

## Regulating Off-label Promotion of Medications: Has the Pendulum Swung Too Far?

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### ABSTRACT

*Prescribing medications off-label is commonplace in dermatology. Recent policy changes on the regulatory abilities of the US FDA and legal precedents regarding this topic have led to intense debate on free speech about off-label drug use by physicians and drug manufacturers. Here, we summarize and discuss the risks and benefits of off-label promotion and how this relates to quality patient care in dermatology.*

**Key words:** labeling, pharmaceutical, promotion, advertising, FDA, regulations, dermatology

### Introduction

Pharmaceuticals are often prescribed for uses beyond those listed on the drug's US Food and Drug Administration (FDA) approved label. This off-label use includes treatments for disorders not formally reviewed by the FDA, dosages or delivery mechanisms not approved by the agency, or use of the agents in patient populations not tested in FDA approved clinical trials.<sup>1</sup> In order for a drug company to market a medicine for a particular use or disease, it must go through rigorous evaluation by the FDA. This entire process, which includes preclinical testing and three clinical phases, takes an average of 8 to 12 years.<sup>2</sup> This course is so rigorous that for every 5,000 to 10,000 compounds that enter preclinical testing, only one is approved for marketing.<sup>3</sup> Off-label prescribing compensates for this scrupulous and time-consuming approval process by allowing physicians to use treatment options that are readily available. The off-label use of drugs has significantly contributed to the therapeutic armamentarium of many different diseases in medicine.

Off-label prescribing is particularly common in dermatology. This can in part be explained by the relative lack of clinical trials evaluating the multitude of therapeutic options for any given dermatologic condition. For many skin diseases, few - if any - medications are FDA-approved, and use of off-label medications is the standard of care in dermatology.<sup>4,5</sup> Off-label prescribing is used in a wide range of dermatologic conditions, from disorders that are common and have multiple treatment options, such as actinic keratosis and acne vulgaris, to the more rare conditions

that have very few if any FDA-approved treatments, such as pyoderma gangrenosum, pemphigus vulgaris, and lichen planus. Off-label options can be used for common conditions when treatment with approved medications have been exhausted or have proved unsuccessful or even when the off-label treatment is deemed better than on-label options.

Increasing prevalence of off-label prescribing has come with a fair share of conflicts between the FDA, insurance companies, physicians and pharmaceutical companies, as the FDA has sought to regulate the pharmaceutical industry's promotion of unapproved therapies. During the past decade, pharmaceutical companies have faced government investigations regarding the marketing and promotion of their products. Companies have been fined billions of dollars for promoting their product for indications other than those listed on the FDA-approved label. Although regulations on the pharmaceutical industry were designed to protect the public, they may have unexpected negative consequences. Branding a drug's particular use as "off-label" not only limits the dissemination of information about the drug, but also decreases patient access to the agent. While patients, physicians not employed by pharmaceutical companies, insurers and government researchers are free to discuss whatever they want about off-label uses, the pharmaceutical company is prohibited from entering the discussion. These limitations on the dissemination of information have become a major topic of controversy in recent years. Because the off-label use of drugs and devices will remain a major part of

the practice of medicine in the future, there needs to be a balance between the regulatory authority of the FDA, the circulation of information coming from the pharmaceutical companies, and the ability of physicians to provide the best possible care for their patients. In this paper we discuss a brief history on the drug approval process and the development of FDA regulations over off-label drug promotion, recent legal cases surrounding off-label drug speech, and the risks and benefits of off-label drug promotion in dermatology (Table 1).

Arguments Against Off-label Promotion	Arguments Supporting Off-label Promotion
Pharmaceutical companies may promote material that is unsubstantiated or factitious.	Increases the dissemination of potentially valuable information to both patients and physicians.
Allowing for off-label promotion may weaken desire to conduct clinical trials to obtain FDA approval.	Drug manufacturers are unlikely to conduct clinical trials for every single use of their product, regardless of whether they are allowed to discuss off-label uses or not.
Without clinical trials, the safety and efficacy of a drug is not as heavily studied.	Allows more patients to be treated with the most up-to-date treatment options without waiting for formal FDA approval.
Some physicians may be swayed to believe any information presented from pharmaceutical companies without judging the quality of evidence.	Physicians are generally good at determining what is scientifically and medically substantial.

