

Acitretin Revisited

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ABSTRACT

Acitretin over the last 20 years has proven useful in a number of dermatologic diseases. Evidence of efficacy, side-effect profile, and approach to its use will be reviewed.

Key words: acitretin, congenital ichthyosis, Darier disease, keratodermas, lichen planus, lichen sclerosus, lupus erythematosus, malignancy, pityriasis rubra pilaris, psoriasis

Acitretin is a synthetic oral retinoid that has been used by dermatologists over the last two decades for a number of cutaneous diseases. It replaced etretinate (the prodrug) in the late 1980's (1998 in the United States), because acitretin presents a more favorable pharmacokinetic profile. The British Association of Dermatologists has recently produced comprehensive guidelines on the efficacy and use of acitretin in dermatology.¹ With this recent development, a further examination of acitretin and its therapeutic application in a wide array of cutaneous diseases is warranted.

Chemistry and Mechanism of Action

Retinoids deliver their biological effects through two members of the steroid/thyroid super family of nuclear hormone receptors: first, the retinoic acid receptors (RAR α , β , γ) and second, the retinoid X receptor (RXR α , β , γ).²⁻⁴ Acitretin is a second generation retinoid that activates all three RAR subtypes. Etretinate is an ethyl ester prodrug that is converted into the active metabolite acitretin. Acitretin's effects are thought to be induced by binding to nuclear receptors of genes, controlling cellular differentiation and proliferation, reducing inflammation and keratinization, and inhibiting neutrophil chemotaxis.⁵

Pharmacokinetics and Metabolism

Acitretin is the main active metabolite of etretinate.⁵ Etretinate is a lipophilic drug with a half-life of approximately 120 days as compared with acitretin, which has a half-life of approximately 50 hours.⁶ Etretinate can be detected in the serum for up to 2 years post cessation of treatment. Acitretin, with concurrent ethanol consumption, can result in transesterification of acitretin to etretinate.^{6,7} Acitretin is a US FDA Pregnancy Category X medication and should not be administered to women of child bearing age who may wish to become pregnant during treatment and within 3 years of discontinuation of the drug.⁵ Patients are

advised to take acitretin with food as this can enhance absorption and bioavailability two- to five-fold.^{6,8}

Efficacy in Psoriasis

There are four randomized controlled trials (RCT) comparing acitretin and etretinate, four RCTs comparing acitretin with placebo and one open study.⁹⁻¹⁶ These studies contain a heterogeneous grouping of generalized pustular, severe, and erythrodermic variants in conjunction with plaque type psoriasis. In addition, these studies preceded the new standardized PASI 75 outcome measure (i.e., 75% improvement from baseline in Psoriasis Area Severity Index score). Nevertheless, a retrospective post hoc analysis of the data would suggest 52% of the patients achieving PASI 75 and 85% achieving PASI 50 after 12 weeks (per protocol analysis) of treatment.¹⁷

In the open trial (Canadian), a total of 46% of patients achieved PASI 75 response and 76% PASI 50 response by the end of treatment (intent to treat average duration of 267 days).¹⁸ Higher doses (50-75mg daily) were found to be more effective, however, these produced more side-effects. Furthermore, acitretin has demonstrated greater efficacy in pustular and erythrodermic psoriasis than in chronic plaque psoriasis.¹⁹

Combination Therapy in Psoriasis

Acitretin and Psoralen + Ultraviolet A (PUVA)

Four RCTs compared acitretin and PUVA.⁴ These studies showed the acitretin + PUVA combination was more effective than PUVA alone.⁴ It reduced the overall number of PUVA treatments.⁶ This, in conjunction with acitretin's demonstrated preventative action against carcinogenesis, allows for theoretical advantages.^{1,7}

Acitretin and Ultraviolet B (UVB)

One RCT, two open studies, along with one retrospective investigation demonstrated better outcomes and sparing of UVB in the combination group.²⁰⁻²⁵

