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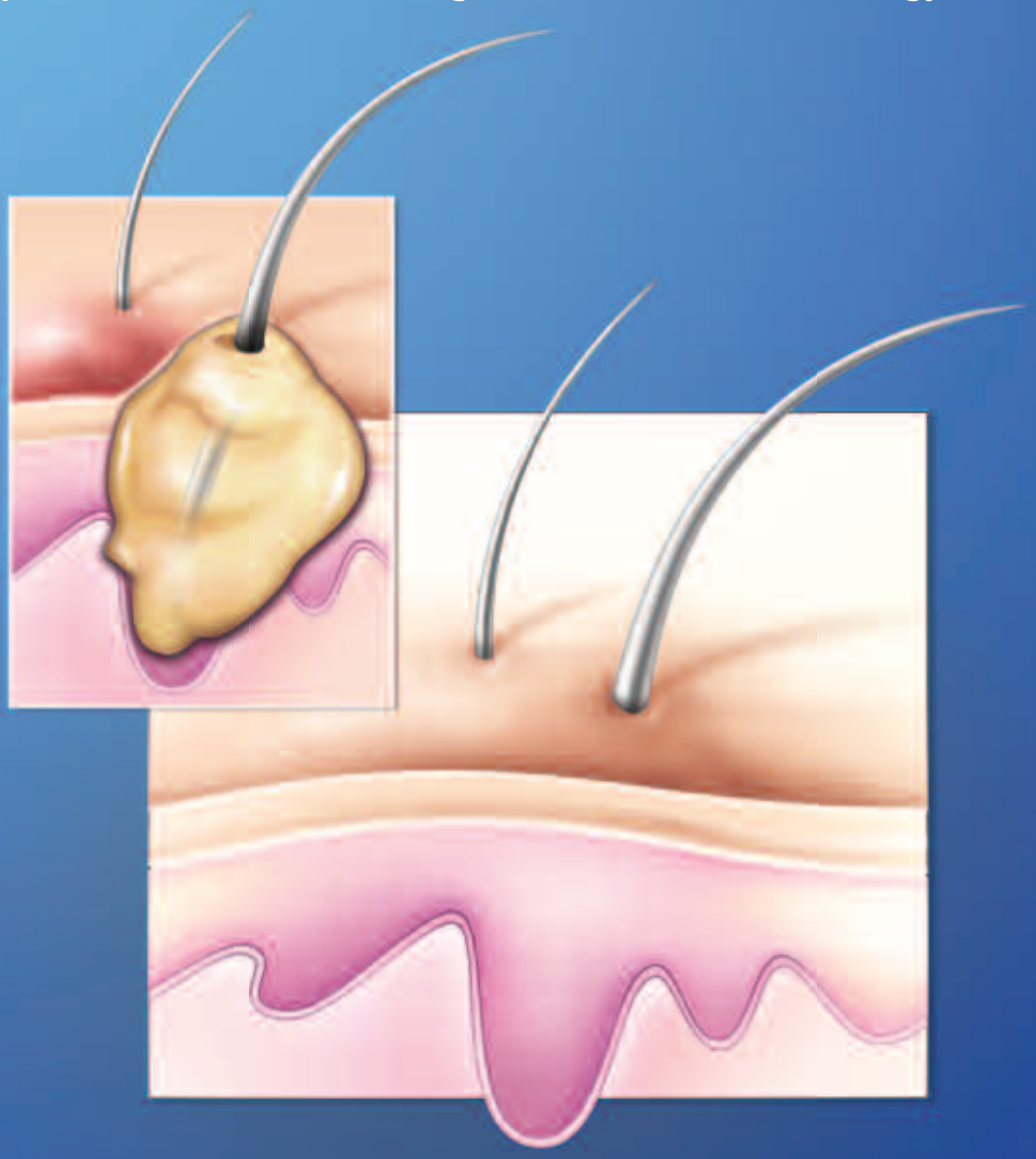
Issues and Advances in Acne Management:

A Special Report from the Annual Meeting of the Canadian Dermatology Association



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Introduction: Acne as a Chronic Disease

Recent decades have witnessed shifting perspectives on acne management, and methods of treating *acne vulgaris*—common or ordinary acne—are reflecting a significant change in approach. Acne was previously perceived as an unfortunate but periodic condition, a mild juvenile affliction to be weathered for a brief time. Now it is increasingly understood by health professionals to be a chronic disease state. As with any chronic condition, successful therapies aim to prevent worsening, shorten the course of any occurrence, and prevent recurrence. Current therapeutic approaches strive to achieve and maintain remission of acne flares via maintenance therapy.

The impact of this perspectival shift should not be underestimated. Acknowledging acne as a chronic condition means appreciating the social, psychological, and emotional impairment that can result from relapses subsequent to treatment.

Issues and Advances in Acne Management

On June 30th, 2006, at the annual meeting of the Canadian Dermatology Association in Winnipeg, physicians participated in a series of interactive talks focussed on acne management. Three speakers led the discussion: Dr. Neil Shear from the University of Toronto, Dr. John Wolf from the Baylor College of Medicine (Houston, Texas), and Dr. Richard Thomas from the University of British Columbia, speaking on behalf of Dr. Jerry Tan. This panel of speakers— all three on the front lines of acne treatment— addressed the complexities and advances in managing acne as a chronic condition.

