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DLQI: Dermatology Life Quality Index; NRI: Non-responder imputation; sPGA: static Physician's Global Assessment; TNF: tumour necrosis factor.

* The efficacy and safety profile of SKYRIZI were assessed in 997 patients with moderate to severe plaque psoriasis in two multicentre, randomized, double-blind studies, ULTIMMA-1 (SKYRIZI: n=304; ustekinumab: n=100; placebo: n=102) and ULTIMMA-2 (SKYRIZI: n=294; ustekinumab: n=99; placebo: n=98). 598 patients were randomized to SKYRIZI 150 mg, 199 to ustekinumab 45 mg (≤100 kg body weight) or 90 mg (>100 kg body weight), and 200 to placebo. Patients received treatment at Week 0, Week 4, and every 12 weeks thereafter.

† NRI was used to impute missing data.

‡ IMMHANCE was a multicentre, randomized, double-blinded study in patients with moderate to severe plaque psoriasis (407 randomized to SKYRIZI 150 mg and 100 to placebo). Patients received treatment at Week 0, Week 4, and every 12 weeks thereafter (Part A). Patients who were originally on SKYRIZI and had a sPGA response of clear or almost clear (0/1) at Week 28 were re-randomized to continue SKYRIZI every 12 weeks or have treatment withdrawn (Part B).

§ Treatment differences, 95% CIs and p-values were based on the Cochran-Mantel-Haenszel test stratified by weight (≤100 kg versus >100 kg) and prior TNF exposure (0 versus ≥1). Type I error rate for the multiple endpoints was controlled using a pre-defined hierarchical testing procedure.

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EDITORS WELCOME

Dear Canadian Dermatology Community,

As we reach the midway point of 2021, we all continue to be affected by the COVID-19 pandemic. On behalf of our editorial board, we hope that you and your families are coping and managing well during these difficult times.

Our readership continues to grow, and we are immensely thankful to all of those who have expressed such positive feedback about the journal over the last 18 months. We continue to welcome ideas about new topics and issues that are germane to your practices.

We have also created a central hub where all our articles are now archived and accessible to all subscribers. Please take a look by visiting www.canadiandermatologytoday.com

In this issue we have many fascinating topics ranging from lichen sclerosus and lichen planopilaris to examining new treatments in pediatric dermatoses and discussing oral supplementation in dermatology.

As always, we hope you find these articles informative and helpful. Please feel free to share our registration link with your peers so that, they too, can subscribe to future issues and access all archived articles!

Best wishes,

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The Product Monograph is also available by calling us at 1-866-502-6436.

References:
1. OTEZLA® Product Monograph. Amgen Canada Inc. August 5, 2020.
2. Amgen Canada Inc. Data on file (AUG2020 MedReg letter).
3. Amgen Canada Inc. Data on file (JAN2020 MedReg Letter).

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Dr. Sibbald is a dermatologist who completed her residency training at the University of Toronto and is board certified in Canada and the US. She completed fellowship training in pediatric dermatology at the Children's Hospital of Philadelphia. She has an MSc in Epidemiology from the London School of Hygiene & Tropical Medicine and a BSc Ph.M. from the University of Toronto. She is a staff physician with research and clinical activities at the Hospital for Sick Children, and recently joined the pyoderma gangrenosum clinic at Women's College Hospital. She is an Assistant Professor at the University of Toronto in the Department of Pediatrics with a cross appointment to the Department of Medicine. Her clinical interests are broad and include alopecia, morphea, and laser treatment of vascular lesions.

WHAT'S NEW AND OLD IN TREATMENTS FOR PEDIATRIC DERMATOLOGY

The past year has seen many new, exciting, approved treatments in pediatric dermatology become commercially available as well as the release of new evidence about existing therapeutic agents. This article will provide the reader with an overview of these treatments and their evidence.

PSORIASIS

Several biologics for the treatment of psoriasis in children have received expanded indications from Health Canada in the past year. Ustekinumab, an IL12/23 inhibitor, was approved in June 2020 for the treatment of chronic, moderate-to-severe plaque psoriasis in patients 6 to 17 years of age who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapy.

The approved dosing is weight- based (**Table 1**) with injections at 0, 4 and then every 12 weeks thereafter. The expanded indication is based on CADMUS Junior, a phase III open-label single arm study of 44 children aged 6 to <12 years with moderate-to-severe psoriasis for at least 6 months and a PASI score of ≥12. At week 12, 77% of patients achieved PGA 0/1, 84% achieved PASI75 and 64% achieved PASI90 response. Ustekinumab's onset of action resulted in approximately 25% of patients achieving PASI75 by week 4, and almost 60% of patients by week 8. The most common adverse effects reported were nasopharyngitis (25%) and infections requiring treatment (27%). Overall, 34 patients (77%) had at least one adverse event.[1]

Agent	Indication	Dose	Frequency	Efficacy	Adverse effects
Etanercept	**4 years and older:** chronic severe PsO who are candidates for systemic therapy or phototherapy	0.8 mg/kg	Once weekly	12 weeks: PASI75 ~60-70% PASI90 ~30-40%	URTI (37.6%) Nasopharyngitis (26%) Headache (21.5%)
Ustekinumab	**6 years and older:** For moderate-to-severe plaque psoriasis, who are candidates for phototherapy or systemic therapy	<60 kg: 0.75 mg/kg 60-100 kg: 45 mg >100 kg: 90 mg	0, 4, then every 12 weeks	12 weeks: PASI75 84% PASI90 64%	Nasopharyngitis (25%) URTI (14%) Infections requiring treatment (27%) ISR (14%)
Secukinumab	**12 years and older:** For severe plaque psoriasis, who are candidates for phototherapy or systemic therapy Must weigh > 50 kg	150 mg	0,1,2,3,4 weeks then monthly	12 weeks: PASI75 77.5-80% PASI90 67.5-72.5%	Neutropenia (2.6%), Candida infections (1.8%) ISR (6.1%)
Ixekizumab	**6 years and older:** For moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy	<25 kg: 40 mg then 20 mg 25-50 kg: 80 mg then 40 mg >150 kg: 160 mg then 80 mg	Every 4 weeks	12 weeks: PASI75 89% PASI90 78%	Infections (32%) Serious infections (0%) Crohn's disease (1%) ISR (12%)

Table 1. Currently Approved Biologics for Pediatric Psoriasis in Canada

The infrequent dosing of ustekinumab coupled with the absence of routine bloodwork enhances its appeal as a treatment option in the pediatric population. However, its efficacy in children with psoriatic arthritis or inflammatory bowel disease has not been studied in trials to date.

In January 2021, secukinumab, an IL-17A inhibitor, was approved by Health Canada for its use in adolescents 12 years and older with severe plaque psoriasis who are > 50 kg. The recommended dose is 150 mg subcutaneously at weekly intervals for the first 5 doses and then monthly thereafter. This dose can be doubled to optimize response. Support for this indication was demonstrated in a phase III multicentre double-blind study of 162 patients with severe psoriasis defined by a minimum PASI of 20, and PGA of 4. Patients were randomized to receive secukinumab (either 150 mg or 300 mg), placebo or etanercept. At week 12, PASI75 response was achieved in 80% of patients receiving high dose, and 77.5% of those receiving low dose. Secukinumab's onset of action resulted in 30-50% of patients achieving PASI75 response by week 4, and roughly 60% of patients by week 8. Among the 114 subjects receiving either dose of secukinumab, adverse reactions within the first year of treatment included neutropenia (2.6%), candida infections (1.8%) and injection site reactions (6.1%).[2]

A trial of children aged 2-17 years with enthesitis-related arthritis or juvenile psoriatic arthritis was completed in 2020, and results may help elucidate the effectiveness of secukinumab in pediatric arthritis (NCT03031782).

The most recent biologic approved in the pediatric population for psoriasis is ixekizumab, approved in March 2021 for children aged 6 to less than 18 years of age with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This approval was based on a phase III multicentre double-blind placebo-controlled trial of pediatric patients with moderate-to-severe plaque psoriasis, defined as a minimum PASI of 12, and sPGA of 3. Patients were randomized to receive ixekizumab every 4 weeks at weight tiered dosing (**Table 1**) or placebo. An etanercept reference arm was added. At week 12, PASI75 response and an IGA of 0/1 were achieved in 89% and 81% of patients receiving ixekizumab respectively. Approximately 35% of patients achieved PASI75 by week 4, and almost 65% by week 8. Adverse events at week 12 included injection site reactions in 12%, and infections in 32% of patients of which none were categorized as serious. Among the 196 patients who received at least one dose of ixekizumab, 1 patient had Crohn's disease at 12 weeks, with another 3 patients during the maintenance period.[3]

There were no cases of inflammatory bowel disease (IBD) in the adolescent psoriasis trial of secukinumab as compared to ixekizumab. However, the study populations for both trials were quite small. A claims-based retrospective case-control study of 7,686 children with psoriasis and 30,744 children without psoriasis revealed an incidence rate per 1000 person years of

0.97 (0.53-1.62) for Crohn's disease and 0.62 (0.28-1.17) for ulcerative colitis. This translated to an incidence rate ratio of 3.34 (1.60-6.86) for Crohn's and 2.70 (1.11-6.27) for ulcerative colitis, $p<0.05$ for both. More data is clearly needed before any conclusions can be drawn about whether these biologics have a true risk of uncovering IBD in a population at risk, and if any factors could help in screening those at increased risk.[4]

ATOPIC DERMATITIS

Dupilumab, a human monoclonal antibody targeting IL-4 and IL-13, is now approved for children with atopic dermatitis starting from the age of 6 years. The dosing is weight-based (**Table 2**). The adolescent phase III trial included 251 patients with moderate-to-severe disease, defined by a minimum IGA of 3, and EASI of 16 at baseline. Of note, patients were not allowed concurrent topical steroids in the trial. By week 16, EASI75 response was achieved in 38-42% of patients, and an IGA of 0/1 in 18-24% of patients. The majority of these participants responded by week 8.[5]

Conversely, the trial in children aged 6-11 years included 367 participants over 16 weeks and required slightly worse dermatitis at baseline, with a minimum IGA of 4 and EASI of 21. Subjects were allowed to use concurrent topical steroids with dupilumab therapy during the study period.[6]

At week 16, 67-69% of participants achieved EASI75 response, and 30-33% of subjects achieved an IGA of 0 or 1. The onset of action was similar to that seen in adolescents, with many participants achieving response 8 weeks after randomization.