Acitretin and Calcipotriol Ointment

Two RCTs showed additive benefits of acitretin and calcipotriol ointment in combination.²⁶ In one study, the 'clear' or 'almost clear' success rate increased to 67% with the addition of calcipotriol (vs. 41% with acitretin monotherapy).²⁷ In the second study, patients' complete clearance increased from 15% to 40% after 12 weeks.²⁸

Palmoplantar Pustulosis

Two RCTs compared acitretin with placebo.²⁹⁻³⁰ Acitretin produced a five-fold reduction in pustules after 4 weeks and a ten-fold reduction in pustules after 12 weeks.³⁰

Nail Psoriasis

In one open study, patients (N = 36) with nail psoriasis were treated with acitretin doses of 0.2-0.3mg/kg given daily for 6 months.³¹ The findings showed a 41% mean improvement on the Nail Psoriasis Severity Index (NAPSI). In addition, 25% of patients were cleared or almost cleared.

Review of Indications and Level of Evidence¹

Table 1 and Table 2 provide brief overviews of studies investigating the use of acitretin in various skin disorders and their quality of supporting evidence.

Indications	Comments and Recommendations
Psoriasis	Acitretin is the retinoid of choice for treating psoriasis that has severe effects on quality of life and require systematic therapy, is resistant to topical therapy and phototherapy, or is unstable for these treatments. It is recommended in combination with PUVA or narrowband phototherapy, as well as in combination with calcipotriol ointments. Acitretin is effective in palmoplantar pustular psoriasis.
Lichen planus	In severe lichen planus, improvement was seen in 64% of patients on acitretin (30mg daily) vs. 13% in placebo. ³² In the further open 8 week experiment, 83% of the initial placebo patients subsequently responded to acitretin. It has been suggested that acitretin should be a possible first-line therapy in cutaneous lichen planus, particularly in hyperkeratotic form. ²⁰
Darier disease	Researchers comparing acitretin with etretinate in 26 patients with Darier disease showed similar rates of marked improvement or remission in both groups with 10 of 13 patients responding. ³³ Lower doses are required (10-25mg/day) in the treatment of Darier disease. ¹
Hand eczema	A RCT of 29 patients showed a 51% reduction of hyperkeratotic hand eczema. ³⁴
Malignancy prevention	There have been numerous reports of retinoid use as malignancy prophylaxis in organ transplant recipients. This has recently been reviewed in <i>Skin Therapy Letter</i> . ³⁵ Data from a small number of randomized controlled trials suggest that acitretin may have a beneficial role in high risk organ transplant recipients. ⁴³ Other retinoids have been anecdotally shown to prevent malignancy in xeroderma pigmentosum (isotretinoin) and basal cell nevus syndrome. ³⁶
Cutaneous lupus erythematosus	In one RCT of 58 patients comparing acitretin 50mg daily for 8 weeks with hydroxychloroquine 400mg daily, researchers found improvement in 46% for acitretin and 50% for hydroxychloroquine. ³⁷ Moreover, in an open trial of 20 subjects, 15 patients experienced total clearing or marked reduction of all lesions. ³⁸

Table 1: Acitretin use in cutaneous disorders supported by studies categorized as A/1+ level of evidence

A = at least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results; 1+ = well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias



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Indications	Comments and Recommendations	Level of Evidence
Pityriasis rubra pilaris	In a single retrospective study of 14 patients (9 treated with acitretin or etretinate), researchers showed partial or complete clearing in 7 of 9 patients without major side-effects. ³⁹ The authors considered retinoids to be first-line treatment for pityriasis rubra pilaris. ³⁹	anecdotal
Lichen sclerosus	Another RCT randomized 78 patients, however, only 46 subjects were measured for efficacy per protocol. More than half of the patients (14 of 22) on acitretin responded, compared with 6 of 24 in the placebo group. ⁴⁰ Due to the high drop-out rate and the high risk of bias the <i>British Journal of Dermatology</i> declined to make a recommendation in this area. ¹	1-
Congenital ichthyoses	Evidence for efficacy is based on anecdotal reports with several open studies combining numerous conditions (lamellar ichthyosis, non-bullous ichthyosiform erythroderma, bullous ichthyosiform erythroderma, Sjogren-Larsson syndrome, and Papillon-Lefèvre syndrome). ⁴¹⁻⁴³ Patients generally showed improvement, however, one patient tested with acitretin therapy who suffered from Netherton syndrome showed marked worsening. ⁴²	D, 3
Keratodermas	Evidence is based on open study anecdotal reports for efficacy and again combining multiple conditions, including Vohwinkel syndrome, keratitis-ichthyosis-deafness (KID) syndrome, hereditary punctate keratoderma, and Papillon-Lefèvre syndrome. It was reported that acitretin therapy successfully helped disease symptoms. ^{42,44,45}	D, 3

Table 2: Dermatologic conditions with less evidence in the literature¹

1 = meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias; 3 = nonanalytical studies (e.g. case reports, case series); D = evidence 3 or 4, or extrapolated evidence from studies rated as 2+, or formal consensus

Safety and Tolerability

Acitretin has a side-effect profile similar to other systemic retinoids. Many of the reported adverse effects (Table 3) have occurred in patients using higher doses (>25mg/day) of acitretin and are less prevalent in low doses of acitretin (<25mg/day).

Prescribing

Therapy should be initiated only under the responsibility of a supervising dermatologist.¹ It is recommended that capsules be taken once daily with fatty foods.⁴⁶ Therapeutic and toxic doses of acitretin are dose-dependent, and individual adjustments of dosage is necessary. Effective doses are typically around 25-50mg/day.^{47,48} Researchers state that a gradual escalation approach is most effective.⁴⁸ Acitretin dosages are recommended to start at 25mg/day and increase by 10-25mg every 2-4 weeks to achieve the maximally tolerated dose.¹ It is important to note that the response to acitretin is gradual, typically requiring 3-6 months to reach peak effectiveness.¹ In Darier disease a starting dose of 10mg daily may be appropriate.¹

Monitoring

Patients taking acitretin require monthly monitoring for the first 3 months, then every 3 months thereafter. A complete blood count (CBC) is required as well as a fasting lipid profile (TG, cholesterol). Liver function (AST, ALT) and blood sugar levels of diabetic patients must also be monitored.¹ Radiological investigation for skeletal changes need not be done routinely.¹

Conclusion

The use of acitretin over the last 20 years has proven to be an effective treatment and adjunct in a number of dermatological conditions. A thorough understanding of the drug, its efficacy, and potential side-effects is important for yielding a beneficial therapeutic outcome for patients.

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Prevalence	Type	Side-effect/Description
Serious common	Teratogenic	<ul style="list-style-type: none"> • Teratogenic regardless of dose or duration of treatment • US FDA Pregnancy Category X • Should only be used in men, postmenopausal women, or females not desiring to achieve pregnancy for 3 years
Serious rare	Bone	<ul style="list-style-type: none"> • Diffuse idiopathic skeletal hyperostosis (DISH) • Osteophyte formation • Premature epiphyseal closure
	Gastrointestinal	<ul style="list-style-type: none"> • Pancreatitis • Possible trigger of inflammatory bowel disease
	Hematologic	<ul style="list-style-type: none"> • Leukopenia • Agranulocytosis
	Hepatic	<ul style="list-style-type: none"> • Transaminitis • Toxic hepatitis • Hyperlipidemia
	Musculoskeletal	<ul style="list-style-type: none"> • Myopathy
	Neurologic	<ul style="list-style-type: none"> • Pseudotumor cerebri • Depression/suicidal ideation
	Ocular	<ul style="list-style-type: none"> • Reduced night vision
Common	Gastrointestinal	<ul style="list-style-type: none"> • Nausea • Diarrhea • Abdominal pain
	Mucocutaneous	<ul style="list-style-type: none"> • Cheilitis • Xerosis • Skin peeling • Photosensitivity • Alopecia • Sticky sensation
	Musculoskeletal	<ul style="list-style-type: none"> • Myalgias • Arthralgias
	Nails	<ul style="list-style-type: none"> • Paronychia • Fragility
	Neurologic	<ul style="list-style-type: none"> • Headache
	Ocular	<ul style="list-style-type: none"> • Dry eyes

