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EDITORS WELCOME

Dear Canadian Dermatology Community,

Welcome to our third issue of 2021! We trust that you and your loved ones have enjoyed a safe summer..

Between the print and digital versions of *Canadian Dermatology Today*, we are reaching almost 72% of Canadian medical and cosmetic dermatologists each and every quarter with content and articles from their peers that we hope is providing value to the community.

As a reminder, we have created a central hub where all our articles are now archived and accessible for all subscribers. Please take a look by visiting www.canadiandermatologytoday.com

In this issue we examine adult female acne, commonly used neuromodulators in clinical practice and complementary and natural therapies in the management of atopic dermatitis. We also have a great article on scar injection and a piece on the growing role that social media is playing in the field of dermatology for both patients and clinicians. Finally, with COVID-19 vaccinations having ramped up across all parts of the country, we are pleased to present an article on important learnings about the COVID-19 virus and the impact of vaccinations in patients with psoriasis.

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

Best wishes,

Kim Papp, MD Jensen Yeung, MD Melinda Gooderham, MD Chih-ho Hong, MD



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SCAR INJECTION: BEYOND TRIAMCINOLONE ACETONIDE

Introduction

Pathological scars, comprising hypertrophic scars and keloids, are both rewarding and challenging to treat in clinical practice. Beyond the cosmetic appearance and the physical reminder of the circumstances of scar formation (**Figure 1**), patients can also experience itch, pain, or even functional limitations. In many ways, the large number of available treatment options highlight that there is no globally accepted therapeutic ladder for this clinical scenario.

Modalities of treatment include scar injections, cryotherapy, surgery, and energy-based device treatments, including lasers or radiation.[1] Laser-assisted drug delivery (LADD), which is the treatment of a scar with low-density fractional ablative laser followed by immediate application of a topical agent, is associated with excellent outcomes.[2-4] However, this approach requires technology that may not be as widely available or as comprehensively reimbursed as scar injections. The objective of this article is to provide an overview of treatment options for scar injections with accessible medications to treat pathological scars, especially for dermatologists who may not have access to advanced technologies and devices for scar treatment in their practice.

Triamcinolone acetonide

Intralesional triamcinolone acetonide (TAC) is commonly used to treat pathological scars. It is widely available at pharmacies, inexpensive, and does not require specialized technology to use. A recent systematic review and meta-analysis of fifteen trials confirmed its effectiveness in the treatment of hypertrophic scars and keloids.[5] Unfortunately TAC can induce apoptosis of fibroblast and atrophy of collagen in adjacent normal skin. Potential side effects of TAC injections include atrophy, telangiectasias, hypopigmentation, and recurrences over time. Scar recurrence can be seen as frequently as in 50% of cases,[6] especially for keloids. Customizing the TAC concentration to patient skin type, size of scar, and location of scar is a strategy that can help mitigate atrophy. Empirically, in the author's practice, the first scar injection with TAC is performed with a concentration of 5-20 mg/cc. Low concentrations are used in patients with Fitzpatrick Skin Phototype V and VI who are at higher risk of hypopigmentation, as well as for treatment of cosmetically sensitive sites (face, décolleté). Careful observation of the scar is recommended during a very slow injection. This is to minimize pain and to enable stopping the injection prior to any extravasation of TAC to surrounding healthy skin. Patients are injected every 4 to 6 weeks and the concentration of TAC can be adjusted at that time – if the clinical response was modest with no adverse events, the concentration may be increased. If early signs of surrounding atrophy are noted and the scar still needs treatment, a lower concentration of TAC may be used.

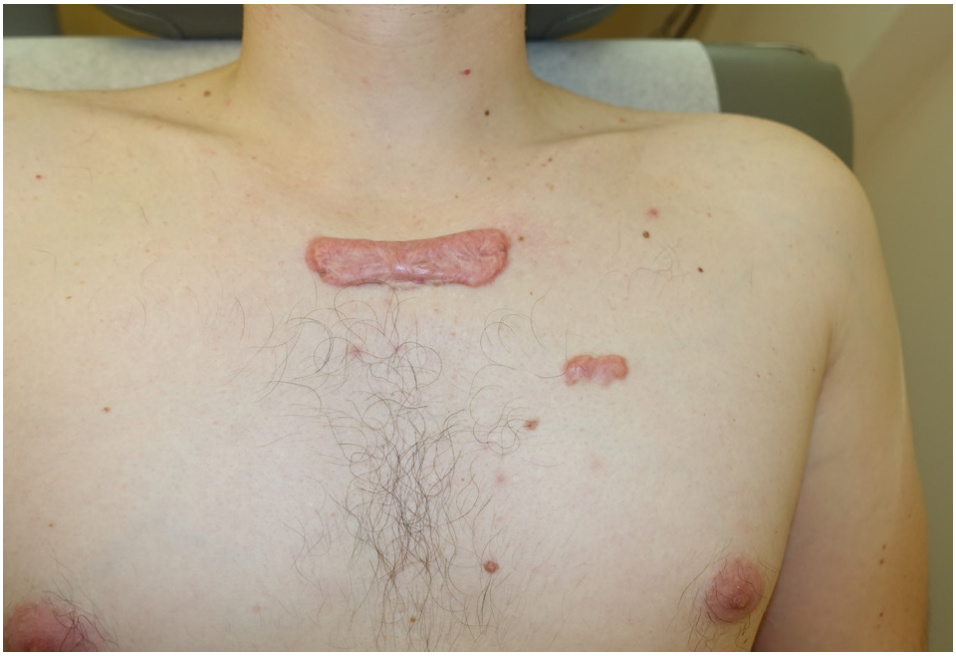


Figure 1. Close up of keloid scar on man's skin; photo courtesy of Vincent Richer, MD

5-fluorouracil

The chemotherapy agent 5-fluorouracil (5-FU) is a pyrimidine analog that suppresses deoxyribonucleic acid synthesis by inhibiting thymidine synthase, effectively halting the proliferation of fibroblasts and the fibroblast-populated collagen lattice.[7] 5-FU is commercially available in 10ml single use vials and 100ml "bulk" vials. When used in monotherapy, the performance of 5-FU at reducing scar thickness is comparable to TAC, however it does not offer the same long-term improvement in scar vascularity.[5] Moreover, injection of 5-FU alone can lead to increased pain and ulcer formation. It is generally recommended to avoid injecting more than 2 cc (e.g. 100 mg) per session to avoid significant systemic exposure and symptoms. While intralesional 5-FU and TAC have both been proven as effective monotherapy, there has been increased interest in their combined synergistic effects.

Combination triamcinolone acetonide and 5-fluorouracil

Compared to TAC alone, using combination TAC and 5-FU produces significant improvement in scar height, pliability, and pigmentation. Additionally, the combination is associated with increased long-term responses (24+ weeks) when compared to TAC alone, suggesting lower rates of scar recurrence.[5] Many combination dosages and treatment intervals have been examined, however, there is currently no consensus on any of them. It is likely that the patient's skin type as well as the size and location of the scar will affect the dosing strategy. Empirically, in the author's practice, up to 2 mL of 50 mg/mL 5-FU are used to dilute down TAC to its desired concentration and patients are injected every 4 to 6 weeks. Dilution of TAC can be as low as 2.5 to 3.3 mg/mL for first-time treatment of small keloids at risky sites for iatrogenic atrophy (e.g. the presternal region). The concentration of TAC may be increased with subsequent treatments or started at 5 to 20 mg/mL for larger keloids at more forgiving anatomical sites (e.g. the helix).[7] Injections are delivered slowly to minimize pain until the scar appears temporarily blanched. Clinicians should take care to interrupt injection if diffusion occurs into adjacent normal skin.

Botulinum toxin-A

Botulinum toxin-A (BTX-A) is a neurotoxin that acts on neurons to inhibit the release of acetylcholine, which inhibits muscle contraction. BTX-A is more expensive than TAC but is widely available and stocked by many dermatologists who offer cosmetic services. Dermatologists are familiar with its cosmetic use to treat dynamic rhytides and its medical indications such as primary hyperhidrosis, but may not be aware that it can also reduce inflammatory stimuli involved in wound healing, thereby affecting scar formation.[8] Moreover, BTX-A may directly regulate the activity of fibroblasts by changing apoptosis, migration, and fibrosis.[6] Since hypertrophic scars and keloids occur at areas of high skin tension, it stands to reason that minimizing these forces in surrounding skin by relaxing muscle tissue may be beneficial. A recent systematic review and meta-analysis concluded that BTX-A was more effective than saline at prevention of postsurgical facial scars.[8] Monotherapy of pathological scars with BTX-A has been studied and shows favorable outcomes when compared with TAC.[6] However, the dosing and treatment sequence reported in the literature are highly heterogeneous.

Combination triamcinolone acetonide and botulinum toxin-A

In a recent network meta-analysis, botulinum toxin-A combined with TAC had the highest predicted efficacy, followed by combination TAC and 5-FU.[6] Further analysis reveals this is based on a handful of studies that compared combination TAC and BTX-A to either treatment as monotherapy.[9] Nonetheless, the evidence supporting BTX-A monotherapy is encouraging,

and adding BTX-A to TAC or TAC + 5-FU combination injections is a viable treatment option. As mentioned above, the optimal dosing and treatment sequence for BTX-A to treat pathological scars has not been determined. Empirically, in the author's practice, 2 units of onabotulinum toxin-A are injected per cm^2 of scar, with injection points extending beyond the scar periphery. Treatment is performed immediately after TAC or TAC + 5-FU combination scar injection during the same visit.