The transition of patients from other systemic treatments to dupilumab have been proposed, with suggestions centering on longer tapers of cyclosporine to avoid a rebound. One published treatment algorithm suggests overlapping therapeutic agents for 8 weeks before tapering by 25% bi-weekly for cyclosporine, and by 50% every 4 weeks for other immunosuppressants.[7]

The guidance for the evaluation of risk and for the management of conjunctivitis and head and neck dermatitis are available for adult patients, and these could be used to inform the approach in pediatric patients. In the adolescent trial, most cases of conjunctivitis occurred in the first 2-3 months after treatment, and none led to the discontinuation of therapy. Interestingly, the rates of conjunctivitis in adolescents being treated with dupilumab for asthma are much lower than the rates of conjunctivitis seen in adolescents being treated with dupilumab for AD, and more research is required to determine possible explanatory factors for this phenomenon.[8] Recommendations for the screening and management of conjunctivitis include baseline assessment of risk factors including high IgE and pre-existing ocular signs or symptoms, use of lubricating drops, and involvement of ophthalmologists when symptoms develop.[9-11]

Head and neck dermatitis may be more common in the younger population, and a diagnostic challenge owing to its broad differential diagnoses. Morphologic distribution can be helpful; with isolated eyelid or periocular involvement more suggestive of allergic contact dermatitis, while involvement of both periocular and perioral regions being more consistent with periorificial dermatitis.[12] Malassezia-associated dermatitis may be more common in the pediatric population, and it is most prominent on the central face, forehead, chin and neck. Successful treatment of post-pubertal adolescents receiving dupilumab with head and neck dermatitis has been reported with systemic fluconazole for a week in a recently-published case series involving five adolescent patients.[13]

Dupilumab is also approved for the treatment of asthma in adolescents and is being studied in many eosinophil-mediated conditions. With JAK inhibitors on the horizon having potential for faster onset of action, concurrent treatment of atopic comorbidities will likely play a role in selecting optimal systemic treatments for children with atopic dermatitis.

Indication	Dose	Efficacy	Adverse effects
6 years and older: For moderate-to-severe atopic dermatitis, not adequately controlled with topical prescription therapies or when those therapies are not advisable	15-< 30 kg: 600 mg then 300 mg every 4 weeks 30-< 60 kg: 400 mg then 200 mg every 2 weeks 60 kg+: 600 mg then 300 mg ever 2 weeks	Age 6-12 years (Week 16) EASI75 ~75%, IGA 0/1 ~30-40% Age 12-17 years (Week 16) EASI75: 42% IGA 0/1: 24%	Age 6-12 years Conjunctivitis ~ 7-15% ISR ~10% Age 12-17 years Conjunctivitis ~ 10-11% ISR 6 - 8.5%

Table 2. Dupilumab indication, dose, efficacy and adverse event profile

Crisaborole 2% ointment remains a non-steroidal topical alternative for atopic dermatitis in children aged 2 years and older. The use of concurrent moisturizers to minimize any burning or irritation with application has been suggested by some clinicians. A small study examined the absorption of crisaborole in an ex vivo abdominal skin model.[14] When applied within 15 minutes after a moisturizer (in a cream or ointment), there was decreased absorption in both the epidermis and dermis. Additionally, there was decreased epidermal absorption of crisaborole when an ointment vehicle was applied immediately after. This small study suggests that waiting at least 15 minutes before applying moisturizers may optimize absorption of crisaborole.

ACNE

Trifarotene, a selective RAR-γ agonist, was recently approved as a 0.005% cream in Canada for treatment of facial and truncal acne in adolescents aged 12 years and older. The approval was supported by two phase III double-blind, randomized, vehicle-controlled, 12-week studies (PERFECT 1 and PERFECT 2) in 2420 patients aged 9 years and older.[15] For the 1214 patients treated with trifarotene and 1206 treated with vehicle, the week 12 facial success rates according to the IGA were 29.4% in PERFECT 1 and 42.3% in PERFECT 2 (vs 19.5% and 25.7% for vehicle [$P < .001$]); trifarotene had statistically significant superior success rates at week 4 (PERFECT 1) and week 8 (PERFECT 2). At week 12, the rates of success with trifarotene according to the truncal PGA were 35.7% in PERFECT 1 and 42.6% in PERFECT 2 (vs 25.0% and 29.9%, respectively for vehicle [each $P < .001$]). An open-label extension demonstrated ongoing improvement past 12 weeks, with an IGA of 0/1 being achieved in almost 70% of patients by 52 weeks.[16] The cream was well-tolerated in the majority of patients, with the main side effect of local irritation peaking in the first week on the face and at 2-4 weeks on the trunk with subsequent improvement over time.

Trifarotene has also been shown to increase expression of transglutaminase 1, which promotes keratinocyte cohesion.[17] Based on this observed effect, it is also being studied in clinical trials at higher concentrations (0.015% and 0.02%) in adolescents aged 12 years and older for lamellar ichthyosis (NCT03738800), but no interim results have been released and recruitment is ongoing.

Spironolactone has been used to treat acne in adults successfully for many years, but there has been limited data in pediatric patients. A recent retrospective review of 80 female patients including the pediatric population (median age 19 years; range 14-20) from a single clinic (Mayo Clinic, Rochester, Minnesota) reported complete response in 22.5% of patients, and a complete or a partial response greater than 50% in 58.8% of subjects.[18] The median dose was 100 mg, and median time to initial and maximal responses were 3 and 5 months respectively. Responders were more likely to have jawline distribution of acne (70.3% vs 56.3%) and cyclic flares (75% vs 56.3%), although this was not statistically significant. Only 3 patients experienced side effects (rash, breast tenderness, diarrhea, and headache) and required discontinuation of treatment. Investigators did not report symptoms of hypotension, although blood pressure and potassium were not routinely checked in the cohort due to a low risk of hyperkalemia in younger patients.

MORPHEA

There is now increasing evidence to support the efficacy and safety of mycophenolate mofetil (MMF) for pediatric morphea. To date, the combination of methotrexate (MTX) with pulse corticosteroids has been a first-line treatment approach for children with morphea requiring systemic treatment to prevent irreversible joint contractures or permanent deformities. However, up to 30% of patients do not respond to this combination treatment. Studies in adult populations suggest MMF may be an effective alternative.[19] In a retrospective study, outcomes of 47 patients treated with MTX were compared to 22 patients treated with MMF because of MTX-refractory disease or intolerance to MTX.[20] After a mean follow-up period of 9.4 years, 90.9% of patients on MMF and 100% of those on MTX had inactive disease.
Full doses of MTX and MMF were 15–17 mg/m2/week and 700-1000mg/m2/day respectively. Side effects of MMF included headache (22.7%), mild increase in transaminases (18.2%), nausea/vomiting (9.1%) and fatigue (9.1%), with none of the reported adverse events leading to drug discontinuation. Given the impressive performance of MMF, its efficacy in treatment-naïve patients compared to a traditional MTX and steroid combination may help secure its place in our treatment algorithm for pediatric morphea.

ALOPECIA AREATA

With the current lack of approval of JAK inhibitors for children with alopecia areata (AA), and challenges with availability and the cost of off-label preparations and compounds, this population remains in need of therapies for this condition. A recent review of five studies reported good or complete response in 34 of 68 children treated with methotrexate.[21] An additional retrospective review from Sunnybrook Health Sciences Centre in Toronto reported partial response in 4 of 7 children treated with MTX.[22] More data would help characterize responders and clarify optimal duration and dose of treatment.

There is also excitement about the potential of dupilumab for the treatment of AA, based on cases of regrowth of AA in patients with atopic dermatitis. A recent case series of 16 children with both atopic dermatitis and AA who were treated with dupilumab reported good regrowth in 4 of 8 children who had follow-up at 4 months.[23] One possible but unproven explanation for the divergent responses to dupilumab involves considering AA in four classifications as described by Ikeda.[24] In patients with severe atopic dermatitis and AA that is being perpetuated by massive interferon release, control of the dermatitis may be enough to allow for resolution of the alopecia. Conversely, in patients without pre-existing AA, treatment with dupilumab may lead to a shift in the immune system, triggering alopecia areata mediated by autoreactive CD8+ T cells.

