Systematic Literature Review and Network Meta-Analysis to Assess the Comparative Efficacy of Topical Fixed-Dose Combinations for Moderate to Severe Acne Vulgaris as Measured by Lesion Counts

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SUMMARY

- Several topical and oral monotherapies/combinations are available for treating moderate to severe acne vulgaris and a few are currently under review by the United States (U.S) Food and Drug Administration (FDA).
- This Systematic Literature Review (SLR)/Network Meta-Analysis (NMA) assessed the comparative efficacy of topical Fixed-Dose Combinations (FDCs) based on the absolute mean reduction in inflammatory and non-inflammatory lesion count among moderate to severe acne patients.
- This NMA demonstrated that the topical triple-agent FDC gel of clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% gel (IDP-126) was superior to other topical FDCs.

INTRODUCTION

- Acne Vulgaris (AV), or acne, is an inflammatory skin disorder characterized by excessive oiliness, blackheads, whiteheads papules, pustules, nodules, and/or pigmentation and scarring. AV is a disease of the pilosebaceous unit that causes clinically noninflammatory lesions (open and closed comedones), inflammatory lesions (papules, pustules, and nodules,) and varying degrees of scarring.[1]
- Globally, it is the eighth most common skin disorder, and the prevalence of acne is estimated at 9.38%, affecting nearly 650 million adolescents and adults.[2]
- Symptoms associated with acne are discomfort, and impaired quality of life in terms of social life, self-esteem, and body image among individuals. It is often associated with psychosocial co-morbidities including depression and anxiety.[3,4]

OBJECTIVE

- This SLR/NMA aimed to identify, collate, and analyze various treatment options and report the best treatment for moderate to severe AV.

