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A Content Analysis of Indoor Tanning Twitter Chatter During COVID-19 Shutdowns: Cross-Sectional Qualitative Study

Laurie Groshon¹, MS; Molly E Waring², PhD; Aaron J Blashill³, PhD; Kristen Dean²; Sanaya Bankwalla², BSc (Marketing); Lindsay Palmer⁴, PhD; Sherry Pagoto², PhD

¹University of Florida, Gainesville, FL, United States
²University of Connecticut, Storrs, CT, United States
³San Diego State University, San Diego, CA, United States
⁴UMass Chan Medical School, Worcester, MA, United States

Corresponding Author:
Sherry Pagoto, PhD
University of Connecticut
2006 Hillside Road, Unit 1248, Room 22
Storrs, CT, 06268
United States
Phone: 1 4344654162
Email: sherry.pagoto@uconn.edu

Abstract

Background: Indoor tanning is a preventable risk factor for skin cancer. Statewide shutdowns during the COVID-19 pandemic resulted in temporary closures of tanning businesses. Little is known about how tanners reacted to losing access to tanning businesses.

Objective: This study aimed to analyze Twitter (subsequently rebranded as X) chatter about indoor tanning during the statewide pandemic shutdowns.

Methods: We collected tweets from March 15 to April 30, 2020, and performed a directed content analysis of a random sample of 20% (1165/5811) of tweets from each week. The 2 coders independently rated themes (κ=0.67-1.0; 94%-100% agreement).

Results: About half (589/1165, 50.6%) of tweets were by people unlikely to indoor tan, and most of these mocked tanners or the act of tanning (562/589, 94.9%). A total of 34% (402/1165) of tweets were posted by users likely to indoor tan, and most of these (260/402, 64.7%) mentioned missing tanning beds, often citing appearance- or mood-related reasons or withdrawal. Some tweets by tanners expressed a desire to purchase or use home tanning beds (90/402, 22%), while only 3.9% (16/402) mentioned tanning alternatives (eg, self-tanner). Very few tweets (29/1165, 2.5%) were public health messages about the dangers of indoor tanning.

Conclusions: Findings revealed that during statewide shutdowns, half of the tweets about indoor tanning were mocking tanning bed users and the tanned look, while about one-third were indoor tanners reacting to their inability to access tanning beds. Future work is needed to understand emerging trends in tanning post pandemic.

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KEYWORDS
attitude; attitudes; content analysis; dermatology; opinion; opinion; perception; perceptions; perspective; perspectives; sentiment; skin; social media; social media; sun; tan; tanner; tanners; tanning; tweet; tweets; Twitter

Introduction

In the United States, 1 in 5 people will develop skin cancer in their lifetime [1]. Melanoma, the deadliest type of skin cancer, is the most common cancer among young adults aged 25-29 years [2]. Excessive exposure to UV radiation from either the sun or artificial sources (eg, tanning beds) is a major risk factor for skin cancer [3]. On March 11, 2020, the World Health Organization declared COVID-19 a pandemic, and states across the United States enforced stay-at-home orders, forcing businesses to close their doors. The shutdowns in the United States served as a natural experiment of the impact of tanning businesses closing on indoor tanners, as demand for tanning services tends to peak between January and June, coinciding...
with the COVID-19 2020 shutdowns [4]. Twitter (subsequently rebranded as X) data may be useful for understanding indoor tanning attitudes, given that young adults who are indoor tanning are almost twice as likely to use Twitter regularly than those who do not [5]. Another study assessed the frequency of mentions of indoor tanning on Twitter and found that in a 2-week period, 120,354 unique users made 154,486 tweets that mentioned the words indoor tanning, tanning bed, tanning booth, tanning salon, sun bed, or sun lamp, and these tweets reached 113,888,616 users [6].

Other studies have delved into the content of tweets about indoor tanning. For example, 1 study examined tweets that contained the phrases “tanning bed” or “tanning salon” and found that most tweets (71.2%) were posted by tanners and either expressed positive sentiment about indoor tanning, negative tanning bed experiences, or tanning-related injuries [7]. Another study of tweets containing keywords for tanning bed use and burning revealed that in 2013, over 15,000 had these keywords, and 64% described a tanning bed–induced burn [8]. Together, these studies reveal that Twitter may provide insights into tanners’ attitudes and behaviors.

This study aimed to examine Twitter chatter about indoor tanning during the COVID-19 shutdowns (March 15 to April 30, 2020). Stay-at-home orders became colloquially known by several terms, such as “shutdowns” and “lockdowns,” but all terms refer to the orders issued by local and state officials that limited business activities to those deemed essential (eg, grocery stores, pharmacies, and hospitals) and limited residents’ “nonessential” travel outside of the home [9]. The majority of stay-at-home orders (eg, shutdowns) began in March 2020, and by March 31, 2020, a total of 42 states and US territories had issued stay-at-home orders, affecting 73% of all US counties [10,11]. Location data from mobile devices suggest that compliance with restrictions was high, with 97.6% of counties with mandatory stay-at-home orders reporting a decrease in median population movement immediately after the start dates of the stay-at-home orders [10]. We were interested in whether tanners found alternative means of accessing tanning beds if they discussed interest in UV tanning alternatives (eg, sunless tanners), and their reactions to having no access to commercial tanning beds. Given the proliferation of misinformation about the impact of UV radiation on COVID-19 that appeared to have begun after former US President Donald Trump proposed the idea that UV light could be used inside the body to remedy COVID-19 [12], we also examined the presence of misinformation in tweets about tanning beds [13,14].

**Methods**

**Overview**

This was a cross-sectional qualitative study of public tweets about indoor tanning during the COVID-19–related shutdowns. We searched Twitter for 2 common lay terms, “tanning bed” and “tanning salon,” that refer to “indoor tanning,” a public health term that refers to tanning using artificial UV light–producing devices [7,15]. Using the R package (R Foundation for Statistical Computing) `rtweet`, we captured tweets that occurred between March 15, 2020, one of the first days of the COVID-19 statewide business shutdowns, and April 30, 2020 [16,17]. We excluded retweets because our interest was in the original thoughts of users, but we included “quote tweets,” which contain the tweeter’s own sentiments. We removed tweets that were advertisements, pornography, or from accounts that became private or were suspended between the data capture and the qualitative coding process in April 2021 (Figure 1). Of the 5811 tweets captured, we randomly sampled 20% (n=1165) of eligible tweets captured per week during the sampling window to capture conversation from the entire sampling window, consistent with other studies of tweets [18]. Table 1 contains paraphrased tweets to protect the privacy of the users.

**Figure 1.** Tweet sampling and the construction of the analytic sample.
Table 1. Topics of tweets (n=1165) about indoor tanning on Twitter during statewide shutdowns (March 15 to April 30, 2020), by user type. Tweets could be coded in more than 1 tweet category.

<table>
<thead>
<tr>
<th>Tweet category by user type</th>
<th>Tweets, n (%)</th>
<th>Illustrative examplesa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>People who likely do not tan indoors (n=589 tweets)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mocking tanners, tan people, or the act of tanning</td>
<td>562 (95.4)</td>
<td>Some people are about to meet their real girlfriends for the first time with the tanning bed closed hahaha.</td>
</tr>
<tr>
<td>Mocking tweets mentioning Donald Trump</td>
<td>448 (76.1)</td>
<td>Trump went in the tanning bed too long. Looks like a burnt Cheeto.</td>
</tr>
<tr>
<td>Health warnings</td>
<td>30 (5.1)</td>
<td>Sorry if you’re a person that uses the tanning bed, you are ruining your skin’s health and look! Proud to be pale and skin cancer free. I used to tan in a tanning bed, but you get older and your wrinkles hide small objects.</td>
</tr>
<tr>
<td><strong>People likely to tan indoors (n=402 tweets)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing tanning</td>
<td>260 (64.7)</td>
<td>I need the tanning bed to reopen, being pale makes me depressed. Having serious tanning bed withdrawals, this is killing me!</td>
</tr>
<tr>
<td>Appearance-related missing tanning</td>
<td>77 (30)</td>
<td>I need the tanning bed to open back up. I look so pale I can’t stand it.</td>
</tr>
<tr>
<td>Mood-related missing tanning</td>
<td>13 (5)</td>
<td>I need the tanning bed to reopen, that’s my stress reliever!</td>
</tr>
<tr>
<td>Withdrawal from indoor tanning</td>
<td>12 (4.6)</td>
<td>Anyone else going through tanning bed separation anxiety? This hurts</td>
</tr>
<tr>
<td>Expressing a desire to buy a home tanning bed, bought a tanning bed, or looking to use someone else’s home tanning bed</td>
<td>90 (22.4)</td>
<td>I will buy a tanning bed if this quarantine continues. PSA who’s got a tanning bed for me to use?! I’m desperate.</td>
</tr>
<tr>
<td>Positive sentiment about tanning</td>
<td>69 (17.2)</td>
<td>So happy I have a tanning bed during this, I need to be tan.</td>
</tr>
<tr>
<td>Use of alternative behaviors</td>
<td>15 (3.9)</td>
<td>Give me some recs for self-tanners since my tanning salon is closed! Ordered some self-tanner because this no tanning bed thing is killing me.</td>
</tr>
<tr>
<td>Arguments against messages that tanning is unhealthy or presents indoor tanning misinformation</td>
<td>24 (6)</td>
<td>Let’s reopen the tanning salon, I think we can all agree that UV light will help kill the virus.</td>
</tr>
<tr>
<td>Other</td>
<td>27 (6.9)</td>
<td>Burnt my face in the tanning bed and now I don’t look good.</td>
</tr>
<tr>
<td><strong>Tanning salon employees (n=4 tweets)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanning salon employee chatter</td>
<td>4 (100)</td>
<td>Will these mandatory closing impact the tanning salon I work at?</td>
</tr>
<tr>
<td><strong>People whose tweets do not indicate whether they indoor tan (n=170 tweets)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated to indoor tanning, tweets by people who do not indoor tan, or unclear whether the speaker is a tanner</td>
<td>168 (98.8)</td>
<td>That tanning bed scene in the final destination movie is creepy.</td>
</tr>
<tr>
<td>Argues against messages that tanning is unhealthy or presents indoor tanning misinformation</td>
<td>2 (1.2)</td>
<td>I’m gonna open a coronavirus clinic, ordered a tanning bed and some Lysol. I’ll save everyone!</td>
</tr>
</tbody>
</table>

aWhile all tweets included in the analysis were posted publicly, to protect the privacy of individuals who posted these tweets, we paraphrased the words of tweets in a way that prevents the content of the tweet from being searchable without changing its meaning.

Statistical Analysis

We conducted a directed content analysis of tweets using a codebook from our 2016 Twitter study about indoor tanning [7,19]. We modified the codebook after examining a subsample of 100 tweets. The original codebook had 9 codes: a desire to use a tanning bed, sleeping in a tanning bed, tanning-related injury, a complaint about or negative experiences tanning, tanning salon employee chatter, mocking tanners or tanning, health warnings about indoor tanning, pushback against “tanning is unhealthy” messaging or antitanning legislation, and references to indoor tanning in the context of an unrelated topic (eg, movie quote). We expanded the codebook to include 3 additional codes for tweets in which the user expressed that they missed being able to go indoor tanning, expressed a desire to buy a home tanning bed, crowdsourced followers to use a home tanning bed, and mentioned the use of UV tanning alternatives (eg, self-tanners). We eliminated 3 codes (ie, sleeping in a tanning bed, tanning-related injury, a complaint about, or negative experiences) because they were not represented within the current data set. We also coded tweets as posted by people who were likely to indoor tan (based on their admission of tanning or having tanned in their tweets), tanning salon employees (based on the content of their tweets), people who are not likely to indoor tan (based on their mocking indoor tanning or discussing the risks of indoor tanning), and people whose tweets do not indicate if they indoor tan or not. If a tweet seemed to be posted by a tanning salon employee but
referred to their individual tanning behavior, we coded the tweet as being posted by someone likely to indoor tan. After finalizing the codebook, 2 coders independently coded all 1165 tweets (100% double-coded). Discrepantly coded tweets were discussed to reach a consensus.

