Demographic studies suggest that onychomycosis affects between 6.1% and 6.9% of the Canadian population. Several risk factors are associated with the development of onychomycosis, including male gender, increasing age, diabetes, peripheral vascular disease, and immunosuppression. With the increasing age of the Canadian population and the high incidence of diabetes, a set of safe and effective options for the treatment of this condition is needed.

**Ciclopirox Nail Lacquer**

Ciclopirox (Penlac™, Dermik) 8% solution is the only topical antifungal approved for onychomycosis in Canada. This compound is fungicidal in vitro against proliferating and dormant fungal cells, and has a broad spectrum of activity. Ciclopirox nail lacquer was recently approved in Canada (April 2004) as part of a comprehensive nail management program, in which the lacquer is applied once daily for 48 weeks and nail debridement is performed under the supervision of a medical professional.

**Mechanism of Action**

Ciclopirox targets a variety of metabolic processes in the fungal cell. It chelates polyvalent cations (Fe+3 and Al+3) that are involved in fungal enzymatic activity, ultimately interrupting intracellular energy production and toxic peroxide degradation. Ciclopirox may also inhibit fungal nutrient uptake, resulting in a depletion of amino acids and nucleotides and a reduction in protein synthesis.
**Pharmacokinetics**

Ciclopirox nail lacquer penetrates the nail plate via a transungual delivery system. When the solvent evaporates, the concentration of ciclopirox increases from 8% to 34.8%, providing a concentration gradient that facilitates the transfer of the drug through the nail plate. This mode of application permits distribution of the active compound throughout the entire nail plate, including the lateral margins and onycholytic portions of the nail. In vitro penetration studies in pigskin, cow horn, sheep hoof plates, and human nails using radiolabelled ciclopirox demonstrated penetration of the active ingredient as deep as 0.4mm into the nail after one application. Pharmacological studies demonstrate that ciclopirox nail lacquer, applied daily for 7-14 days, penetrates the nail at concentrations that exceed the in vitro minimum inhibitory concentrations (MICs) for most fungal species.

**Safety**

**Drug-Drug Interactions**

Ciclopirox has no reported interactions with other systemic drugs.

**Adverse Events**

Ciclopirox treatment-emergent adverse events (TEAE) reported in US pivotal trials were localized to the treatment area. Nine percent of patients treated with ciclopirox nail lacquer and 7% of patients treated with vehicle reported TEAEs considered by the investigator to be related to the test material. The most common TEAE was a mild rash at the application site (5% ciclopirox, 1% vehicle). Other attributable TEAEs included nail disorders such as shape change, irritation, ingrown toenail, and discolouration.

**Systemic Absorption**

Low levels of ciclopirox are recovered systemically. The mean systemic absorption of ciclopirox is less than 5% of the applied dose.

**Efficacy**

**In Vitro**

The efficacy of ciclopirox has been demonstrated against a broad spectrum of proliferating and dormant fungal strains. The MIC (mean ± SEM) for ciclopirox was 0.04±0.02mg/ml against dermatophytes, 0.05±0.02mg/ml against yeasts, and 1.04±2.62mg/ml against other nondermatophytes.

**In Vivo**

Two double-blind, vehicle-controlled, multicenter pivotal US clinical trials assessing the use of ciclopirox nail lacquer for mild-to-moderate onychomycosis (20%-65% surface involvement of the target toenail) demonstrated significant mycological efficacy of the active compound when compared with the vehicle. The mycological cure (negative KOH and culture) rate for ciclopirox nail lacquer applied once daily for 48 weeks was 29% (ciclopirox) vs. 11% (vehicle) in the first trial and 36% (ciclopirox) vs. 9% (vehicle) in the second trial. Data from a meta-analysis of 10 trials conducted worldwide showed a mean (±SE) mycological cure rate of 52.6%±4.2% (range: 46.7%-85.7%). Although the parameters of these studies were different, these results were consistent with the US results. These studies and US pivotal trials establish the efficacy of ciclopirox nail lacquer for the treatment of onychomycosis.

Successful treatment of onychomycosis caused by nondermatophyte molds with ciclopirox nail lacquer has been reported. These results demonstrate the broad spectrum of activity of ciclopirox nail lacquer in vivo.

