

Examining Over-the-Counter Acne Treatments

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In 2001, consumers spent approximately \$100 million on over-the-counter (OTC) products for the treatment of acne.¹ This rapidly expanding market is changing the practice of dermatology. Patients that present for acne treatments have more severe diseases and have already tried a variety of mass-market products and treatment regimens purchased at cosmetic counters or through infomercials. Therefore, it is worthwhile to obtain a better understanding of the ingredients used in OTC acne treatments.

Some OTC antiacne products are cosmetics. These products do not have an active ingredient listed on the packaging. When acne products list an active ingredient, the US Food and Drug Administration classifies these products as OTC drugs. Only certain ingredients can be used in acne products, which are listed in the final monograph for topical antimicrobial drug products for OTC human use.² These ingredients aim to reduce the number of acne blemishes, pimples, blackheads, and whiteheads. Ingredients approved for this use on the monograph include salicylic acid, sulfur, sulfur combined with resorcinol, and benzoyl peroxide.² These ingredients can only be used singly and not in combination. Other botanical extracts that are not on the monograph are also used, such as hydroxy acids, retinol, triclosan, and tea tree oil. The utility of these ingredients in the treatment of acne is discussed.

Benzoyl Peroxide

The most effective and commonly used active ingredient in OTC acne preparations is benzoyl peroxide. Twenty-three percent of persons aged 13 to 27 years have used an OTC benzoyl peroxide product.³ It is a member of the organic peroxide family consisting of 2 benzoyl groups joined by a peroxide group. Benzoyl peroxide is prepared

by reacting sodium peroxide with benzoyl chloride to yield benzoyl peroxide and sodium chloride. It is a radical initiator, possible tumor promoter, and mutagen. It is also highly flammable and explosive.

Benzoyl peroxide was not originally developed for medical purposes. It first appeared in 1917 as an ingredient to bleach flour white. It was first used medically to treat leg ulcers in the 1960s and then to treat acne in the 1970s. Other applications include its use as a tooth whitening solution and an active agent in hair dyes.

Benzoyl peroxide has many properties pertinent to acne, including antibacterial, anti-inflammatory, and comedolytic effects.⁴ When benzoyl peroxide touches the skin, it breaks down into benzoic acid and oxygen, neither of which is problematic. It has antimicrobial properties against *Propionibacterium acnes*, as demonstrated by a 2- \log_{10} decrease in *P. acnes* concentration after 2 days of topical applications of benzoyl peroxide 5%.⁵ This same antimicrobial effect was also observed with benzoyl peroxide 10%, resulting in a mean 2- \log_{10} decrease in organisms after applying benzoyl peroxide 10% cream for 3 days. However, after 7 days no further decline in *P. acnes* level was observed.⁶

These are interesting studies because they point to several facts about topical benzoyl peroxide. The first finding is that benzoyl peroxide 5% and 10% may be equally efficacious.⁴ This means that the increased skin irritation experienced with the higher concentration may not be necessary to improve acne resolution. Furthermore, initial improvement in acne may be seen with topical benzoyl peroxide as *P. acnes* are destroyed. Eventually, no further decline in organisms is possible. The patient may notice a decrease in acne lesions for a short period, but other factors will not improve. This accounts for the common patient-perceived phenomenon where the product worked well initially, but eventually resistance occurred and no further improvement was noted. This is why many consumers change from one OTC acne product to the next as each successive treatment loses potency. However, there is no loss in potency. It is simply that the benzoyl peroxide has done what is possible and further improvement requires the addition of another ingredient from either the OTC or prescription realm.⁷

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The author reports no conflict of interest in relation to this article.

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Benzoyl peroxide is an important antimicrobial, with more *P acnes* destroyed than any other topical antibiotic (eg, erythromycin or clindamycin) alone. However, unlike topical antibiotics, benzoyl peroxide does not result in resistant organisms.⁸ This is the rationale for the currently popular combination of benzoyl peroxide and clindamycin in cream or gel prescription formulations.⁹ Even a benzoyl peroxide cleanser can suppress the development of resistant organisms.¹⁰ Thus, benzoyl peroxide is ubiquitously found in many acne treatment regimens.