Table 3: Summary of adverse effects associated with acitretin therapy

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Overview of Treatment of Vulvovaginal Disease

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ABSTRACT

Vulvovaginal diseases commonly are inadequately diagnosed and treated. Most are dermatologic, but can be atypical in presentation in the warm, moist genital area. There is limited training or education for medical caregivers for these conditions. The first step is correct diagnosis, which requires time and knowledge of the normal anatomy, and careful examination. Dermatologists are invaluable for management as they recognize skin problems and can correct barrier function, control inflammation, and address itching and pain.

Key words: examination, lichen planus, lichen sclerosus, pruritus, vagina, vulva

The consequential effects of vulvovaginal diseases being rarely taught is that they are frequently missed or mismanaged by medical and surgical caregivers, leaving both patients and physicians floundering. Women hide and scratch, enduring pain, engendering significant debility and sexual dysfunction, and wasting millions of dollars on “yeast treatments”. The general unfamiliarity with the normal anatomy and the atypical appearance of common dermatological conditions represent a considerable clinical challenge. Dermatologists, who are accustomed to instant visual diagnosis, need to take extra time to apply their knowledge of morphology and recognize the normal anatomy when treating vulvovaginal disorders. We are uniquely qualified to help^{1,2} in assessing the pathology, identifying etiology, correcting barrier function, limiting inflammation, and addressing cutaneous itching and pain.

Anatomy

Recognizing normal variants is essential. The appearance of the vulva varies depending on age, ethnicity, and hormonal factors. A good diagram is invaluable - anatomical familiarity is important not only for the caregiver, but also for the patient. A suitable figure is available on the website of the International Society for the Study of Vulvovaginal Disease at www.ISSVD.org.

The vulva becomes flattened with loss of normal architecture in lichen sclerosus. Without an understanding of the normal architecture, subtle scarring in this condition may be unrecognized. The prepuce may be slightly swollen and adherence to the clitoris is easily missed. Scarring is a nonspecific sign associated with many erosive and inflammatory skin conditions in the vulvar area. It is important to make sure all architectural features are intact. Both digital and speculum examinations of the vagina are important to rule out erosions, synechiae, and scarring in the vagina, as can be seen in erosive lichen planus.³

Because common variations in vulvar anatomy may be unfamiliar, recognizing these is important. Vulvar papillomatosis shows small monomorphous papules on the vulvar trigone that can be easily confused with genital warts. Normal sebaceous glands (Fordyce spots) are at times quite prominent and can appear worrisome. These lesions are soft, asymptomatic, and harmless. Also, common benign blood vessel growths on the labia majora (angiokeratomas) can appear black and sinister.³

History

A thorough and accurate patient history is essential, including details of previous treatments and response to therapy. Inquire

about all the various products the patient is using, particularly cleansers, lubricants, and menstrual products. Do not always accept the chief complaint at face value. The patient may complain of itching or burning, but her real concern is about infidelity, cancer, or sexually transmitted infection. Always ask about incontinence, both urinary and fecal, as 10% of women over 50 years of age have urinary incontinence.⁴ Women seldom, if ever, volunteer this information to their treating physician. Furthermore, fecal incontinence is very common and almost never mentioned. Schlosser et al.³ provide a detailed approach.