**Combination Therapy**

Ciclopirox has demonstrated synergy in vitro when combined with oral agents. Synergy between ciclopirox and terbinafine was demonstrated against 5 of 6 nondermatophyte species tested. Synergy, additivism, and indifference were observed between ciclopirox and itraconazole. No antagonism was observed for either combination.

Mycological cure rates in patients receiving 8 weeks of terbinafine (250mg/day) plus ciclopirox nail lacquer (once daily for 48 weeks) compared with patients receiving 12 weeks of terbinafine monotherapy (250mg/day) suggest that combination therapy of ciclopirox nail lacquer with lower doses of terbinafine may be effective. At the end of 48 weeks, mycological cure was reported in 66.7% of patients treated for 8 weeks with terbinafine and ciclopirox, 70.4% of patients receiving 12 weeks terbinafine and ciclopirox, and 56.0% for those treated with 12 weeks of terbinafine alone (p>0.05).

**Candidates for Treatment**

Patients not eligible for systemic treatment due to safety issues (i.e., the elderly and patients with hepatic dysfunction), those using multiple medications, or patients unwilling to use systemic treatment are candidates for topical antifungal therapy using ciclopirox nail lacquer. In patients with onycholysis, the lacquer may penetrate to onycholytic regions that may not receive adequate drug from conventional oral therapy. In cases of dermatophytoma, a subungual mass of densely packed thick-walled fungal hyphae,
a combined approach of oral/topical/mechanical therapies may increase efficacy rates. In lateral onychomycosis, the concentration of the oral antifungal agent is lower in the lateral portion of the nail plate, and combining it with ciclopirox nail lacquer may help improve efficacy by providing drug to this area of the nail.15

Patients may benefit from the use of ciclopirox nail lacquer applied twice weekly7,11 as a means of preventing recurrence. However, the benefit of prophylactic treatment needs to be confirmed in controlled trials.

Cost
Pharmaco-economic analysis16 suggests that ciclopirox nail lacquer may be a cost-effective option for the management of dermatophyte onychomycosis. The wholesale price of the lacquer in Canada is $89.95/6g bottle, which offers more than 1,000 applications.17

Conclusion
Ciclopirox nail lacquer is the only approved topical agent for the treatment of mild-to-moderate onychomycosis. The choice of antifungal therapy depends on several factors: efficacy, spectrum of activity, convenience, cost, and patient/physician preference. Combination therapy using ciclopirox nail lacquer and terbinafine may be a consideration in moderate-to-severe cases of onychomycosis.

References
5. Penlac® (Ciclopirox) topical solution 8% [Canadian prescribing information] (2004) Laval, Quebec.
While cosmetic evaluation needs to address the face as a harmonious whole, it can be divided into the lower, middle, and upper face. Recently, the upper third, consisting of the eyes, brows, and forehead has drawn increased attention from esthetic surgeons. This renewed interest may reflect the perception that an individual’s face begins with the eyes, underscoring the notion that the “eyes are the windows of the soul.”

The hallmarks of upper third facial aging are: lowered brows; lines of expression on the forehead glabellar and periorbital regions; and lateral hooding, dermatochalasis, and fat pseudoherniation in the medial aspect of the upper eyelids. In the lower eyelids, there may be a tear drop deformity, pseudoherniation of the three fat compartments, and rhytides. These changes in the lower eyelid, combined with malar hollowing, leads to the so-called “double bubble” irregularity, a telltale sign of the aging face.

The majority of patients who end up requiring an upper or lower blepharoplasty or both will give the chief complaint of “looking tired or not alert” even when they are rested and alert. Some will state that their eyes appear much smaller. Many women will also relate that they have no upper eyelid platform upon which to place make-up. Some patients who have significant upper hooding will have reduced lateral visual acuity. Lower eyelid bags will accentuate the tired look and may appear as unsightly dark circles.

Essentially, the goals of blepharoplasty should be to restore a rested appearance to the eyes with a wider palpebral aperture and greater smoothness and symmetry. When there is visual compromise, the aim is increased temporal vision. Depending on the patient, resection of skin, muscle, and fat will achieve these objectives. However, in recent years, most cosmetic surgeons have reduced the amount of skin and fat removed from both the upper and lower eyelids. Too aggressive an approach may lead to hollowing of the eyelids and a “cadaveric” appearance. In some patients, particularly those with a nasojugal depression, a fat pedicle or filler may be necessary. Some practitioners have advocated fat transfer to both the upper and lower eyelids, which may tighten the skin, decrease hollowing, and provide a more youthful appearance.