Benzoyl peroxide also acts as an anti-inflammatory agent by reducing oxygen radicals. Furthermore, its ability to reduce the *P acnes* population also reduces inflammation due to lessened bacterial-induced monocytes producing tumor necrosis factor- α , interleukin-8, and interleukin-1 β .¹¹ This anti-inflammatory effect is perceived by the patient as reduced redness and pain.

Finally, benzoyl peroxide is also a comedolytic, capable of producing a 10% reduction in comedones.⁵ Comedolytics allow the plug in the pore to loosen from the surrounding follicle, which restores the normal flow of sebum to the skin's surface. It was originally thought that higher concentrations of benzoyl peroxide preparations provided superior comedolytic benefits. However, it now appears that even benzoyl peroxide 2.5% is effective. Higher concentrations of benzoyl peroxide may only increase skin irritation, resulting in peeling and redness.¹² In addition, benzoyl peroxide is a cause of allergic contact dermatitis in 1% to 2.5% of consumers, resulting in redness, swelling, oozing, and pain.¹³ Benzoyl peroxide can also bleach clothing and hair.

One of the major unresolved concerns regarding benzoyl peroxide is its safety. Benzoyl peroxide is a highly reactive molecule capable of causing explosions in concentrations of 20% or higher. The manufacturing of benzoyl peroxide products requires a special facility, and stability problems are common in new formulations. Benzoyl peroxide is capable of producing DNA strand breaks, but rodent carcinogenicity studies have been negative.³ No correlation has been shown between benzoyl peroxide use and skin cancer in humans.

Current trends in benzoyl peroxide formulation have focused on the use of less irritating hydrogel formulations and benzoyl peroxide with smaller particles.¹⁴ Raw benzoyl peroxide is a particulate that must be solubilized into solution. Only benzoyl peroxide that touches the skin surface is active in killing *P acnes*. Larger particles yield higher concentrations in the formulation, but most of the benzoyl peroxide does not touch the skin. Smaller particle size allows better skin coverage with less irritation because the concentration is reduced. It is possible

to create a benzoyl peroxide 2.5% formulation with equal efficacy to a benzoyl peroxide 10% formulation based on skin contact with the active ingredient. Careful, creative formulation can minimize tolerability issues with OTC benzoyl peroxide formulations.

Salicylic Acid

The other major comedolytic used as an active ingredient in OTC acne treatments is salicylic acid in concentrations up to 2%.¹⁵ Salicylic acid is a colorless, crystalline, oil-soluble, phenolic compound originally derived from the willow tree *Salix*. It is a β -hydroxy acid where the hydroxyl group is adjacent to the carboxyl group. Synthesis of the compound involves the treating of sodium phenolate, the sodium salt of phenol, with carbon dioxide at 100 atm pressure and 116.85°C temperature followed by acidification with sulfuric acid.

Salicylic acid, also known as 2-hydroxybenzoic acid, has a rich history in medicine. It is used as an anti-inflammatory, inhibiting arachidonic acid because it is chemically related to aspirin, a flavoring agent with the characteristic wintergreen taste, a liniment for sore muscles, and an acne treatment. In the 5th century BC, Hippocrates wrote about a bitter powder extracted from the willow bark that would ease pain and reduce fever. The active extract of the willow bark, called salicin, was isolated in crystalline form by Henri Leroux, a French pharmacist, in 1828.

Salicylic acid can penetrate into the follicle and dislodge the comedonal plug from the follicular lining. However, it does not kill *P acnes* and does not prevent the development of antibiotic resistance. Salicylic acid may be less effective than benzoyl peroxide as an acne treatment, but it is also less irritating and less allergenic. Some proprietary salicylic acid preparations have shown parity to benzoyl peroxide 5%.¹⁶ Salicylic acid is sometimes used in hypoallergenic acne treatments and acne treatments for mature individuals.