**Table 1:** Arguments for and against off-label promotion.

### A Brief History of Drug Regulation

The process of bringing to market a new drug or new use of a drug is rigorous, involving preclinical testing with animals, three phases of human clinical trials, and two stages of approval from the FDA. This process is a multi-year, multi-stage course and generally costs millions of dollars. If a drug survives all three phases of clinical trials, a New Drug Application (NDA) containing all the preclinical and clinical information obtained during testing is submitted to the FDA. The FDA then performs an independent review, after which a NDA may be approved or rejected. After FDA approval for a given disease, a medication is often subject to phase 4 post-marketing studies, which are designed to evaluate long-term efficacy and safety in a larger patient population and a longer time period. It is reported that this entire process from lab to patient may take as long as 10 to 15 years, with clinical trials accounting for 7 of those years, and may cost an average of \$1.2 billion per drug.<sup>6</sup> Even when drug manufacturers desire to obtain FDA approval for an off-label use that is similar to

indications listed on the label, they must submit a “supplemental new drug” application. The drug then has to undergo extensive clinical trials to determine the efficacy of this off-label use. While the FDA claims they are speeding up the supplemental new drug approval process, the data show there are still long delays.<sup>7</sup>

The first federal laws to regulate the sale and content of food and drugs came in 1906 with the Pure Food and Drug Act. Since then, the passage of over 200 laws has created a stringent regulatory system with the goal of protecting consumers.<sup>8</sup> The federal Food, Drug and Cosmetic Act (FDCA) of 1938 was one of the major milestone laws that gave the FDA authority to regulate promotional materials of the pharmaceutical companies. The FDCA indirectly prohibits the promotion of off-label use in two ways: 1) By prohibiting drug manufacturers from introducing a new drug into interstate commerce unless both the drug and the label have gained FDA approval, and 2) By prohibiting the drug manufacturer from introducing a “misbranded” drug. A drug is considered misbranded if the label contains information about unapproved uses or misleading information. Visual aids and handouts used by sales representatives are considered part of the drugs label even if they are not packaged with the product.<sup>1</sup> The FDA has long held to these rules when reviewing promotional materials of pharmaceutical companies. The off-label promotion of drugs was further restricted by the indirect effects of the 1962 Amendments, which gave the FDA stricter control over how companies performed clinical trials.<sup>8</sup> These amendments were a major contribution in shaping the rigorous structure that is currently in place for FDA approval.

The FDA’s strict regulations on the promotion of unapproved drugs have become slightly more permissive over time. While the FDA previously had an absolute authority to prohibit the dissemination of off-label information, newer guidelines under the FDA Modernization Act of 1997 (FDAMA) allow drug manufacturers to distribute reprints of peer-reviewed articles that describe unapproved use of their products.<sup>9</sup> However, even this change of policy came with its fair share of regulations. The FDA imposed a list of conditions to be met before companies could circulate the articles. Some of these requirements include: the information must be published in a peer-reviewed scientific or medical journal, the company must submit a supplemental new drug application and they must provide the FDA with advance copies of the articles they intend to redistribute.<sup>1</sup> Despite the series of laws and amendments, there remains a considerable amount of uncertainty about what exactly manufacturers are able to promote.

### Recent Legal Precedents

There are now more than one hundred ongoing civil and criminal investigations involving the US Department of Justice and the US Department of Health and Human Services. These investigations, in which pharmaceutical companies were accused of off-label promotion, held companies liable under both the FDCA and the False Claims Act (FCA).<sup>10</sup> The FCA makes it unlawful to file a false claim with the government. This theory has been applied to off-label promotion, regardless of whether the information about off-label use is truthful or not. These legal actions have had a major hit on pharmaceutical companies, with settlements

ranging from tens of millions to hundreds of millions of dollars and occasionally even jail time for company executives.<sup>1</sup>

A recent legal case could have broad ramifications for the pharmaceutical industry and the role of off-label promotion in medicine. In this landmark case of *United States v. Caronia*, No. 09–5006–CR, 2012 WL 5992141 (2d Cir. December 23, 2012), the US Court of Appeals for the Second Circuit overturned the conviction of a pharmaceutical sales representative who was accused of promoting a drug for its off-label uses. The Court's holding, in full, reads: "[W]e decline to adopt the government's construction of the [Food, Drug, and Cosmetic Act's (FDCA's)] misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech. We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs." *Ibid.*, 15. The case has led to an increased focus on the issues that exist with the FDA's regulation on off-label use of drugs, and the negative impact this has had on healthcare. There is a distinction between truthful communication about off-label drug uses, many of which are proven efficacious and safe by the medical community, and claims that are not validated or are simply factitious. References to the First Amendment have hampered the FDA's ability to regulate off-label promotion and will likely have an impact on the future of off-label drug discussions.