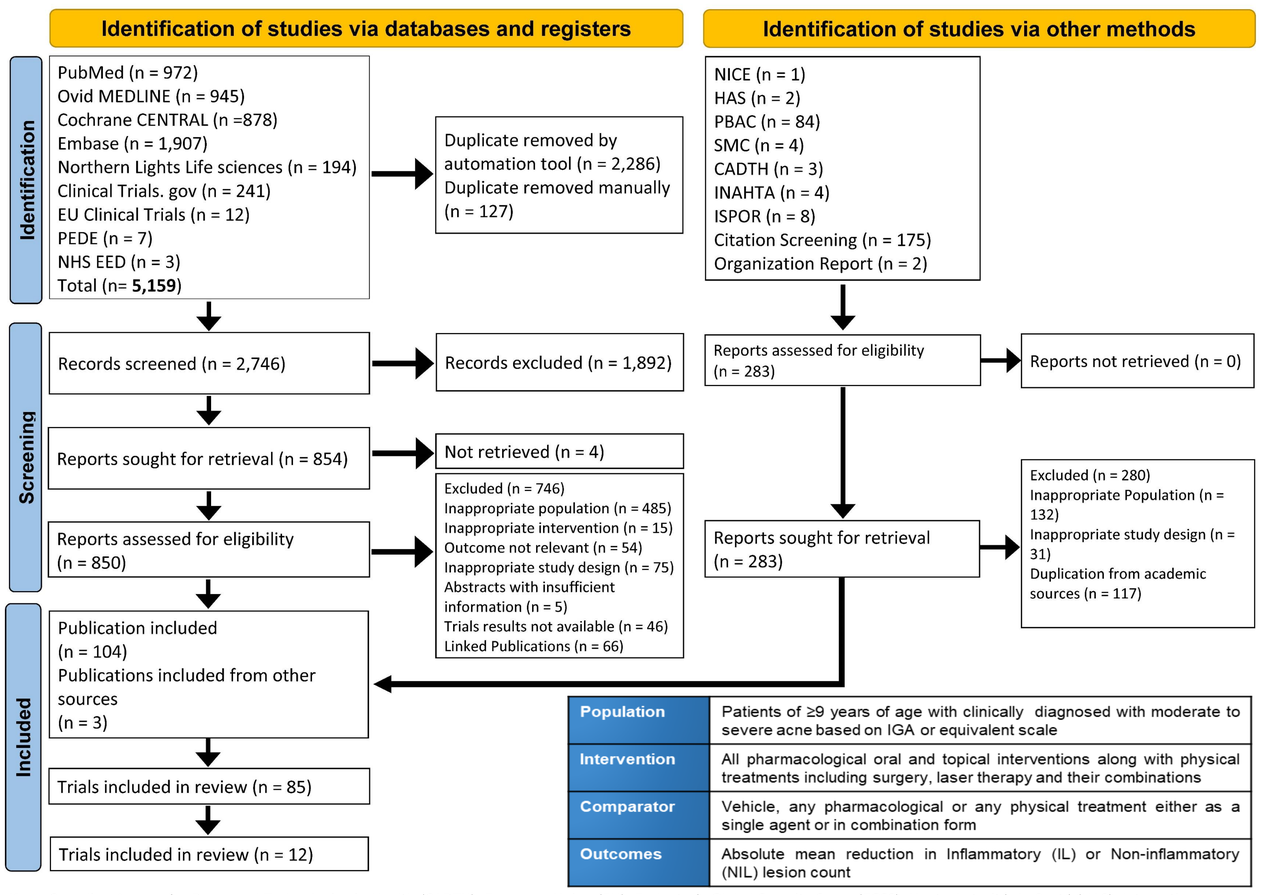
METHODS

- Academic (MEDLINE, Embase, Cochrane CENTRAL, Paediatric Economic Database Evaluation, and National Health Service Economic Evaluation Database) and non-academic databases (Health Technology Assessment databases, conference abstracts, and trial registries) were searched in May 2022, for identifying Randomized Controlled Trials (RCTs), with ≥1 topical FDC (currently approved/under review with FDA).
- Search terms used while searching across the databases were “acne vulgaris”, “acne”, “acneiform eruptions », “benzoyl peroxide”, “topical retinoid”, “adapalene”, “tretinoin”, “isotretinoin”, “topical antibiotic”, “erythromycin”, “clindamycin”, “comedone extraction”, “low-level Light Therapy”, “chemical peel”, “photodynamic therapy”.
- Title-abstract and full-text screening were conducted by two independent reviewers and reconciled by a third senior reviewer.
- Studies were selected based on the predesigned inclusion and exclusion criteria followed by data extraction.
- RCTs included in the analysis evaluated acne severity using the Investigator's Global Assessment Scale (IGA), the Evaluator's global acne severity scale (EGSS), or the Investigator's Static Global Assessment (ISGA). These scales are consistent in accordance with the IGA scales as suggested by the FDA.[5]
- A Bayesian network meta-regression was conducted using the proportion of patients with moderate acne at baseline as covariates for acne severity.
- The Bayesian simulation approach was used to develop a posterior rank order to assess the most efficacious treatment.
- The risk of bias was assessed with Cochrane Risk of Bias (RoB) v2.0 for quality assessment.

RESULTS

- The SLR identified 12 Phase II/III/IV RCTs comprised of 10,313 patients across eight treatment groups that were included for NMA from 5,442 citations (Figure 1 & Table 1).

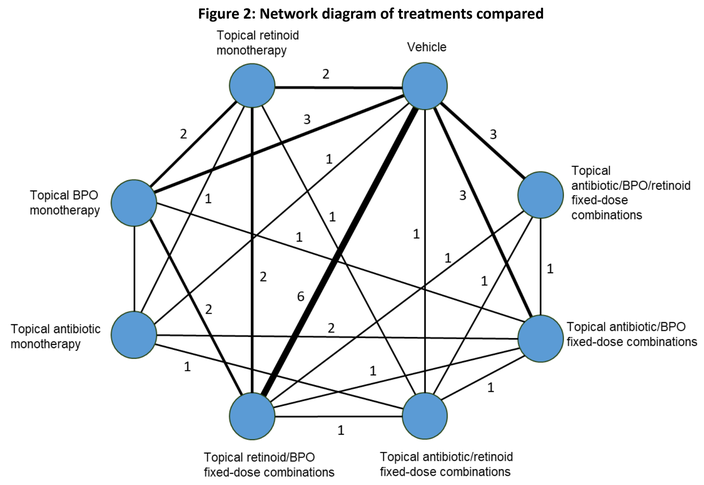
Figure 1: PRISMA diagram for inclusion of studies



Keys: Canadian Agency for Drugs and Technologies in Health (CADTH), European Union (EU), Evaluator's Global Severity Score (EGSS), Haute Autorité de Santé (HAS), International Network of Agencies for Health Technology Assessment (INAHTA), Investigator's Global Assessment (IGA), Investigator’s Static Global Assessment (ISGA), National Health Service Economic Evaluation Database (NHS EED), National Institute for Health and Care Excellence (NICE), Paediatric Economic Database Evaluation (PEDE), Pharmaceutical Benefits Advisory Committee (PBAC), Population Intervention Comparator Outcome (PICO), Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Scottish Medicines Consortium (SMC), Systematic Literature Review (SLR), The Professional Society for Health Economics and Outcomes Research (ISPOR)

- Among the 12 trials, seven were of high quality (low risk of bias), four were of medium quality (some concern for risk of bias), and one trial of low quality (high risk of bias).
- The network diagram for 12 studies consisting of eight treatment groups is presented in (Figure 2).
- Topical FDC of clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide (the first triple-agent FDC), was clinically superior to other fixed-dose combinations for reducing inflammatory and non-inflammatory lesion counts.

