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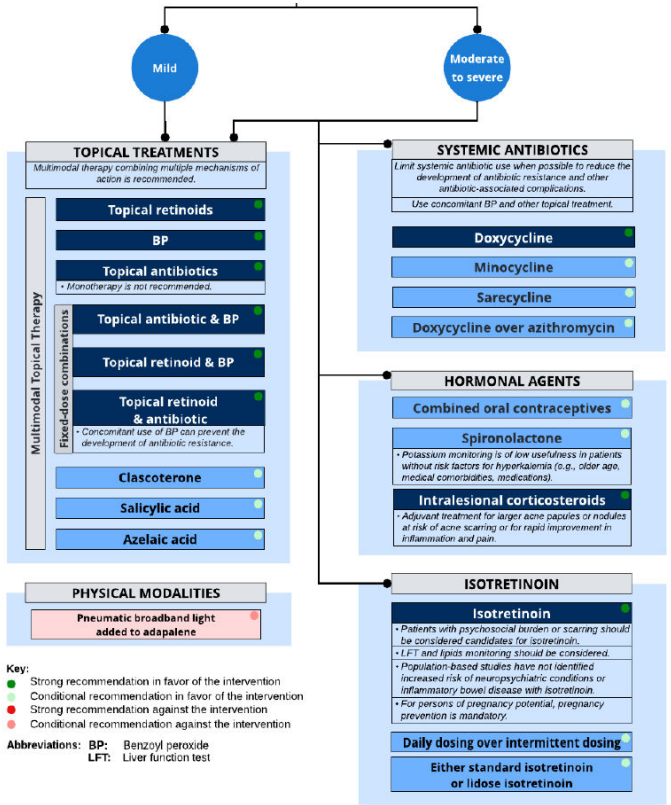
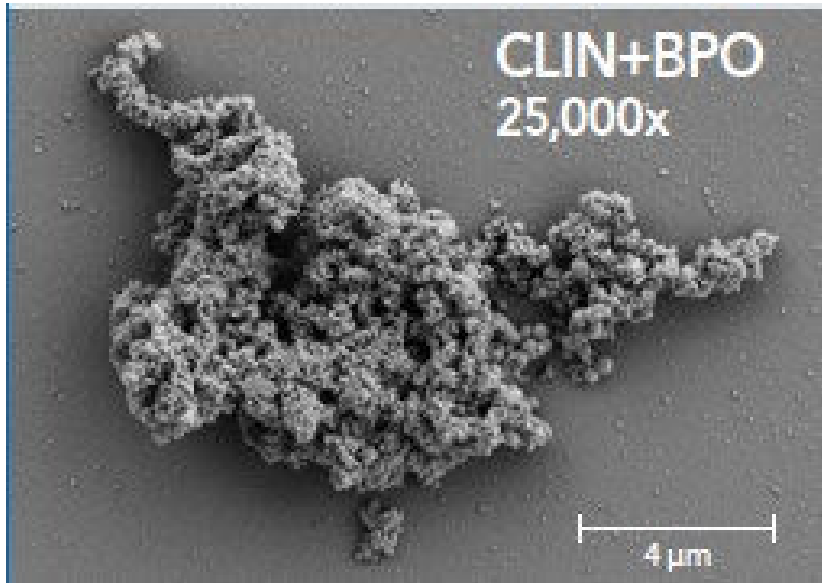
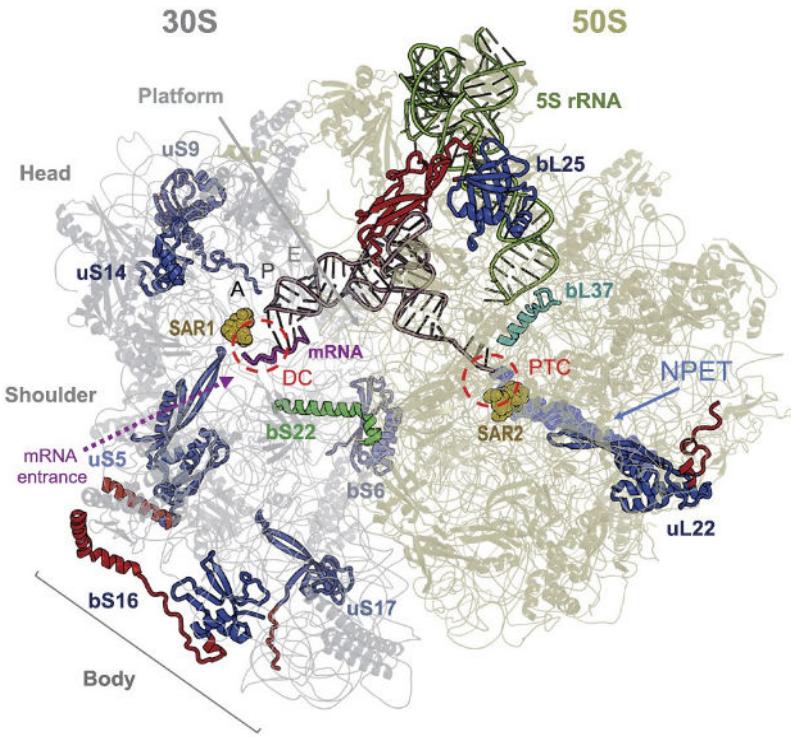
Acne vulgaris: Medical and Procedural Interventions







Christopher G. Bunick, MD, PhD

Associate Professor of Dermatology & Program in Translational Biomedicine

Yale School of Medicine

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Acne vulgaris: Medical and Procedural Interventions

DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Abbvie: Investigator, Consultant
Almirall: Investigator, Consultant
Apogee: Investigator, Consultant
Arcutis: Consultant
Eli Lilly: Consultant
LEO Pharma: Investigator, Consultant
Novartis: Consultant

Ortho Dermatologics: Investigator, Consultant
Palvella: Investigator
Pfizer: Consultant
Sanofi-Regeneron: Consultant
Sun Pharma: Investigator, Consultant
Timber: Investigator
UCB Pharma: Consultant

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2024 Update to AAD Acne Guidelines

https://doi.org/10.1016/j.jaad.2023.12.017

Management of Acne Vulgaris

Adults, adolescents, and preadolescents (≥ 9 years) with acne vulgaris

Baseline Evaluation

SEVERITY ASSESSMENT:

- Acne objective severity should be assessed consistently, using the Physician Global Assessment (PGA) or other scales
- Assess satisfaction with appearance, extent of scar / dark marks, treatment satisfaction, long-term acne control, and impact on quality of life.

Routine microbiological and endocrine testing are not indicated

Mild

Moderate to severe

TOPICAL TREATMENTS

Multimodal therapy combining multiple mechanisms of action is recommended

Multimodal Topical Therapy

- Topical retinoids
- BP
- Topical antibiotics
  - *Monotherapy is not recommended*

Fixed-dose combinations

- Topical antibiotic & BP
- Topical retinoid & BP
- Topical retinoid & antibiotic
  - *Concomitant use of BP can prevent the development of antibiotic resistance.*
- Clascoterone
- Salicylic acid
- Azelaic acid

PHYSICAL MODALITIES

- Pneumatic broadband light added to adapalene

SYSTEMIC ANTIBIOTICS

Limit systemic antibiotic use when possible to reduce the development of antibiotic resistance and other antibiotic-associated complications.

Use concomitant BP and other topical treatment

- Doxycycline
- Minocycline
- Sarecycline
- Doxycycline over azithromycin

HORMONAL AGENTS

- Combined oral contraceptives
- Spironolactone
  - *Potassium monitoring is of low usefulness in patients without risk factors for hyperkalemia (e.g., older age, medical comorbidities, medications).*
- Intralesional corticosteroids
  - *Adjuvant treatment for larger acne papules or nodules at risk of acne scarring or for rapid improvement in inflammation and pain.*

ISOTRETINOIN

- Isotretinoin
  - *Patients with psychosocial burden or scarring should be considered candidates for isotretinoin.*
  - *We recommend monitoring only LFT and lipids*
  - *Population-based studies have not identified increased risk of neuropsychiatric conditions or inflammatory bowel disease with isotretinoin.*
  - *For persons of pregnancy potential, pregnancy prevention is mandatory.*
- Daily dosing over intermittent dosing
- Either lidose-isotretinoin or standard isotretinoin

Key:

- Strong recommendation in favor of the intervention
- Conditional recommendation in favor of the intervention
- Strong recommendation against the intervention
- Conditional recommendation against the intervention

Abbreviations: BP: Benzoyl peroxide; LFT: Liver function test

2024 AAD Acne Guidelines

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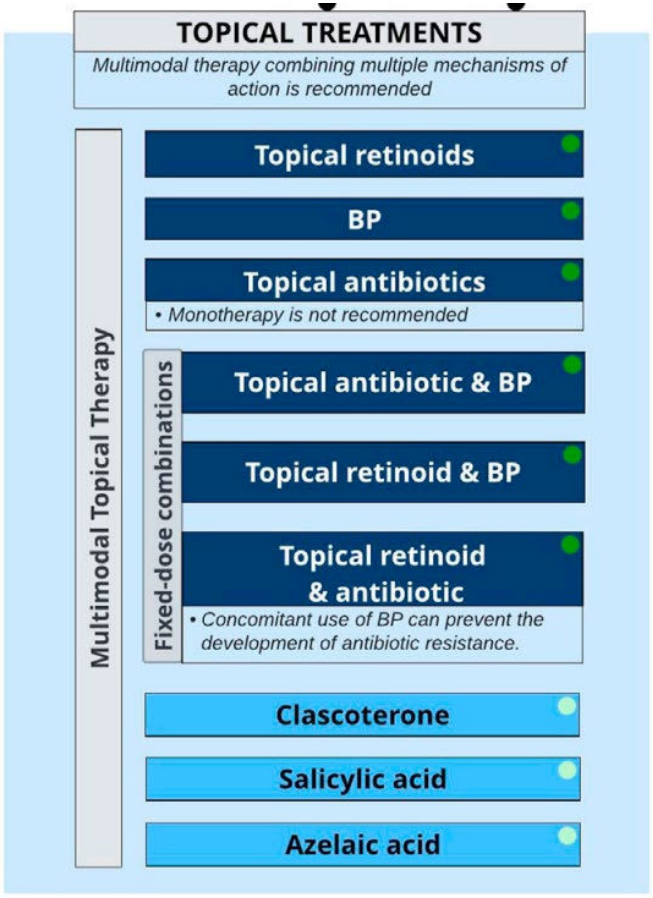
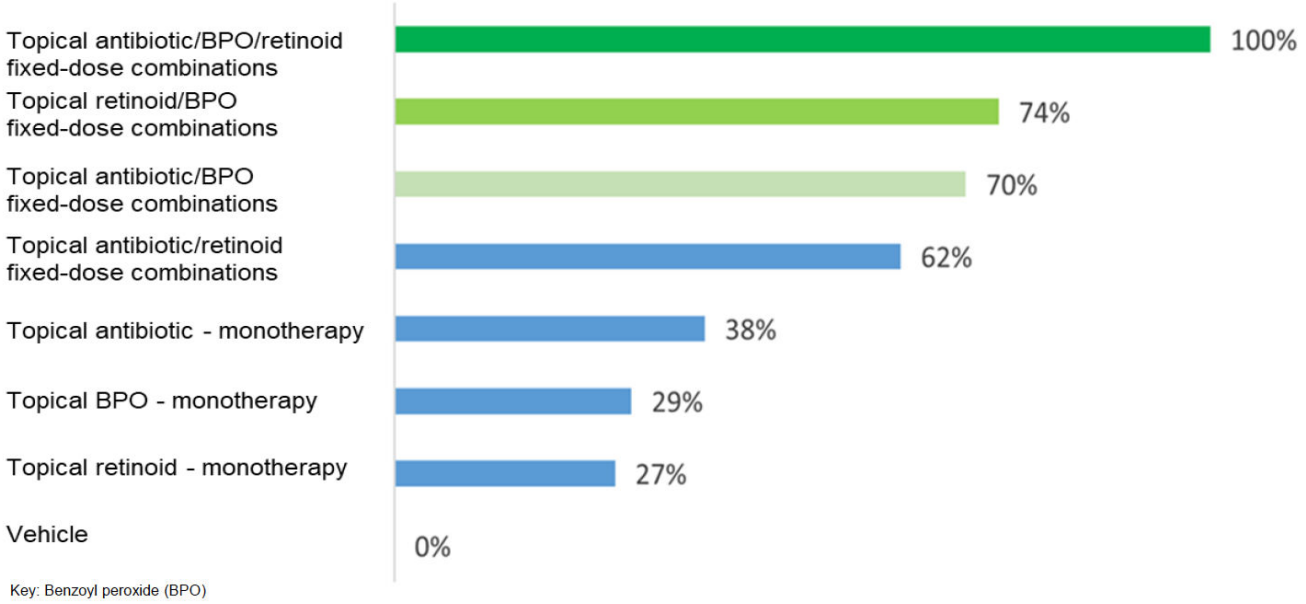
2024 AAD Acne Guidelines: Topical Therapy



Harper J, et al. A systematic literature review and network meta-analysis of comparative efficacy of topical fixed-dose combination treatments for moderate to severe acne vulgaris.

Bausch Health, Poster, Fall Clinical Meeting, Las Vegas, NV, 2023.



- A Surface Under the Cumulative Ranking (SUCRA) value of 100% indicates that the topical triple-agent FDC has the highest probability of being the most effective among all the comparators in the NMA

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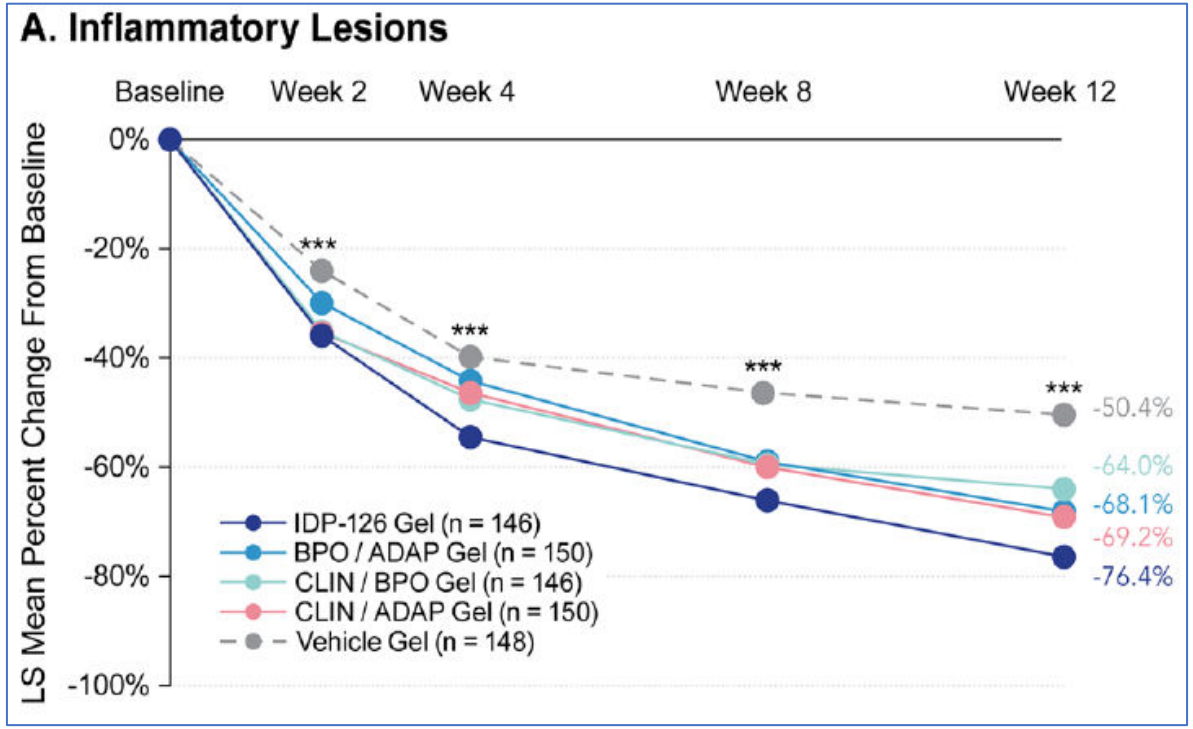
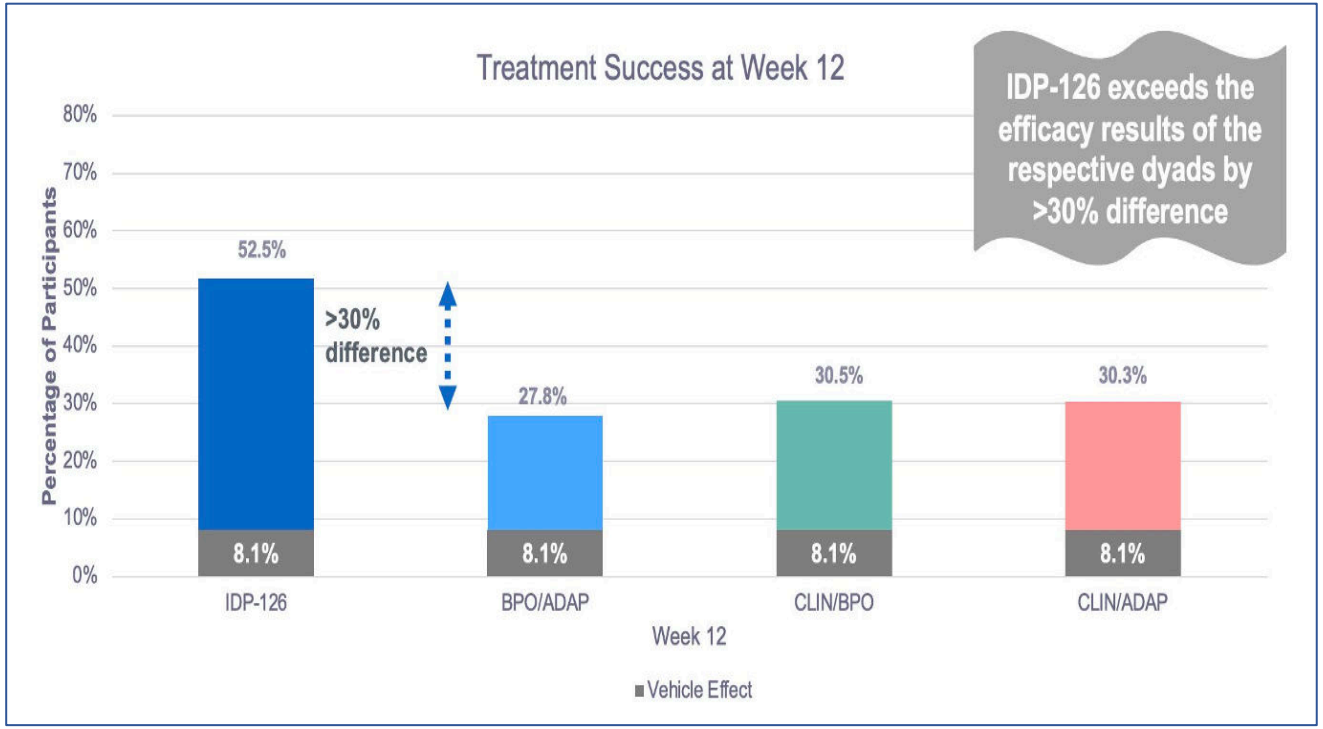
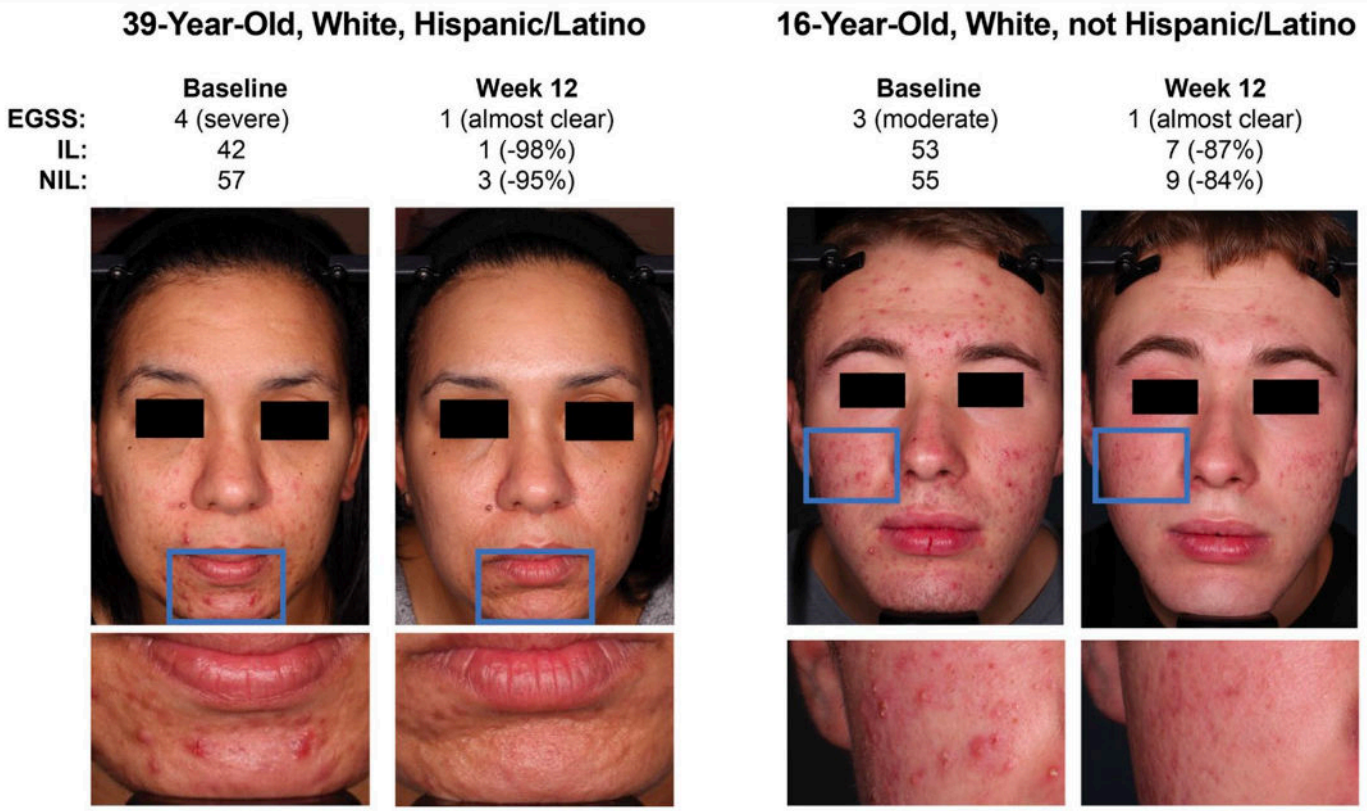
FDA-Approved: triple combination topical Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel enhances efficacy and may increase patient compliance





