Percutaneous Egression: What Do We Know?

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Keywords
Percutaneous egression · Diffusion · Wick effect · Administration · Drug

Abstract

Background: The process by which drugs leave the bloodstream to enter the skin compartments is important in determining appropriate routes of delivery and developing more efficacious medications. We conducted a general literature review on percutaneous egression mechanisms. Summary: Studies demonstrate that the stratum corneum (SC) is a compartment for systemically delivered drugs. Upon reviewing the available literature, it became apparent that there may be multiple mechanisms of percutaneous egression dependent upon drug physiochemical properties. These mechanisms include, but are not limited to, desquamation, sebum secretion, sweat transport, and passive diffusion. While drugs often utilize one major pathway, it is possible that all mechanisms may play a role to varying extents. Key Messages: Available literature suggests that hydrophilic substances tended to travel from blood to the upper layers of the skin via sweat, whereas lipophilic substances utilized sebum secretion to reach the SC. Upon reaching the skin surface, the drugs spread laterally before penetrating back into the skin as if they were topically administered. More data are warranted to identify additional percutaneous egression mechanisms, precise drug action sites, and accelerate drug development. © 2022 The Author(s).

Introduction

Treatment of skin disease frequently requires systemic medications, which according to mainstream belief, are generally more potent than topical therapeutics [1]. Both delivery modes have advantages and disadvantages. For example, systemic dosing may be more ideal for skin disease involving a larger body surface area but often involves a greater risk of toxicity. Topicals have relatively fewer adverse effects but can be associated with poor adherence and must have physiochemical properties that allow them to adequately penetrate the skin layers to reach their action site [1].

Of particular interest to dermatologists is the mechanism by which systemically administered drugs enter skin compartments because a drug must be present in the ex-
act tissue compartment in adequate amounts in order to exert therapeutic action. Percutaneous egression is a term we neologized to describe this process by which drugs in the bloodstream enter the skin [2]. In contrast, percutaneous absorption describes the opposite passage of substances from the epidermis into the bloodstream. Quantifying drug concentrations in various epidermal levels, however, is challenging and studies on drug disposition from the bloodstream to the skin are few. As a result, little is known about how drugs reach the skin compartments to exert therapeutic effect after systemic administration.

Here, we discuss the current knowledge regarding the precise mechanism of percutaneous egression to the skin in humans; percutaneous egression of drugs to the hair, nails, and sweat and animal studies are beyond the defined scope of this article. We conducted a general literature review of articles through PubMed, Google Scholar, Embase, and Scopus from date of database inception until 2021 using terms: “transepidermal” or “epidermal” or “cutaneous” or “skin” or “percutaneous” and “egression” or “mechanism” or “inverse” or “penetration” [3]. Citation chaining was also used to identify relevant studies on the topic of percutaneous egression. In the sections below, we first summarize the common methods used to evaluate drug penetration into skin and determinants of cutaneous concentrations of systemic drugs before evaluating the latest data on percutaneous egression mechanisms.

**Common Methods to Evaluate Drug Penetration into Skin**

**Tape Stripping**

Tape stripping is widely used in studies investigating the cutaneous concentrations of systemically administered medications. The cell layers of the stratum corneum (SC) are sequentially removed from the skin with adhesive tape and then the drug content of the tape strips is measured. The amount of SC removed depends upon the size of the corneocytes, thickness of SC, age, and lipid composition, among other factors [4].

This method is simple, quick, inexpensive, and noninvasive. However, variations in the pressure applied during application, force used during removal, and velocity of tape removal can influence detection data [4]. Tape stripping also cannot measure drug concentrations in deeper layers such as the dermis and can decrease the skin barrier, leading to artificially increased skin drug levels.

**Skin Biopsy**

Skin biopsy cuts deep into the skin; a shave biopsy contains epidermis and some dermis while a punch biopsy contains epidermis, dermis, and parts of subcutaneous tissue. The SC can also be optionally removed with tape stripping before a punch biopsy is performed to prevent surface contamination. This method is advantageous because a punch biopsy allows analysis of in vivo drug concentration in all skin layers. However, this is the most invasive method and can leave a scar. Contamination can also arise if the biopsy tool introduces the drug from the skin surface into deeper layers [5].

