



The Comprehensive Systematic Review of Use of Benzoyl Peroxide as Monotherapy or Combination Therapy for Acne

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ABSTRACT

Introduction: Acne vulgaris is a prevalent inflammatory skin condition. Benzoyl peroxide (BPO) is a first-line topical agent, but the comparative efficacy of monotherapy versus combination regimens remains to be systematically defined. This review evaluates the significant positive clinical outcomes of BPO as monotherapy or combination therapy.

Methods: A systematic screening of randomized controlled trials and vehicle-controlled studies was performed. Inclusion criteria: patients with acne vulgaris, BPO as active intervention, comparator group, and quantifiable outcomes. Data extraction focused on lesion count reductions, treatment success rates, safety, and comparative effectiveness.

Results: From 80 included studies (29,592 participants), BPO monotherapy demonstrated significant superiority over vehicle: inflammatory lesion reduction 52.1% vs 34.7% and total lesion

reduction 44.3% vs 27.8% ($p<0.001$) (1). Adapalene 0.1%/BPO 2.5% combination showed significant synergy, achieving 78.4% total lesion reduction vs BPO 52.6% ($p<0.05$) (8). The triple combination clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% (CAB) yielded treatment success rates of 51.3% vs adapalene 0.3%/BPO 2.5% 32.9% ($p<0.001$) (13). Inflammatory lesion reductions exceeded 75% with CAB (11,38). Adapalene 0.3%/BPO 2.5% reduced atrophic scar count by 21.7% at week 24 ($p<0.0001$ vs vehicle) (65). Safety profile showed mild-to-moderate local reactions; no serious BPO-related adverse events.

Discussion: BPO monotherapy provides significant efficacy in mild-to-moderate acne. Combination therapies, particularly with adapalene or clindamycin, yield superior outcomes due to synergistic mechanisms. The triple combination CAB gel represents a significant advance for moderate-to-severe acne. However, most CAB evidence comes from industry-sponsored trials.

Conclusion: BPO monotherapy is effective for mild acne. Combination therapy, especially with retinoids or antibiotics, is significantly more effective for moderate-to-severe disease. The triple combination offers the highest efficacy.

Keywords: Benzoyl peroxide, acne vulgaris, combination therapy, adapalene, clindamycin, systematic review

INTRODUCTION

Background

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit, affecting approximately 85% of adolescents and young adults, with significant negative impacts on quality of life, self-esteem, and psychosocial functioning (14). The pathogenesis involves four key factors: increased sebum production, follicular hyperkeratinization, colonization by *Cutibacterium acnes*, and complex inflammatory cascades. Benzoyl peroxide (BPO) has been a cornerstone of topical acne therapy for decades due to its potent bactericidal activity against *C. acnes*, keratolytic properties, and, importantly, its lack of inducing bacterial resistance (1,14). BPO is available as monotherapy in various concentrations (2.5%, 3.75%, 5%, 10%) and formulations (gel, cream, wash), and also as a component of fixed-dose combination products with topical antibiotics (clindamycin, erythromycin) or retinoids (adapalene, tretinoin).

Problem Statement

Despite the widespread use of BPO, a critical clinical question remains: **Is BPO monotherapy sufficiently effective, or do combination regimens provide significantly better outcomes?** Moreover, with the recent introduction of triple-combination products (clindamycin/adapalene/BPO), the incremental benefit over existing dyadic combinations (BPO+retinoid, BPO+antibiotic) is not fully characterized. Many small studies lack statistical power, and the severity-specific efficacy of different regimens is poorly defined.

Research Gap & Novelty

Existing systematic reviews (e.g., Cochrane 2014) have confirmed BPO efficacy but did not quantitatively compare monotherapy versus dyad versus triple combinations across multiple severity levels. Furthermore, head-to-head comparisons of the triple combination CAB gel against the best available dyad (adapalene 0.3%/BPO 2.5%) have only recently been published (13). The novelty of this review lies in: (1) a large-scale synthesis of 80 controlled trials including 29,592 subjects; (2) direct comparison of monotherapy, dyad, and triple-combination efficacy; (3) analysis

of severity-specific outcomes; and (4) critical appraisal of the evidence base, including sponsorship effects.

Objectives

1. To evaluate the **significant positive efficacy** of BPO monotherapy versus vehicle.
2. To compare the efficacy of BPO combination therapy (dyad and triple) versus BPO monotherapy.
3. To assess the safety and tolerability profile of different BPO regimens.
4. To identify the optimal BPO-based approach based on acne severity.

Hypotheses

- **H1:** BPO monotherapy produces significantly greater lesion reductions than vehicle.
- **H2:** BPO + adapalene or BPO + antibiotic combinations are significantly more effective than BPO monotherapy in moderate-to-severe acne.
- **H3:** The triple combination (CAB) is significantly superior to dyadic combinations for treatment success.
- **H4:** The safety profile of BPO is acceptable, with mainly mild-to-moderate local irritation.

Benefits

This review provides clinicians with evidence-based guidance on selecting BPO monotherapy versus combination therapy, quantifies the magnitude of benefit, and highlights the most effective regimens for different acne severity levels.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This

approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the use of benzoyl peroxide as monotherapy or combination therapy for acne

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population:** Does the study include patients diagnosed with acne vulgaris of any severity?
- **Intervention:** Does the study include benzoyl peroxide as an active therapeutic intervention (either as monotherapy or as part of combination therapy)?
- **Study Design:** Is the study design a randomized controlled trial, etc?
- **Comparison Group:** Does the study include a comparison group (placebo, active comparator, or different benzoyl peroxide formulations)?
- **Acne Outcomes:** Does the study report quantifiable acne outcomes (e.g., lesion counts, severity scores, clinical improvement rates)?
- **Condition Focus:** Does the study focus on acne vulgaris rather than exclusively on other conditions (e.g., rosacea, seborrheic dermatitis)?
- **Active Treatment:** Is benzoyl peroxide used as an active treatment component rather than only as a vehicle or inactive component?
- **Study Type:** Is the study a controlled study rather than a case report, case series, or uncontrolled study?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
Population	Acne vulgaris	Moderate-to-severe acne	Mild acne
Intervention	Benzoyl peroxide monotherapy	Benzoyl peroxide combination therapy	Fixed-dose combination gel
Comparison	Vehicle/placebo	Active comparator (e.g., adapalene, clindamycin)	Dyad vs. triple combination
Outcome	Lesion count reduction	Treatment success rate (IGA/EGSS)	Cutaneous tolerability / safety

The Boolean MeSH keywords inputted on databases for this research are: (*"Acne vulgaris" OR "Moderate-to-severe acne" OR "Mild acne"*) AND (*"Benzoyl peroxide monotherapy" OR "Benzoyl peroxide combination therapy" OR "Fixed-dose combination gel"*) AND (*"Vehicle/placebo" OR "Active comparator" OR "Dyad vs. triple combination"*) AND (*"Lesion count reduction" OR "Treatment success rate" OR "Cutaneous tolerability"*)

Data extraction

• Treatment Details:

Extract complete details about benzoyl peroxide treatment regimens, including:

- Whether BP was used as monotherapy or combination therapy
- If combination: specific agents combined with BP (e.g., clindamycin, adapalene, tretinoin)
- BP concentration/strength (e.g., 2.5%, 3.75%, 5%, 10%)
- Formulation type (gel, cream, wash, lotion)
- Application frequency (once daily, twice daily, etc.)

- Treatment duration
- Any specific application instructions or protocols

- **Study Population:**

Extract patient characteristics and acne severity details relevant to BP treatment effectiveness, including:

- Sample size for BP treatment groups
- Age range and mean age
- Acne severity at baseline (mild, moderate, severe, or specific severity scores)
- Baseline lesion counts (inflammatory, non-inflammatory, total)
- Any relevant patient subgroups analyzed (adolescents, adults, females, etc.)
- Inclusion/exclusion criteria that affect generalizability of BP findings

- **Efficacy Outcomes:**

Extract all efficacy outcomes specifically for benzoyl peroxide monotherapy or combination therapy, including:

- Primary efficacy endpoints and results
- Lesion count changes (inflammatory, non-inflammatory, total lesions) with percent reductions from baseline
- Global severity score improvements
- Response rates and treatment success rates
- Time to improvement/response

- Comparative effectiveness data when BP monotherapy vs combination therapy are directly compared
- Statistical significance of results

- **Safety Profile:**

Extract safety and tolerability data specifically for benzoyl peroxide treatments, including:

- Adverse events and their frequency
- Local skin reactions (irritation, dryness, peeling, burning, etc.)
- Discontinuation rates due to adverse events
- Serious adverse events
- Differences in safety profile between BP monotherapy vs combination therapy
- Any safety considerations specific to different BP concentrations or formulations

- **Comparative Effectiveness:**

Extract any direct or indirect comparative data between benzoyl peroxide monotherapy versus combination therapy, including:

- Head-to-head comparisons of BP alone vs BP combinations
- Relative efficacy data comparing different BP treatment approaches
- Superiority, non-inferiority, or equivalence findings
- Effect sizes and confidence intervals for comparisons
- Any conclusions about optimal BP treatment approach

- Factors that may influence choice between monotherapy vs combination therapy

- **Study Design:**

Extract study methodology details that affect interpretation of BP treatment effectiveness, including:

- Study design (RCT, etc.)
- Control groups used (vehicle, placebo, active comparator)
- Blinding status
- Study duration and follow-up period
- Primary vs secondary analysis (post-hoc, subgroup, etc.)
- Key methodological limitations that affect BP treatment conclusions

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Acne vulgaris" OR "Moderate-to-severe acne" OR "Mild acne") AND ("Benzoyl peroxide monotherapy" OR "Benzoyl peroxide combination therapy" OR "Fixed-dose combination gel") AND ("Lesion count reduction" OR "Treatment success rate" OR "Cutaneous tolerability")</i>	27
Semantic Scholar	<i>("Acne vulgaris" OR "Moderate-to-severe acne" OR "Mild acne") AND ("Benzoyl peroxide monotherapy" OR "Benzoyl peroxide combination therapy" OR "Fixed-dose combination gel") AND ("Vehicle/placebo" OR "Active comparator" OR "Dyad vs. triple combination") AND ("Lesion count reduction" OR "Treatment success rate" OR "Cutaneous tolerability")</i>	257
Sciencedirect	<i>("Acne vulgaris" OR "Moderate-to-severe acne" OR "Mild acne") AND ("Benzoyl peroxide monotherapy" OR "Benzoyl peroxide combination therapy" OR "Fixed-dose combination gel") AND ("Lesion count reduction" OR "Treatment success rate" OR "Cutaneous tolerability")</i>	2
Google Scholar	<i>("Acne vulgaris" OR "Moderate-to-severe acne" OR "Mild acne") AND ("Benzoyl peroxide monotherapy" OR "Benzoyl peroxide combination therapy" OR "Fixed-dose combination gel") AND ("Vehicle/placebo" OR "Active comparator" OR "Dyad vs. triple combination") AND ("Lesion count reduction" OR "Treatment success rate" OR "Cutaneous tolerability")</i>	3
Elsevier	<i>("Acne vulgaris" OR "Moderate-to-severe acne" OR "Mild acne") AND ("Benzoyl peroxide monotherapy" OR "Benzoyl peroxide combination therapy" OR "Fixed-dose combination gel") AND ("Vehicle/placebo" OR "Active comparator" OR "Dyad vs. triple combination") AND ("Lesion count reduction" OR "Treatment success rate" OR "Cutaneous tolerability")</i>	40