HIDRADENITIS SUPPURATIVA (HS)

Adalimumab has been approved for the treatment of adolescent HS for several years, but the indication was not based on clinical trial data, thereby limiting our knowledge of its efficacy and onset of action in this patient population. A recent retrospective chart review of adolescents treated with biologics included seven patients aged 8-13 with Hurley Stage 2-3 disease treated with adalimumab.[25] Four patients responded with a minimum of 50% reduction in total abscess and inflammatory nodule count at 4 months, while the other 3 were switched to other biologics due to a failure in achieving Hidradenitis Suppurativa Clinical Response (HiSCR) on their original biologic therapy. No patients reported adverse events.

It is clearly an exciting time for pediatric dermatology, and the momentum is likely to continue with many new therapeutic options in the pipeline and new evidence emerging to optimize our treatment of dermatoses in this patient population.

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AN OVERVIEW OF LICHEN SCLEROSUS

INTRODUCTION

Lichen sclerosus (LS) is a chronic, inflammatory disease that typically affects the genital skin, and less frequently on other skin sites. It is characterized by white, shiny, scar-like atrophy. Symptoms include pruritus, burning, progressive atrophy, and in severe cases, loss of normal genital architecture, and functional impairment.

Synonyms: kraurosis vulvae, balanitis xerotic obliterans (in males), lichen sclerosus et atrophicus

EPIDEMIOLOGY

The exact incidence and prevalence of lichen sclerosus are not known due to a lack of population-based data in the literature. One previous review of a general gynecology practice estimated the prevalence of vulvar LS to be around 1.7%[1] and a Dutch cohort study estimated the incidence rate of lichen sclerosus to range from 7.4 to 14.6 per 100,000 woman-years between 1991 and 2011.[2] Peak incidence occurs in postmenopausal women, with a second peak in prepubertal girls, followed by men in their fourth decade.[3]

ETIOLOGY/PATHOGENESIS

The cause of LS remains unknown. Several HLA haplotypes have been associated with the disease and identified in the peer-reviewed literature.
(HLA-DQ3, HLA-DQ7, HLA-DRB1*12, HLA-DRB1*0301/04/DQB1*0201/02/03, among others).[4-6] Autoantibodies against extracellular matrix protein 1 (ECM-1) have also been identified in LS patients. Indeed, autoimmunity is believed to play a primary role in the disease, and several autoimmune comorbid conditions have been associated with LS, including autoimmune thyroiditis, alopecia areata, vitiligo, pernicious anemia, celiac disease, and morphea.[7,8] *Borrelia burgdorferi sensu lato* species has also been implicated in the pathogenesis of lichen sclerosus, with one study detecting *Borrelia* species in 63% (38 of 60 cases) of lichen

sclerosus tissue specimens.[9] Other triggers, such as influenza vaccination[10], surgery[11] , and genital piercing[12] have been described as well in the form of single case reports.

CLINICAL FEATURES

LS can affect both the genital and extragenital skin. The classic morphology is characterized by ivory white, porcelain-like, sclerotic, atrophic papules and plaques. These lesions may also have telangiectasias, follicular plugging, erosions, purpura, and haemorrhagic bullae. In the anogenital region in women, a "figure-of-eight" configuration has been described, with circumferential lesions involving the vulva, perineum and anus. In advanced cases, the normal architecture of the labia minora, labia majora, and clitoral hood may be resorbed, resulting in narrowing of the vaginal introitus. In men, lesions may similarly present as sclerotic, shiny, white lesions, often on the glans penis and inner aspect of the foreskin. Constriction, phimosis, paraphimosis, and recurrent balanitis are complications of LS in men. In advanced stages, patients may also have urinary obstruction. Patients with LS, both men and women, often have significant dyspareunia, pruritus, dysuria, and general soreness and discomfort.

Because of the chronic inflammatory state of LS, there is a risk of malignancy in longstanding lesions. The 10-year vulvar squamous cell carcinoma incidence in women with lichen sclerosus was associated with concurrent vulvar intraepithelial neoplasia and age at time of lichen sclerosus diagnosis (5.9% in women of ≥70 years, 3% in women between 50 and 70 years, and 1.8% in women <50 years).[2]

DIFFERENTIAL DIAGNOSIS

Lichen sclerosus must be delineated from a variety of other diseases of the anogenital region, including morphea, erosive lichen planus, and graft vs host disease. In men, Erythroplasia of Queyrat, balanitis, and extramammary Paget's must all be considered. In young children, it is important to rule out sexual abuse.[3,13,14]

PATHOLOGY

Biopsies of lichen sclerosus will typically show a thinned epidermis and a lichenoid interface dermatitis characterized by vacuolar degeneration of the basal layer and a band-like lymphocytic infiltrate.[13-16] Macrophages and mast cells can also sometimes be seen in the infiltrate. Follicular plugging may be seen and rete ridges may be flattened. Below this, in the dermal level, lesions may demonstrate homogenized dermal collagen and edema. The key differentiating feature between lichen sclerosus and morphea is the loss of elastic fibers, which is seen in LS but not morphea.[14-16]

TREATMENT

The current standard of care for LS patients is a high potency topical steroid such as clobetasol propionate 0.05% daily or alternating with a non-steroidal topical or rest period.[3,14,17] For recalcitrant cases, or for patients unable to apply topical steroids, intralesional steroid injections can be helpful.[17] The most commonly used non-steroidal alternatives are tacrolimus and pimecrolimus. One study of sixteen patients (10 with anogenital and six with extragenital localization) were treated with topical tacrolimus ointment twice daily. Results demonstrated improvement in a majority of genital LS patients[18], but none in patients with extra-genital LS.

No adverse effects were observed in this study. Due to a black box warning regarding lymphoma risk associated with tacrolimus and the risk of squamous cell carcinoma (SCC) arising in LS, clinicians should consider counselling patients about this theoretical risk However, no studies have shown development of SCC as a result of topical calcineurin inhibitors in patients with LS.

Although topical estrogen and progesterone preparations have been used for post-menopausal dryness and dyspareunia, there is no evidence to support the use of such preparations in LS.[17] Topical testosterone is also not recommended and has been shown to be inferior to clobetasol.[17] Furthermore, studies have demonstrated unacceptable adverse effects of topical testosterone including clitoral hypertrophy, hirsutism, acne, and menstrual abnormalities.[17,19,20]

Phototherapy has long been considered in the treatment of LS. The most evidence exists for the use of PUVA/UVA1, but the data is limited to a few case series, and patients should be warned about risk of carcinoma with PUVA.

The use of systemic treatments such as prednisone, cyclosporine, and methotrexate have been elucidated through case reports in the literature. The largest study of methotrexate was a retrospective review of 28 patients who had previously failed topical therapies. The authors found improvement in 75% of patients who received weekly doses of methotrexate ranging from 2.5 mg to 17.5 mg (median= 10 mg), however several patients had to discontinue methotrexate due to side effects.[21]

There are conflicting case reports involving the use of hydroxychloroquine and thus a recent review of treatment strategies for LS[17] did not recommend this medication.

There is some evidence for the use of systemic retinoids in LS. One randomized controlled trial[22] found a significantly higher number of responders in patients receiving 35 mg of acitretin daily (14 of 22 patients), compared with the placebo group (6 of 24 patients). Another randomized, double-blind, placebo controlled trial done in males with LS[23] also found some positive effect of acitretin. In this study of 49 completers who were eligible for statistical analysis, complete response was achieved by 36.4% (12 of 33) of the acitretin group vs 6.3% (1 of 16) of the controls, while 36.4% (12 of 33) vs 12.5% (2 of 16) achieved partial resolution, respectively.

A potential hypothesis for the treatment of LS centers on the use of systemic antibiotics, which links back to the theory that *Borrelia* species may trigger LS. One retrospective study of 15 men and women with steroid-resistant LS were treated with one of: intramuscular penicillin and oral penicillin, intramuscular cephalosporin, oral penicillin, or oral cephalosporin.[24] The authors noted that all patients showed significant response within a few weeks, particularly those who had received intramuscular antibiotics, with significant reduction in pain, pruritus, and burning. Though not a first-line treatment approach, clinicians may consider the use of intramuscular ceftriaxone 1 gram every two weeks for three doses, then once a month on a PRN basis; or intramuscular penicillin G benzathine suspension dosed at 2.4 million units every 2 weeks for three doses, then once a month on a PRN basis in resistant LS cases.[17]

Newer, investigative treatments include the use of fractional carbon dioxide laser (i.e. MonaLisa Touch®) which is currently being investigated at Sunnybrook Health Sciences Centre. The published data on this treatment modality is limited, with mostly case reports reported in the literature.[25-28] The largest published study of forty women with LS who failed clobetasol propionate demonstrated improvement in vulvar itching, dryness, sensitivity during intercourse and dyspareunia. Itching relief was noted after only one treatment in several patients.[29] No systemic or local adverse reactions were reported in this study. Fractional CO2 laser has also been studied in males, with improvement noted in DLQI scores, symptoms of LS, sexual function, and no relapse at the 6-month follow-up mark.[30] This study also reported that the fractional laser was well-tolerated, with no significant adverse effects. Some patients experienced edema, short duration of burning, and erythema, all of which resolved within hours to days.