**Skin Blister Induction**

There are three main methods of generating a skin blister: suction blister technique, cantharidin-induced blisters, and blister formation with ammonium hydroxide. The first involves a negative pressure suction cup of 300–350 mm Hg applied to skin for approximately 2 h that leads to cleavage of the epidermal basement membrane from the dermis and produces a blister [6]. The fluid within the blister corresponds to interstitial fluid [5]. The second method involves first placing a filter paper disc on the skin before saturating the paper disc with 0.1% cantharidin solution in acetone [7]. A blister dressing is applied after the disc dries, and the blister fluid can then be collected 24 h after cantharidin application [7]. The third method involves applying a 0.5 mL 1:1 solution of aqueous ammonium hydroxide in a one-well plastic block strapped to the skin using tourniquets [8]. A painless intraepidermal blister is generated in a mean time of 13 min; the skin heals without scarring [8].

The skin blister method is advantageous because many drugs targeting the skin are situated at the epidermal/dermal junction [5]. It allows for in vivo analysis and is relatively noninvasive. However, concentrations measured reflect that in experimentally induced fluids, which vary with blister size and surface-to-volume ratio [9]. In addition, the technique is not capable of continuous drug concentration measurement unless multiple blisters are produced [9]. Lipophilic drugs may also bind to skin tissue resulting in low drug levels in blister fluid.

**Cutaneous Microdialysis**

Cutaneous microdialysis allows continuous sampling of unbound drug in tissues [9]. A probe is first inserted horizontally into the dermis then continuously perfused with a physiologic perfusate, allowing solutes to cross the membrane by passive diffusion [10]. Since large molecules such as proteins are prevented from diffusing...
through the probe membrane, this enables analysis of unbound drug in the tissue.

One major advantage of cutaneous microdialysis is that it can provide detailed chronological pharmacokinetic data since several sites can be sampled simultaneously. It is a useful technique for studying skin metabolism, more specific compared to other objective measures of cutaneous drug sampling, and does not require sample clean-up prior to analysis given there is a lack of protein in dialysate. However, the method is limited by the sensitivity of the analytical assay since drug concentrations can be especially low with lipophilic substances and requires careful calibration of flow rate. Insertion of the probe can also elicit a tissue reaction which can impact skin absorption. Furthermore, microdialysis only samples the dermis and is therefore unsuitable for epidermal analyses.

Confocal Laser Scanning Microscopy

Confocal laser scanning microscopy (CLSM) enables an “optical biopsy” to allow spatial drug distribution analysis. In this method, laser from the confocal microscope is directed toward fluorescently labeled samples; the resulting fluorescence emission from the focal plane returns to the scanning system and is focused onto a detector. A spatial filter removes light from nonfocal planes, enhancing the signal to background ratio [11]. Point scanning the area and altering the plane of focus produces a series of high-resolution images that allow detection of substances that have penetrated the skin throughout various depths.

The noninvasive nature and ability to image thick samples with high resolution is a major advantage of CLSM. However, this method only allows for qualitative, not quantitative analysis. It is also dependent on autofluorescent drug compounds or dyes or labels [12].

Confocal Raman Spectroscopy

Confocal Raman spectroscopy is a newly validated method for quantitative detection of pharmaceuticals in the skin [13]. It takes advantage of the Raman effect, characterized by a linear correlation of scattering intensity and molecular concentration of the drug of interest [13]. First, laser radiation focuses on a point in the skin sample; the light that is scattered by the tissue and/or substance is then focused onto an optical fiber connected to a spectograph [14]. The spectra are collected and the relative concentrations of the substances of interest are then calculated [15].

A major advantage of confocal Raman spectroscopy is that it allows for real-time monitoring of in vivo drug penetration into SC with high depth-resolution [15]. It is noninvasive and unlike CLSM, non-reliant on labels and dyes. An important limitation is that the substance studied must have a specific absorption spectrum separate from that of SC.

Fourier Transform Infrared-Attenuated Total Reflection Spectroscopy

This vibrational spectroscopy tool is among the most widely used spectroscopic methods to assess drug penetration in skin [14]. It involves emitting an infrared beam through an infrared-transparent crystal, into the skin sample placed on the crystal. The drug of interest in the sample then absorbs the infrared radiation at frequencies corresponding to its absorption spectrum, allowing the substance to be subsequently quantified.