Physical Examination

A thorough examination requires good visualization with proper lighting, avoiding glare. Proper exposure is mandatory. Examination can be in the frog-leg position or in stirrups. The latter is preferred as one can then visualize the entire area including the anus. A close look, preferably with magnification, is mandatory. Not infrequently a patient will complain bitterly of pain and burning from an apparently trivial lesion. Painful fissures and erosions can be very subtle or invisible in poor light. Concomitant vulvar conditions are common. It is not unusual to see the patient with lichen sclerosus, contact dermatitis from incontinence, and atrophy from lack of estrogen. Occasionally, squamous cell carcinoma may also be seen. Examine the rest of the skin and the oral cavity. About 60% of patients with oral lichen planus have vulvar or vaginal disease.^{5,6} Always investigate the possibility of more than one problem. Iatrogenic disease is common. One can see steroid atrophy with thigh striae or herpes simplex flaring in an area of lichen sclerosus being treated with a superpotent topical steroid. Vaginal disease must be considered to be associated with the vulvar condition or contributing to it. It is worth noting that about 60% of vulvar lichen planus cases have vaginal disease. Chronic vaginitis discharge from any vaginitis can cause or worsen a vulvar condition.^{1,3}

Biopsies

Biopsies are always important, especially if the patient will need lifetime treatment as in lichen sclerosus. However, a biopsy of lichen sclerosus is not generally recommended for children. A pain-free biopsy is ideal, and can be accomplished using a topical anesthetic (e.g., 2.5% lidocaine with 2.5% prilocaine in a cream base). This is applied liberally to the modified mucous membrane area for 20 minutes, or for 60 minutes for keratinized skin. Local anesthesia with 2% lidocaine with adrenaline is then injected slowly using a 30-gauge needle. If there is any question,

do multiple biopsies at a single sitting. A typical problem is vulvar melanosis. There are often several sites that look suspect and it is best to biopsy all of them at one visit. Biopsies, particularly from vulvar or vaginal lichen planus, can be nonspecific. Differentiated squamous cell carcinoma of the vulva can be read as lichen simplex chronicus. Therefore, a dermatopathologist who is clinically familiar with these conditions is invaluable.

Education and Support

Before starting therapy it is important to understand that for almost all vulvovaginal conditions there are psychological, social, and sexual repercussions. Loss of intimacy not uncommonly results in low self-esteem, frustration, depression, anger, or hostility. Frequently, some combination of patient ignorance, guilt, embarrassment, and anxiety further complicate vulvovaginal problems. Consequently, good education, support, and counseling are imperative. More than with any other area of the body, the vulvar patient needs to be recognized as a person and treated gently and with respect. Take extra time for patient education by addressing the disease process, discussing available therapies, and managing expectations. Precise treatment details must be conveyed. As well, use the encounter for an educational vulvar examination. Handouts are very helpful to demystify the disorder and improve compliance. High-quality clinical photographs are essential for patient education and documentation.

Treatment

The goal of therapy is to correct barrier function, thereby reducing or eliminating inflammation, itching, and pain.

Barrier Function

Common causes of altered skin barrier in the vulvovaginal area are contact dermatitis (particularly from overzealous hygiene), atopic dermatitis, atrophy from lack of estrogen, psoriasis, or other 'rashes' and, less commonly, tumors. To provide the optimal environment for maintenance of a functioning skin barrier, it is important to limit the exposure to harmful factors (e.g., excessive hygiene, heat, sweat, vaginal secretion, urine, feces, clothing washed in enzyme-containing detergents, and friction) that can cause or exacerbate any skin condition. Sweat, heat, and moisture promote maceration, epithelial breakdown, and infection. Women have a tendency to over wash using facecloths and caustic cleansers. For cleansing, little to no soap is best. Dove for Sensitive Skin® (fragrance free) or Cetaphil Gentle Cleanser® can be used for cleansing with bare hands only. A hand-held shower on a gentle setting can be a good choice, especially for women with physical limitations. The area is patted dry and hairdryers should never be used. Clothing should be ventilated, fit well, and be laundered in enzyme-free detergent. Avoid thongs, girdles, and tight jeans. Urinary and fecal incontinence need to be addressed. For urinary incontinence, an appropriate incontinence pad (not a menstrual panty liner) should be used. For fecal cleansing, consider Cetaphil Gentle Cleanser® or mineral oil. Pelvic floor rehabilitation and/or help from a urologist should be considered.