Stein Gold L, et al.
Efficacy and Safety of a Fixed-Dose **Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel** for Moderate-to-Severe Acne: A Randomized Phase II Study of the First Triple-Combination Drug.
Am J Clin Dermatol. 2022 Jan;23(1):93-104.

Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne

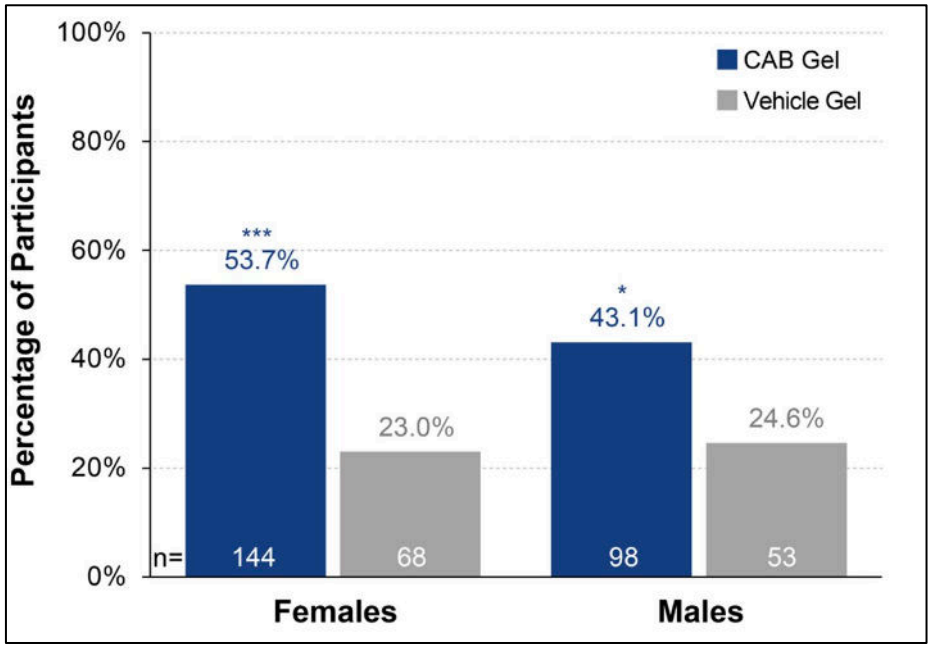


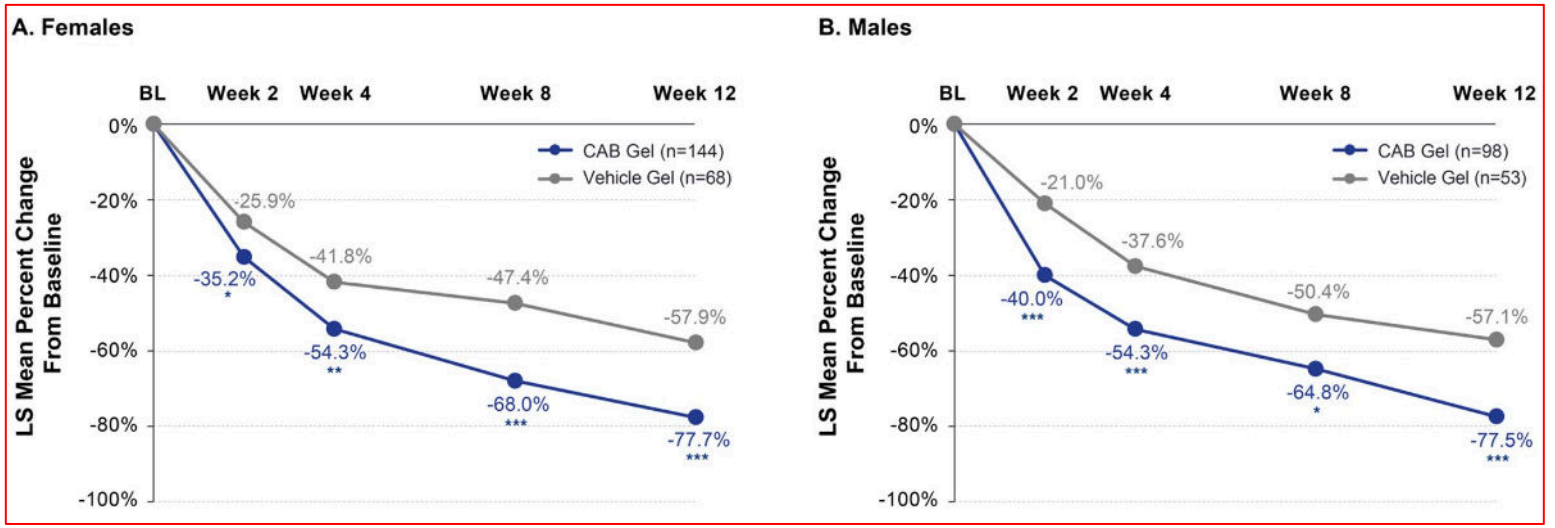
Acne improvements with clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% (IDP-126). Individual results may vary.
EGSS Evaluator's Global Severity Score (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe)

Stein Gold L, et al. Efficacy and Safety of a Fixed-Dose Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: A Randomized Phase II Study of the First Triple-Combination Drug. Am J Clin Dermatol. 2022 Jan;23(1):93-104.

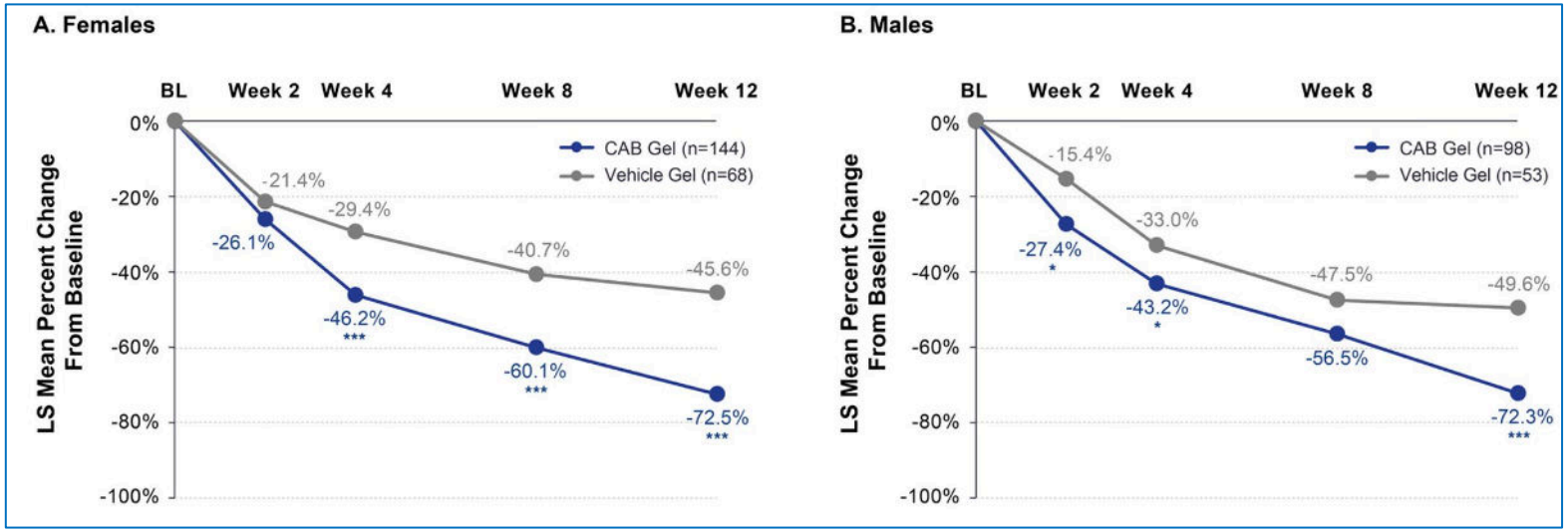
Lain ET, Bhatia N, Kircik L, Gold LS, Harper JC, Bunick CG, Guenin E, Baldwin H, Feldman SR, Rosso JQD. Clindamycin Phosphate 1.2%/Adapalene 0.15%/Benzoyl Peroxide 3.1% Gel for Male and Female Acne: Phase 3 Analysis. J Drugs Dermatol. 2024 Oct 1;23(10):873-881.

Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: Gender Differences





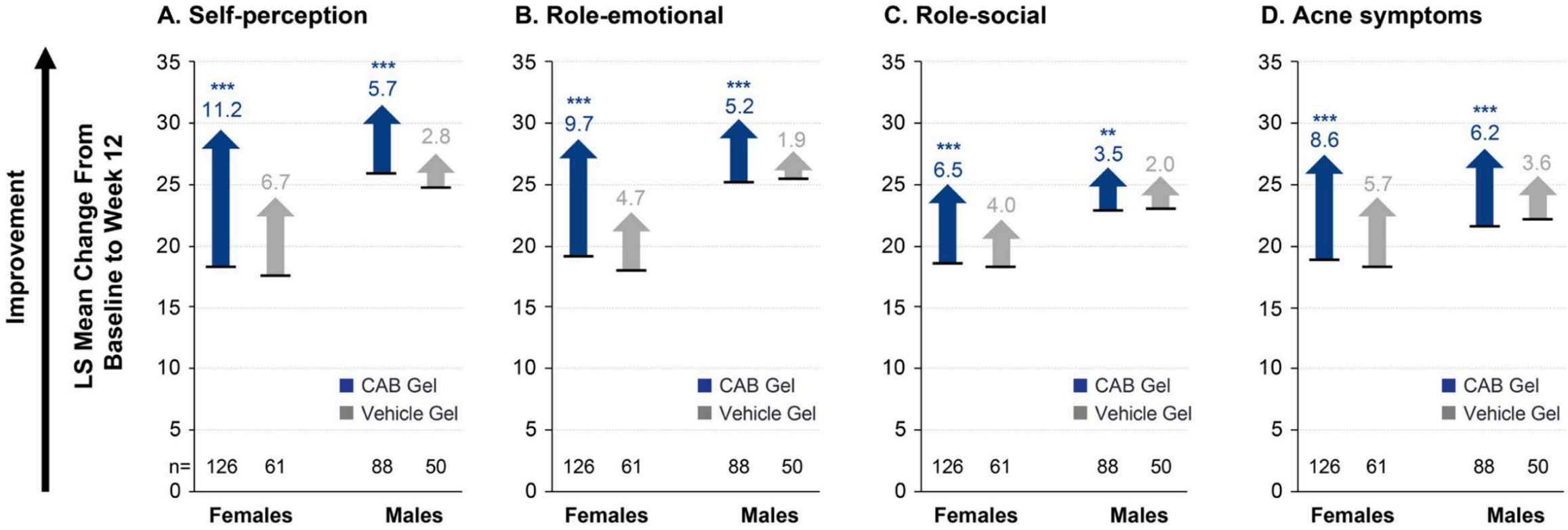
Inflammatory Lesion Reduction



Non-Inflammatory Lesion Reduction

Lain ET, Bhatia N, Kircik L, Gold LS, Harper JC, Bunick CG, Guenin E, Baldwin H, Feldman SR, Rosso JQD. Clindamycin Phosphate 1.2%/Adapalene 0.15%/Benzoyl Peroxide 3.1% Gel for Male and Female Acne: Phase 3 Analysis. J Drugs Dermatol. 2024 Oct 1;23(10):873-881.

Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: QOL improvement



Lain ET, Bhatia N, Kircik L, Gold LS, Harper JC, Bunick CG, Guenin E, Baldwin H, Feldman SR, Rosso JQD. Clindamycin Phosphate 1.2%/Adapalene 0.15%/Benzoyl Peroxide 3.1% Gel for Male and Female Acne: Phase 3 Analysis. J Drugs Dermatol. 2024 Oct 1;23(10):873-881.

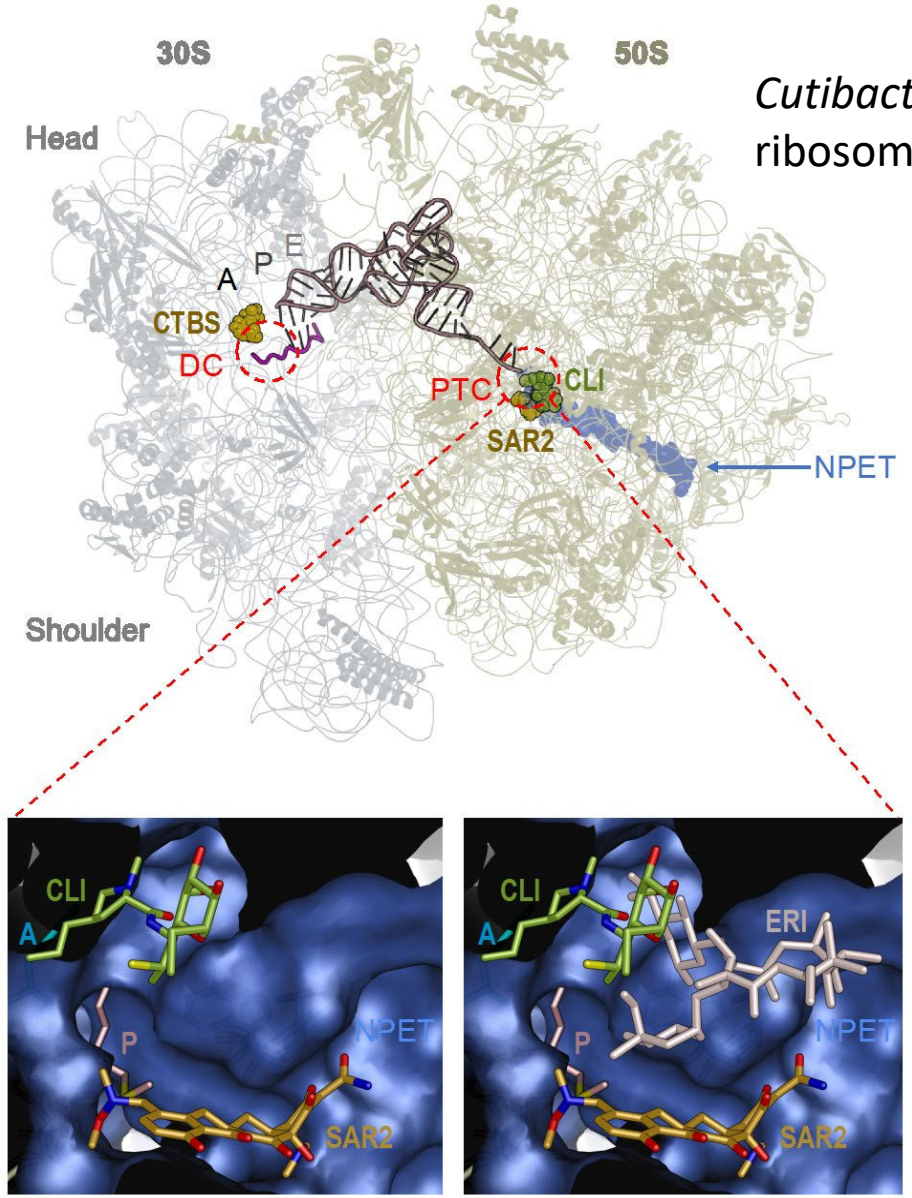
Benefits of clindamycin in triple-combination acne topical