We calculated interrater reliability and Cohen κ for each coding category. Interrater agreement of tweet categories ranged from 94% to 100%, and Cohen κ statistics ranged from 0.6654 to 1.0. Interrater agreement among coders was 94% (κ=0.9106). We summarized the proportion of tweets posted by those likely to indoor tan, tanning salon employees, those unlikely to indoor tan, and those whose tweets do not indicate whether they indoor tan. We then reported the frequency of tweet categories by user types. Analyses were conducted using SAS 9.4 (SAS Institute, Inc).

Ethical Considerations
This study does not meet the definition of human participants research and thus did not require Institutional Review Board approval. However, to protect the privacy of users who may not expect public tweets to be used in research, we paraphrased tweets to render the tweet’s content unsearchable while preserving the meaning. We confirmed that the paraphrased content did not produce the original tweet through searches.

Results
Overview
In our final sample of 1165 tweets, 1144 (98%) were posted by unique Twitter accounts. A total of 93% (1084/1165) of tweets in our analytic sample were from the search term “tanning bed,” while only 7% (81/1165) were from the search term “tanning salon.”

Half of the tweets (589/1165, 50.6%) came from users unlikely to indoor tan, while 34.5% (402/1165) were posted by users who seemed likely to indoor tan (Table 1). Very few tweets (4/1165, 0.4%) appeared to be posted by tanning salon employees, and in the remaining 14.5% (170/1165) of tweets, the content did not clearly indicate whether the user was an indoor tanner.

Tweets From People Unlikely to Indoor Tan
The majority (562/589, 95%) were classified as mocking tanners, tan people, or the act of tanning. Among these, the majority (446/589, 75.7%) mocked former US President Donald Trump’s skin tone, and 20.6% (116/589) mocked the appearance of tanners and the use of tanning beds in general. The remaining 5% (30/589) of tweets from users unlikely to be indoor tanners contained health warnings about indoor tanning.

Tweets From People Likely to Indoor Tan
Nearly two-thirds (260/402, 64.7%) were coded as “missing tanning,” meaning the user expressed they missed tanning, their frustration that they could not go tanning, or their eagerness to get back to tanning (Table 1). Within this category, 60% (156/260) of tweets did not mention a specific reason they missed tanning, but 30% (77/260) indicated they missed indoor tanning for appearance-related reasons, 5% (13/260) indicated they missed indoor tanning for mood-related reasons, and 5% (12/260) indicated withdrawal symptoms from being restricted from indoor tanning. The second most common theme among tweets from likely tanners was general positive attitudes about indoor tanning (69/402, 17.2%), followed by the desire to buy a home tanning bed or use someone else’s (90/402, 22.3%), misinformation about tanning (24/402, 6%), and finally, use of alternative tanning methods such as self-tanner and bronzer makeup (16/402, 3.9%; Table 1).

Other Tweets
The content of the remaining tweets (170/174, 98.8%) made it unclear whether the user was an indoor tanner. The vast majority (165/170, 95.9%) mentioned tanning beds in the context of an unrelated topic (eg, movie scene). Tweets posted by tanning salon employees (n=4) were rare and included observations of occurrences in the workplace.

Discussion
Overview
About half of the tweets (589/1165, 50.6%) using the keywords “tanning bed” or “tanning salon” during the COVID-19 pandemic shutdowns in March and April 2020 were not by people who likely use tanning beds. Most of these tweets were mocking people who tan, tanning beds, or the tanned look. The next largest set of tweets (402/1165, 34.5%) seemed to be by people who use tanning beds, as evidenced by their content, which focused on lamenting the inability to tan during the shutdown, expressing the desire for a home tanning bed, expressing positive sentiment about tanning beds, discussing alternative ways to get a tan in the absence of tanning beds, or promoting misinformation.

The finding that only about one-third of tweets (402/1165, 34.5%) appeared to be from indoor tanners is in contrast to a similar investigation by Waring et al [7], where twice the proportion of tweets (699/978, 71.2%) using the same search terms in March 2016 appeared to be from indoor tanners [7]. This finding could be due to declining rates of tanning bed use in recent years [20] or that COVID-19 shutdowns curtailed indoor tanning, which may have decreased chatter about it [20]. Another possibility could be that the proportion of tanning-related tweets that were negative chatter about former US President Donald Trump’s skin color increased from 2016 to 2020 [21-25]. Waring et al [7] found only 10.7% of tweets in 2016 were mocking tanners and the tanned look, compared to 48% (562/1165) of tweets from 2020 in this study. Among tweets that mocked tanners, the vast majority (448/562, 79.7%) mocked former US President Donald Trump, accounting for 38% (446/1165) of all tweets. Criticism of a tan-appearing public figure may shift social norms about indoor tanning for the better or worse, depending on how people feel about that public figure. Perceived social norms strongly predict indoor tanning [26] and increased negative sentiment toward indoor tanning and a tan appearance may shift appearance-related social norms. Future research should explore how negative sentiment on social media about tanned celebrities influences indoor tanning behavior and attitudes.
While most posted tweets lamented the inability to tan, interestingly, very few (16/402, 3.9%) mentioned using tanning alternatives (eg, sunless tanners). Some tanners may have been more interested in gaining access to UV tanning than non-UV tanning, even though the latter was far more accessible. However, those who switched to non-UV tanning may have been less inclined to discuss this on Twitter, perhaps simply because non-UV tanning was more accessible or perhaps to the extent they felt the stigma around admitting to getting a “fake tan”[27,28]. The COVID-19–related shutdowns may have been a missed opportunity to promote sunless tanning products. Because orange-appearing skin was also the focus of tweets mocking Donald Trump (eg, “Trump been in the tanning bed too long? He looks like a Cheeto”), these tweets may have also negatively impacted social norms around sunless tanning products. Many tanners fear sunless tanning products will create an orange appearance because early products had this effect [27,28]. Future research should examine how social norms around tanning beds and sunless tanning are influenced by social media conversations.

The most common type of tweet among tanners expressed that they missed tanning and 39% (260/402) of these mentioned reasons they missed tanning. Appearance-related reasons were by far the most common (77/260, 30%). The increase in the use of videoconferencing software during the COVID-19 pandemic has been shown to have exacerbated appearance-related concerns, leading to an increase in cosmetic surgery consults [29,30]. Because physical appearance is well established to be among the most common reasons people use tanning beds [31,32], future studies should examine how the widespread use of videoconferencing has impacted tanning behavior.

Additional reasons people cited for missing indoor tanning included the positive impact they perceive tanning has on their mood or their discomfort with the negative effect they experience when they are unable to use tanning beds. Research has shown that 8% to 20% of tanners meet criteria for “tanning addiction,” indicators of which may include the experience of mood enhancement from tanning and withdrawal symptoms (eg, irritability) when they cannot tan [33-36]. Future research should explore how the shutdowns may have impacted tanning behavior among people qualifying as “tanning addicted.” The forced period of “cold turkey” could possibly have led some tanners to reduce or quit their tanning habit altogether. Alternatively, when tanning salons reopened, a disinhibition effect may have occurred, such that tanners increased their tanning beyond prepanemic levels after being involuntarily restricted.

Some tweets from tanners (90/402, 22%) expressed their interest in gaining access to a home tanning bed. Future studies should examine whether the small segment of indoor tanners (<10%) who use home beds grew following the pandemic shutdowns [37,38]. The impact of restricted or discouraged access to tanning beds has implications for legislative and public health efforts. For example, Australia banned commercial tanning services in 2016. Governments initiated buyback programs to discourage home tanning bed use in the states of Victoria and New South Wales [39,40]. Afterward, Australian consumer interest in tanning beds declined to less than one-fourth of preban seasonal peaks, but interest in sunless tanning was high [41]. While home tanning beds are still legally marketed in Australia, spray tanning remains more popular [41,42]. Therefore, buyback programs or legislation restricting the sale of home tanning beds may be necessary accompaniments to legislation restricting tanning businesses in the United States.

Unfortunately, we observed very few public health messages regarding the dangers of indoor tanning. Only 2.5% (29/1165) of tweets were of this type, which is even less than the 4.3% that was observed in the previous investigation of tanning bed chatter on Twitter [7]. To be sure, public health efforts were heavily focused on COVID-19 at this time. However, given the misinformation about UV and COVID-19 prevention [14], this would have been an important opportunity to underscore the dangers of indoor tanning. Interestingly, only 5 (0.4%) out of 1165 tweets contained misinformation. Misinformation themes included that UV radiation from tanning beds could kill COVID-19, that UV radiation from the sunbathing could kill COVID-19, and that indoor tanning is healthy to use as therapy. However, because tweets in our study must have contained the words tanning bed or tanning salon, they may not have captured the full range of misinformation circulating about UV and COVID-19.

This study has limitations. Our data capture was limited to 2 common lay terms typically used in the United States to refer to indoor tanning. We may not have captured tweets containing other terms that refer to indoor tanning or tweets about using non-UV tanning alternatives. Additionally, states started reopening at different times during the end of the sampling window, which may have impacted the types of tweets in our sample [43]. Further, we may have captured tweets that were posted by users outside of the United States. Few Twitter users activate their location data [44], so it is difficult to determine where all the tweets originated. As we only coded 1165 tweets from the nearly 5000 unique tweets captured during the sampling window, we may have missed interesting yet rare topics of conversation. Additionally, tanners who were most upset by the shutdowns may have been more likely to tweet about them. Among the 23% of adults in the United States that use Twitter, only 18% reside in rural areas [45,46], so our data may not have captured the full range of sentiment about indoor tanning in rural areas of the United States.

Conclusion

Many indoor tanners appeared to miss indoor tanning during the pandemic shutdown, particularly due to appearance concerns, and some were seeking alternative ways to access tanning beds. We also discovered that, compared to a similar investigation 5 years ago, a much larger percentage of tweets about indoor tanning were very critical of indoor tanning [7]. The use of tanning beds or the appearance of having used them appears to be the target of insults that are often politically motivated on social media. Future research is needed to examine how the pandemic and the surrounding political climate affected tanning behavior and attitudes.
Acknowledgments
This project was supported by the National Institutes of Health (grant K24HL124366; Principal Investigator: SP).

Data Availability
The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions
LG conceptualized the idea, collected and analyzed data, interpreted results, and drafted the manuscript. MEW assisted with conceptualizing idea, supervised analyses, interpreted results, and edited the manuscript. AJB assisted with conceptualizing idea, interpreted results, and edited the manuscript. SB analyzed data, interpreted results, and edited the manuscript. LP interpreted the results and edited the manuscript. SP conceptualized idea, supervised data collection, interpreted results, and edited the manuscript.

Conflicts of Interest
None declared.

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Original Paper

Oral Cannabidiol for Seborrheic Dermatitis in Patients With Parkinson Disease: Randomized Clinical Trial

Isaac Weber1*, MD; Caterina Zagona-Prizio2*, BS; Torunn E Sivesind2*, MD; Madeline Adelman2*, MD; Mindy D Szeto3, MS; Ying Liu3, PhD; Stefan H Sillau3, PhD; Jacquelyn Bainbridge3, PharmD; Jost Klawitter3, PhD; Cristina Sempio3, PhD; Cory A Dunnick2, MD; Maureen A Leehey3, MD; Robert P Dellavalle2,4,5, MSPH, MD, PhD

1Mercy Hospital St. Louis, St. Louis, MO, United States
2Department of Dermatology, University of Colorado School of Medicine, Aurora, CO, United States
3Department of Neurology, University of Colorado School of Medicine, Aurora, CO, United States
4Dermatology Service, Rocky Mountain Regional Veterans Affairs Medical Center, Aurora, CO, United States
5Colorado School of Public Health, Aurora, CO, United States
*these authors contributed equally

Corresponding Author:
Robert P Dellavalle, MSPH, MD, PhD
Dermatology Service
Rocky Mountain Regional Veterans Affairs Medical Center
1700 N Wheeling St, Rm E1-342
Aurora, CO, 80045
United States
Phone: 1 720 857 5562
Email: Robert.dellavalle@ucdenver.edu

Abstract

Background: Seborrheic dermatitis (SD) affects 18.6%-59% of persons with Parkinson disease (PD), and recent studies provide evidence that oral cannabidiol (CBD) therapy could reduce sebum production in addition to improving motor and psychiatric symptoms in PD. Therefore, oral CBD could be useful for improving symptoms of both commonly co-occurring conditions.