Other drugs for scar injection

Verapamil has also been extensively studied for the treatment of pathological scars. It appears to have comparable efficacy to TAC in improving scar height over time, however it may not achieve similar outcomes on the domains of scar vascularity and pliability.[5] In the network meta-analysis mentioned previously, verapamil had the lowest order of efficacy as compared to the above treatment options.[6] The body of evidence to support the use of bleomycin, hyaluronic acid, hyaluronidase, platelet rich plasma or collagenase is less robust and beyond the scope of this article.[1]

Scar injection versus laser-assisted drug delivery

With the advent of LADD, has scar injection been fully supplanted? A large number of peer-reviewed articles compare ablative fractional laser (AFLX) alone versus AFLX with LADD.[2] However, data comparing intralesional (IL) injection versus LADD of a medication are scarce. Only two studies comparing IL injection to LADD of a medication were found in the literature. Abd El-Dayem et al.[10] compared four IL TAC treatment sessions at 4-week intervals vs fractional Er:YAG-assisted delivery of topical betamethasone in 30 keloids. While both treatments showed significant improvement three months after the last treatment, there was no significant difference between the outcomes and there was a higher incidence of telangiectasia, dermal atrophy and dyspigmentation with IL TAC, although this difference was not statistically significant. Sabry et al.[11] compared once-monthly treatments of IL BTX-A for four consecutive months to four sessions of fractional CO2-assisted delivery of topical BTX-A in 10 keloids and 10 hypertrophic scars. In the hypertrophic scars group, both treatments showed overall significant improvement at the six-month follow-up mark, with more improvement on the LADD-treated side than the IL injection side. Interestingly, in the keloid group, IL injections were favored over LADD of BTX-A for vascularity and pliability. The limitations of these studies include a small sample size as well as scoring by evaluators who were not blinded. While these two studies help support the role of LADD in the management of pathological scars and potentially elucidate a better safety profile compared to IL injections of TAC, they do not obviate the role of scar injections.

Conclusion

Of the many treatment options available to treat pathological scars, scar injection is widely available and requires no specialized technology. Though TAC is most commonly used for scar injection, 5-FU and BTX-A have been studied as monotherapy and in combination with TAC. Notably, duration of treatment response may be longer with combination TAC and 5-FU. Both 5-FU and BTX-A carry the added benefit of reducing the risk of skin atrophy associated with high-concentration TAC. Combining 5-FU and/or BTX-A with TAC may allow for effective treatment of pathological scars while maintaining lower concentrations of TAC to minimize side effects. Additional randomized trials are necessary to further optimize combination scar injection therapy and to guide resource allocation.

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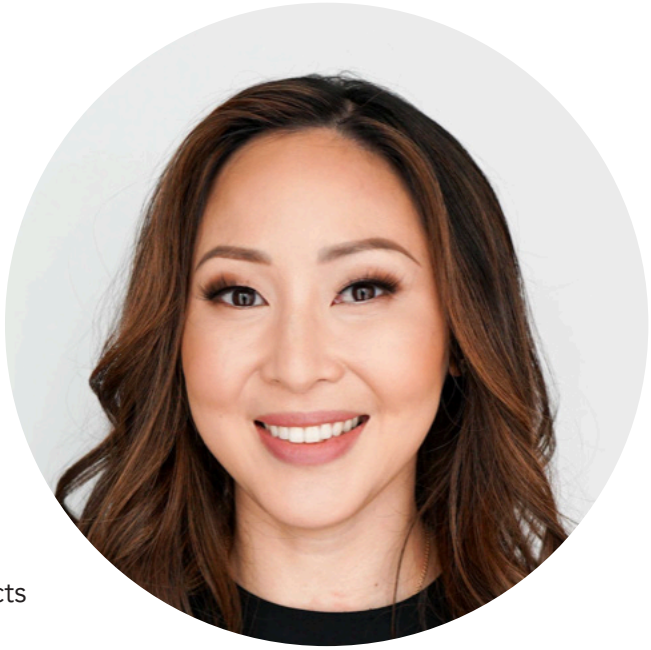
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MY APPROACH TO COMPLEMENTARY AND NATURAL THERAPIES IN MANAGING ATOPIC DERMATITIS

Compared to other chronic cutaneous diseases, atopic dermatitis (AD) has gained much attention in the complementary and alternative realms of medicine. In a questionnaire-based study from Norway, 51% of patients with eczema reported use of one or more forms of alternative medicine (homeopathy, health foods, and herbal remedies) to help treat their condition.[1] Some patients may look for alternative options when their disease is chronic, when explanations are unsatisfying, or when treatments are felt to be unsafe (i.e. in the case of steroid-phobia in the treatment of AD).

An increasing number of patients are using complementary and alternative medicine and asking for 'natural' options particularly when dealing with recalcitrant eczema. As we enter an exciting new chapter for the treatment of moderate-to-severe AD with new biologics and small molecules on the horizon, we must keep in mind that these treatments are not a cure and patients may experience flares in their disease even when on therapy. I believe we should adapt and be open to providing 'integrative dermatology'- which combines conventional and complementary approaches to disease management together in a safe and evidence-based fashion.

This article includes complementary therapies that I recommend in my practice, with evidence provided in a table (**Table 1**) for the readers. Even though there are numerous complementary and alternative medicine options available, the peer-reviewed evidence supporting their use through methodologically robust clinical studies is scarce. The aim of this article is to serve as a resource when you are having discussions with your patients about the potential use of 'natural' options. The complementary treatment options have been grouped into the four pillars of conventional AD treatment: **moisturization, anti-inflammatories, anti-bacterials, and anti-pruritics.**

Moisturization and Wet Wraps

Moisturization is one of the most important components of AD therapy. It helps to maintain hydration and protect the skin barrier, decrease trans-epidermal water loss (TEWL), and prevent irritants and/or allergens from entering the skin. There is no 'best' emollient and clinicians must keep in mind patient preferences, cost of emollients, disease state, and patient skin type. Some patients feel comfortable using natural oils to moisturize their skin because it is a 'natural' ingredient or because of lower cost. Not all oils are interchangeable and there are a few key features to consider, particularly the type of oil and the processing of the oil (i.e. cold pressed vs. heat pressed).

Two oils that clinicians may wish to consider are virgin coconut oil and virgin sunflower seed oil. Most 'virgin' oils are cold pressed meaning the seed or nut is processed through high pressure at a specific temperature to extract the oil without the use of chemicals or heat.[2]

Virgin sunflower seed oil (VSO)- Virgin sunflower seed oil is composed mainly of linoleic acid, which is thought to decrease inflammation in the skin and restore the skin barrier by increasing the synthesis of ceramides.[3] A study of 19 adults with and without a history of atopic dermatitis compared the use of olive oil and sunflower seed oil on opposite arms through two randomized forearm-controlled studies. Sunflower seed oil was shown to preserve the stratum corneum, improve hydration, and did not cause erythema. Conversely, olive oil decreased the stratum corneum, increased TEWL, and caused mild erythema.[4]

Virgin coconut oil (VCO)- Virgin coconut oil is an effective emollient and a natural antibacterial against *S. aureus*.[5,6] Virgin coconut oil is made by a wet-milled, cold pressed process that preserves the active components (antioxidants and fatty acids). There have been no reported cases of allergic contact dermatitis with virgin coconut oil in a review of the literature.[7] A study of 117 patients showed virgin coconut oil as superior to mineral oil in SCORAD (SCORing of Atopic Dermatitis) and TEWL assessments compared to baseline.[7]

Wet Wraps are an easy and effective way to enhance moisturization. My recommended protocol is as follows:

1. Apply emollient cream or ointment on damp skin,
2. Apply layer of damp Tubifast® garments or wrap gauze,
3. Apply final layer of dry Tubifast® garment or wrap gauze on top, and
4. re-wet the garments/gauze every 2-3 hours but stop rewetting overnight[9]

This form of occlusive moisturization can significantly improve water absorption and skin barrier at least for the short-term and prevent scratching by blocking access to the skin.[8] A review of wet wraps in 2006 concluded that they can be used as a short-term treatment in children with severe and/or refractory AD.[10] Long-term occlusion with wet or dry garments can increase the number of bacteria on the skin and folliculitis can be a common complication of wet wrap therapy. It may be beneficial to use diluted bleach baths or antiseptic cleansers prior to applying the wet wraps.

Anti-inflammatories

Topical corticosteroids (TCS) are the mainstay of topical anti-inflammatory therapy in AD. There is a growing concern with side effects of long term topical steroid use (i.e. skin atrophy, striae, dyspigmentation and hypertrichosis), causing 'steroid phobia' especially in the treatment of pediatric AD. Patients will often ask for alternative and natural topical options that may decrease inflammation in eczema and some patients may refuse treatment with TCS. There are two topical vitamins that may help alleviate the inflammation caused by AD and may be used as an alternative to topical steroids or during periods of steroid holidays.

Vitamin B5 (Pantothenic acid)- Vitamin B5, in the alcohol derivative form of Provitamin B5 (panthenol) is an effective humectant. It prevents TEWL and promotes healing of the skin by inducing keratinocyte proliferation and increasing glutathione in the skin.[11] There are many products containing panthenol that can be recommended to patients. A small study comparing dexpanthenol 5% ointment and hydrocortisone 1% ointment concluded that dexpanthenol 5% ointment may be just as efficacious as hydrocortisone 1% and can be used as an alternative to topical corticosteroids.[12]

Vitamin B12 (Cobalamin)- Topical Vitamin B12 has shown some success in small clinical trials for the treatment of AD. It is not commercially available but can be compounded by a pharmacist. This is a topical therapy that may be suitable for those patients that are reluctant to try conventional therapy options. It is thought to decrease symptoms and

inflammation by reducing nitric oxide production in the skin.[13] Topical Vitamin B12 was found to be superior to placebo in reducing the extent and severity of AD in one study.[14] While there are many compounds of B12, a simple compound for topical Vitamin B12 is 0.07% of cyanocobalamin (B12) powder in any moisturizer base.