Surgical interventions have also been studied in LS. In men, surgical intervention such as circumcision can often be curative in mild-to-moderate cases.[13,17] In women with advanced LS, perineotomy and lysis of adhesions can provide symptomatic relief.[17] Platelet-rich plasma has also been studied in a non-randomized setting, with excellent response rates in subjects ranging from 62%-100%.[31-35]

SUMMARY

Lichen sclerosus is a chronic, inflammatory disease that primarily affects the anogenital area in both men and women. Treatment is essential to prevent progression of the disease, which can lead to permanent deformity and decreased quality of life. The mainstay of treatment includes potent topical steroids and in some cases, surgery can be curative. In cases unresponsive to topical steroids, systemic treatments such as systemic retinoids, methotrexate, and antibiotics may be utilized. Fractional laser and platelet-rich plasma are promising new treatments and may be considered in recalcitrant cases.

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† ORION: Multicentre, phase 3, double-blind, placebo-controlled study to evaluate TREMFYA® administered with the patient-controlled One-Press injector in adults with moderate to severe plaque psoriasis (i.e., IGA score ≥3; PASI score ≥12; BSA involvement ≥10% for ≥6 months prior to screening). Patients were randomized 4:1 to either TREMFYA® 100 mg at Weeks 0, 4, and every 8 weeks thereafter, or placebo at Weeks 0, 4,and 12, with crossover to TREMFYA® 100 mg at Week 16. SC injections for both treatment arms done with One-Press device. Co-primary endpoints: Proportion of patients achieving IGA 0/1 and PASI 90 responses at Week 16.

PASI=Psoriasis Area Severity Index; NRI=non-responder imputation; IGA=Investigator's Global Assessment; BSA=body surface area; SC=subcutaneous.

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AN UPDATE ON TREATMENTS FOR LICHEN PLANOPILARIS

Lichen planopilaris (LPP) is an immune-mediated cicatricial alopecia that is often challenging to treat. In LPP, hair follicles are selectively destroyed by a chronic lymphocytic inflammatory process, leading to irreversible scarring and permanent hair loss (**Figure 1 and 2**). Several variants of LPP have been described in the literature including the classic form, the Graham-Little-Piccardi-Lassueur syndrome, frontal fibrosing alopecia, and recently, a new clinical variant, lichen planopilaris diffuse pattern.[1]

LPP is associated with a high burden of disease and causes significant psychological distress to patients. In addition to visible hair loss, many patients experience burning, itching, and scalp tenderness which contribute to the quality of life impairment associated with the condition. The understanding that it is an incurable disease and that there are no consistently effective treatment options can also make coping with LPP difficult for patients. A recent retrospective review of 215 women with LPP with a mean age of 59.8 years found a high incidence of depression (45.7%), anxiety (41.8%), and sleep disturbance (29.2%).[2]

When approaching the management of LPP, patient selection and clear communication around treatment expectations are essential. Patients most likely to benefit from treatment are those with active disease—the presence of perifollicular scale and erythema, progressive hair loss, symptoms, and an inflammatory process on scalp biopsy compatible with LPP indicate that the condition is active. Conversely, end-stage lesions of LPP are unlikely to respond to treatment. With respect to treatment expectations, patients should understand that the goal of therapy is to stop disease progression and alleviate symptoms. Due the scarring nature of LPP, hair regrowth in areas of existing alopecia is not expected.

Treatment of LPP remains difficult. Due to a lack of high-quality evidence on therapies and the unpredictable clinical course of the disease, the best approach to the treatment of LPP is currently unclear. The absence of consistent methods to assess the response to treatment in the literature has also contributed to uncertainty about treatment efficacy. As a result, treatment varies widely.

Traditional first-line therapy for limited disease involves the use of topical and intralesional corticosteroids. Common systemic therapies include hydroxychloroquine and systemic antibiotics such as doxycycline. Despite the initial effectiveness of these treatments, relapses are common.[2,3] As a result, a range of other therapeutic options has been investigated. In addition to the treatments discussed in this article, data suggest that methotrexate, cyclosporine, oral retinoids, pioglitazone, and 5-alpha reductase inhibitors such as finasteride and dutasteride could be helpful in the treatment of LPP.

The objective of this article is to review recent data published in the literature on therapeutic modalities for LPP.

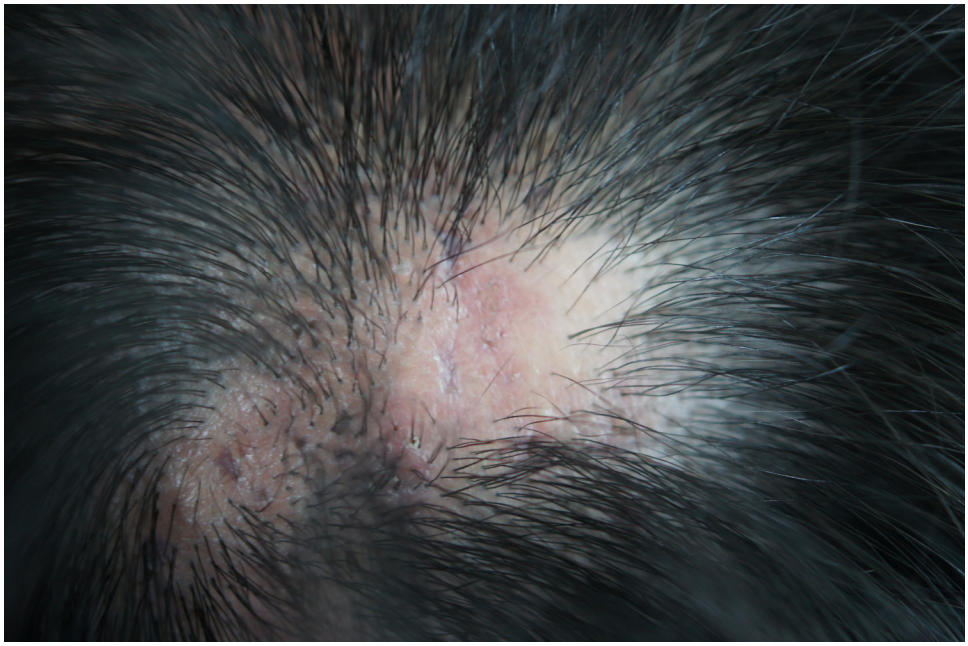

Figure 1. Lichen planopilaris of the scalp characterized by perifollicular scale, perifollicular erythema, and scarring

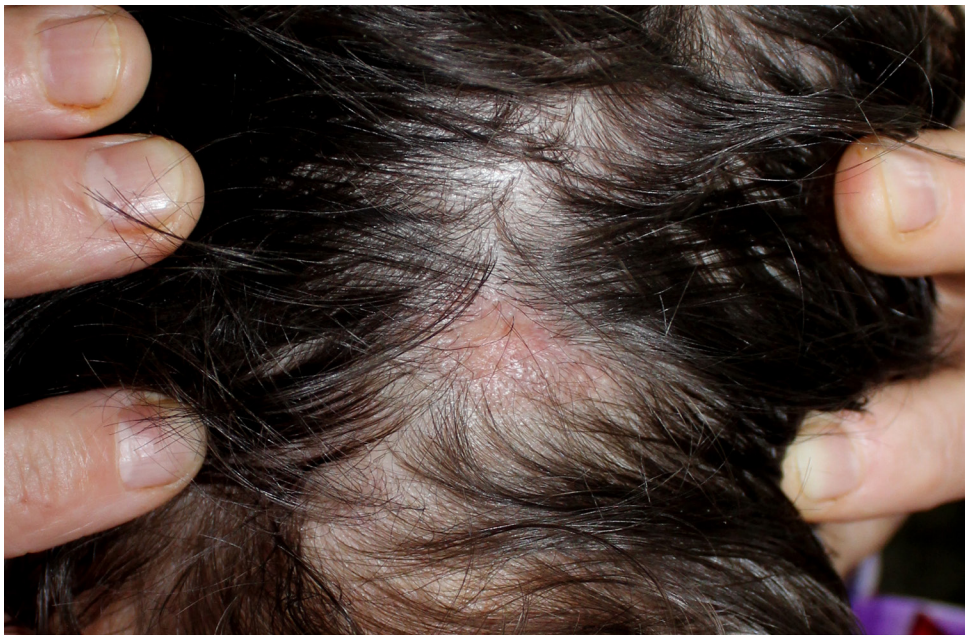

Figure 2. A case of lichen planopilaris in a female patient

ORAL MINOXIDIL

Oral minoxidil is a systemic vasodilatory agent which has demonstrated efficacy in the treatment of androgenetic alopecia and chronic telogen effluvium. A recent retrospective review evaluated the role of low dose oral minoxidil (LDOM) in increasing hair thickness in patients with LPP.[4] LDOM was started at a dose of 0.25 to 1 mg and gradually uptitrated over a minimum treatment duration of 6 months. Subjects' change in global hair thickness was assessed before and after LDOM treatment. The study found that hair thickness improved in 39% of patients, remained stable in 53% of patients, and worsened in only 8% of patients. LDOM was generally well-tolerated, with mild adverse events such as hypertrichosis, postural hypertension, tachycardia, and weight gain being reported in a minority of patients.

The study concluded that LDOM can help to maintain or improve hair thickness in most patients with LPP, with an acceptable safety profile. The increase in background hair thickness generated by LDOM might provide better concealment of adjacent areas of hair loss, thus reducing patient disease burden. Although there were limitations of the study, including its small sample size (n = 51) and retrospective design, LDOM may be a promising therapeutic option to add to the treatment armamentarium for patients with LPP.

