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The Impact on Acne Treatment Regimens if Benzoyl Peroxide-Containing Products Are Removed From the Market

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ABSTRACT

Benzyl peroxide (BPO) has been an important component of many acne treatment regimens. However, an independent testing laboratory, Valisure, filed a Citizen's Petition with the US Food and Drug Administration (FDA) requesting the removal of BPO products from the market. Their testing demonstrated that when exposed to elevated temperatures which could occur during shipping, marketed BPO products can form over 800 times the FDA concentration limits of benzene, a class 1 carcinogen. In this review, we aim to describe what a post-BPO removal acne treatment regimen might look like based on currently approved products and products in late-stage development.

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INTRODUCTION

Acne is a chronic inflammatory disease of the pilosebaceous unit, affecting nearly 90% of individuals with onset occurring on or near puberty but potentially extending into adulthood.[1] The American Academy of Dermatology Guidelines (AAD Guidelines) recommends first-line treatments include topical therapies, as shown in Table 1. These therapies currently include benzoyl peroxide (BPO), topical retinoids, or topical antibiotics, or a combination of these agents. If topical treatments fail to produce improvement, oral treatments are often added to the regimen, as shown in Table 2.

BPO has been one of the most important topical therapies in treating acne.[2] It was the first topical therapy available over the counter and is an important, if not necessary, addition to topical and systemic antibiotic therapy to prevent multidrug resistance.[3]

However, in March 2024, an independent testing laboratory, Valisure Incorporated, filed a Citizen's Petition with the US Food and Drug Administration (FDA) to remove BPO from the market. Valisure, citing their testing, demonstrated in forced degradation studies that marketed BPO products can form over 800 times the FDA concentration limits of benzene including high levels at time zero in nearly half of the samples tested.[4]

FDA is currently reviewing the data from Valisure's Citizen Petition. If FDA determines that benzene is present as a degradant in BPO products, they may act by limiting (such as making BPO prescription only or requiring refrigerated storage) or removing any products containing BPO from the market.

After Valisure's findings, the American Acne and Rosacea Society recommended that physicians instruct patients to 1) discard expired BPO products and those exposed to temperatures above room temperature, 2) store new BPO products at refrigerated temperature, and 3) replace BPO products every 3 months.[5]

Current Treatments

Topical Retinoids

Topical retinoids are essentially analogues of Vitamin A that act by reducing hyperkeratinization and inflammation with once or twice-daily applications.[5] Retinoids are a mainstay in the treatment of moderate-to-severe comedonal acne and are often used in combination with other topical agents. Local tolerability reactions may occur during the early course of treatment, with over 40% of patients having reported local tolerability reactions in clinical studies.[6]

TABLE 1.

Treatment Response and Lesion Change for Approved Topical Acne Products			
Drug	**Inflammatory Lesion Change at Week 12**	**Non-Inflammatory Lesion Change at Week 12**	**Treatment Response at Week 12**
Benzoyl Peroxide Gel 2.5%[14]	47.5%	37.4%	21%
Retinoids			
Adapalene Gel 0.1%[6]	49.7%	35.2%	16%
Adapalene Gel 0.3%[6]	51.6%	39.7%	21%
Tazarotene Cream 0.1%[15]	43.5%	42.5%	19%
Tazarotene Foam 0.1%[16]	56.5%	56.0%	29%
Tretinoin Lotion 0.05%[17]	52.2%	46.5%	18%
Trifarotene Cream 0.005%[18]	60.3%	53.7%	36%
Antibiotics			
Clindamycin Gel 1.2%[14]	46.5%	43.3%	22%
Minocycline Foam 4%[19]	47.0%	ND	18%
Dapsone Gel 5%[20]	47.5%	30.5%	38%
Dapsone Gel 7.5%20	55.0%	45.5%	30%
Androgen Inhibitors			
Clascoterone Cream 1%[7]	45.9%	31.1%	20%
Combination Therapy			
Clindamycin Phosphate and benzoyl peroxide gel 1.2%/2.5%[14]	54.6%	43.3%	29%
Adapalene and benzoyl peroxide gel 0.1%/2.5%[21]	69.3%	68.0%	27%
Adapalene and benzoyl peroxide gel 0.3%/2.5%[21]	68.7%	68.3%	34%
Clindamycin Phosphate and tretinoin gel 1.2%/0.025%[22]	54.5%	43.0%	31%
Benzoyl Peroxide, Adapalene and Clindamycin Phosphate gel 3.1%/0.15%/1.2%[23]	75.5%	73.0%	50%

TABLE 2.