While some may believe that dermatologists are free from the FDA litigations over off-label promotion, this is not necessarily true for physicians who participate in clinical trials or promote products on behalf of manufacturers. In January 2010, the FDA sent a warning to a Florida dermatologist for mentioning in interviews with magazines that an anti-wrinkle drug she was conducting a clinical trial on had demonstrated to work better than a competitor's product.<sup>11</sup> Upsetting the FDA by promoting an off-label indication in dermatology may have far worse consequences than a warning letter. In 2004, oral tazarotene for the treatment of psoriasis was denied FDA approval. While the advisory board claimed there was not enough data to support that the benefits outweigh the risks, the committee repeatedly asked Allergan about how they had promoted the off-label of oral tazarotene for acne via posters at an American Academy of Dermatology conference.<sup>12</sup> Approval for oral tazarotene, a product that had the potential to benefit patients with psoriasis, was eventually denied, perhaps in part because of concerns over off-label promotion. Although physicians are supposedly free to discuss any off-label indications with colleagues and patients, this freedom is limited when the physician is acting as an agent of a pharmaceutical company. With the FDA's authoritative power in approving medication uses, a company could potentially win a First Amendment battle over off-label promotion but lose a war if the FDA chose to delay or not to approve future products.

### **Risks with Off-Label Promotion**

Before regulations on the content and promotion of pharmaceutical agents, drug makers were able to produce and sell products that would seem criminal in today's day and age. For instance, "Peter's Specific, The Great Blood Purifier System Regulator" was recommended as a treatment for dermatologic disease and as an alternative tonic, invigorator and blood

purifier.<sup>13</sup> While drug manufacturers are no longer able to make scientifically unfounded claims, many physicians prescribe off-label for uses that lack significant scientific support.<sup>14</sup> By "word of mouth" marketing, highly influential academic physicians may, for better or worse, indirectly help pharmaceutical companies promote products' off-label uses.<sup>15</sup> This promotion often comes in the form of industry-sponsored abstracts, posters and publications. If a poster demonstrates promising preliminary results but the follow-up studies show no benefit, the negative findings may not get widespread notice. This leaves the medical community with the potential for an incomplete, overly favorable, impression of the product. The spread of invalid data is not only the fault of pharmaceutical companies, but also of physicians who may try and promote new off-label uses out of desperation when all conventional therapies have failed. While many efficacious treatment strategies are discovered by trial and error, this also lends to the potential widespread use of products that are not beneficial. In 2008, topical bimatoprost (Latisse®) was approved for the treatment of eyelash hypotrichosis. Since then, some have advocated the use of bimatoprost to stimulate hair growth in other areas such as the scalp or eyebrows, despite the lack of any published scientific evidence on this use.<sup>16</sup> Furthermore, allowing drug manufacturers to redistribute information about off-label uses may disincentivize companies to conduct clinical trials to gain FDA approval.<sup>17</sup> Without the rigorous scientific scrutiny that comes with FDA approval, the safety and efficacy of off-label uses may not be well elucidated. Limiting manufacturers from promoting off-label use is the primary method used by the FDA to "protect the public from promotional claims that are unsubstantiated at best, and false at worst."<sup>18</sup> The FDA regulations are designed to protect not only patients, but also physicians as they prevent them from receiving biased information that may inappropriately influence their prescription choices. However, limiting the dissemination of information may be harmful to public health as it decreases the data readily available to physicians when making treatment decisions.