Anti-inflammatory Properties of Clindamycin

Proinflammatory Factors and Components	Study Type: Acne[b]	Study Type: Other	Inhibits: Yes	Inhibits: No	Enhances[a]: Yes	Enhances[a]: No
Propionibacterium acnes growth	X[72]		X[72]			
P acnes protein synthesis (50S ribosomal subunit binding)		X[26,70]	X[26,70]			
P acnes lipase production	X[73]		X[73]			
P acnes and the release of follicular free fatty acids	X[15,74]		X[15,74]			
Proinflammatory Chemokines (Attractants)						
P acnes release of leukocyte chemotactic components	X[23,56,75,76]		X[23,56,75,76]			
IL-8	X[46,c]			X[46,c]		
Phagocytosis						
Opsonization of bacteria for enhanced phagocytosis		X[77-80]			X[77-80]	
Enhances and potentiates phagocytosis		X[77,81,82]			X[77,81,82]	
Respiratory burst (ROS as O_2^-, H_2O_2)		X[83,84]	X[83,84]			
iNOS enzymes		X[85]	X[85]			
Protein kinase C enzyme/granuloma formation	X[86]			X[86]		
Proinflammatory Cytokines (Primarily Monocytes)						
IL-1α	X[46,c]			X[46,c]		
IL-1β	X[46,d]	X[87-89]	X[46,87-89,d]			
IL-6	X[46,c,e]		X[46,c,e]			
IL-12p70	X[46,d]			X[46,d]		
IFN-γ	X[46,d]		X[46,d]			
TNF-α	X[46,d]	X[85,87-90]	X[85,87-90]	X[46,d]		
Keratinocyte Cytokines (Stimulants)						
GM-CSF	X[46,c,e]		X[46,c,e]			

Abbreviations: ROS, reactive oxygen species; O_2^-, superoxide; H_2O_2, hydrogen peroxide; iNOS, inducible nitric oxide synthase; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor α; GM-CSF, granulocyte-macrophage colony-stimulating factor.
[a]In several instances, clindamycin can actually enhance rather than inhibit a process associated with inflammation. These enhancements can actually be beneficial therapeutically and therefore can be ranked as anti-inflammatory in nature.
[b]Acne related based on available understanding of inflammatory mechanisms involved in pathogenesis.
[c]From human keratinocytes activated by heat-killed *P acnes*.
[d]From human monocytes activated by heat-killed *P acnes*.
[e]Inhibits at high concentration; however, the investigators suggest that the high concentration of clindamycin used "may be achievable in acne lesions after single topical application . . ."[46]

Del Rosso JQ, Schmidt NF. A review of the anti-inflammatory properties of clindamycin in the treatment of acne vulgaris. *Cutis*. Jan 2010;85(1):15-24.

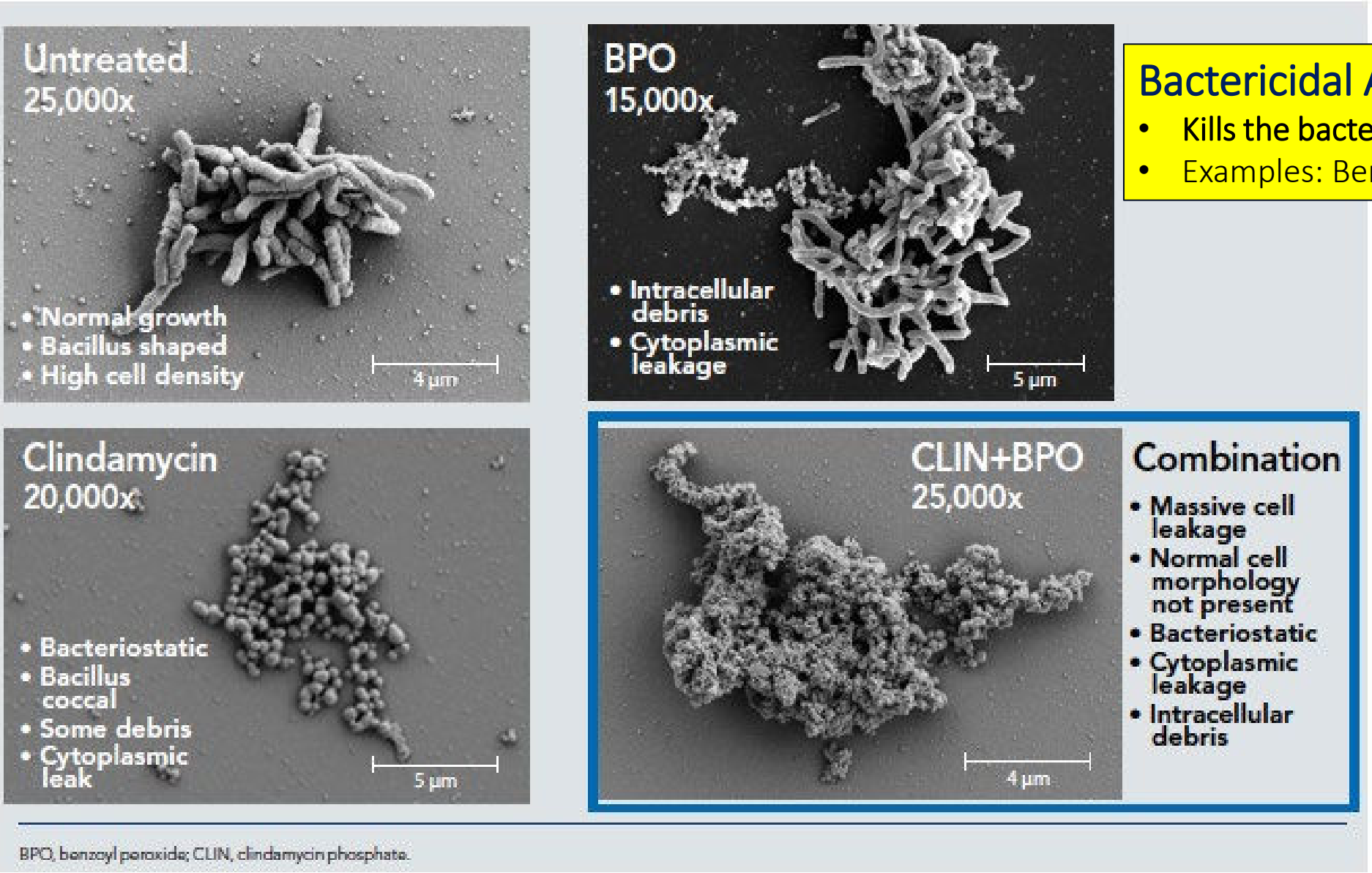


Cutibacterium acnes ribosome

Armillei MK, Lomakin IB, Del Rosso JQ, Grada A, Bunick CG. Scientific Rationale and Clinical Basis for Clindamycin Use in the Treatment of Dermatologic Disease. Antibiotics (Basel). 2024 Mar 17;13(3):270.

Clindamycin and BPO damages *C. acnes*

Scanning Electron Microscopy



Bactericidal Agent

- Kills the bacteria
- Examples: Benzoyl Peroxide

Ghannoum M, et al. Avoiding the danger of rising resistance in C. acnes: criticality of BPO and Antibiotic Fixed Combinations. Bausch Health, Poster, Fall Clinical 2023.

BPO degrades into Benzene

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Benzoyl Peroxide Drug Products Form Benzene

Kaury Kucera,[1] Nicola Zenzola,[1] Amber Hudspeth,[1] Mara Dubnicka,[1] Wolfgang Hinz,[1] Christopher G. Bunick,[2] Arash Dabestani,[3] and David Y. Light[1]

[1]Valisure, LLC, New Haven, Connecticut, USA
[2]Yale University, New Haven, Connecticut, USA
[3]Long Island University, Brooklyn, New York, USA

https://doi.org/10.1289/EHP13984

Introduction

Benzoyl peroxide (BPO) is a diacyl peroxide with bactericidal activity used in topical drug products up to 10% concentration and is available through prescription or over-the-counter (OTC) for treatment of acne vulgaris (acne).[1] Acne drug treatments commonly include topical creams, gels, or other drug product formulations that are left on the skin daily. Wash-away cleansers are also available, as are microencapsulated formulations that aim to stabilize benzoyl peroxide.[2] Most products are applied daily and consistent use ranges from months to years where patients are chronically exposed to drug products with BPO.

BPO, produced as a crystalline powder, is known to thermally decompose to form two molecules of benzoyloxy radicals that can further decompose to benzoic acid or phenyl radicals with liberation of carbon dioxide. Depending on the chemical environment, the phenyl radicals produce end products that include benzene, phenyl benzoate, and biphenyl.[3] A degradation mechanism from BPO ($(C_6H_5CO)_2O_2$) to benzene (C_6H_6) is shown below:

$$(C_6H_5CO)_2O_2 \rightleftharpoons 2C_6H_5CO_2\bullet$$
$$C_6H_5CO_2\bullet \rightarrow C_6H_5\bullet + CO_2$$
$$C_6H_5\bullet + H^+ \rightarrow C_6H_6$$

There is no safe level of benzene exposure to humans and US Food and Drug Administration (FDA) guidance specifies that drug products should not contain benzene because of its unacceptable toxicity and benzene is permissible up to 2 ppm only for products where benzene is required for manufacturing.[4] Since 2021, independent studies identifying benzene contamination have led to global recalls of consumer drug products, including hand sanitizers, sunscreens, antifungal sprays, and antiperspirants.[5]

To investigate both benzene concentrations produced within the topical drug products and gaseous benzene released into the surrounding air, orthogonal analytical techniques of gas chromatography–mass spectrometry (GC-MS) and selected-ion flow-tube MS (SIFT-MS) were used. Incubation temperature of 37°C (98.6°F) was used to evaluate effect of standard body temperature, 50°C (122°F) was used to evaluate shelf-life performance as an accelerated stability testing temperature for pharmaceuticals,[6] and 70°C (158°F) was used to evaluate transportation/passenger vehicle excursion temperature.[7]

Materials and Methods

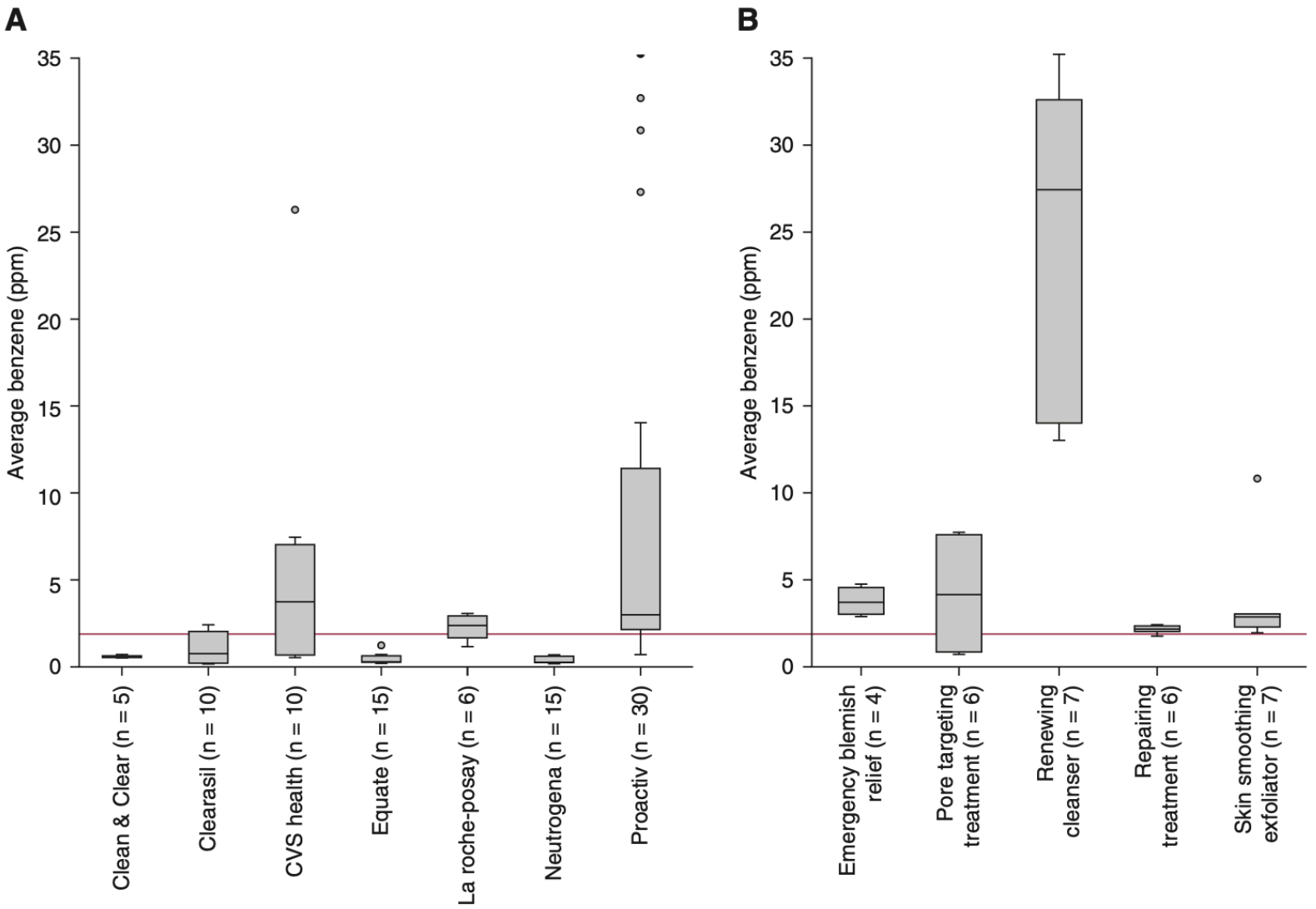
Single lots of seven differently formulated and branded BPO products were selected based on availability from national retailers. The products used are listed with their packaged volume and unique product codes (UPCs) for *a*) GC-MS studies: Equate Beauty 2.5% BPO cleanser 4 oz (118 mL) UPC 681131200066, Neutrogena 10% BPO cleanser 5 oz (148 mL) UPC 070501024638, CVS Health 10% BPO face wash 6.6 oz (195 mL) UPC 050428326930, Walgreens 10% BPO cream 1.12 oz (33 mL) UPC 049022657021, Clean & Clear 10% BPO cleanser 5 oz (148 mL) UPC 38137-0032892; and *b*) SIFT-MS: Equate Beauty 10% BPO acne wash 5.5 oz (163 mL) UPC 681131436496, and Proactiv 2.5% BPO cleanser 4 oz (118 mL) UPC 842944102170.

GC-MS

GC-MS methodology in this investigation followed that previously used by Valisure's laboratory for the analysis of benzene in consumer products, including the use of solvent blanks and isotopically labeled benzene in representative samples of consumer products.[8] Benzene-$^{13}C_6$ (99.8% Sigma-Aldrich) was

Kucera K, Zenzola N, Hudspeth A, Dubnicka M, Hinz W, Bunick CG, Dabestani A, Light DY. **Benzoyl Peroxide Drug Products Form Benzene**. Environ Health Perspect. 2024 Mar;132(3):37702.

BPO degrades into Carcinogen Benzene



- 111 BPO products sourced from 6 states across United States
- 34% of OTC BPO drug products exceeded the FDA's conditional limit

FDA conditional limit: 2 ppm

Kucera K, Zenzola N, Hudspeth A, Dubnicka M, Hinz W, Bunick CG, Girardi M, Dabestani A, Light DY. Evaluation of Benzene Presence and Formation in Benzoyl Peroxide Drug Products. J Invest Dermatol. 2024 Oct 7:S0022-202X(24)02155-9.

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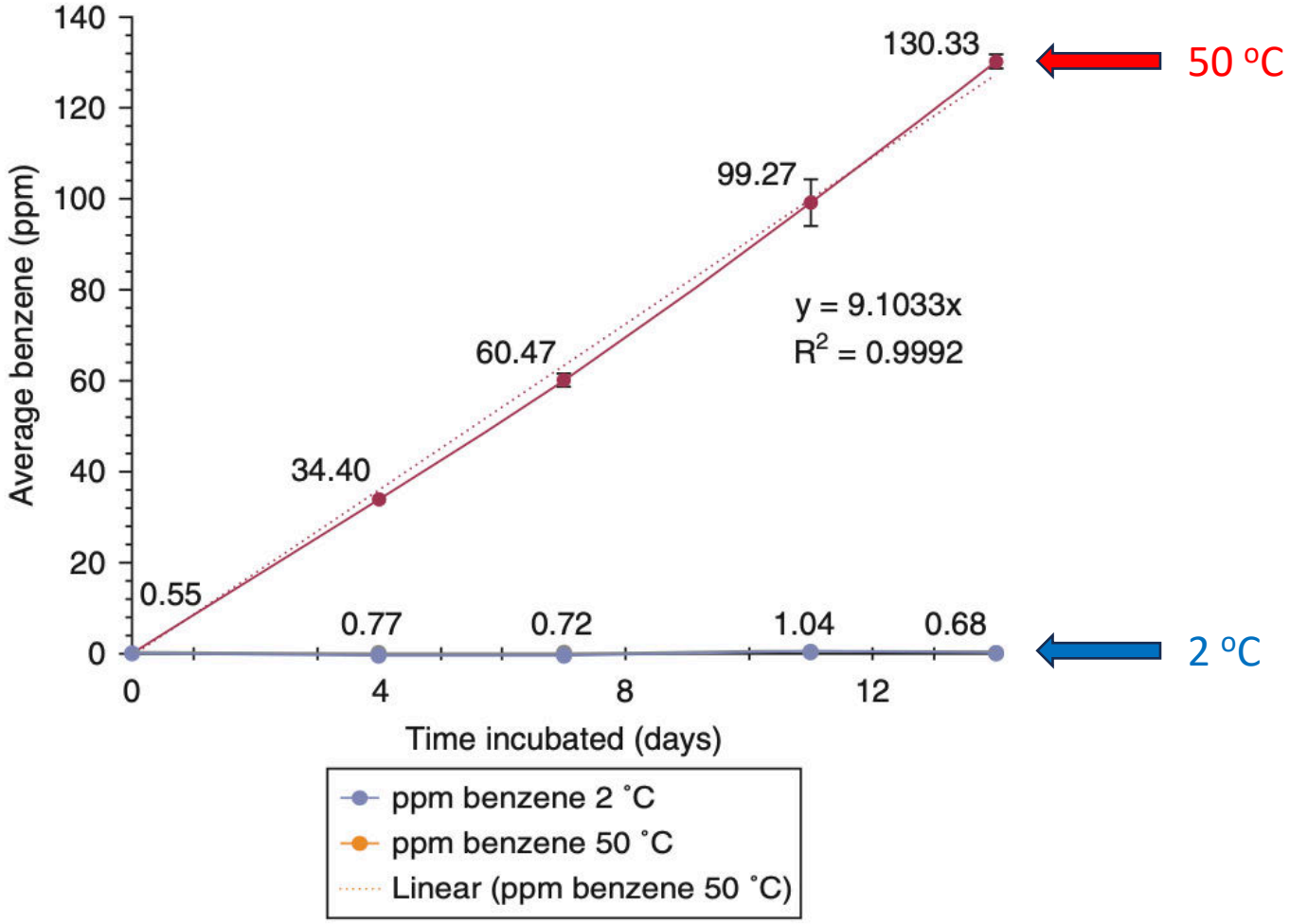
Cold temperature reduces BPO degradation into Benzene

Encapsulated BPO drug product



Kucera K, Zenzola N, Hudspeth A, Dubnicka M, Hinz W, Bunick CG, Girardi M, Dabestani A, Light DY. Evaluation of Benzene Presence and Formation in Benzoyl Peroxide Drug Products. J Invest Dermatol. 2024 Oct 7:S0022-202X(24)02155-9.

