Itching is a sensation that, if sufficiently strong, will provoke scratching or the desire to scratch. It is a frequent and distressing symptom of various dermatological (see Table 1) and systemic diseases (see Table 2). It can also occur in some patients without any skin symptoms. Knowledge has accumulated about the initiation of itch by external stimuli, but the neuronal substrate in the skin has not been completely identified. This has fortunately changed to some degree since a group of histamine-sensitive C-fibers were recently identified, which probably represent the afferent units that mediate itch sensations. Histamine, derived from mast cells, is the best known pruritogen. It induces different degrees of itching when applied in different concentrations into the skin. In most dermatological and systemic diseases, except urticaria, histamine is not the main mediator. There are other proinflammatory mediators to consider such as substance P, proteases, interleukin-2, acetylcholine, vasoactive intestinal peptide (VIP) and opioid peptides. The different types of pruritus (see Table 2) have different etiological factors, which in most cases have not yet been clarified. As well, the mechanisms of excitatory and inhibitory processing in the central nervous system are not defined.

Drugs With Antipruritic Potency

Antihistamines

Histamine acts as a neuromediator via three receptors: H₁ receptors, which are located in the brain and the central nervous system, H₂ receptors, which mediate the secretion of gastric acid and other hormones, and H₃ receptors, which are involved in vasodilation and vasoconstriction of blood vessels. Classic sedating antihistamines, the newer nonsedating antihistamines, and tricyclic antidepressants can be used to block pruritis caused by histamine. Tricyclic antidepressants will be discussed separately.

Antihistamines are one of the most widely used medications in the world. They are helpful for treating diseases in which histamine plays a central role such as urticaria. But in most pruritic disorders they have only sedative and placebo effects. Exception should be made, however, for antihistamines such as cetirizine that show an additional inhibitory effect on eosinophils. These play an important role in mediator release in a variety of allergic disorders and atopic eczema. Due to the limited and
controversial antipruritic effect of antihistamines within the great variety of itching dermatoses, and the large number of papers on antihistamines, this will not be discussed here in further detail. In particular, evidence based studies fulfilling Cochrane’s criteria in atopic dermatitis have never been performed.

**Opiate Antagonists**
Severe itching can follow epidural and intraspinal analgesia. This is due to the presence of µ-opioid receptors in the central nervous system, and can be antagonized by naloxone. Opiate antagonists have also shown some antipruritic potency in etiologically different types of pruritus such as cholestatic4,5, uremic6, butorphanol-induced7, histamine-induced8 pruritus and in itching associated with urticaria and atopic dermatitis9.

**Serotonin Receptor Antagonists**
Since 1993, several reports have been published on the improvement of cholestatic10, uremic10 and opioid-induced11 pruritus by ondansetron, a serotonin (5HT3) receptor antagonist. Under experimental conditions this antipruritic potency could not be verified12. Further investigations showed that tropisetron, another 5-HT3 receptor antagonist, has some antipruritic potency in mast cell depleted skin13.

**Tricyclic Antidepressants**
Tricyclic antidepressants bind to H1 receptors with a high degree of affinity, and to a lesser extent to H2 receptors. Droxepin has demonstrated antihistaminergic, antimuscarinic, antiserotonergic, anti-alpha-adrenergic and sedative activity14,15. Tricyclic antidepressants may also have some effects on neurogenic and psychogenic itching. Oral doxepin proved to reduce itching in patients suffering from chronic idiopathic urticaria. Due to its pharmacokinetic profile doxepin can be applied topically, reducing systemic adverse effects such as drowsiness, dryness of the mouth and eyes, and constipation15.

**Tacrolimus (FK 506)**
Tacrolimus is a macrolide immunosuppressive agent, which suppresses the T-cell mediated immune response. It mediates pruritus via the modulation and suppression of T-cell invasion, and the release of mediators that can provoke pruritus. Systemic administration of tacrolimus (FK 506) is effective for the treatment of psoriasis, Behcet’s disease, pyoderma gangraenous and Crohn’s disease16. A topical formulation of tacrolimus (Protopic/Fujisawa) is undergoing regulatory evaluation in the US and Canada for use in atopic dermatitis and other inflammatory dermatoses16.

**Ascomycin**
Ascomycin derivatives represent a new class of compounds with immunomodulating properties. SDZ ASM 981 is the first ascomycin macrolactam derivative to be developed for the treatment of inflammatory skin diseases, especially atopic dermatitis17. It selectively inhibits the release of inflammatory cytokines. This derivative can only penetrate damaged skin. To our knowledge there are no data on its systemic effects in pruritus and pruritic skin diseases.