Decision-Making

Upper Eyelid

The basic decisions involved in upper eyelid blepharoplasty include whether to extend the incision laterally and superiorly if there is lateral hooding, and whether to remove fat in addition to the skin-muscle excision. Some surgeons warn against lateral extension of the blepharoplasty incision since it may invite visible scarring. In most cases, however, this scar can be hidden in the periorbital crow’s feet. While there has been a trend toward removal of skin rather than fat, if there is pseudoherniation, particularly in the medial fat pad, not removing fat will produce an unsatisfactory result.

When performing a four-lid blepharoplasty, there are no hard and fast rules for the order. Many surgeons will perform the upper blepharoplasty first, particularly if there has been a browlift. The author

ABSTRACT

A telltale sign of the aging face is upper eyelid skin redundancy and lower eyelid bags. These changes can contribute to a “tired” appearance. Upper and lower blepharoplasty procedures can correct these processes. By removing skin and muscle, an upper eyelid blepharoplasty can give the eye a larger appearance. A lower blepharoplasty can remove pseudoherniated fat, or transpose it to provide a smooth infraorbital contour. It appears that a transconjunctival approach for the lower blepharoplasty will lead to a lower incidence of eyelid malposition. An adjunctive procedure such as laser resurfacing may be appropriate. Patients should be counseled on all potential complications, including visual loss from muscle injury or hematoma, as well as the extent of postoperative recuperation.

Key Words: blepharoplasty, dermatochalasis, transconjunctival
performs blepharoplasties under local anesthesia with oral sedation, and finds it preferable to perform the upper and then lower lids because the patient may be more attentive initially in keeping his/her eyes closed. Another basic issue in performing upper and lower blepharoplasties is determining which cutting device to use: cold steel vs. cautery vs. radiofrequency vs. laser. Again, there is no correct answer. Laser may result in better hemostasis and less collateral damage, but many surgeons prefer the tactile feel of scalpel or electrocautery/radiofrequency. The author uses cold steel for the upper blepharoplasty and a Colorado needle for the lower transconjunctival blepharoplasty. It has been reported that radiofrequency may result in less collateral damage and less risk of injury to orbital structures. The diamond scalpel has also been used successfully for blepharoplasties.

Lower Eyelid

Similar to the upper eyelid, the lower eyelid should have a smooth contour. This contour may be disrupted by pseudoherniated fat, a reduction in volume in the nasojugal groove, static rhytides in the periorbital region, and crow’s feet. The overall aging process creates an unevenness of the lower eyelid and an undulation between the periorbital cosmetic unit and the malar region of the cheek. Therefore, the goal of rejuvenating the lower eyelid should be to create a uniform contour and surface.

If the patient has crow’s feet and static periorbital rhytides with only mild bulging, the best option would be to combine laser resurfacing with botulinum toxin A (BOTOX®, Allergan). If fat is to be removed, then a transcutaneous or transconjunctival approach can be chosen. Though technically more demanding, the latter technique reduces the likelihood of postoperative lower lid malposition. There is also no visible scar. While fat will generally need to be removed from each of the three fat pockets, the philosophy again is to remove less rather than more. Experimentally, injections of phosphatidylcholine have been used to reduce a small amount of fat. If there is a tear drop deformity, then a fat pedicle will have to be raised and mobilized in the subperiosteal space. A bulge in a portion of the lower lid, particularly in men, is usually due to orbicularis oculi hypertrophy, and a partial resection will need to be considered. The disadvantage of the transconjunctival approach is that it will not remove excess skin. Therefore, on practically all of the author’s patients, peri orbital laser resurfacing is performed; however, if a patient has festooning, this procedure will not be adequate and some skin resection will be necessary. A small group of patients has undergone radiofrequency treatment of the lower eyelid for redundant periorbital skin with reasonable results and minimal downtime.