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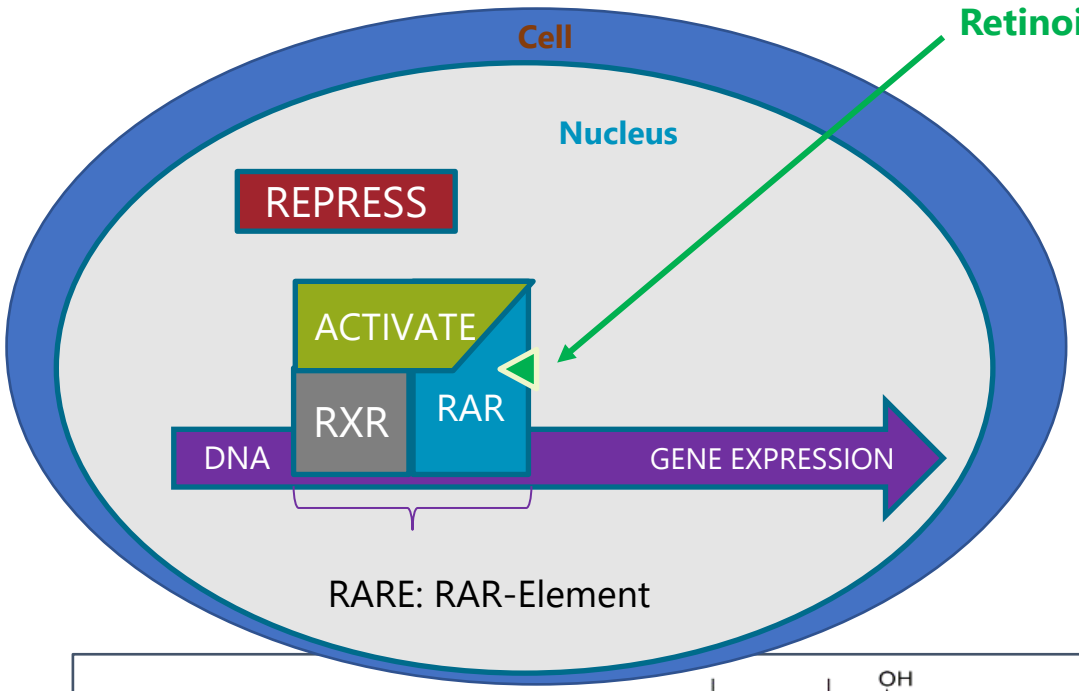
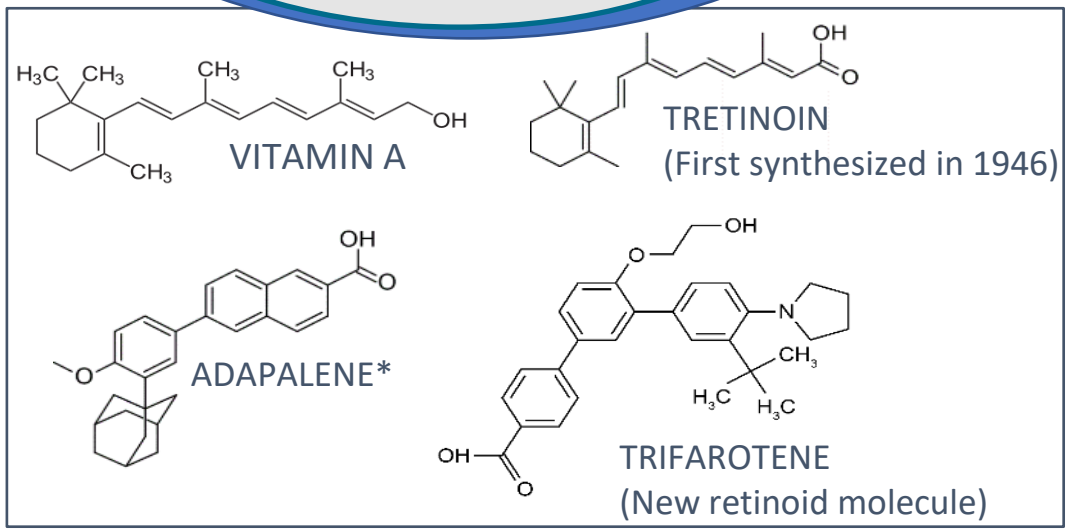
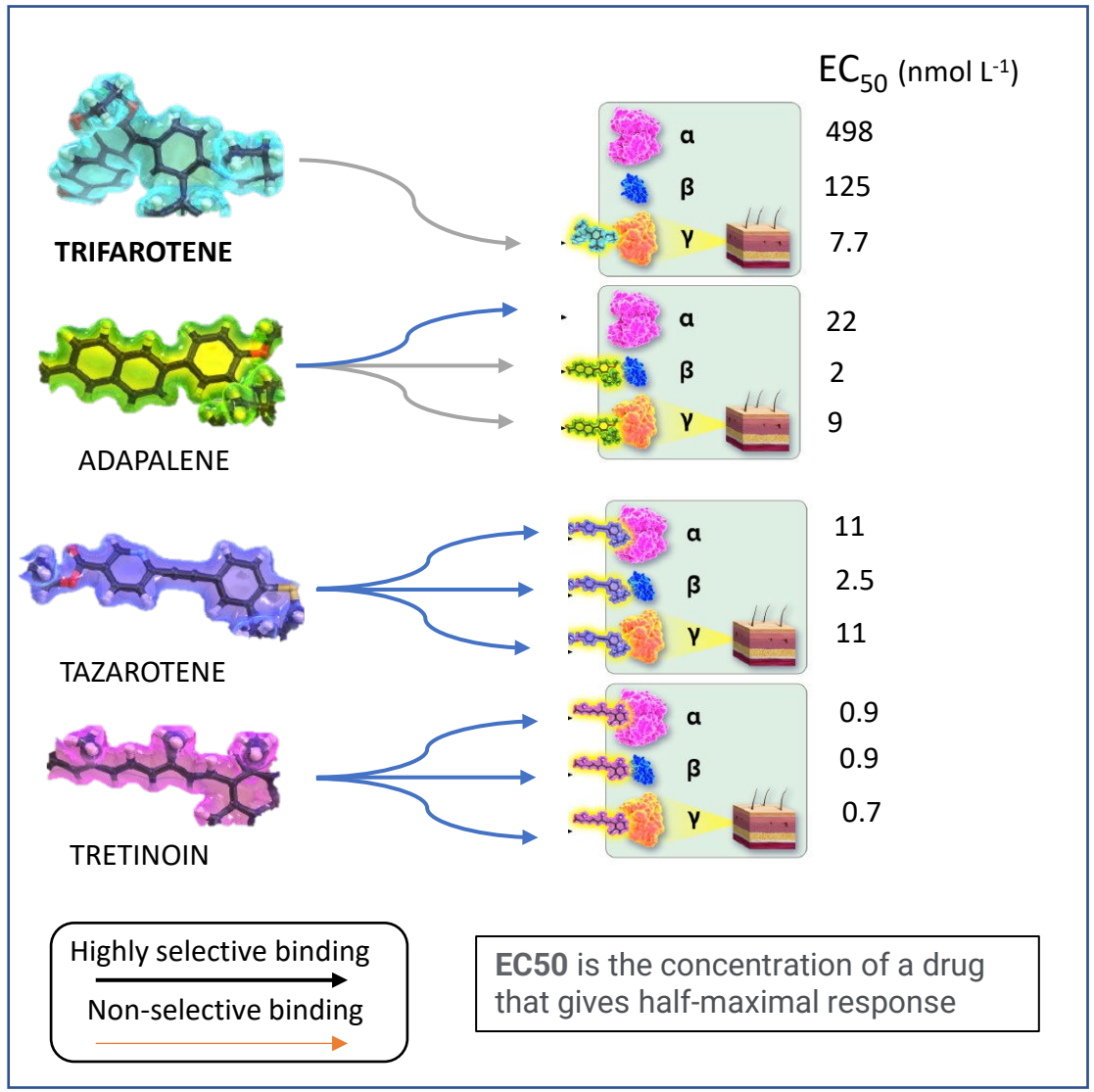
What do Dermatologists Do Now?

1. All prior BPO containing products subjected to hot showers, cars, or other heated environments should be discarded.
2. All expired benzoyl peroxide products should be discarded.
3. For those physicians and patients who wish to continue using benzoyl peroxide products, consider storing them at 4C, or refrigerator temperature. This will not necessarily eliminate the risk of benzene but should slow any temperature-dependent degradation of benzoyl peroxide.
4. Replace your benzoyl peroxide product regularly, such as every 3 months to avoid long-term accumulation of benzene.
5. Industry and pharmacy should consider "cold chain" 4C storage throughout the entire lifecycle of benzoyl peroxide products: from manufacturer, to pharmacy/shelf, to patient/consumer homes.
6. As further information and guidance comes, we as a dermatology community can move forward with what is always in the best interest of our patients.

Update on Topical Retinoids







Trifarotene is a potent agonist of RAR, binding specifically to the γ subtype of RAR receptors, which is the predominant receptor type in the skin (~90%)

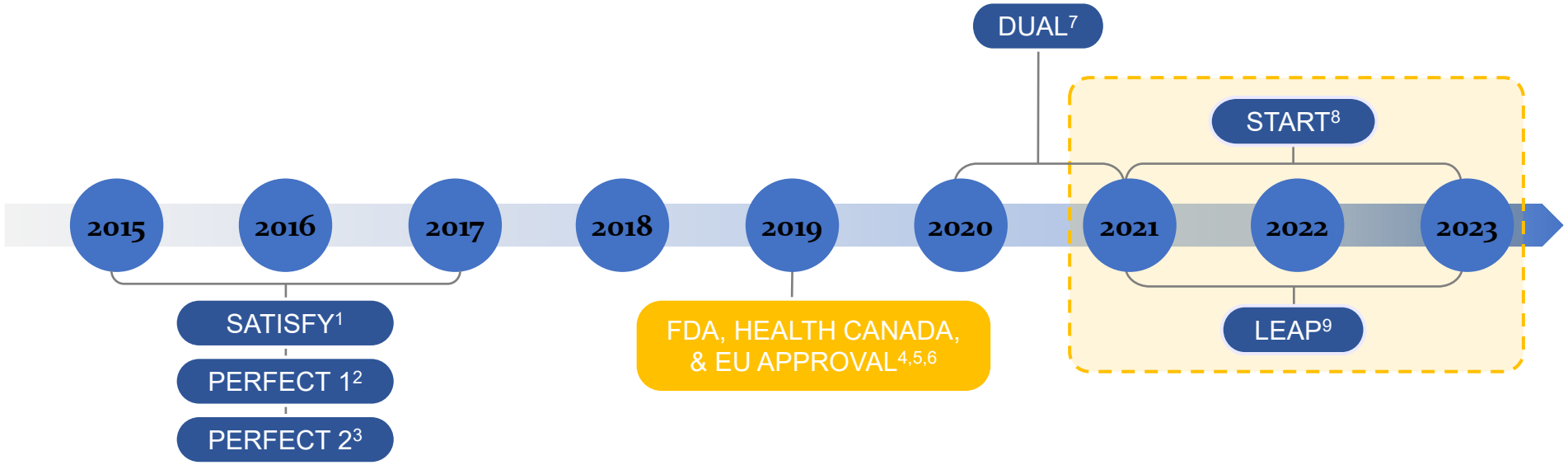
Slide information and figures courtesy Galderma.

Czernielewski J, *et al. J Eur Acad Dermatol Venereol.* 2001;15(suppl 3):5-12; ; Thoreau E, *et al. Bioorg Med Chem Lett.* 2018;28(10):1736-1741; Drugbank. https://www.drugbank.ca/drugs/DB12808 (last accessed January 2019); Nagpal S, *et al. Cur Pharm Design.* 2000;6:919-931; Aubert J, *et al. Br J Dermatol.* 2018;179:442–456; Huang P *et al. Chem Rev.* 2014;8;114(1):233-54; Fisher GJ, *et al. FASEB J.* 1996;10:1002-1013

Trifarotene Cream 0.005%: Phase 4 Studies of Acne Sequelae

LEAP: A Study of Acne-Induced Hyperpigmentation

START: A Study of Acne-Induced Scarring

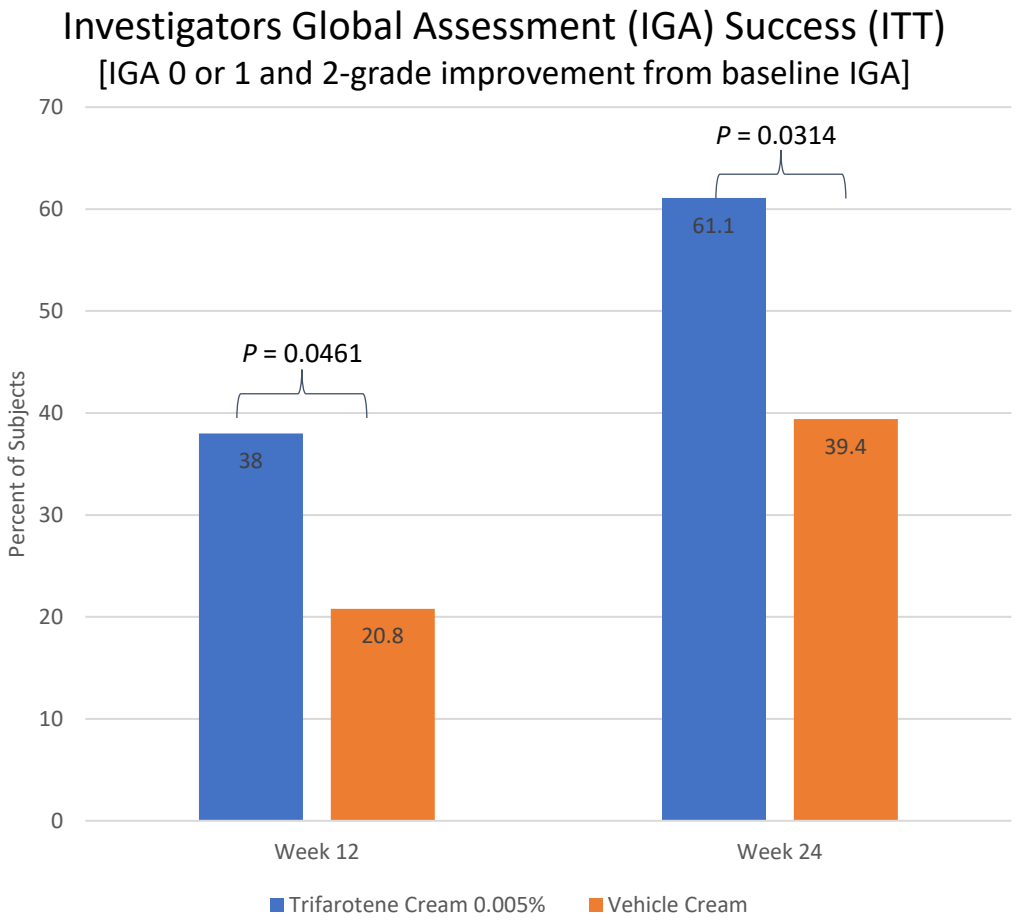


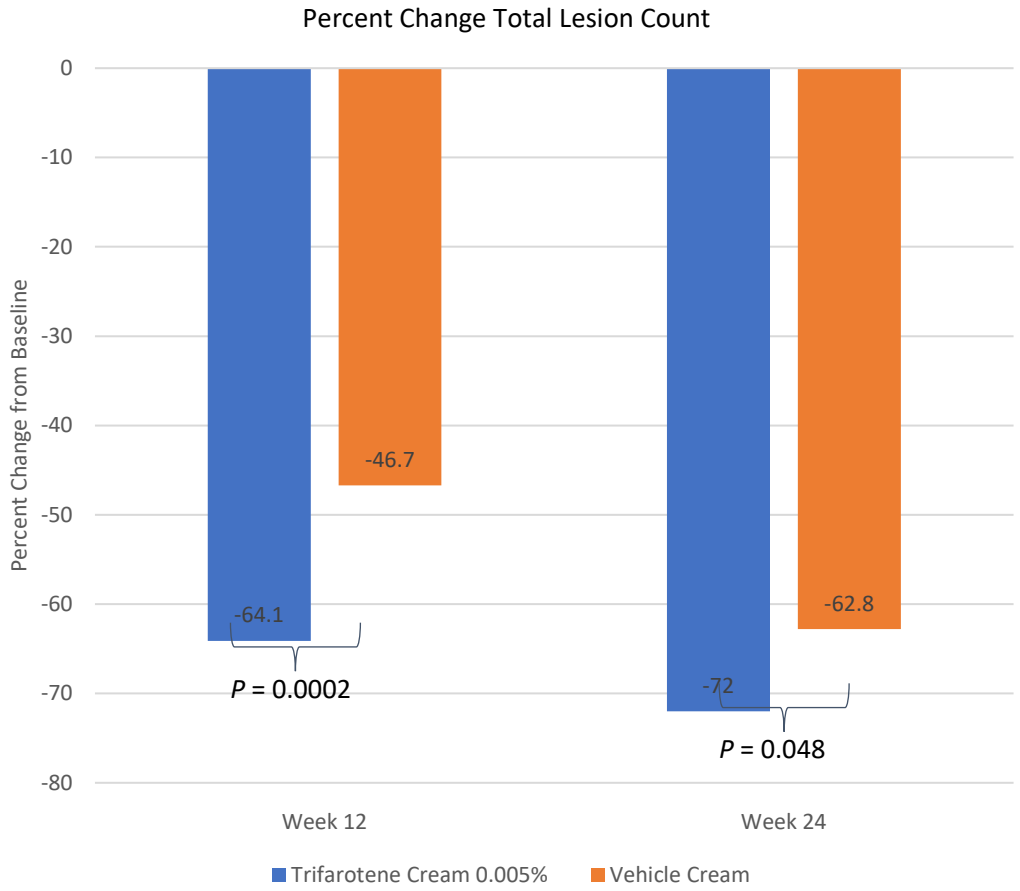
Slide courtesy Galderma

LEAP: (ak**L**ief **E**valuation in **A**cne-induced **P**ost-inflammatory hyperpigmentation)