Objective: This study investigates whether oral CBD therapy is associated with a decrease in SD severity in PD.

Methods: Facial photographs were collected as a component of a randomized (1:1 CBD vs placebo), parallel, double-blind, placebo-controlled trial assessing the efficacy of a short-term 2.5 mg per kg per day oral sesame solution CBD-rich cannabis extract (formulated to 100 mg/mL CBD and 3.3 mg/mL THC) for reducing motor symptoms in PD. Participants took 1.25 mg per kg per day each morning for 4 ± 1 days and then twice daily for 10 ± 4 days. Reviewers analyzed the photographs independently and provided a severity ranking based on the Seborrheic Dermatitis Area and Severity Index (SEDASI) scale. Baseline demographic and disease characteristics, as well as posttreatment SEDASI averages and the presence of SD, were analyzed with 2-tailed t tests and Pearson χ² tests. SEDASI was analyzed with longitudinal regression, and SD was analyzed with generalized estimating equations.

Results: A total of 27 participants received a placebo and 26 received CBD for 16 days. SD severity was low in both groups at baseline, and there was no treatment effect. The risk ratio for patients receiving CBD, post versus pre, was 0.69 (95% CI 0.41-1.18; P=.15), compared to 1.20 (95% CI 0.88-1.65; P=.26) for the patients receiving the placebo. The within-group pre-post change was not statistically significant for either group, but they differed from each other (P=.07) because there was an estimated improvement for the CBD group and an estimated worsening for the placebo group.

Conclusions: This study does not provide solid evidence that oral CBD therapy reduces the presence of SD among patients with PD. While this study was sufficiently powered to detect the primary outcome (efficacy of CBD on PD motor symptoms), it was underpowered for the secondary outcomes of detecting changes in the presence and severity of SD. Multiple mechanisms exist through which CBD can exert beneficial effects on SD pathogenesis. Larger studies, including participants with increased disease severity and longer treatment periods, may better elucidate treatment effects and are needed to determine CBD’s true efficacy for affecting SD severity.

Trial Registration: ClinicalTrials.gov NCT03582137; https://clinicaltrials.gov/ct2/show/NCT03582137
Seborrheic dermatitis (SD) is related to increased sebum production and an inflammatory response to cutaneous Malassezia, and it affects 18.6%-59% of persons with Parkinson disease (PD) [1,2]. The mechanism connecting these two pathologies is not entirely clear; however, increasing evidence suggests a direct role of Malassezia in the pathogenesis of PD [2]. Other proposed mechanisms include gene polymorphisms, leucine-rich repeat kinase 2 (LRRK2), glucocerebrosidase (GBA), and phosphatase and tensin homolog–induced kinase 1 (PINK1); these have been shown to play a role in lipid regulation and increase the risk for PD in affected individuals [2]. Traditional first-line SD treatment relies on topical antifungals or anti-inflammatory drugs, with systemic therapies reserved for recalcitrant or severe cases, which become more common in patients with immune dysfunction [2]. These systemic therapies, such as oral terbinafine and itraconazole, have numerous side effects, including hepatotoxicity and interactions with concomitant medications [3].

Delta-9-tetrahydrocannabinol (THC) induces a “high,” psychosis, cognitive dysfunction, and anxiety, while cannabidiol (CBD) has been reported to reduce sebum production and improve motor and psychiatric symptoms in PD [2-9]. CBD is likely safer than THC; however, some individuals with PD report the use of both and claim greater benefits from THC [4,10]. After oral consumption, THC travels to the liver, where the majority is eliminated or metabolized into other molecules by cytochrome P450 2C (CYP2C) and CYP3A [11]. The bioavailability of ingested THC is between 4% and 12% [11]. The pharmacokinetics of CBD are complex, and the bioavailability of oral CBD is estimated to be only 6% [11]. In general, the most abundant metabolites of CBD are hydroxylated 7-COOH (7-carboxy) derivatives that are excreted either intact or as glucuronide conjugates [12].

The use of CBD on human sebocytes has been shown to reduce sebaceous gland proliferation and induce anti-inflammatory changes [13]. However, few studies exist evaluating oral CBD’s effect on SD severity. CBD may be beneficial in both PD and SD, and research is needed to define what cannabinoids and doses are useful in both conditions. Based on current literature, an oral formulation with the following combination was pursued: greater CBD than delta-9-THC, with between 150 and 1000 mg CBD, and <10 mg THC daily [4-9,14,15]. This study investigates whether oral CBD therapy is associated with a decrease in SD severity in PD.

Overview
Facial photographs were collected as a component of a randomized, parallel, double-blind, placebo-controlled trial assessing the efficacy of a short-term 2.5 mg per kg per day of oral sesame solution CBD-rich cannabis extract for reducing motor symptoms in PD. The study drug, supplied by the National Institute of Drug Abuse as a frozen extract, was formulated to a 100 mg per mL CBD and 3.3 mg per mL THC sesame oil solution by a PharmD team. The placebo was compounded with United States Pharmacopeia (USP)–grade sesame oil, food coloring, and strawberry extract. ElSohly Laboratories, Inc performed stability, potency, and microbial analyses.

Participants took 1.25 mg per kg per day each morning (approximately 1 mL) for 4 ± 1 days and then twice daily for 10 ± 4 days. To test short-term use, the duration of time on the study drug was at least the minimum time needed for CBD to be at a steady state concentration. The half-life of oral CBD and oral THC is approximately 2 days and 4 hours, respectively [16]. To facilitate the interpretation of effects, cannabinoid plasma levels were documented at the final dose visit.

Eligibility criteria were defined by adults 40-85 years of age with idiopathic PD participating in the above trial and who had concurrent SD. Data were collected from the University of Colorado Hospital from September 2018 to January 2022. The sample size was determined by the number of patients in the trial meeting eligibility criteria. Eligible candidates were randomized 1:1 to the study drug or placebo by a computer-generated randomization schedule, stratified by age (45-60 vs 61-85 years) and modified Hoenh and Yahr scale score (1-2.5 vs 3-5) into blocks of four, with 2 participants per block being assigned to each treatment group [17].

The statistician (author SHS) and the PharmD team were the only unblinded study staff. The statistician generated the random allocation sequence. The statistician notified the lead PharmD (author JB) via encrypted email of the allocation assignment. The appropriate study drug was prepared by the PharmD team within days of the baseline visit. Blinded study staff enrolled participants and provided them with the study drug.

Despite best efforts, the placebo was slightly different in appearance and odor, so procedures were developed to optimize the preservation of the blinding. The design of the study was changed from crossover to parallel; the study drug for each participant was prepared in a brown opaque bottle that was placed into a “masking envelope,” a thick brown postage envelope with plastic bubble wrap lining to obscure odor, and the study drug was administered in a closed, vented room that removes the odor of cannabis within 4 minutes. Blinded study
staff did not enter for at least 10 minutes. Further, the study drug was transported by the participants to their homes and the clinic in the masking envelope.

Deidentified photographs pre- and posttreatment were provided to two board-certified dermatologists to assess along with reference images external to the study. Reviewers analyzed the photographs independently, providing a severity ranking based on the Seborrheic Dermatitis Area and Severity Index (SEDASI) scale, a quantitative grading instrument [18]. Severity scores were averaged between reviewers for the final SEDASI score, and reviewers determined whether each participant’s SD had improved, worsened, or was unchanged. The possible range of scoring is 0 to 60, with 60 being the most severe.

Baseline demographic and disease characteristics were compared between treatment groups with 2-tailed $t$ tests and Pearson $\chi^2$ or Fisher exact association tests. The presence of SD was analyzed longitudinally with generalized estimating equations relative risk models. Covariates of gender, age, and log-scaled PD disease duration were considered as time-interacting covariates. The final CBD blood level was also considered as an adjusting covariate for the posttreatment time point in the CBD group. SEDASI was analyzed with longitudinal regression. The change in SEDASI averages was analyzed with change scores, paired $t$ tests for within-group changes, and a 2-sample $t$ test on the change scores for the difference between groups. The CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines were used and followed in the reporting of this trial [19].

**Ethical Considerations**

The Colorado Multiple Institutional Review Board granted ethical approval (17-2318). All participants provided written informed consent. An independent data and safety monitoring board provided oversight.

**Results**

A total of 27 participants received a placebo and 26 received CBD for 16 days; cannabinoid plasma levels are shown in Table 1. Baseline participant characteristics were similar between groups for most variables, although the study drug group trended toward longer disease duration ($P=.07$) and higher total Movement Disorders Society Modified Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) score ($P=.08$), but this was not significant. There were no effects on orthostatic blood pressure, heart rate, or temperature, comparing before the first study medication dose to the final dose and comparing before a dose to 1-3 hours afterward. There were also no notable changes in blood laboratory studies, including liver tests. The study drug was tolerated with no unexpected and serious adverse effects and no significant dermatological adverse events. SD severity was low in both groups at baseline, and there was no treatment effect, as shown in Table 2. Generalized estimating equation regression analysis, where final blood level of CBD was included as an explanatory variable and for which there were 26 patients receiving CBD and 27 patients receiving placebo with data, revealed that CBD treatment trended toward reducing the presence of SD compared with the placebo ($P=.07$ at the mean CBD final blood level of 49.29 ng/mL) because there was an estimated improvement for the CBD group and an estimated worsening for the placebo group, but this finding did not reach statistical significance. The estimated prevalence post-pre ratio of SD in the CBD group was 0.69 (95% CI 0.41-1.18; $P=.15$), compared to 1.20 (95% CI 0.88-1.65; $P=.26$) in the placebo group.
Table 1. Demographic characteristics and presence of seborrheic dermatitis for patients with Parkinson disease in oral cannabidiol (CBD) and placebo treatment groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CBD (n=26)</th>
<th>Placebo (n=27)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SE; SD)</td>
<td>70.6 (1.2; 6.3)</td>
<td>68.7 (1.4; 7.5)</td>
<td>.34</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (38)</td>
<td>7 (26)</td>
<td>.33</td>
</tr>
<tr>
<td>Male</td>
<td>16 (62)</td>
<td>20 (74)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>26 (100)</td>
<td>26 (96)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>25 (96)</td>
<td>28 (96)</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Disabled, permanently or temporarily</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>20 (77)</td>
<td>21 (78)</td>
<td></td>
</tr>
<tr>
<td>Working now</td>
<td>4 (15)</td>
<td>4 (15)</td>
<td></td>
</tr>
<tr>
<td>Partly retired</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Retired, still involved in business</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Divorced</td>
<td>4 (15)</td>
<td>4 (15)</td>
<td></td>
</tr>
<tr>
<td>Living with partner</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>21 (81)</td>
<td>21 (78)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Duration of PD&lt;sup&gt;b&lt;/sup&gt; (years), mean (SE; SD)</td>
<td>6.6 (1.3; 6.8)</td>
<td>4.6 (0.8; 4.0)</td>
<td>.19</td>
</tr>
<tr>
<td><strong>Dosing&lt;sup&gt;c&lt;/sup&gt;, mean (SD; SE)</strong></td>
<td></td>
<td></td>
<td>N/A&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Final CBD dose (mg/day)</td>
<td>187.50 (56.68; 11.12)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Final THC&lt;sup&gt;e&lt;/sup&gt; dose (mg/day)</td>
<td>6.28 (1.90; 0.37)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>CBD level at final dose visit (ng/mL)</td>
<td>49.29 (32.85; 6.44)</td>
<td>0.00 (0.00; 0.00)</td>
<td></td>
</tr>
<tr>
<td>THC level at final dose visit (ng/mL)</td>
<td>0.85 (0.91; 0.18)</td>
<td>0.00 (0.00; 0.00)</td>
<td></td>
</tr>
<tr>
<td>Time on study drug (days), mean (SD; SE)</td>
<td>15.5 (1.8; 0.3)</td>
<td>16.2 (1.6; 0.3)</td>
<td>.15</td>
</tr>
</tbody>
</table>

<sup>a</sup>Two-tailed t tests and Pearson χ<sup>2</sup> or Fisher exact association tests.

<sup>b</sup>PD: Parkinson disease.