Although this method is rapid and noninvasive, Fourier transform infrared-attenuated total reflection spectroscopy is highly sensitive to small movements and irregularity of the skin sample surface [14]. The infrared beam also has a low penetration of 1–2 μm. Therefore, it is often utilized in combination with tape stripping so that successive SC layers can be placed against the ATR crystal, allowing the entire SC to be studied.

Major Factors Impacting Percutaneous Egression

Climate

Many factors can influence the cutaneous content of systemically administered substances and the route of transport to the skin. Two studies of griseofulvin levels in skin after oral administration revealed that climate can impact griseofulvin concentration in SC [16, 17]. There was a more rapid buildup of drug and a higher plateau during summer than winter [16]. In particular, concentration was three to four times higher during summer than winter [16]. Epstein et al. [16] postulated that this is likely because griseofulvin can dissolve in perspiration during warmer temperatures. As water and perspiration evaporates from skin, this can result in drug deposition in perspiration during warmer temperatures. Water and perspiration evaporates from skin, this can result in drug deposition in perspiration during warmer temperatures. As water and perspiration evaporates from skin, this can result in drug deposition in perspiration during warmer temperatures.
relatively higher free drug concentration in the blood, but many other substances such as itraconazole, terbinafine, and griseofulvin travel through the blood bound to albumin [16, 18]. After drug discontinuation, the amount of unbound drug in the plasma decreases quickly, generating a concentration gradient that causes drug diffusion back into the skin from skin tissue [16]. However, the cutaneous concentration has been shown to be less dependent on plasma concentration after multiple systemic administrations [19].

**Drug Properties and Vasoconstriction**

Drug properties also influence percutaneous egression. Those with a high volume of distribution tend to redistribute more readily to the skin from the plasma. Alkalotic molecules can leave the systemic circulation more easily compared to acidic molecules given that the former have higher binding affinity with the negatively charged phospholipid heads [20, 21]. Lipophilicity can also promote dermal drug accumulation [19]. While albumin has a propensity to bind to lipophilic drugs, these molecules have a higher lipid membrane permeability and are therefore more likely to leave the plasma. Overall, drugs that are lipophilic have a higher volume of distribution.

Vasoconstriction, which can be induced as a physiologic reaction to cold temperatures or pharmacologic substances such as adrenaline, reduces drug concentration in the skin [10]. This is due to decreased blood flow which decreases transport of molecules from the bloodstream to the target site.

**Percutaneous Egression Mechanisms**

In 1960, Roth and Blank [22] became the first to study percutaneous egression in humans and demonstrated the presence of orally administered griseofulvin at various SC depths. In the study, nine subjects received 1 g of griseofulvin daily for 18–56 days; individuals were tested at a maximum of 72-h intervals, and the SC was stripped down to depths of 25%, 50%, 75%, and 100% until the tape no longer contained any components from the SC [22]. To determine the presence of griseofulvin, a pure suspension of *Microsporum gypseum* was applied to each skin depth in addition to intact skin, and direct in vivo biassays were performed within 72 h after the first oral dose and repeated at intervals of 3–5 days [22]. Abnormal histologic characteristics such clubbing, curling, contortion, ballooning, and lateral branching of germ tubes indicated griseofulvin presence in SC, but Roth and Blank did not measure the relative concentration of griseofulvin at each skin depth [22]. Furthermore, the mechanism by which griseofulvin was transported into the SC was still unclear.

Since then, scientists have postulated a few theoretical paths that drugs can take to reach the skin from the bloodstream. The first route is through desquamation, or incorporation of substances from blood into epidermal basal layer cells which then move toward the surface and eventually cornify into SC [23]. A second mechanism involves sebum secretion [23]. These two processes typically occur over 3–4 weeks [23]. Passive diffusion across the dermal-epidermal barrier into the SC and transport via sweat glands are faster alternative mechanisms [23]. Upon literature review, it appears that drug properties can determine percutaneous egression routes and that multiple mechanisms may be at play simultaneously. Detailed characteristics of the studies reviewed are included in Table 1.