LEAP

Acne Improvement





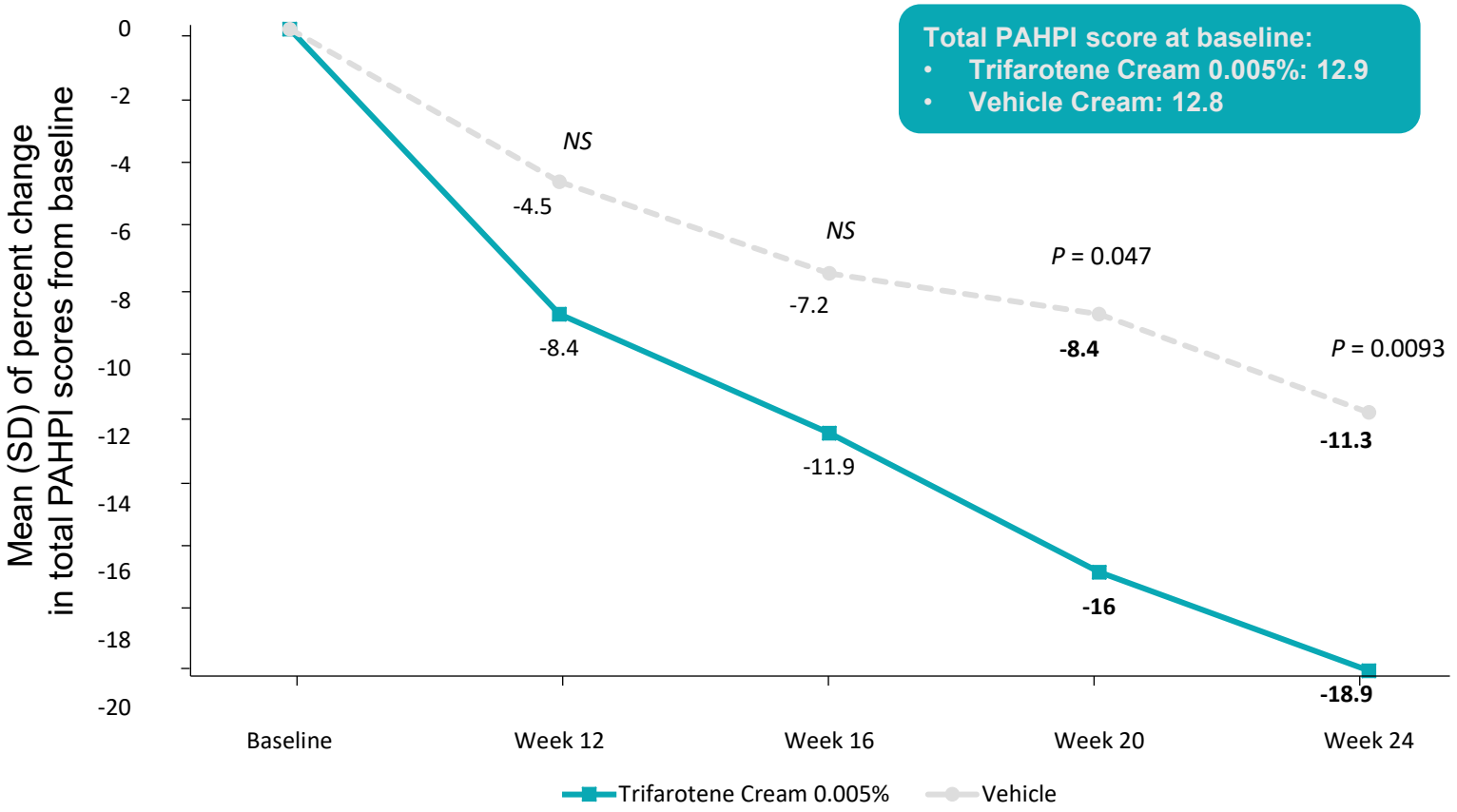
Missing data imputed using multiple imputation under the assumption of missing at random (ITT population).
BL, baseline; CI; confidence interval; IGA, investigators global assessment; ITT, intention-to-treat; MI, multiple imputation.
Galderma. Data on File RD.06.SPR.204245

Slide courtesy Galderma

Post-acne Hyperpigmentation Index (PAHPI; size, intensity, number)

LEAP

Percent change from baseline in PAHPI of the face total score (ITT)[1]



Scoring the Post-Acne Hyperpigmentation Index (PAHPI)	
Weighted score (S)	Median lesion size
2	< 3 mm
4	3 – 6 mm
6	7 – 10 mm
8	> 10 mm
Weighted score (I)	Median lesion intensity
3	Slightly darker than surrounding skin
6	Moderately darker than surrounding skin
9	Significantly darker than surrounding skin
Weight score (N)	Number of lesions
1	1 – 15
2	16 – 30
3	31 – 45
4	46 – 60
5	> 60

BL, baseline; ITT, intention-to-treat; PAPHI, postacne hyperpigmentation index; SD, standard deviation.
Galderma Data on File RD.06.SPR.204245

Slide courtesy Galderma

LEAP

Patient photographs

Vehicle group

Vehicle

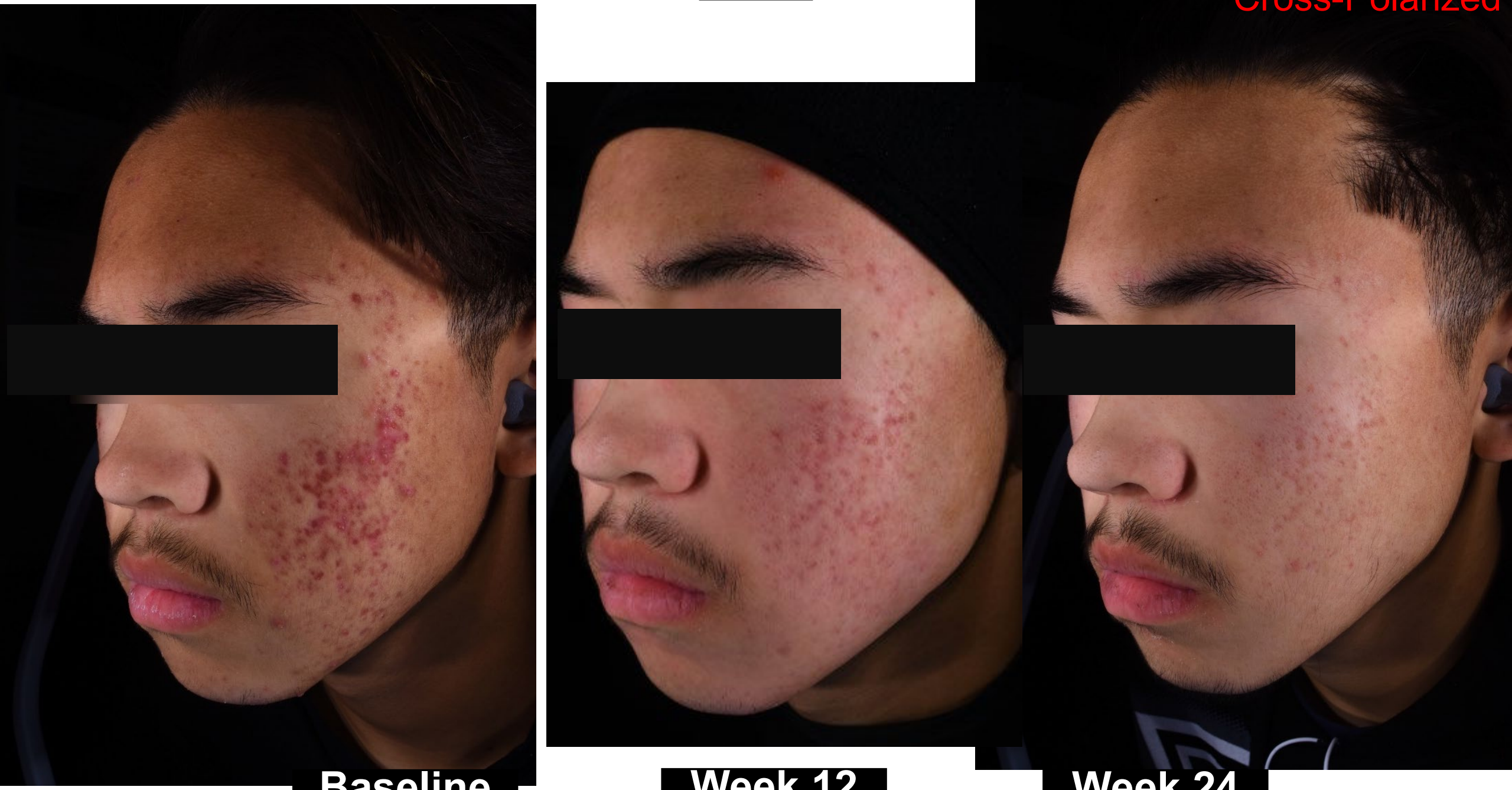
LEAP

Patient Photographs

Trifarotene Group

Trifarotene

Cross-Polarized



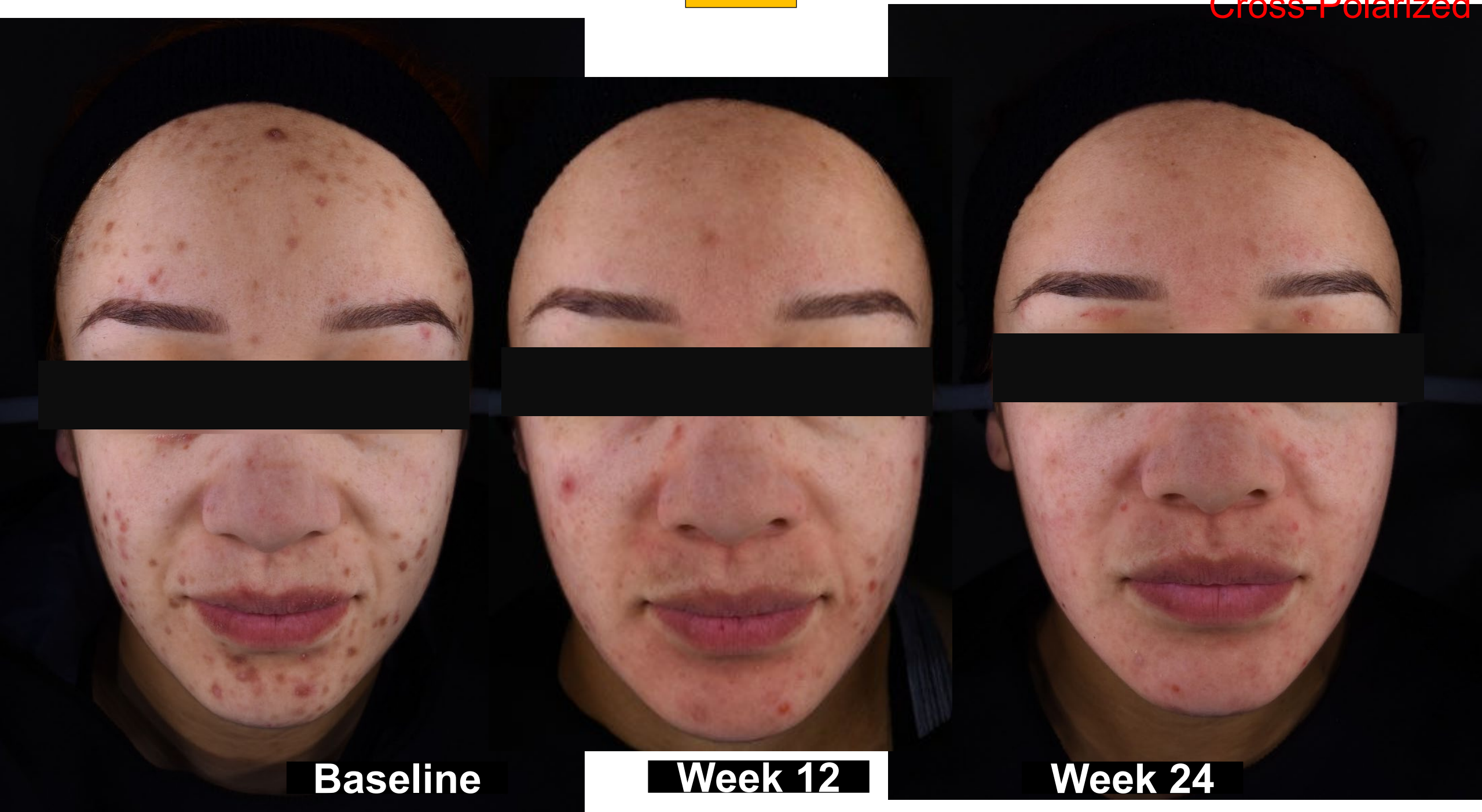
Baseline

Week 12

Week 24

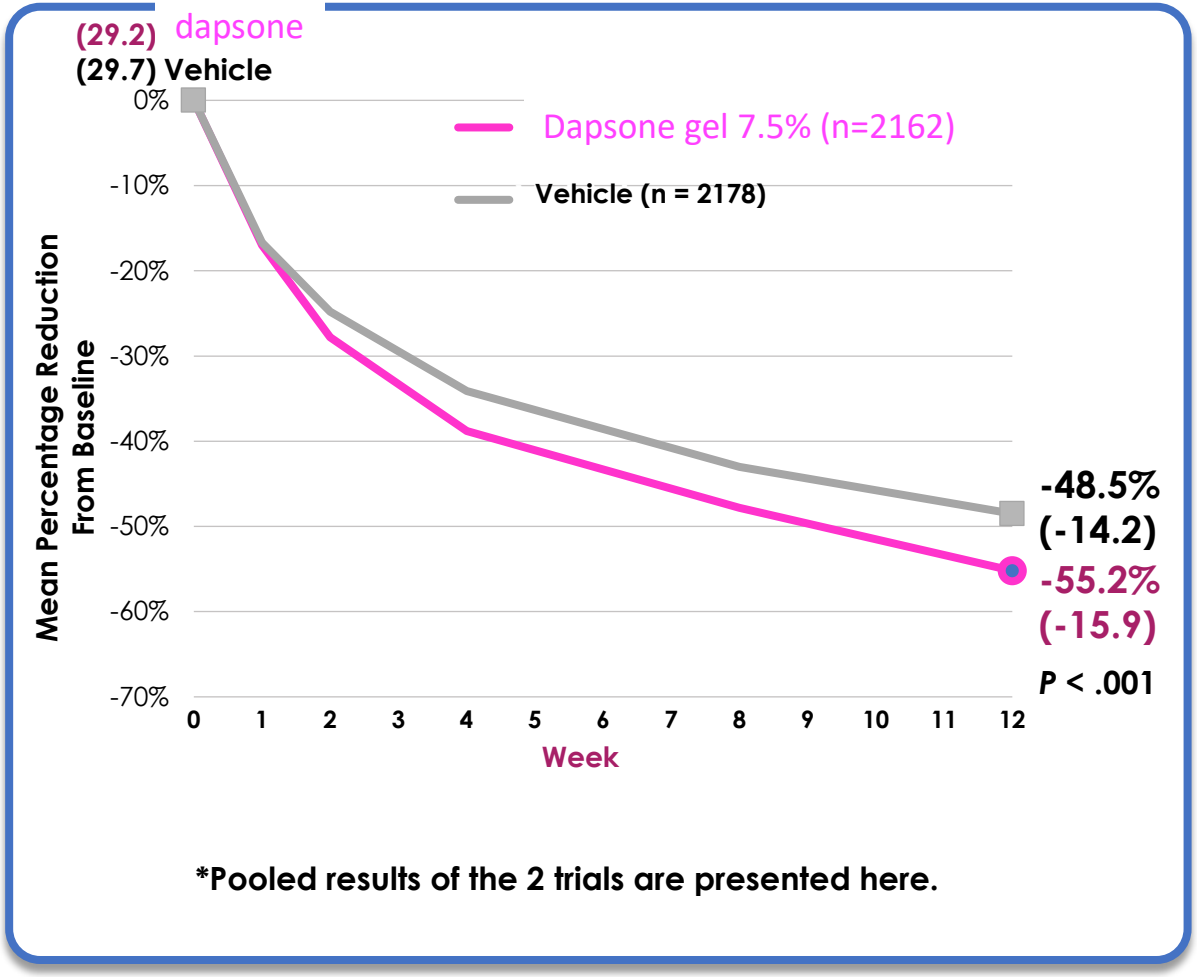
Trifarotene

Cross-Polarized



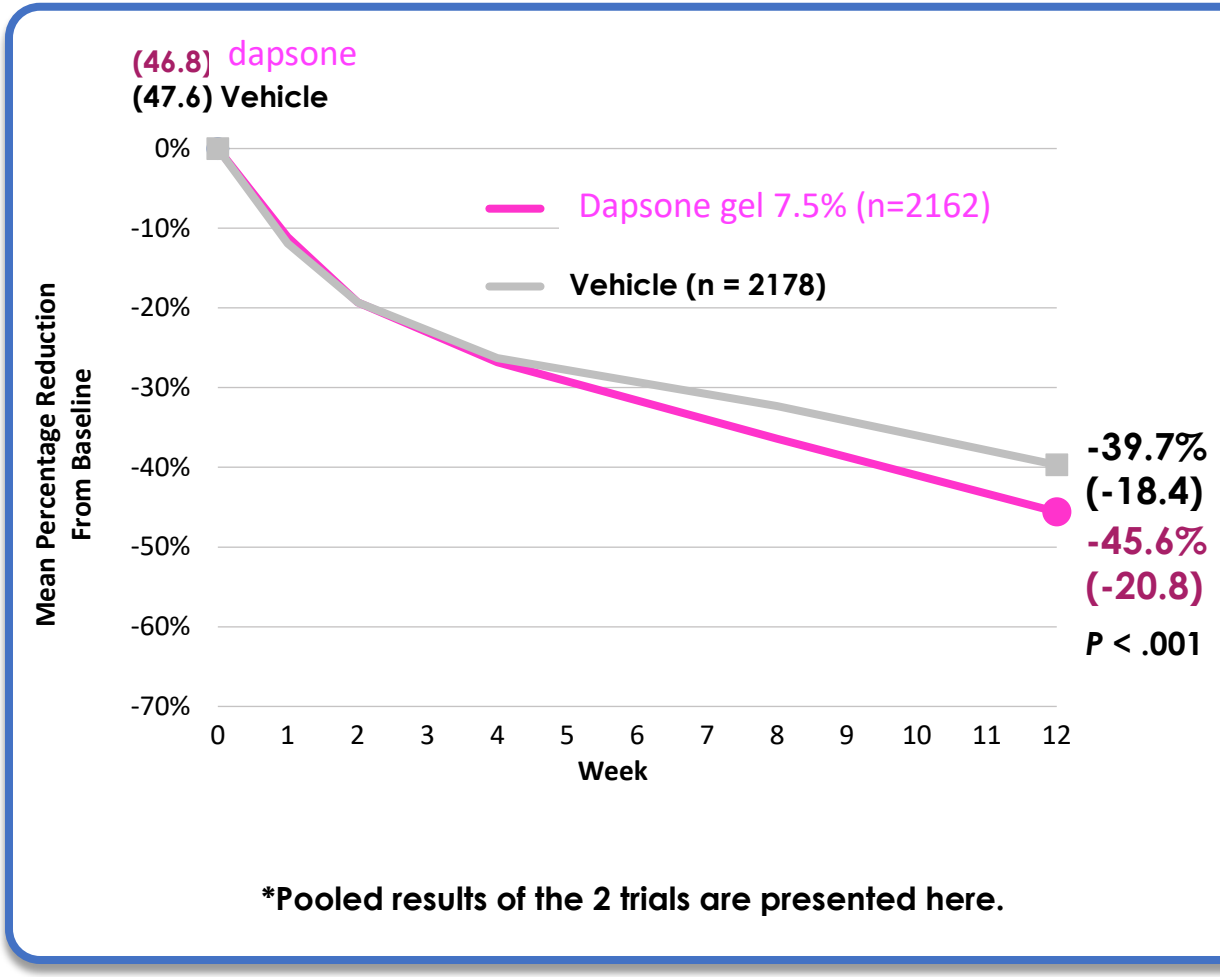
Efficacy of Dapsone 7.5% gel

Inflammatory Lesion Count Reduction at Week 12*



*Pooled results of the 2 trials are presented here.