Antiseptic use and dilute bleach baths

S. Aureus colonization in AD has been linked with worsening of disease activity. Since a landmark study in 2009 suggested the use of diluted bleach baths to decrease the bacterial load of *S. Aureus* on the skin, it has been commonly used as an antibacterial therapy in the management of AD.[15] A meta-analysis in 2017 of four studies evaluating the efficacy of bleach baths and bath water demonstrated that there was no significant difference between the two in terms of impact on *S. aureus* density or severity of AD.[16] While this recent evidence may raise doubt about the benefits of diluted bleach baths, I regularly recommend diluted bleach baths for my patients with moderate-to-severe AD as an adjunct because the risks with this therapy are relatively low and I have had favourable outcomes in my clinical practice.

Antiseptics are used to decrease or slow the growth of microorganisms on surfaces. They can represent an alternative to topical antibiotics in patients with AD and frequent skin infections with *S. aureus*. The use of antiseptics is not substantiated through good clinical studies. Some advantages of antiseptics over antibiotics include the low potential of inducing bacterial resistance and rarely causing delayed hypersensitivity reactions or allergies.[17] One of the antiseptics that I often recommend is chlorhexidine gluconate (dexiden 4% detergent or 0.5-1% chlorhexidine added to an emollient). The patient can apply the chlorhexidine in emollient daily or use the antiseptic wash twice-weekly when bathing.

Textiles and Anti-pruritics

Clothing fabrics interact directly with our skin and can sometimes be the cause of irritation and induce itching. Fabric selection for eczema sufferers is an important component of counselling.

There are new synthetic fabrics that may combine anti-microbial, anti-inflammatory, moisture wicking and soothing properties for a patient suffering with AD. Cotton, bamboo and silk have historically been the fabrics that I recommend to most of my patients with AD. Fabrics such as large fibre wool and polyester may cause irritation and induce itch. Small fibre wools, such as ultra or superfine merino wool can be tolerated well by patients with AD and are a good alternative warm fabric in the autumn and winter months.[18] A recent meta-analysis looking at fabric selection in AD found that some emerging fabrics that can potentially reduce atopic dermatitis severity and *S. aureus* burden include, silver-coated, chitosan-coated, and cellulose-based fabrics.[19] I recommend silver-coated clothing for patients with frequent cutaneous infections that use TENCEL technology (a cellulose-based fibre embedded with chitosan) especially for pediatric patients with moderate-to-severe AD.

Itch associated with AD is complex and treatment can be challenging and disappointing. Treatment strategies are aimed at decreasing inflammation in the skin, treatment of bacterial infections and creating a physical barrier to prevent scratching. There are several household products that clinicians may wish to consider as an adjunct therapy to help relieve itch.

Baking Soda (Sodium bicarbonate)- Baking soda has been used to soothe and relieve itch and has been investigated as an antimicrobial agent and treatment option for aquagenic pruritus and psoriasis.[20,21] Sodium bicarbonate has many useful properties including balancing the skin's pH, reducing inflammation, and acting as a natural antibacterial agent.[22] The National Eczema Association recommends using a ¼ cup of baking soda in a full tub of warm water and soaking for 10-15 minutes, then rinsing off with warm water and locking in moisture with an emollient.

Colloidal Oat (Avena sativa)- Colloidal oat is the finely ground form of uncooked oatmeal and can readily absorb water and easily mix with creams and lotions.[2] Colloidal oatmeal helps to provide a skin barrier by holding moisture through its hydrophilic polysaccharides and hydrocolloids. Studies have demonstrated that avenanthramides (a component of whole grains) are responsible for the oat's anti-inflammatory, antioxidant, and antihistaminic activity.[23,24] Patients may purchase commercially available packaged bath treatments or take oat and grind it in a food processor or coffee grinder until a fine powder consistency is achieved. I recommend using a cup of colloidal oat and sprinkling it into a tub of warm water as the tub is

PILLAR OF AD MANAGEMENT	TREATMENT	RECOMMENDATION	EVIDENCE
Moisturization	Virgin sunflower seed oil	Apply VSO to damp skin twice daily	VSO improved skin hydration and preserved stratum corneum integrity, while olive oil reduced stratum corneum integrity and induced erythema.[4]
	Virgin coconut oil	Apply VCO to damp skin twice daily	A study comparing topical VCO vs. mineral oil showed significant improvements in SCORAD, TEWL and skin capacitance scores compared with baseline. VCO was superior on all accounts compared with mineral oil after 8 weeks[7]
	Wet Wraps	1) Apply emollient cream or ointment on damp skin 2) Apply layer of damp Tubifast® garments or wrap gauze 3) Apply final layer of dry Tubifast® garment or wrap gauze on top 4) rewet the garments/gauze every 2-3 hours but stop rewetting overnight	A review of wet wraps concluded that they can be used as an efficacious short-term intervention treatment in children with severe and/or refractory AD[10].
Anti-inflammatories	Vitamin B5	Apply commercially available products available for use on active areas of eczema (ie La Roche Posay Cicaplast Baume B5) or compound panthenol 5% in moisturizer of choice	A small study of 30 patients comparing dexpanthenol 5% ointment and hydrocortisone 1% ointment concluded the effectiveness of dexpanthenol 5% ointment may be equal to that of hydrocortisone 1% and can be used as an alternative treatment in mild to moderate AD[12]
	Vitamin B12	Topical B12 Cream: 0.07g cyanocobalamin (Vit B12), 46g persea gratissima oil (avocado oil), 45.42g water, 8g TEGO care PS or methyl glucose stearate (an emulsifier), 0.26g potassium sorbate (preservative), 0.25g citric acid OR 0.07% cyanocobalamin in moisturizer of choice	A small study of 49 patients compared topical Vitamin B12 to placebo and was found to be superior in regard to reducing the extent and severity of AD[14]
Antibacterials	Dilute bleach bath	¼ cup of bleach in full tub of water, 10-15min soak, then rinse and apply emollient	Bleach baths are effective in decreasing the severity of AD but a recent meta-analysis of four small, randomized trials (116 patients) found that bleach baths were not more effective than plain water baths at 4 weeks in decreasing severity of AD[16]
	Antiseptics	chlorhexidine gluconate (dexiden 4% detergent or 0.5-1% chlorhexidine added to emollient); apply the chlorhexidine in emollient daily or use the antiseptic wash when bathing twice weekly	A systematic review found that topical antibiotics and antiseptics reduced the colonization of skin with *S.aureus* but could not prove whether treatment with these agents in combination with TCS induced greater clinical improvements compared to TCS alone[17]
Antipruritics	Textiles	Recommended fabrics for AD: cotton, silk, bamboo, ultra or super fine merino wool functional fabrics: silver-coated, chitosan-coated and cellulose-based fabrics	A meta-analysis looking at fabric selection in AD found that some emerging fabrics that could potentially reduce atopic dermatitis severity and *S. aureus* burden include silver-coated, chitosan-coated and cellulose-based fabrics[19]
	Baking soda bath	¼ cup of baking soda in a full tub of warm water and soaking for 10-15 minutes, then rinsing off with warm water and locking in moisture with an emollient.	Baking soda baths have been used successfully in relieving itch associated with aquagenic pruritus[26]; There are no studies evaluating baking soda baths and AD although, it is often recommended as a bath additive for symptomatic relief by experts and recommended as part of treatment guidelines for the management of AD in the 2012 Joint Task Force Practice Parameter update[27]
	Colloidal oat bath	1 cup of colloidal oat sprinkled into a tub of warm water as it is filling, soaking for 10-15 minutes then patting dry and locking in moisture with an emollient	Colloidal oatmeal powder added to baths or cold wet packs led to complete clearance (29%) and great improvement (22%) of active AD lesions and some improvements in 41% of patients.[25]

Table 1. Complementary Therapies used for Atopic Dermatitis and evidence ; courtesy of Angela Law, MD

filling, soaking for 10-15 minutes then patting dry and locking in moisture with an emollient. Anecdotally, patients with open wounds and painful lesions prefer oatmeal baths to bleach baths because of superior tolerability and lack of irritation. In one study, children with AD who bathed with colloidal oatmeal powder achieved marked improvement in their active lesions.[25]

AD is a challenging disease to treat, and there is no uniform approach for patients. Conventional treatments can offer relief for many patients, but symptoms often relapse, and treatments are not without risk. Some of the complementary options mentioned above are relatively harmless, affordable, and easy enough to incorporate into a patient's regimen. These options are not meant to replace conventional therapies but instead are supplementary therapy to provide more relief for AD patients.

