Effective management of dermatological disorders requires patient adherence and buy-in to the treatment plan. Along with accurate diagnosis and treatment, the clinician and his/her team are charged with assessing and driving patient compliance. In the instant gratification web-based world that we live in, compounded with mounting clinician pressures, time constraints and dwindling reimbursement rates, assessing and managing patients’ compliance can be easily overlooked. This is especially true in management of acne vulgaris. The acne population is at risk for provider-hopping and reports high dissatisfaction rates. Rarely does an acne patient present to a dermatology provider that has not been seen previously by a physician or prescribed other therapies that they deem a treatment failure. It is not uncommon for patients to present with multiple tubes of topical medicines that they have discontinued. Patient frustration and dissatisfaction regarding topical interventions are common barriers to care. As with all other medical interventions, once a patient deems a therapy a failure, it is difficult to get them to re-initiate any similar therapies.

In the formative teenage years, acne and other inflammatory skin disorders can have significant negative impact on self-esteem and self-image. Adolescent acne patients are at higher risk for depression, anxiety and obsessive compulsive disorder. There is considerable evidence suggesting that those with inflammatory skin diseases are at higher risk of psychological morbidity, which is often undetected, undiagnosed, and undertreated. Miller, Maletic, and Raison published data further supporting the notion that inflammation has been extended to neuropsychiatric disorders such as major depression and anxiety disorders. (For more on the psychological aspects of skin disease, see the September/October edition online at PracticalDermatologyPeds.com).

Understandably, acne patients and their parents have

Pearls for Optimizing Topical Retinoid Therapy in Pediatric Acne

Retinoids are a cornerstone of acne therapy, but their efficacy comes with potential irritation. Patient education along with use of coping strategies can enhance the therapeutic experience.

By Diane Hanna, ARNP-c and Tracy Clark, ARNP-c

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In the formative teenage years, acne and other inflammatory skin disorders can have significant negative impact on self-esteem and self-image. Adolescent acne patients are at higher risk for depression, anxiety and obsessive compulsive disorder. There is considerable evidence suggesting that those with inflammatory skin diseases are at higher risk of psychological morbidity, which is often undetected, undiagnosed, and undertreated. Miller, Maletic, and Raison published data further supporting the notion that inflammation has been extended to neuropsychiatric disorders such as major depression and anxiety disorders. (For more on the psychological aspects of skin disease, see the September/October edition online at PracticalDermatologyPeds.com).

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Take-Home Tips. Retinoids are the foundation for acne vulgaris therapy with established safety and efficacy. Cutaneous irritation secondary to retinoids is a normal and expected result in the treatment of acne. Overcoming barriers to patient compliance and easing the burden of adverse events can pave the way to increased patient compliance and improved outcomes. Strategies include dose escalation/titration, use of moisturizers, careful vehicle/formulation selection, and good patient education.
a sense of urgency to have their acne resolved. So why then is compliance so difficult to obtain?

**Acne Myths versus Facts**

It is common to see a paternal generational approach to the etiology of acne. Common misperceptions that influence compliance tend to be centered on hygiene, diet and foods. Parents often believe that acne is under the total control of the teen and is a result of poor hygiene and or diet. While more research is needed to closely examine the link between diet and acne vulgaris as a trigger or exacerbating factor, it is not the cause. The lack of understanding and oversimplification of acne can be a two-fold barrier to compliance affecting both parent and adolescent.

The pathogenesis of acne is multifactorial. There is a strong genetic link. The presence of maternal and paternal acne markedly increases the risk of developing acne in children. It is theorized that the genetic component is responsible for follicular epidermal hyperploration that leads to follicular plugging. During puberty, heightened androgen production is responsible for stimulation of androgen receptors located in the sebaceous gland. This activation leads to increased sebum production. Growth hormone and insulin like growth factor influence the activity of sebaceous glands. This fits the clinical picture of children with metabolic x syndrome and the presence of acne without precocious puberty. The hormonal activity is postulated to have an end organ effect on those individuals with the genetic predisposition.