Applying the Global Consensus Guidelines in Practice

A Change in Therapeutic Practice

Although acne is nearly universal, until recently there were few comprehensive guidelines to direct its treatment. Dr. Shear commenced with discussing the application of the global consensus guidelines as reported by the Global Alliance to Improve Outcomes in Acne, or Global Acne Alliance (GAA), published in 2003.[1] The guidelines, which were evidence-based and the product of international collaboration, gave a comprehensive overview of acne therapy. The GAA's recommendations now "form the basis for more uniform therapeutic strategies throughout the world, enhanced patient compliance and more effective use of healthcare resources."[1] Those strategies were based on an understanding of acne as, indeed, a chronic disease.

Dr. Shear advised listeners to appreciate the profound change that the consensus guidelines represent—it changes the treatment approach. That new focus is behind Dr. Shear's recommendation to his audience that "it's important, when you're looking at a chronic condition, to think about preventing subsequent lesions from replacing the current ones."

As maintenance therapy is increasingly folded into the standard treatment approach, it should help resolve frustrations that dermatologists often experience. Unlike many other physicians, dermatologists have longstanding relationships with patients and often manage their skin problems over years of duration.

Global Consensus Guidelines: Mild-to-Moderate Acne

Internationally accepted guidelines are now available, but are Canadian dermatologists following these parameters? The meeting's touchpad response technology allowed Dr. Shear to query his listeners as he presented the GAA's treatment guidelines across multiple grades of severity. Prior to exploring a case of mild acne, he questioned listeners' familiarity with the guidelines. Just over half of the audience members stated that their first-line therapeutic recommendation for

Topical Retinoids: The Cornerstone of Acne Treatment

The most authoritative guidelines are clear: current best practice adds topical retinoids such as adapalene at the onset of therapy in all types of acne (not just comedonal acne). The Global Acne Alliance consensus recommendations advocate initiating topical retinoid therapy as a first-line management approach. Retinoids are a key component of the combination therapies that compose the treatment for moderate and severe cases of acne. Finally, they are essential to maintenance therapy.

Topical retinoids reverse abnormal desquamation of follicular corneocytes, inhibit the microcomedones that are the precursor lesions in acne, clear mature comedones, and enhance skin penetration of other medications, most importantly topical antimicrobials. They also have an anti-inflammatory effect.[1,2]

mild-to-moderate acne was a topical retinoid along with a topical antibiotic and a benzoyl peroxide (BPO) agent. The GAA's treatment algorithm (Table 1) from the guidelines gives practitioners clear direction: mild-to-moderate papular/pustular acne calls for the use of a topical retinoid plus a topical antimicrobial. Topical retinoids alone are the recommended therapy for mild comedonal acne and the basis of treatment for the next level of severity. Combination therapy is advantageous because it simultaneously addresses multiple dimensions of pathophysiology. Consensus guidelines provide for therapy plus or minus a BPO for moderate/nodular acne as a more aggressive treatment. Maintenance therapy calls for the use of a topical retinoid.

Guidelines further prescribe that moderate-to-severe acne should be treated with a topical retinoid and BPO plus oral antibiotics, and the audience's touchpad response proved that the guidelines had been integrated into standard practice.

Case 1: A Case of Mild Acne: The "Pre-Prom" Consult

Dr. Shear described a common "pre-prom" consult with an athletic 17-year-old female student who is concerned about her acne. The prom is 10 weeks away and she is troubled by her appearance. She presents with multiple open comedones and a few erythematous papules (Figure 1).

In considering the optimal therapy for this case, Dr. Shear discussed the effects of various classes of therapies. According to the GAA guidelines, comedonal acne should be treated with a topical retinoid, and papular/pustular acne with a combination of topical retinoid and topical antimicrobial agent (Table 1). The guidelines emphasize that most patients with acne benefit from the use of a retinoid, the preferred agent for maintenance therapy (Table 2). The guidelines seek to minimize the use of antibiotics in acne treatment. As Dr. Shear explained, "When thinking about treatment [for this patient], we think about the advantages of topical retinoids and the reduction of comedones because the microcomedo is the primary lesion in our current model of how this disease occurs. And if we can control and get rid of these microcomedones, we're in business."

The retinoid, Dr. Shear explained, should be used early for best results as it inhibits the microcomedones (the precursor lesions), clears mature comedones, and heals inflammatory lesions. Used in the long term as a maintenance therapy, retinoids can aid in combatting the return of acne. The patient was started on adapalene 0.1% gel and benzoyl peroxide 5%. She experienced significant clearing in the 10-week period.