### **Benefits of Off-Label Promotion in Dermatology**

"FDA restrictions on off-label promotion has made it more difficult for physicians to learn about new uses of drugs and devices."<sup>19</sup> The medical community, federal courts and even the FDA all agree that drug manufacturers are often the best source of information on the data regarding the risks and benefits of off-label drug uses. Any speech on off-label use is subject to the same penalties, regardless of whether or not the information is true. With the wide range of dermatologic disorders and the limited number of well-designed clinical trials assessing the multitude of therapeutic options, off-label prescribing is now commonplace in dermatology. Clinical trials often reveal significant evidence supporting the benefit of off-label uses long before these agents gain FDA approval. This lag time to FDA approval is evident in a wide variety of dermatologic disorders, most recently in the treatment of complicated infantile hemangiomas. On March 17th, 2014, Pierre Fabre Dermatologie obtained marketing authorization from the FDA for the pediatric drug Hemangeol™ (propranolol hydrochloride), making it the first and only FDA approved treatment for proliferating infantile hemangioma requiring systemic therapy.<sup>13</sup> However, since 2008, when the efficacy of propranolol for hemangiomas was first proposed,

propranolol has proven efficacious in accelerating the involution infantile hemangiomas through a wide variety of case series and clinical trials.<sup>20</sup> Also common in dermatology is the wide spread use of products to treat conditions well beyond those reflected on their FDA approved label. Tacrolimus (Protopic™), while only FDA approved for the treatment of atopic dermatitis, has been used off-label to treat many other skin disorders including lichen planus, allergic contact dermatitis, seborrheic dermatitis, vitiligo, pyoderma gangrenosum, and balanitis xerotica obliterans.<sup>21,22</sup> While some of these uses are based on small case series, there is statistically significant evidence from multiple randomized, double-blind studies that supports the use of 0.1 % tacrolimus ointment in some forms of psoriasis.<sup>23,24</sup> Despite this proven efficacy in a multitude of conditions, the manufactures are confined to only discussing the product's one FDA approved use. These restrictions may contribute to the underuse of products that have tremendous potential to help other patients.

### Moving Forward

The increasing popularity of off-label prescribing combined with recent law proceedings that have undermined the FDA's ability to regulate off-label marketing activities, has led to some concerns about how to most effectively keep physicians informed while still protecting patients. The FDA's concerns over protecting physicians from inappropriate influence by pharmaceutical companies are often seen as unnecessary and even insulting to the practitioners. With the recent legal cases highlighting protection under the First Amendment, there may be an increase in the free speech by pharmaceutical companies. The necessity of clinical trial transparency and a greater emphasis on improving research quality will become even more important in this setting. The requirements of advanced registration for clinical trials and the stipulation that summary results of clinical trials must be published have made it more difficult to hide negative studies, ensuring that physicians and patients will have access to the most honest and up to date information.<sup>25</sup>

Many have proposed that to decrease off-label drug use and promotion the FDA must modify their approval system into a streamlined process for approving new uses of drugs. However, such changes to the regulatory system are not likely to occur anytime soon. Off-label promotion will continue to be a necessity as the FDA's current drug approval process is unlikely to keep pace with the rapid expansion of therapeutic options in dermatology. The evolving nature of the FDA's regulatory guidelines on the dissemination of information regarding off-label uses, combined with efforts to improve research quality and transparency, will hopefully expand the realm of knowledge available to physicians, allowing for the best possible management of their patients' dermatologic conditions. Allowing for open discussion about off-label uses should be seen not as a form of pharmaceutical promotion but as a form of education.

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# Current Management of Scalp Psoriasis

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## ABSTRACT

*The scalp is involved in up to 80% of individuals with psoriasis. Eighty percent of those with scalp psoriasis experience a negative impact on quality of life. Topical treatment with corticosteroids with or without vitamin D3 analogues is the mainstay of treatment. Topical therapy most suitable for the scalp is formulated as a solution, lotion, gel, foam, spray, oil, or shampoo. Twice weekly maintenance in frequent relapsers may decrease the time to first relapse. Intralesional steroids, phototherapy and the excimer laser are occasionally used for resistant cases. In patients with moderate-to-severe psoriasis, apremilast, adalimumab and etanercept have been shown to significantly improve scalp psoriasis. They should be considered in patients who have failed topical therapy.*

**Key words:** biologics, laser and light therapies, scalp dermatoses, scalp psoriasis, steroids, vitamin D derivatives

## Introduction

Up to 80% of individuals with psoriasis have scalp involvement, and 80% of those with scalp psoriasis experience a negative impact on quality of life.<sup>1</sup> Topical therapy is first-line treatment, with both the active ingredient(s) as well as the vehicle affecting efficacy, tolerability and treatment adherence.<sup>2</sup> In 2009, the US National Psoriasis Foundation recommended intralesional corticosteroids as second-line treatment, and phototherapy, conventional systemics and biologics as third-line treatments.<sup>3</sup>