Propionibacterium acnes, are an anaerobic gram positive rod and are part of normal skin flora that flourish in the fatty acid-rich sebum. Additionally P. acnes are active in recruitment and chemotaxis of inflammatory mediators by activating toll like receptor 2 (TL2), pro-inflammatory mediators located on monocytes and neutrophils. Additionally P. acnes activate IL-8, IL-12, TNF-α and other pro-inflammatory cytokines.

**Single Agent Approach**

In the majority of acne cases, a poly-pharmacy approach is needed. It is well established that compliance decreases with increased dosing and use of multiple modalities. In the treatment of acne this is compounded by the use of multiple topical single- and combination-medications; The adverse effects of topical medications that alone can cause cutaneous irritation—such as retinoids or benzoyl peroxides—are compounded with the addition of multiple therapeutic modalities. Conversely, in inflammatory acne, the single agent approach is rarely efficacious and a multi-therapeutic approach is required. Add in to the mix a lack of disease state understanding and education, and a less then stellar treatment response is right around the corner at the next office visit.

The purpose of this article is to provide commonly used clinical pearls for the optimization of retinoid therapy. Topical retinoids are the cornerstone of acne treatment. According to the National Ambulatory Medical Care Survey, pediatricians accounted for 4.6 million acne visits from 1995-2005. Dermatologists reported 18.1 million acne visits for the same time frame. In 46.1 percent of the dermatology office visits a topical retinoid was prescribed versus 12.1 percent is the pediatric office. Retinoids have known efficacy for both inflammatory and non-inflammatory acne lesions. Equally as well known are the cutaneous adverse events. Depending on which package insert is reviewed, the most common reported adverse events are: Erythema, stinging, peeling, and flaking, summed up as cutaneous irritation. Variability is demonstrated based on the initial phase III clinical trials, dependent on the intent to treat population, acne grading scoring, primary endpoints and vehicle and other vari-
Topical Retinoids

Variability is also demonstrated in efficacy and time to clear. The primary endpoint for acne clinical trials is three months, the time point at which safety and efficacy is measured for Food and Drug Administration (FDA) approval. From this data, it has been extrapolated that in order to see efficacy or improvement in acne, patients need the arbitrary number of three months of treatment. Three months of daily treatment can appear to be an insurmountable amount of time for impatient teens. Therefore, prior to tackling the potential adverse events associated with retinoids, setting proper patient expectations is key.

There is a widely accepted range in common protocols for follow-up after the start of therapy. The variation in follow-up can vary from six to 12 weeks. Follow-up at more frequent intervals provides the opportunity for accurate clinical assessment of improvement as well as patient compliance and adherence to treatment to protocol. One approach is to have a monthly office visit for the first three months in order to effectively coach the patient through compliance issues and properly manage expectations. This approach allows early changes and modifications to the treatment plan.

Formulations and Cutaneous Irritation

Skin irritation is the major deterrent to compliance, but is an entirely expected and normal response. Assessing skin sensitivity and concern regarding cutaneous irritation can help mold the right treatment regimen. Set patient expectations that cutaneous irritation is a normal part of the process, transient, and perhaps most importantly a needed process to bring acne to a resolution. The patients’ natural skin color or Fitzpatrick score is not an adequate indicator or predictor for skin sensitivity with the use of retinoids. Most often, cutaneous affects are seen in the first few weeks of the initiation of therapy or after a prolonged drug holiday and subsequent re-initiation of therapy. After the first few weeks of treatment, the skin acclimates and the cutaneous irritation resolves. Coaching patients through the initial phase of treatment is critical to enhancing patient outcome.