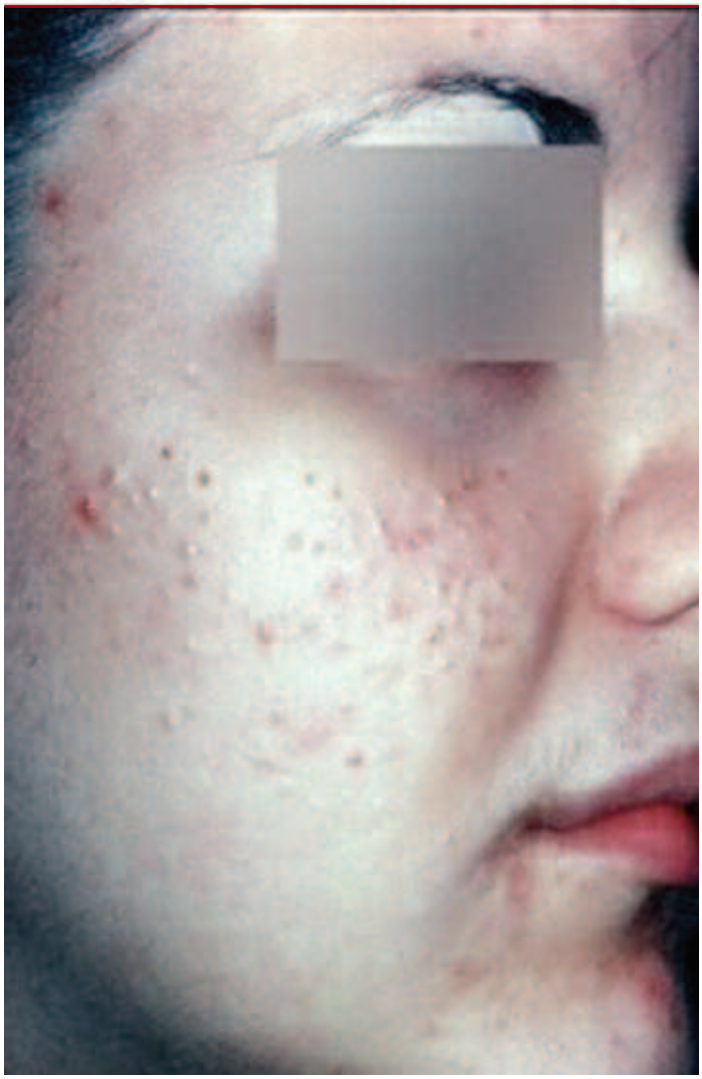
The pathophysiology of common acne such as experienced by the young woman in Case 1, as well as the role of topical retinoids in active and maintenance therapy, are illustrated in Figure 2.

Table 1: Global Acne Alliance Algorithm

Severity	Type	Treatment
mild	comedonal	topical retinoid
	papular/pustular	topical retinoid + topical antimicrobial
moderate	papular/pustular	topical retinoid + oral antibiotic +/- BPO
	nodular	topical retinoid + oral antibiotic + BPO
severe	nodular	oral isotretinoin

Source: Gollnick H et al., 2003.[1]

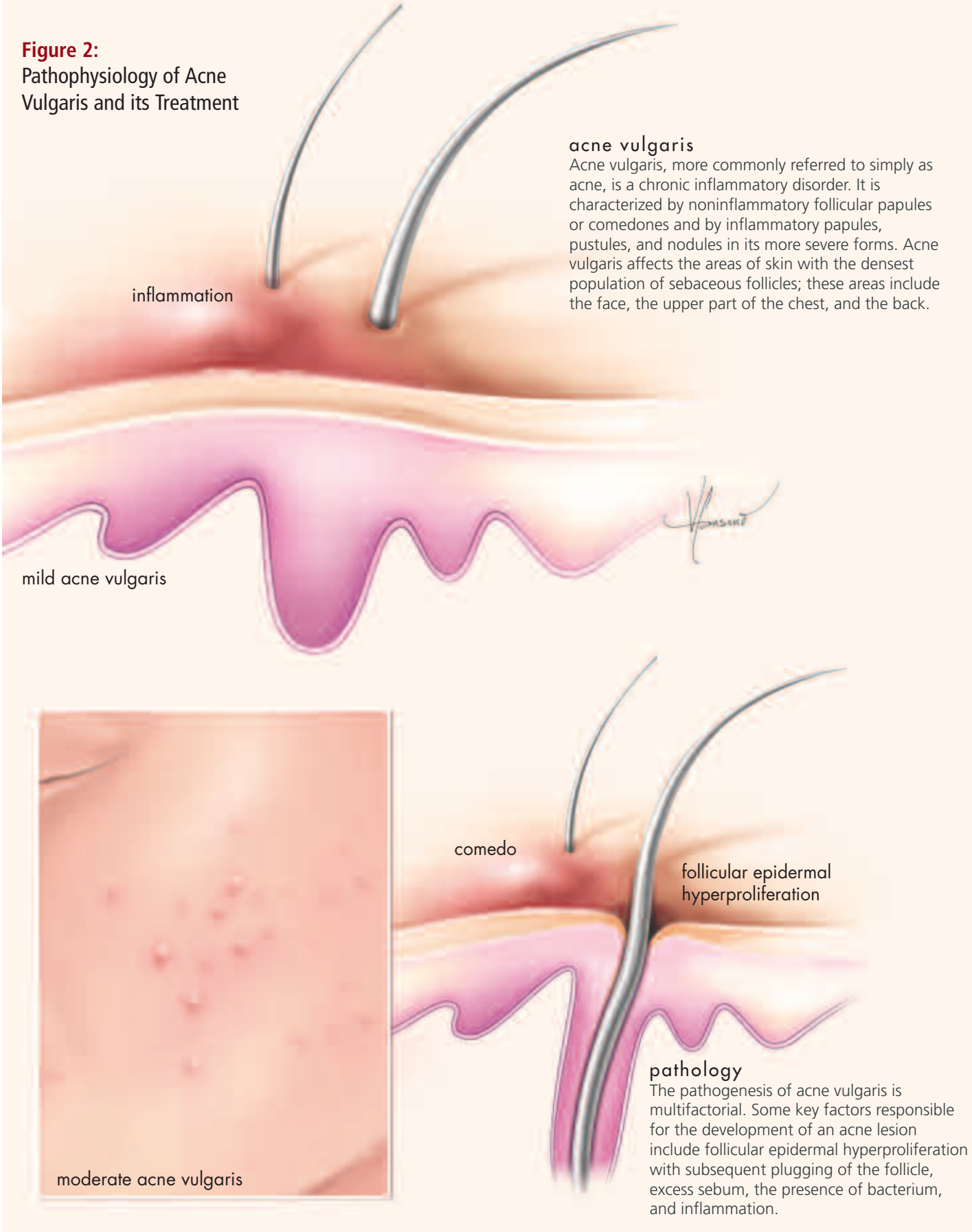
Figure 1: The "Pre-Prom" Consult (Case 1)