Figure 2: Network diagram of treatments compared



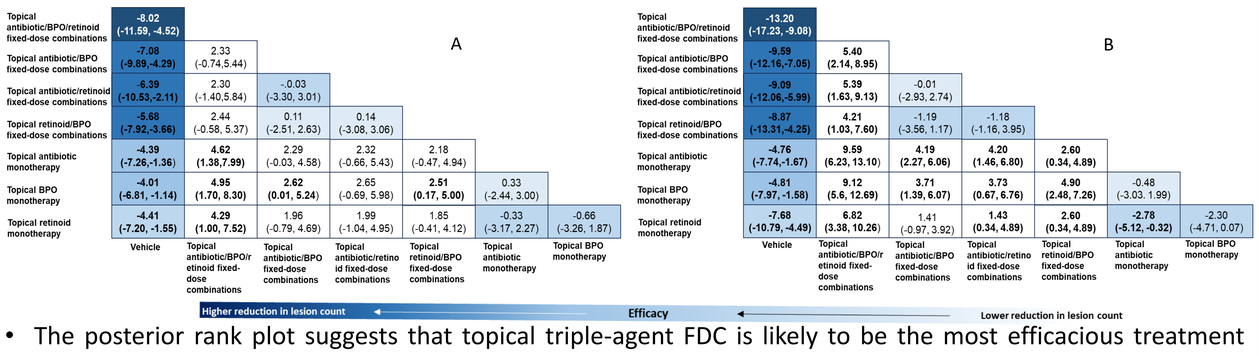
Keys: Benzoyl Peroxide (BPO)

Table 1: Quality of included trials and their baseline characteristics

Study	Phase	Quality of Trials	Intervention	Moderate patients (%)	Age (mean)	Female (%)	ILS (mean)	NILS (mean)
Thiboutot et al. 2008[11]	III	Medium	Topical clindamycin 1.2% / benzoyl peroxide 2.5%	80.70%	19.2	51.20%	26.4	47.4
			Topical clindamycin phosphate 1.2%	80.40%	19.6	51.70%	26.3	45.3
			Topical benzoyl peroxide 2.5%	82.40%	19.1	56.20%	25.8	46.8
			Vehicle	80.80%	19.4	48.60%	26.1	44
Gollnick et al. 2009[9]	III	High	Topical adapalene 0.1% / benzoyl peroxide 2.5%	100.00%	19.5	56.30%	26	45
			Topical adapalene gel 0.1%	100.00%	18.5	54.80%	27	46
			Topical benzoyl peroxide 2.5%	100.00%	18.9	55.40%	26	45
			Vehicle	100.00%	19.2	58.40%	26	46
Schmidt et al. 2011[14]	III	Low	Topical clindamycin phosphate 1.2% / tretinoin 0.025%	74.70%	19.1	48.90%	30.6	49
			Topical clindamycin phosphate 1.2%	74.60%	19	54.60%	30.9	48.9
Pariser et. al. 2014[13]	III	High	Topical clindamycin Phosphate 1.2% / benzoyl peroxide 3.75%	83.80%	18.2	48.60%	27.2	38.3
			Vehicle	81.60%	19.3	48.60%	26.7	37.2
Stein Gold 2016[7]	III	High	Topical adapalene 0.3% / benzoyl peroxide 2.5%	51.20%	20.1	52.10%	39.2	58.9
			Vehicle	48.40%	18.5	52.20%	36.4	60.7
Dréno et al. 2018[8]	IV	High	Topical adapalene 0.3% / benzoyl peroxide 2.5%	92.50%	21.5	65.70%	17.8	22
			Vehicle	92.50%	21.5	65.70%	18	22
Webster et al. 2020[16]	II	Medium	Topical benzoyl peroxide 3%	85.60%	22	61.90%	27.9	42.7
			Topical tretinoin 0.05%	86.40%	22	65.30%	26.7	41.7
			Topical tretinoin 0.1%	90.70%	23	69.50%	26.2	42.4
			Topical retinoid 0.05% / benzoyl peroxide 3%	88.90%	22.4	64.10%	27.8	43.4
			Topical retinoid 0.1% / benzoyl peroxide 3%	87.90%	21.9	58.60%	26.7	42.9
			Vehicle	88.70%	21.2	60.90%	28.6	42.5
Stein Gold et al. 2021[6]	II	High	Topical IDP-126 gel (clindamycin phosphate 1.2% / benzoyl peroxide 3.1% / adapalene 0.15%)	**84.90%**	**19.9**	**64.40%**	**39**	**51.8**
			Topical benzoyl peroxide 3.1% / adapalene 0.15%	79.30%	19.2	57.30%	39	48
			Topical clindamycin phosphate 1.2% / benzoyl peroxide 3.1%	84.90%	19.6	62.30%	40	49.2
			Topical clindamycin phosphate 1.2% / adapalene 0.15%	86.00%	19.4	62.00%	38.2	51.1
			Vehicle	85.80%	19.6	60.10%	38.2	50.7
Del Rosso et al. 2021[15]	III	Medium	Topical benzoyl peroxide 3% / tretinoin 0.1%	89.80%	20.5	61.00%	30.9	46.6
			Vehicle	92.70%	20.8	55.80%	30.5	46
Dogra et. al. 2021[12]	III	Medium	Topical tretinoin microsphere 0.04% / clindamycin 1%	87.30%	20	37.0%%	28	35
			Topical tretinoin 0.025%	88.30%	20	44.70%	28	35
			Topical clindamycin phosphate 1%	86.70%	20	38.00%	28	35.5
Stein Gold et al. 2023[10]	III	High	Topical IDP-126 gel (clindamycin phosphate 1.2% / benzoyl peroxide 3.1% / adapalene 0.15%)	**87.70%**	**20.2**	**61.50%**	**36.4**	**50.7**
			Vehicle	95.10%	19.8	50.80%	37.1	45.9
Stein Gold et al. 2023[10]	III	High	Topical IDP-126 gel (clindamycin phosphate 1.2% / benzoyl peroxide 3.1% / adapalene 0.15%)	**90.80%**	**20.2**	**57.50%**	**37.4**	**48.2**
			Vehicle	95.00%	21.4	61.70%	37.7	49.3