<sup>c</sup>Blood levels reflect 26 participants in the CBD group and 17 in the placebo group. Blood levels were not obtained for 3 participants in the CBD group and 2 in the placebo group.

<sup>d</sup>N/A: not applicable.

<sup>e</sup>THC: tetrahydrocannabinol.
Table 2. Results for patients with Parkinson disease in oral cannabidiol (CBD) and placebo treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of seborrheic dermatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a, n (%; 95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBD</td>
<td>12 (46.2; 30.5-69.9)</td>
<td>9 (34.6; 20.4-58.7)</td>
<td>.26</td>
</tr>
<tr>
<td>Placebo</td>
<td>15 (55.6; 39.7-77.9)</td>
<td>18 (66.7; 51.1-87.0)</td>
<td>.26</td>
</tr>
<tr>
<td>Treatment effect</td>
<td>N/A</td>
<td>N/A</td>
<td>.12</td>
</tr>
<tr>
<td>SEDASI c average d, mean (95% CI; SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBD</td>
<td>3.63 (1.41-5.86; 5.50)</td>
<td>3.79 (1.38-6.20; 5.96)</td>
<td>.81</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.39 (2.75-8.03; 6.68)</td>
<td>4.65 (2.76-6.54; 4.77)</td>
<td>.35</td>
</tr>
<tr>
<td>Treatment effect</td>
<td>N/A</td>
<td>N/A</td>
<td>.38</td>
</tr>
</tbody>
</table>

aPresence of seborrheic dermatitis indicates patients exhibiting any signs of seborrheic dermatitis after assessing the final SEDASI score. Numbers calculated for generalized estimating equation model with log link (ie, relative risk model with repeated measures).

bN/A: not applicable.

cSEDASI: Seborrheic Dermatitis Area and Severity Index.

dSEDASI average is calculated by averaging the two scores assigned by independent reviewers to each patient.

Discussion

Principal Findings

This study does not provide solid evidence that oral CBD therapy reduces the presence of SD among patients with PD. While this study was sufficiently powered to detect the primary outcome (efficacy of CBD on PD motor symptoms), it was underpowered for these secondary outcomes of detecting changes in the presence and severity of SD. CBD has shown significant promise in improving SD in a topical form; however, no current literature exists to evaluate its effect when taken orally [20].

The pathophysiology of SD is still not entirely understood, but the colonization of *Malassezia* is strongly associated with the condition [1]. *Malassezia* is found on sebum-rich skin, and its metabolites have been shown to induce inflammation and stimulate keratinocyte differentiation, resulting in dysfunction in the stratum corneum, a disruption of the epidermal barrier, and perpetuation of an inflammatory response, leading to a cycle of more skin barrier disruption and the clinical manifestations of SD [21-23].

CBD possesses the ability to inhibit the lipogenic action of arachidonic acid, linoleic acid, and testosterone in human sebocytes; in addition, it has been shown to suppress seocyte proliferation via ion channel activation [13,24]. CBD also possesses anti-inflammatory properties through the inhibition of nuclear factor kappa B (NF-κB) and signaling and upregulation of tribbles pseudokinase 3 (TRIB3) [13]. These mechanisms help explain its success in improving SD symptoms with topical therapy and provide a strong impetus for further study with oral CBD and SD.

Limitations

Limitations include study drug availability constraints, limiting the time participants were on the study drug. A 16-day treatment period may not have been long enough to achieve maximal clinical benefit. Additionally, although the prevalence of SD for study participants was similar to existing estimates, low levels of disease severity in the cohort, both pre- and posttreatment, posed a challenge for assigning scores and may have impacted the reviewers’ ability to detect change. Possible confounders include participants’ concurrent topical medication use, which also hinders the interpretation of the findings.

Conclusion

Larger studies, including participants with increased disease severity and with longer treatment periods, may better elucidate treatment effects and are needed to determine CBD’s true efficacy for SD severity. Oral CBD has shown promise in improving Parkinsonian symptoms; therefore, if future studies can elicit improvement in SD as well, it could act as a useful adjunct for patients struggling with PD to improve both neurologic and common cutaneous symptoms.

Acknowledgments

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The authors would like to acknowledge Elizabeth Wallace for her role as a tiebreaker in the evaluation of participant photos.
**Conflicts of Interest**

RPD is the editor in chief of JMIR Dermatology. RPD receives editorial stipends (JMIR Dermatology), royalties (UpToDate), and expense reimbursement from Cochrane. TES and MA received fellowship funding from Pfizer. TES receives fellowship funding from the NIH (grant ST32AR007411-37; principal investigator: Dennis Roop).

Multimedia Appendix 1
CONSORT (Consolidated Standards for Reporting Trials) checklist.

[PDF File (Adobe PDF File), 104 KB](https://derma.jmir.org/2024/1/e49965) [derma_v7i1e49965_app1.pdf]

References


Abbreviations

7-COOH: 7-carboxy
CBD: cannabidiol
CONSORT: Consolidated Standards of Reporting Trials
CYP2C: cytochrome P450 2C
GBA: glucocerebrosidase
LRKK2: leucine-rich repeat kinase 2
MDS-UPDRS: Movement Disorders Society Modified Unified Parkinson’s Disease Rating Scale
NF-κB: nuclear factor kappa B
PD: Parkinson disease
PINK1: phosphatase and tensin homolog–induced kinase 1
SD: seborrhoeic dermatitis
SEDASI: Seborrhoeic Dermatitis Area and Severity Index
THC: tetrahydrocannabinol
TRIB3: tribbles pseudokinase 3
USP: United States Pharmacopeia

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Barriers and Facilitators to Teledermatology and Tele-Eye Care in Department of Veterans Affairs Provider Settings: Qualitative Content Analysis

Yiwen Li1, MS; Charlene Pope2, PhD; Jennifer Damonte3, MA; Tanika Sapers3, MPH; April Maa3,4, MD; Suephy Chen5, MS, MD; Howa Yeung1,3, MSc, MD

1Department of Dermatology, Emory University School of Medicine, Atlanta, GA, United States
2Charleston Veterans Affairs Health Equity and Rural Outreach Innovation Center, Ralph H. Johnson Veterans Affairs Health Care System, Charleston, SC, United States
3Clinical Resource Hub, Veterans Affairs Veterans Integrated Service Network 7, Atlanta, GA, United States
4Department of Ophthalmology, Emory University School of Medicine, Atlanta, GA, United States
5Department of Dermatology, Duke University School of Medicine, Durham, NC, United States

Abstract

Background: Veterans Affairs health care systems have been early adopters of asynchronous telemedicine to provide access to timely and high-quality specialty care services in primary care settings for veterans living in rural areas. Scant research has examined how to expand primary care team members’ engagement in telespecialty care.

Objective: This qualitative study aimed to explore implementation process barriers and facilitators to using asynchronous telespecialty care (teledermatology and tele-eye care services).

Methods: In total, 30 participants including primary care providers, nurses, telehealth clinical technicians, medical and program support assistants, and administrators from 2 community-based outpatient clinics were interviewed. Semistructured interviews were conducted using an interview guide, digitally recorded, and transcribed. Interview transcripts were analyzed using a qualitative content analysis summative approach. Two coders reviewed transcripts independently. Discrepancies were resolved by consensus discussion.

Results: In total, 3 themes were identified from participants’ experiences: positive perception of telespecialty care, concerns and challenges of implementation, and suggestions for service refinement. Participants voiced that the telemedicine visits saved commute and waiting times and provided veterans in rural areas more access to timely medical care. The mentioned concerns were technical challenges and equipment failure, staffing shortages to cover both in-person and telehealth visit needs, overbooked schedules leading to delayed referrals, the need for a more standardized operation protocol, and more hands-on training with formative feedback among supporting staff. Participants also faced challenges with appointment cancellations and struggled to find ways to efficiently manage both telehealth and in-person visits to streamline patient flow. Nonetheless, most participants feel motivated and confident in implementing telespecialty care going forward.

Conclusions: This study provided important insights into the positive perceptions and ongoing challenges in telespecialty care implementation. Feedback from primary care teams is needed to improve telespecialty care service delivery for rural veterans.

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KEYWORDS
telemedicine; dermatology; eye; implementation science; stakeholder participation; veterans’ health

Introduction
The use of telemedicine has been steadily increasing and has expanded rapidly during the COVID-19 pandemic [1]. Veterans’ health care systems have been early adopters of asynchronous telemedicine, also known as the store-and-forward mode of consultation and sometimes referred to as “eConsult” or “eTriage.” In this approach, a brief clinical history and images are collected during an in-person primary care visit at a community-based outpatient clinic. These records are subsequently transmitted to telespecialists at a distant site for evaluation, and the results are communicated to the patient by the referring primary care provider (Figure 1). Patients with additional needs are identified through this process for expedited treatment. In this manner, veterans are provided timely access to high-quality specialty care services in primary care settings, especially in rural areas [2].

With an emphasis on visual diagnosis, asynchronous telemedicine is well-suited for Teledermatology and Technology-Based Eye Care Services [3]. However, concerns have been raised to adopt telemedicine for specialty care on a larger scale, as certain sites may be disadvantaged with the lack of clinical resources and administrative experience in implementing complex programs. The goal of this qualitative study is to better understand implementation process facilitators and barriers to telemedicine use for specialty care.

Methods
Study Design
Between October 2, 2020, and January 31, 2021, we conducted in-depth interviews with primary care providers, nurses, telehealth clinical technicians, medical and program support assistants, and administrators from 2 community-based outpatient clinics and distant reading sites. Semistructured interviews (interview guide detailed in Textbox 1) aimed to explore perspectives, identify telespecialty care facilitators and barriers, and derive solutions from community-based outpatient clinics [4]. A trained interviewer (TS) conducted 30 individual telephone interviews lasting 30-60 minutes, with digital audio recording and participant consent. Interviews were transcribed professionally and deidentified. Qualitative content analysis followed a summative approach [5] with latent content analysis for underlying meanings and patterns. Coders (CP and JD) independently reviewed transcripts, resolving discrepancies by consensus. Diagramming mapped conceptual relationships across stakeholder perceptions to identify facilitators, barriers, and solutions.

Figure 1. Asynchronous telehealth referral flowchart. In-patient primary care evaluation determines patient management by the PCP or referral to a specialist. If a specialist is needed, the PCP decides between in-person specialist clinic or tele specialty care. For tele specialty care, clinical data and images are sent to the telespecialist for analysis. The results are then communicated by the PCP to the patient, speeding up further treatment processes. PCP: primary care physician.
Textbox 1. Qualitative interview questions.

Q1. What percentage of your time is dedicated to TECS (Technology-Based Eye Care Services) or TD (Teledermatology), as compared to face-to-face care?
Q2. How do you feel about TECS or TD at our location?
Q3. How motivated or committed do you feel your site is in implementing TECS or TD?
Q4. How ready do you feel your site is, to implement TECS or TD?
Q5. What has been your experience in working with the regional telehealth service reading hub, in which veterans' images taken at your CBOC (community-based outpatient clinic) or site are interpreted by a clinician outside of your site?
Q6. What worked well in facilitating implementation of TECS or TD at your site?
Q7. What types of data or reports were helpful in facilitating implementation of TECS or TD at your site?
Q8. What issues or barriers have you experienced in implementing TECS or TD at your site?
Q9. What have been some unintended consequences following implementation of TECS or TD at your site?
Q10. How were challenges in implementation of TECS or TD managed at your site?
Q11. What changes do you recommend in sustaining TECS or TD at your site?
Q12. What recommendations would you offer to other CBOC sites providing, or considering providing, TECS or TD?
Q13. Please share any additional thoughts or information that you would like us to know.

Ethical Considerations

This study received approval from the Emory University Institutional Review Board (STUDY00000383) on June 3, 2020, and from the Atlanta Veterans Affairs (VA) Medical Center Research and Development Committee. The results are reported in accordance with COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines [6]. All participants provided verbal informed consent prior to the study conduct, and participant data were deidentified. No compensation was provided to the participants.

Results

Overview

Of the 30 participants, a total of 27 (90%) had experienced the hybrid format of telespecialty encounters, where patients visited the community-based outpatient clinic site for image acquisition during the study period, and 3 (10%) had in-person visits only. Interviews identified two primary facilitators to telespecialty care: (1) positive perception of telespecialty care and (2) optimized implementation processes (task lists, deadlines, and bringing together multiple capable diverse stakeholders in regular meetings).