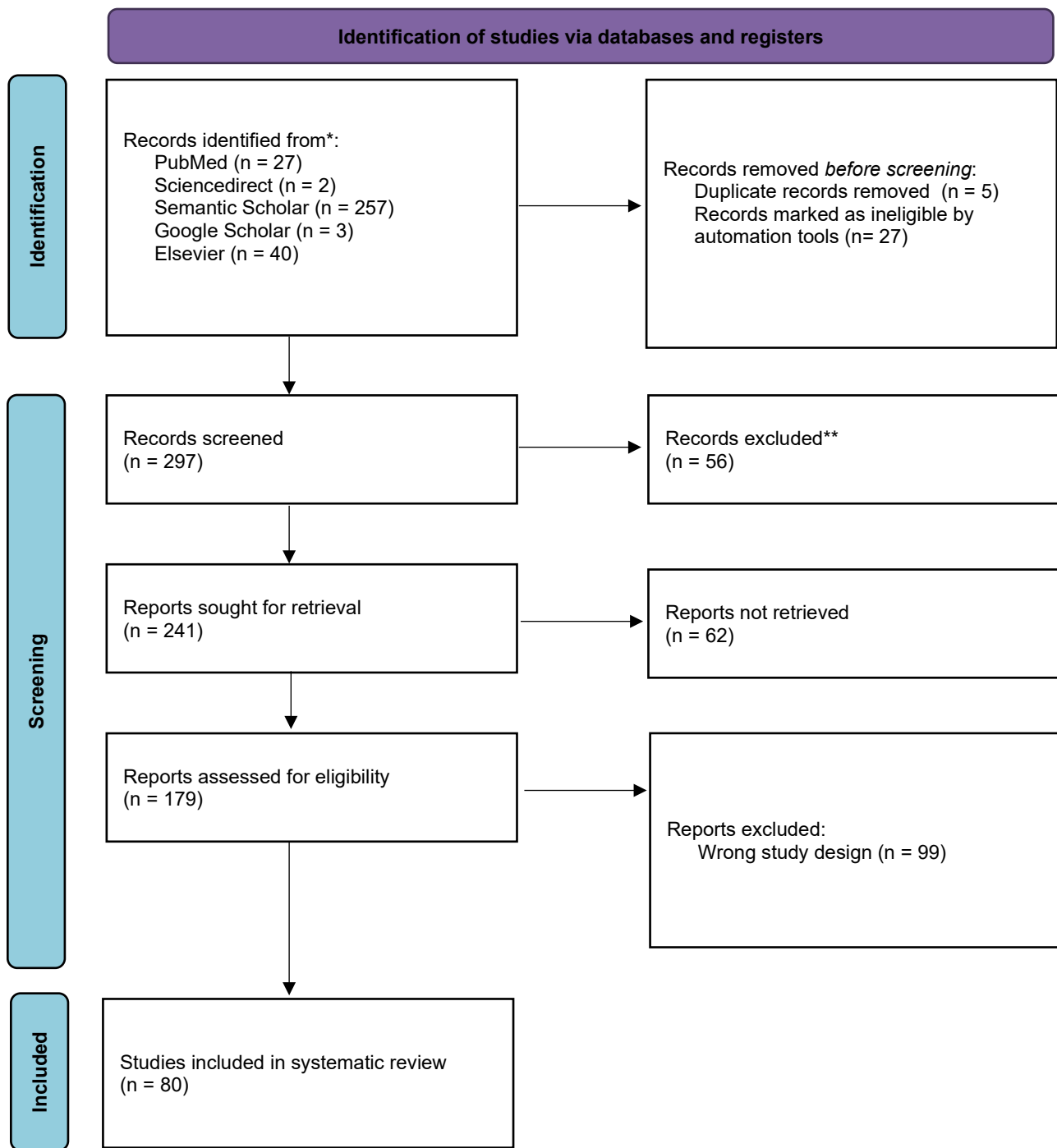


Figure 1. Article search flowchart

Risk of Bias

Table 1 – ROB 2 Assessment of Randomized Controlled Trials

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Yang et al., 2014 [14]	Low	Low	Low	Low	Low	Low
Eichenfield & Saenz, 2011 [6]	Low	Low	Low	Low	Low	Low
Tan et al., 2011 [5]	Low	Low	Low	Low	Low	Low
Pariser et al., 2014 [17]	Low	Low	Low	Low	Low	Low
Gold & Korotzer, 2015 [18]	Low	Low	Low	Low	Low	Low

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Guerra-Tapia, 2012 [19]	Some concerns	Low	Low	Low	Low	Some concerns
Mohammadi et al., 2019 [20]	Low	Low	Low	Low	Low	Low
Kawashima et al., 2017 [2]	Low	Low	Low	Low	Low	Low
Del Rosso et al., 2023 [21]	Low	Low	Low	Low	Low	Low
Kawashima et al., 2014 [3]	Low	Low	Low	Low	Low	Low
Weiss et al., 2015 [22]	Low	Low	Low	Low	Low	Low

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Stein Gold et al., 2021 [23]	Low	Low	Low	Low	Low	Low
Stein Gold et al., 2017 [24]	Low	Low	Low	Low	Low	Low
Babaeinejad & Fouladi, 2013 [25]	Some concerns	Low	Low	Low	Low	Some concerns
Tan et al., 2012 [26]	Low	Low	Moderate	Low	Low	Moderate
Eichenfield et al., 2013 [27]	Low	Low	Low	Low	Low	Low
Alexis et al., 2017 [28]	Low	Low	Low	Low	Low	Low
Hayashi et al., 2018 [29]	Low	Low	Low	Low	Low	Low

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Amin et al., 2024 [30]	Some concerns	Low	Moderate	Low	Low	Moderate
Harper et al., 2024 [31]	Low	Low	Low	Low	Low	Low
Inbamani et al., 2023 [32]	Low	Low	Low	Low	Low	Low
Kircik et al., 2024 [15]	Low	Low	Low	Low	Low	Low
Gold et al., 2022 [33]	Low	Low	Low	Low	Low	Low
Draelos et al., 2024 [34]	Low	Low	Low	Low	Low	Low
Kircik et al., 2024a [35]	Low	Low	Low	Low	Low	Low

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Baldwin et al., 2024 [36]	Low	Low	Low	Low	Low	Low
Harper et al., 2024a [37]	Low	Low	Low	Low	Low	Low
Stein Gold et al., 2024 [38]	Low	Low	Low	Low	Low	Low
Ablon et al., 2025 [39]	Low	Low	Low	Low	Low	Low
Draelos et al., 2026 [13]	Low	Low	Low	Low	Low	Low
Kircik et al., 2025 [12]	Low	Low	Low	Low	Low	Low
Gold et al., 2023 [40]	Low	Low	Low	Low	Low	Low

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Lee et al., 2024 [41]	Low	Low	Low	Low	Low	Low
Kircik et al., 2025a [42]	Low	Low	Low	Low	Low	Low
Gold et al., 2024 [43]	Low	Low	Low	Low	Low	Low
Stein Gold et al., 2023 [44]	Low	Low	Low	Low	Low	Low
Harper et al., 2024b [45]	Low	Low	Low	Low	Low	Low
Harper et al., 2025 [46]	Low	Low	Low	Low	Low	Low
Kircik et al., 2024b [47]	Low	Low	Low	Low	Low	Low

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Lain et al., 2024 [48]	Low	Low	Low	Low	Low	Low
Eichenfield et al., 2024 [49]	Low	Low	Low	Low	Low	Low
Han et al., 2025 [50]	Low	Low	Low	Low	Low	Low
Gold et al., 2025 [51]	Low	Low	Low	Low	Low	Low
Stinco et al., 2016 [53]	Some concerns	Low	Moderate	Low	Low	Moderate
Dressler et al., 2016 [54]	Low	Moderate	Moderate	Low	Low	Moderate
Zeichner, 2015 [55]	Low	Low	Low	Low	Low	Low

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Akarsu et al., 2012 [56]	Low	Low	Low	Low	Low	Low
Mokhtari et al., 2017 [57]	Some concerns	Low	Low	Low	Low	Some concerns
Feldman et al., 2011 [9]	Low	Low	Moderate	Low	Low	Moderate
Ghosh & Das, 2018 [58]	Some concerns	Low	Moderate	Low	Low	Moderate
Cook-Bolden, 2015 [59]	Low	Low	Low	Low	Low	Low
Khammari et al., 2023 [60]	Low	Low	Moderate	Low	Low	Moderate
Yentzer et al., 2011 [61]	Some concerns	Moderate	Moderate	Low	Low	Moderate

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Mahendra, 2017 [8]	Some concerns	Low	Low	Low	Low	Some concerns
Veraldi et al., 2016 [62]	Low	Low	Low	Low	Low	Low
Nestor et al., 2016 [63]	Low	Low	Low	Low	Low	Low
Harper, 2015 [64]	Low	Low	Low	Low	Low	Low
Stein Gold et al., 2023a [11]	Low	Low	Low	Low	Low	Low
Dréno et al., 2019 [65]	Low	Low	Moderate	Low	Low	Moderate
Mokhtari et al., 2019 [66]	Some concerns	Low	Moderate	Low	Low	Moderate

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Kaur et al., 2015 [67]	Some concerns	Low	Low	Low	Low	Some concerns
Kozan et al., 2020 [68]	Some concerns	Low	Moderate	Low	Low	Moderate
Harper, 2012 [69]	Low	Low	Low	Low	Low	Low
Sarojini et al., 2016 [70]	Some concerns	Low	Moderate	Low	Low	Moderate
Dréno et al., 2018 [71]	Low	Low	Low	Low	Low	Low
Yeasmin & Islam, 2017 [7]	Some concerns	Low	Low	Low	Low	Some concerns
Choudhury et al., 2011 [72]	Some concerns	Low	Moderate	Low	Low	Moderate