MYCOPHENOLATE MOFETIL

While the pathophysiology of LPP remains poorly understood, the disease is thought to result from a T-lymphocyte-mediated cytotoxic immune reaction to

follicular antigens. Mycophenolate mofetil (MMF) is an antimetabolite that blocks de novo guanine nucleotide synthesis by inhibiting inosine monophosphate dehydrogenase. Both T and B lymphocytes lack purine scavenger mechanisms and consequently, their DNA replication pathways are inactivated by MMF. Recently, a systematic review and meta-analysis was published regarding the outcomes of MMF in LPP.[5] Based on a total of six studies comprising 94 LPP patients, the pooled proportion of any good response (either partial or complete) was 69.2% (95% CI 47.8 – 77.0). Side effects occurred in 16.9% of cases, which included elevated liver function tests, edema, hyperlipidemia, anaemia, herpes zoster infection, photosensitivity, and urinary tract infection. Based on these findings, it was concluded that MMF is reasonably effective and well-tolerated in the treatment of LPP, with fewer associated adverse events than other immunosuppressive medications such as cyclosporine. Although the current evidence for MMF remains limited, it appears to be a potential therapeutic option for patients with severe or recalcitrant LPP who have failed hydroxychloroquine and other immunosuppressants.

PLATELET-RICH PLASMA

Platelet-rich plasma (PRP) has emerged as a popular treatment option for non-scarring alopecias such as androgenetic alopecia. Until recently, its effectiveness in treating cicatricial alopecias including lichen planopilaris was largely unknown. Over the last two years, there has been increasing evidence to support its clinical benefits in the treatment of LPP.[6,7] A recent retrospective analysis examined the effect of PRP in 10 patients with LPP.[6] After an average of four treatments, four out of ten patients demonstrated improvement in LPP, defined by disease stabilization and/or attenuated symptoms, and three out of ten patients demonstrated neither improvement nor worsening. While the exact mechanism of action of PRP remains unclear, it is thought to promote hair growth via its effects on platelets, growth factors, and anti-inflammatory mediators. There have been concerns regarding the potential for PRP to cause new areas of disease (i.e., koebnerization) in patients with LPP. However, this retrospective review concluded that PRP need not necessarily be avoided for LPP patients and that it may result in clinical improvement without koebnerization. Future studies are needed to better understand the role of PRP in the treatment of LPP.

TOFACITINIB

Tofacitinib is a pan-Janus kinase (JAK) inhibitor approved for the treatment of moderate-to-severe rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. It has been used off-label in its topical and systemic forms for the treatment of various dermatologic conditions including psoriasis and vitiligo, as well as in the non-scarring alopecia, alopecia areata.[8] Two recent retrospective review studies found that tofacitinib was an effective therapeutic option for patients with LPP. Responses in both studies were evaluated based on patient-reported symptoms and physical examination findings. The first retrospective case series, published in 2018, included six females and four males and the average age at presentation was 55 years (range 33–68 years). The diagnosis of LPP was biopsy proven in five patients and was a clinical diagnosis in the remaining five patients. This study reported that eight out of ten patients treated with oral tofacitinib 5 mg twice daily or three times daily for 2-19 months as either monotherapy or adjunctive therapy had clinical improvement as measured by lichen planopilaris activity index (improvement ranged from 30% to 94%). Adjunctive therapies were used in five patients and included intralesional triamcinolone (two patients), hydroxychloroquine (one patient), intralesional triamcinolone and hydroxychloroquine (one patient), and intralesional triamcinolone and tacrolimus ointment (one patient).[9] Tofacitinib was well tolerated by all patients.

In the second retrospective review, published in 2020, topical and oral tofacitinib were used adjunctively in nine patients with LPP.[10] Three of four patients receiving topical therapy (2% cream twice daily) achieved a positive response, and all patients receiving systemic therapy (5 mg twice daily or three times daily) demonstrated a favourable response. Minor laboratory abnormalities were noted in patients on systemic therapy and included mild, transient hemoglobin and creatinine abnormalities, and mildly elevated triglyceride and cholesterol levels, but none required treatment. No other adverse events were reported. Despite these promising results, further investigation of tofacitinib in the setting of LPP is warranted.

NALTREXONE

Naltrexone is a long-acting opioid antagonist. At a low daily dose of between 1 and 5 mg, naltrexone exhibits both analgesic and anti-inflammatory effects and has been used successfully in treating a variety of inflammatory conditions. In the context of dermatology, low-dose naltrexone (LDN) has

demonstrated benefit in the treatment of pruritus, Hailey-Hailey disease, Grover disease, and Darier disease.[11] In a case series of 4 patients with LPP treated with 3 mg of naltrexone daily, a reduction in pruritus, clinically evident scalp inflammation, and disease progression was seen in all patients. Improvements were noted within 1 to 2 months of starting therapy and no adverse events were reported.[12] LDN is an interesting treatment option for LPP as it is relatively inexpensive, well-tolerated, and does not require laboratory monitoring. Further studies are required to better understand its potential role in the treatment of LPP.

CONCLUSION

In conclusion, new data continues to emerge on therapeutic options for LPP. As with other challenging and refractory dermatologic conditions, LPP will likely require a multimodal treatment approach involving the combination of therapeutic agents to achieve optimal outcomes. Although there is still a need for high quality data, the promising therapies reported in the literature in recent years will likely be a useful addition to our clinical repertoire.

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ORAL SUPPLEMENTATION IN DERMATOLOGY

INTRODUCTION:

Canadians purchase approximately $1.2 billion of oral vitamins and supplements, also known as 'nutraceuticals', each year.[1] Global retail sales of nutraceuticals have been valued at over $382 billion in 2019.[2] Health Canada does not review natural health products with the same rigor as over-the-counter and prescription drugs[3], and many of these products claim to have medical benefits for the skin, hair, and/or nails. As dermatologists, our patients often ask questions regarding the possible benefits of various oral supplements. These inquiries are related to topics ranging from skin rejuvenation, hair and nail health, photoprotection, to anti-oxidant and anti-inflammatory effects in conditions such as eczema, psoriasis, acne, and hidradenitis suppurativa. With growing patient interest and market share, there are an increasing number of clinical studies examining the potential effects of oral supplements on the skin. While there are thousands of products available, the scope of this article is centered on reviewing the evidence for three of the more commonly encountered ones: collagen, *polypodium leucotomos*, and omega-3 fatty acids. The ensuing discussion about the evidence for each one of these agents will be summarized according to the quality of studies[4] and the level of evidence outlined in **Table 1**.

COLLAGEN:

Oral collagen has been a popular product for many years. In 2016, the collagen market was valued at around $3.7 billion USD and is projected to reach $6.6 billion USD by 2025.[6] Commercially available products are typically derived from various origins such as marine, bovine and porcine sources. Oral collagen has been linked with both antioxidant and anti-inflammatory properties, as well as being associated with UV protection, skin hydration, and improvements in nail strength.[7] Collagen-derived products are metabolized in the gastrointestinal system into amino acids (most commonly di- and tri-peptides) before being absorbed into the blood circulation, but there is growing evidence to suggest that they might also be absorbed directly.[8] Animal studies have demonstrated that maximal absorption in the skin is reached at 12 hours after consumption, and that more than 85% disappears from the blood after 24 hours.[9]

Levels of Evidence for Therapeutic Studies*

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCTs (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study)
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

**From the Centre for Evidence-Based Medicine, http://www.cebm.net.*

Table 1: Levels of Evidence for Therapeutic Studies[5]

A recent systematic review and meta-analysis published in March 2021 evaluated the effects of oral collagen supplementation on skin; it included 19 randomized, double-blind, and controlled trials (RCTs) with a total of 1,125 participants aged between 20 and 70 years. It showed favorable results of collagen supplementation in terms of skin hydration (measured by corneometry in 10 out of 13 studies), elasticity (measured by cutometry in 11 out of 15 studies), and wrinkles (measured by silicone skin replicas with 3D topography analysis in 2 out of 4 studies, and photographic analysis in 2 out of 4 studies) after 90 days of use.[10]

Another 2019 systematic review examined the effects of collagen-derived dietary supplements on the skin and included 11 RCTs with a total of 805 patients.[11] That review concluded that these supplements are generally safe. Eight studies used collagen hydrolysate, at 2.5 grams per day (g/d) to 10 g/d, for 8 to 24 weeks, for the treatment of pressure ulcers, xerosis, skin aging, and cellulite. Two studies used collagen tripeptide, 3 g/d for 4 to 12 weeks, with notable improvement in skin elasticity and hydration. The last study using collagen dipeptide showed a dose-dependent relationship to anti-aging efficacy.[12] The majority of these 11 RCTs also used cutometry and corneometry to measure elasticity and skin hydration respectively. These systematic reviews suggest benefit for oral collagen supplements in skin aging. The level of evidence for using oral collagen supplementation for this is therefore 1A. Further studies are needed to elucidate medical use in skin barrier diseases such as atopic dermatitis and to determine optimal dosing regimens

POLYPODIUM LEUCOTOMOS:

There are a few manufacturers of this oral supplement available which is a South American species of fern plant, and claims to have antioxidant, photoprotective,

and anti-aging properties by inhibition of UV-induced reactive oxygen species generation.[13] There have been a number of studies that suggest evidence for photoprotection and photoaging with *polypodium leucotomos*.[14,15,16]

Although it has gained more "hype" in recent years, extracts of this fern have been used for the treatment of a variety of skin conditions since the 1970s, including psoriasis, atopic dermatitis, polymorphic light eruption, and melasma. To date, there is weak or no scientific evidence to support these uses.[17,18,19,20]

Only two RCTs evaluating this oral supplement have shown statistically significant outcomes. One randomized, double-blind, placebo-controlled study with 40 subjects demonstrated that 240 mg of *P. leucotomos* taken twice daily for 60 days resulted in an increased minimal erythema dose (MED) and reduced UV-induced erythema intensity at day 28.[21] Another recently published randomized, assessor-blinded prospective study with 44 vitiligo patients showed that 480 mg of oral *P. leucotomos* taken twice daily along with NB-UVB phototherapy demonstrated improved repigmentation as well as increased response rate to NB-UVB treatment compared to those on placebo and NB-UVB treatment.[22] The level of evidence to use oral *P. leucotomos* for UV protection and adjunctive therapy for vitiligo is therefore 1B.