Topical retinoids are inherently irritating and the response appears to be dose-, concentration- and patient-dependent. The molecular weight for the drug class is small and allows for rapid penetration into the skin. With most topicals, vehicles matter, but this is even more emphasized with the retinoid class. Vehicle formulation and selection influence the degree of cutaneous irritation as well as efficacy. Many of the branded drug formulations have altered the vehicles in order to decrease the rate of penetration, minimize irritation, and promote use; this is, something generic versions have not done. Microspheres and microsuspensions, are just a few of the vehicle alterations that

Table 1. Topical Retinoid Formulations for Acne

<table>
<thead>
<tr>
<th>Retinoid</th>
<th>Concentration</th>
<th>Vehicle</th>
<th>Brand Name</th>
<th>Generic</th>
<th>Application Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tretinoin</td>
<td>0.04%</td>
<td>Gel, Microsphere</td>
<td>Retin-A Micro</td>
<td>None</td>
<td>Pea-size amount/1-2 pumps</td>
</tr>
<tr>
<td></td>
<td>0.1%</td>
<td>Gel, Microsphere</td>
<td>Retin-A Micro</td>
<td>None</td>
<td>Pea-size amount</td>
</tr>
<tr>
<td></td>
<td>0.025%</td>
<td>Cream</td>
<td>Retin-A, Tretin-X</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.05%</td>
<td>Cream</td>
<td>Retin-A, Tretin-X</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1%</td>
<td>Cream</td>
<td>Retin-A, Tretin-X</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.01%</td>
<td>Gel</td>
<td>Retin-A, Tretin-X</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0375%</td>
<td>Gel</td>
<td>Tretin-X</td>
<td>None</td>
<td>“Cover...lightly”</td>
</tr>
<tr>
<td></td>
<td>0.05%</td>
<td>Gel</td>
<td>Atralin</td>
<td>None</td>
<td>Pea-size amount</td>
</tr>
<tr>
<td>Adapalene</td>
<td>0.1%</td>
<td>Cream, Gel, Lotion</td>
<td>Differin</td>
<td>Cream, Gel</td>
<td>“Thin film”</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
<td>Gel</td>
<td>Differin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Tazarotene</td>
<td>0.05%</td>
<td>Gel, Cream</td>
<td>Tazorac</td>
<td>None</td>
<td>Thin film/(2 mg/cm)</td>
</tr>
<tr>
<td></td>
<td>0.1%</td>
<td>Gel, Cream</td>
<td>Tazorac</td>
<td>Cream</td>
<td></td>
</tr>
</tbody>
</table>
are present in the branded drugs that rapidly affect absorption but are not present in the generic formulations. Additionally, generic formulations have different bioequivalent ranges and properties with the same concentration and can elicit an exaggerated skin response.

**Titration**

Erythema, flaking, burning, stinging and skin sensitivity are the clinical signs of irritation most often reported. Titrating retinoids is a common approach to treatment that promotes adherence. The nasojugal grooves, lateral canthus of eye, and lateral corners of the mouth (Fig. 1) and eyes are especially prone to dryness and flaking.

Even more important than reviewing the signs and symptoms of cutaneous irritation is teaching patients what to do if the symptoms become a barrier to compliance. One often effective approach to driving compliance is titrating retinoids from the onset of therapy. This minimizes skin irritation but conversely has an inverse relationship on efficacy. Dose application escalation is common. Dependent on skin sensitivity and patient motivation, an every-other-day approach is widely accepted by both practitioners and patients, gradually increasing to daily application over several weeks. Stair-stepping patients allows for them to modify their dose in response to any irritation and manage their symptoms for the first several weeks.

**Dose Escalation**

Another approach is to start on a lower concentration every other day, increase applications as the patient is able to tolerate, then increasing the dose. Titration of medicine increases the total cost for therapy, keeping in mind that most insurance polices will more often than not direct patients towards a generic formulation.

If a patient encounters cutaneous irritation that is not manageable, it is important to instruct the patient to temporarily discontinue therapy until signs and symptoms have resolved and then slowly reinitiate therapy as tolerated and slowly build up to every other day or daily use.