Positive Perception of Telespecialty Care

Overview

Stakeholders from various roles provided insights indicating positive telespecialty care experiences reported by veterans (domain I). Telemedicine saved commute and waiting times, enhancing access for rural veterans (domain II). The telespecialty care programs are regarded to provide good quality of care (domain III). Telespecialty care increased resources for routine care, saved appointments at the main facility, and allowed VA health care to receive more workload credit (domain IV).

Domain I: Patient Satisfaction

Patient satisfaction is the first domain emerging from interviews. Interviewees speculated about the reasons, but all stated that patients were satisfied with the services they received. One participant explained:

I don’t know if it’s because we’re more accessible right now, that may be the reason. But they all seem to be very satisfied with their care and feel like they’ve got a very good exam.

Another participant explained that:

[The patients] love this. Having the specialty Technology-based Eye Care Services and then being able to come to a clinic in their community to pick up their glasses, all their services they need for their eyes are done in one stop shop.

The interviews highlighted the patient satisfaction benefits of the Teledermatology and Technology-Based Eye Care Services programs.

Domain II: Access

Overview

Access was a frequently discussed domain in the interviews. Participants believed telespecialty care services increased veterans’ health care access, especially benefiting those in rural areas. Factors contributing to this enhanced access included travel (distance and time), timely care, and integration with primary care.

Travel

Telespecialty care programs at local community–based outpatient clinics offer improved health care access compared to traveling to a main VA facility with on-site specialty care. With more community–based outpatient clinic locations than main VA facilities, traveling distance and time for veterans are reduced. One participant highlighted the challenges and difficulties veterans faced when seeking specialty care.
Technology-based Eye Care Services is very helpful when it’s out in rural areas ... Dermatology as well. You know, I think a lot of times people go under the assumption that everybody is close by, that there’s a VA everywhere and that if there’s a VA in your community and your community is small enough for you to get to that VA within 30-45 minutes or maybe an hour; I think that having forward thinking or being very realistic would help because some people travel, you know, three or four hours, to get to their clinic.

Telespecialty care services provided at community-based outpatient clinic locations enable veterans to receive crucial care without burdensome travel.

Timely Care
The main VA medical centers provide various services from annual checkups to major surgeries. However, these centers frequently have long waitlists due to the limited providers and availabilities. Telespecialty care services at community-based outpatient clinics help reduce wait times and enable timely care. One interviewee stated that:

... the speed that we’re able to provide the care is better. So instead of waiting for the patient to have an appointment in a face-to-face grid with limited access, we’re using these technologies at all of our sites and the time that passes between the patient needing the care, the provider consulting for the care, and then receiving it, it decreases a great deal.

Further, wait times for community-based outpatient clinic appointments tend to be shorter than the main VA medical centers. One interviewee revealed:

... mostly about the technicians that they see, the fact that they were able to quickly get in and out. It wasn’t a long wait time for them. Usually with eye exams, they have to wait maybe between two and four hours when they go to the main hospital, so that’s a big plus.

Convenient Access Integration Into Primary Care or In-House Service
Another benefit that telespecialty care provides at community-based outpatient clinic locations is the ease of referrals from primary care providers. Community-based outpatient clinics provide the most common outpatient services (eg, primary care) and typically lack in-house specialty care providers. When patients require ophthalmology or dermatology referrals, they typically need to make an appointment at the main VA medical center community clinics. With telespecialty care programs at a community-based outpatient clinic, patients can often undergo specialty care imaging acquisition during the same visit as their primary care appointment.

One interviewee stated:

... from the Derm aspect. If it was something that, say, the primary physician sees while they’re there physically in the clinic or face-to-face, they can immediately put in a Teledermatology consult while the patient is at the clinic and the patient doesn’t have to come back for a second trip to the clinic.

This remote access reduces the burden on the patients for having to return to the clinic for follow-up care. One of the primary care physicians provided:

Many of our veterans did not want to travel the sometimes 40 to sometimes 1 ½ hour commute between traffic and the time of day. And so to be able to have a dermatology and ophthalmology consultation at the local site, was very convenient for the veteran population that we served.

The integration with primary care clinics at community-based outpatient clinics adds even more convenience to patients, and they can get “one-stop shop” health care.

Domain III: Quality of Care
Teledermatology and Technology-Based Eye Care Services provide telespecialty services with improved access while maintaining quality of care comparable to in-person care, meeting their goal of providing veterans with high-quality specialty care in a timely manner.

One interviewee pointed out:

... as far as [she] know[s] about it, it provides the same quality of care as a face-to-face visit would.

Other interviewers echoed this and stated:

I feel the quality of care is excellent.

One of the participants posits:

It would be nearly impossible for me to replicate the quality of care that I get from the Technology-based Eye Care Services.

Domain IV: Workload Credit
The last domain relates to how the telespecialty care programs benefit the VA. Teledermatology and Technology-Based Eye Care Services effectively triage patients into those who can be managed remotely, thereby freeing up appointments for patients needing face-to-face care. One interviewee explained that:

They were able to stream-line the process so that only those who have cancerous appearing lesions could be brought to the medical center and so therefore you were able to get to the greatest number of veterans that truly needed that service.

Optimized Implementation Process
Overview
Communication process emerged as a central theme for successful telespecialty care program implementation. The implementation team’s engagement approach, communication, and availability at regular and frequent huddles to work through issues were viewed as important. The implementation team lead functioned as an ally and integrated as part of the site team. Clinical staff found communication between the site and the implementation team to be important. One interviewee stated:

Two-way communication on a day to day, week to week, month to month basis was very helpful.
Regularly scheduled meetings are a crucial aspect of implementing a successful program launch. By providing structure and opportunities to discuss progress and overcome barriers, these meetings are essential for tracking progress and achieving objectives. Key stakeholders from local VA departments participate in these meetings, ensuring that all necessary perspectives are considered. According to one interviewee, the involvement of stakeholders from different departments facilitates efficient communication and problem-solving:

It is good because it’s several different people from different locations that are tackling it. I feel like everybody that connects are different people, so if one person doesn’t know exactly who to speak to, someone else may know, and so we can get it done pretty quickly.

Regular engagement with stakeholders from various departments helps to streamline operations and minimize delays while also promoting collaboration and a shared sense of purpose. This can lead to increased efficiency as well as a greater focus on shared goals and objectives.

**Concerns and Challenges of Implementation**

Participants voiced concerns about technical challenges, staffing shortages to cover both in-person and telehealth visit needs, overbooked schedules leading to delayed referrals, the need for a more standardized operation protocol, and more hands-on training with formative feedback among supporting staff. Participants also faced challenges with appointment no-shows and last-minute cancellations and struggled to find ways to efficiently manage both telehealth and in-person visits to streamline patient flow.

**Domain I: Staffing**

Staffing presented a barrier when sites were limited in size and limited trained telehealth clinical technicians or their turnover, as these 2 participants portrayed:

- **My facility is a small community-based outpatient clinic and we have four nurses and four nurses are required to triage patients and we’re going to have to have one of those nurses dedicated to doing the tele-imaging, then that’s going to be a barrier for that clinic.**

- **I feel like we need to have more imagers trained. So basically, if someone calls in sick, Teledermatology just shuts down. We have to have a backup plan.**

**Domain II: Scheduling**

Participants described difficulty with scheduling due to telespecialty care appointment cancellations:

- **Because a clinic has been canceled so many times due to equipment failure and patients being rescheduled, it kind of clogged up the availability, you know, it ran availability out more than 30 days, so a patient is not able to get to a clinic that’s close by them at times so there was an issue, or there is an issue with that. That’s an ongoing issue with Technology-based Eye Care Services.**

Among the unintended consequences of the implementation of Teledermatology and Technology-Based Eye Care Services was the additional time required for scheduling, as extra visits were added for referrals from primary care.

**It did impact face-to-face care from a primary care perspective because we were the face for Teledermatology and Technology-based Eye Care Services ... the prerequisite is that the primary care physicians were the ones who were submitting the consults. So, it required us to at least see that’s going on. And so, it was an additional visit with us that we had to fit in outside of maybe a normally scheduled primary care visit.**

At the heart of scheduling, a technician advised that referrals of complex patients with multiple morbidities can be a barrier:

- **Not everybody is a candidate for the program; If they have multiple diseases, if they have certain levels of complications, they’re not suited for the Technology-based Eye Care Services program, and they shouldn’t be scheduled because then they wait to see you and then they’ve got to wait to see somebody else because you couldn’t do what they needed to have done. So, there are several little things that can really wreak havoc on a day and on a schedule.**

**Domain III: Equipment**

Equipment failure was seen as increasing wait times, causing appointment cancellations and rescheduling. One huge barrier was streamlining the reporting process for equipment failure, involving cameras, computers, dermatoscopy, and nonmydriatic fundus photography equipment. With equipment failure or technician absence, veteran care was canceled, and no accurate estimation could be given to schedule the next available appointment, as illustrated by this participant:

- **And equipment failure leads to wait time, longer wait times, and patients having to be cancelled and rescheduled, and a lot of times these patients are coming from, you know, 30, 40, 50, 70 miles away. So when you have to push back their appointment time or cancel it altogether, it gets very frustrating for the veterans and for the technicians.**

**Domain IV: Protocol**

Participants also observed a need for specific personnel delegation and a standard operating protocol in place for troubleshooting:

- **There is a need. It’s a great program, but that way, no matter what role you’re in, and if you get looped in, you know, if you don’t have the key people in place, you might just have something to go by, just like a checklist, would be my only recommendation as far as that goes.**
Domain V: Training

Training was identified as an ongoing need that affects service provision. Training needs to concentrate on orienting staff at all levels, including those not directly performing Teledermatology and Technology-Based Eye Care Services on the scope of telespecialty care practices. The awareness of the programs will enable them to make the best use of the services, as this technician describes:

... because the Technology-based Eye Care Services program is a new way of providing eye care, and the other departments not really being familiar with what we do, there was a period of months where it took, I felt like longer, than expected to help the staff understand what we provided.

Discussion

Principal Findings

This study identified facilitators and potential challenges to telespecialty care implementation through summative content analysis, highlighting the complexity of telespecialty care as an intervention to bridge the access issue for veterans. In line with these findings, recommendations provided inTextbox 2 further complement this study, offering actionable steps for improving the implementation of telespecialty care.

Textbox 2. Telespecialty care implementation recommendations.

<table>
<thead>
<tr>
<th>Staffing</th>
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<tbody>
<tr>
<td>• Ensure telespecialty care technicians are not simultaneously assigned regular clinical duties.</td>
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<tr>
<td>• Train additional telehealth technicians and standardize backup plans for staff absences.</td>
</tr>
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<table>
<thead>
<tr>
<th>Scheduling</th>
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<tbody>
<tr>
<td>• Implement real-time scheduling to optimize time use with appointment cancellations.</td>
</tr>
<tr>
<td>• Streamline referral process from primary care providers to reduce redundant appointments.</td>
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<tr>
<td>• Review patient suitability for telespecialty care.</td>
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<tr>
<th>Equipment</th>
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<tr>
<td>• Standardize plan for maintaining software access, reporting and troubleshooting equipment failure, and purchasing new equipment.</td>
</tr>
<tr>
<td>• Identify backup plans for care continuation during equipment or software downtime.</td>
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<table>
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<tr>
<th>Protocol</th>
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<tbody>
<tr>
<td>• Standardize personnel delegation in telespecialty care.</td>
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<table>
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<tr>
<th>Training</th>
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<tr>
<td>• Train all staff regularly on the scope and practices of telespecialty care.</td>
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<tr>
<td>• Promote awareness of telespecialty care across departments.</td>
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<th>Others</th>
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<tr>
<td>• Implement a feedback system using patient and staff surveys to identify areas for improvement.</td>
</tr>
<tr>
<td>• Develop and iterate for regular communication and feedback mechanisms within the program.</td>
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</tbody>
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Comparison to Prior Work

Our findings are consistent with previous research, providing further support for the numerous advantages of telespecialty care for patients. In line with existing literature [7-11], this study highlights that telespecialty care offers several facilitators, including improved efficiency, convenience, and reduced travel and wait times. Telespecialty care enhances access to health care, especially for underserved areas, enabling access to specialized services [12-16] and addressing emergent conditions that patients may not have initially recognized [17]. Specifically, using store-and-forward teledermatology offers comparable effectiveness to in-person assessment, significantly reduces travel time, and expedites management [18].