The patient presented with multiple open comedones, and few erythematous papules.

Photos courtesy of Dr. Neil Shear

Figure 2:
Pathophysiology of Acne Vulgaris and its Treatment

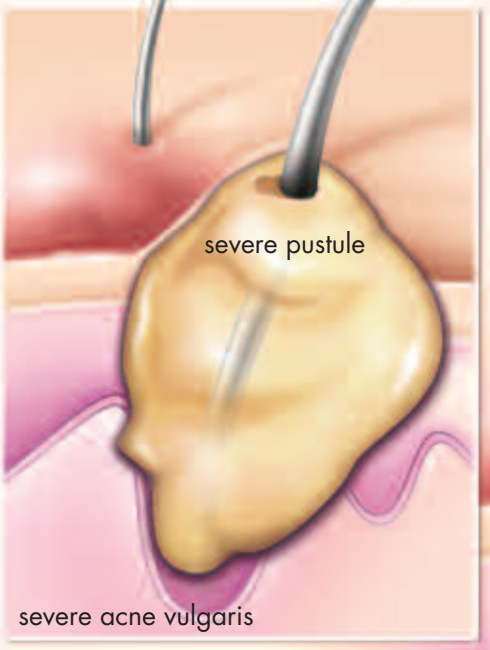


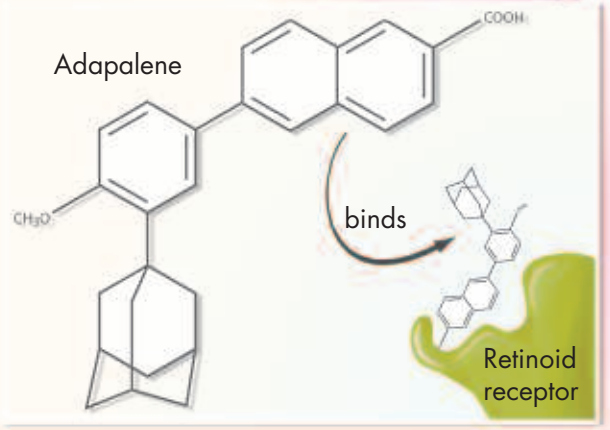
acne vulgaris

Acne vulgaris, more commonly referred to simply as acne, is a chronic inflammatory disorder. It is characterized by noninflammatory follicular papules or comedones and by inflammatory papules, pustules, and nodules in its more severe forms. Acne vulgaris affects the areas of skin with the densest population of sebaceous follicles; these areas include the face, the upper part of the chest, and the back.

pathology

The pathogenesis of acne vulgaris is multifactorial. Some key factors responsible for the development of an acne lesion include follicular epidermal hyperproliferation with subsequent plugging of the follicle, excess sebum, the presence of bacterium, and inflammation.





pustule

keratinization
a process by which epithelial cells lose their moisture and are replaced by horny tissue

therapy

Topical retinoids are the recommended therapeutic choice for mild-to-moderate acne (comedonal and inflammatory acne). These drugs are highly effective comedolytic agents that help restore normal desquamation, prevent occlusion of follicles, promote drainage of comedones, and prevent formation of new microcomedones and inflammatory lesions.

Papular/pustular acne should be treated with a topical retinoid in combination with an antimicrobial agent.

Topical retinoids are critical for the maintenance therapy of acne vulgaris.

mechanism of action

Adapalene, a topical retinoid, acts on retinoid receptors. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes, all of which represent important features in the pathology of acne vulgaris.

Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene normalizes the differentiation of follicular epithelial cells, resulting in decreased microcomedo formation.

skin clarity is maintained with the use of topical retinoid therapy

Case 2: A Patient with Moderate-to-Severe Acne

The acute psychological impact that distinguishes recurrent acne was apparent in the case Dr. Shear next highlighted—that of a 21-year-old woman experiencing a repeated bout of inflammatory acne. She experienced acne as a child that cleared when she began taking oral contraceptives at age 17. She reported having stopped the contraceptives due to the development of classical migraines and, three months later, the lesions flared again (Figure 3). She attempted over-the-counter creams without success. Over time she had become increasingly embarrassed about her acne and reported skipping university classes and social functions when her lesions would flare.

The patient presents with multiple erythematous papules, pustules, and comedones; one nodule; and no increase in facial hair.

According to the GAA guidelines (Table 1), which the audience followed at nearly 90% according to touchpad response, this case of moderate-to-severe inflammatory and comedonal acne should be treated with topical retinoid plus an oral antibiotic plus or minus a BPO. As there is some nodular expression, she could be treated with oral isotretinoin; however, the patient refused this treatment. Oral isotretinoin should be used only in severe and refractory acne, including severe nodular or conglobate acne. Thus, she was initiated on a combination therapy of doxycycline 100 mg/day, BPO 5% gel qam, and adapalene 0.1% gel qhs, seeing significant clearing over a 10-week period. She was later prescribed ongoing maintenance therapy and adjunctive skin care.

Consensus Guidelines on Inflammatory Acne

In the second woman's case, Dr. Shear emphasized that the retinoid has an important and clear role: retinoids such as adapalene are part of the first-line therapeutic response as well as—in Dr. Shear's terms—a "safety net" for future skin care. Here they speed the action of the antibiotic—crucial given that the latest recommendations advise limiting the duration of active therapy. Dr. Shear underlined that adapalene plus an oral antibiotic is significantly more effective than an oral antibiotic alone. He noted that while practitioners previously did not consider retinoids for inflammatory lesions such as this patient was experiencing, they are a key component of the therapy as they are able to target the lesion. As incidences of antibiotic resistance increase, their role is more central than ever.

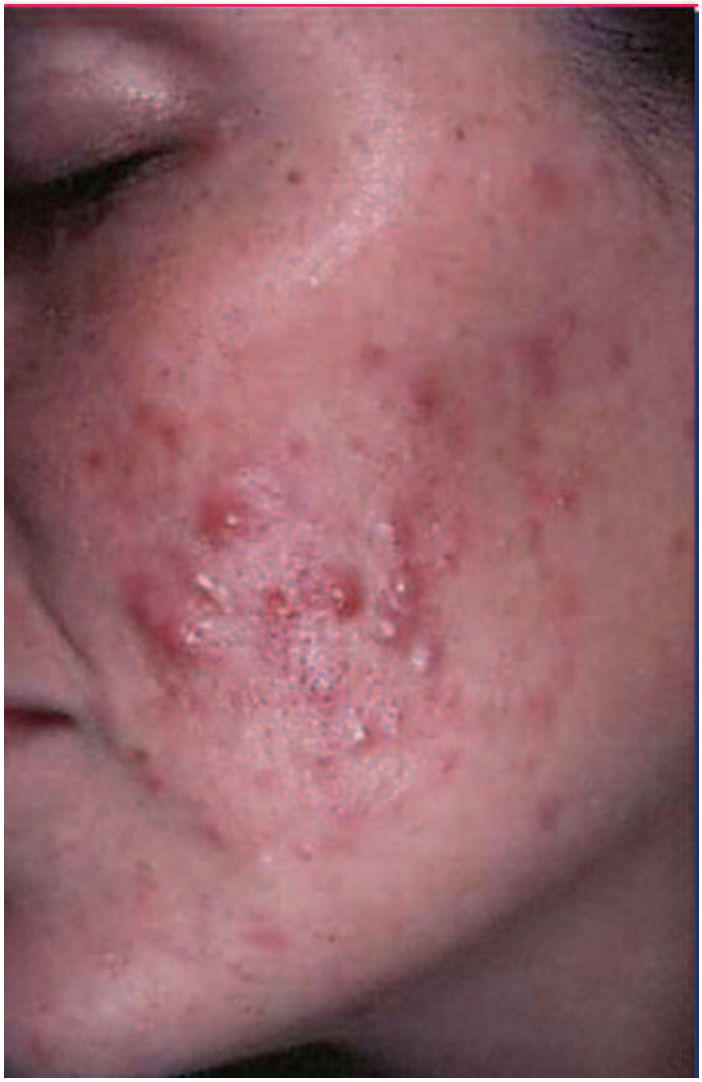
Dr. Shear closed by emphasizing three key points from the GAA's guidelines: pathophysiology directs treatment; combination therapies target multiple pathogenic factors involved in flaring from mild to severe; and retinoids are fundamental to acne therapy and the maintenance of lesion-free skin.

Table 2: Consensus—Topical Retinoids Have Multiple Anti-Acne Actions

Inhibit the formation of and reduce the number of microcomedones (precursor lesions)
Reduce mature comedones
Reduce inflammatory lesions
Promote normal desquamation of follicular epithelium
Some may have an anti-inflammatory effect
Likely to enhance penetration of other drugs
Likely to maintain remission of acne by inhibiting microcomedo formation, thus preventing new lesions

Source: Gollnick H et al., 2003.[1]

Figure 3: Flare-Up After Stopping Oral Contraceptive (Case 2)



The patient presented with multiple erythematous papules, pustules, and comedones.