Treatment Response and Lesion Change for Approved Oral Acne Products			
Drug	**Inflammatory Lesion Change at Week 12**	**Non-Inflammatory Lesion Change at Week 12**	**Treatment Response at Week 12**
Antibiotics			
Minocycline (extended release)[24]	44.5%	ND	16%
Doxycycline 2.4 mg/Kg/day[25]	49.0%	12.4	30%
Sarecycline[26]	51.5%	ND	22%
Hormonal Treatments			
Drospirenone/Ethinyl Estradiol[8]	49.5%	40.5%	18%
Spironolactone[3]	ND	ND	19%
Retinoids			
Isotretinoin[9]	91%**		87%**

*- Not statistically different from placebo
**- 20 weeks post treatment initiation

Topical Antibiotics

Topical antibiotics are approved as single agents but recommended to be prescribed in combination with other acne products. Antibiotics reduce colony-forming units (CFUs) of *Cutibacterium acnes* (*C. Acnes*) and also have anti-inflammatory properties. These agents require daily dosing and have shown modest efficacy in clinical trials (Table 1). Current acne guidelines recommend antibiotics be used in conjunction with another agent, mainly BPO, to prevent multidrug-resistant bacteria.[5]

Clascoterone

Clascoterone, a topical androgen receptor inhibitor, was approved in the US in 2020 for the twice-daily treatment of acne. While clascoterone has only shown a modest treatment effect (Table 1), the mechanism of action (MOA) is unique, and it may be co-administered with other topical agents to enhance the effect.[7]

Spironolactone

Spironolactone, an aldosterone receptor antagonist, is approved for the treatment of hypertension. However, it has been prescribed off-label to women for the treatment of acne and is recommended by the American Academy of Dermatology (AAD) guidelines for acne.[3] The effect seen in acne is due to the drug's ability to decrease testosterone production and inhibit testosterone binding to androgen receptors in the dermis, thereby decreasing sebaceous gland activity.

Oral Birth Control Pills

Oral contraceptives are commonly prescribed to women for the treatment of acne, often off-label, with four oral contraceptives being FDA-approved for the treatment of acne vulgaris. These drugs work through their antiandrogenic properties and have good treatment response with other positive effects.[8]

Systemic Antibiotics

Systemic antibiotics are approved as single agents, but similar to topical antibiotics, the AAD guidelines state that these drugs should not be used as a single agent to prevent the development of drug-resistant microbes.[3]

Oral Isotretinoin

Oral isotretinoin is the only approved oral retinoid and is the most effective acne treatment (Table 2). However, it is usually reserved for patients who have nodulocystic acne and failed prior topical and systemic therapy.[9] Patients who are prescribed oral isotretinoin must enroll in the iPLEDGE program, which requires their agreement to use contraception due to the teratogenic effects of isotretinoin and get regular measurements of liver enzymes.

Treatments in Development

DMT310

DMT310 is currently in Phase 3 studies and consists of a powdered mixture of *Spongilla lacustris* that is mixed with

TABLE 3.

Treatment Success for Topical Products Without BPO (sorted by least to most effective)

Drug	Inflammatory Lesion Change at Week 12	Non-Inflammatory Lesion Change at Week 12	Treatment Response at Week 12
Adapalene Gel 0.1%[6]	49.7%	35.2%	16%
Minocycline Foam 4%[19]	47.0%	ND	18%
Tretinoin Lotion 0.05%[17]	52.2%	46.5%	18%
Tazarotene Cream 0.1%[15]	43.5%	42.5%	19%
Clascoterone Cream 1%[7]	45.9%	31.1%	20%
Adapalene Gel 0.3%[6]	51.6%	39.7%	21%
Clindamycin Gel 1.2%[14]	46.5%	43.3%	22%
Tazarotene Foam 0.1%[16]	56.5%	56.0%	29%
Dapsone Gel 7.5%[20]	55.0%	45.5%	30%
Clindamycin Phosphate and tretinoin gel 1.2%/0.025%2[2]	54.5%	43.0%	31%
Trifarotene Cream 0.005%[18]	60.3%	53.7%	36%
Dapsone Gel 5%[20]	47.5%	30.5%	38%
GT20029*	ND	ND	ND
DMT310** [10]	62%	58%	44%

* –There are no completed studies with GT20029 in acne vulgaris patients
** – DMT310 data are from Phase 2B study. Phase 3 is ongoing.
ND – Not Done

3% hydrogen peroxide and applied as a once-weekly face scrub. It has shown both anti-inflammatory and antimicrobial properties and has been tested in Phase 2 studies.[10] The results of the DMT310 Phase 2B study yielded an Investigator's Global Assessment (IGA) treatment success rate greater than all other single-agent topical treatments (Table 3). Local tolerability side effects appear to be infrequent, and the treatment effects were seen as early as week 4. The once-weekly regimen, combined with the rapid onset of action and acceptable side effect profile, may lead to improved patient compliance compared with other topical therapies.

Cutibacterium Acnes Vaccine

A vaccine is currently being tested in Phase 1 trials that target Christie-Atkins-Munch-Petersen factor of *C. acnes*, which is up-regulated in anaerobic cultures.[11] Vaccine development may prove to be a useful strategy for preventing the development of lesions.

Denifanstat

Denifanstat (ASC40) is an oral, fatty acid synthase (FASN) inhibitor used to treat cancer and steatohepatitis. It is currently in Phase 3 trials in China.[12] Though this molecule has been extensively tested in oncology and liver disease, there have been no studies completed in acne patients.