Comedonal Lesion Count Reduction at Week 12*



*Pooled results of the 2 trials are presented here.

1. Data on file, Allergan, 2016; Integrated Summary of Effectiveness.

Acne accounts for an almost 2.5-fold higher proportion of dermatology visits among adult females compared to adult males in the United States: A study of the national ambulatory medical care survey from 2002–2016

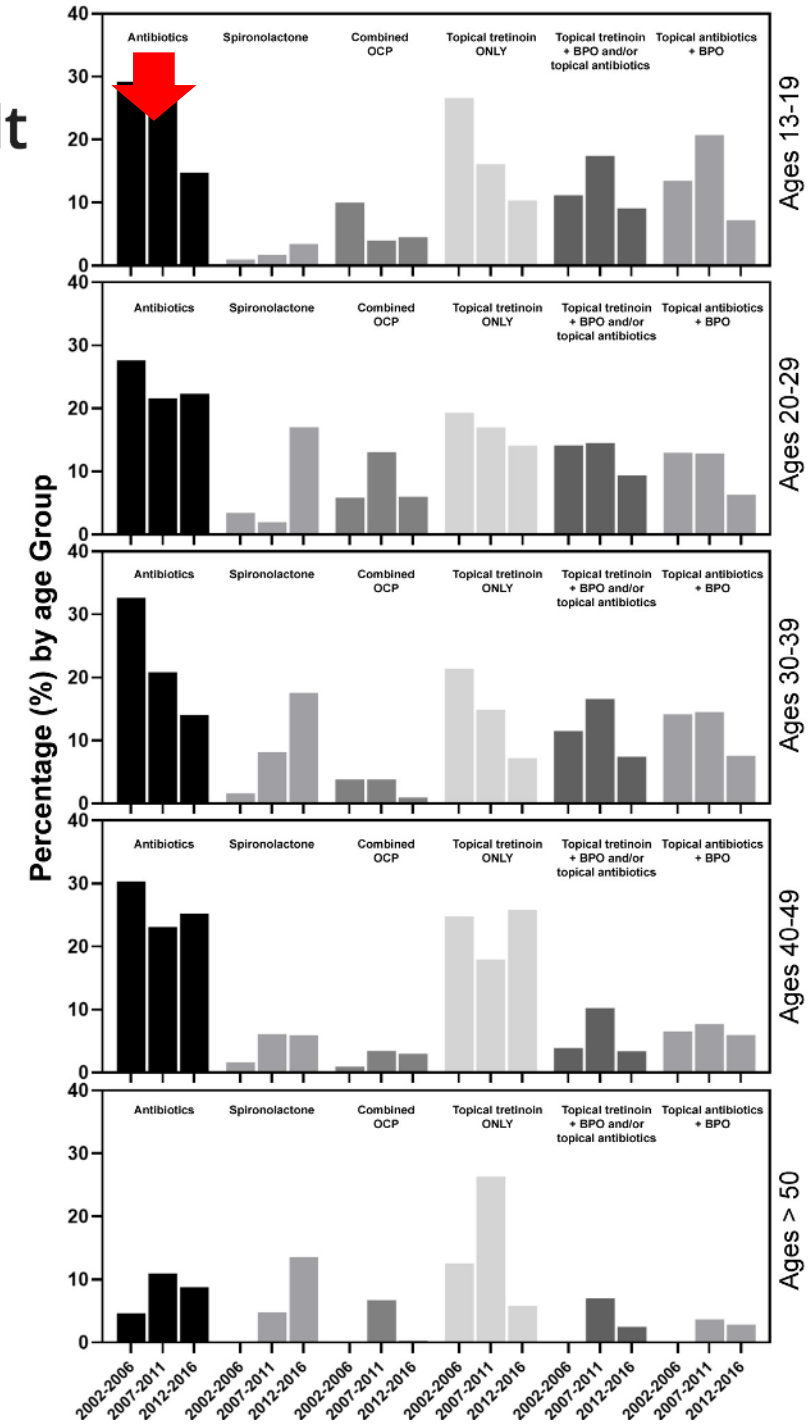
Jungsoo Chang, Michael R. Nock, Jeffrey M. Cohen, Christopher G. Bunick

Published: September 21, 2023 • https://doi.org/10.1371/journal.pone.0290763

Age groups	Total Dermatology Visits by Females	Diagnosis of Acne in Females	%	Total Dermatology Visits by Males	Diagnosis of Acne in Males	%	P value*
13–19	22,313,895	13,918,161	62.37	19,334,773	13,473,081	69.68	
20–29	24,561,556	10,899,975	44.38	13,942,660	3,637,344	26.09	<0.001
30–39	33,215,926	7,607,845	22.90	16,471,046	1,977,692	12.01	<0.001
40–49	39,504,477	4,890,284	12.38	22,461,687	1,128,227	5.02	<0.001
>50	163,191,246	2,875,150	1.76	145,500,032	1,306,024	0.90	<0.001
Total	282,877,917	40,191,415	14.21	217,710,198	21,522,368	9.88	<0.001

* Prevalence of dermatology visits related to acne were compared between males and females using $\chi 2$ tests.

https://doi.org/10.1371/journal.pone.0290763.t001



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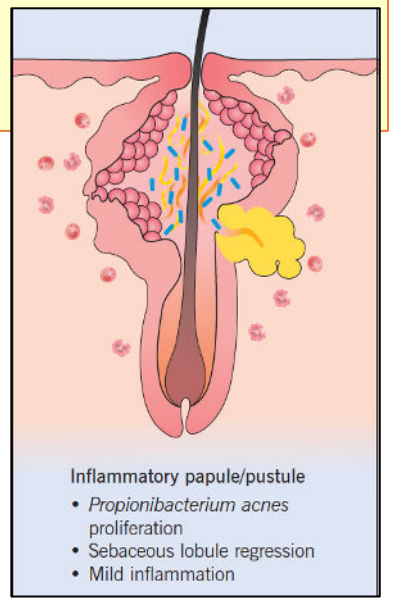
Why do we use oral antibiotics in acne?

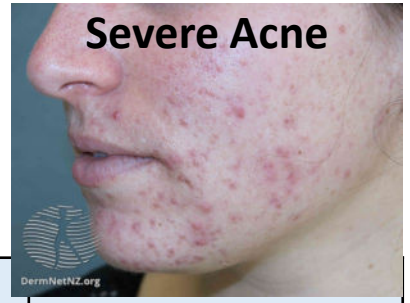
1. Bacterial pathogenesis

Interaction of four main pathogenic factors

- **Follicular hyperkeratinization**
- **Increased sebum production**
- ***Cutibacterium acnes* (C. acnes) an anaerobic G+ that is a normal component of skin flora**
- **Inflammation**

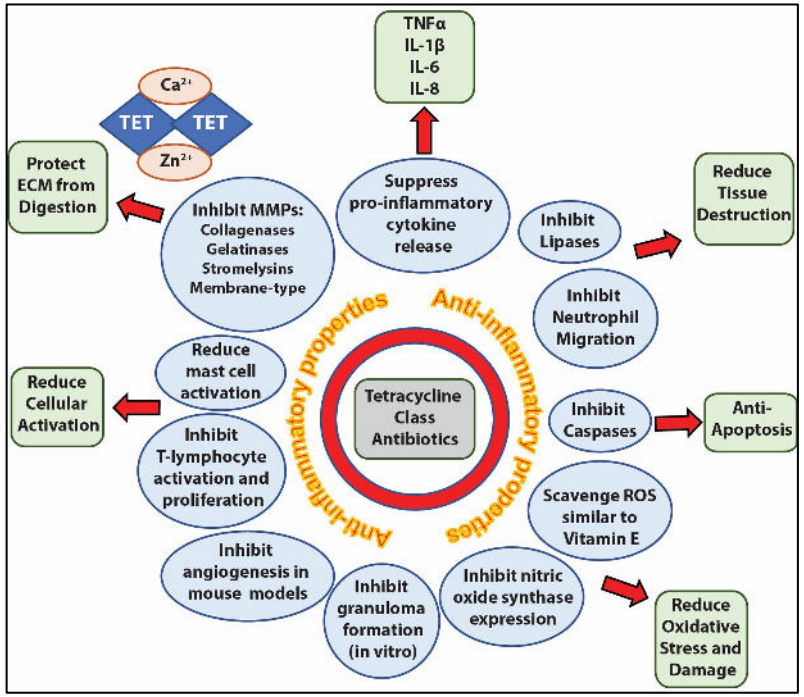


2. 2016 AAD Acne Guidelines



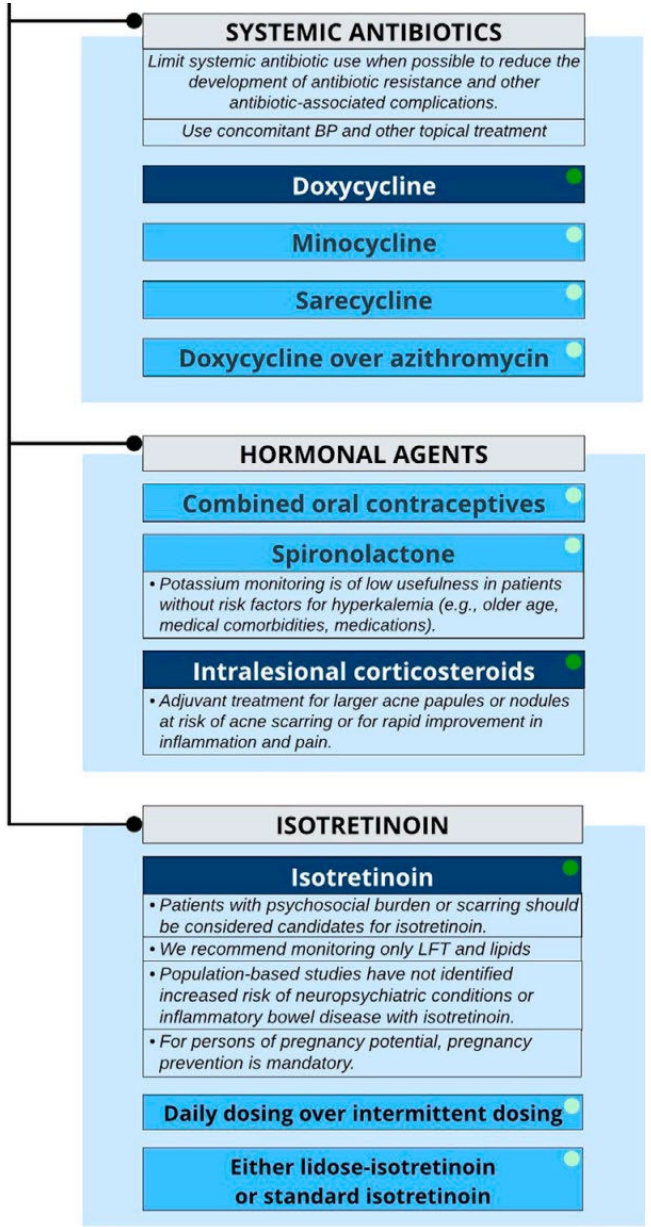
Moderate Acne	Severe Acne
1st-Line Treatment Topical Combination Therapy* BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- **Oral Antibiotic** + Topical Retinoid + BP -or- **Oral Antibiotic** + Topical Retinoid + BP + Topical Antibiotic	**1st-Line Treatment** **Oral Antibiotic** + Topical Combination Therapy* BP + Antibiotic or Retinoid + BP -or- Retinoid + BP + Antibiotic -or- Oral Isotretinoin
Alternative Treatment Consider Alternate Combination Therapy -or- Consider Change in **Oral Antibiotic** -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin	**Alternative Treatment** Consider Change in **Oral Antibiotic** -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin

3. Anti-inflammatory



Grada et al. Antibiotics. 2022 May 27;11(6):722.

2024 AAD Acne Guidelines: Oral Therapy



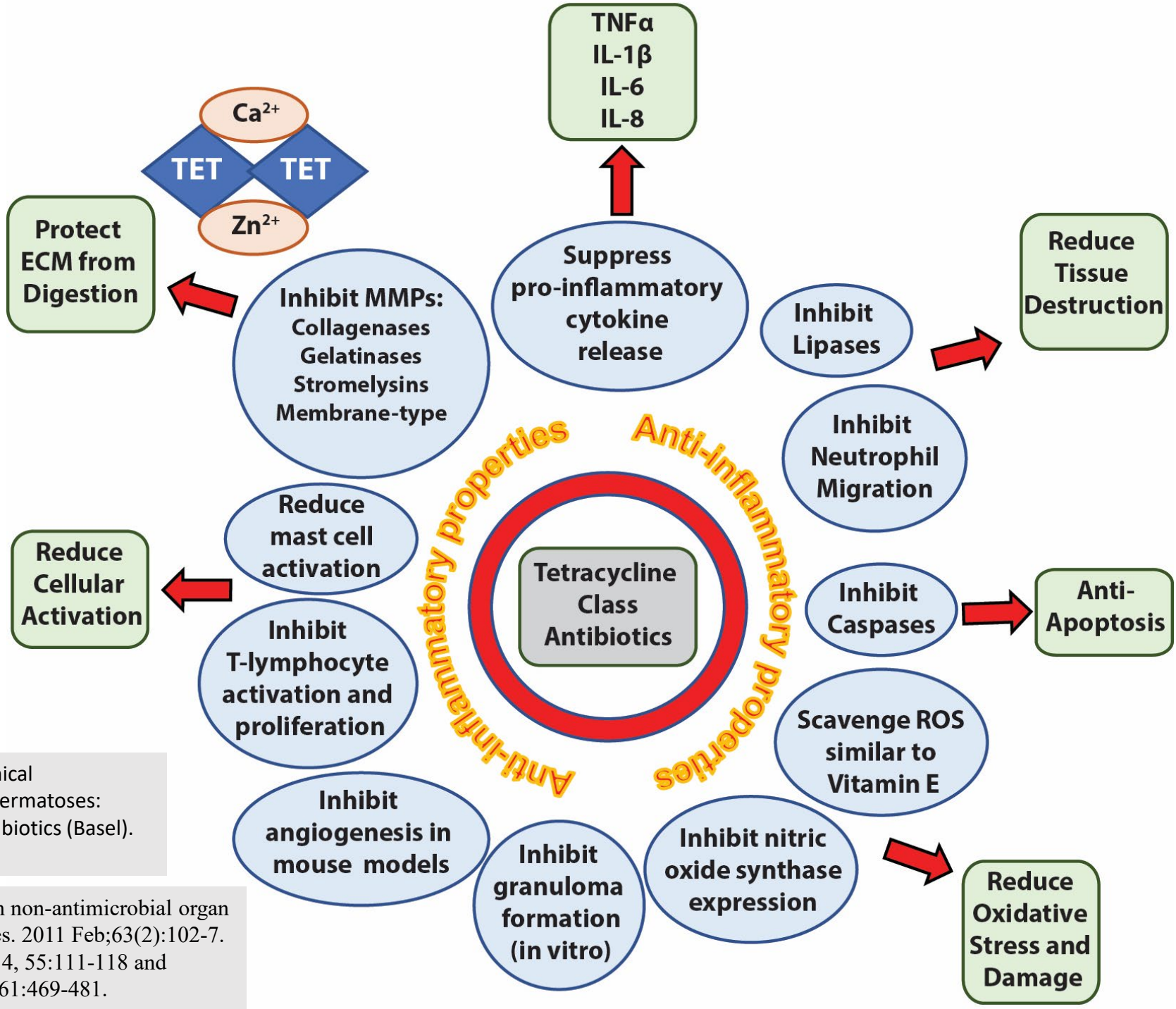
AAD Acne Guidelines, 2024

Oral Antibiotic Use 2014-2016

Tetracyclines	73.4%
Doxycycline	36.7%
Minocycline	36.5%
Tetracycline	0.2%
Penicillins	11.4%
Amoxicillin	
Cephalexin	
Macrolides	4.1%
Azithromycin	
Erythromycin	
Others	10.9%
Clindamycin	
Trimethoprim	
Trimethoprim-sulfamethoxazole	

Grada A, Armstrong A, **Bunick C**, Salem R, Feldman S. Trends in Oral Antibiotic Use for Acne Treatment: A Retrospective, Population-Based Study in the United States, 2014 to 2016. J Drugs Dermatol. 2023 Mar 1;22(3):265-270.