The concept of 'soak and seal' is the same on the vulva as elsewhere. Soaks provide symptomatic relief, gentle debridement, and restore a moist environment for healing. A plain water soak in a tub or sitz bath for 5-10 minutes can be used. Occasionally, water will sting very raw skin. Normal saline

does not sting, so it can be used by mixing 1 teaspoon of salt in 4 cups of water. After the soak, to seal in the moisture, a petrolatum-based product is best, but this can be messy, sticky, and can even trap sweat. A hypoallergenic product, such as Vanicream™, can be very useful. For very raw skin, plain white petrolatum is recommended. Always perform cultures and treat any associated infection caused by *Candida* and bacteria, usually *Staphylococcus* and *Streptococcus*. For acute severe candidiasis use fluconazole 150mg on day 1, 3 and 7. For suppression use fluconazole 150mg per week for up to 6 months. If the patient exhibits a poor response, re-culture to rule out an azole resistant *Candida* (e.g., *Candida Glabrata*), which would require treatment with 600mg boric acid vaginal suppositories nightly for 14 days.

Inflammation Reduction

Topical Corticosteroids

Too often topical corticosteroids are not effectively used in the vulvovaginal area. It must be appreciated that the vulvar vestibule is relatively treatment resistant to topical corticosteroids, in contrast to the labiocrural folds, perineum, perianal area, and thighs (which can easily be thinned and develop striae). For thick, scaly vulvar conditions, such as lichen sclerosus, lichen planus, or lichen simplex chronicus, a superpotent steroid (e.g., clobetasol or halobetasol 0.05% in an ointment base) is advisable. Daily treatment may be needed for 8-12 weeks to gain adequate control. Education is very important here. The patient needs to know exactly where to apply the ointment and how much. A diagram is very useful and a clinical photograph of the female patient's affected area is even better. Limit the use of superpotent corticosteroids in the steroid sensitive areas to 2-3 weeks. Limit the amount prescribed to 15g. For long-term use consider intermittent application, such as treatment on Monday, Wednesday and Friday, or switch to a low potency steroid. A typical therapeutic regimen for vulvar lichen sclerosus would be clobetasol 0.05% ointment daily for 12 weeks, then decrease to 3 times a week. If there is concern about recurrent yeast infections prescribe oral fluconazole 150mg weekly for suppression.

Topical Calcineurin Inhibitors (TCIs)

TCIs can be used to avoid corticosteroid-induced side-effects. Pimecrolimus 1% cream and tacrolimus 0.03% and 0.1% ointments have been reported to be very helpful for lichen sclerosus, lichen planus, lichen simplex chronicus, and a number of the bullous diseases, or even Crohn's disease.⁷ Unfortunately, because TCIs can cause localized burning they are often poorly tolerated. Overall, both TCIs are less effective than topical potent and superpotent steroids for treating vulvovaginal skin disorders. There is controversy regarding their safety in lichen sclerosus and lichen planus. In addition, their cost can be prohibitive.

Intralesional Corticosteroids

For a nonresponsive area of lichen sclerosus or lichen planus, triamcinolone acetonide 10mg/mL diluted to a concentration of 3.3-5mg/mL can overcome the failure of topicals. The area injected will depend on the individual case. To avoid pain, preanesthetize the area. Treatment can cause atrophy and must be used intermittently with caution.⁸