Many hydrophilic substances tended to utilize eccrine sweat glands to reach skin from blood. Fluconazole, for example, accumulated rapidly in the skin after oral ingestion, with highest concentration in the SC, followed by eccrine sweat [24]. Faegermann and Laufen [25] produced similar results, suggesting that sweat secretion is one of the major mechanisms by which fluconazole is transported to the skin surface from blood. Other hydrophilic drugs such as anthracyclines have also shown preference for reaching the skin via sweat. While investigating the pathogenesis of anthracycline-induced palmar-plantar erythrodysesthesia, Jacobi et al. [26] noted that 3 h after intravenous doxorubicin administration; fluorescence was detected on the skin surfaces of all five body sites studied (forearm, palm, sole, axilla, and forehead). In addition, the drug was observed inside excretory ducts of sweat glands and around the opening of the sweat gland in the upper skin layers [26]. The hydrophilic liposomal coat encapsulating doxorubicin likely favored this route. These results were later reproduced using laser scanning microscopy on nine body sites (forehead, both axilla, palms, soles, and underarm areas) in Martschick et al. [27] who demonstrated that doxorubicin and epirubicin were found inside the sweat duct and around its opening on the skin after intravenous administration. Upon arrival to the surface, doxorubicin, and epirubicin were then visualized to spread out laterally on the surface before penetrating back into the SC, as if they had been topically applied [27]. This confirmed secretion via sweat glands as a percutaneous egression mechanism.

Lipophilic substances may favor delivery to the skin surface via sebum. After oral ivermectin administration to 5 patients with scabies, Haas et al. [28, 29] measured...
Table 1. Summary of key studies dedicated to understanding percutaneous egression mechanisms

| Study                  | Subjects | Substance | Dose                                      | Skin collection method | Extraction method | Detection method in skin (quantitative/qualitative) | Sebum   | Sweat        | Skin                  |
|------------------------|----------|-----------|-------------------------------------------|------------------------|-------------------|-----------------------------------------------------|---------|--------------|-----------------------|
| Roth and Blank [22]    | 9        | Griseofulvin (oral) | One gram daily for 18–56 days              | Tape stripping         | N/A               | Microsporum gypseum was applied to SC; abnormal hyphal characteristics indicated griseofulvin presence | N/A     | N/A          | Griseofulvin detected |
| Wildfeuer et al. [24]  | 21       | Fluconazole (oral) | Twelve volunteers: 50 mg daily for 12 days | Skin scrapings, punch biopsy | Five milliliters of ethyl acetate, then fluconazole and internal standard were back-extracted into 2 mL of 1 M HCl, alkalinized with 5 M NaOH and re-extracted into 5 mL ethyl acetate | Capillary gas chromatography with electron capture detection | N/A     | 50 mg dose   | 4.58 μg/mL           |
|                        |          |           | Nine volunteers: 200 mg daily for 5 days   |                        |                   |                                                     |         | 200 mg dose  | SC: 73 μg/g          |
|                        |          |           |                                            |                        |                   |                                                     |         | SC: 127 μg/g |                      |
| Faergemann et al. [30–32] | 23      | Fluconazole (oral) | Twelve volunteers: 50 mg daily for 12 days | Skin scrapings, punch biopsy | Five milliliters of ethyl acetate, then fluconazole and internal standard were back-extracted into 2 mL of 1 M HCl, alkalinized with 5 M NaOH and re-extracted into 5 mL ethyl acetate | Capillary gas chromatography with electron capture detection | N/A     | 50 mg dose   | 4.6 μg/mL            |
|                        |          |           | Eleven volunteers: 150 mg weekly for 2 weeks |                        |                   |                                                     |         | 150 mg dose  | SC: 66.4 μg/g         |
|                        |          |           |                                            |                        |                   |                                                     |         | SC: 23.4 μg/g | Demis-epidermis: 2.93 μg/g |
|                        |          |           |                                            |                        |                   |                                                     |         | SC: 4.62 μg/g | Demis-epidermis: 4.62 μg/g |
| Jacobi et al. [26]     | 15       | Doxorubicin (intravenous) | 20–25 mg/m² every 2 weeks                | N/A                    | N/A               | CLSM                                                | N/A     | Doxorubicin detected in sweat duct | Doxorubicin detected in SC |
| Martschick et al. [27] | 12       | Doxorubicin (intravenous) | Six volunteers: doxorubicin at medium dose 23.3 mg/m² (20–40 mg/m²) | N/A                    | CLSM               | N/A                                                 | N/A     | Doxorubicin and epirubicin detected inside sweat duct and around its opening on the skin | Doxorubicin and epirubicin detected in SC |
| Study | Subjects | Substance | Dose | Skin collection method | Extraction method | Detection method in skin (quantitative/ qualitative) | Sebum | Sweat | Skin |
|-------|----------|-----------|------|------------------------|-------------------|------------------------------------------------|-------|-------|------|
| Haas et al. [28, 29] | 5 | Ivermectin (oral) | Single 200 μg/kg dose | Skin rubbed with porous ceramic plates that collect squames | Samples were vaporized by heating and ionized | N/A | N/A | Seborrheic areas 39.2±40.2 mg/kg Non-seborrheic areas 25.9 11.2 mg/kg |
| Faergemann et al. [30] | 10 | Terbinafine (oral) | 250 mg daily for 12 days | Skin scrapings, punch biopsy | SM NaOH and heat to hydrolyze SC; extraction of terbinafine and internal standard into ethyl acetate, then centrifuged and evaporated before residues were re-dissolved in ethyl acetate | HPLC | 45.1 μg/mL | 0 | SC: 9.1 μg/g Demis-epidermis: 0.3 μg/g |
| Faergemann et al. [31] | 12 | Terbinafine (oral) | 250 mg daily for 28 days | Skin scrapings, punch biopsy | SM NaOH and heat to hydrolyze SC; extraction of terbinafine and internal standard into ethyl acetate, then centrifuged and evaporated before residues were re-dissolved in ethyl acetate | HPLC | 56.1 μg/g | N/A | SC: 14.4 μg/g Demis-epidermis 1.03 μg/g |
| Faergemann et al. [32] | 16 | Terbinafine (oral) | Eight volunteers: 250 mg daily for 7 days Eight volunteers: 250 mg daily for 14 days | Skin scrapings, punch biopsy | SM NaOH and heat to hydrolyze SC; extraction of terbinafine and internal standard into ethyl acetate, then centrifuged and evaporated before residues were re-dissolved in ethyl acetate | HPLC | Day 7 19.02 μg/mL Day 14 21.83 μg/mL | N/A | Day 7 SC: 2.52 μg/g Day 14 SC: 7.64 μg/g |
### Table 1 (continued)