Prescribers and patients should note that concentration of a retinoid does not indicate its potency. While there have been attempts to compare the efficacy of various retinoids, generally speaking, most clinicians identify no significant differences in overall efficacy between tretinoin, adapalene, or tazarotene for their indicated acne intent to treat populations demonstrated in their respective phase 3 trials. It is important to note that while retinoids are indicated for acne, each retinoid is indicated based on the intent to treat population that was defined in their pivotal trials. The first in class has the hardest hill to climb for FDA approval. Tretinoin when compared to other available retinoids had that most severe intent to treat population and had the most rapid onset of efficacy, where statistical significance was demonstrated at week seven and clinical significance was noted at week two. However, while tretinoin is the gold standard for efficacy, it has the well-known dependable events of cutaneous irritation.

Clinician preferences tend to revolve around perceived tolerability or suspected benefits in particular clinical settings. However, while topical adapalene is available in 0.1% and 0.3% concentrations and tazarotene is available in 0.1% concentration, tretinoin is marketed in branded formulations at concentrations as low as 0.04% and 0.05% (0.1% gel microsphere is also available; See Table for more information).

**Application**

Historically it has been a widely accepted practice to apply retinoids at nighttime. In a clinical study sponsored by OrthoDermatologics, oily skinned patients using micronized or microspheres containing formulations had a reduction in shine with the introduction of QAM application. Traditionally the standard application amount is referred to as a pea size amount. Because of relationship between dosage and irritation, application amount is key. However, it the pivotal trials each retinoid has a varied dosage regiments. See Table 1 for dosing as indicated in each PI.

**Vehicle Selection**

There are many different vehicle choices for retinoids. Oily skin patients are more likely to be able to withstand an alcohol based gel (note that many gels are...
now water-based), whereas more sensitive skinned patients tend to fair better with cream formulations. However, patients may have preferences for a particular vehicle, and it may be worthwhile to question patients prior to choosing a therapy.

**Moisturizers**

Another common practice is the introduction of moisturizer to help manage cutaneous symptoms. No pharmacodynamics, placebo-controlled, safety and efficacy studies have been done to understand the impact on co-application or mixing of moisturizers with topical retinoids. Still, it is a widely accepted practice. One approach is to apply the moisturizer prior to the application of topical retinoids. The application of a physical barrier is thought to slow down the penetration and absorption of the molecule and decrease irritation. A commonly reported approach is to mix the topical retinoid with a moisturizer, again for the purpose of the creation of a barrier to slow down absorption. Some clinicians instruct patients not to combine moisturizer with their medication and encourage frequent use of moisturizer as desired throughout the day.

In the winter months, in areas of the country where humidity drops, the skin naturally becomes dry. Moisturizers that focus on barrier repair, such as Restoraderm or Cetaphil (Galderma), and CeraVe (Corias Laboratories), are useful in protecting the skin from the elements and managing side affects. These specific moisturizers are non-greasy, non-comedogenic and contain lipids and ceramides that keep moisture and essential fats in the skin.

**Patient Handout**

Clinicians are well aware that patients have limited capacity to absorb and retain information given in a 10-minute office visit. Written clarification is a helpful tool, and many brand specific handouts are available to providers.

Having a simple office based handout that mimics the provider’s generalized treatment approach is helpful in reinforcing the message. Key points to include are:

1. Expected time for global improvement
2. Application time (am or pm)
3. Dosing schedule (daily, every other day, etc.)
4. Recommended moisturizers and how to apply them
5. What to do if irritation occurs (call office, decrease dosing).

**Increased Compliance, Improved Outcomes**

In summary, cutaneous irritation secondary to retinoids is a normal and expected result in the treatment of acne vulgaris. Retinoids are the foundation for acne therapy and have established safety and efficacy. Overcoming the barriers to patient compliance and easing the burden of adverse events can pave the way to increased patient compliance and improved outcomes.

The authors have no relevant disclosures.

6. Acne Vulgaris by James Fulton Jr, MD, PhD, Center for Cosmetic Dermatology; Consultant, Vivant Pharmaceuticals, LLC.