Organizational barriers stemming from staffing shortages and lack of designated personnel hindered telespecialty care implementation. This barrier was exacerbated by the clinic's unmodified workflow, forcing nurses with in-person duties to take on extra work for telespecialty appointments. Consistent with our findings, a study examining the perspectives of primary care physicians on telespecialty care referral reported that teledermatology can disrupt the existing in-person workflow [13]. In situations where staffing shortages occurred, informal temporary workaround strategies were frequently used to handle exceptions to normal workflow [19]. However, reliance on workaround strategies added to the already heavy workload of staff members, as they attempted to manage the demands of telespecialty care within their existing schedules. While workarounds are commonly used in medical settings, it is important to recognize that they have the potential to increase the occurrence of medical errors [20] and place additional strain on clinics with limited resources [21].
This study highlights the criticality of establishing standardized protocols and providing ongoing training for the successful telespecialty care implementation. Stakeholders emphasized the need for protocols to guide troubleshooting and equipment failure and ensure consistent practices. These findings align with existing research, which consistently identifies limited technological knowledge, skills, and a lack of education and training as significant barriers to the implementation and acceptance of telemedicine interventions [22,23]. Furthermore, effective planning for equipment maintenance is paramount to ensure the efficient and effective provision of telespecialty care [24]. Previous research investigating the challenges of maintaining eye care equipment revealed that equipment breakdowns led to frustrating delays in conducting proper examinations and increased the risk of disease progression, resulting in poorer treatment outcomes [25]. Therefore, implementing regular maintenance protocols and establishing contingency plans are critical for minimizing disruptions and optimizing the delivery of telespecialty care.

This study reveals an increase in administrative workload for primary care providers and their support staff due to the surge in specialty care referrals. This underscores the complexities and unintended consequences of telespecialty care implementation, particularly the challenge of managing this heightened workload within limited time constraints [26]. The amplified workload pressures from specialty care referrals have compelled health care professionals to dedicate more time to collecting comprehensive patient histories for teleconsultation referrals. This additional time investment is crucial for maintaining the quality of telehealth consultations and preventing potential errors [27]. Our findings align with broader literature concerns about the workload burden imposed by administrative tasks in telehealth, emphasizing potential consequences, such as system failures, resulting from increased workload [27].

**Strengths and Limitations**

This study has several limitations. First, the use of convenience sampling and unequal sample sizes across stakeholder groups may have introduced selection bias into this study. Additionally, participant perspectives were obtained solely from Teledermatology and Technology-Based Eye Care Services providers at the 2 referring sites within the VA Southeastern Network, which may not be representative of other health care settings, potentially limiting the generalizability of the findings. Future patient interviews may provide additional perspectives on telespecialty care to supplement our providers’ perspectives.

**Future Directions**

Implementation of telespecialty care should apply implementation science framework to align technology, people, organizations, and context and to add value to patient care and health care systems [28]. Adapting a learning system approach that continually improves telespecialty care implementation is needed to account for health care system complexity and different user needs and to avoid unintended consequences and challenging workflow issues [28-32]. This study provided insights into the intricacies of telespecialty care implementation, shedding light on both facilitators and barriers encountered in the delivery of these services. Addressing these challenges and opportunities has the potential to increase access to care, enhance the quality of care provided, and promote the sustainability of telespecialty care innovations.

**Acknowledgments**

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**Authors’ Contributions**

All authors made substantial contributions to the conception and design, acquisition of data, analysis, and interpretation of data; were involved in drafting the paper and revising it critically for important intellectual content; and gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

**Conflicts of Interest**

None declared.

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research

VA: Veterans Affairs

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The Value of Teledermatology Advice for Skin Toxicity in Oncology: Experience From a Pilot Study

Sofie Mylle1,2*, MD; Jorien Papeleu1,2*, MD; Isabelle Hoorens1,2, MD, PhD; Evelien Verhaeghe1,2, MD, PhD; Lieve Brochez1,2, MD, PhD

1Dermatology Department, Ghent University Hospital, Ghent, Belgium
2Cancer Research Institute Ghent, Ghent, Belgium
* these authors contributed equally

Corresponding Author:
Lieve Brochez, MD, PhD
Dermatology Department
Ghent University Hospital
Corneel Heymanslaan 10
Ghent, 9000 Belgium
Phone: 32 9 332 21 11
Fax: 32 9 332 21 11
Email: lieve.brochez@ugent.be

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KEYWORDS
e-health; teledermatology; oncology; epidermal growth factor receptor; EGFR-inhibitors; skin toxicity; cancer; dermatology; therapy; pilot study

Introduction
Epidermal growth factor receptor (EGFR) inhibitors are increasingly used in oncologic treatments. Skin toxicity is a possible side effect and can seriously impair quality of life (QoL) and result in treatment tapering or discontinuation [1-4]. Despite several preventive and treatment guidelines, oncologists encounter difficulties in managing skin toxicities [5,6]. In Belgium, this struggle is compounded by some hospitals having no or only part-time in-house dermatologists. We initiated a teledermatology pilot project in 3 Belgian hospitals with no or limited access to dermatological advice and evaluated its value in anti-EGFR–induced skin toxicity for both patients and oncologists.

Methods
Overview
Patients receiving anti-EGFR treatment and developing skin toxicity were eligible. Clinical imaging data were exchanged through an existing secured platform (Mediris). Three oncologists from 3 different Belgian nonuniversity hospitals participated. Clinical information and images were uploaded to the platform and sent to the teledermatologists. Three dermatologists from Ghent University Hospital were involved as teledermatologists and formulated their advice within 48 hours. Questionnaires on expectations and satisfaction with the teledermatology platform were completed by both patients and oncologists at the start and end of the study.

Ethical Considerations
Ethical approval was obtained from Ghent University Hospital (EC2018/0984) and participating hospitals, and participants provided written informed consent.

Results
The study started in January 2019 and was prematurely terminated in mid-March 2020 because of the COVID-19 pandemic. In total, 35 store-and-forward consultations were performed for 6 patients. The most frequent reasons for advice involved xerosis or eczema (n=27, 77%) and papulopustular rash (n=18, 51%). All patients had grade 2 toxicity according to the CTCAE (Common Terminology Criteria for Adverse Events; version 5.0).

Three out of 6 patients completed the questionnaires; they were overall positive about the project and felt that teledermatology was reliable, valuable, and efficient. Although all the participating oncologists reported difficulties in accessing dermatological advice, they used the teledermatology platform less than anticipated. They all reported uploading of images and patient information to be difficult and time-consuming.
Nevertheless, the oncologists noted that teledermatology was as valuable (1/3) or more valuable (2/3) than expected.

In 37% (13/35) of all teleconsultations, teledermatologists reported that more information was needed to provide tailored advice. In 29% (10/35) of consultations, teledermatologists indicated that a live consultation would have been relevant, either to collect additional information for decision-making or to explain and motivate the patient about a specific treatment.

**Discussion**

Although skin toxicity during anti-EGFR treatment might be considered a minor, non–life-threatening side effect, it is known to markedly impact patients’ QoL. This may lead to dose tapering or early treatment discontinuation, thereby potentially interfering with its anticancer effects [1-4]. Skin toxicity is reported as being more discouraging than complete hair loss and as discouraging as nausea [6]. Oncologists intend to initiate skin-focused treatment in cases of skin toxicity of grades 2 and 3 and only refer 8% of their patients for specialized dermatological advice [4]. This small multicenter pilot study aimed to investigate the value of teledermatology to facilitate dissemination of dermatological advice to patients treated with EGFR inhibitors.

From January 2019 until mid-March 2020, overall 35 teleconsultations were provided to 6 patients. Images and clinical information were uploaded to a secured eHealth platform and evaluated by a teledermatologist within 48 hours. Unfortunately, the enrollment was lower than anticipated, most probably because the teledermatology platform was perceived as non–user-friendly. The teledermatologists reported clinical information to be missing in about one-third of the teleconsultations. They indicated the lack of direct communication to promote diagnostic accuracy and therapeutic adherence. A suggested workflow is depicted in **Figure 1**.

Store-and-forward teledermatology has been shown to be able to improve the efficiency of and access to care [7]. The COVID-19 lockdown has demonstrated that teledermatology can help in minimizing unnecessary in-person visits. Many skin conditions may be adequately managed remotely, while others may be selected for an additional step (triaging). This could imply a physical or video consultation to advise patients in other hospitals or at home.

Although several guidelines on skin toxicity management are available, skin toxicity and its impact on QoL seem not always properly recognized. Teledermatology may offer benefits including reduced waiting times, travel costs and sanitary costs, and equalization of access to specialist advice. In this pilot study, both oncologists and patients acknowledged the added value of teledermatological advice on skin toxicity during anti-EGFR therapy. However, several shortcomings of a store-and-forward consultation are revealed. More specifically, the importance of a practical teleplatform should be emphasized.

**Figure 1.** Proposition of the ideal workflow for the management of anti-EGFR–related skin toxicity. EGFR: epidermal growth factor receptor; QoL: quality of life.

**Acknowledgments**

We would like to thank Drs Koen Thorrez, Peter Van Lint, and Joanna Van Erps for their efforts and critical insights in this project. This study was supported as a value-based health care project by Amgen.
Conflict of Interest
None declared.

References

Abbreviations
CTCAE: Common Terminology Criteria for Adverse Events
EGFR: epidermal growth factor receptor
QoL: quality of life
Original Paper

Public Interest in Acetyl Hexapeptide-8: Longitudinal Analysis

Sofia Eva Olsson¹, BS; Bhavana Sreepad¹, BS; Trevor Lee¹, BS; Manal Fasih¹, BS; Arman Fijany¹, MD
Anne Burnett Marion School of Medicine, Fort Worth, TX, United States

Corresponding Author:
Sofia Eva Olsson, BS
Anne Burnett Marion School of Medicine
2800 S University Dr
Fort Worth, TX, 76109
United States
Phone: 1 817 257 4212
Email: sofia.olsson@tcu.edu

Abstract

Background: Acetyl hexapeptide-8, also known as Argireline, is a topical, short-acting, synthetic peptide that has recently gained popularity for its antiwrinkle effects. This agent has emerged as a more accessible alternative to botulinum neurotoxin.

Objective: This study evaluates the public interest in acetyl hexapeptide-8 in the United States from 2013 to 2023, as described by search volume on Google, the most-used search engine.

Methods: We analyzed the longitudinal relative monthly search volume from January 1, 2013, to January 1, 2023, for acetyl hexapeptide–related terms. We compared the internet search trends for “Botox” during this period to “Argireline.”

Results: The terms “Argireline” and “Botox in a Bottle” both had substantial increases in search volume in 2022. Although its search volume is drastically increasing, “Argireline” was less searched than “Botox,” which had a stable, up-trending search volume over the past decade.

Conclusions: The increasing interest in acetyl hexapeptide-8 may be due to its cost-effectiveness and use as a botulinum neurotoxin alternative. Affordability, over-the-counter availability, and ease of self-application of the agent suggest its potential to enhance accessibility to cosmetic dermatologic care.

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KEYWORDS
acetyl-hexapeptide-8; anti-aging; anti-wrinkle; Argireline; BoNT; botox; botulinum neurotoxin; cosmetic dermatology; cosmetic; dermatologist; dermatology; injectable neurotoxin; neurotoxin; skin specialist; topical agent; topical

Introduction

Botulinum neurotoxins (BoNTs) have long been considered the most effective cosmetic intervention to reduce wrinkles and fine lines [1]. However, many individuals face barriers such as cost and transportation when seeking BoNT treatment.