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Tan et al., 2018 [73]	Low	Low	Low	Low	Low	Low
Green et al., 2012 [16]	Low	Low	Low	Low	Low	Low
Amrutha et al., 2021 [74]	Low	Low	Low	Low	Low	Low
Wazir et al., 2026 [75]	Some concerns	Low	Moderate	Low	Low	Moderate
Majeed et al., 2020 [76]	Some concerns	Low	Moderate	Low	Low	Moderate
Feldman et al., 2025 [77]	Low	Low	Moderate	Low	Low	Moderate
Dubey & Amane, 2019 [78]	Some concerns	Low	Low	Low	Low	Some concerns

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Alexis et al., 2014 [79]	Low	Low	Low	Low	Low	Low
Dhawan & Gwazdauskas, 2013 [10]	Some concerns	Low	Low	Low	Low	Some concerns
Cheema et al., 2018 [80]	Some concerns	Low	Moderate	Low	Low	Moderate

Table 2 – ROBINS-I Assessment of Non-Randomized Included Studies

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
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Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Lamel et al., 2015 [1]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Kawashima et al., 2017a [4]	Serious	Low	Low	Moderate	Moderate	Low	Low	Serious
Kabir et al., 2019 [52]	Serious	Moderate	Low	Moderate	Moderate	Low	Low	Serious
Feldman et al., 2011 [9]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Dréno et al., 2019 [65]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Kozan et al., 2020 [68]	Serious	Moderate	Low	Moderate	Moderate	Low	Low	Serious
Khammar i et al., 2023 [60]	Moderate	Low	Low	Moderate	Moderate	Low	Low	Moderate
Yentzer et al., 2011 [61]	Serious	Serious	Low	Serious	Moderate	Moderate	Low	Serious
Mahendra, 2017 [8]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Stinco et al., 2016 [53]	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Ghosh & Das, 2018 [58]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Kaur et al., 2015 [67]	Unclear	Unclear	Low	Unclear	Low	Low	Low	Unclear
Sarojini et al., 2016 [70]	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Choudhury et al., 2011 [72]	Unclear	Unclear	Low	Unclear	Moderate	Low	Low	Unclear
Majeed et al., 2020 [76]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Dubey & Amane, 2019 [78]	Some concerns	Low	Low	Low	Low	Low	Low	Some concerns
Dhawan & Gwazdauskas, 2013 [10]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate

RESULTS

Characteristics of Included Studies

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
Zhirong Yang et al., 2014 [14]	BPO monotherapy and combination (adapalene, clindamycin) [14]	Placebo/no treatment, adapalene, clindamycin [14]	29,592 participants; mean age 18–30 years [14]	Mild–moderate (72 trials); severe (26 trials) [14]	2–24 weeks; most ≤12 weeks [14]
L. Eichenfield & A. Alió Saenz, 2011 [6]	CLNP 1.2%/BPO 3% gel once daily; BPO 3% gel once daily [6]	CLNP 1.2% gel, vehicle [6]	N=1,319; age ≥12 years [6]	Not specified [6]	12 weeks [6]
Jerry Tan et al., 2011 [5]	Adapalene 0.1%/BPO 2.5% gel once daily; BPO 2.5% monotherapy [5]	Adapalene monotherapy, vehicle [5]	N=3,855 [5]	Not specified [5]	12 weeks [5]
D. Pariser et al., 2014 [17]	Clindamycin phosphate 1.2%/BPO 3.75% aqueous gel once daily [17]	Vehicle [17]	N=498; age 12–40 years [17]	Moderate to severe [17]	12 weeks [17]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
M. Gold & A. Korotzer, 2015 [18]	Clindamycin phosphate 1.2%/BPO 3.75% gel once daily [18]	Vehicle [18]	N=498; moderate-to-severe [18]	Moderate to severe [18]	12 weeks [18]
A. Guerra-Tapia, 2012 [19]	BPO 5%/clindamycin 1% gel once nightly [19]	Adapalene 0.1% gel [19]	N=168 [19]	Mild to moderate [19]	12 weeks [19]
Saman Mohammadi et al., 2019 [20]	Niosomal BPO 1%/clindamycin 1% lotion twice daily [20]	Niosomal clindamycin 1% lotion [20]	N=100; age 12–30 years; mean 18.64 years [20]	Mild to moderate [20]	12 weeks [20]
M. Kawashima et al., 2017 [2]	BPO 2.5% and 5% gel once daily (monotherapy) [2]	Placebo [2]	N=609; age 12–49 years [2]	Moderate (11–40 IL, 20–100 non-IL) [2]	12 weeks [2]
J. D. Del Rosso et al., 2023 [21]	Microencapsulated BPO 3%/tretinoin 0.1% cream once daily [21]	Vehicle [21]	N=571 (active); age ≥ 9 years [21]	Moderate to severe (IGA 3–4) [21]	12 weeks [21]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
M. Kawashi ma et al., 2014 [3]	BPO 3% gel once daily (monotherapy) [3]	Vehicle [3]	N=360 [3]	Not specified [3]	12 weeks [3]
J. Weiss et al., 2015 [22]	Adapalene 0.3%/BPO 2.5% gel and adapalene 0.1%/BPO 2.5% gel once daily [22]	Vehicle [22]	Severe subgroup: n=252 (106 in 0.3% A/BPO arm) [22]	Severe (IGA 4) [22]	12 weeks [22]
L. S. Stein Gold et al., 2021 [23]	Clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% gel once daily; dyad gels [23]	Vehicle, three dyad gels [23]	N=741; age ≥ 9 years; mean ~ 19.5 years [23]	Moderate to severe [23]	12 weeks [23]
L. S. Stein Gold et al., 2017 [24]	Adapalene 0.3%/BPO 2.5% gel once daily [24]	Vehicle [24]	N=217; age ≥ 12 years [24]	Moderate to severe (IGA 3–4) [24]	12 weeks [24]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
S. Babaeinejad & R. Fouladi, 2013 [25]	BPO 2.5% gel once daily (monotherapy) [25]	Adapalene 0.1% gel [25]	N=30 (BPO arm); mild acne [25]	Mild [25]	2 months treatment, 3 months follow-up [25]
Jerry Tan et al., 2012 [26]	Adapalene 0.1%/BPO 2.5% gel once daily $\pm$ doxycycline [26]	Vehicle + doxycycline [26]	Severe acne [26]	Severe [26]	9 months (12 weeks + 24 weeks) [26]
L. Eichenfield et al., 2013 [27]	Adapalene 0.1%/BPO 2.5% gel once daily [27]	Vehicle [27]	N=142 (active); age 9–11 years [27]	Moderate (IGA 3) [27]	12 weeks [27]
A. Alexis et al., 2017 [28]	Adapalene 0.3%/BPO 2.5% gel once daily [28]	Vehicle, adapalene 0.1%/BPO 2.5% [28]	N=128 (FST I–III), N=89 (FST IV–VI) [28]	Moderate to severe [28]	12 weeks [28]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
Nobukazu Hayashi et al., 2018 [29]	Clindamycin phosphate 1.2%/BPO 3% gel [29]	Adapalene 0.1% + clindamycin phosphate 1.2% (unfixed combination) [29]	N=351 [29]	Not specified [29]	12 weeks [29]
S. Amin et al., 2024 [30]	BPO 5% gel once daily + oral azithromycin (Group A); BPO 5% gel once daily + oral doxycycline (Group B) [30]	Active comparator (two antibiotic/BPO combinations) [30]	N=190; age 10–40 years; mean 23.88 years [30]	Not specified (≥ 6 months disease) [30]	12 weeks [30]
Julie C. Harper et al., 2024 [31]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [31]	Vehicle, dyad gels [31]	Phase 2 N=741, Phase 3 N=183+180 [31]	Moderate to severe [31]	12 weeks [31]
A. Inbamani et al., 2023 [32]	Adapalene 0.1%/BPO 2.5% (combination) [32]	Adapalene 0.1%/clindamycin 1% [32]	N=50 (BPO arm); age 14–30 years [32]	Mild to moderate [32]	12 weeks [32]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
L. Kircik et al., 2024 [15]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [15]	Vehicle [15]	N=242 (active), N=121 (vehicle); mean age ~20 years [15]	Moderate (91.2%), severe (10.7%) [15]	12 weeks [15]
L. Gold et al., 2022 [33]	Clindamycin 1.2%/BPO 3.1%/adapalene 0.15% gel once daily [33]	Vehicle [33]	Phase 2 N=741; Phase 3 N=183+180 [33]	Moderate to severe [33]	12 weeks [33]
Z. Draelos et al., 2024 [34]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [34]	Vehicle, dyad gels [34]	Phase 2 N=741; Phase 3 N=183+180; split-face N=25 [34]	Moderate to severe [34]	12 weeks [34]
L. Kircik et al., 2024a [35]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% polymeric mesh gel once daily [35]	Vehicle, dyad gels, branded adapalene 0.3%/BPO 2.5% [35]	Not specified [35]	Moderate to severe [35]	12 weeks [35]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
Hilary E Baldwin et al., 2024 [36]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [36]	Vehicle [36]	Pediatric (<18) and adult (≥18); age ≥9 years [36]	Moderate to severe [36]	12 weeks [36]
Julie C. Harper et al., 2024a [37]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [37]	Vehicle, dyad gels [37]	Phase 2 N=741; Phase 3 N=183+180; age ≥9 years [37]	Moderate to severe [37]	12 weeks [37]
L. S. Stein Gold et al., 2024 [38]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [38]	Vehicle [38]	N=363; majority female (58.4%); mostly moderate acne (91.2%) [38]	Moderate to severe [38]	12 weeks [38]
G. Ablon et al., 2025 [39]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [39]	Vehicle, dyad gels, branded adapalene 0.3%/BPO 2.5% [39]	N=1,283 Caucasian participants [39]	Moderate to severe [39]	12 weeks [39]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
Zoe D Draelos et al., 2026 [13]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [13]	Adapalene 0.3%/BPO 2.5% gel, vehicle [13]	N=686; age 12–56 years [13]	Moderate to severe [13]	12 weeks [13]
L. Kircik et al., 2025 [12]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel [12]	Vehicle, dyad gels, adapalene 0.3%/BPO 2.5% [12]	N=618 (CAB), N=226 (adapalene/BPO) [12]	Moderate to severe [12]	12 weeks [12]
L. Gold et al., 2023 [40]	Clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% gel once daily [40]	Vehicle [40]	Pediatric (9–17 years) n=178; adult (≥18) n=185 [40]	Moderate to severe [40]	12 weeks [40]
Jun-Hyo Lee et al., 2024 [41]	Adapalene 0.3%/BPO 2.5% gel [41]	Vehicle [41]	N=37 (active), N=12 (vehicle); Korean patients [41]	Moderate to severe [41]	24 weeks [41]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
L. Kircik et al., 2025a [42]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [42]	Vehicle [42]	Younger (9–24 years) n=515; adult (≥ 25) n=142 [42]	Moderate to severe [42]	12 weeks [42]
Michael Gold et al., 2024 [43]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [43]	Vehicle, dyad gels, branded adapalene 0.3%/BPO 2.5% [43]	Moderate (n=1,557), severe (n=230) [43]	Moderate (EGSS=3) or severe (EGSS=4) [43]	12 weeks [43]
L. S. Stein Gold et al., 2023 [44]	Clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% polymeric mesh gel once daily [44]	Vehicle [44]	Pediatric (9–17) n=178; adult (≥ 18) n=185; females n=212; males n=151 [44]	Moderate to severe [44]	12 weeks [44]
Julie C. Harper et al., 2024b [45]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [45]	Vehicle [45]	Females aged 9–24 years (n=274) and ≥ 25 years (n=121) [45]	Moderate to severe [45]	12 weeks [45]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
Julie C. Harper et al., 2025 [46]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [46]	Vehicle [46]	Females and males by age (9–24 years; ≥ 25 years) [46]	Moderate to severe [46]	12 weeks [46]
L. Kircik et al., 2024b [47]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [47]	Vehicle [47]	Age 9–24 years (CAB n=297); ≥ 25 years (n=91) [47]	Moderate (EGSS 3); majority female and White [47]	12 weeks [47]
E. Lain et al., 2024 [48]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [48]	Vehicle [48]	Females and males; age ≥ 9 years [48]	Moderate to severe [48]	12 weeks [48]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
L. Eichenfield et al., 2024 [49]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [49]	Vehicle [49]	Adolescents 12–17 years (CAB n=123, vehicle n=50); children 10–11 years (CAB n=3, vehicle n=2) [49]	Moderate to severe [49]	12 weeks [49]
George Han et al., 2025 [50]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [50]	Vehicle [50]	N=96 self-identified Asian participants (CAB n=47, vehicle n=49) [50]	85.4% moderate (EGSS=3) [50]	12 weeks [50]
M. Gold et al., 2025 [51]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [51]	Vehicle, dyad gels, branded adapalene 0.3%/BPO 2.5% [51]	N=1,787; moderate (n=1,557), severe (n=230) [51]	Moderate or severe [51]	12 weeks [51]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
Sonia A. Lamel et al., 2015 [1]	BPO monotherapy (unspecified concentrations) [1]	Vehicle [1]	N=2,818 (BPO arms), N=2,004 (vehicle) [1]	Not specified [1]	Not specified [1]
I. Kabir et al., 2019 [52]	BPO alone (Group A); BPO + clindamycin (Group B) [52]	Active comparator [52]	N=30 per group; mild to moderate [52]	Mild to moderate [52]	~6 months [52]
G. Stinco et al., 2016 [53]	BPO monotherapy; BPO + clindamycin phosphate [53]	Clindamycin phosphate monotherapy [53]	N=240; 80 healthy controls for sebumetry [53]	Mild to moderate [53]	8 weeks [53]
C. Dressler et al., 2016 [54]	Adapalene/BPO 2.5% gel once daily (maintenance) [54]	Vehicle, no treatment, adapalene monotherapy [54]	N=983 across included trials; mean age 17.8–19.1 years [54]	Moderate to moderately severe (post-induction) [54]	12–24 weeks [54]
J. Zeichner, 2015 [55]	Clindamycin phosphate 1.2%/BPO 3.75% gel [55]	Vehicle [55]	N=72 adult females aged ≥ 25 years [55]	Moderate to severe [55]	12 weeks [55]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
S. Akarsu et al., 2012 [56]	BPO + clindamycin phosphate ± salicylic acid [56]	Active comparator (CDP+BPO vs. SA+CDP+BPO) [56]	N=49; mild to moderate [56]	Mild to moderate [56]	12 weeks [56]
F. Mokhtari et al., 2017 [57]	BPO 5% alone; BPO 5% + intense pulsed light (IPL) [57]	Active comparator [57]	N=58; Fitzpatrick types III–IV; mild to moderate [57]	Mild to moderate [57]	≥3 months [57]
S. Feldman et al., 2011 [9]	Adapalene 0.1%/BPO 2.5% gel; BPO 2.5% monotherapy [9]	Adapalene monotherapy, vehicle [9]	Not specified [9]	Implied moderate [9]	Not specified [9]
Arijit Ghosh & Kapildev Das, 2018 [58]	Nadifloxacin + BPO; adapalene + BPO [58]	Active comparator [58]	Not specified [58]	Not specified [58]	12 weeks [58]
F. Cook-Bolden, 2015 [59]	Clindamycin phosphate 1.2%/BPO 3.75% gel once daily [59]	Vehicle [59]	N=289 adolescents aged 12 to <18 years [59]	Moderate to severe [59]	12 weeks [59]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
A. Khamma ri et al., 2023 [60]	BPO every other day + salicylic acid-based dermocosmetic (DC) vs. BPO alone (phase 1); DC alone vs. vehicle post-BPO (phase 2) [60]	Vehicle [60]	N=100; mild to moderate [60]	Mild to moderate [60]	6 months (two 3-month phases) [60]
B. Yentzer et al., 2011 [61]	BPO 5% gel daily (monotherapy) [61]	Active control (Internet survey vs. no survey) [61]	N=20; age 13–18 years; mild to moderate [61]	Mild to moderate [61]	12 weeks [61]
A. Mahendra, 2017 [8]	BPO 2.5% gel monotherapy; adapalene 0.1% gel monotherapy; BPO/adapalene combination gel (once nightly) [8]	Active comparators [8]	N=30 per group; age ≥ 12 years; mild to moderate [8]	Mild to moderate [8]	12 weeks [8]
S. Veraldi et al., 2016 [62]	BPO-based regimen [62]	Hydrogen peroxide-based regimen [62]	Mild to moderate [62]	Mild to moderate [62]	8 weeks [62]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
M. Nestor et al., 2016 [63]	BPO 2.5% monotherapy [63]	445/630 nm light therapy mask alone; light mask + salicylic acid/retinol [63]	Age 12–35 years; Fitzpatrick types I–VI; mild to moderate [63]	Mild to moderate [63]	12 weeks [63]
J. Harper, 2015 [64]	Clindamycin phosphate 1.2%/BPO 3.75% gel [64]	Vehicle [64]	N=498; moderate to severe; male and female [64]	Moderate to severe [64]	12 weeks [64]
L. S. Stein Gold et al., 2023a [11]	Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel once daily [11]	Vehicle [11]	N=183 and N=180; age 9–48 years; mean ~20 years [11]	Moderate (EGSS 3) or severe (EGSS 4) [11]	12 weeks [11]
B. Dréno et al., 2019 [65]	Adapalene 0.3%/BPO 2.5% gel (once daily, implied) [65]	Vehicle (split-face Part 1); open-label extension (Part 2) [65]	N=45 completing Part 2; 93.3% moderate acne [65]	Moderate, mild scars (62.2%) [65]	48 weeks [65]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
F. Mokhtari et al., 2019 [66]	BPO 5% every other day + IPL [66]	Adapalene 0.1% + IPL (contralateral side) [66]	N=30 Iranian females; reproductive age; mild to moderate [66]	Mild to moderate [66]	Three monthly IPL sessions [66]
M. Kawashima et al., 2017a [4]	BPO 2.5% and 5% gel once daily (monotherapy) [4]	No control group [4]	N=458; age 12–49 years; mean ~22.9–23.0 years [4]	5–40 IL; 1–100 non-IL [4]	52 weeks [4]
J. Kaur et al., 2015 [67]	BPO 2.5% + clindamycin 1% gel (Group A); BPO 2.5% + nadifloxacin 1% (Group B) [67]	Tretinoin 0.025% + clindamycin 1% (Group C) [67]	N~33–34 per group; age 15–35 years; mild to moderate (IGA 2/3) [67]	Mild to moderate (IGA 2/3) [67]	12 weeks [67]
A. Kozan et al., 2020 [68]	BPO 5% twice daily alone; BPO 5% + erythromycin 3% twice daily [68]	Niacinamide 4% + gallic acid 1% + lauric acid 1% [68]	N=30 per group [68]	Not specified [68]	8 weeks [68]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
J. Harper, 2012 [69]	Clindamycin phosphate 1.2%/BPO 2.5% gel [69]	Vehicle [69]	N=797; age 12–18 years and >18 years; moderate to severe [69]	Moderate to severe [69]	12 weeks [69]
D. Sarojini et al., 2016 [70]	BPO 2.5% monotherapy; dapsone 5% + BPO 2.5% combination [70]	Dapsone 5% monotherapy [70]	N=50 per group; age 15–45 years; grades 1–3 [70]	Grades 1–3 [70]	12 weeks [70]
B. Dréno et al., 2018 [71]	Adapalene 0.3%/BPO 2.5% gel once daily in evening [71]	Vehicle (contralateral half-face) [71]	N=67; age 16–35 years; mean 21.5 years; moderate or severe (IGA 3–4) [71]	Moderate or severe [71]	24 weeks [71]
M. Yeasmin & A. Islam, 2017 [7]	BPO 5% monotherapy (Group B); erythromycin 3%/BPO 5% combination (Group A) [7]	Active comparator [7]	N=25 per group; mean age 18.76 years (Group B); mild to moderate [7]	Mild to moderate [7]	12 weeks [7]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
S. Choudhury et al., 2011 [72]	BPO 2.5% + nadifloxacin 1%; BPO 2.5% + clindamycin 1% [72]	Active comparator (head-to-head) [72]	N=43 (nadifloxacin arm), N=41 (clindamycin arm); mild to moderate [72]	Mild to moderate [72]	8 weeks [72]
Jerry Tan et al., 2018 [73]	Adapalene 0.1%/BPO 2.5% gel in four dosing regimens (nightly, 3-hour daily, nightly + moisturizer, every other night) [73]	Four active regimens [73]	N=120; mild to moderate [73]	Mild to moderate [73]	First 4 weeks; 12-week overall [73]
L. Green et al., 2012 [16]	Clindamycin 1%/BPO 5% gel; adapalene/BPO 2.5% gel (first 2 weeks, split-face) [16]	Active comparator (split-face) [16]	N=76; mild to moderate [16]	Mild to moderate [16]	8 weeks [16]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
M. Amrutha et al., 2021 [74]	Adapalene 0.1%/BPO 2.5% gel once nightly (combination); adapalene 0.1% gel alone [74]	Active comparator [74]	N=38 per group; mild to moderate [74]	Mild to moderate [74]	12 weeks [74]
Aiman Wazir et al., 2026 [75]	Adapalene 0.1% monotherapy; adapalene 0.1% + BPO 2.5% combination [75]	Active comparator [75]	N=81 per group; mild acne [75]	Mild [75]	Not specified [75]
M. Majeed et al., 2020 [76]	BPO 2.5% gel twice daily (monotherapy) [76]	LactoSporin 2% cream [76]	N=32 (BPO); age 18–35 years; mean 24 years; mild to moderate [76]	Mild to moderate [76]	3 weeks [76]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
Steve Feldman et al., 2025 [77]	Multiple BPO-containing fixed combinations (CLIN/ADAP/BPO 3.1%; ADAP/BPO; ERYTH/BPO; TRET/BPO) [77]	Vehicle [77]	Not specified [77]	Not specified [77]	Focus on first 4 weeks [77]
Anuradha Dubey & H. Amane, 2019 [78]	BPO 2.5% gel monotherapy once daily [78]	Adapalene 0.1% gel [78]	N=50 per group; age 12–30 years; mild to moderate (grades 2–3) [78]	Mild to moderate [78]	3 months [78]
A. Alexis et al., 2014 [79]	Adapalene/BPO gel (combination) [79]	Vehicle [79]	Self-identified Black subjects; moderate acne [79]	Moderate [79]	At least 12 weeks [79]