Anti-inflammatory properties of tetracycline-class antibiotics

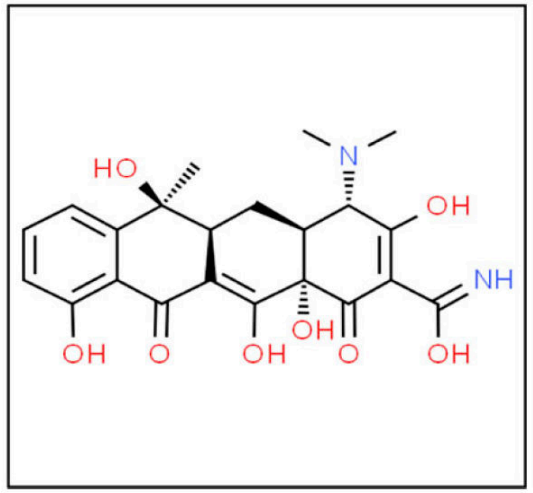
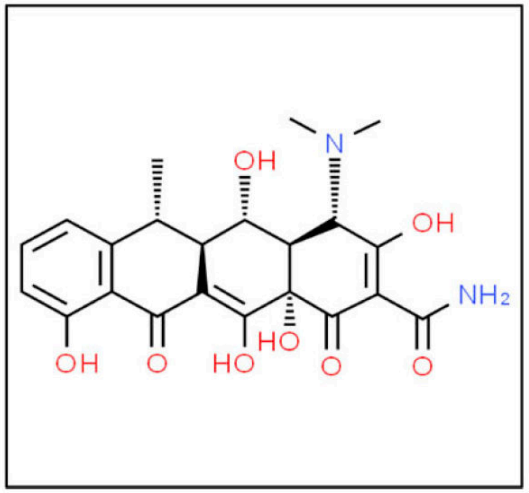
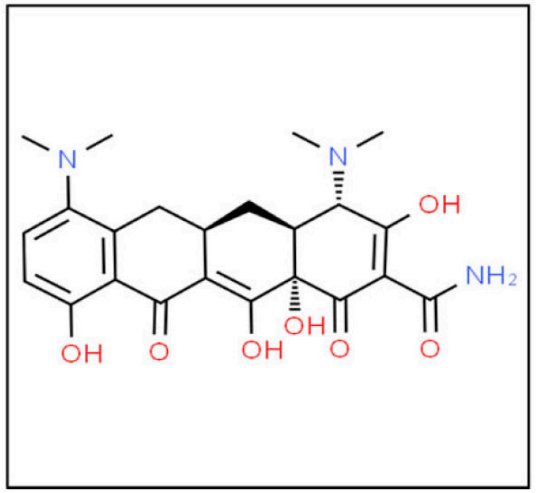
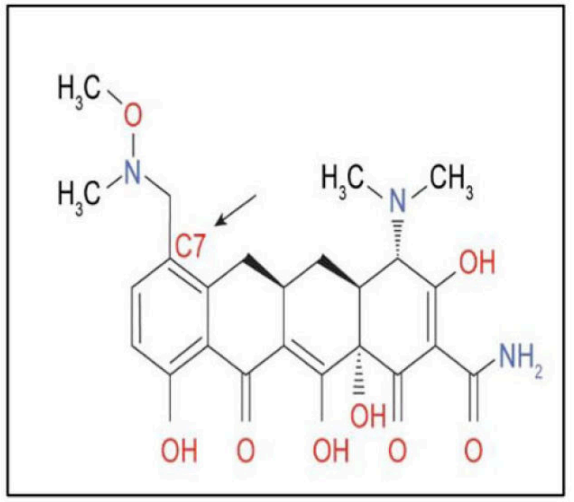


Grada A, Ghannoum MA, **Bunick CG**. Sarecycline Demonstrates Clinical Effectiveness against Staphylococcal Infections and Inflammatory Dermatoses: Evidence for Improving Antibiotic Stewardship in Dermatology. Antibiotics (Basel). 2022 May 27;11(6):722.

Griffin MO, Ceballos G, Villarreal FJ. Tetracycline compounds with non-antimicrobial organ protective properties: possible mechanisms of action. Pharmacol Res. 2011 Feb;63(2):102-7.
Adapted from: Perret LJ, Tait CP, *The Australasian J Dermatol* 2014, 55:111-118 and Pradhan S, Madke B, Kabra P, Singh AL, *Indian J Dermatol* 2016, 61:469-481.

2024 AAD Acne Guidelines: What about Antibiotic Stewardship?

Broad Spectrum → **Narrow Spectrum**

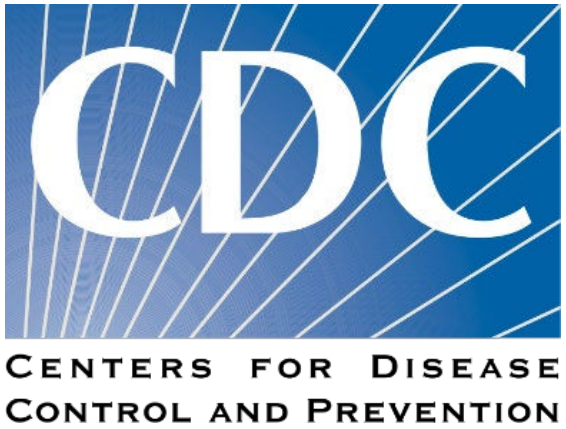
First Generation	Second Generation		Third Generation
Tetracycline	**Doxycycline**	**Minocycline**	**Sarecycline**
FDA-approved 1953	FDA-approved 1967	FDA-approved 1971	FDA-approved 2018
			

Longest and largest C7 moiety gives Sarecycline unique properties

FDA, United States Food and Drug Administration.

Graber E. Dermatol Rev. 2021;2:221-230.

Antibiotic Stewardship



"*and facilitate use of narrow-spectrum antibiotics whenever possible*" – CDC

Source: Antibiotic Stewardship Statement for Antibiotic Guidelines – Recommendations of theHICPAC

"Core principles of antibiotic stewardship include selecting narrow-spectrum agents when feasible, using antibiotics only when necessary, and prescribing antibiotics for the shortest effective duration,"

Source: https://www.cidrap.umn.edu/news-perspective/2020/04/stewardship-resistance-scan-apr-09-2020

Due to concerns regarding antimicrobial resistance, the Centers for Disease Control and Prevention (CDC) has **stressed antibiotic stewardship**. This is an initiative to promote the appropriate use of antibiotics where patients receive the **right dose** of the **right antibiotic** at the **right time** for the **right duration**

Source: Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, Bowe WP, Graber EM, Harper JC, Kang S, Keri JE. Guidelines of care for the management of acne vulgaris. Journal of the American Academy of Dermatology. 2016 May 1;74(5):945-73.

Antimicrobial Resistance in *C. acnes*

Percentages of antibiotic-resistant *C. acnes* isolated from acne patients

Country	Clindamycin	Erythromycin	Oxytetracycline	Doxycycline
United States (1983)	79	81	63	**57**

Dreno B, Thiboutot D, Gollnick H, Bettoli V, Kang S, Leyden JJ, Shalita A, Torres V. Antibiotic stewardship in dermatology: limiting antibiotic use in acne. European Journal of Dermatology. 2014 May 1;24(3):330-4.

Antibiotic	Concentration (µg)	Sensitive n(%)	Resistant n(%)
Doxycycline	30	63 (63)	37 (37)
Tetracycline	30	64 (64)	36 (36)
Erythromycin	15	27 (27)	73 (73)
Clindamycin	2	41 (41)	59 (59)
Trimethoprim/Sulfamethoxazole	12/5/23.75	69 (69)	31 (31)
Levofloxacin	5	85 (85)	15 (15)
Minocycline	30	97 (97)	3 (3)

Alkhawaja E, Hammadi S, Abdelmalek M, Mahasneh N, Alkhawaja B, Abdelmalek SM. Antibiotic resistant Cutibacterium acnes among acne patients in **Jordan**: a cross sectional study. BMC dermatology. 2020 Dec;20(1):1-9.

Antibiotic	Resistant n(%)
Doxycycline	19.4
Tetracycline	8.3
Erythromycin	25
Clindamycin	16.7
Minocycline	11.1

Sheffer-Levi S, Rimon A, Lerer V, Shlomov T, Coppenhagen-Glazer S, Rakov C, Zeiter T, Nir-Paz R, Hazan R, Molcho-Pessach V. Antibiotic Susceptibility of Cutibacterium acnes Strains Isolated from **Israeli** Acne Patients. Acta Dermato-venereologica. 2020 Oct 20;100(17):adv00295-.

Protecting the host microbiome

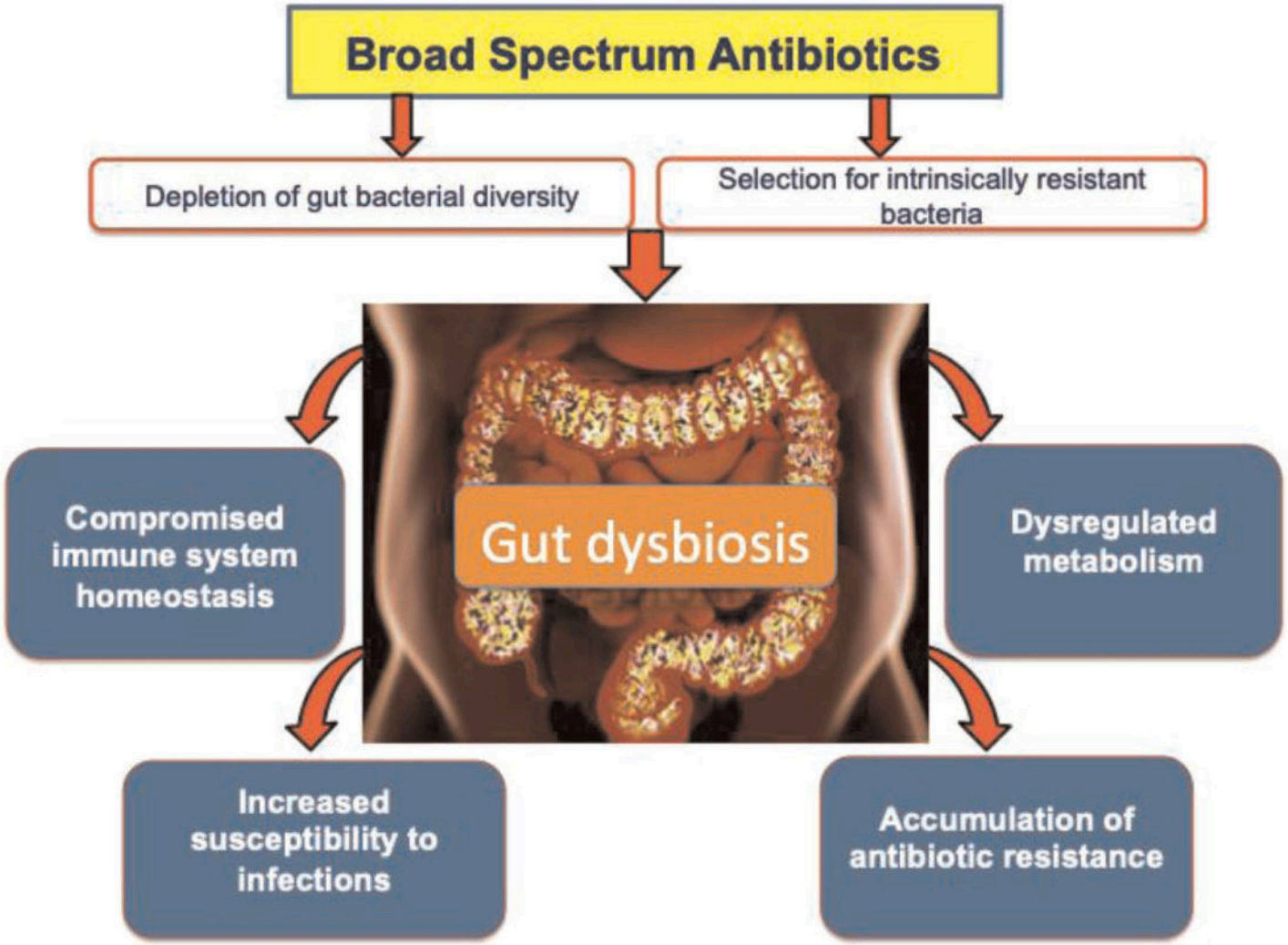
Narrow-spectrum Sarecycline protects the patient's gut microbiome

- Use of broad-spectrum antibiotics may cause depletion of gut bacterial diversity and selection for intrinsically resistant bacteria
- These changes are referred to as gut dysbiosis

Of the 100 trillion microbes that exist in our bodies, about **80% live in the gut**

The gut microbiome is essential in the development/regulation of:

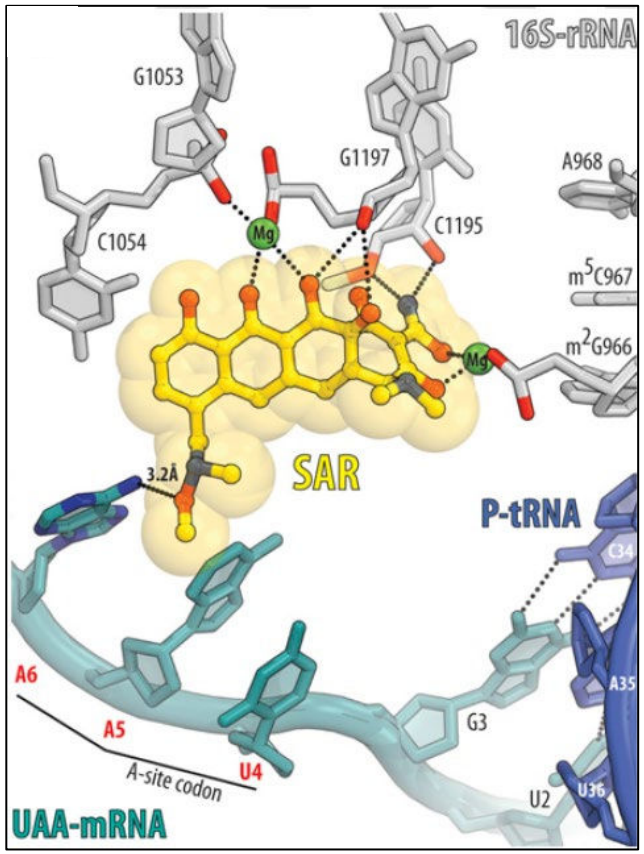
- ✓ **Immunity, Nutrition, Digestion, Hormone secretion, Inflammation**



Graber E. *Dermatol Rev*. 2021;2:221-230.

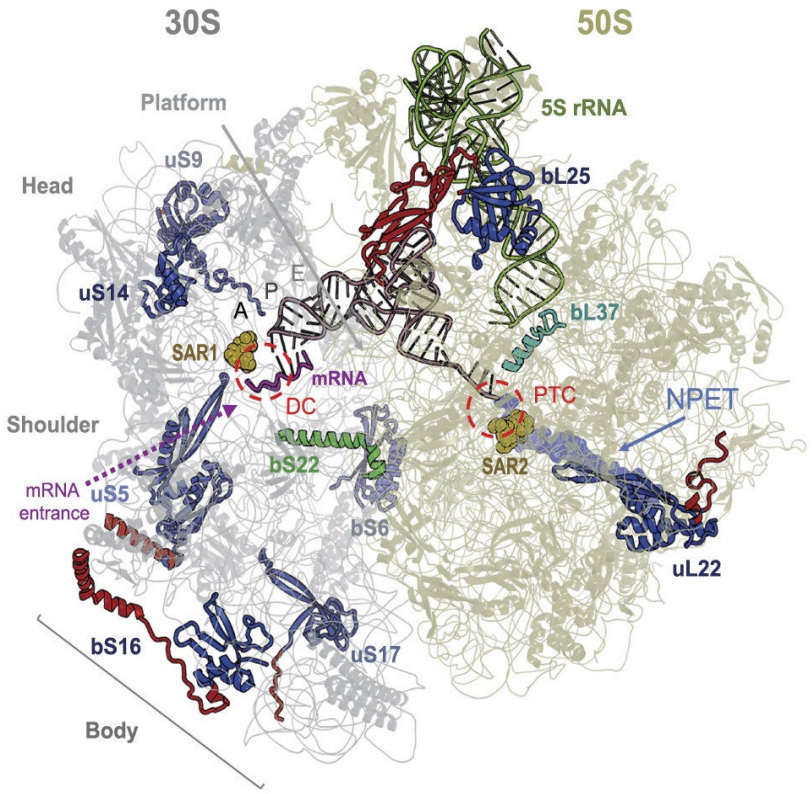
Narrow spectrum Sarecycline is molecularly distinct from Doxy and Mino

Sarecycline uniquely contacts mRNA in ribosome



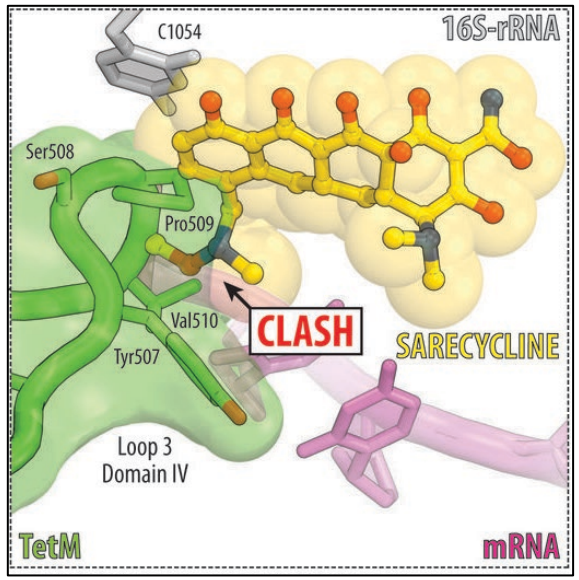
Batool Z, Lomakin IB, Polikanov YS**, Bunick CG**. **Sarecycline interferes with tRNA accommodation and tethers mRNA to the 70S ribosome**. Proceedings of the National Academy of Sciences. 2020 Aug 25;117(34):20530-7.

Sarecycline has novel 50S subunit exit tunnel binding site



Lomakin IB, Devarkar SC, Patel S, Grada A, **Bunick CG**. **Sarecycline inhibits protein translation in Cutibacterium acnes 70S ribosome using a two-site mechanism.** Nucleic Acids Res. 2023 Apr 11;51(6):2915-2930.