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TREATING ADULT FEMALE ACNE

Adult female acne (AFA) is a common and challenging condition to treat, often resistant to conventional acne treatments. AFA is a type of hormonal acne that affects women, typically peaking in the 20s and slowly declining with age. A 2015 survey documenting the self-reported prevalence of acne in 540 adult females showed that 50.9% of women in their 20s, 35.2% of women in their 30s, 26.3% of women in their 40s and 15.3% of women in their 50s are affected.[1] A 1997 article in the *British Journal of Dermatology* elucidated the increasingly common phenomenon of acne in adults older than 25 years of age and reported that approximately 75% of women (mean age = 35.5 years) report acne as being continuous or intermittent from adolescence while 18.4% report no history of adolescent acne.[2]

While AFA can affect any area on the face and upper body, it typically occurs in a u-shaped pattern on the lower cheeks, jawline and neck. It is characterized by inflammatory papules and cysts as well as comedones. Patients often complain of facial cysts that fail to come to a head, are painful, last for months and resolve with longstanding dyspigmentation. Sequelae are similar to adolescent acne and can involve scarring (20%), post-inflammatory pigmentary change and even depression (10%).[1]

Although the diagnosis of AFA is usually quite straightforward for the dermatologist, the management can be challenging. These patients are characterized by failure with standard topical therapies and disease recurrence after repeat courses of antibiotics and isotretinoin. As well, hormonal intrauterine devices (IUDs) and certain birth control pills can exacerbate or trigger the acne.

Of the four pathogenic factors causing acne: abnormal follicular keratinization, *cutibacterum acnes* colonization (previously known as *proprionibacterium acnes*), inflammatory events, and hormones; the hormonal element is the predominant causative factor in AFA. The sebaceous glands are androgen dependent. Androgens and end organ receptor sensitivity are responsible for gland activity and the resultant acne. Progesterones have varying degrees of androgenicity, and the degree of androgenicity plays a significant role in AFA.[3]

Successful disease management of AFA centers on the targeting of hormones. This includes using combined oral contraceptive pills (COC) and/or spironolactone. Topical agents should be used for optimization of therapy. Topical retinoids are often used for treating the comedomal aspect of AFA, and have been shown to help with post-inflammatory pigmentation and scarring, in addition to the anti-aging benefit many women in this age group seek. Efficacy in AFA has also been demonstrated for clindamycin-retinoid and benzoyl peroxide-retinoid combination gels. Additionally, dapsone 5% gel has shown efficacy in women with AFA, as has azelaic acid 15% gel, which has the added benefit in this patient population of being safe for women of child-bearing age and/or those who are pregnant.[2]

All COC pills have a net antiandrogen effect; however, they do not all have the same efficacy with respect to the treatment of acne. COCs contain the estrogen ethinyl estradiol (EE) which increases levels of sex hormone-binding globulin, resulting in lower levels of free testosterone.

Progesterones, which vary significantly in content by COC, are divided into 4 generations based on their androgenicity (**Figure 1**).[4] The first generation progesterones, such as norethindrone, have a marked intrinsic androgen effect, which worsens acne. This type of progesterone is found in many commonly-prescribed COCs and is also found in the 'minipill' which is progesterone-only, without the added anti-androgen benefit of estrogen. All of these first generation treatment options tend to worsen or trigger acne in women. Clinicians may be interested to learn that some commonly used treatments to abate menopausal symptoms, such as patches and tablets, contain estrogen in combination with norethindrone and can trigger or exacerbate acne in this older population of women.

Second generation progesterones such as levonorgestrel and norgestrel have varying androgenic effects and variable effects on acne. These progesterones are found in commonly prescribed COCs. While these commonly prescribed COCs (and their generic equivalents) are approved for both contraception and acne, they are not as effective at treating acne as COCs containing more anti-androgenic progesterones.[5]

Levonorgestrel is also the progesterone found in all currently available hormonal IUDs. These IUDs do not contain estrogen. The rates of acne demonstrated with these agents ranges from 1-10% and, in some instances, greater than 10% based on the data found in their Health Canada approved product monographs.[6] Retrospective studies have shown increased acne exacerbation with levonorgestrel containing IUDs than with COCs.[7,8] Additionally, a small survey of 51 respondents on levonorgestrel containing IUDs showed that there was significant

Generations of Progesterone and Treatment of Acne	
1st Generation-marked intrinsic androgenic effect • metabolize to norethindrone (such as Lolo, Ortho, Demulen) • Micronor, Depo-provera • Menopausal treatments (such as Estralis, Activella)	Worsen/cause acne
2nd Generation- varying androgenic effect • Norgestrel/levonorgestrel (Ovral, Triphasil, Seasonalle, Alesse, Alysena, Triquilar) • Also IUD's Mirena, Kylena	May or may not worsen/cause acne
3rd Generation - Least androgenic • Desogestrel, norgestimate, gestodene (Marvelon, Tricyclen, Linessa, Cyclen) • Etonogestrel in Nuvaring (related to desogetrel) • Norelgestromin in Evra Patch	Effectively treat acne

Synthetic Progestins- Antiandrogenic
• Cyproterone acetate: inhibit 5 alpha reductase and block androgen
  • Diane 35 and generics
• Drospirenone: inhibits ovarian production of androgen and blocks androgen R in skin
  • Yaz, Yasmin and generics
  • Synthetic spironolactone analogue equivalent to ~25 mg spironolactone
	Most effective for treating acne

Figure 1. Generations of progesterone and treatment of acne; adapted from Apgar et al, 2000

(P = .0005) change in acne severity upon IUD placement with 35% of women reporting worsening of acne.[9]

Third generation progesterones such as desogestrel, norgestimate and gestodene are the least androgenic of the first three generations and can be very effective at treating acne and are the progesterones found in commonly prescribed pills and their generic equivalents. In addition, the Evra™ Patch (norelgestromin) and the NuvaRing® (etonogestrel) contain third generation progesterones with estrogen and can be good alternatives for contraception and acne control in those who do not want to take COC.[3,4]

Finally, the fourth generation 'synthetic progesterones' are anti-androgenic and are the most effective for treating acne.[3] These include drospirenone and cyproterone acetate. Drospirenone is a synthetic analogue of spironolactone which is equivalent to about 25 mg of spironolactone[10] and works by blocking both the androgen receptor and inhibiting ovarian androgen production.[10] It is found in combination with EE in commonly-prescribed COCs and their generic equivalents, which are approved for both contraception and acne.

Cyproterone acetate blocks the androgen receptor and inhibits 5 alpha-reductase.[10] This is found in combination with EE in some COCs and their generic equivalents, which are approved for treatment of acne but not for contraception.

The use of COCs is not without risk, including the risk of venous thromboembolic (VTE) events. The risk of VTE in women of reproductive age who are COC non-users is estimated at 4- 5/10,000 women per year (WPY). Women on COCs have been estimated to have an increased risk of 9-10/ 10,000 WPY.[11,12] This risk is felt to be associated with the estrogen more than the progesterone. Additionally, the risk of VTE is higher with COCs containing a higher dose of EE (> 30 mcg). There has been controversy regarding whether there is a slightly increased risk of VTE with COCs using third and fourth (synthetic) generation progesterones.[11,12] Epidemiological studies demonstrate a slight increase in the risk of VTE, but these observational studies do not fully control for confounding in their methodology. Prospective studies, conversely, do not show an increased risk of VTE. The Society of Obstetricians and Gynecologists of Canada (SOGC) states that for cyproterone acetate/ estrogen COC users, the risk of VTE is very low and comparable to that of other combined hormonal contraceptives and that for the majority of women, the benefits outweigh the risks. Similarly, for drospirenone the SOGC suggests that users of COCs should be advised that the highest quality evidence available at this time does not suggest any difference in VTE risk based on the type of progestin in the COC.[11] Additionally, the risk of VTE from COCs is low relative to the risk of VTE in pregnancy (29/10,000 WPY) and post partum (up to 300-400/10,000 WPY).[10-12] When counseling women about the risk of VTE with COCs, it is important to consider relative risks, as well as other risk factors for VTE such as age, polycystic ovary syndrome, obesity, smoking, air travel, surgery, and personal and family history of VTE.[10-12]

Spironolactone is an anti-androgen therapy that acts at the androgen receptor and is also an

Spironolactone drug interactions

- **Amiloride (X - avoid combination)**
- **Bromperidol (X)**
- **Cyclosporine (X)**
- **Triamterene (X)**
- Amifostine, ammonium chloride, cosyntropin, eplerenone, mitotane, obinutuzumab, potassium salts, sodium phosphates (all D- modify regimen)
- Abiraterone, alfuzosin, Alpha/beta agonists, **amphetamines, ACE inhibitors, ARBs, atypical anti-psychotics, ASA, atorvastatin, barbituates**, benperidol, **brimonidine (topical)**, cardiac glycosides, **ciprofloxacin**, cholestyramine, diacerein, diazoxide, **digoxin**, **drospirenone**, duloxetine, **heparin**, some herbs, levodopa, **lithium**, lormetazepam, molsidomine, naftopidil, non-depolarizing neuromuscular blocking agents, nicergoline, nicarandil, **nitrofurantoin**, nitroprusside, **NSAIDs**, **opioids**, **pentoxifylline**, pholcodine, PDE5 inhibitors, prostacyclin, quinagolide, quinidine, tacrolimus (systemic), tolvaptan, trimethoprim, yohimbine, canagliflozin, mianserin, mirabegron, oxymetazoline (topical), protirelin, Vitamin K antagonists (category C- monitor therapy)

Figure 2. Spironolactone drug interactions; adapted from Plavanich et al and Azarchi et al.