## Topical Therapy

### Topical Steroids

Topical steroids are the most commonly prescribed scalp treatments.<sup>4</sup> They are more efficacious than calcipotriol, coal tar and tazarotene.<sup>3</sup> The scalp is relatively resistant to atrophy induced by topical steroids.<sup>3</sup>

Clobetasol propionate (CP) in various formulations appears to be highly efficacious for scalp psoriasis. In a vehicle-controlled, randomized, double-blind study, after 4 weeks of twice daily application, 85% of patients on CP spray were clear/almost clear compared to 13% on vehicle ( $p < 0.001$ ).<sup>5</sup> Another study showed that CP 0.05% solution was superior to 0.05% betamethasone dipropionate solution.<sup>6</sup> In another study involving 142 individuals with scalp psoriasis, after 4 weeks, CP 0.05% shampoo was more effective than vehicle in reducing total severity score ( $p < 0.001$ ) and 42.1% treated with CP were clear/almost clear compared to 2.1% in the vehicle arm.<sup>7</sup> After an initial daily treatment for 4 weeks, twice weekly maintenance use of this shampoo over 6 months decreased the median time to first relapse (141 days vs. 30.5 days for vehicle,  $p < 0.0001$ ).<sup>8</sup>

The formulation of the topical steroid can make a difference. Foams have the following cosmetic advantages including drying quickly, easy application, and minimal residue after application.<sup>9</sup> In addition, the human cadaver skin model showed greater

absorption of CP foam than solution, with a more than double peak rate.<sup>10</sup> In a 14-day study of 26 patients with moderate-to-severe psoriasis involving  $>20\%$  body surface area (BSA), both the CP foam and CP ointment caused similar reversible hypothalamic-pituitary-adrenal (HPA) axis suppression (3 in each group) as has been noted with other class I topical corticosteroids.<sup>10</sup> In a double-blind study involving 188 adults with moderate-to-severe scalp psoriasis, greater reduction in scaling was noted at day 15 with CP (Olux®) foam than with CP solution ( $p = 0.0142$ ); the difference was maintained over the next 14 days despite no additional treatment.<sup>10</sup> Seventy-four percent on CP foam, 63% on CP solution, and 4% and 10% in the placebo groups were clear/almost clear after 14 days of treatment.<sup>10</sup>

Similarly, in the human cadaver skin study, after 12 hours, the bioavailability of betamethasone valerate (BMV) was 300% greater with the foam than the lotion.<sup>11</sup> However, a study in atopic dermatitis in which the foam was applied to 30% or more of BSA showed that BMV foam had little propensity to induce hypothalamic-pituitary axis suppression.<sup>11</sup> In a twice daily 4 week study comparing BMV 0.12% (Luxiq®) foam to BMV lotion, placebo foam and placebo lotion, 72% on BMV foam were clear/almost clear compared to 47% on BMV lotion, and 21% on placebo foam ( $p < 0.05$ ).<sup>11</sup> In a cross-over study involving 210 patients, 88% on BMV foam were clear/almost clear compared to 66% on standard therapy [other topical steroids in 55% of cases [mometasone (70%), betamethasone dipropionate (25%), BMV (3%), and hydrocortisone butyrate (2%)], or calcipotriol lotion in 45% of cases;  $p < .001$ ].<sup>12</sup> Feldman et al found similar efficacy between once and twice daily BMV foam in the treatment of scalp psoriasis, suggesting that once daily application should be sufficient.<sup>13</sup>

### Vitamin D Derivatives

Vitamin D derivatives may cause irritation, but do not cause atrophy.<sup>3</sup> It takes longer to see optimal improvement with vitamin D

derivatives (8 weeks) than with steroids (2-3 weeks).<sup>14</sup> In a large (n=3396) observational study of scalp psoriasis, 80% of individuals treated with calcipotriol solution had 'good' or 'very good' improvement after 8 weeks.<sup>15</sup> One study showed similar efficacy between calcipotriol solution and BMV 1% lotion,<sup>16</sup> although in another study involving 474 patients with scalp psoriasis, more patients (75%) were clear or markedly improved with BMV 0.1% solution than with calcipotriol 50 mcg/ml solution (58%, p<0.001) and there was a greater reduction in the total sign score (61% and 45% respectively, p<0.001).<sup>17</sup> An additional study showed that calcipotriol solution was also inferior to clobetasol propionate shampoo.<sup>18</sup>