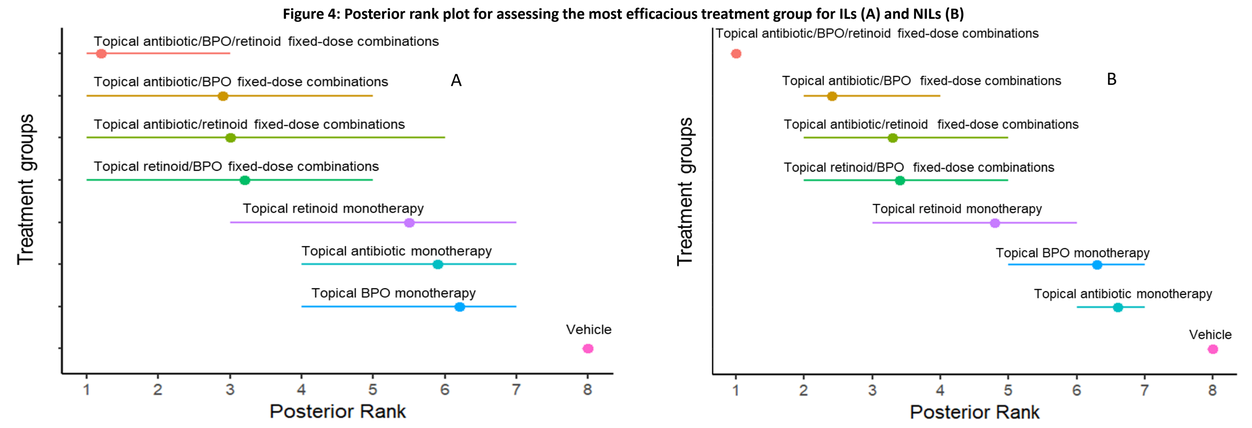
- The topical triple-agent FDC demonstrates an additional reduction of 8.02 inflammatory lesions (95% Credible Interval: -11.59 to -4.52) when compared to the Vehicle gel (Figure 3).
- The topical triple-agent FDC demonstrates an additional reduction of 13.20 non-inflammatory lesions (95% Credible Interval: -17.23 to -9.08) when compared to the Vehicle gel (Figure 3).

