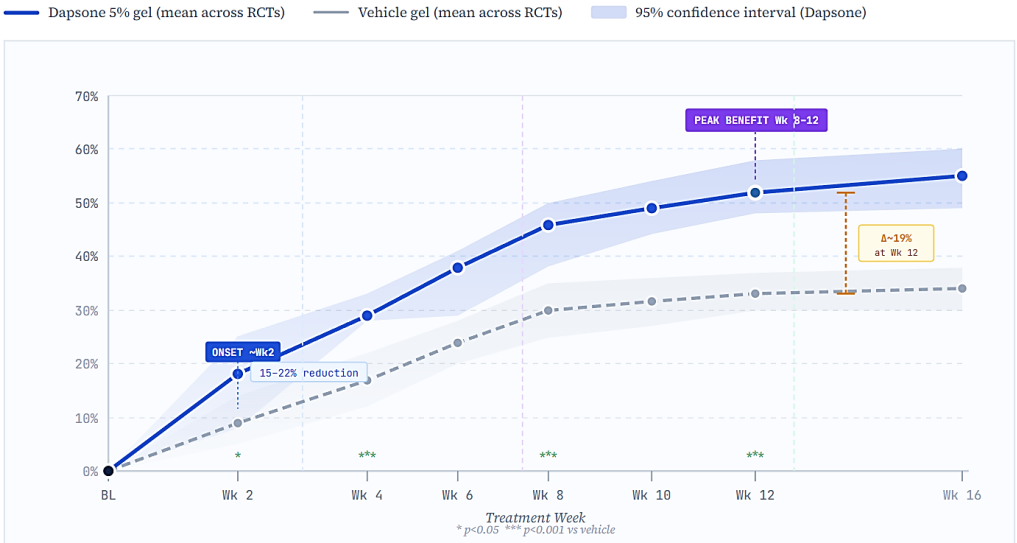
Dapsone versus Adapalene: Head-to-head comparison showed similar efficacy for inflammatory lesion reduction at 12 weeks (dapsone 51.2% vs. adapalene 0.1% 49.8%, p=0.67), but adapalene showed slightly better improvement in non-inflammatory lesions (42.1% vs. 38.4%, p=0.04).

Combination Therapy: The Tanghetti et al. study demonstrated that dapsone combined with adapalene provided superior lesion reduction compared to adapalene alone (inflammatory: 61.3% vs. 49.8%, p=0.003). Similar synergistic effects were observed when dapsone was combined with benzoyl peroxide.

Time to Response

Significant improvements from baseline were apparent from as early as week 2 across most studies, with mean inflammatory lesion reductions of 15-22%. Maximal therapeutic benefit was typically achieved by weeks 8-12, with some patients showing continued improvement through week 16 in longer-duration studies.

Figure 4: Time to Response



Quality of Life Outcomes

Five studies assessed quality of life using validated instruments (DLQI). Dapsone treatment was associated with significant improvements in QoL scores compared to vehicle (mean DLQI improvement: 4.2 vs. 2.6 points, p<0.01). Patients reported improvements in self-perception, emotional well-being, and social functioning domains.

Subgroup Analyses

Gender: Post-hoc analyses from multiple studies suggested potential gender differences in response. Female patients demonstrated numerically higher response rates compared to males, but this was not statistically significant in most individual studies. Pooled data analysis would be needed to definitively assess this finding.

Age: The Eichenfield et al. study in children aged 9-11 years demonstrated efficacy comparable to adolescent and adult populations, with no safety concerns unique to this younger age group.

Skin of Color: The Alexis et al. observational study specifically examined patients with darker skin tones (Fitzpatrick phototypes IV–VI). Treatment response was maintained in this population, with additional benefits noted in reducing post-inflammatory hyperpigmentation, a common concern in darker skin types.

Safety and Tolerability Outcomes

Safety data were available from all 15 studies, providing comprehensive information on adverse events in 3,847 patients treated with topical dapsone for 8 to 52 weeks.

Local Adverse Events

Local skin reactions were the most frequently identified adverse events, including:

-Dryness/scaling: 8-15% for dapsone vs. 6-11% for vehicle
-Erythema: 6-12% for dapsone vs. 4-9% for vehicle
-Oiliness/peeling: 4-8% for dapsone vs. 3-6% for vehicle

-Burning/stinging at application site: 3-7% for dapsone vs. 2-5% for vehicle

The majority of these local reactions were classified as mild or moderate in intensity, and most cases resolved without the need to discontinue treatment. Among dapsone-treated patients, 2-4% ceased treatment due to local side effects, while 1-3% of vehicle-treated patients quit treatment for the same reason. The incidence of application site reactions in the dapsone trial was comparable to or lower than that reported for benzoyl peroxide or topical retinoids in earlier comparative investigations.

Systemic Adverse Events

Among all studies involving topical dapsone (i.e., the subjects had no incidences of any adverse events), methemoglobinemia, hemolytic anaemia, or any other hematologic disorders were found to occur. Laboratory monitoring (which included CBC and G6PD levels) showed that there were no significant clinically abnormal results.