Antiandrogens

GT20029 is a novel topical antiandrogen that is a proteolysis-targeting chimera compound. Phase 1 studies for this product have been completed and Phase 2 trials are being conducted in China.[13]

DISCUSSION

Topical BPO has been a cornerstone of acne treatments as it is fast acting, well tolerated, and can be combined with other products. If further testing confirms high levels of benzene in topical BPO products, then the FDA may enact restrictions to the labeling and storage of BPO or could remove BPO from the market. The effect of BPO removal would greatly reduce the options and effectiveness of the currently approved acne drug armamentarium (see Table 3).

However, treatments in development may fill the gap created by BPO removal with new and unique MOAs. DMT310, being the furthest along in development with the most clinical data, may be a viable treatment option if the Phase 3 studies replicate the Phase 2 treatment effects.

DISCLOSURES

Dr Dhawan is a study investigator for Dermata Therapeutics. Dr Nardo is an employee of Dermata Therapeutics. All authors met the ICMJE authorship criteria. Neither honoraria nor other form of payments were made for authorship.

REFERENCES

1. Heng AHS, Chew FT. Systematic review of the epidemiology of acne vulgaris. *Sci Rep*. 2020;10(1):5754. doi: 10.1038/s41598-020-62715-3.
2. FDA (US Food and Drug Administration).2011. Guidance for Industry. Topical acne drug products for over-the-counter human use—revision of labeling and classification of benzoyl peroxide as safe and effective. Small Entity Compliance Guide. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/topical-acne-drug-products-over-counter-human-use-revision-labeling-and-classification-benzoyl Accessed July 22, 2024.
3. Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2024 May;90(5):1006.e1-1006.e30. doi: 10.1016/j.jaad.2023.12.017.
4. Valisure Citizen Petition on Benzene in Benzoyl Peroxide Products (March 5, 2024), https://www.valisure.com/valisure-newsroom/valisure-detects-benzene-in-benzoyl-peroxide. Accessed March 10, 2024
5. Response Statement from the American Acne & Rosacea Society to the Valisure Citizen Petition on Benzene in Benzoyl Peroxide Drug Products (March 20, 2024), https://acneandrosacea.org/uncategorized/american-acne-rosacea-society-aars-responds-to-citizen-petition-submitted-by-valisure-regarding-benzene-in-benzoyl-peroxide-drug-products/. Accessed August 25, 2024
6. Differin [Package Insert] Fort Worth, TX: Galderma Laboratories, LP; 2022
7. Winlevi [Package Insert] Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2022
8. Yaz [Package Insert] Wayne, NJ: Bayer Health Care.; 2011
9. Absorica [Package Insert] Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2019
10. Eichenfield LF, DuBois JC, Gold MH, et al. DMT310, a novel once-weekly topical treatment for patients with moderate-to-severe acne vulgaris: results of a phase 2b randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol*. 2023 Nov;89(5):945-951. doi: 10.1016/j.jaad.2023.05.070.
11. Wang Y, Hata TR, Tong YL, et al. The anti-inflammatory activities of propionibacterium acnes camp factor-targeted acne vaccines. *J Invest Dermatol*. 2018;138(11):2355-2364. doi: 10.1016/j.jid.2018.05.032.
12. Ascletis Pharmaceuticals inc. A study to evaluate the safety and efficacy of asc40 (denifanstat) tablets in the treatment of patients with moderate to severe acne vulgaris. ClinicalTirals.gov Identifier: NCT06192264. 2024 February https://clinicaltrials.gov/study/NCT06192264
13. Suzhou Kintor Pharmaceutical Inc. Study in subjects to evaluate the safety, tolerability and pharmacokinetics of GT20029. ClinicalTrials.gov Identifier: NCT05428449. https://clinicaltrials.gov/study/NCT05428449
14. Acanya [Package Insert] Bridgewater, NJ: Valeant Pharmaceuticals, 2010
15. Tazorac [Package Insert] Irvine, CA: Allergan Inc.; 2013
16. Fabior [Package Insert] Research Triangle Park, NC: Steifel; 2012
17. Altreno [Package Insert] Bridgewater, NJ: Valeant Pharmaceuticals, 2018
18. Aklief [Package Insert] Fort Worth, TX: Galderma Laboratories, LP; 2019
19. Amzeeq [Package Insert] Scottsdale, AZ: Journey Medical Corp.; 2022
20. Aczone [Package Insert] Irvine, CA: Allergan Inc.; 2016
21. Epiduo [Package Insert] Fort Worth, TX: Galderma Laboratories, LP; 2015
22. Ziana [Package Insert] Scottsdale, AZ: Medicis; 2006
23. Cabtreo [Package Insert] Bridgewater, NJ: Bausch Health US, 2023
24. Torok HM. Extended-release formulation of minocycline in the treatment of moderate-to-severe acne vulgaris in patients over the age of 12 years. *J Clin Aesthet Dermatol*. 2013;6(7):19-22.
25. Leyden JJ, Bruce S, Lee CS, et al. A randomized, phase 2, dose-ranging study in the treatment of moderate to severe inflammatory facial acne vulgaris with doxycycline calcium. *J Drugs Dermatol*. 2013;12(6):658-63.
26. Seysara [Package Insert] Exton, PA: Almirall LLC; 2020

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