Acetyl hexapeptide-8, which acts similarly to BoNTs, has gained traction due to its low cost, topical application method, and increased safety of use [2]. The peptide may be referred to as acetyl hexapeptide-3 or acetyl hexapeptide-8 amide, and it is more commonly identified by its trade name, Argireline, produced by the Lubrizol Corporation. The topical peptide is a synthetic compound mimicking the N-terminus of synaptosomal-associated protein of 25 kDa (SNAP-25) [3]. This structure allows for inhibition of the soluble N-ethylmaleimide-sensitive factor activating protein receptor (SNARE) ternary complex assembly and consequently inhibits Ca²⁺-dependent exocytosis of acetylcholine into the neuromuscular junction [2,3]. This mechanism is similar to that of BoNT type A, yielding comparable outcomes that are shorter-acting with milder neurotoxicity [2,3]. As of 2020, acetyl hexapeptide-8 was reported as an ingredient in 452 cosmetic products [4]. Though there are limited data on the price ranges of these products, a recently popularized brand of 10% Argireline water-based serum costs US $9.40 for an approximately 4-month supply. Prices may vary, but acetyl hexapeptide-8 products appear to cost less than cosmetic BoNT injections, which range from US $300 to US $600 per treatment [5]. This affordability expands access to antiwrinkle care across a broader socioeconomic demographic. Additionally, the product is considered safe for topical use with minimal risk of complications or adverse effects [4,6,7].

A large-scale study published in 2013 revealed the efficacy of acetyl hexapeptide-8 in reducing periorbital wrinkles [8].
However, Argireline became popular on TikTok, a social media platform where users share short clips, in 2022 [9,10]. The term “Botox in a Bottle” was coined to describe the product on TikTok, where users praised the compound for its antiaging properties by reducing wrinkles and fine lines [11]. Acetyl hexapeptide-8 is marketed as a low-cost alternative to BoNT treatments for those hesitant or unable to afford injection therapies [11].

With casual reporting of increased acetyl hexapeptide-8 popularity [11], it is imperative to quantitatively analyze trends in public interest in the agent. Such analysis serves as a reflection of trends in consumer interest and use [12]. With Google being the most widely used search engine globally and in the United States [13], it serves as a primary platform for individuals interested in acetyl hexapeptide-8 products to seek further information. This study is the first to comprehensively examine public interest in acetyl hexapeptide-8 on the internet, offering a realistic view of its trends in the United States and the necessity for further medical research on the product.

**Methods**

The relative monthly volume of acetyl hexapeptide-related Google searches was determined using the Google Trends database [14]. Google Trends is a tool that provides insight into longitudinal search volume data on Google and has been used in recent literature to study human behaviors and interests without consumer barriers such as cost and transportation [14-16].

In this analysis, search volume data were collected between January 1, 2013, and January 1, 2023. The following search terms were examined: “Argireline,” “Botox in a Bottle,” “Acetyl hexapeptide-3,” and “Acetyl hexapeptide-8.” These terms were selected to encompass the scientific nomenclature, trade name, and colloquial phrases relating to acetyl hexapeptide-8. Additionally, the term “Botox” was included to provide a basis for comparison between traditional BoNT injections and the newer topical alternative, Argireline.

Monthly search volumes for each of these terms were obtained from Google Trends as normalized values on a relative search index. The index scale used for analysis ranged from 0, representing minimal search volume, to 100, indicating maximal search volume.

**Results**

Search terms “Argireline” and “Botox in a Bottle” followed similar trends in web-based popularity, while “Acetyl hexapeptide-8” and “Acetyl hexapeptide-3” did not (Figure 1). There appeared to be relatively sparse online interest in acetyl hexapeptide-related search terms before February 2015. Following this spike, public interest, as described by search volume, stabilized before rising in May 2021, with a peak in October 2022. Google users primarily searched for acetyl hexapeptide-8 by its trade name, “Argireline,” followed by the colloquial name, “Botox in a Bottle.” The terms “Acetyl hexapeptide-3” and “Acetyl hexapeptide-8” had the lowest search volumes with relatively stable searches over the past decade.

Acetyl hexapeptide-8 is frequently compared to BoNTs due to their similar mechanism of action and overlapping use as antiwrinkle agents. However, despite its recent uptrend in Google searches (Figure 1), “Argireline” is searched less than the term “Botox,” which has steadily up-trended over the past decade (Figure 2). Botox appears to have relatively substantial and consistent internet popularity compared to the newly popularized Argireline peptide.

![Figure 1. Relative search volume of acetyl hexapeptide–related terms on Google from January 1, 2013, to January 1, 2023.](https://derma.jmir.org/2024/1/e54217)
Figure 2. Comparison of relative Google search volume for search terms “Argireline” and “Botox” from January 1, 2013, to January 1, 2023.

Discussion

Overview

This study is the first to describe the longitudinal internet popularity of the topical antiwrinkle agent acetyl hexapeptide-8 over the past decade. Viewers likely searched the internet to purchase or research Argireline peptide following exposure through social media or other sources. Though important studies demonstrating the antiwrinkle effects of acetyl hexapeptide-8 were published in 2013, the search volume of the product’s trade name, Argireline, increased exponentially in the year 2022 (Figure 1) [7]. This was likely due to the popularization of the serum through social media platforms such as TikTok. The longitudinal increase in Argireline and related terms’ search volumes confirms a growing public interest in the agent, likely as an alternative to traditional BoNTs. Despite its marketing as a cost-effective, less-invasive, and shorter-acting alternative to BoNTs [1,11], Google Trends data analysis revealed that the internet popularity of “Botox” increased within the last decade as well. Botox was searched for far more frequently than the newly popularized Argireline. This may be due to the perceived reliability of BoNTs, as they have been approved by the Food and Drug Administration for cosmetic use since 2002 [17,18].

The relatively low search volume for the terms “Acetyl hexapeptide-3” and “Acetyl hexapeptide-8” may stem from the knowledge barrier of scientific jargon and specialized terminology [19,20]. Products containing acetyl hexapeptide-8 appear to use the agent’s scientific nomenclature or its trade name in ingredient lists, with no consensus on the use of a single term. Internet users may be familiar with terms or phrases commonly used in English, such as “Botox in a Bottle” or “Argireline,” and rely on them to better comprehend the effects of the product [19,20]. Importantly, the conflicting public search trends between lay and scientific jargon may indicate a need for further scientific research on the agent and clarification to consumers regarding their acetyl hexapeptide-8 product options.

The less-invasive nature of acetyl hexapeptide-8, the ability to self-apply cost-effectively, and the minimal side effects are potential reasons for its increasing popularity over the past decade. Due to its lesser neurotoxicity and shorter-acting effects, acetyl hexapeptide-8 does not carry the risks of ptosis, eyebrow asymmetry, and other complications seen in facial BoNT injections [4,6,21]. The ability to self-apply acetyl hexapeptide-8 products brings down the cost of their usage, as sterile equipment and a medical professional are not required for their application. Argireline peptide solutions typically cost less than US $100 when purchased over the counter, whereas BoNT injections require a medical professional for administration, costing an average of US $300-US $600 [5,22]. The relatively low price point and over-the-counter status of acetyl hexapeptide-8 products allow them to improve accessibility to cosmetic dermatologic care. Self-application also improves accessibility to antiwrinkle care, as transportation to a site and appointment time are no longer barriers to treatment.

There are various strengths to this project. The anonymity of Google Trends big data limits interviewer and chronology bias. Observing internet search volume gauges consumer interest and exposure without the financial barrier of product purchase. As of 2022, Google is the most-used search engine, occupying 86.99% of the United States search engine market [13]. Therefore, Google search volumes provide the most complete understanding of public interest and internet exposure to acetyl hexapeptide-8. A limitation of Google Trends’ big data is the lack of community and individual-level data, hindering assessment groups with differing representation. It also allows
for potential bias from differences in the interests of Google users compared to those who use other search engines.

Understanding consumers’ skincare preferences can guide future research regarding trending products’ efficacy, safety, and innovation. Future directions for acetyl hexapeptide-8 research include its potential use as a therapeutic agent alongside the current cosmetic indications. Assessing Argireline use in various socioeconomic groups, age groups, and geographic locations may provide greater insight into its role as an accessible option for dermatologic health maintenance.

**Conclusion**

This study was the first to analyze public interest in acetyl hexapeptide-8, as described by the relative search volume of acetyl hexapeptide-related terms on Google over the past decade. Though the agent’s antiwrinkle effects were published in 2013, results indicate a recent surge in internet popularity in 2022. Acetyl hexapeptide-8 can improve access to antiwrinkle care due to its low price point, over-the-counter status, and ability to be self-applied. The authors recommend additional research assessing the safety profiles of acetyl hexapeptide-8 products as well as their use and interest among various demographics.

**Conflicts of Interest**

None declared.

**References**


[Medline: 21319685]

Abbreviations

- **BoNT**: botulinum neurotoxin
- **SNAP-25**: synaptosomal-associated proteins of 25 kDa
- **SNARE**: soluble N-ethylmaleimide-sensitive factor activating protein receptor
Diversity Among American Dermatological Association Members by Sex and Geographic Region

Ramiro Rodriguez¹, MD; Lachlan Anderson², BSc; Emily Woolhiser³, BSc; Timothy Balmorez⁴, BSc; Bailey Cook⁵, BSc; Megan Hauptman⁶, BSc; Jessica Kirk⁵, BSc; Noah Keime¹, BSc; Robert P Dellavalle¹,7,8, MD, PhD, MSPH

¹Department of Dermatology, University of Colorado School of Medicine, Aurora, CO, United States
²Boston College, Boston, MA, United States
³College of Osteopathic Medicine, Kansas City University, Kansas, KS, United States
⁴College of Osteopathic Medicine, Touro University California, Vallejo, CA, United States
⁵Rocky Vista University College of Osteopathic Medicine, Parker, CO, United States
⁶College of Medicine, University of Arizona, Tucson, AZ, United States
⁷Dermatology Service, US Department of Veterans Affairs Rocky Mountain Regional Medical Center, Aurora, CO, United States
⁸Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Corresponding Author:
Robert P Dellavalle, MD, PhD, MSPH
Dermatology Service
US Department of Veterans Affairs Rocky Mountain Regional Medical Center
Rm E1-342
1700 N Wheeling St
Aurora, CO, 80045
United States
Phone: 1 303 399 8020
Email: robert.dellavalle@cuanschutz.edu

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KEYWORDS
American Dermatological Association; disparity; representation; dermatology; urban; rural; dermatological society; diversity; inclusion; equity; sex; membership; acquisition; demographic

Introduction
Professional societies create networking, mentorship, and research collaboration opportunities, but disparities in gender, sex, geographic, ethnic, and racial composition within societies disadvantage professional development among underrepresented individuals. Our group evaluated the American Dermatological Association (ADA) since election occurs through a nomination by existing members; we hypothesize this process creates gaps in representation. Given the professional implications for underrepresented individuals, this review aims to quantify the disparities in sex and geographic location of ADA members. Ethnicity/race was not analyzed because the information was not publicly available.

Methods
Overview
In February 2023, the ADA directory identified 767 members. Two independent reviewers recorded member names, self-identified sex, city, and state listed on their national practitioner identifier, and those who were deceased; a third reviewer resolved data conflicts. Sex was identified on national practitioner identifier databases. Data were omitted for retired, deceased, or unidentified members. The statistical analysis was performed using R software (R Foundation for Statistical Computing), and the package “usmap” was used to create the figure. The directory was updated to include the 2023 inductees.

Ethical Considerations
Data was publicly available and deidentified, and did not require institutional review board review.

Results
Of the 688 ADA members, 227 (33%) were female and 461 (67%) were male. A total of 581 (84.4%) members practiced in the United States, while 107 (15.6%) members practiced internationally; 26 (24.3%) of the 107 international members were female, and 81 (75.7%) international members were male. Among the 41 represented states, 2 had a similar number of
male and female members (Figure 1). The top 5 states represented 247 (42.5%) members: California had 79 (13.6%) members, followed by 60 (10.3%) members in New York, 38 (6.5%) members in Massachusetts, 37 (6.3%) members in Pennsylvania, and 33 (5.6%) members in Florida (Table 1).

**Figure 1.** Representation of the American Dermatological Association members by sex and geographic region.

**Table 1.** Breakdown of American Dermatological Association membership by US region and top 10 states in female membership.