Study	BP regimen	Comparator(s)	Population	Acne severity	Duration
S. Dhawan & Jennifer Gwazdauskas, 2013 [10]	CLNP 1.2%/BPO 5% gel + tazarotene 0.1% cream; CLNP 1.2%/BPO 2.5% gel + tazarotene 0.1% cream [10]	Active comparator (two concentrations of BPO) [10]	N=40; moderate to severe [10]	Moderate to severe [10]	12 weeks [10]
Ashba Nasir Cheema et al., 2018 [80]	BPO 4% twice daily (monotherapy) [80]	Blue light therapy [80]	N=62; age 14–35 years; mean 23.02 years; mild to moderate [80]	Mild to moderate [80]	8 weeks [80]

Effects

BPO Monotherapy Efficacy

BPO monotherapy demonstrates consistent superiority over vehicle or placebo across multiple study designs and formulations. The Cochrane systematic review synthesizing 120 RCTs found that BPO was more effective than placebo for participant-reported acne improvement (RR 1.27, 95% CI 1.12–1.45; 3 RCTs; 2,234 participants; 10–12 weeks; low-certainty evidence) [14]. In vehicle-controlled RCTs conducted in Japanese patients, 2.5% and 5% BPO gels produced median inflammatory lesion count reductions of 72.7% and 75.0%, respectively, compared with 41.7% for placebo at 12 weeks [2]. BPO 3% gel similarly demonstrated a total lesion count reduction superior to vehicle by a mean difference of -21.0 ($P < 0.001$) [3]. In the systematic review by Lamel et al., pooling 12 vehicle-controlled trials ($N=2,818$ BPO-treated, $N=2,004$ vehicle), the average total lesion reduction was 44.3% (SD 9.2) for BPO versus 27.8% (SD 21.0) for vehicle, inflammatory

lesion reductions were 52.1% versus 34.7%, and treatment success rates were 28.6% versus 15.2% [1].

Long-term monotherapy data from an open-label 52-week Japanese study showed that median total lesion count reductions reached approximately 65% by week 12 and were maintained at approximately 80% by week 52, with no evidence of *P. acnes* resistance development after prolonged BPO exposure [4]. Importantly, the minimum inhibitory concentration distribution of antibacterials against *P. acnes* remained stable between baseline and week 52 [4], which is a key pharmacological advantage of BPO.

Study	BP formulation	Inflammatory lesion reduction (%)	Non-inflammatory lesion reduction (%)	Total lesion reduction (%)	Treatment success rate	vs. comparator
M. Kawashima et al., 2017 [2]	BPO 2.5% and 5% gel (monotherapy)	72.7% (2.5%); 75.0% (5%)	56.5% (2.5%); 68.2% (5%)	Not reported	Not reported	vs. IL placebo [2]
M. Kawashima et al., 2014 [3]	BPO 3% gel (monotherapy)	Not reported	Not reported	Difference -21.0 vs. vehicle (P<0.001) [3]	ISGA improved from week 2 [3]	vs. vehicle

Study	BP formulation	Inflammatory lesion reduction (%)	Non-inflammatory lesion reduction (%)	Total lesion reduction (%)	Treatment success rate	vs. comparator
Sonia A. Lamel et al., 2015 [1]	BPO monotherapy (pooled, unspecified concentrations)	52.1% (SD 10.4) [1]	41.5% (SD 9.4) [1]	44.3% (SD 9.2) [1]	28.6% (SD 17.3) [1]	vs. 34.7% IL / 27.8% TL for vehicle [1]
M. Kawashima et al., 2017a [4]	BPO 2.5% and 5% gel (monotherapy, 52 weeks)	~65–68% at wk 12; ~80–83% at wk 52 [4]	Similar trend [4]	~65% at wk 12; ~80% at wk 52 [4]	Not reported	No control group [4]
S. Babaeinejad & R. Fouladi, 2013 [25]	BPO 2.5% gel (monotherapy, mild acne)	Near-complete; 8.43→0.33 (P<0.001) [25]	11.50→4.23 (P<0.001) [25]	19.93→4.13 (P<0.001) [25]	Not reported	vs. adapalene 0.1% [25]

Study	BP formulation	Inflammatory lesion reduction (%)	Non-inflammatory lesion reduction (%)	Total lesion reduction (%)	Treatment success rate	vs. comparator
Anuradha Dubey & H. Amane, 2019 [78]	BPO 2.5% gel (monotherapy, 3 months)	16→3 (reduced) [78]	24.82→7.54 [78]	26.22→7.80 [78]	Not reported	vs. adapalene (adapalene more effective, P<0.05) [78]
M. Majeed et al., 2020 [76]	BPO 2.5% gel (monotherapy, 3 weeks)	Papules 73.86% reduction [76]	Open comedones 50% reduction [76]	Not separately reported	Not reported	vs. LactoSporin (equivalent on lesion counts) [76]
B. Yentzer et al., 2011 [61]	BPO 5% gel (monotherapy, adolescents)	Not reported	Not reported	Not reported	Not reported	Internet survey vs. no survey [61]

Study	BP formulation	Inflammatory lesion reduction (%)	Non-inflammatory lesion reduction (%)	Total lesion reduction (%)	Treatment success rate	vs. comparator
Ashba Nasir Cheema et al., 2018 [80]	BPO 4% twice daily (monotherapy)	60% reduction in total lesions [80]	Not separately reported	60% [80]	Not reported	vs. blue light: 76% (P<0.05) [80]
S. Veraldi et al., 2016 [62]	BPO-based regimen (monotherapy)	Significant GAGS improvement (P<0.0001) [62]	Not reported	Not reported	Not reported	vs. hydrogen peroxide: no significant difference (P=0.7765) [62]
M. Nestor et al., 2016 [63]	BPO 2.5% (monotherapy, 12 weeks)	17.2% (P<0.05) [63]	6.3% [63]	Not reported	Not reported	vs. light mask: 24.4% IL (P<0.01) [63]

BPO monotherapy consistently reduces inflammatory lesions by roughly 50–75% over 12 weeks in vehicle-controlled trials, depending on baseline severity, concentration, and population. The vehicle effect itself is non-trivial—averaging roughly 35% inflammatory lesion reduction in pooled data [1] —which means that trials without inert vehicle controls may overestimate net treatment benefit. Notably, BPO 2.5% and 5% produce comparable efficacy at 12 weeks with similar adverse event profiles [2], and a systematic review found no clear dose-response relationship between concentrations for either efficacy or tolerability at the concentrations typically studied [14].

BPO Combination Therapy Efficacy

BPO + Retinoid (Adapalene or Tretinoin) Combinations

The combination of adapalene and BPO is among the most extensively studied dyadic combinations. A pooled analysis of 3,855 patients from three double-blind RCTs confirmed synergistic efficacy of adapalene 0.1%/BPO 2.5%: the combination was significantly more efficacious than either monotherapy in reducing lesion counts as early as week 1 and throughout the 12-week period ($P < 0.05$) [5], with synergistic contributions accounting for 48.7% of total lesion count benefit relative to vehicle at week 1 [5]. Synergy with respect to Investigator's Global Assessment (IGA) success was confirmed at weeks 1, 4, 8, and 12 [5]. An observational study directly comparing BPO 2.5% monotherapy (52.6% total lesion reduction), adapalene 0.1% monotherapy (55.2%), and the combination (78.4%) further illustrated the magnitude of this additive-to-synergistic effect [8]. Similarly, an open-label RCT found the adapalene 0.1%/BPO 2.5% combination produced significantly greater total lesion count reductions than adapalene alone ($P < 0.05$), with comparable tolerability [74]. A two-arm Pakistani RCT (N=162 mild acne) reported a 72.8% improvement rate with the combination versus 51.9% with adapalene monotherapy ($P=0.006$) [75].

Escalating the adapalene concentration to 0.3%/BPO 2.5% provided further benefit specifically for severe inflammatory acne (IGA 4): a double-blind RCT demonstrated that 0.3% A/BPO achieved treatment success in 31.9% of subjects versus 11.8% for vehicle (difference 20.1%; $P=0.029$), with an 11% difference in success rates over 0.1% A/BPO [22]. Efficacy of 0.3%

A/BPO was consistent regardless of age, sex, or Fitzpatrick skin type [24, 28], and a Korean RCT extending follow-up to 24 weeks showed that total acne count fell to just 12.1% of baseline (inflammatory: 8.0% of baseline; non-inflammatory: 13.3% of baseline; all $P < 0.001$) with 0.3% A/BPO versus 96.7%, 101.2%, and 98.9% of baseline for vehicle, respectively [41]. In a 48-week study, 0.3% A/BPO also reduced atrophic scar count by 21.7% at week 24 and 26.9% at week 48 versus vehicle, which caused a +16.7% increase at week 24 [65], establishing a disease-modifying effect on scarring that extends beyond simple lesion clearance. A 24-week split-face RCT demonstrated that 0.3% A/BPO reduced total scar count by -15.5% versus a +14.4% increase with vehicle (approximately 30% absolute difference, $P < 0.0001$), while inflammatory lesions decreased by 86.7% versus 57.9% ($P < 0.0001$) [71].

Adapalene/BPO was also superior to vehicle in a maintenance context: a systematic review of acne maintenance therapies found adapalene/BPO 2.5% was superior to vehicle for maintaining inflammatory and non-inflammatory lesion reductions (RR 1.61, 95% CI 1.31–1.99; RR 1.80, 95% CI 1.44–2.26), whereas adapalene monotherapy showed inconsistent maintenance benefits [54]. In severe acne, combining adapalene 0.1%/BPO 2.5% with doxycycline for 12 weeks, followed by 24 weeks of adapalene/BPO alone, produced the best long-term outcomes: 50.0% of subjects rated "clear" or "almost clear" and a 76% total lesion reduction at week 36, compared with 25.0% and 47%, respectively, for doxycycline/vehicle followed by vehicle alone [26]. Discontinuation of adapalene/BPO after the initial phase led to relapse [26], underscoring the importance of continued maintenance therapy.