antagonist of aldosterone which is used as a potassium-sparing diuretic. While it is approved by Health Canada for the treatment of essential hypertension, edematous conditions, primary hyperaldosteronism and hypokalemia, it is commonly used off-label to treat AFA at doses of 25-200 mg daily (the typical starting dose is 100 mg).[13] New evidence shows that in healthy women less than 50 years of age taking spironolactone for acne, routine potassium monitoring is not necessary as rates of hyperkalemia in the spironolactone-treated population are equivalent to those found in the general population. Potassium monitoring is recommended if there are other risk factors for hyperkalemia such as renal impairment or use of other medications which cause hyperkalemia (**Figure 2**).[14,15] Additionally, while contraindicated in pregnancy, spironolactone is safe in lactation. Intense diuresis can suppress lactation, but this is unlikely to occur with acne dosing.[16] Additionally, large registries have failed to show increased risk of breast cancer previously suggested by early animal studies, supporting the safety of this therapy.[14,15]

The future treatment horizon for AFA includes a new topical androgen receptor inhibitor, clascoterone 1% cream, which will soon be available for clinicians. This topical agent reduces oil in the skin and has demonstrated efficacy in treating both inflammatory and comedomal lesions in patients with moderate-to-severe acne in phase III clinical trials.[17]

Adult female acne is a common entity and a challenging condition to treat, often failing conventional acne treatments. Topical agents alone are rarely effective for AFA but have a role as adjunctive therapy. Anti-androgen COCs, specifically those containing a synthetic progesterone (drospirenone or cyproterone acetate), are the most effective COCs for treating acne, followed by those containing third generation progesterones. First and second generation COCs may not help and can even exacerbate or cause hormonal acne. Hormonal IUDs are also known to induce and worsen acne. Spironolactone is a safe and effective therapy for AFA and can be used with an anti-androgen oral contraceptive pill in a complementary fashion to further improve results.[10]

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WHAT TO KNOW ABOUT COVID-19 AND ITS IMPACT ON PATIENTS WITH PSORIASIS

Introduction:

Coronavirus disease 2019 (COVID-19) is an acute systemic illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This novel coronavirus was first identified in Wuhan, China in late 2019 and has since had a major impact on global health after being declared a pandemic in the spring of 2020 by the World Health Organization. To date, there have been over 180 million confirmed infections and over 4 million deaths worldwide across multiple 'waves'.[1]

COVID-19 has had a major impact on dermatology practice in Canada with a shift towards virtual care and a reluctance to prescribe some immunosuppressive medications.[2] However, since those early days, there has been growing comfort with continuing such medications in most cases.

The primary objective of this article is to review the impact of both COVID-19 and COVID-19 vaccination on patients with psoriasis who are taking oral agents and biologics (anti-tumour necrosis factor (TNF), anti-interleukin (IL)-17 and anti-interleukin (IL)-23 inhibitors).

Impact of COVID-19 On Patients with Psoriasis on Oral Agents or Biologics:

Psoriasis is a chronic and immune-mediated skin disease that affects 2-3% of the population.[3] It can range from mild to severe with worse cases often requiring systemic immunomodulatory therapy. This may include oral small molecules (apremilast, methotrexate, cyclosporine) and injectable biologics (TNF-α, IL-17 and IL-23 inhibitors).

Early in the pandemic, it was unknown what impact psoriasis may have on COVID-19, especially for those patients taking oral or biologic therapy. As data has begun to emerge, it has become clear that certain co-morbidities may predict a worse outcome for patients with COVID-19 such as cardiac disease, diabetes mellitus, and obesity, all of which are more common in psoriasis patients.[4] Several studies have shed light on the use of oral and biologic medications including a large and sophisticated cohort study which was conducted by examining over 50 million unique patient records across multiple countries to evaluate the impact of methotrexate and anti-TNF agents on COVID-19-related outcomes.[5] The researchers identified 214 patients within their database with COVID-19 who had recent anti-TNF or methotrexate exposure compared with 31,862 with COVID-19 who had not had recent methotrexate or anti-TNF exposure. Using propensity matching, the researchers did not identify any increased risk of COVID-19 hospitalization between the anti-TNF group vs no anti-TNF group (anti-TNF: risk ratio (RR) = 0.73 [95% CI 0.47 to 1.14], p = 0.1594) nor for those in the methotrexate group vs the no methotrexate group (RR = 0.87 [95% CI 0.62 to 1.23], p=0.4272). Similarly, a large cohort in Northern Italy found similar results.[6] This retrospective cohort study followed a large number of patients with chronic plaque psoriasis taking biologic therapy (n = 6501). The authors found that the incidence rate of hospitalization from COVID-19 was similar among the general population compared to those with psoriasis taking biologics (11.7 per 10,000 person-months in patients with psoriasis (95% CI, 7.2 to 18.1) vs 14.4 in the general population (95% CI, 14.3 to 14.5). Interestingly, the risk of death from COVID-19 trended lower among those on biologics (1.3 per 10,000 person-months in patients with psoriasis (95% CI, 0.2 to 4.3) vs 4.7 in the general population (95% CI, 4.6 to 4.7).[6]

Currently, the National Psoriasis Foundation does not recommended withholding or delaying treatment due to the pandemic in patients without active COVID-19 infection.[7] Based on these and other studies it appears there are no clear safety signals among patients using immunomodulatory therapy without active signs of infection.

COVID-19 Vaccination & Psoriasis:

Currently four vaccines are approved in Canada for inoculation against SARS-CoV-2. The two mRNA-based vaccines use a lipid nanoparticle that encodes for the SARS-CoV-2 spike protein. The Pfizer-BioNTech (BNT162b2) vaccine is delivered as a series of two doses (0.3mL each) 21 days apart.[8] Phase III studies (n=43,448) demonstrated 95% efficacy in preventing COVID-19 (95% CI: 90.3 to 97.6) . National-level real world data from Israel demonstrates a similar efficacy level of 94% for symptomatic infection.[9] The Moderna (mRNA-1273) vaccine showed similar results in their phase III study (n=30,351) with 94.1% efficacy in preventing COVID-19 (95% CI, 89.3 to 96.8%; P<0.001) with two 0.5 mL doses at weeks 0 and 4.[10] Both vaccines are well-tolerated with injection site reactions, fatigue, and headache being the most common adverse effects.

Two adenovirus vector vaccines are available that both use replication-deficient chimpanzee adenoviral vector that encodes for part of the SARS-CoV-2 spike protein. The University of Oxford and AstraZeneca developed a two-shot vaccine (AZD1222). In the pivotal clinical trial (n=23,848) participants had a reported 70.4% efficacy (95.8% CI: 54.8–80.6; 66.9%; adjusted 95% CI, 59.0 to 73.4).[11] Johnson & Johnson also developed a one-shot vaccine based on similar technology.[12] Due to concerns about vaccine-induced immune thrombotic thrombocytopenia (VITT), adenovirus vector vaccines are not being commonly administered in Canada.[13]

It is unclear at this time if biologic therapy should be interrupted for COVID-19 vaccination. Theoretically, since these vaccines work partially through T-cell immunity, there may be a reduced immune response. A study of inflammatory bowel disease patients (n=48) in New York examined vaccine antibody response in patients receiving either anti-TNF or IL-23 inhibitors[14] and found that in those who completed two-doses, all subjects produced an immune response above the level thought to confer protection from COVID-19. A subgroup analysis in patients who received 2 vaccine doses revealed no association between timing of infusion and antibody response.

In contrast to biologics, there is some data to suggest that methotrexate may reduce immune response to vaccination. A cohort study in New York of patients (n=51) who received the Pfizer-BioNTech mRNA vaccine examined the antibody response of patients taking methotrexate for immune-mediated inflammatory diseases, including psoriasis.[15] The

a priori hypothesis included the assumption that antibody response would be attenuated in patients receiving a mRNA vaccine for COVID-19 since similar effects had been observed with the influenza vaccine. The authors found that there was a significantly lower level of 'adequate' antibody titres in those taking methotrexate with immune-mediated inflammatory diseases vs those not taking methotrexate with immune-mediated inflammatory diseases (92.3% vs 72.0%, p<0.001).

Vaccine Recommendations for Patients on Oral or Biologic Therapy:

The current guidelines from the National Psoriasis Foundation recommend that "patients who are to receive an mRNA-based COVID-19 vaccine continue their biologic or oral therapies for psoriasis and/or psoriatic arthritis in most cases".[7] The guidelines note that although there may be some reduced response to influenza vaccination in patients on methotrexate and/or anti-TNF agents, there is no apparent similar effect for anti-IL-12/23 or IL-17 inhibitors. Because patients on immunomodulatory therapy were excluded from clinical trials for COVID-19 vaccination, we have minimal data at this time.

In contrast, the American College of Rheumatology (ACR) recommends holding methotrexate for one week after receiving mRNA-based vaccines.[16] The ACR based their recommendation on the same data showing reduced antibody response to influenza vaccination and additional data suggesting no major disease flares. In addition, they recommend patients taking biologic therapy continue treatment as they normally would.

Direct Impact of COVID-19 Vaccination on Skin Disease in Psoriasis:

COVID-19 has the potential to flare skin disease. Anecdotal reports from patients suggest that there can be mild, transient flares of pre-existing skin disease such as psoriasis and atopic dermatitis. A single case report of a patient in his 40s with psoriasis who had a severe flare of inflammatory psoriasis, became febrile and required admission to the hospital, despite being on a TYK2 inhibitor, has been reported.[17] This flare occurred a few days after his second dose of the Pfizer-BioNTech mRNA vaccine. Thus far, such severe reactions appear rare.