OMEGA-3 FATTY ACIDS:

Most of the scientific research on oral omega-3 fatty acids (O3FAs) focuses on alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). ALA is found in plant oils such as flaxseed, walnuts, soy, and canola oils, while EPA and DHA are found in fish, krill and fish oils (originally synthesized by microalgae).[23] Studies have suggested that O3FAs have antioxidant and photoprotective properties in the skin and may benefit eczema and psoriasis patients.

Although a deficiency of O3FAs can lead to skin disease such as dermatitis, there is no known lower threshold for the serum concentrations of O3FAs below which dermatitis can manifest.[24]

A review of 38 studies which met the eligibility criteria was published in 2020 examining the role of omega-3 supplementation in various dermatological conditions, The review included double-blind RCTs that showed statistically significant benefits in psoriasis, atopic dermatitis, acne, and skin ulcers.[25] The level of evidence for using omega-3 supplementation in these conditions is therefore 1B.

CONCLUSION:

The role of oral nutraceutical supplementation in skin health is a frequent source of patient inquiry and physician uncertainty. There is limited evidence for the efficacy and safety of many supplements in the treatment of dermatologic diseases, and I do not recommend them over the use of medically prescribed therapies. This article reviews the currently available evidence for three of the more common oral supplements that patients may inquire about. With the appropriate patients, I would discuss the potential benefit of oral supplementation, in addition to prescribed therapies, especially if they are not obtaining adequate amounts in their diet. For example, omega-3 supplementation is unlikely to clear a patient's psoriasis or dermatitis as monotherapy, but there is some evidence to suggest benefit. Similarly, *P. leucotomos* can be used as an adjunct to, not a substitute for, sunscreen and UV-protective clothing for photoprotection. I may suggest it to some of my vitiligo patients undergoing phototherapy in light of the recent publication. The use of supplements is not without cost, and so before a patient relies solely on oral collagen for anti-aging, it is important to ensure the patient understands the importance of healthy lifestyle choices (e.g. sun protection, not smoking, eating healthy, getting good sleep, regular exercise, and perhaps the use of a topical retinoid). In suitable patients, it may be reasonable to supplement collagen, *P. leucotomos*, and/or O3FAs given their ease of administration, low risk of adverse effects, and growing body of evidence to indicate their potential benefits.

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NEW ANATOMICAL INSIGHTS INTO PREVENTING BROW PTOSIS WITH BOTULINUM TOXIN-A USE

INTRODUCTION

Botulinum toxin-A (BTX-A) injections were the most commonly performed non-surgical procedure in 2020 according to the Aesthetic Plastic Surgery National Databank Statistics.[1] Between 2019 and 2020, the number of neurotoxin injections performed in the United States has risen 1.5 fold from 1,712,994 to 2,643,366.[1,2] When utilizing BTX-A in the upper face, the incidence of eyebrow ptosis varies widely and has been quoted in the literature at upwards of 20%.[3-6] This adverse event is not exclusively seen post-treatment of the frontalis muscle but can also occur through inadvertent diffusion of the neurotoxin when treating the glabellar complex.[6] Over the past year, new anatomic considerations to help injectors optimize results and reduce the risk of eyebrow ptosis with frontalis and glabellar BTX-A injections have been published.[7-9] This paper aims to summarize three such publications which may help to positively impact injectable outcomes in the clinician's day-to-day practice.

THE LINE OF CONVERGENCE

The frontalis muscle acts as the sole elevator of the eyebrows, thereby making injectors proceed with caution when treating this area with BTX-A for fear of eyebrow ptosis. To minimize this risk, it is recommended to focus treatment on the upper portion of the frontalis despite a lack of evidence for why this produces a more desirable clinical outcome.[7-10]

In 2020, Cotofana et al. helped shed light on this clinical phenomenon by introducing the concept of the Line of Convergence (C-line).[7] Twenty-seven healthy volunteers (11 men and 16 women) with a mean age of 37.5 ± 13.7 years (range, 22 to 73 years) and of diverse ethnicity (14 Caucasians, four African Americans, three Asians, and six of Middle Eastern descent) had the pattern of their forehead movement during eyebrow

elevation analyzed. The mean forehead height was found to be 65 ± 8.1 mm and 53.4 ± 9.2 mm for men and women, respectively. The median number of horizontal forehead rhytids independent of sex was four.[7]

The investigators found that all patients had a bimodal movement of forehead skin with elevation of the eyebrows and depression of the hairline. The C-line was the name given to the stable horizontal forehead line. The position of the C-line was found at approximately 60% of the total forehead height when moving superiorly from the eyebrows. This location also corresponded to the second forehead line when counting in the inferior direction from the hairline **(Figure 1)**. Interestingly, there were no statistically significant variations between sexes or ethnicities.[7]

This paper helped to elucidate the role of the frontalis muscle and its bidirectional movement. The lower ~60% appears to act as an eyebrow elevator, whereas the upper ~40% depresses the hairline. Clinically, the concept of the C-line can help injectors reduce the risk of eyebrow ptosis by using a lower dosage in the lower 60% of the forehead when appropriate.

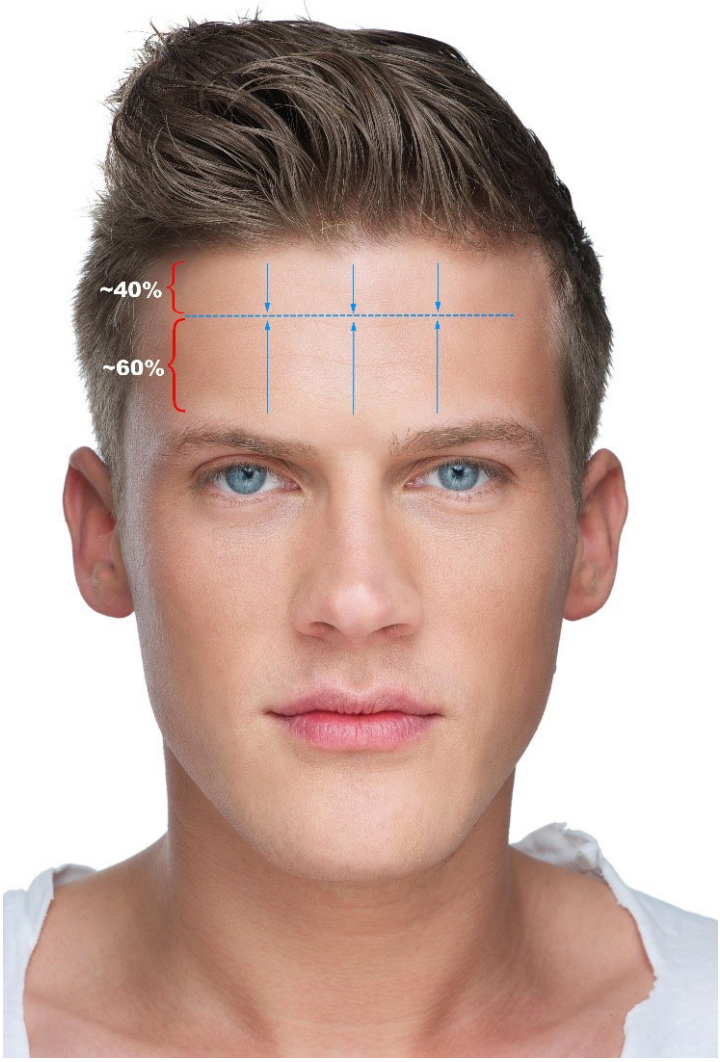

Figure 1: The approximate location and movement of the Line of Convergence; courtesy of Matthew Sandre, MD

DEPTH OF INJECTION WHEN TREATING THE FRONTALIS

Similarly, clinicians must also consider the depth of injection when treating the forehead to minimize the risk of brow ptosis. Superficial/dermal injections of BTX-A on the forehead have been previously shown to result in a lower number of eyebrow ptoses when compared to deeper/intramuscular injections.[8,11,12]A recently- published , prospective interventional, split-face study assessed the depth of BTX-A injections in the treatment outcomes of horizontal forehead lines.[8] The results demonstrated how a blended-depth injection technique is supported by the forehead's fascial anatomy and may lead to a more optimal aesthetic result.[8]

Fourteen patients with a mean age of 35.71 (7.8) years and mean body mass index of 21.9 (3.0) kg/m^2 had their foreheads treated with abo-BTX-A. There were 8 injection points per frontalis (4 per side) which were landmarked as mirror images of each other. The dose injected varied between patients based on their frontalis muscle activity with a mean value of 25.73 international units of abo-BTX-A. One side was treated with superficial injections in order to place product superficial to the frontalis muscle. This was accomplished placing the needle at a 45° angle and producing a bleb with product injection. The contralateral side was treated with deep injections perpendicular to the skin surface, placing product in the supraperiosteal plane. This depth was confirmed by the injectors hearing a 'click' to indicate that they pierced the subfrontalis fascia.[8]

The treatment outcome was rated by the physician and by two independent observers according to a forehead line severity scale (0-4) at 14 and at 30 days. The results found that the deep injections produced a superior outcome in reducing horizontal forehead line severity at days 14 and 30 compared to the contralateral side that received more superficial BTX-A injections.[8] No eyebrow or eyelid ptoses were observed with either injection technique.