| Study | Subjects | Substance | Dose | Skin collection method | Extraction method | Detection method in skin (quantitative/qualitative) | Sebum | Sweat | Skin |
|-------|----------|-----------|------|------------------------|-----------------|-------------------------------------------------|-------|-------|------|
| Cauwenbergh et al. [33] | 3 | Itraconazole (oral) | Two volunteers: 100 mg daily for 4 weeks<br>One volunteer: 200 mg daily for 7 days | Epidermal shaving | N/A | HPLC | Day 7<br>4.64 μg/mL | Day 7<br>0.072 μg/mL | Day 7 SC<br>Palms: 0.053 mg/g<br>Beard region: 0.444 mg/g<br>Back: 0.389 mg/g |
| Thiele et al. [34] | 9 | Vitamin E | N/A | Tape stripping | Extracted with 4 mL hexane | HPLC, gas chromatography-mass spectrometry | Upper arm (after 1 h)<br>5.1±1.2 pmol/mL<br>Cheek (after 1 h)<br>76.5±13.4 pmol/mL | N/A | Upper arm: upper-most SC: 0.7±0.3 pmol/mg<br>Cheek: 13.7±5.1 pmol/mg |
| Epstein et al. [16] | 13 | Griseofulvin (oral) | Seven volunteers: 500 mg twice daily for 25 days<br>Six volunteers: Three 500 mg tablets at 12 h intervals | Skin scrapings | Extracted with ether | Gas-liquid chromatography with electron capture detector | N/A | N/A | Outermost level I: 16.4±2.7 ng/mg<br>Level II: 9.7±1.5 ng/mg<br>Innermost level III: 4.5±1.9 ng/mg |
| Shah et al. [17] | 38 | Griseofulvin (oral) | 500 mg twice a day for 3 days | Skin scrapings | Extracted with ether | Gas-liquid chromatography with electron capture detector | N/A | 200–340 ng/mL | Outermost level I: 20.8±1.5 ng/mg<br>Level II: 10.0±1.5 ng/mg<br>Innermost level III: 7.5±2.2 ng/mg |
| Harris et al. [23] | 17 | Ketoconazole 400 mg daily for various lengths of time | Skin scrapings | Extracted with heptane-isoamyl alcohol | HPLC | Day 7<br>0 μg/mL<br>Day 14: 0 μg/mL<br>≥9 months: 4.7 μg/g | Day 7<br>0.059 μg/mL<br>Day 14<br>0.084 μg/mL | Day 7<br>4.59 μg/g<br>Day 14<br>5.18 μg/g |