Cutaneous Reactions to COVID-19 Vaccination:

Although COVID-19 vaccination is considered safe, there is a risk of cutaneous adverse effects. A large cohort study (n=414) in the United States tracked reactions to both the Pfizer-BioNTech and Moderna mRNA vaccines and found local reactions to be the most frequent reported adverse event.[18] Drug eruptions, either urticarial or morbilliform, were also common and there were a number of rare cutaneous reactions that resembled those reported with actual COVID-19 infection such as chilblains and pityriasis rosea. These were typically transient and resolved on their own. Less than half of patients who experienced these reactions after their first dose had a recurrence after their second dose.

Conclusion:

COVID-19 is a potentially serious and lethal infection that has impacted physical and mental health, and the global economy. Patients with severe psoriasis taking immunomodulatory agents appear to have similar outcomes as the general population. Effective and safe mRNA-based vaccines exist for COVID-19. At this time, medical organizations recommend these vaccines for patients taking either oral or biologic agents for psoriasis without interruption of treatment. The only exception is methotrexate which some suggest holding for one week. Local reactions to the vaccine are common and on occasion atypical cutaneous eruptions may occur which dermatologists should be aware of in the event that they arise.

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RECONSTITUTING NEUROMODULATORS IN CLINICAL PRACTICE

Neuromodulators have been used in clinical practice for decades, for both therapeutic and cosmetic applications. They are neuromuscular blocking agents that inhibit acetylcholine (ACh) release. In dermatology, they are typically used for temporary improvement in the appearance of dynamic, and to an extent, static lines. Facial aging is a result of a host of both extrinsic and intrinsic factors, including ultraviolet radiation, gravity, atrophy and remodeling of adipose, osseous, and cartilaginous structures, and changes in the muscle activity of facial musculature.[1] Neuromodulators can be used to treat muscle hyperactivity, unwanted muscle movement contributing to wrinkle formation, asymmetries, and can also be used to treat hyperhidrosis.

Botulinum neurotoxin (BoNT) works by binding cholinergic receptors selectively and irreversibly in the nerve terminals, thereby blocking ACh release through enzymatic cleavage of the SNAP-25 protein.[1] This prevents muscular contraction of the treated muscles by blocking the nervous impulses that cause the depolarization of the muscle membrane and sweat production by blocking ACh release in the autonomic cholinergic fibers from sympathetic fibers of the sweat glands.[1] There are seven different serotypes, denominated A – G.[1] Botulinum neurotoxin-A (BoNT-A) and botulinum neurotoxin-B (BoNT-B) are approved for use in humans. Different BoNT-A products are commercially available in Canada for cosmetic use.

Onabotulinumtoxin-A (ONA) (BOTOX COSMETIC®, Allergan Inc, Irvine, CA), branded as Botox®, was the first neuromodulator approved for anti-aging. It was the only therapeutic agent of its kind available for many years. It has become a leading cosmetic treatment for improving the appearance of unwanted wrinkles and other manufacturers have since entered the market. Abobotulinumtoxin-A (ABO) (DYSPORT AESTHETIC™, Ipsen Ltd, Maidenhead, UK), and incobotulinumtoxin-A (INCO) (XEOMIN COSMETIC™, Merz Pharmaceuticals, Frankfurt, Germany) are two commonly used competitors, which have also had great success in clinical practice for their cosmetic applications.

Although they are all BoNT-A neuromuscular paralytic agents, there are differences in the manufacturing processes of these commercially available neuromodulators that give them unique properties. Differences in the purification methods, and the added inactive ingredients, can play a role in determining the characteristics of each product, such as the affinity for their target, effects on muscle paralysis, antigenicity, and the duration of efficacy.

The dose of each BoNT-A product is measured in units (U) of biological activity. The biological activity is determined in animals. One unit is calculated as the median lethal dose (LD50) of reconstituted product in mice injected intraperitoneally.[2] The potency of each BoNT-A product is different, thus the labelled units of one product cannot be converted directly into another and are not interchangeable between products.[3-5]

The products are all packaged in a lyophilized powdered state and must be reconstituted before use.[3-5] INCO is a visible white powder, whereas ONA and ABO are more colourless. ONA should be kept frozen (<5°C), ABO in the fridge (2 – 8°C) and INCO can be kept at room temperature (<25°C) until reconstituted.[3-5] The product monographs of all three products recommend reconstitution with 0.9% preservative-free sterile saline (NaCl).[3-5] In clinical practice, NaCl with preservatives is often used off-label however, as preservatives tend to significantly decrease the pain, discomfort and burning of the injections for the patient. Studies have demonstrated that preservatives do not compromise the efficacy of these agents and that they increase the duration of the storage period after reconstitution and reduce the risk of bacterial contamination.[6]

A 20-27 gauge beveled needle can be used to draw up the NaCl in a syringe for reconstitution before injection.[4-5] The exposed portion of the rubber stopper on the vial should be cleaned with alcohol before the needle is inserted vertically into the vial through the rubber stopper. Once the needle of the syringe containing the diluent is put into the vial, it should pull the diluent into the vial. The syringe is then removed from the vial, and the neuromodulator and NaCl is mixed by carefully rotating the vial for ONA and ABO, and by swirling and inverting the vial to ensure all of the white powder is dissolved for INCO.[3-5] If the diluent is not easily pulled into the vial and the seal is broken, the vial should be discarded.[3-5] Neurotoxins can be denatured with strong agitation, foaming, or bubbling, thus the NaCl diluent should be introduced gently into the vial. The reconstituted product should be a clear, colourless solution, and free of particulate matter. The date and time can be recorded on the label, or in practice, on the box.

Health Canada has approved various reconstitutions for all three products. ONA can be reconstituted as per the approved indication for wrinkles with 0.9% sterile non-preserved NaCl 1.3 - 4.0 milliliters (mL) per 100 U vial, resulting in dilutions of 7.5 - 2.5 U, per 0.1 mL (**Table 1**).[3] The product monograph recommends dilutions between 4.0 – 7.0 U per 0.1 mL, and the package insert suggests using 2.5 mL to dilute a 100 U vial for a resulting dose of 4 U per 0.1 mL.[2-3] Generally, a lower reconstitution volume with a higher concentration is desired for cosmetic injections. This allows for more precision while injecting the product, thereby lowering the risk of diffusion and complications. In practice, many clinicians use a dilution of 10.0 U per 0.1 mL for ONA, which corresponds to 1 U per 0.01 mL marking on a syringe. This formula for dilution is not specified in Health Canada's approved labelling or in the package insert for ONA but is specified for ONA therapeutic which has many different indications.[7] The on-label recommended reconstitution for ONA for axillary hyperhidrosis is 4.0 mL for a 100 U vial (**Table 1**).[7] In practice, it is common to dilute ONA with 5.0 mL NaCl for hyperhidrosis, as more spread and diffusion is desirable. For INCO, the approved dilutions in the product monograph result in 10.0 – 2.5 U per 0.1 mL, with dilutions of 1.0 – 4.0 mL NaCl for a 100 U vial (**Table 1**). For ABO, the recognized dilutions on the product monograph result in 20 U – 10 U per 0.1 mL, with dilutions of 1.5 mL – 3.0 mL NaCl for a 300 U vial (**Table 1**).[5]

Although the units are not equivalent between different commercially available neuromodulators, equivalence ratios can be used to determine comparable dosing and clinical outcomes. Studies suggest that 1 U of ONA is equivalent to 2-2.5 U of ABO, based on efficacy, intensity, safety, and duration of the desired paralysis or anhidrosis.[8-10] Another study demonstrated that a dose equivalence ratio of 2:1 U (ABO:ONA) results in similar field effects on muscle and sweat gland activity, but at a higher dose equivalence of 2.5:1 (ABO:ONA), ABO affects a greater area and horizontal diameter.[11] This should be taken into consideration when injecting this product to

Product	Units per vial	Volume of diluent	Dilution per 0.1 mL
ONA (BOTOX COSMETIC®)[1]	100 U	4.0 mL	2.5 U
		2.0 mL	5.0 U
		1.3 mL	7.5 U
ONA (BOTOX®)[2]	100 U	4.0 mL	2.5 U
INCA (XEOMIN COSMETIC™)	100 U	4.0 mL	2.5 U
		2.5 mL	4.0 U
		2.0 mL	5.0 U
		1.25 mL	8.0 U
		1.0 mL	10.0 U
ABO (DYSPORT AESTHETIC™)	300 U	3.0 mL	10.0 U
		2.5 mL	12 U
		1.5 mL	20 U

Table 1. Health Canada approved reconstitution volumes with preservative free sterile saline.[3-5,7]
Notes: (1) For facial lines (2) For axillary hyperhidrosis.

prevent unwanted spread and complications.

The same dose of ONA or INCO will typically achieve comparable results.[12-14] In practice, many clinicians reconstitute a 300 U vial of ABO with 1.0 mL, 1.1 mL or 1.2 mL of bacteriostatic NaCl for an approximate ratio of 1:3 (ONA:ABO), which is considered comparable to 1 mL of diluent for a 100 U vial of ONA or a 100 U vial of INCO. These commonly used off-label dilutions allow for the same volumes of ABO and ONA to be injected, to achieve the same clinical results. The equivalence ratios for ABO of 1:2, 1:2.5 or 1:3 (ONA:ABO) can be achieved with the following volumes in **Table 2.1-2.3**, respectively.