Injections above the C-line (in the upper 40% of the forehead), can be injected deep in order to help maximize neurotoxin effect on the frontalis muscle. Comparatively, BTX-A injections below the C-line, or in areas where one wishes to have less effect on the frontalis muscle activity, can be placed more superficial to reduce the possibility of eyebrow ptosis.[8]

A recently-published paper demonstrated the clinical utility of a 3-point glabellar injection technique to reduce the possibility of medial eyebrow ptosis and excessive lateral eyebrow lifting/"Spocking". The approach centers on understanding the detailed anatomy of the procerus and corrugator supercilii muscles and targeting their bony origin, reducing the frequency of indirectly affecting the lower frontalis.[9]

Box. 1 New Potential Strategies to Prevent Eyebrow Ptosis with BTX-A Injections

- When injecting the frontalis:
  - » Consider placing the majority of the units above the C-line
  - » Injections below the C-line can be placed more superficial to lessen the effect on frontalis muscle activity
  - » Injections above the C-line can be placed deep on bone to maximize effect on frontalis muscle activity
- When injecting the glabella:
  - » Inject deep on bone at the origin of the procerus and corrugator supercilii
  - » Avoid injections above the level of the hairy eyebrow

Anatomically, the superficial injection places BTX-A above the suprafrontalis fascia which acts as a partial barrier between the product and the frontalis muscle.[8,13] In contrast, the perpendicular deep injections not only place the product deep to the subfrontalis fascia but also create a vertical channel for the BTX-A to travel retrograde along and therefore come in direct contact with the frontalis muscle.[8] Davidovic et al. highlighted that this retrograde travel of fluids has also been documented previously using fillers with different viscoelastic properties.[14-16]

3-POINT GLABELLAR INJECTION TECHNIQUE

Glabellar injection techniques frequently differ between practitioners depending on variables such as injector preference, the patient's desired outcomes, and glabellar contraction patterns.[9,17-20] Many injection techniques target both the medial and lateral corrugator supercilii muscle, and the placement of these injection points can occasionally allow product to diffuse to the lower frontalis muscle fibers increasing the risk of an eyebrow ptosis.[9,17,18]

A total of 105 patients (27 males and 78 females) with a mean age of 40.90 ± 9.2 years were included between the different participating centres. A standardized 2D and 3D injection technique was used but injectors were allowed to vary the number of units between patients and select the type of BTX-A used. Injection of the procerus was completed using a midline injection point at a vertical height of a line connecting the medial canthal ligaments. The needle was inserted perpendicular to the skin and product was injected deep on bone. The corrugator supercilii injection was also deep on bone at the medial inferior eyebrow. The needle was inserted at a 45°

angle to both the midline and frontal bone. No injection points were above the line of the hairy eyebrow.[9] **(Figure 2)**

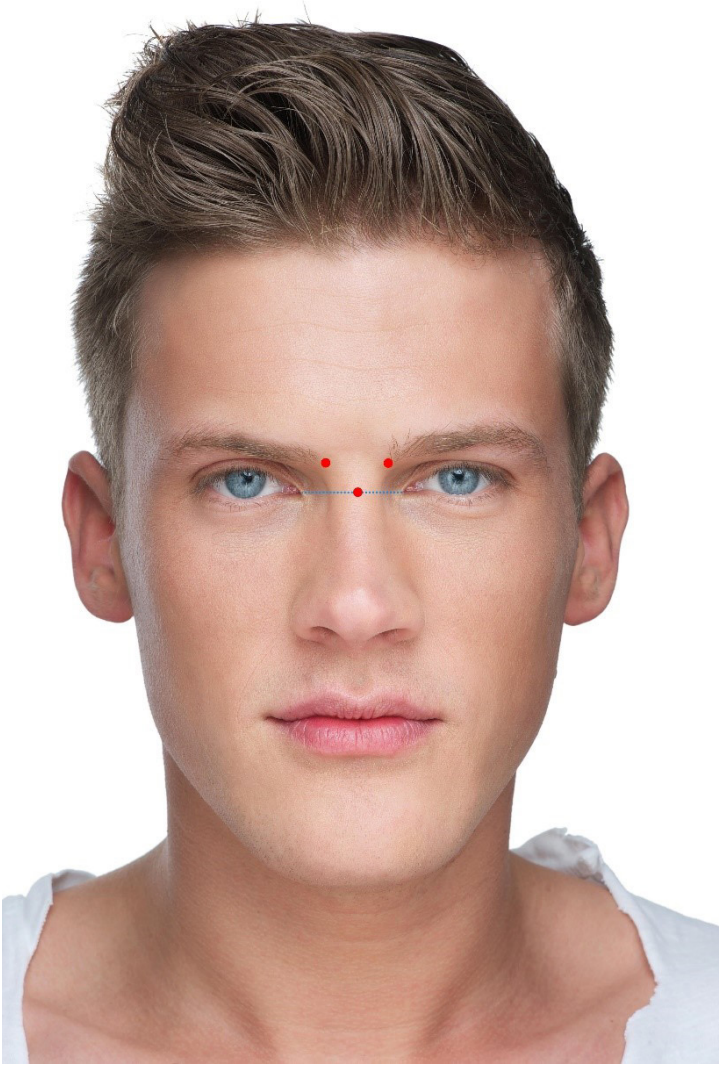

Figure 2: The three-point glabellar complex injection technique; courtesy of Matthew Sandre, MD.

The procerus muscle was injected with an average of 5.23 ± 2.5 units of ona-/inco-BTX-A or 12.90 ± 6.3 units of abo-BTX-A. Each corrugator supercilii muscle was injected with an average of 13.27 ± 5.7 units ona-/inco-BTX-A or 33.17 ± 14.2 abo-BTX-A. A statistically significant reduction in median glabellar wrinkle score was seen with this injection technique (median score before treatment = 3; median score at 14 days = 0). There were no cases of eyebrow ptosis, eyelid ptosis, or "Spocking" of the lateral eyebrow. An increase in medial eyebrow height of 1.21 ± 2.8 mm was also observed.[9]

Clinically, this newly-proposed 3-point technique appears to have the potential to reduce the risk of eyebrow ptosis while still achieving desirable glabellar wrinkle reduction. Furthermore, less injection sites also reduce patient discomfort and the risk of bruising, making it appealing for injectors and patients alike.

CONCLUSION/DISCUSSION

The demand for non-surgical aesthetic procedures continues to rise in dermatology practices and BTX-A injections may offer patients an effective treatment option for many commonly encountered facial aesthetic concerns. Although facial BTX-A injections carry a relatively low rate of complications, expert injectors are continuously looking for new ways to optimize patient outcomes and minimize risk. This paper highlights three recent publications that aim to expand our anatomic knowledge of the forehead and glabellar complex and how it relates to BTX-A injection techniques. However, it is critical that clinicians remain cognizant of variations in patients' anatomy and aesthetic goals which are essential to consider during every patient encounter.

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- No adequate and well-controlled studies have been conducted in pregnant women.
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NIHB: Non-Insured Health Benefits Program; PASI: Psoriasis Area Severity Index; IL-17: interleukin-17; SC: subcutaneous
*Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, Québec, Saskatchewan. Please refer to the respective formularies for coverage information.
†Fictitious patient. May not be representative of all patients.
‡AMAGINE-2 study: A randomized, double-blind, active comparator trial assessing the efficacy and safety of SILIQ in adult patients with moderate to severe plaque psoriasis, defined as a minimum body surface area of 10%, a PASI score ≥ 12, a static Physician's Global Assessment score ≥ 3 on a severity scale of 0 to 5 in the overall assessment, and who were candidates for systemic therapy or phototherapy. Patients received either SILIQ (210 mg SC at Weeks 0, 1, and 2, followed by the same dose every two weeks through Week 12; n=612), ustekinumab (45 mg SC for patients ≤ 100 kg, or 90 mg SC for patients > 100 kg at Weeks 0, 4, and 16, followed by same dose every 12 weeks; n=300), or placebo (n=309).
§Comparative clinical significance is unknown.

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ABOUT THE AUTHOR

Nicole Hawkins, MD

Dr. Hawkins grew up in Calgary, Alberta. She attended Acadia University where she earned a research-based Honours Bachelor of Science degree in Nutrition. She went on to attend Queen's School of Medicine and completed her residency training in Dermatology at the University of Saskatchewan and University of Toronto. She is dual board certified in dermatology in both Canada and the US. Dr. Hawkins obtained her certificate in the Fundamentals of Clinical and Translational Research from Harvard while running a busy clinical and research practice in Saskatoon. In 2019, she relocated to Calgary and now splits her time, practicing medical dermatology in Okotoks, and cosmetic dermatology at Dermapure in Calgary. She enjoys seeing patients of all ages and stages of life. She is a medical advisor for the Canadian Skin Patient Alliance. Dr. Hawkins spends her free time skiing, playing tennis, and spending time with her husband and two young sons.