If laser resurfacing is to be performed on a more mature patient who has pre-existing lid laxity, then it would be prudent to incorporate a canthopexy procedure. This procedure can also be used to produce a slightly more “almond” shaped eye as well as increasing the canthal tilt. Both of these anatomic characteristics communicate youthfulness and are accentuated in the female eye.
While the decisions in blepharoplasty focus on the removal of tissue, there is a school of thought that emphasizes replacement of tissue since facial aging does indeed cause volume loss. This loss can be replaced by fat transfer. The lateral brow can be elevated by injecting fat just inferior to the brow. Injecting fat into the upper eyelid sulcus will create fullness, while making the redundant upper eyelid skin taut. In the lower eyelid, fat injections can diminish hollowing, or potentially, even out the valleys between the pseudoherniated fat pads. This fat contouring will eliminate the “double bubble” and create a more youthful appearance. The disadvantages of fat transfer are that it is temporary and that it requires multiple treatments. It should be reserved for the subset of patients who have only mild dermatochalasis, and where hollowing of the lower lids predominates over fat pad protuberance. In addition, this technique should be performed only by those who have a great deal of experience in fat transfer techniques.

Recently, other fillers such as hyaluronic acid, calcium hydroxyapatite and l-polylactic acid have been used in these areas, particularly in the tear trough. These injections offer ease of use and less downtime than fat transfer. However, there has not been long-term follow-up for these techniques, and they may provide only a short-term effect. Importantly, injections of these substances in this cosmetic unit are considered an off-label use.

Figure 1A, B: Pre- and post-operative images of patient with lower eyelid pseudoherniated fat pads and 3 months following transconjunctival blepharoplasty and erbium: YAG laser resurfacing of the infraorbital region.

Outcomes

Long-term outcome studies for upper eyelid blepharoplasty have not been performed. Yet, with natural senescence, the positive effects of an upper blepharoplasty should last at least a decade. If fat is appropriately removed, it is unlikely that there will be additional pseudoherniated fat for a substantial number of years. As mentioned, the opposite effect, that of hollowing, will be the major challenge in the ensuing years. An important factor determining the longevity of an upper lid blepharoplasty is the descent of the eyebrows. This phenomenon will create a pseudoredundancy of upper eyelid skin and will increase hooding. This descent is genetic-, expression- and photodamage-related. Because of this natural descent, a minimally invasive transblepharoplasty browpexy may be indicated.

Transcutaneous vs. Transconjunctival Approaches

An unpublished review of the literature since 1970 compared 4,460 transcutaneous blepharoplasties with 3,438 patients who underwent the transconjunctival approach. In terms of complications, lid malposition was the most frequent in patients who received a transcutaneous blepharoplasty, occurring in 1.4% vs. 0.7% in the transconjunctival patients. However, the latter had significantly more edema, i.e., 18.4% vs. 0.2% for the transcutaneous blepharoplasties. Hematoma and inferior oblique injury were also more common in the transconjunctival approach, as were inadequate fat removal and overcorrection. Both of the latter occurred in 1.2% of the patients. Wrinkling of the lower eyelid remained in a far greater number of those undergoing the transconjunctival blepharoplasty, i.e., 11.4% vs. 2.4% in the transcutaneous group. Consequently, adjunctive procedures such as chemical peels and laser resurfacing were much more common, i.e., 32% vs. 1.5% with the transconjunctival approach. Yet, a large majority of the patients, 90.4%, were ultimately satisfied with the transconjunctival approach. There was minimal data in this outcome for those undergoing the transcutaneous blepharoplasty. Despite the higher rate of potential complications, the transconjunctival approach and an adjunctive resurfacing procedure was preferred by most practitioners in this review of the literature. The approach's steeper learning curve may account for some of its complications. Because the transconjunctival approach dramatically reduces the potential for ectropion (lid malposition was probably under-reported for the transcutaneous approach), it is a more versatile technique, particularly for elderly patients.

Counseling Patients

As with any procedure, appropriate patient expectations is one of the keys to a satisfactory outcome. The patient should understand that a blepharoplasty will not elevate the brows, or reduce rhytides or lines of expression. An upper blepharoplasty will make the eyes appear larger and more prominent in the upper third of the face. The patient will appear more alert, and, if female, have a larger platform on which to apply make-up. This aspect will provide a rejuvenating effect, but middle-aged patients should not expect to appear as they did in their third decade. Similarly, a lower
Blepharoplasty will produce a smoother infraorbital contour and make the patient appear well rested. It will not affect a sagging malar eminence directly below this cosmetic subunit. A mid facelift would be needed to elevate the malar area and diminish a “double bubble” effect.