If reconstituted with preservative free NaCl, the product should be refrigerated between 2°C and 8°C.[3-5] The products should not be frozen once reconstituted. The product monographs recommend using the products within 24 hours of reconstitution. Studies suggest that some of these products (ONA and ABO) are still effective and safe to use for 2 – 6 weeks, however.[15-17]

Various syringes can be used to administer the reconstituted product intramuscularly for lines, or intradermally for hyperhidrosis.[7] For patient comfort and to minimize complications, such as bleeding, bruising, and inadvertent placement of the product, a short, small bore, sterile needle is recommended. The ONA monograph recommends a 1.0 mL tuberculin syringe, the ABO monograph a 30-gauge needle, and the INCO monograph a 13 mm long 30 – 33-gauge needle.[3-5] In clinical practice, a 0.3 mL, or 0.5 mL, BD Ultra-Fine II syringe with a short 30-gauge needle works well. It is precise, and the small bore minimizes patient discomfort.

There are several other subtleties between ABO, INCO and ONA that make each product unique. Many factors are important to consider when making the proper selection for patients to meet their needs.

The onset of action of ONA and INCO starts within 1 week and can take up to 2 weeks for full onset, whereas the onset of action of ABO is shorter. Muscle relaxation for INCO can be observed between 2 – 5 days, with a median onset at 7 days, maximum effect at 2 weeks, and a duration of 9 – 16 weeks.[4] ONA reduces the severity of facial lines for up to 120 days.[3] The onset of ABO is the fastest, with observable results as early as 24 hours, and a median time to onset of three days.[5] This is a good option for patients looking to achieve results quickly. The effects of ABO last up to 4 months.[5] The clinical effect of ABO is known to locally migrate further than ONA or INCO, which also needs

Diluent for 100 U of ONA (BOTOX COSMETIC® or BOTOX®) (mL)	Diluent for 100 U of INCO (XEOMIN COSMETIC™) (mL)	Diluent for a 300 U vial of ABO (DYSPORT AESTHETIC™) (mL)
1	1	1.5
2	2	3
2.5	2.5	3.75

Table 2.1. Regular dilutions of 0.8 mL, 1 mL, 2 mL and 2.5 mL for ONA and INCO to achieve the 1:2 U equivalent dosing for ABO; courtesy of Dr Chloé E. Ward

Diluent for 100 U of ONA (BOTOX COSMETIC® or BOTOX®) (mL)	Diluent for 100 U of INCO (XEOMIN COSMETIC™) (mL)	Diluent for a 300 U vial of ABO (DYSPORT AESTHETIC™) (mL)
1	1	1.2
2	2	2.4
2.5	2.5	3

Table 2.2. Regular dilutions of 0.8 mL, 1 mL, 2 mL and 2.5 mL for ONA and INCO to achieve the 1:2.5 U equivalent dosing for ABO; courtesy of Dr Chloé E. Ward

Diluent for 100 U of ONA (BOTOX COSMETIC® or BOTOX®) (mL)	Diluent for 100 U of INCO (XEOMIN COSMETIC™) (mL)	Diluent for a 300 U vial of ABO (DYSPORT AESTHETIC™) (mL)
1	1	1 – 1.2
2	2	2
2.5	2.5	2.5

Table 2.3. Regular dilutions of 0.8 mL, 1 mL, 2 mL and 2.5 mL for ONA and INCO to achieve the 1:3 U equivalent dosing for ABO; courtesy of Dr Chloé E. Ward

to be considered in dosing. It is a good option in anatomical areas where several injections are needed, but this migration must be considered by clinicians in anatomical areas where spread needs to be minimized to prevent complications. Anecdotally, it has been described that effects of INCO can wear off more quickly in some patients, however, several clinical studies comparing INCO to ONA for axillary hyperhidrosis, blepharospasm, cervical dystonia, and facial rhytides, including a split face study, did not reveal any significant differences in the duration of clinical efficacy. Results will vary from patient to patient and are dose dependent. Injection volume, injection angle and speed, needle size, muscle mass and skin thickness are also thought to have an effect on the field of treatment.

ONA and ABO contain an accessory protein to carry the botulinum toxin, and it is thought that antibody formation can occur over time, diminishing the efficacy with continued use. INCO in comparison, is marketed as a product that does not contain additives or accessory proteins, as the therapeutic component of the toxin complex is isolated from accessory proteins, thereby reducing the risk of immunogenicity or allergic reaction to the accessory protein that other products contain. Although there are differences

Generic name	onabotulinumtoxinA	incobotulinumtoxinA	abobotulinumtoxinA
Brand name	BOTOX COSMETIC®/ BOTOX®	XEOMIN COSMETIC™	DYSPORT AESTHETIC™
Health Canada approved dermatologic Indications	• Hyperhidrosis of the axilla in patients ≥ 18 years of age • Upper facial rhytides, including forehead, lateral canthus, and glabellar lines in adults	• Moderate-to-severe horizontal forehead lines, lateral canthal lines, and glabellar lines in adults	• Moderate-to-severe glabellar lines and/ or lateral canthal lines (crow's feet) in adults < 65 years of age
Contraindications	• Hypersensitivity • Infection at the proposed injection site(s)	• Hypersensitivity • Infection or inflammation at the proposed injection site(s) • Generalized disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome)	• Hypersensitivity • Infection at the proposed injection sites • Cow's milk protein allergy • Generalized disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome or amyotrophic lateral sclerosis)
Purified neurotoxin complex molecular weight	900 kD	150 kD	150 kD
Active substance	BoNT-A with complexing proteins	BoNT-A free from complexing proteins	BoNT-A with complexing proteins
Number of units per vial	100	100	300
Suggested equivalent dosing ratio for 1 U ONA	1 U	1:1	1:2 – 1:3
Toxin protein load in dose equivalence range	5 ng/100 U	0.6 ng/100 U	2.7 ng/300 U
Frequency of dosing	Every 3 months	Every 3 months	Every 3 months
Storage before reconstitution	-5°C	< 25°C	2–8°C
Storage once reconstituted with NaCl (preservative-free)	2–8°C	2–8°C	2–8°C
Shelf-life (unopened)	36 months	36 months	24 months
Shelf-life reconstituted	< 24 hours	< 24 hours	<24 hours
Excipients	·Human albumin 0.5 mg ·NaCl 0.9 mg	·Human albumin 1 mg ·Sucrose 4.7 mg	·Human albumin 0.125 mg ·Lactose 2.5 mg

Table 3. Comparison of commonly used commercial preparations of BoNT-A in Canada[1-5,7]
Notes: Kilodaltons (kD), unit (U), nanogram (ng), milligram (mg), degrees Celsius (°C)

in the molecular weights of the purified protein complexes, the variance in size among the products is now thought to be inconsequential with respect to clinical outcomes.[1] One study demonstrated that dilution of the concentrated ONA and ABO complexes with normal saline, results in dissociation or release of 85% or more of the free 150 kDa neurotoxin, prior to treatment injection.[18] If a patient stops responding to ONA over time, the patient can still be treated with ABO or INCO, and vice versa.

In terms of cost, the dosing of INCO is most similar to ONA, but the cost is typically slightly lower. ABO requires higher units of the product to achieve the same outcomes, however, the cost per unit is lower than ONA.

In summary, ONA, ABO and INCO are all considered safe and effective cosmetic treatments for wrinkles and facial asymmetries, and, with good patient selection, injector experience and expertise, clinicians can be confident of achieving excellent outcomes for their patients. They all originate from the same bacterium source, clostridium botulinum and are synthesized as BoNT-A formulations. Their safety and efficacy have been demonstrated through clinical trials, regulatory oversight and approval, and extensive worldwide use. Although there are subtle differences between the commercially available products, similar results of temporarily paralyzing targeted muscles to improve the appearance of wrinkles and asymmetries can be similarly achieved with all three products.

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SKIN ON SOCIAL: THE INFLUENCE OF SOCIAL MEDIA ON DERMATOLOGY

For medicine as a whole and especially for dermatology, few cultural shifts have had as monumental an effect as the rise of social media. It is quickly becoming evident in our clinical practices that with unprecedented access to reams of online information, clinicians are no longer the primary source of skin health information for patients. With social media platforms like YouTube, Instagram, and TikTok, patients can peruse millions of pieces of dermatology and skin-related content; overwhelmingly created by non-dermatologists, and of varying quality and accuracy. In order to understand and engage our patients, we must be aware of the information they consume and take part in the education process. It is now well-documented that social media has a significant influence on our patients' treatment decisions.[1]

With over three billion active social media users worldwide, the sheer number of online platforms allow for unprecedented communication and spread of information.[2] With the general public increasingly turning to social media for health information, many physicians are sharing information directly with the public, and dermatologists are among the group of physicians with a growing social media presence. However, with much of the skin-related content on social media created by non-dermatologists, it is important to consider why and how this media is consumed by patients, particularly given the recent rise in dermatology interest and content.