Vitamin D/steroid combination: Dovobet® gel (formerly Xamiol®; also called Daivobet® and Taclonex®) contains calcipotriol 0.005% and betamethasone dipropionate 0.05%.<sup>4</sup> It has a fast onset of action and is superior to its individual ingredients,<sup>4</sup> and calcipotriol scalp solution.<sup>19</sup> More than twice as many patients treated with Dovobet® gel (68.6% vs. 31.4% on calcipotriol scalp solution) had absent/very mild disease after 8 weeks of use.<sup>19</sup> Absent or very mild disease is achieved by approximately 60% of patients after just 2 weeks of therapy and 70% after 8 weeks.<sup>4</sup> Dovobet® gel is efficacious for very severe scalp psoriasis. After 8 weeks, 36.4% who had very severe disease at baseline, demonstrated absent/very mild disease compared to none treated with calcipotriol solution.<sup>19</sup>

Two long-term 52-week studies showed that Dovobet® gel is efficacious and well tolerated.<sup>20,21</sup> Absent/very mild/mild disease was noted in 92.3% of visits with Dovobet® gel vs. 80% with calcipotriol in the first study, while in the second study, the median number of visits with clear/minimal/mild disease was 100%.

Dovobet® gel is well tolerated with no reports of atrophy, striae, purpura, or significant changes in serum calcium in trials.<sup>4</sup> Some patients, however, have had difficulty removing Dovobet® gel from their hair. Application of shampoo, particularly a clarifying shampoo, to dry hair where Dovobet® gel was applied, prior to entering the shower and wetting the hair, aids significantly in the removal of gel.

### Other Topical Treatments

Due to its keratolytic effect, salicylic acid may enhance penetration of topical corticosteroids.<sup>3</sup> The National Psoriasis Foundation recommends tazarotene as first-line therapy based on its efficacy off the scalp.<sup>3</sup> Scalp studies are lacking, but the author has successfully used the gel formulation in resistant cases.

### Topical Shampoos Other Than Steroid Shampoos

Tar and imidazole antifungal shampoos have modest, at best, efficacy in scalp psoriasis.<sup>22</sup> In an 8-week randomized, open-label study involving 475 patients, a 1% coal tar/1% coconut oil/0.5% salicylic acid shampoo was found to be inferior to calcipotriol (p<0.001). Tar's malodor, hair staining and drying, poor efficacy and carcinogenicity limit its use.<sup>3,22</sup> Imidazole antifungals have been tried since pityrosporon overgrowth has been associated with psoriasis, however, not all studies have shown efficacy.<sup>22</sup>

## Systemic, Light and Laser Therapies

### Intralesional Corticosteroids

There are no studies of intralesional corticosteroids in scalp psoriasis, although anecdotal reports support their use for localized disease.<sup>3</sup>

### Phototherapy and Excimer Laser Treatment

Treatment of scalp psoriasis with phototherapy or laser is difficult since hair shields the scalp from ultraviolet (UV) radiation. UV combs have been developed for scalp use, and blow dryers may help expose the scalp for excimer laser (308 nm) treatment, but large controlled trials are lacking and treatment may be cumbersome.<sup>2,3</sup>

### Systemic/Biologic Treatment

Although the traditional systemic agents methotrexate, cyclosporine and acitretin have been used in patients with moderate-to-severe psoriasis with scalp involvement,<sup>22</sup> studies in scalp psoriasis are lacking.

Apremilast, an oral phosphodiesterase 4 inhibitor, which has recently received approval for treatment of moderate-to-severe plaque psoriasis, improves scalp psoriasis. In the ESTEEM I phase 3 trial, at week 16 [n=374 on apremilast and n=189 on placebo, who had a baseline Scalp Physician's Global Assessment (ScPGA) score of at least 3; 66.7% of total patients], 46.5% on apremilast achieved an ScPGA of 0 or 1 compared to 17.5% on placebo (p<0.0001).<sup>23</sup> At week 52, ScPGA response was achieved by 73% of apremilast patients.<sup>23</sup>

A subanalysis of the phase 3 adalimumab BELIEVE trial showed that by week 8, 76.5% of patients with scalp psoriasis at baseline had achieved a Psoriasis Scalp Severity Index (PSSI) response (PSSI 4 or less). At week 16, the median and mean decreases in PSSI were 100% and 77.2% respectively.<sup>24</sup> Patients with scalp involvement had a lower Psoriasis Area and Severity Index (PASI) 75 response early in treatment, but differences declined with time and at week 16, PSSI scores correlated with PASI 75.<sup>24</sup>