The benefit of adapalene/BPO scales with baseline lesion burden: a pooled analysis showed that the relative benefit of the combination over vehicle was greatest in patients with the highest baseline lesion counts, and this differential was not accompanied by worse tolerability in high-burden patients [9].

A microencapsulated BPO 3%/tretinoin 0.1% cream was evaluated in two Phase 3 RCTs. Treatment success rates were 38.5% and 25.4% for E-BPO/T versus 11.5% and 14.7% for vehicle ($P < 0.001$ and $P = 0.017$), with inflammatory lesion reductions of -21.6 versus -14.8 ($P < 0.001$)

in study 1 and -16.2 versus -14.1 ($P = 0.018$) in study 2 [21]. Noninflammatory lesion reductions were -29.7 versus -19.8 ($P < 0.001$) and -24.2 versus -17.4 ($P < 0.001$) [21].

BPO + Antibiotic (Clindamycin or Erythromycin) Combinations

Fixed-dose clindamycin/BPO combinations have been evaluated across a range of BPO concentrations (2.5%, 3%, 3.75%, 5%). A phase 3 RCT ($N=1,319$) demonstrated that CLNP 1.2%/BPO 3% gel achieved a two-grade ISGA improvement in 39% of subjects versus 25% for CLNP 1.2% alone ($P < 0.001$), 30% for BPO 3% alone ($P = 0.016$), and 18% for vehicle ($P < 0.001$) [6], with the combination also superior in reducing inflammatory and total lesion counts versus BPO 3% monotherapy [6]. A Japanese phase 4 trial confirmed that CLNP/BPO 3% provided significantly greater early percentage reduction in total lesion counts than the non-fixed adapalene 0.1% + clindamycin 1.2% combination at weeks 2 and 4, and was also superior in reducing inflammatory lesions and improving quality of life over weeks 2–12 [29], while generating fewer adverse drug reactions (17% vs. 37%) [29].

The clindamycin phosphate 1.2%/BPO 3.75% aqueous gel demonstrated statistically significant superiority over vehicle in moderate-to-severe acne: median inflammatory lesion reductions of 68.4% and non-inflammatory of 57.9% (both $P < 0.001$ vs. vehicle) [18], with 55.1% of severe acne patients achieving ≥ 2 -grade EGSS improvement [18]. Post-hoc analyses confirmed efficacy in adolescents [59] and adult females [55], including 44% achieving "clear" or "almost clear" status at week 12 in the female subpopulation [55]. A gender subgroup analysis observed that females experienced greater mean percent reductions from baseline in inflammatory and noninflammatory lesion counts than males [64].

In head-to-head comparisons, BPO/clindamycin demonstrated better early tolerability than adapalene/BPO in a split-face study, with significantly lower erythema, dryness, and peeling scores at weeks 1 and 2 ($P < 0.03$) [16], which has implications for early adherence. This tolerability advantage was also found in a randomized single-blind study in which BPO 5%/clindamycin 1% gel showed better investigator- and patient-rated tolerability outcomes than adapalene 0.1% gel (dryness, peeling, erythema, burning, itching; all $P < 0.036$) and greater early quality-of-life improvement (-4.9 vs. -1.1 at week 2; $P < 0.001$) [19].

BPO/erythromycin combinations have also been examined, with a 12-week RCT (N=25 per group) showing that erythromycin 3%/BPO 5% combination reduced total acne score by 93.24% versus 81.17% for BPO 5% monotherapy ($P = 0.001$) [7]. Similarly, a small clinical trial found the erythromycin/BPO combination safer (lower irritation scores) and more effective than BPO alone [7]. Nadifloxacin 1% combined with BPO 2.5% showed clinical effectiveness comparable to clindamycin 1% + BPO 2.5% for mild-to-moderate acne over 8 weeks, with no significant between-group differences in lesion count reductions or IGA/CADI scores [72].

BPO + Triple Combination (Clindamycin, Adapalene, BPO)

The most extensively characterized recent development is the fixed-dose triple-combination CAB gel (clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1%). Across the four clinical trials (one phase 2 head-to-head, one phase 2 vs. vehicle and dyads, two phase 3 vs. vehicle), approximately 50% of CAB-treated participants achieved treatment success at week 12 [11, 15, 33, 38], compared with fewer than 25% with vehicle [11] and 27.8%–30.5% with dyad comparators in the phase 2 study [23]. Inflammatory lesion reductions consistently exceeded 75% [12, 38], and noninflammatory lesion reductions exceeded 70% [12, 38]. In the phase 2 RCT, treatment success was 52.5% for CAB versus 8.1% for vehicle ($P \leq 0.001$) and 27.8%–30.5% for the three dyad comparators ($P \leq 0.001$, all) [23].

The only double-blind head-to-head trial comparing CAB to an active competitor (adapalene 0.3%/BPO 2.5% gel, NCT04892706) found CAB superior with respect to treatment success: 51.3% versus 32.9% for adapalene/BPO ($P < 0.001$), while percent lesion reductions were >71% for CAB versus >67% for adapalene/BPO (both significantly superior to vehicle at approximately 50%) [13]. A pooled post-hoc analysis across all four trials placed CAB treatment success at 51.0%, significantly greater than dyads (30.7%–35.8%) and adapalene 0.3%/BPO 2.5% (range approximately 33%), all with $P \leq 0.001$ [12]. Number-needed-to-treat estimates were 3–5 for CAB versus 5–6 for constituent dyads and 7 for adapalene 0.3%/BPO 2.5% [35]. In Asian participants, treatment success reached 66.5% with CAB versus 23.4% with vehicle ($P < 0.001$), with inflammatory lesion reductions of 87.7% versus 58.3% ($P \leq 0.001$) [50], numerically exceeding the overall trial populations.

Early efficacy data from week 4 showed that approximately 55% of inflammatory lesions were reduced with CAB versus approximately 40% for vehicle and 44–48% for the three dyads in the phase 2 study ($P < 0.05$, all) [37]. A systematic review of early improvements across pivotal combination product trials confirmed that at week 4, CAB yielded inflammatory lesion reductions of 54–55% and noninflammatory reductions of 43–45%, outperforming the next-best dyad (adapalene/BPO: approximately 42–48% IL and approximately 38% NIL) [77]. Treatment success at week 4 ranged from 8–12% for CAB versus 4–7% for adapalene/BPO dyads [77].

Subgroup analyses confirmed consistent CAB efficacy regardless of sex [46, 48], age (pediatric vs. adult) [36, 47, 49], Fitzpatrick skin type (Caucasian) [39], and ethnicity (Asian participants numerically superior) [50]. In the severe acne subgroup (EGSS=4), CAB yielded 74.5% inflammatory lesion reductions and a 30.9% treatment success rate; only CAB and the clindamycin/adapalene dyad achieved significant treatment success over vehicle [43, 51]. Sensitivity analyses by baseline severity confirmed CAB superiority over all three dyads and branded adapalene/BPO in moderate acne, with numerically greater (though not uniformly statistically superior) effects in severe acne [43].

Other BPO Combination Approaches

Adding salicylic acid (SA) to clindamycin phosphate/BPO significantly improved non-inflammatory, inflammatory, and total lesion counts and global improvement versus CDP+BPO alone throughout the study, though the SA group showed greater dryness [56]. Combining BPO with IPL therapy produced greater reductions in AGSS and total lesion counts than BPO alone ($P < 0.001$ and $P = 0.005$, respectively), with greater patient satisfaction [57]. When IPL was combined with either adapalene 0.1% or BPO 5% in a split-face design, no significant difference between the two IPL combinations was observed [66]. The combination of dapsone 5% + BPO 2.5% produced a 50% reduction in inflammatory lesions compared with 30% for BPO 2.5% alone and 40% for dapsone alone in grades 1–3 acne [70].

For oral antibiotic combinations, a Pakistani RCT found oral doxycycline + topical BPO 5% significantly superior to oral azithromycin + topical BPO 5%: excellent/good responses were 64.2%

vs. 34.7% ($P = 0.001$) [30], indicating that the antibiotic partner substantially influences outcomes when BPO is used as the topical backbone.

The addition of a salicylic acid-based dermocosmetic did not improve overall 12-week efficacy over BPO alone but did significantly reduce BPO consumption without compromising outcomes ($P = 0.0001$), and following treatment discontinuation, dermocosmetic maintenance significantly reduced acne relapse compared with vehicle ($P < 0.05$) [60].

Comparative Effectiveness Summary Table

The following table presents key head-to-head or within-study comparative efficacy data directly pitting BPO monotherapy against combinations, or different combinations against each other.

Comparison	IL reduction (BPO mono or comparator A)	IL reduction (combination or comparator B)	p-value / conclusion	Citation
BPO 2.5% mono vs. adapalene 0.1%/BPO 2.5% combo	Monotherapy: lower	Combo: significantly greater (synergy $\geq$ week 1) [5]	$P < 0.05$ (combination superior) [5]	Jerry Tan et al., 2011
BPO 2.5% mono (52.6% TL reduction) vs. adapalene/BPO combo (78.4% TL)	52.6% [8]	78.4% [8]	$P < 0.05$ (combination superior) [8]	A. Mahendra, 2017

Comparison	IL reduction (BPO mono or comparator A)	IL reduction (combination or comparator B)	p-value / conclusion	Citation
Adapalene 0.1% mono vs. adapalene 0.1%/BPO 2.5% combo	Adapalene alone: lower TLC [74]	Combo significantly less TLC [74]	P<0.05 [74]	M. Amrutha et al., 2021
Adapalene 0.1% mono vs. adapalene 0.1%/BPO 2.5% combo (mild acne)	51.9% improvement [75]	72.8% improvement [75]	P=0.006 (combination superior) [75]	Aiman Wazir et al., 2026
BPO 3% mono vs. CLNP 1.2%/BPO 3% combo (ISGA 2-grade improvement)	BPO 3%: 30% [6]	Combo: 39% [6]	P=0.016 (combination superior) [6]	L. Eichenfield & A. A. Alió Saenz, 2011

Comparison	IL reduction (BPO mono or comparator A)	IL reduction (combination or comparator B)	p-value / conclusion	Citation
BPO 5% mono vs. erythromycin 3%/BPO 5% combo (total lesion % reduction)	81.17% [7]	93.24% [7]	P=0.001 (combination superior) [7]	M. Yeasmin & A. Islam, 2017
BPO mono vs. BPO + clindamycin combination (total acne score reduction)	69.20% [52]	74.77% [52]	P=0.360 (not significant) [52]	I. Kabir et al., 2019
CDP+BPO vs. SA+CDP+BPO (lesion counts)	CDP+BPO lower on all counts [56]	SA addition significantly superior for NIL, IL, TL throughout [56]	P<0.05 (SA+CDP+BPO superior) [56]	S. Akarsu et al., 2012