Salicylic acid can be applied to the skin in a variety of different formulations.¹⁷ It can be applied as a solution in an alcohol-detergent vehicle or in the form of an impregnated pad.^{18,19} It can be formulated as a salicylic acid 2% scrub with clinical data demonstrating a reduction in open comedones.²⁰ Salicylic acid 10% and 20% peels are also used to promote comedolysis.

Some individuals experience allergic reactions when salicylic acid is ingested. However, it is generally accepted as a safe ingredient. An overdose of salicylic acid can lead to salicylate intoxication, presenting as a state of metabolic acidosis with a compensatory respiratory alkalosis. This has not been reported with topical applications and

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salicylic acid acne preparations are considered safe and effective, even during pregnancy.

Sulfur

The oldest treatment for acne, predating benzoyl peroxide and salicylic acid, is sulfur. Sulfur is a known bacteriostatic and antifungal ingredient.²¹ It is a yellow, nonmetallic element that has been used for centuries to treat various dermatologic conditions. A Roman physician first described the use of a sulfur mineral bath for the treatment of acne in an early medical text named *De Medicina*. The mechanism of action for sulfur is not completely understood, but it is thought to interact with cysteine in the stratum corneum, causing a reduction in sulfur to hydrogen sulfide. In turn, hydrogen sulfide degrades keratin, which produces the keratolytic effect of sulfur.²² Sulfur has been labeled as a comedogen, but this is controversial.²³

Sulfur is available in concentrations of 3% to 8% in OTC acne formulations. It has a characteristic foul odor and unusual yellow color. It stains clothing and is typically formulated as a thick paste. This limits its utility. However, it is commonly used in prescription formulations in combination with sodium sulfacetamide, a topical sulfur antibiotic.

Other Nonmonographed Acne Treatments

In addition to the monographed acne treatment ingredients of salicylic acid, sulfur, and benzoyl peroxide, other substances have been used to improve the appearance of acne-afflicted skin. These substances include hydroxy acids, retinol, triclosan, and tea tree oil.

Hydroxy Acids

Hydroxy acids, such as glycolic acid, have also been used in acne treatments as desquamating agents. Glycolic acid is the smallest α -hydroxy acid, appearing as a colorless, odorless, hygroscopic, crystalline solid. While glycolic acid can be obtained from the fermentation of sugar cane, it is more commonly synthesized by reacting chloroacetic acid with sodium hydroxide, followed by reacidification.

The efficacy of glycolic acid in treating acne is related to the free acid concentration.²⁴ The free acid is able to dissolve the ionic bonds between the corneocytes, forming the stratum corneum. This desquamation can remove the comedonal plugs. However, the water-soluble glycolic acid cannot enter the oily milieu of the pore. For this reason, salicylic acid is a much better comedolytic.

Glycolic acid can be delivered to the skin in the form of a cleanser, moisturizer, or peel. Cleansers that rinse off

the skin and contain glycolic acid are less effective in acne therapy than leave-on moisturizers. Higher concentrations of glycolic acid, from 20% to 70%, can be delivered to the skin in the form of a peel that is left on for 3 to 5 minutes followed by rinsing. The peels also can be used to improve dark scarring associated with acne, known as postinflammatory hyperpigmentation.²⁵

Triclosan

Topical antimicrobials also may be used in the treatment of acne. One common antimicrobial used in deodorant soaps and waterless hand sanitizers is triclosan. Triclosan is not on the US monograph for OTC acne drugs, but is used for the treatment of acne in other countries, such as England. Triclosan decreases *P acnes* counts on the skin's surface, which accounts for dermatologists' recommendation that patients with acne use deodorant soap as part of an acne treatment regimen. Other delivery methods for triclosan, including hydrogel patch delivery, have been published.²⁶

Retinols

Vitamin A derivatives, known as retinoids, are used in the treatment of acne, both in the prescription and OTC realm. The 3 prescription acne treatment retinoids include adapalene, tretinoin, and tazarotene. Unfortunately, prescription retinoids have the unwanted side effect of dryness, peeling, and irritation of the skin.