A double-blind, placebo-controlled study of etanercept in 124 adults with moderate-to-severe psoriasis involving 10% or more body surface area, a PASI score of at least 10, and 30% or more scalp involvement with a PSSI of at least 15, showed 86.8% improvement in PSSI after 12 weeks of etanercept 50 mg twice weekly compared to 20.4% for the placebo arm.<sup>25</sup> From week 12 to 24, the etanercept arm was stepped down to 50 mg once a week, while the placebo arm was treated with etanercept 50 mg twice weekly. At week 24, the mean PSSI improvements were 90.6% for the etanercept/etanercept arm and 79.1% for the placebo/etanercept arm.

## Conclusion

Topical steroids with or without calcipotriol are the mainstay of therapy for scalp psoriasis. There are a number of newer formulations including foams, shampoos, gels and sprays which enhance cosmetic acceptability and adherence. Twice weekly treatment should be considered as maintenance therapy for patients who relapse quickly.<sup>26</sup> Systemic treatment should be considered for recalcitrant cases. Studies have shown excellent efficacy with apremilast, adalimumab and etanercept.

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Name/Company	Approval Dates/Comments
<p><b>Varicose vein procedure n-butyl-2-cyanoacrylate adhesive polymer + delivery system components</b> <i>VenaSeal™ Closure System</i> Covidien LLC Medtronic</p>	<p>The US FDA approved the first adhesive varicose vein treatment in February 2015. VenaSeal™ closure system is the only non-tumescent, non-thermal, non-sclerosant procedure to permanently treat varicose veins of the legs by sealing the affected superficial veins using an adhesive agent. Treatment is intended for patients with superficial varicose veins of the legs that cause symptoms. The sterile kit is made up of an adhesive, a specially formulated n-butyl-2-cyanoacrylate, and delivery system components that include a catheter, guide wire, dispenser gun, dispenser tips, and syringes. Treatment can be performed in an office or outpatient setting. A trained healthcare professional inserts the catheter through the skin into the diseased vein to allow injection of the adhesive, a clear liquid that polymerizes into solid material. The healthcare professional monitors proper placement of the catheter using ultrasound imaging during delivery of the adhesive into the diseased vein to seal it. Because the VenaSeal™ system does not incorporate heat application or cutting, patients experience less bruising and can promptly return to their normal activities.</p>
<p><b>Dermal filler with calcium hydroxylapatite (CaHA) + integral 0.3% lidocaine</b> <i>Radiesse® (+)</i> Merz North America</p>	<p>In March 2015, the FDA approved Radiesse® (+) injectable implant dermal filler that contains a small quantity of the local anesthetic lidocaine. Radiesse® (+) is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. This new preparation enhances patient comfort and eliminates the need for in-office lidocaine mixing.</p>
<p><b>Dalbavancin for IV injection</b> <i>Xydalba™</i> Durata Therapeutics Actavis plc</p>	<p>In March 2015, the European Commission approved dalbavancin, a novel second-generation lipoglycopeptide antibiotic, for the treatment of adults with skin infections. Treatment is indicated for acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive microorganisms, such as <i>Staphylococcus aureus</i> (including methicillin-susceptible and methicillin-resistant strains) and <i>Streptococcus pyogenes</i>. To reduce the development of drug-resistant bacteria and maintain its efficacy, use should be limited to the treatment of infections that are proven or strongly suspected to be caused by susceptible bacteria. This drug is marketed in the US under the trade name Dalvance®.</p>
<p><b>Pembrolizumab for IV infusion</b> <i>Keytruda®</i> Merck &amp; Co.</p>	<p>The United Kingdom's Medicines and Healthcare Products Regulatory Agency cleared pembrolizumab for early access in March 2015 to treat adults and children ≥12 years of age with advanced melanoma. Treatment is indicated for patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The drug acts by targeting the programmed cell death 1 (PD-1) receptor. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with programmed cell death 1 ligand 1 (PD-L1) and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including anti-tumor immune response. Pembrolizumab is the first treatment to be accepted under the UK's new Early Access to Medicines Scheme (EAMS), which is similar to the US FDA's Breakthrough Therapy Designation for accelerated drug approval.</p>