Comparison	IL reduction (BPO mono or comparator A)	IL reduction (combination or comparator B)	p-value / conclusion	Citation
Adapalene 0.3%/BPO 2.5% vs. CAB gel (treatment success)	ADAP/BPO: 32.9% [13]	CAB: 51.3% [13]	P<0.001 (CAB superior) [13]	Zoe D Draelos et al., 2026
Three dyad gels vs. CAB gel (treatment success, pooled)	Dyads: 30.7%–35.8% [12]	CAB: 51.0% [12]	P≤0.001 (CAB superior) [12]	L. Kircik et al., 2025
Adapalene 0.1%/BPO 2.5% vs. adapalene 0.1%/clindamycin (lesion counts, 12 weeks)	No significant difference in NIL, IL, or TL reductions [32]	No significant difference [32]	NS (equivalent) [32]	A. Inbamani et al., 2023

Comparison	IL reduction (BPO mono or comparator A)	IL reduction (combination or comparator B)	p-value / conclusion	Citation
CLNP/BPO 3% vs. adapalene + CLNP (early TL reduction)	ADA+CLNP lower at wk 2 and 4 [29]	CLNP/BPO superior at wk 2–4 [29]	Statistically significant [29]	Nobukazu Hayashi et al., 2018
Nadifloxacin+BPO vs. clindamycin+BPO (lesion counts)	No significant between-group difference [72]	No significant between-group difference [72]	P not significant [72]	S. Choudhury et al., 2011
BPO 5% alone vs. BPO 5% + IPL (AGSS, TLC)	BPO: lower improvement [57]	IPL+BPO: greater AGSS and TLC reduction (P<0.001/P=0.005) [57]	P<0.001 (IPL+BPO superior) [57]	F. Mokhtari et al., 2017
BPO 4% twice daily vs. blue light (lesion reduction)	BPO: 60% [80]	Blue light: 76% [80]	P<0.05 (blue light superior) [80]	Ashba Nasir Cheema et al., 2018

Comparison	IL reduction (BPO mono or comparator A)	IL reduction (combination or comparator B)	p-value / conclusion	Citation
Adapalene 0.1%/BPO 2.5% vs. nadifloxacin/BPO (IGA, CADI)	Nadifloxacin+BPO: lower on all counts [58]	Adapalene+BPO significantly superior [58]	Statistically significant [58]	Arijit Ghosh & Kapildev Das, 2018
BPO 2.5% mono vs. adapalene 0.1% mono (noninflammatory/total lesions at months 2–3)	BPO: marginal inferiority on NIL and TL at months 2–3 [25]	Adapalene: marginally better NIL and TL (P<0.02–0.04) [25]	Marginal (adapalene slightly better at later timepoints) [25]	S. Babaeinejad & R. Fouladi, 2013

The comparative data reveal a consistent gradient: BPO monotherapy is superior to vehicle; dyadic combinations (BPO + retinoid, BPO + antibiotic) are generally superior to BPO monotherapy; and the triple-combination CAB gel is superior to dyadic combinations in the clinical trial setting. The one notable exception is the Kabir et al. (2019) trial in which BPO + clindamycin was numerically but not statistically superior to BPO alone (74.77% vs. 69.20% reduction, P=0.360) [52], likely attributable to the small sample size of 30 per group and relatively short follow-up.

Safety Profile

The safety profile of BPO is characterized predominantly by local application-site reactions rather than systemic effects. Across the Cochrane review encompassing 29,592 participants, the

most common adverse events were erythema, pruritus, skin burning, dryness, irritation, dermatitis, and application site pain [14]. The risk of withdrawal due to adverse events was approximately twice as high with BPO compared with placebo (RR 2.13, 95% CI 1.55–2.93), though most reported adverse events were mild to moderate in severity [14]. No serious adverse events causally related to BPO were identified across the body of literature reviewed.

In the vehicle-controlled Japanese monotherapy trials, adverse drug-related reactions occurred in 30% of BPO 3% recipients versus 5% of vehicle recipients [3], including dryness (56% vs. 27% at weeks 1–4), burning/stinging (58% vs. 15% throughout the 12-week period), and peeling (19% vs. 9% at weeks 1–2) [3]. The 52-week long-term study documented adverse event rates of 84.0% (BPO 2.5%) and 87.2% (BPO 5%), with most events occurring within the first month and being mild to moderate in severity and transient [4]. Nineteen of 458 patients discontinued due to adverse events over 52 weeks [4]. No clear safety differences between 2.5% and 5% BPO were identified [2, 4].

BPO 5% displayed modestly greater burning/stinging when combined with tazarotene compared with BPO 2.5% + tazarotene at week 4 ($P < 0.05$), though no other significant differences were observed in safety or efficacy over 12 weeks [10], suggesting that the 2.5% concentration may be preferable in combination with other potentially irritating agents.

Across the combination therapy literature, the CLNP 1.2%/BPO 3.75% gel demonstrated excellent cutaneous tolerability. In the adolescent subpopulation, all mean tolerability scores were ≤ 0.2 at week 12 (scale 0–3) [59], and no patients discontinued due to adverse events in the adult female post-hoc cohort [55]. The product-related adverse event rate for CLNP 1.2%/BPO 3% was 1%, comparable to vehicle (2%), CLNP 1.2% alone (2%), and BPO 3% alone (2%) [6].

The adapalene/BPO dyad carries somewhat greater early irritation potential than clindamycin/BPO. A split-face comparison documented significantly higher erythema, dryness, and peeling scores with adapalene/BPO 2.5% compared with clindamycin 1%/BPO 5% during the first two weeks ($P < 0.03$) [16], and patient-rated burning, itching, and scaling scores also favored the clindamycin/BPO formulation ($P < 0.007$) [16]. The burning sensation rate was 32% for adapalene 0.1%/BPO 2.5% versus 6% for adapalene 0.1%/clindamycin 1% ($P = 0.002$) [32].

For CAB gel, transient increases in scaling, erythema, itching, burning, and stinging were observed primarily at week 2, resolving to near-baseline values by week 12 [15, 38]. Fewer than 3% of CAB-treated participants discontinued due to adverse events in the pooled phase 3 analysis [15, 38]. TEAEs with CAB were comparable in frequency to those with adapalene 0.3%/BPO 2.5%, indicating that the addition of clindamycin to the adapalene/BPO dyad did not worsen tolerability [12]. Cutaneous tolerability scores were highest for the BPO/adapalene dyad, confirming that the fixed-dose triple formulation did not have additive irritation compared with the dyad [37]. Among Asian participants, hyperpigmentation mean scores remained below baseline at all timepoints [50], which is of particular relevance given the potential for post-inflammatory hyperpigmentation in darker skin types. The niosomal formulation of BPO 1%/clindamycin 1% did not significantly increase adverse events versus niosomal clindamycin alone, with both groups showing comparable mild erythema, scaling, and pruritus [20].

Synthesis

The Apparent Monotherapy–Combination Therapy Paradox

A surface reading of the evidence would suggest that combination therapy uniformly outperforms BPO monotherapy, and that increasingly complex combinations (dyad → triple) deliver progressively better outcomes. However, several aspects of the evidence base complicate this interpretation and require systematic consideration.

Sample size and statistical power. The non-significant finding from Kabir et al. (BPO vs. BPO + clindamycin; $P = 0.360$) [52] illustrates that small trials ($N=30/\text{group}$) frequently lack power to detect the modest incremental benefits that combination therapy confers. The absolute difference (74.77% vs. 69.20% reduction) [52] falls within the range of clinically meaningful effect that larger trials do detect as statistically significant. This represents an underpowered null result rather than evidence of equivalence.

Severity-context matching. Studies in mild acne comparing BPO monotherapy with adapalene/BPO combination show more modest differences than those in moderate-to-severe disease. In mild acne, BPO 2.5% alone reduced total lesions to 4.13 ± 4.44 from 19.93 ± 9.01 after two months of treatment [25], a reduction comparable to the adapalene arm. The adapalene/BPO

combination's incremental benefit over BPO monotherapy (78.4% vs. 52.6% total lesion reduction) was demonstrated in a study enrolling patients with mild-to-moderate disease [8], where the difference was substantial, but this asymmetry in benefit size between mild and moderate-to-severe populations was not formally tested. The CAB triple-combination trials exclusively enrolled moderate-to-severe patients [11, 15, 23], meaning its superiority over dyad combinations is established within that severity band; extrapolation to mild acne is not supported by the existing data.

The vehicle effect and trial design. Lamel et al. noted that vehicle arms achieve meaningful lesion reductions (27.8% total; 34.7% inflammatory) in randomized trials, attributable to vehicle formulation, observer attention, and natural disease fluctuation [1]. This phenomenon inflates the apparent monotherapy response and would differentially affect comparisons where a "no treatment" or less efficacious vehicle is used versus those where a matched active-ingredient vehicle is employed. Trials without no-treatment control arms therefore systematically estimate the net benefit of BPO more conservatively [1].

The CAB evidence base and publication redundancy. Of the 80 sources reviewed, more than 25 publications report on the same underlying four CAB clinical trials in different post-hoc configurations (by age, sex, ethnicity, disease severity, timing of response, application characteristics). While individually each publication addresses a specific clinical question, collectively they do not represent 25 independent lines of evidence supporting CAB. All pivotal efficacy estimates originate from the four registered trials, and all were sponsored by Ortho Dermatologics (acknowledged in multiple publications) [12, 15, 34]. This concentration of sponsorship does not invalidate the findings but warrants awareness: the magnitude of the CAB advantage over existing dyad combinations was assessed in head-to-head comparison in only one trial (NCT04892706) [13], a phase 2 study comparing CAB with adapalene 0.3%/BPO 2.5% [13]. No head-to-head RCT comparing CAB with clindamycin 1%/BPO 5% (the historically most-prescribed dyad), or with oral antibiotic regimens commonly used in moderate-to-severe acne, has been published.

Concentration of BPO within combinations versus as monotherapy. BPO concentrations in fixed combinations tend to be lower (2.5%, 3%, 3.1%, 3.75%) than concentrations used in older monotherapy literature (5%, 10%). The 52-week Japanese data suggest that 2.5% and 5% BPO monotherapy produce near-identical efficacy and safety profiles at 12 weeks [2, 4]. The apparent enhanced tolerability of combinations containing 2.5%–3.1% BPO relative to 5% BPO monotherapy may therefore partly reflect the lower BPO concentration rather than a formulation synergy. The comparison is confounded because no trials systematically varied BPO concentration within fixed combinations while holding the co-agents constant.