Photos courtesy of Dr. Neil Shear

Sustaining Acne Remission

The need for new guidelines on acne therapy arose in the absence of internationally accepted guidelines. In his talk on "Sustaining Acne Remission," Dr. John Wolf described how new guidelines have foregrounded the significance of maintenance therapy. Nonetheless, many physicians today rely on outdated prescribing habits. Dr. Wolf would once have counted himself among this group: as early as a few years ago, Dr. Wolf explained, he treated flare-ups, wished his patients well, and said goodbye. The growing amount of data on the value of retinoid therapies was revelatory for him.

Dr. Wolf reiterated Dr. Shear's emphasis on acne as a chronic disease—"a Sisyphean challenge" for dermatologists, he suggested. He drew listeners' attention to the dramatic psychosocial sequelae patients experience from flaring and relapses. "Acne is a chronic disease and is one where intervention can make a very significant difference both clinically and emotionally. It follows quite logically that maintenance therapy is vitally important."

Turning to the guidelines, he reminded his audience that 1) topical retinoids should be first-line therapy for acne. They are first-line therapy for all forms of acne—inflammatory as well as comedonal acne; 2) combined therapy (retinoids plus antimicrobials) is key; and 3) maintenance therapy is critical.

Dr. Wolf presented study results showing the clearing effect of topical retinoids on closed comedones and microcomedones (see Figure 4). Dr. Wolf candidly stated that these data changed the way he viewed acne patients. When topical retinoids were withdrawn, the patients' lesions returned. At that point, he saw the tremendous value in maintenance therapy.

At the 2005 meeting of the GAA, it was agreed that an increasing number of persistent cases were emerging that were often chronic or episodic. Defining acne as a chronic condition was further supported by Dr. Wolf's report of two studies of maintenance treatment over a 16- and 12-week period.

Adapalene in Combination with Oral Antibiotics

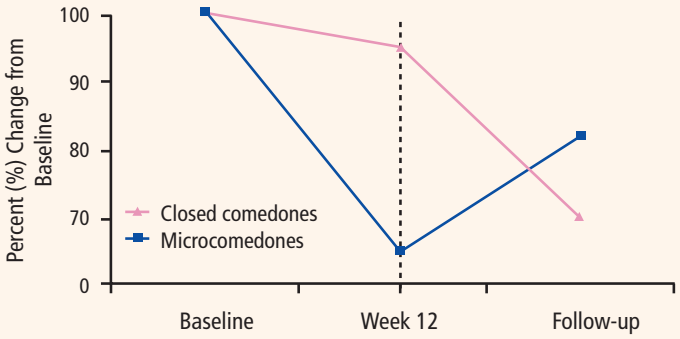
In the first study,[3] subjects were randomly treated with one of two regimens: either adapalene plus doxycycline or doxycycline plus vehicle. After 12 weeks, subjects who had achieved "treatment success" (that is, had achieved 50% or more improvement during the acute phase) were re-randomized and again assigned one of the two prior regimens.

The results were significant. The adapalene combination treatment outperformed the vehicle in terms of both inflammatory and noninflammatory lesion counts throughout the study (Figure 5a). And, at the end of the 16-week period, maintenance of remission was greater in the adapalene group (Figure 5b). As Dr. Wolf noted, "The adapalene was very helpful in maintaining the degree of control achieved in the first part of the trial."

Adapalene in Combination with Topical Antibiotics

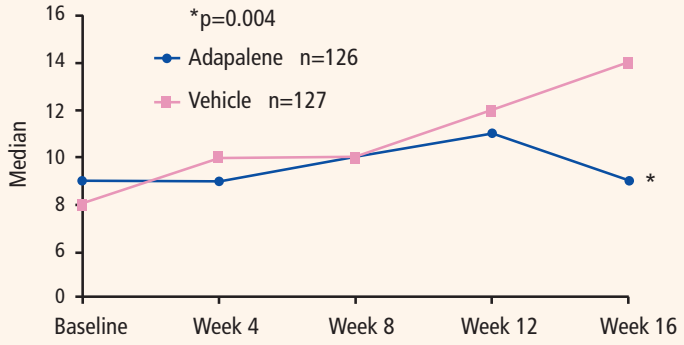
The second study described by Dr. Wolf[4] was similar in design. Subjects were randomized to treatment with either adapalene plus clindamycin or clindamycin alone for 12 weeks. Following this stage, all subjects with moderate clinical improvement (defined as an improvement score of 2 or more on a scale

Figure 4: Topical Retinoid Maintenance Therapy to Prevent Recurrence



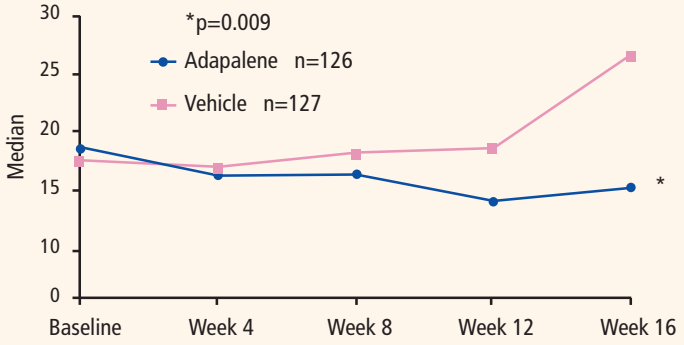
Source: Gollnick et al., 2003.[1]