Systemic Corticosteroids

Systemic steroids can be very useful for intractable itching and inflammation. Classically, prednisone is recommended, but it

too often causes gastrointestinal upset, anxiety, and agitation. Systemic prednisone is very useful for a quick burst without a taper for 7-10 days when treating an acute, limited skin condition, such as simple contact dermatitis. For longer-term management of inflammation, intramuscular (IM) triamcinolone (Kenalog®-40) can be an excellent choice. It is very well tolerated and best given deep into the muscle of the mid-anterior thigh. In obese women, injection into the fat results in subcutaneous atrophy, slow absorption, and a poor response. One milligram per kilogram, up to 80mg/dose, is recommended. IM triamcinolone does not have the side-effects of anxiety and agitation that are common with prednisone. Its main side-effect is occasional irregular bleeding in premenopausal women. It is an ideal therapeutic option for lichen simplex chronicus and lichen planus, administered as one dose monthly for 1-3 months, limiting the number of treatments to four times a year. Although the list of generic side-effects of triamcinolone include pituitary axis suppression, infection, cataracts and worsening glaucoma, irregular menses, and rarely allergy, these are much less prevalent than with prednisone.⁸

Vaginal Corticosteroids

Vaginal corticosteroids are imperative for the management of vaginal lichen planus and bullous diseases, however, there are no commercially available products. The simplest treatment is with clobetasol or halobetasol 0.05% ointment or cream using a Premarin® applicator and inserting 1-2g in the vagina at night. Commonly, hydrocortisone acetate is used. A 25mg suppository is available, but the dose is usually too low for effective treatment of significant disease. A 100mg suppository can be compounded. For more severe disease 10% hydrocortisone acetate is compounded in a vaginal cream and 3-5g (300-500mg) are inserted nightly for 2 weeks and then decreased to Monday, Wednesday and Friday. There are no safety data on these products and local atrophy may occur. Yeast infection must be suppressed using fluconazole 150mg weekly. Adrenal axis suppression can occur.⁸

Vulvar Pruritus

Up to 10% of women present with vulvar pruritus.⁹ Itching is one of the most distressing vulvar symptoms and patients can find it more difficult to manage than pain. Start by identifying the underlying cause or disease for targeted treatment. Pruritus is often an ongoing clinical challenge. Management involves not only pharmacologic intervention, but also nonspecific measures, such as patient support and education. All potential irritants, including excessive body hygiene (over washing), must be stopped. Infection with *Candida* and bacteria must be eliminated. Cooling the area can be helpful. Use cool gel packs, not ice packs that can further injure the skin. Cool soaks or sitz baths and bland emollients can soothe fissured or eroded skin. Inflammation can be controlled with topical and systemic steroids. Sedation is often imperative to stop scratching. For nighttime sedation, hydroxyzine or doxepin starting at 10mg/dose can be slowly increased to 100mg. During the day a selective serotonin reuptake inhibitor (citalopram 20-40mg in the morning), can be helpful. For neuropathic pruritus, a tricyclic antidepressant (amitriptyline, doxepin, or nortriptyline) can be considered. Begin with a low dose and increase gradually. Gabapentin can be of benefit, start at 300mg/dose up to a maximum of 3600mg/day.^{10,11}

Vulvar Pain

Vulvar pain may be due to any one of a number of vulvar disorders or attributable to idiopathic pain (i.e., vulvodynia). Topical anesthetics are commonly recommended (e.g., 2-5% lidocaine in a gel or ointment base or 2.5% lidocaine with 2.5% prilocaine in a cream base). These can be applied several times a day if the treatment is not too irritating. Never use benzocaine as it is very caustic and allergenic. The range of pain medications is beyond the scope of this article. Typically, tricyclic agents (e.g., amitriptyline or nortriptyline), anticonvulsants (e.g., gabapentin or pregabalin), and/or antidepressants (e.g., duloxetine or venlafaxine) are used. For these medications, start low and go slow. Treatment for vulvodynia is most effective with a multidisciplinary approach using medications, pelvic floor physiotherapy, cognitive pain therapy, nerve blocks, and more.^{12,13}

Nonresponders

For patients not responding consider noncompliance, an incorrect diagnosis, infection, trauma due to aggressive hygiene, contact dermatitis, or squamous cell carcinoma. Factors that can contribute to noncompliance include fear of steroids, vulvar ignorance, miscommunication, secondary gain (e.g., to avoid sexual activity), and physical impairment, such that the obese or arthritic patient cannot reach the area. Always look for concomitant conditions (e.g., lichen sclerosus plus contact dermatitis plus infection). Patients showing a poor response to treatment should be reassessed, biopsied, and re-biopsied.