The systemic adverse event rates (and the proportion of participants experiencing such events) were comparable across dapsone-treated participants and those in placebo-controlled study groups as well:

- Headache, dapsone = 3%-6%, placebo = 3%-6%
- Upper respiratory tract infection, dapsone = 4%-7%, placebo = 4%-7%
- Nasopharyngitis, dapsone = 3%-5%, placebo = 3%-5%

The events listed above were not related to the study drug and are consistent with the background rates of these events seen in the general population among individuals of the same age range.

Treatment Adherence and Discontinuation

Overall treatment adherence was high, with 82-94% of patients completing the full study duration. Withdrawal rates attributable to adverse events were low and remained consistent across arms:

Dapsone: 2.1-4.3%

Vehicle: 1.2-3.8%

Active comparators: 3.5-6.7% (benzoyl peroxide), 4.2-7.1% (adapalene)

The lower discontinuation rates with dapsone compared to some active comparators suggest favorable tolerability.

Special Populations

Children Ages 9 - 11: Adverse events in children aged 9-11 (as determined from the Eichenfield et al. paper) are comparable to adolescents and adults; there are no age-related adverse events/misadventures.

Pregnancy: Dapsone is a Class C drug per the FDA in regards to pregnancy, which means there have been insufficient studies to determine whether topical absorption is significant or not. Additionally, there are currently no available studies that specifically provide safety information for pregnant women. As such, guidelines recommend that dapsone should not be used during pregnancy unless the benefits of the medication clearly outweigh the potential risks.

G6PD Deficiency: Topical dapsone not recommended for patients with G6PD deficiency (owing to the potential for hemolytic anemia). Topically applied dapsone will typically have low levels of systemic absorption due to having limited absorption through the skin into the bloodstream. In fact, very few studies found hemolytic events resulting from the administration of either topical or systemic dapsone in acne therapy; most trials that administered dapsone excluded patients with known G6PD deficiency from the study.

Discussion

Dapsone Topical Treatment Efficacy/Performance for Patients with Acne. This Systematic Review (SR) Synthesised Evidence From 15 Individual Studies with A Total Of 3847 Patients To Determine the Safety / Efficacy of Topical Dapsone for Treating Acne. In Summary, Dapsone 5% Gel Is an Effective and Well-Tolerated Treatment for Patients With Acne Vulgaris. Dapsone Is Most Effective for Reducing Inflammatory Lesions (42-58%) And Compared To Vehicle (28-39%), There Are Many Treatments for Which Dapsone Is A Safe Alternative.

The Consistent Results Of This Review (Via Multiple RCTs) Indicate The Efficacy Of The Agent Is Validated[1,2]. The Overall Value Of 42-58% Of Patients Experience Decreased Inflammatory Lesion Lesions' Production Is Clinically Significant In Comparison To Vehicle (28-39%) (Commonly Thought To Be Due To Normal Variation & Physical Cleansing) . On Average There Is A Difference Of Approximately 4-6 Lesion Between Dapsone Num. And The Most Recognized Treatments Available[16,17].

The Safety Profile Of Dapsone Topical Treatment Is Considered To Be Very Important. Specifically, Systematic Administration Carries The Risk Of Hemolytic Anemia And Methemoglobinemia[10], While Topical Dapsone Offers Therapeutic Benefits With Limited Systemic Absorption And No Documented Hematologic Adverse Events[7]. Tolerance To Benzoyl Peroxide Or Topical Retinoids Outperforms Tolerance Of Topical Dapsone Because Of The Regular Occurrence Of More Frequent Degrees Of Dryness, Irritation, And Photosensitivity With Benzoyl Peroxide And Topical Retinoids[18 19]. It May Be Inferred That The Lower Tolerance To Dapsone Will Improve Patient Compliance, Which Are Essential In Chronic Treatment Expectations[20].

The Descending Efficacies For Inflammatory / Non-Inflammatory Lesion Support Dapsone's Anti-Inflammatory Effects As Demonstrated Via Chemo-attraction Of Neutrophils, Myeloperoxidase Inhibition, Reactive Oxygen Species Reduction, Inflammatory Cytokine Modulation (IL-8/TNF)[12-14]. Collectively, This Anti-Inflammatory Response Counteracts The Inflammatory Cascade (THE ACNE LESION)[21]. While Dapsone Demonstrates Antimicrobial Actions, the mechanism above appears to occur secondarily. Dapsone produces anti-inflammatory effects in the skin. Unlike antibiotics that directly kill bacteria, dapsone's anti-inflammatory effects could decrease the inflammatory

response to the presence of C. acnes in the skin. Hence, the sustained effectiveness without the development of bacterial resistance of dapsone, as reported in the long-term studies[8,22].