HPLC, high performance liquid chromatography.
significantly higher concentrations of the drug in seborrheic (forehead and retroauricular areas) than non-seborrheic skin (forefinger, antithenar, axilla, and abdomen), suggesting a sebum secretion pathway for ivermectin from the bloodstream. Three different studies by Faergemann et al. [30–32] demonstrated that after daily oral 250 mg terbinafine, the highest concentrations were achieved in sebum and SC, respectively. Plasma and dermis-epidermis (without SC) concentrations were significantly lower, and terbinafine was not found in sweat [30–32]. Similarly, sebum concentrations of itraconazole were 10 times that of the peak plasma after oral administration; consistent with other studies, the SC had the second highest drug concentration, and itraconazole did not appear in sweat until a much higher (200 mg vs. 100 mg) dose [33]. As in Haas et al. [28, 29] Cauwenbergh et al. [33] also noted higher accumulation of itraconazole in seborrheic skin areas such as the beard and back compared to palmar skin. Sebum secretion is also vitamin E’s major route of percutaneous egression. Using high performance liquid chromatography analysis of α-tocopherol (vitamin E) and squalene (sebum marker) concentrations in tape-stripped SC samples and sebum, Thiele et al. [34] discovered that there was a significant correlation between vitamin E and co-secreted squalene. In addition, the α-tocopherol concentration was 20 times higher in seborrheic (cheek) than non-seborrheic (upper arm) skin [34]. Collectively, these results support sebum as an additional percutaneous egression mechanism. The pattern of highest drug concentrations in sebum followed by SC after systemic administration suggest that, as with hydrophilic drugs, lipophilic medications may also penetrate back into the SC upon arrival at the skin surface.

Griseofulvin and ketoconazole are lipophilic drugs that reach the skin surface mainly via sweat. Using gas-liquid chromatography with electron capture, Epstein et al. [16] and Shah et al. [17] demonstrated that evaporation of sweat from the skin deposited systemically administered griseofulvin, resulting in a higher concentration in the SC than can be achieved through diffusion alone [16, 17]. In Harris et al. [23] study, ketoconazole content in palmar SC, sweat, sebum, and serum was measured with HPLC. Ketoconazole was detected in eccrine sweat and palmar sweat within 1 h after oral ingestion [23]. In contrast, ketoconazole was only detected in sebum after prolonged (greater than 9 months) treatment [23]. These results suggest that the slower epidermal basal cell incorporation mechanism is less likely because ketoconazole was detectable in the skin at 7 days after oral ingestion [23]. Sebum secretion is also unlikely, because ketoconazole appeared in palmar SC, and palmar skin lacks sebaceous glands [23]. Harris et al. [23] concluded that although passive diffusion from plasma into SC is a possibility, eccrine sweat is a major route for percutaneous egression. One explanation for delivery of lipophilic ketoconazole and griseofulvin to the SC via sweat is that ketoconazole is first converted into a hydrophilic substance by gastric acid before systemic absorption [23]. Griseofulvin, on the other hand, has poor water-solubility but is highly lipid-soluble, an essential feature required for drugs to readily diffuse from blood through sweat gland epithelium into sweat [17].

**Conclusion**

There are multiple percutaneous egression mechanisms, including but not limited to, sweat transport, sebum secretion, desquamation, and passive diffusion [23]. The route preferred depends heavily on drug physiochemical properties, but all pathways may be relevant. Since this topic has not been extensively investigated, the extent of each mechanism’s contribution to the delivery of systemically administered drugs to the skin is still unclear. More data on percutaneous egression is needed to accelerate the development of efficacious drugs for dermatologic diseases.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

**Funding Sources**

None.

**Author Contributions**

Qisi Sun conceptualized and wrote the manuscript; Caitlin G. Purvis assisted with literature search and reviewed the manuscript; Sahir N. Iqbal reviewed the manuscript and assisted with creating a table; Veronica K. Emmerich reviewed the manuscript; Steven R. Feldman reviewed the manuscript; Howard Maibach provided the idea for and reviewed the manuscript.
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