PANNING FOR PANDEMIC GOLD: PERSONAL LESSONS AND OBSERVATIONS

A recent article published in one of Canada's national newspapers asked, "Will life soon return to normal?"[1] It was one of the more optimistic pieces I have read this year. The authors – all of them infectious disease physicians – opined on the eventual return to our normal activities, made possible by the roll-out of COVID-19 vaccines. This past year brought such rapid change to our lives and to those of our patients and communities. I started to reflect on some of the changes that might persist beyond this "return to normal" and what follows is a recounting of my own experiences and those of my dermatology colleagues I have communicated with -- via text, phone, and zoom -- over the past few months.

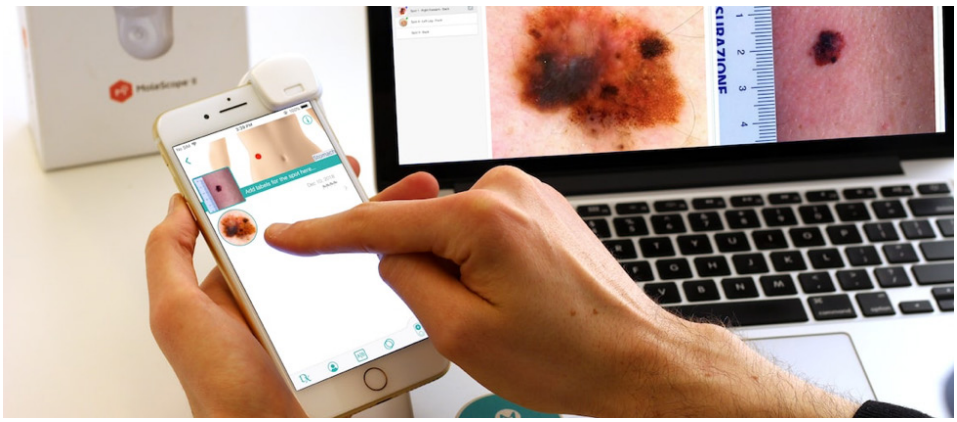
PERSONAL DECISIONS AND PERSONAL SPACE.

In previous winters, I typically caught a cold or two. In residency, it was more often. But this year, with more attention to handwashing and hand hygiene for patients and physicians, physical distancing, and masking, I have fared better. At the onset of the pandemic, tables were separated, stickers were affixed to floors everywhere, and even the big, illuminated signs on the overpass above my commuter route reminded us to "Stay apart to stay safe". Since then, a general awareness of where our bodies are in physical relation to other people seems to have taken root remarkably quickly. In clinic, most of my patients know to reschedule appointments when they are feeling unwell, and if they need to cough or sneeze in clinic, they do so masked and into their elbow. We have all become more aware of our own droplets, and where they land. "I hope the culture shifts so that, when doctors or patients are sick, they don't come in", states Dr. Jori Hardin of Calgary. I could not agree more. The chain of COVID-19 infection can be broken with the single decision to just stay home. This year, our clinic started booking "open days"– one each month – so that, if patients need to be rebooked because a clinician or a family member is sick, the patients can be rebooked to the open day.

Another observation that I have made during this pandemic is that I have also found patients to be more understanding when it comes to rescheduling clinic. And I hope this continues long after we have all been vaccinated.

TELEDERMATOLOGY – AND A RECOGNITION OF ITS BEST USES.

When public health orders triggered the shut-down of many dermatology clinics in 2020, most of us adapted by offering virtual care. The various technology platforms and software to deliver telehealth appointments has existed for years, but now, with no other means to see patients – and a fee schedule that supported it



– many dermatologists were able to justify its use. Our clinic had the usual issues with photo quality and video feeds but managed to see a reasonable number of patients for follow up appointments, and we were even able to undertake some new consults.

Certain conditions were easily managed virtually, but the inability to biopsy or excise patients proved to be terribly frustrating. As clinicians, we had no idea when we would be able to open again, and in what capacity. A recent study by Canadian dermatologists Leis, Fleming and Lynde[2] evaluated dermatologists' experiences during the summer of 2020 and found that 58% of dermatologists surveyed were dissatisfied with teledermatology, and 74% reported decreased job satisfaction. The broad takeaway from this study is that many of us went into medicine, and specifically dermatology, to see patients and help people. As we move forward and reimagine telehealth in a post-pandemic world, the technology can be reliably used to enhance care in many situations, such as to reach patients in remote communities, or to follow up with patients who are stable on long-term medications. But, unless we can engage with our patients in real life, how will we experience the satisfaction of extracting a massive, dilated pore of Winer?

WAITING ROOMS.

Before the pandemic, our waiting rooms were full of uncomfortable patients seated cheek-to-jowl. Now, our waiting rooms are empty. Instead, patients are outdoors in their cars listening to a podcast or taking a work call, going for a walk around the neighbourhood, or having a socially-distanced coffee outside with a companion. They receive a text when it is time for them to be brought into an exam room, at which time they enter the clinic and are greeted by a team member. This process seems so much more civilized, and I think, so much more respectful of our patients' time.

Another waiting room evolution shared with me by dermatologist Dr. Kim Tran has been the implementation of software that simplifies and accelerates the patient's intake form. In our clinic, we always asked patients to fill out a questionnaire in the waiting room prior to their visit, which was then scanned into the chart and reviewed by the team. Some of the newer software simplifies this process by emailing a secure link to the patient a few days prior to their appointment through which they provide their history, update their contact information, and add prior treatments and other details that they consider germane to their upcoming visit. The patient's responses are uploaded to the EMR and automatically linked to their chart. Dr. Tran has found that she is better prepared to see each patient, offers more efficient and thorough care, and that patients are very happy with the process

DRESS CODE.

After having children, I started to wear scrubs to work. My cosmetic practice in Calgary, however, had a tonier dress code. So, when I started working there, I had to revert back to the world of business casual clothing during the workday. That all changed with COVID-19 as scrubs were mandated in our workplace. Many other clinics turned to wash-and-wear for infection control, and many of these dermatologists will continue to wear scrubs on an ongoing basis. Dr. Angela Law of Vancouver tells me that she has no plans to switch back from scrubs. She lists the many benefits including the fact that scrubs are affordable, machine-washable, and are easily worn with clogs or another work-appropriate footwear. Much has been published over the years about health care worker apparel,

including studies that demonstrate home- versus hospital-laundered scrubs harbor similar numbers of bacterial pathogens[7,8], but patients have shown in the past that they prefer doctors to wear professional attire. It remains to be seen whether this perception will change post-pandemic.

LAB MONITORING.

In recent years, much has been written about lab monitoring for commonly used dermatologic medications, specifically spironolactone[3] and isotretinoin. The onset of the pandemic and the rapid closure and then limited re-opening of community labs, has caused many dermatologists to re-evaluate which patients need to be tested and when. Barbieri and colleagues concluded that "there are opportunities to improve the quality of care among patients being treated with isotretinoin by reducing the frequency of lipid and liver function monitoring and by eliminating complete blood count monitoring".[4] While the landscape continues to change in regard to the availability of community labs, clinicians can rely on follow up calls and screening questions with their patients to determine the safety of continuing medications and renewing prescriptions. The key learning is that the changes necessitated by the COVID-19 pandemic have forced us to consider what tests we order and why.

EMPATHY.

I am fortunate to work alongside six wonderful family physicians, who have shared with me that patients have increasingly been reporting mental health-related issues over the past year. The scientific literature has shown an increased incidence of anxiety, depressive symptoms, anger and fear over the past twelve months.[5,6] This has affected patients of all ages, particularly children and adolescents, and the elderly. Many folks in our community are struggling with job losses, home schooling, and social isolation. On an ongoing basis, it is important to remind ourselves that patients are struggling with more than their skin disease, something that we may not have always considered before the COVID-19 pandemic.

REBALANCING.

The pandemic has affected us all in many ways. I returned to the clinic in a reduced capacity to enable more time for proper infection control of the clinic rooms and found that I have enjoyed this relaxed pace very much. I am doing more thorough histories and exams, finishing my clinic day on time, and feel less harried during the workday. Several dermatologist colleagues have told me similar stories – that they are adding a telehealth day once a week so they can work from home, that the lockdown and home schooling helped them re-engage with their children, or that a reduced number of patients in their clinic has improved their outlook. Dr. Angela Law tells me that she will continue to see patients in 15-minute appointment times, as it has improved her relationships with patients and helped with staff morale.
Dr. Jori Hardin has found that the reduced number of extracurricular activities for her children, and the commensurate increase in "family time" has contributed to her well-being. She hopes to continue this post-pandemic. These small anecdotes demonstrate that selectively choosing certain aspects of our 'new' professional world, may lead to the betterment of our own mental health. We have all been touched in some way by the COVID-19 pandemic. This article is not to marginalize or diminish the pain and suffering that so many have experienced over the past 12 months, but rather to find an opportunity to use small lessons that can improve our practices and, by extension, the care we deliver to our patients. I wish you all good health this year, and a safe and happy practice.

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