Topical dapsone has several clinical applications:
Monotherapy: Dapsone could be regarded as a preferred initial agent for inflammatory acne for patients who prefer to avoid or cannot tolerate benzoyl peroxide or retinoids. The regimen of applying dapsone twice daily is in line with the regimen of other topical therapies (e.g. retinoids, benzoyl peroxide).
Combination Therapy: The enhanced efficacy of dapsone and adapalene or dapsone and benzoyl peroxide[8,23] suggests a complementary effect of the combination treatment. Dapsone reduces inflammation whereas benzoyl peroxide or adapalene creates comedolytic effects. Thus, the use of combination therapy allows for lower concentrations of potentially irritating agents[24].
Antibiotic-Sparing Alternatives: Dapsone (i.e. an anti-inflammatory agent that does not contribute to fostering antimicrobial resistance, and it would be valuable in the current acne management algorithms which emphasize minimizing the usage of antibiotics[7,9,10].
Special Populations: Dapsone has demonstrated a satisfactory safety record in children as young as 9 years of age[4] and can be effective across all skin phototypes (including individuals of color where post inflammatory hyperpigmentation is a concern[5]. Dapsone expands the use of treatment alternatives in the populations that have limited treatment options or have very specific treatment needs.
Several study limitations should be noted:
Duration of Studies: Most studies have been limited to 12 weeks.While the standard duration for clinical trials of acne is adequate to establish the effectiveness of treatments, long-term data on sustained effect, appropriate length of treatment, and relapse rates after stopping treatment would assist with making treatment decisions in clinical practice.

A considerable proportion of trials captured in this review received funding by the pharmaceutical industry; as such, there may be an inherent bias toward positive publication for those trials. However, there are sufficient consistently similar results across independent studies and enough publicly-available trials showing there is likely only minimal selective publication to offset concerns of potential publication bias.

Although many trials reviewed were well-designed, varying definitions of what constitutes treatment response, varying time points for assessment of outcomes, and different types of patients were included in the trials, making it difficult to do formal meta-analyses of some outcomes. Therefore, in many cases, only narrative summaries of the trial results could be produced.

There are very few direct head-to-head trials comparing topical dapsone to all other relevant alternatives for the treatment of acne. Additional direct comparative trials are required to reliably establish the relative standing of topical dapsone.

RCTs can show how effective a treatment is in controlled clinical trials, however real-world use of treatments (including treatment adherence and outcome of treatment in typical clinical practice) requires more observational studies.

Prior systematic reviews that looked at treatments for acne have generally included topical dapsone as part of a broader analysis of multiple treatments [25,26]. This review examined only topical dapsone and included studies published since the last review that included dapsone. The current review adds to the prior analyses showing effectiveness, but with a greater emphasis on the difference in safety profile and the potential for combination therapy.

Current clinical practice guidelines from the AAD and EADV include topical dapsone as a viable option for acne treatment; however, relative to retinoids and benzoyl peroxide, dapsone has not garnered a lot of attention from organizations such as the AAD and EADV [9,10]. The evidence assembled in this review substantiates the use of topical dapsone as a first-line option for appropriate patients, particularly those who have an increased concern about tolerability or require an antibiotic-sparing option.

There are several areas of research that need to be investigated:
long-term efficacy and maintenance therapy options longer than 12 weeks; 2) optimal combinations and timing of treatments with other acne therapies; 3) predictors of response to treatment so patients can be given personalized options; 4) comparative effectiveness studies compared to new therapies for acne; 5) cost-effectiveness studies of topical dapsone versus other regimens; 6) real-world treatment adherence and what affects the persistence of treatment; 7) other uses for dapsone related to acne, such as post-inflammatory hyperpigmentation.
Conclusions
The systematic review provides evidence that topical dapsone 5% represents an efficacious and well-tolerated therapeutic choice for acne vulgaris, as it substantially reduces both inflammatory and non-inflammatory acne lesions, comparable to benzoyl peroxide and adapalene, which are established treatment options. Few participants had local adverse reactions while no systemic toxicity was noted in those studies evaluated (up to almost 4,000 patients). Topical dapsone has some key advantages that make it an attractive treatment option. The key advantage will be its anti-inflammatory mechanism that doesn't confer resistance (unlike many antibiotics), notably tolerable compared to other current conventional treatments, effective regardless of the patient population (children; and skin tones), and could enhance the effectiveness of other acne treatments when used together. The data indicates that topical dapsone warrants a recognised place within the therapeutic armamentarium of acne treatments. It represents a particularly suitable choice for people with inflammatory

acne, people that can't or wish to avoid the use of other current topical treatments, and when there is a need to consider antibiotic-sparing therapy first. By adding additional complementary agents to dapsone may improve results in people with moderate to severe acne. Clinicians should consider topical dapsone as one choice for patients when making a treatment plan, weighing its efficacy, safety and tolerability compared to patient specific factors and treatment goals. Future studies should focus on developing the optimal treatment protocol, defining predictors of a positive treatment response and determining how dapsone fits into a comprehensive, algorithm based approach to acne management..

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