Table 1: Some dermatological disorders associated with pruritus

<table>
<thead>
<tr>
<th>Skin disease</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infestation</td>
<td>Scabies, Pediculosis, Insect bites</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Atopic dermatitis, Irritant or allergic contact dermatitis, Urticaria, Mastocytosis, Bullous diseases, Psoriasis, Parapsoriasis, Polymorphic light eruption, Lichen simplex chronicus</td>
</tr>
<tr>
<td>Infections</td>
<td>Mycosis, Bacterial infections, Viral infections</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Cutaneous T-cell Lymphoma, Hodgkin’s disease</td>
</tr>
<tr>
<td>Hereditary/congenital</td>
<td>Darier-White disease, Hailey-Hailey disease, Inflammatory Linear Verrucous Epidermal and Nevus (ILVEN)</td>
</tr>
<tr>
<td>Other</td>
<td>Xerosis, Eczema Craquelé, Anogenital pruritus, Amyloidosis, Mucinosis</td>
</tr>
</tbody>
</table>

continued on page 5
Topical immunotherapy using diphencyprone (DPCP) is considered by many dermatologists to be the treatment of choice for extensive alopecia areata. Unfortunately, DPCP is not officially approved anywhere mainly because there is not enough evidence to support its safety.

**DPCP**

DPCP has been used throughout the world since 1983 for the treatment of extensive (>40%) alopecia areata. It is a compound used topically to induce an allergic contact dermatitis. Its exact mechanism of action is still unknown, but researchers hypothesize that the inflammatory reaction that is created diverts the immune system away from the hair follicle, thereby allowing new hair to grow.

The average response rate varies among patients with alopecia areata, but seems to be around 40% for cosmetically acceptable regrowth. Forty percent of those who respond will maintain a cosmetically acceptable head of hair even 6 months after DPCP has been stopped. The most common side effects are mild eczema, cervical lymphadenopathy and skin pigment changes.

The US FDA is concerned that there are too many unknowns regarding DPCP. However, there are some encouraging data in favour of its safety. DPCP was not detected in the serum or urine of patients treated topically for alopecia areata, and no major side effects have been reported since its initial use.

### Indication

Treatment of alopecia areata when more than 40% of scalp hair is lost.

### Technique of application

Sensitization with 2% DPCP followed by weekly application of a lower concentration that will be slowly increased each week until a mild eczema is elicited.

### Maximum duration of treatment if no response

6 months

### Initial response

12 weeks

### Cosmetically acceptable regrowth

24 weeks

### Overall response rate:

- 40–99% involvement
- 100% involvement
  - 40%
  - 5%

### Relapse rate

60% at six months in patients who experienced a cosmetically acceptable regrowth.

### Side effects

- Allergic contact dermatitis
- Cervical lymphadenopathy
- Pigment changes

**Table 1:** Summary.

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**ABSTRACT**

Topical immunotherapy with diphencyprone (DPCP) for the treatment of severe alopecia areata has been used since 1983 and is felt to be the treatment of choice by many dermatologists. Although there have been no major side effects reported since its initial use, there remain some unknowns regarding its safety. Because DPCP has at least a 40% success rate for cosmetically acceptable regrowth in extensive alopecia areata, its availability is an important matter for patients with alopecia areata.

**Key Words:** topical immunotherapy, diphencyprone, alopecia areata
Drug Warnings

**Skin Cap Spray** – In March 2000, HPB-Ottawa announced that Skin-Cap Spray (Cheminova Internacional, Madrid, Spain) was found to contain an undeclared and potent corticosteroid at a class 1 hazard level, and should not be used without medical supervision. The corticosteroid in question is betamethasone-21-butyrate-17-propionate.

Skin-Cap Spray was approved in Canada as an OTC anti-dandruff preparation, but the product was mislabelled to treat seborrheic dermatitis and mislabelled as to the contents.

Dermalabs Inc., the Canadian distributor for this product, has voluntarily initiated a recall. Health Canada is not aware of any reports of illness and has received no complaints associated with the current distribution of this product, which was only recommenced in mid-January 2000. This is the second time HPB-Ottawa has issued a warning about Skin-Cap because it contained an undeclared corticosteroid. The first time was in 1997, when it was found to contain clobetasol, another potent corticosteroid. Skin-Cap is sold in many countries worldwide.

**Miralex Skin Cream** – Another product that was found to contain an undeclared corticosteroid (clobetasol propionate), and was subsequently withdrawn by HPB-Ottawa is Miralex Skin Cream. It was sold as a corticosteroid-free natural product.

A class action suit has been commenced in British Columbia, Canada, against the distributors of this product. If you or your patients would like to learn more about the class action, contact Mr. Ward Branch at the law firm of Branch MacMaster (604) 654-2966, e-mail <wbranch@branmac.com>. At this time, the class action is only proposed on behalf of BC residents. However, Mr. Branch indicates that if someone from outside BC comes forward, the action could be expanded to include persons from outside BC.

**The Future**

Although alopecia areata is a medically benign condition, it can cause extreme distress in a large number of patients.

After weighing the pros and the cons, the National Alopecia Areata Foundation and the US FDA are considering the possibility of making DPCP available as an investigational new drug. At this time, a decision has not been made as to whether the investigation will be done in a multi-center study, or by issuing “packets” that will be available to physicians in the US who want to take part. In Canada, once again, this whole process is not mandatory.