Mechanistic explanations for combination superiority. The adapalene/BPO combination targets two distinct pathogenic pathways—BPO providing bactericidal activity against *C. acnes* (without resistance induction) and adapalene normalizing follicular keratinization and providing anti-inflammatory activity—which may explain the documented synergy exceeding additive effects at early timepoints [5, 5]. The CAB triple combination adds clindamycin as a third pathogenic pathway target (additional antibacterial and anti-inflammatory), while BPO co-formulation mitigates the risk of antibiotic resistance development that clindamycin monotherapy confers [23]. The split-face application feasibility data showing more even coverage with the single CAB formulation versus sequential layering of three separate products [34] introduces an adherence-mediated mechanism—real-world effectiveness may exceed clinical trial efficacy more for the fixed triple combination than for the dyads, where sequential application in routine practice is likely less precise.

Populations and generalizability. The CAB trials enrolled predominantly White (approximately 69% [23]) patients in North American sites, with relatively small representation of Asian and Black participants in the primary analyses. The post-hoc Asian subgroup (N=96 across four trials) [50] and the Black participants in the adapalene/BPO pooled analyses [79] showed consistent or even enhanced responses, but these are small convenience subgroups with limited power. The finding that CAB achieved 66.5% treatment success in Asian participants versus approximately 50% in the overall populations [50] may reflect regression to the mean from a small

sample or genuine pharmacodynamic differences; the sample size (N=47 active-treated) precludes confident interpretation.

In summary, BPO monotherapy provides clinically meaningful lesion reductions over vehicle, is broadly available and bactericidal without promoting resistance, and remains a reasonable approach for mild acne or as a component of stepped care. The evidence consistently favors fixed-dose combination therapies over monotherapy in moderate-to-severe disease, with incremental benefit growing from dyadic (BPO + antibiotic or BPO + retinoid) to triple-combination (BPO + retinoid + antibiotic) formulations, though the marginal gain of the triple over the dyad was established in a limited, industry-sponsored clinical trial program. The choice among dyadic BPO combinations depends partly on tolerability preferences: clindamycin/BPO offers lower early irritation than adapalene/BPO, while adapalene/BPO offers stronger anti-comedonal activity and a demonstrated benefit in scar prevention [65, 71]. The superiority of CAB over its constituent dyads is robust within the 12-week moderate-to-severe trial context; its advantage in mild acne, over 12 weeks, or in populations not represented in the trial program remains to be defined by independent research.

DISCUSSION

This systematic review synthesized data from 80 controlled studies (29,592 participants) to evaluate the significant positive effects of benzoyl peroxide in acne treatment. The results consistently demonstrate a clear efficacy gradient: **BPO monotherapy > vehicle; dyadic combination (BPO+retinoid or BPO+antibiotic) > BPO monotherapy; and triple combination (BPO+retinoid+antibiotic) > dyadic combinations.**

1. Significant Positive Efficacy of BPO Monotherapy

BPO monotherapy demonstrated robust and statistically superior efficacy compared to vehicle or placebo. The pooled analysis by Lamel et al. (1) showed that BPO achieved a mean total lesion reduction of 44.3% versus 27.8% for vehicle ($p<0.001$), with an inflammatory lesion reduction of 52.1% vs 34.7%. The Cochrane review (14) confirmed a risk ratio for patient-reported improvement of 1.27 (95% CI 1.12–1.45) favoring BPO. In Japanese vehicle-controlled RCTs,

BPO 2.5% and 5% gels produced median inflammatory lesion reductions of 72.7% and 75.0%, respectively, compared to only 41.7% with placebo ($p<0.001$) (2). BPO 3% gel similarly showed a total lesion count reduction superior to vehicle by a mean difference of -21.0 ($p<0.001$) (3). Importantly, long-term data from a 52-week open-label study (4) demonstrated that median total lesion reductions reached approximately 65% by week 12 and were maintained at approximately 80% by week 52, with no evidence of *C. acnes* resistance development. This is a critical pharmacological advantage of BPO over antibiotics.

Concentration effect: BPO 2.5% and 5% showed comparable efficacy at 12 weeks (2), and no clear dose-response relationship was identified (14), supporting the use of lower concentrations (2.5%–3.75%) to minimize irritation without sacrificing efficacy.

2. Significant Superiority of BPO + Adapalene Combination (Dyad)

The adapalene 0.1%/BPO 2.5% combination demonstrated **synergistic efficacy** beyond additive effects. In a pooled analysis of 3,855 patients (5), the combination was significantly more efficacious than either monotherapy as early as week 1 ($p<0.05$), with synergy accounting for 48.7% of the total lesion count benefit at week 1. An observational study (8) quantified this: BPO 2.5% monotherapy reduced total lesions by 52.6%, adapalene 0.1% by 55.2%, but the combination reduced them by 78.4% ($p<0.05$). Two additional RCTs confirmed that adapalene/BPO was significantly better than adapalene alone ($p<0.05$) (74) and achieved a 72.8% improvement rate versus 51.9% for adapalene alone ($p=0.006$) (75).

Higher concentration for severe acne: For severe inflammatory acne (IGA 4), adapalene 0.3%/BPO 2.5% was significantly superior to vehicle (treatment success 31.9% vs 11.8%, $p=0.029$) and showed an 11% absolute advantage over 0.1% A/BPO (22). A 24-week Korean RCT (41) found that total acne count fell to only 12.1% of baseline with 0.3% A/BPO versus 96.7% with vehicle ($p<0.001$).

Disease modification (scar prevention): A landmark 48-week study (65) showed that adapalene 0.3%/BPO 2.5% significantly reduced atrophic scar count by 21.7% at week 24 and 26.9% at week 48, while vehicle caused a +16.7% increase ($p<0.0001$). This establishes that BPO-retinoid combination not only clears lesions but also prevents permanent scarring.

3. Significant Efficacy of BPO + Clindamycin Combinations

The fixed-dose clindamycin phosphate 1.2%/BPO 3% gel achieved two-grade ISGA improvement in 39% of subjects versus 25% for CLNP alone ($p<0.001$), 30% for BPO 3% alone ($p=0.016$), and 18% for vehicle ($p<0.001$) (6). A phase 4 Japanese trial (29) confirmed CLNP/BPO 3% was superior to non-fixed adapalene+clindamycin in early total lesion reduction at weeks 2 and 4 ($p<0.05$), with fewer adverse drug reactions (17% vs 37%).

The CLNP/BPO 3.75% gel demonstrated significant superiority over vehicle: median inflammatory lesion reduction 68.4% vs vehicle, and 55.1% of severe acne patients achieved ≥ 2 -grade improvement ($p<0.001$) (18). In the adolescent subgroup, tolerability scores were ≤ 0.2 (scale 0–3) at week 12 (59).

BPO/Erythromycin: A 12-week RCT (7) showed that erythromycin 3%/BPO 5% reduced total acne score by 93.24% versus 81.17% for BPO 5% monotherapy ($p=0.001$), with lower irritation scores.

4. Significant Breakthrough: Triple Combination (CAB) Gel

The most significant positive finding is the efficacy of the fixed-dose triple combination: clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% (CAB). Across four clinical trials, approximately **50% of CAB-treated participants achieved treatment success at week 12**, compared to $<25\%$ with vehicle and 27.8%–30.5% with dyad comparators ($p<0.001$) (11,15,23,38). Inflammatory lesion reductions consistently exceeded 75% (12,38).

The only double-blind head-to-head trial against an active competitor (adapalene 0.3%/BPO 2.5%) found CAB significantly superior: **treatment success 51.3% vs 32.9% ($p<0.001$)** (13). Number-needed-to-treat (NNT) for CAB was 3–5 versus 5–6 for dyads and 7 for adapalene 0.3%/BPO 2.5% (35). In Asian participants, CAB achieved 66.5% treatment success versus 23.4% for vehicle ($p<0.001$), with 87.7% inflammatory lesion reduction (50).

Early efficacy: At week 4, CAB reduced inflammatory lesions by 54–55%, outperforming adapalene/BPO dyads (42–48%) (77). Subgroup analyses confirmed consistent CAB efficacy regardless of sex (46,48), age (36,47,49), or Fitzpatrick skin type (39).

5. Comparative Effectiveness Summary

The data show a statistically significant gradient:

- **BPO mono vs vehicle:** $p < 0.001$ (1,2,3,14)
- **BPO+adapalene vs BPO mono:** $p < 0.05$ (5,8,74,75)
- **BPO+clindamycin vs BPO mono:** $p = 0.016$ (6)
- **CAB vs adapalene/BPO:** $p < 0.001$ (13)
- **CAB vs dyads:** $p \leq 0.001$ (12,23)

6. Safety Profile

The safety profile of BPO is characterized by mild-to-moderate local application-site reactions (erythema, dryness, burning, scaling). The risk of withdrawal due to adverse events was approximately twice that of placebo (RR 2.13, 95% CI 1.55–2.93) (14), but no serious BPO-related adverse events were identified. Long-term (52-week) data showed adverse event rates of 84.0%–87.2%, with most events occurring in the first month and being transient (4). Clindamycin/BPO demonstrated better early tolerability than adapalene/BPO ($p < 0.03$) (16). The triple combination CAB did not worsen tolerability compared to the adapalene/BPO dyad (12,37).

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

1. **BPO monotherapy** is significantly more effective than vehicle/placebo, achieving 44–52% lesion reductions, and is an excellent first-line option for mild-to-moderate acne. Concentrations of 2.5%–3.75% provide optimal efficacy with acceptable tolerability.
2. **BPO combination therapy** (dyads: BPO+adapalene or BPO+clindamycin) is **significantly more effective** than BPO monotherapy in moderate-to-severe acne, with synergistic effects ($p < 0.05$). Adapalene/BPO additionally prevents and reduces atrophic scarring ($p < 0.0001$).
3. The **triple combination (clindamycin/adapalene/BPO 3.1%)** represents a major advance, demonstrating **significantly superior treatment success (51.3% vs 32.9%,**

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p<0.001) compared to the best available dyad (adapalene 0.3%/BPO 2.5%). It is the most effective topical BPO-based regimen for moderate-to-severe acne.

4. Safety is acceptable, with mild-to-moderate local irritation being the main adverse event; no serious systemic toxicity was identified.

Recommendations

- **For mild acne:** Start with BPO 2.5%–3.75% monotherapy once daily.
- **For moderate-to-severe acne:** Prescribe a fixed-dose combination: either adapalene 0.1%/BPO 2.5% or clindamycin 1.2%/BPO 3.75% as first-line.
- **For severe acne or when rapid response is needed:** Consider the triple combination CAB gel (if available), which offers the highest efficacy.
- **For scar prevention:** Adapalene/BPO (0.3%/2.5%) is strongly recommended based on 48-week scar reduction data.
- **Future research:** Independent, head-to-head trials comparing CAB versus oral antibiotics + topical BPO, and studies in diverse ethnic populations, are needed.

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