Patients do not always use social media as their primary source of health information in an attempt to circumvent their physician as a credible source of information, but aim to use it as a complement to the traditional physician-patient exchange of information. Their motivation is to use social media as an attempt to fill the gap that they feel cannot be met by their healthcare professional. As physicians, we often summarize and filter information for our patients, whereas the preference by patients is increasingly centered on being informed about all options. These patients also believe that their doctor might not be aware of the latest breakthroughs[3] and are thus moved to investigate themselves. More concerning is that one of the leading reasons patients join online health communities is due to their physician's inability to meet their emotional and informational needs.[4]

For these patients, online social media communities are able to provide a variety of support, along with helping to bridge the gap around medical information about their condition and their everyday lives. The most common type of health-related social media use by patients is social support, with patients exchanging personal experiences and information to improve coping, esteem, belonging and competence.[5]

While social networks can provide patients with emotional support, esteem support, information, and network support[1], it can also allow for what is known as "emotional expression", which is the unique opportunity that social media allows, for patients to express their emotions freely, and without inhibitions or the concern about the immediate feelings or reactions of others, as one would experience in a face-to-face situation.[6]

A systematic review of the impact of social media on patients and their relationship with their physician shows that the most common consequence of social media use for health related reasons is patient empowerment, represented by enhanced subjective well-being, psychological well-being, and improved self-management and control. However, this review also noted worsening of patient subjective well-being, a loss of privacy and the risk of addiction to social media, along with the potential to be targeted for advertising as some of the downsides.[1]

Increased social media use by patients may also lead to an interesting effect on the patient-physician relationship. Health-related social media use by patients leads to more equal communication between the patient and the healthcare professional, as well as more harmonious relationships between physicians and patients. However, it has also been shown to increase switching of healthcare providers and, in some instances, suboptimal interaction between the patient and their physician.[1]

Armed with information they have learned from social media sites, patients feel more confident about their treatment options and feel they can more easily communicate with their physicians. However, a physician's negative reaction to what a patient learned from social media leaves the patient feeling disempowered and lowers their subjective well-being.[4] Specifically, negative reactions like discounting the accuracy of the online information, discouraging their online research, or suggesting the doctor should be the patient's primary source of information, made patients seek a second opinion or be less likely to share what they had learned with their physicians. These reactions however do not ultimately change a patient's online behaviour.[4]

Social media use can also be risky for both patient and doctor. Physicians cannot control the quality or accuracy of the information that patients are exposed to, but as physicians we have some responsibility for the decisions taken by patients under our care.[6] Therefore, to the extent possible, it is important for us to have an awareness of the social media content our patients consume.

Instagram, one of the most popular image-sharing platforms for both patients and dermatologists alike has 1.074 billion active users on a monthly basis.[10] With 67% of users falling within the 18-34 age range, there is an almost equal distribution between males and females.[7] Top hashtags (words or phrases used to group or promote subjects) among this group of users in descending order are "acne, "Botox," "laser,", and "filler", with procedural or cosmetic dermatology-related hashtags being used over 50% more frequently than those of medical dermatology (**Table 1**).[8] Of the medical dermatology hashtags, "acne" was used most frequently, followed by "eczema" and "alopecia".[9]

On Instagram in particular, some of our own have 'gone viral', with dermatologists like Dr. Sandra Lee, aka Dr. Pimple Popper, propelled to superstardom; bringing with them positive visibility to dermatology, and accessible satisfying medical education to patients around the world. At the time of publication, Dr. Lee has 4.4 million followers for whom she posts a breadth of both medical and cosmetic dermatology content. A study looking at the top 10 dermatology influencers on Instagram showed that educational posts had the greatest presence, making up about 50% of sampled content, followed by 30% being comprised of personal posts and 10% each being comprised of accomplishments and advertisements. YouTube dermatology posts on the other hand were almost entirely educational in nature (90%). Of the social media platforms, Instagram users have the highest user engagement as well as the highest median subscriber count.[11] In addition, it appears that educational content is exactly what social media followers

Most Common Dermatologic Diagnosis		Most Common Dermatologic Procedures	
Acne	1,852,029	Botox	1,847,196
Eczema	406,904	Laser	1,398,163
Alopecia	291,652	Filler	626,494
Hairloss	287,587	Juvederm	398,056
Psoriasis	227,413	Restylane	226,889
Pimples	209,775	Laser hair removal	186,149
Rosacea	78,502	Dysport	136,821
Cyst	72,112	Tattoo removal	112,993
Rash	68,833	Coolsculpting	108,295
Melanoma	68,743	Body contouring	105,485
Skin Cancer	65,776	Acne scars	105,134
Hyperpigmentation	47,027	Melasma	98,248
Atopic Dermatitis	5,132	Sun Damage	73,332
Seborrheic Dermatits	2,016	Laser Tatt0o removal	52,611
Contact Dermatitis	1,833	Dermalfillers	130,429
Folliculitis	820	Kybella	45,166
Tinea	800	Radiesse	39,865
Benigntumour	641	Chemicalpeel	76,009
Actinic Keratosis	504	Radiofrequency	37,393
Molluscum Contagiousum	259	Ultherapy	36,481
Total Medical Dermatology-Related	3,722,970	Total Procedural Dermatology-Related	5,893,190

Board Certified Dermatologist	716
Dermatologist	166,150
Dermatology	415,858
Total Hashtags Queried	10,197,884

Table 1. Top Hashtags related to medical and procedural dermatology on Instagram; adapted from Park et al.

crave, as educational posts by dermatologists had the highest median engagement.

Medical organizations have also started to see the value of social media, with the American Academy of Dermatology, the Journal of the American Academy of Dermatology and the Canadian Dermatology Association all maintaining a social media presence. It seems, however, some techniques may be a little dated. A recent look at skin cancer prevention messaging via Facebook found that most messages from professional dermatology organizations were didactic in nature and focused on a strategy of fear appeal, which has been proven ineffective in gaining social media influence.[12]

This 'influence', in terms of popularity and transmissibility on social media, is key for effective transmission of health information. The dissemination of accurate and high-quality information by a board-certified dermatologist is pivotal to public skin health education, as well as dispelling false and potentially harmful misinformation. Unfortunately, dermatologists only make up a fraction of those providing dermatology information on social media platforms, with board-certified dermatologists comprising only 4% of all Instagram accounts with popular dermatology content.[13] Even more concerning is that 93% of all Instagram influencers featured self-promotional posts or directly promoted brands, products, or

services[13] , raising significant conflicts of interest of which patients may not be aware.

Further concerns lurk across the other social media landscapes. With acne affecting an estimated 80% of young Canadians aged 12-24, this social-media savvy generation is a ravenous consumer of acne health information via social media, with YouTube as their platform of choice.[14] A study looking at acne videos on YouTube showed that in comparison to healthcare-sourced videos, non-health care sources were less accurate, and of lower quality, but had a higher mean number of views. They were more engaging than health care sources, despite the fact that videos by universities and professional organizations were most accurate and had the highest quality and viewer experience.[15]

With misinformation rampant, significant time and resources are required of dermatologists to dispel the inaccuracies patients learn from social media. A recently-published survey of patients at a U.S. medical clinic showed that of 130 respondents, 45% consulted social media for acne treatment, interestingly with higher rates (51%) in adults than in adolescents (41%). As expected YouTube and Instagram were the most commonly used platforms, and women were 75% more likely to seek out acne treatment advice on social media. The advice provided to them online, unfortunately, did not hit the mark, with only 7% reporting significant improvement in their acne from social media acne treatment advice. Concerningly, most of the advice encouraged users to try over-the-counter products (81%) and/or dietary modification (40%). Of the study subjects, 17% started an oral supplement on the advice of a social media personality. Only 31% of those following social media advice made changes which were consistent with the AAD clinical guidelines.[16]

TikTok, the world's fastest growing social media platform (**Table 2**)[17] where users share short-form videos, is no better. In *Pediatric Dermatology*, Zheng et al reviewed the top 100 acne videos on TikTok using DISCERN, a validated instrument for the evaluation of consumer health information. The overall content quality rating of the videos indicated "information with serious-to-potentially-important shortcomings".[18] With this in mind, it is alarming to note that by the completion of their study, videos on TikTok with "#acne" were viewed 1.8 billion times.

With potentially dangerous misinformation flooding social media, how do dermatologists ensure that patients are exposed to up-to-date, valid, and accurate information from ethical sources? We know that patients use social media to make decisions regarding treatment[1] so it is important that the medical information provided on social media comes from reliable sources.

Dermatologists are uniquely positioned to provide patients with the valid and accurate information they seek, and evidence is mounting for social media as a burgeoning vehicle for public health education and awareness. As an example, a 2016 study identified an important opportunity to deliver skin cancer prevention information via social media given the high correlation between young adult females who use Instagram and/or Twitter with indoor tanning behaviors.[7]

Hashtag	Number of views as of 9/18/2020	Number of views as of 2/9/2021
Acne	3.0 billion	6.7 billion
Alopecia	407.8 million	1.1 billion
Cyst	315.3 million	649.4 million
Warts	33.7 million	39.5 million
Skin cancer	35 million	43.2 million
Eczema	32.6 million	74.5 million
Rosacea	31.6 million	80.6 million
Psoriasis	29.5 million	84.0 million

Table 2. Number of views for top dermatologic diagnosis on Tiktok in September 2020 and in February 2021.

Large research gaps still remain in this domain, however, information is quickly emerging which will allow us to advance the strategic use of social media to inform patients. In order to share information with the public, effective dissemination, specifically message transmission in the form of "shares" and "retweets" is key. Including media formats such as videos and photos has been shown to be one of the most effective methods of retransmission, with videos retransmitted 63% more often, and photos 27% more often. Including a hashtag increased shares by 12%, and actionable information is also known to be shared at a higher rate.[19] Some engagement features, such as the inclusion of URLs, have been shown to decrease message transmission. Regardless, from a public education perspective, URLs are a powerful tool and the use of hyperlink integration in posts can direct users to other reliable online resources for additional health information.

In summary, social media provides us with the unique opportunity to engage with our patients and the wider community and affords us the opportunity to disseminate accurate, quality and informative medical information to patients. As medicine evolves, the physician's duty to engage and inform patients must move beyond the clinic space, and into the digital space of social media where patients are seeking reassurance and information.

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