**Conclusion**

Within the next few years, the collection of all combined worldwide data, including Canada, should allow the US FDA and HPB – Ottawa to assess safety issues more accurately in order to ultimately gain full regulatory approval.

**References**


## Update on Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncologic Agent</strong></td>
<td><strong>Bexarotene Capsules</strong></td>
<td>The US FDA approved <em>Targretin</em> capsules in February 2000, to be taken orally once/day, for the treatment of all stages of cutaneous T-cell lymphoma (CTCL) in patients who are refractory to &gt; 1 prior systemic therapy. In November 1999, Ligand submitted a marketing application to the European Union (EU) seeking marketing clearance for treatment of CTCL.</td>
</tr>
<tr>
<td><strong>Targretin</strong></td>
<td><strong>Ligand Pharmaceuticals</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Temozolomide</strong></td>
<td><strong>Temozolomide</strong></td>
<td>Schering-Plough has withdrawn its EU marketing application for this oncologic agent for the treatment of advanced malignant melanoma (an additional indication). The EU authorities said that additional studies will be needed for approval. It is already approved in the US and Europe for anaplastic astrocytoma.</td>
</tr>
<tr>
<td><strong>Temodal</strong></td>
<td><strong>Schering-Plough</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mequinol 2%/Tretinoin</strong></td>
<td><strong>0.01%</strong></td>
<td>The US FDA approved this drug in December 1999, for the treatment of solar lentigines.</td>
</tr>
<tr>
<td><strong>Solasge</strong></td>
<td><strong>Bristol-Myers Squibb</strong></td>
<td></td>
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<tr>
<td><strong>Linezolid</strong></td>
<td><strong>Zyvox</strong></td>
<td>A US FDA advisory committee in March 2000, recommended approval of linezolid injection, tablets, and oral suspension for skin and skin structure infections, hospital-acquired pneumonia, and for infections caused by vancomycin-resistant <em>Enterococcus</em>.</td>
</tr>
<tr>
<td><strong>Pharmacia &amp; Upjohn</strong></td>
<td></td>
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<tr>
<td><strong>Amphotericin B Liposome for Injection</strong></td>
<td><strong>Ambisome</strong></td>
<td>HPB - Ottawa approved this antifungal agent in March 2000, for the treatment of systemic or disseminated infections due to <em>Candida</em>, <em>Apergillus</em> or <em>Cryptococcus</em> in patients who are refractory to or intolerant of conventional amphotericin B therapy, or suffer renal impairment.</td>
</tr>
<tr>
<td><strong>Fujisawa Canada</strong></td>
<td></td>
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<tr>
<td><strong>Terbinafine HCl 1% Solution</strong></td>
<td><strong>Lamisil</strong></td>
<td>The US FDA has approved the switch of this drug from prescription to OTC status. <em>Lamisil</em> is the only OTC antifungal liquid indicated for the treatment of interdigital athlete’s foot, jock itch and ringworm.</td>
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<tr>
<td><strong>Novartis</strong></td>
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<tr>
<td><strong>Oncologic Agent</strong></td>
<td><strong>re: Panretin Gel</strong></td>
<td>Phase III trials for Ligand’s alitretinoin 1% gel (<em>Panretin</em>) for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi’s sarcoma were reported in December 1999. Ligand reported that 35% of patients treated in this 12-week multicenter, vehicle controlled study had at least 50% improvement in their cutaneous lesions.</td>
</tr>
<tr>
<td><strong>Antifungal Agent</strong></td>
<td><strong>re: Sporanox</strong></td>
<td>The labelling for <em>Sporanox</em> (Itraconazole) was changed in March 2000, to indicate this drug’s inhibition of the CYP 3A4 isoenzyme. Serious cardiovascular events have occurred in patients using astemizole, cisapride, pimozide or quinidine concomitantly with CYP 3A4 inhibitors.</td>
</tr>
<tr>
<td><strong>Solarase</strong></td>
<td><strong>SkyePharma PLC</strong></td>
<td>SkyPharma PLC signed an agreement with Bioglan Pharma PLC in March 2000, for the manufacture and European marketing and distribution rights to <em>Solarase</em>, a topical gel for actinic keratosis.</td>
</tr>
<tr>
<td><strong>re: Drug Interactions</strong></td>
<td></td>
<td>Patients should be cautioned about taking herbal products along with pharmaceuticals. Mixing them can lead to side-effects which include bleeding, increased psychiatric effects and hypertension. For example, patients who have clotting disorders or are awaiting surgery should avoid gingko, danhen, dongquai, papaya, or garlic. Phenoxyzine users should avoid ginseng and those on tricyclic antidepressants should avoid yohimbine. Patients taking cyclosporin, serotonin reuptake inhibitors, or digoxin should avoid St. John’s Wort. St. John’s Wort has also been reported to compromise the effectiveness of the HIV drug indinavir.</td>
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