Figure 5a: Adapalene in Combination with Oral Antibiotics[3] Inflammatory Lesion Counts (ITT)



Source: Thiboutot DM et al., 2006.[3]

Figure 5b: Non-Inflammatory Lesion Counts (ITT)



Source: Thiboutot DM et al., 2006.[3]

Table 3: Acne-Q4

This scale consists of 4 items. The Acne-Q4 is a condensed version of Acne-QoL that is highly correlated with results from the 19-item test (R^2 0.985).
Feeling upset
Dissatisfied with appearance
Concern about meeting new people
Concern about scarring from facial acne

Source: Tan J et al., 2006.[5]

Table 4: Cardiff Acne Disability Index (CADI)[6]

The CADI is a condensed version of the Acne Disability Index (ADI).
Have you been aggressive, frustrated, or embarrassed?
Has your acne interfered with your daily social life, social events, or relationships with members of the opposite sex?
Have you avoided public changing facilities, or wearing swimming costumes because of your acne?
Describe your feelings about the appearance of your skin over the last month.
Indicate how bad you think your acne is now.

Source: Motley RJ et al., 1992.[6]

from -1="worse" to 5="clear") at 12 weeks were re-randomized to either adapalene gel 0.1% or control.

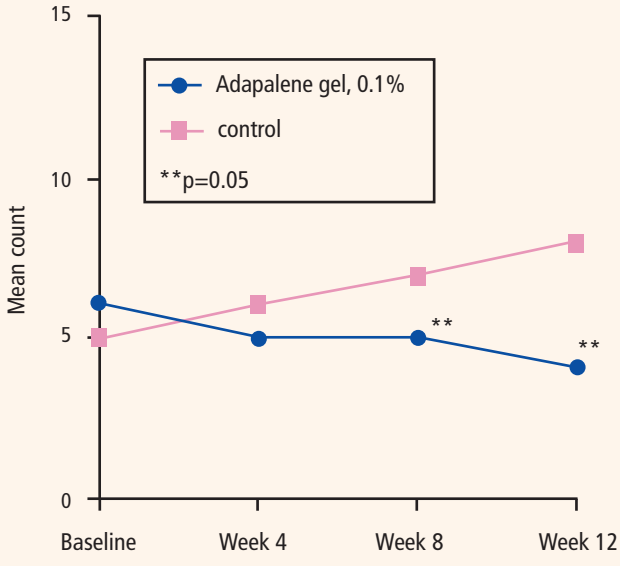
Again, the results were significant. Adapalene combination treatment outperformed control in terms of both inflammatory and noninflammatory lesion counts throughout the study (Figures 6a & b). And as before, the end of the 12-week maintenance period saw prolonged remission in the adapalene group (Figure 7). The synergistic effects of adding a retinoid to an antimicrobial are clear—Dr. Wolf described it as "very interesting" that not only are the clearing benefits maintained but there is augmented improvement in the long term: "Acne recurs when treatment is stopped." This was the point Dr. Wolf pressed his listeners to take home: Adapalene applied once daily for four months maintains the improvement obtained after topical antibiotic therapy (administered alone or in combination with adapalene).

Many among Dr. Wolf's audience seemed to share his revelatory experience once they were presented with his study data that upheld the rationale for the GAA's recommendations. At the outset only 35% of his listeners acknowledged that they consistently used maintenance therapy in their clinical practice. According to touchpad data subsequent to his presentation, 47% said they would do so all of the time henceforward.

The Psychosocial Impact of Acne and the Role of Adjunctive Acne Therapy

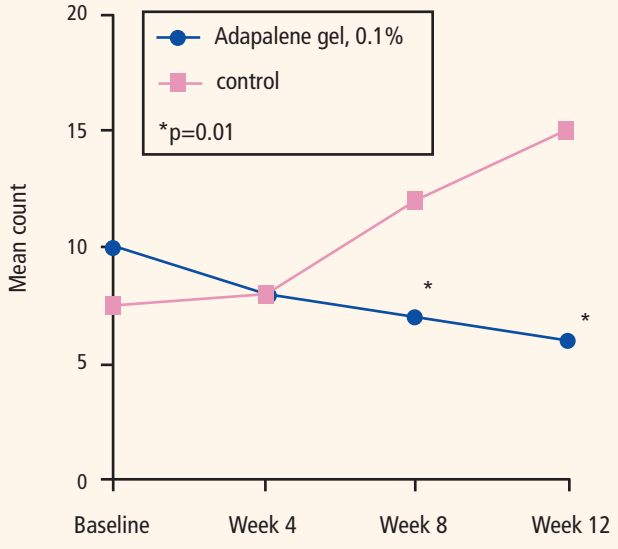
Because acne has a predilection for affecting the face, it can be a profound source of embarrassment and concern,