Figure 3: League table for pair-wise efficacy comparison between treatments for ILs (A) and NILs (B)



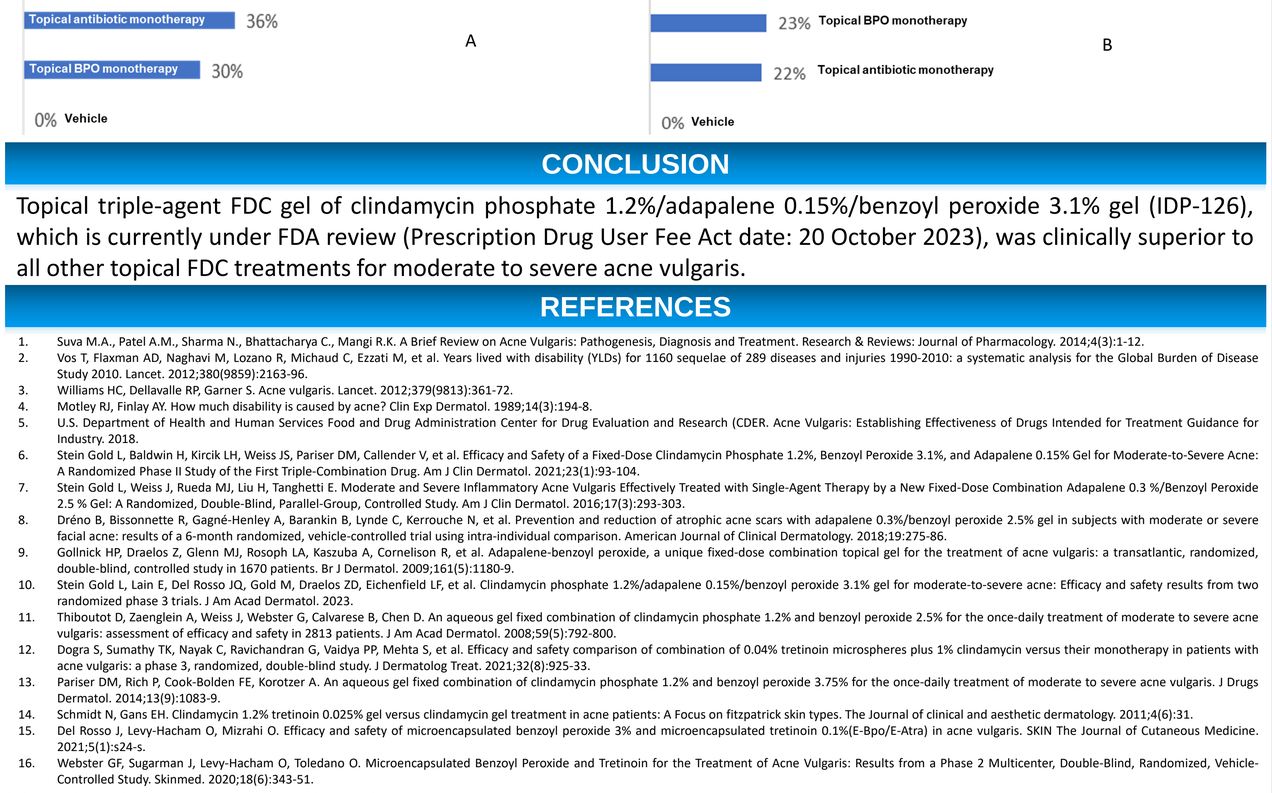
- The posterior rank plot suggests that topical triple-agent FDC is likely to be the most efficacious treatment among all topical FDCs with lower uncertainty around its superiority (Figure 4).
- In terms of reducing inflammatory lesion counts, the topical triple-agent FDC stands out as the most effective treatment, with a posterior mean rank value of 1.02 (95% Credible Interval: 1 to 3). It also performs exceptionally well in reducing non-inflammatory lesion counts, with a posterior mean rank value of 1.01 (95% Credible Interval: 1 to 1.03).

Figure 4: Posterior rank plot for assessing the most efficacious treatment group for ILs (A) and NILs (B)



- A Surface Under the Cumulative Ranking (SUCRA) value represents the overall ranking performance of each treatment. The topical triple-agent FDC gel is the most effective treatment for reducing both inflammatory and non-inflammatory lesion counts with SUCRA values of 87% and 97% respectively.
- The highest SUCRA values indicate that topical triple-agent FDC gel has the highest probability of being the most effective among all the comparators in the NMA (Figure 5).

Figure 5: SUCRA for assessing the most efficacious treatment group ILs (A) and NILs (B)



CONCLUSION

Topical triple-agent FDC gel of clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% gel (IDP-126), which is currently under FDA review (Prescription Drug User Fee Act date: 20 October 2023), was clinically superior to all other topical FDC treatments for moderate to severe acne vulgaris.

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DISCLOSURE: This study was funded by Bausch Health, LLC., The sponsor was involved in several aspects of the research, including study design, the interpretation of the data, and the production of the poster.