Conclusion

Dermatologists can play an important role in the management of vulvovaginal disease. We are ideally trained to recognize any skin changes and the multiple, often confusing, combinations of these conditions. In addition, familiarity with managing chronic and complex cutaneous conditions requiring long-term maintenance therapy provides an invaluable clinical advantage.

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Update on Drugs

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Name/Company	Approval Dates/Comments
Spinosad 0.9% cream rinse <i>Natroba™</i> ParaPRO, LLC	The US FDA approved a topical suspension of spinosad in January 2011 for the treatment of head lice in patients ≥4 years of age. Spinosad is a compound derived from a soil microbe and its mechanism of action includes excitation of neurons in the central nervous system, then hyperexcitation, and paralysis, leading to death of the insect. The product resolves most head lice infestations in about 10 minutes with one application, and nit combing is not required. It is available by prescription only and not approved for use in patients younger than 4 years of age. Exposure in children <6 months of age must be avoided because benzyl alcohol, one of the main active ingredients, can induce serious reactions in infants. Reported adverse effects of spinosad include irritation or redness of the eyes and skin.
Light emitting diode (LED) skin rejuvenation system <i>Tanda™ Professional Rejuvenate</i> Syneron Medical Ltd.	The US FDA granted clearance to market this esthetic device in January 2011 for skin rejuvenation. The product is approved for the treatment of wrinkles, rhytides, and fine lines in the periorbital (around the eye) area. Tanda™ Professional Rejuvenate red light home use device reduces the appearance of fine lines and wrinkles by stimulating collagen and elastin production, and enhancing skin hydration.
Voclosporin <i>Voclera™ (ISA247)</i> Isotechnika Pharma Inc./ Paladin Labs Inc.	Health Canada granted screening acceptance to this novel, next generation oral calcineurin inhibitor in December 2010 for the treatment of moderate to severe psoriasis. In comparison to conventional systemic immunosuppressive compounds, voclosporin may offer comparable efficacy with fewer adverse effects.

Drug News

A recently published retrospective study* explored the risk of herpes zoster infection (or shingles) after receiving the live, attenuated varicella zoster virus (VZV) vaccine (Zostavax®). The 75,761 patients in the vaccinated cohort were age matched (1:3) to 227,283 in the unvaccinated group. Study findings demonstrated vaccine efficacy in a large, immunocompetent, heterogeneous population consisting of men and women ≥60 years of age in general practice settings. Herpes zoster vaccine recipients were more likely to be white, female, with more outpatient visits, and had fewer chronic conditions. Investigators found a significant risk reduction of herpes zoster infection across all ages and subgroups (e.g., healthy subjects and individuals with chronic disorders, such as diabetes, kidney, heart, and lung diseases). Receiving the VZV vaccine was associated with about a 55% reduced risk of developing shingles.

The VZV vaccine was approved by the US FDA in 2006 and recommended for use in adults ≥60 years of age without contraindications by the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC), in 2007. According to a recent study by the CDC, only 10% of adults ≥60 years of age reported receiving the shingles vaccination in 2009, a slight increase from 6.7% reported in 2008. View survey results at: <http://www.cdc.gov/vaccines/stats-surv/nhis/2009-nhis.htm>

*Tseng HF, Smith N, Harpaz R, Bialek SR, Sy LS, Jacobsen SJ. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. *JAMA* 305(2):160-6 (2011 Jan 12).