A variety of OTC retinoids exist that may be helpful to combat acne. These retinoids include retinol and retinaldehyde. Retinol can be absorbed by keratinocytes and reversibly oxidized into retinaldehyde. Retinaldehyde is irreversibly converted into all-*trans*-retinoic acid, known as tretinoin, a potent prescription retinoid. Tretinoin is transported into the keratinocyte nucleus modulating cellular behavior and normalizing follicular keratinization.

There are no large, multicenter trials that evaluate the efficacy of OTC retinoids. In general, retinols are 20 times less potent than topical tretinoin, but exhibit greater penetration than tretinoin.²⁷ Topical retinol 0.25% induces cellular and molecular changes similar to those observed with tretinoin 0.025%, without causing the irritation typical of tretinoin.

Tea Tree Oil

Tea tree oil is the most common herbal essential oil used for acne treatment. Tea tree oil, obtained from the Australian tree *Melaleuca alternifolia*, contains several antimicrobial substances including terpinen-4-ol, α -terpineol and α -pinene.²⁸ It appears as a pale,

golden oil with a fresh, camphoraceous odor. It is used for medicinal purposes as an antiseptic, antifungal, and antibacterial.²⁹

The antibacterial activity of tea tree oil 10% has been shown against *Staphylococcus aureus*, including methicillin resistant *S aureus*, without resistance.³⁰ However, lower concentrations have demonstrated bacterial resistance. Tea tree oil has been found to be as effective in the treatment of acne as benzoyl peroxide 5% based on a reduction in comedones and inflammatory acne lesions. Though, in comparison, the onset of action was slower for tea tree oil.³¹ The tea tree oil group did experience fewer side effects than the benzoyl peroxide group. Another randomized, 60-subject, placebo-controlled study in participants with mild to moderate acne found topical tea tree oil 5% produced a statistically significant reduction in total lesion count and acne severity index as compared to placebo.³² Tea tree oil may also reduce the amount of inflammation present around acne lesions, thereby reducing redness.³³

Tea tree oil is toxic when swallowed. It also has produced toxicity when applied topically in high concentrations to cats and other animals.³⁴ Its use topically in low concentration for the treatment of acne has not produced toxicity problems. However, tea tree oil is a known cause of allergic contact dermatitis. An Italian study of 725 participants patch tested with undiluted tea tree oil 0.1% and 1% found that 6% of participants experienced a positive reaction to undiluted tea tree oil, 1 participant experienced an allergic reaction to tea tree oil 1%, and no participants experienced a reaction to the 0.1% dilution.³⁵ Thus, the incidence of allergic reactions to tea tree oil is concentration dependent.

Conclusion

Over-the-counter acne treatments have become commonplace. Most patients who present to the dermatologist for acne therapy have tried one or more acne cleansers and treatment creams. The current trend is to package acne products as a 3-pack. Thus, an acne regimen consists of a cleanser, treatment product, and a moisturizer containing sunscreen. Each product contains a different active agent designed to improve primarily comedonal acne. For example, the cleanser may contain salicylic acid 2%, the treatment product may include benzoyl peroxide 2.5%, and the moisturizer containing sunscreen may include tea tree oil. Each of these active ingredients combines to provide added efficacy while increasing sales because the patient must purchase 3 products instead of one.

The dermatologist should learn how to combine OTC acne therapies with prescription medications to

maximize patient satisfaction and compliance. Many patients like their OTC products because they possess excellent aesthetics. Products may smell and feel more desirable in OTC formulations than the prescription formulations. One compromise may be to substitute prescription medications for the acne treatment product, allowing the patient to use the cleanser and moisturizer in addition to oral medication if it is required. This enhances efficacy while maximizing aesthetics.

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