Sarecycline resists ribosomal protection proteins



P. acnes strains displayed a **low propensity for the development of resistance** to sarecycline, with spontaneous mutation frequencies being 10^{-10} at 4 – 8 × MIC

Doxycycline vs Minocycline vs Sarecycline

TABLE 3. Reduction in inflammatory lesions with various treatment times*

ENDPOINT	DOXYCYCLINE	MINOCYCLINE	SARECYCLINE	AZITHROMYCIN	TMP-SMX
3 weeks	NA	65%[59]	NA	55%[59]	NA
4 weeks	25–46% [17,21,60]	32%[36]	NA	23%[60]	NA
5 weeks	NA	NA	NA	NA	62%[+6]
6 weeks	NA	51%	NA	NA	NA
8 weeks	39%[60]	41%–69%[17,21,36]	NA	36%[60]	NA
10 weeks	NA	NA	NA	NA	48% [+56]
12 weeks	48%–75%[17,60]	27%–91%[13,17,36]	50%–52%[43,44]	55%[60]	NA
16 weeks	23% to 51%[17,44,60]	NA	NA	NA	NA
18 weeks	NA	22%[13,17]	NA	NA	NA
20 weeks	NA	52%[13,17]	NA	NA	NA
24 weeks	50%[17,21]	74%[13,17,21]	NA	NA	NA

NA: not available
+TMP-SMX study did not evaluate absolute number of inflammatory lesions but rather a grade based on number and severity of lesions[56]
*Doses may differ across studies

Baldwin H. Oral Antibiotic Treatment Options for Acne Vulgaris. J Clin Aesthet Dermatol. 2020 Sep;13(9):26-32. Epub 2020 Sep 1. PMID: 33133338; PMCID: PMC7577330.

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Evolving Treatment Paradigm for Oral Antibiotics in Acne Vulgaris

Past

Broad-spectrum antibiotics target many different types of organisms

Broad-spectrum antibiotic

- Atypicals
- Gram (+) bacilli
- Gram (+) cocci
- Gram (-) bacilli
- Gram (-) cocci

Present & Future

Narrow-spectrum antibiotics target fewer species

Narrow-spectrum antibiotic

- **Enhanced antibiotic stewardship**
- **Host microbiome protected**
- **Reduced antibiotic resistance**
- **Effective against moderate to severe inflammatory acne**

Zhanel et al. *Antimicrob Agents Chemother.* 2018;63:e01297-18.

Antibiotic Interactions With OCPs

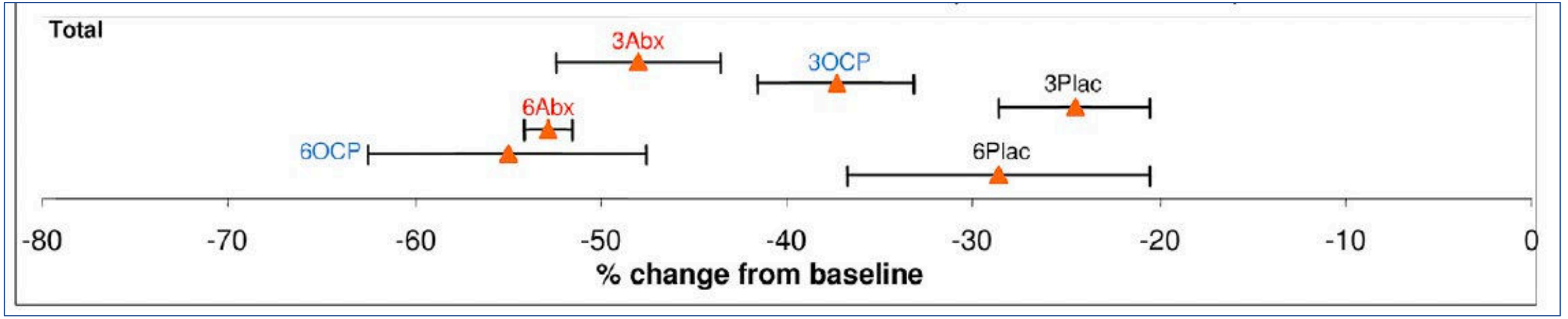
- Rifampin and griseofulvin are the only anti-infectives that interact with combined OCPs, lessening their effectiveness.

- The tetracycline class of antibiotics has not been shown to reduce the effectiveness of COCs when taken concomitantly.
  - OCP failure rate with perfect use = less than 1%
  - OCP failure rate with typical use = 7 – 9%

ACOG Committee on Practice Bulletins-Gynecology. ACOG practice bulletin. No. 73: Use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol. 2006;107:1453-1472.
Katsambas AD, Dessinioti C. Hormonal therapy for acne: why not as first line therapy? facts and controversies. Clin Dermatol. 2010;28:17-23.

Efficacy of Oral Antibiotics versus OCPs at 3 months and at 6 months

- After 6 months of use, combined OCPs are as effective as oral antibiotics in treating acne
- Oral antibiotics seem to have faster onset of efficacy



Koo, E. B., Petersen, T. D., & Kimball, A. B. (2014). Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris. *Journal of the American Academy of Dermatology*, *71*(3), 450-459.

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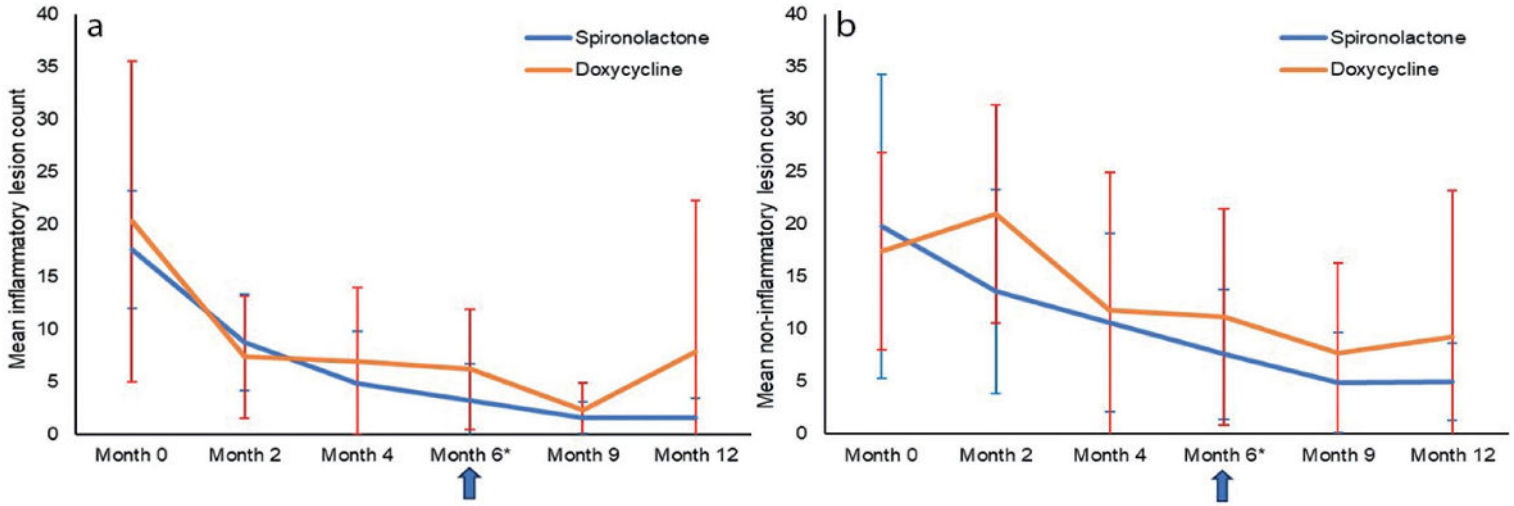
Head-to-head: Doxycycline vs Spironolactone



Treatment outcome was superior with spironolactone compared with doxycycline, with an OR of 1.37 (95% CI 0.60–3.12; p = 0.579) and an OR of 1.371 (95% CI of 1.37–5.99; p = 0.007) at month 4 and month 6, respectively, with spironolactone being 1.37-times and 2.87-times more successful compared with doxycycline at month 4 and month 6.

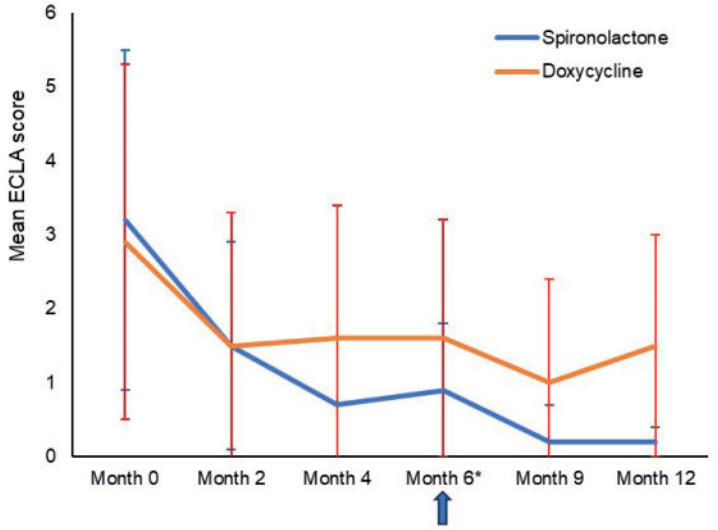


Fig. 5. Evolution of the Échelle de Cotation des Lésions d'Acné or. Acne Lesion Score Scale (ECLA) score over time. *Evaluation of treatment outcome (success or failure).

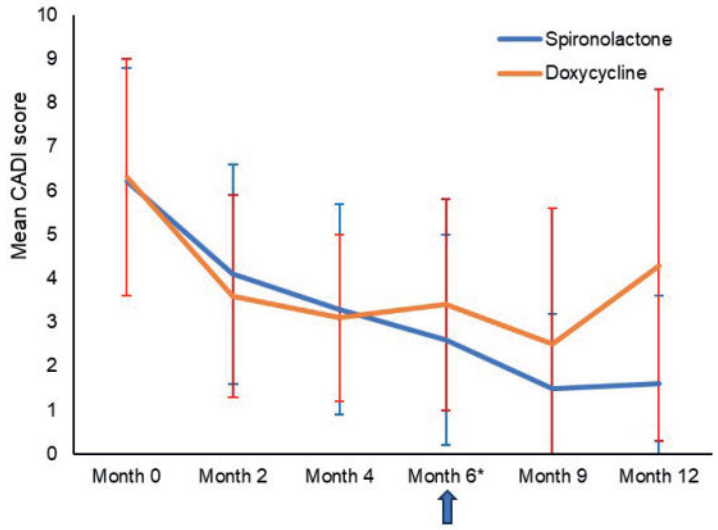
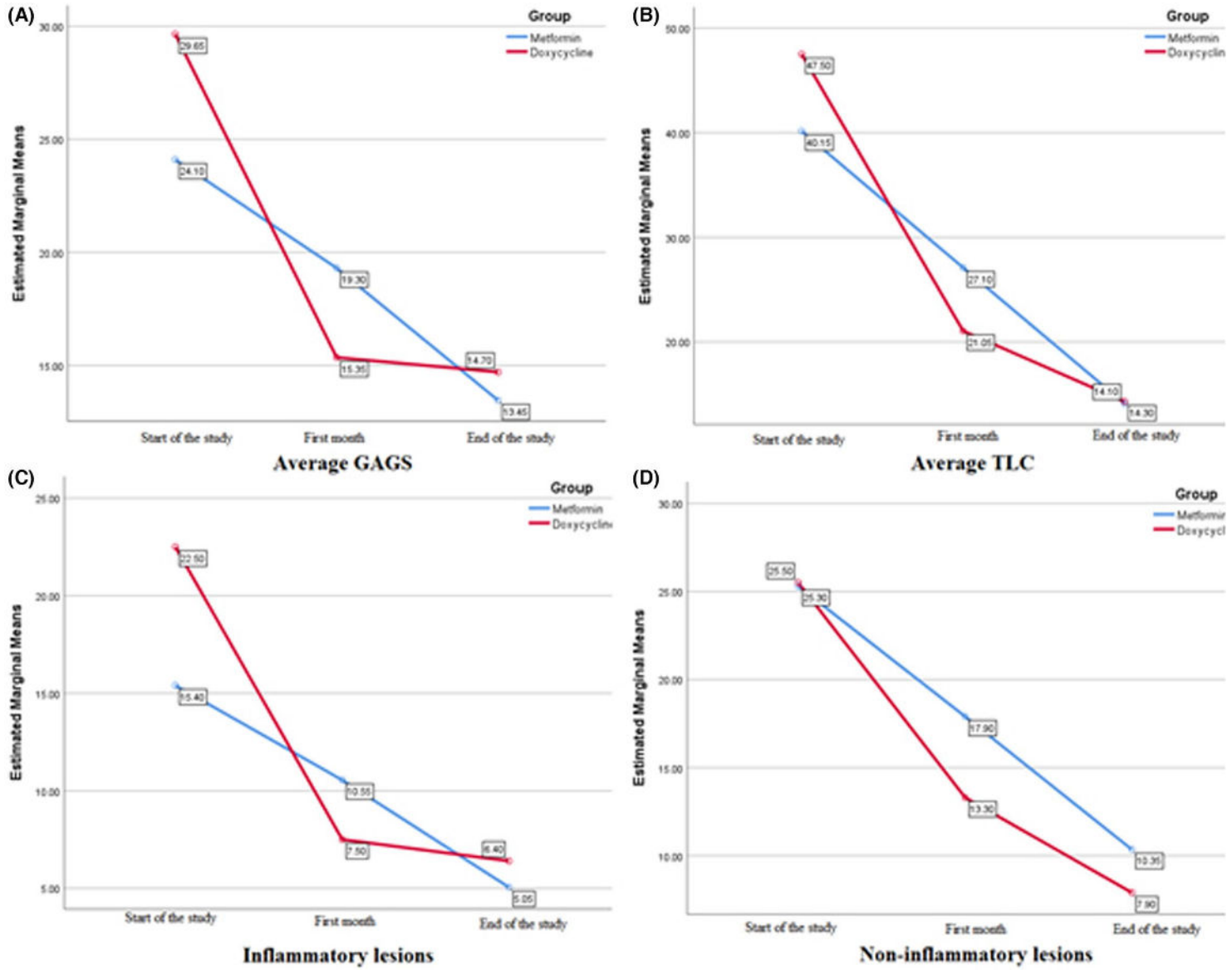


Fig. 7. Evolution of Cardiff Acne Disability Index (CADI) score over time. *Evaluation of treatment outcome (success or failure).

Dréno B, Nguyen JM, Hainaut E, Machet L, Leccia MT, Beneton N, Claudel JP, Célérier P, Le Moigne M, Le Naour S, Vrignaud F, Poinas A, Dert C, Boisrobert A, Flet L, Korner S, Khammari A. Efficacy of Spironolactone Compared with Doxycycline in Moderate Acne in Adult Females: Results of the Multicentre, Controlled, Randomized, Double-blind Prospective and Parallel Female Acne Spironolactone vs doxyCycline Efficacy (FASCE) Study. Acta Derm Venereol. 2024 Feb 21;104:adv26002. doi: 10.2340/actadv.v104.26002. PMID: 38380975; PMCID: PMC10910526.

Head-to-head: Doxycycline vs Metformin



Metformin

Doxycycline

Global Acne Grading System (GAGS) score,
Total Lesion Count (TLC) score

Sadati MS, Yazdanpanah N, Shahriarirad R, Javaheri R, Parvizi MM. Efficacy of metformin vs. doxycycline in treating acne vulgaris: An assessor-blinded, add-on, randomized, controlled clinical trial. J Cosmet Dermatol. 2023 Oct;22(10):2816-2823. doi: 10.1111/jocd.15785. Epub 2023 May 2. PMID: 37128834.

Updates on Oral Isotretinoin: Higher cumulative dose reduces acne relapse

Lai J, Barbieri JS. Acne Relapse and Isotretinoin Retrial in Patients With Acne. JAMA Dermatol. 2025 Jan 15. doi: 10.1001/jamadermatol.2024.5416. Epub ahead of print. PMID: 39813053.

Table 5. Characteristics of Patients With Acne, Stratified by Isotretinoin Daily and Cumulative Dosage

Characteristic	Isotretinoin treatment					
	Maximum daily, mg/kg/d			Cumulative dosage, mg/kg		
	Low (<0.5)	Conventional (0.5-1.0)	High (>1.0)	Low (<120)	Conventional (120-220)	High (>220)
Patients, No.	777	10 527	8603	8328	10 778	801
Age at isotretinoin initiation, mean (SD), y	27.3 (12.0)	21.1 (8.1)	19.4 (6.5)	21.6 (8.6)	20.0 (7.2)	18.8 (7.0)
Female, No. (%)	383 (49.3)	5649 (53.7)	4472 (52.0)	4262 (51.2)	5786 (53.7)	456 (56.9)
Male, No. (%)	394 (50.7)	4878 (46.3)	4131 (48.0)	4066 (48.8)	4992 (46.3)	345 (43.1)
Individuals with a dermatologist practitioner, No. (%)	653 (84.0)	9205 (87.4)	7453 (86.6)	7209 (86.6)	9401 (87.2)	701 (87.5)
Isotretinoin course duration, mean (SD), mo	6.0 (2.3)	5.6 (1.7)	5.5 (1.5)	4.9 (1.2)	5.9 (1.5)	8.3 (2.6)
Isotretinoin maximum daily dose, mean (SD), mg/kg/d	0.4 (0.09)	0.78 (0.14)	1.2 (0.18)	0.76 (0.22)	1.0 (0.21)	1.3 (0.33)
Isotretinoin cumulative dosage, mean (SD), mg/kg	65.4 (29.1)	115.1 (34.5)	159.6 (45.9)	91.7 (20.8)	154.3 (24.8)	259.4 (52.3)
Individuals with acne relapse, No. (%)	235 (30.2)	2382 (22.6)	1865 (21.7)	2175 (26.1)	2129 (19.8)	178 (22.2)
Time to acne relapse, mean (SD), mo	7.5 (7.1)	9.3 (7.8)	10.0 (8.1)	8.4 (7.8)	10.6 (7.9)	9.5 (7.8)
Individuals with isotretinoin retrial, No. (%)	126 (16.2)	898 (8.5)	615 (7.1)	1056 (12.7)	539 (5.0)	44 (5.5)
Time to second isotretinoin course, mean (SD), mo	4.1 (3.3)	5.2 (4.7)	5.4 (5.0)	4.5 (4.3)	6.4 (5.3)	6.7 (5.1)
Follow-up time, mean (SD), mo	24.7 (8.7)	24.7 (8.8)	25.2 (8.7)	25.4 (9.1)	24.7 (8.4)	23.6 (7.7)

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