Figure 6a: Adapalene Combination Treatment Inflammatory Lesion Counts (ITT)



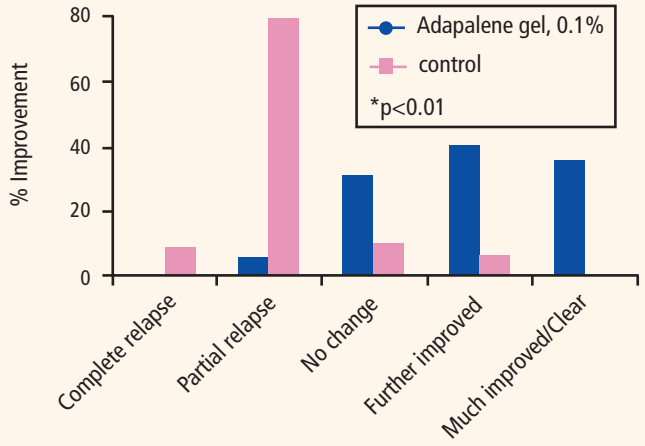
Source: Zhang JZ et al., 2004.[4]

Figure 6b: Adapalene Combination Treatment NonInflammatory Lesion Counts (ITT)



Source: Zhang JZ et al., 2004.[4]

Figure 7: Adapalene in Combination with Topical Antibiotics



Source: Zhang JZ et al., 2004.[4]

especially for those in the formative years of physical growth and self-image development, when acne is most likely to appear.

Dr. Richard Thomas from University of British Columbia, speaking on behalf of Dr. Jerry Tan and presenting the latter physician's research, discussed the social impact of acne. While common, acne is an affliction that can leave the sufferer with physical and emotional scars that may persist lifelong. Dr. Tan is among the few physicians who have worked to quantify those psychosocial effects. Touchpad responses to Dr. Thomas's query indicated that while listeners appreciate acne's psychological impact, most do not formally substantiate that impact in their practice via acne-specific quality of life (QoL) instruments. Eighty-five percent of the polled practitioners use only informal questions or "intuition" to assess the effect of this chronic condition, and a plurality say they would be prepared to pose no more than two questions touching on this area.

Quality of Life Instruments: Under-utilized Tools in Clinical Practice

In an appearance-oriented society, an individual affected by acne may endure feelings of embarrassment, lack of self-confidence, and concerns about social interactions. Social withdrawal can have wide-ranging effects; Dr. Thomas suggested the individual may become so inhibited as to bypass professional and employment opportunities. "The impact on patients is central," he stated.

As most of the audience had indicated that they would be prepared to seek answers to no more than 3–5 questions to determine the psychosocial impact of acne it is unsurprising that most available QoL instruments have not been adopted on a wide scale; many comprise between 15 and 50 items. Dr. Thomas stressed the need for a more condensed tool and highlighted two of them: the Acne-Q4 (Table 3),[5] a brief, validated questionnaire authored by Dr. Tan, and the Cardiff Acne Disability Index (CADI) (Table 4).[6]

Dr. Thomas also reminded the audience that while, from the physician's perspective, severity refers to the clinical grade and count of the condition, from the patient's perspective quality of life and psychological impact of the acne may be more important considerations.

Adjunctive Treatments

Dr. Thomas went on to detail some recent developments in adjunctive acne treatments. These agents support the effects of the first- and second-line treatments as validated by the consensus guidelines. That these advances in adjunctive therapies have appeared is a sign of the seriousness with which acne is increasingly regarded.

Lipohydroxy Acid

In a half-face trial lipohydroxy acid (LHA), a lipophilic derivative of salicylic acid, reduced microcomedone number and size ($p<0.01$).[7] Further, 2% LHA used on alternating nights with tretinoin 0.025% cream in mild acne was as efficacious as tretinoin alone but resulted in less irritation.

Retinaldehyde + Glycolic Acid

The combination of retinaldehyde, which is comedolytic and antibacterial, and glycolic acid, which is comedolytic and increases the absorption of retinaldehyde, has been tested in a RCT. The trial evaluated treatment of acne with a combination of retinaldehyde + glycolic acid,[8] and found a decrease in comedone and inflammatory counts when compared to placebo.

Connecting Psychosocial Issues to Practice

As Dr. Wolf reminded the audience during the panel's closing moments, "In terms of the severity of the psychological impact of disease, it's important that we always remember that mild acne can have a very severe psychological impact." Practitioners would be well-advised not to extrapolate the formally graded severity of the acne to a corresponding degree of psychosocial effect.

Physicians may find that patients will discuss their experiences more openly if they perceive that their quality of life is being taken seriously. Thoughtful questioning can facilitate that, and validated questionnaires are available.

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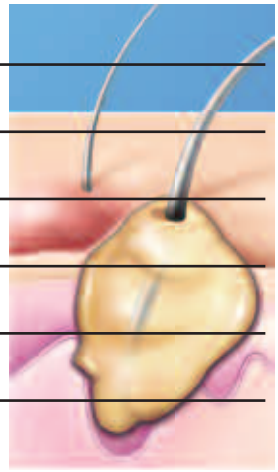
Notes



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