During the preoperative appointment, all complications, from conjunctival irritation and bruising to muscle injury and retrobulbar hematoma, should be explained. The possible visual consequences should also be discussed. There is an art to explaining these potential complications without having the patient forego the surgery. These explanations should be outlined in the informed consent. Postoperative care and length of recuperation also need to be discussed and reiterated. Optimally, a handout should be given to the patient that details what to expect following the surgery. While bandaging is minimal for blepharoplasty, the upper lid incision will be highly visible for at least 1 week. Swelling in both upper and lower eyelids may take months to resolve. Antibiotic ointment may cause a contact dermatitis, and the patient should be educated about this possibility. For a lower lid blepharoplasty, there may be conjunctival irritation and dry eyes. Artificial tears may be needed for several weeks, particularly if the patient has a history of this condition. If laser resurfacing is to be performed, then the patient needs to be educated about prolonged erythema and wound care. Most importantly, because of possible swelling, the final results of the surgery may not be fully apparent for 3 months.

Conclusions

Blepharoplasty is indicated for patients who have pseudoherniated fat pads in the upper and lower eyelids as well as those with redundant skin and hooding in the upper eyelids. While the outcomes of the device used—cold steel vs. laser—aren’t definitive, it does appear that in the lower lid, the transconjunctival approach is preferred. However, an adjunctive procedure such as laser resurfacing may be required. Patients should expect to appear less tired after these procedures, and should be counseled as to the complications and the postoperative recovery of blepharoplasty.

References


### Antiviral Agent

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<thead>
<tr>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
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<tbody>
<tr>
<td>Zoster Vaccine Live</td>
<td>The US FDA received a Biologics License Application in April 2005 for this investigational vaccine for the prevention of herpes zoster, the prevention of postherpetic neuralgia, and the reduction of acute and chronic shingles-associated pain in adults.</td>
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<tr>
<td>Zostavax™</td>
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<td>Oka/Merck</td>
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### Wound Management

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<th>Name/Company</th>
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<tr>
<td>Antimicrobial Barrier Dressing</td>
<td>The US FDA approved this product in May 2005 for wound care as a barrier to bacterial penetration, featuring the patented Silcryst™ nanocrystalline silver technology.</td>
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<tr>
<td>ACTICOAT* Moisture Control</td>
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<td>Smith &amp; Nephew</td>
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### Antibacterial Agent

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<td>Meropenem for Injection</td>
<td>The US FDA approved this antibiotic in May 2005 for the treatment of complicated skin and skin structure infections in adults and children.</td>
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<td>MERREM®</td>
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<td>AstraZeneca</td>
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### Antipsoriatic Agent

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<td>Etanercept</td>
<td>The US FDA approved an additional indication for this tumor necrosis factor receptor in June 2005 to improve physical function in patients with psoriatic arthritis.</td>
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<td>Enbrel®</td>
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<td>Amgen/Wyeth Pharmaceuticals</td>
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### Drug News

#### Cancer Vaccine

CancerVax, in April 2005, announced plans to discontinue the Phase III clinical trial of Canvaxin™ in patients with Stage IV melanoma on the basis of the recommendation of the Independent Data and Safety Monitoring Board (DSMB). The DSMB, after a limited review of the trial found that the data are unlikely to provide significant evidence of a survival benefit for Canvaxin-treated patients with Stage IV melanoma vs. those receiving placebo. There were no safety issues identified, and the recommendation to close the study was not made because of any potential safety concern. It is anticipated that the final analysis of data from this clinical trial will take place after the required number of clinical events have occurred, currently estimated to take place in mid-2006.

#### Antipsoriatic Agent

Serono, in April 2005, announced the discontinuation of a Phase III clinical trial program for onercept (recombinant tumor necrosis factor binding protein) in moderate-to-severe psoriasis. Investigators reported two patients who were diagnosed with sepsis, one of whom subsequently died. Sepsis is a recognized potential risk for patients treated with anti-tumor necrosis factor therapies. The Independent Data and Safety Monitoring Board (DSMB) evaluated the available blinded efficacy data at 12 weeks, and data from the first 12 weeks of an open-label trial. Based on these aggregate data, they determined that the efficacy response observed for onercept was less than that observed in the earlier phase II trial, and with other available treatments. As a consequence of its unfavorable risk-benefit profile, the DSMB recommended discontinuation of the clinical development of onercept in moderate-to-severe psoriasis.