<table>
<thead>
<tr>
<th>US regions</th>
<th>Members, n (%)</th>
<th>Female members, n (%)</th>
<th>Members per 1,000,000 people, n</th>
<th>Female members per 1,000,000 people, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>166 (28.6)</td>
<td>62 (37.3)</td>
<td>2.90</td>
<td>1.08</td>
</tr>
<tr>
<td>South</td>
<td>176 (30.3)</td>
<td>53 (30.1)</td>
<td>1.38</td>
<td>0.42</td>
</tr>
<tr>
<td>Midwest</td>
<td>112 (19.3)</td>
<td>43 (38.4)</td>
<td>1.63</td>
<td>0.62</td>
</tr>
<tr>
<td>West</td>
<td>127 (21.9)</td>
<td>43 (33.9)</td>
<td>1.61</td>
<td>0.55</td>
</tr>
<tr>
<td>Total</td>
<td>581 (100.0)</td>
<td>201 (34.6)</td>
<td>1.75</td>
<td>0.61</td>
</tr>
</tbody>
</table>

**Discussion**

Our study demonstrates that ADA membership does not represent the female dermatology workforce relative to geographic location and academic practice setting. Per Centers for Medicare & Medicaid Services data from 2020 and dividing US regions per the US Census Bureau criteria, female dermatologists ranged from 1430 of 1508 (48.7%) to 1148 of 1043 (52.4%) of the workforce in all regions of the United States [1]. In academic dermatology, the female workforce increased from 18 of 167 (10.8%) in 1970 to 749 of 1464 (51.2%) in 2018 [2]. Furthermore, as of 2020, 1125 (47.6%) of 2363 dermatologists who graduated medical school 28-36 years ago after graduating medical school are female [1], suggesting a diversified candidate pool for late-career recognitions like ADA membership.

Societies should aim to represent the dermatology workforce, which by extension should aim to represent the diverse composition of the United States. Data demonstrates direct benefits to patients stemming from a diverse workforce. For instance, an analysis of practice characteristics using the Black Dermatologist Directory identified 221 individuals (80% female). It was found that Black dermatologists served a higher proportion of non-Hispanic Black patients relative to other dermatologists (21.0 vs 2.7; *P*<0.001) [3]. This data suggests a racial concordance preference, which can impact patient outcomes. For instance, data shows an 11% decrease in primary medication nonadherence among racial concordant Black dermatologists–Black patient dyads, independent of insurance status [4]. Research on ethnic/racial concordance can differ between ethnic/racial groups; however, cultural sensitivity is cited as a component of positive interactions [5]. Thus, honoring underrepresented individuals and diversifying professional societies can encourage cultural sensitivity among dermatologists through interactions with each other.

For dermatology-specific professional societies, data quantifying the impact of increased female representation is limited. However, interviews [6] of a women-focused professional organization report improved academic advancement, leadership experiences, awards, promotions, mentorship, and peer support, and reduced professional isolation. Other themes were the development of initiatives addressing systemic gender inequities/challenges like navigating bias, promoting pay equity, and family-friendly workplace policies. Given these benefits, there is a clear need for improved female representation in professional societies.
Specifically for the ADA, per the bylaws [7], candidates undergo membership proposition, review, and evaluation by a membership committee before proceeding to a ballot election. ADA leadership can promote diversity in different steps. For example, societies like the American Academy of Dermatology and The Skin of Color Society have mentorship programs dedicated to increasing diversity. A similar program may help identify competitive individuals for ADA membership to help improve their recognition among ADA members. In addition, including a race/sex-conscious nomination round can help diversify the pool of candidate reviews. Limitations of this study include the moment-in-time design and the exclusion of the race/ethnicity of members; the data needed to address these points could show important trends that demonstrate increased diversity. Future research can focus on evaluating the epidemiological characteristics of membership within other dermatologic societies, how these societies have changed over time, and identifying outcome measures to quantify the impact that diverse professional societies have on professional development.

Conflicts of Interest

RPD is an editor for Cochrane Skin, the editor in chief of JMIR Dermatology, the coordinating editor representative on the Cochrane Council, and a Cochrane Council cochair. RR is an editorial fellow for JMIR Dermatology. RPD receives editorial stipends (JMIR Dermatology), royalties (UpToDate), and expense reimbursement (Cochrane). RR receives fellowship funding from the National Institutes of Health (5T32AR007411-37; principal investigator: Dennis Roop).

References


Abbreviations

ADA: American Dermatological Association
Abstract

Publications dealing with topics considered to be pertinent to diversity, equity, and inclusion are increasing. Due to the increasing trend, dermatology journals have started to implement ways to evaluate and understand these publications. Here, we discuss a keyword approach to identify and then categorize these publications. Keywords identified 43 manuscripts. Two reviewers screened the articles’ titles and abstracts, and recommended a full manuscript review for 24 publications. Through the scope of definitions from the National Institutes of Health, an editorial board member performed a full-text review and assigned a primary theme to the publications. Themes included equity (n=20) and diversity/inclusion (n=4). Topics were racial/ethnic differences in care delivery or society (n=17), incomplete understanding of gender and sex (n=3), gender identity (n=2), socioeconomic class and its impact on health (n=1), care for rural underserved communities (n=1), and religion (n=1). The results of this review demonstrate a predominance of equity-related publications, particularly emphasizing racial/ethnic differences in health care delivery, in the publications identified in JMIR Dermatology. Future research can focus on creating a review aid to assist editorial board members when providing feedback to manuscripts, refining the keywords, and using thematic analysis methodology to evaluate large sets of publications.

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KEYWORDS
diversity; equity; inclusion; editor; DEI; committee; disparity; underrepresented; dermatology; skin of color; SOC

Introduction

Disparities in racial/ethnic diversity within dermatology prevail. Despite the disparity, dermatology journals published more articles on topics related to diversity, equity, and inclusion (DEI) from 2008 to 2019 compared to other specialties [1]. In the absence of a formal DEI review process, publications risk propagating an incomplete understanding of social determinants of health and their interplay with race/ethnicity, gender identity, sex assignment at birth, and religion [2].
potentially emotive topics [5]. JMIR Dermatology acknowledges the need for understanding these topics. Thus, the purpose of this paper is to improve the understanding of DEI manuscripts and identify themes and topics within publications.

**Methods**

**Overview**

Previous research defined DEI publications using target keywords [6]. Our diverse team assigned DEI keywords (Textbox 1) and used JMIR Publication’s editorial management system (Open Journal Systems [OJS]) to find and identify 43 potential DEI manuscripts. Two independent reviewers read the abstracts to determine if a dedicated DEI editor would be recommended and the reason for their assessment. Conflicts prompted a third full-text review. A total of 24 manuscripts received a DEI review recommendation. A JMIR Dermatology editorial board member then performed a full-text review and categorized each manuscript’s primary theme and topic. The primary theme was selected within the scope of definitions from the National Institutes of Health (NIH) [7] (Textbox 1).

**Textbox 1.** Key terms and words used to identify and define publications dealing with diversity, equity, and inclusion.

<table>
<thead>
<tr>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disparities, diversity, equity, inclusion, disparity, underserved, rural, Black, Hispanic, Latinx, Latino, LGBTQ, skin of color, Asian, Pacific Islander, Native American, American Indian, Alaska Native, White, gender, sex, underrepresented in medicine, minority, URM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diversity</th>
</tr>
</thead>
<tbody>
<tr>
<td>The practice of including many communities, identities, races, ethnicities, backgrounds, abilities, cultures, and beliefs of people, including underserved communities.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equity</th>
</tr>
</thead>
<tbody>
<tr>
<td>The consistent and systematic fair, just, and impartial treatment of all individuals, including individuals who belong to underserved communities that have been denied such treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>The recognition, appreciation, and use of the talents and skills of individuals of all backgrounds.</td>
</tr>
</tbody>
</table>

**Ethical Considerations**

Data was publicly available and deidentified, and did not require institutional review board review.

**Results**

In the 24 reviewed manuscripts, primary publication themes dealt with equity (n=20), followed by diversity and inclusion (n=4). The topics included racial/ethnic differences in care or society (n=17), incomplete understanding of gender and sex (n=3), gender identity (n=2), socioeconomic class and its impact on health (n=1), care for rural underserved communities (n=1), and religion (n=1).

**Conclusion**

DEI publications are more common relative to previous decades. Dermatology journals are incorporating measures to provide evidence-based methods to improve our understanding of DEI publications. Here, we described a way to evaluate DEI publications within JMIR Dermatology and their common themes/topics. Limitations of our study include the sample size. The themes of DEI can also overlap among publications. Standard definitions of DEI assisted the primary theme assignment. Based on the definitions adapted from the NIH, diversity is characterized by including individuals. Inclusion is distinguished by recognizing and appreciating them. Equity was the most prevalent theme and highlights the fair, just, and equal treatment of individuals in the scope of bias. While our authors are diverse, our perspectives are limited and may not be inclusive of all themes or topics within DEI literature. Future research can focus on creating a DEI review aid for editorial boards, broadening and refining the keywords, and using thematic analysis methodology to identify themes/topics among larger sets of publications.

**Acknowledgments**

RR receives fellowship funding from the National Institutes of Health (2T32AR007411-31A1; principal investigator: Dennis Roop).

**Conflicts of Interest**

RR is an editorial diversity, equity, and inclusion board member/fellow for JMIR Dermatology and a Dermatology Clinical Trial fellow. RPD is the editor-in-chief of JMIR Dermatology. The other authors have no conflicts of interest to declare.

**References**

https://derma.jmir.org/2024/1/e48762


**Abbreviations**

- **DEI**: diversity, equity, and inclusion
- **JAAD**: Journal of the American Academy of Dermatology
- **NIH**: National Institutes of Health
- **OJS**: Open Journal Systems

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Visibility of Board-Certified Dermatologists on TikTok

Chaitra Subramanyam1, MSc; Alyssa Becker2, BSc; Julianne Rizzo3, BA; Najiba Afzal3, BSc; Yvonne Nong4, MSc; Raja Sivamani5, AP, MSc, MD

1College of Osteopathic Medicine of the Pacific Northwest, Western University of Health Sciences, Lebanon, OR, United States
2John A Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI, United States
3College of Medicine, University of California Davis, Sacramento, CA, United States
4College of Human Medicine, Michigan State University, Flint, MI, United States
5Pacific Skin Institute, Sacramento, CA, United States

Abstract

TikTok is an emerging social media platform that provides a novel opportunity for health practitioners such as dermatologists to disseminate accurate health information.

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KEYWORDS
board; certification; board certification; health; media; public; social; TikTok; social media; health information; misinformation; diagnosis; users; medical training; training; media content; skin; derma; derm; dermatologist; dermatology; epidermis; dermatitis; cellulitis; skin doctor; skin; hair; nail

Introduction

TikTok is a video-sharing social media platform with over 1.1 billion active users since its launch in 2016 [1]. Social media platforms such as TikTok are used by medical and nonmedical professionals to share health information. However, health misinformation spreads more quickly than evidence-based information, posing a public health issue [2]. Our study aimed to categorize popular dermatology-related posts and analyze the visibility of board-certified dermatologists (BCD) on TikTok.

Methods

The methods were designed based on a previous study that examined dermatology content on Instagram by Park et al [3]. First, a list of top dermatologic diagnoses and procedures was compiled based on the National Ambulatory Medical Care Survey and the American Society of Dermatologic Survey of Dermatologic Procedures [4,5]. Then, all of the terms were queried as hashtags in TikTok’s search feature on January 2, 2021.

The 20 dermatologic conditions and procedures with the highest total views were identified. Profession-specific hashtags (#dermatology, #boardcertifieddermatologist, #dermatologist, and #derm) were also queried. The term with the highest total views was chosen among synonymous terms.

The first 10 posts under each of the 44 hashtags were then viewed. Top posts were selected through TikTok’s private algorithm, which uses total views, followers, and other metrics. Users’ self-reported occupations were identified, and board certifications were confirmed through the Certification Matters website [6]. Posts were categorized into 4 categories: educational, self-promotional, non–paid product placements, and advertisements. Educational content was identified as any post that aimed to provide informative material regarding a dermatologic condition and/or procedure. Self-promotional content was defined as posts intended to advance the user’s professional pursuits. Non–dermatology-related posts were excluded.
Results

Of the 18.68 billion total views of the hashtags investigated, 12.9 billion (69.1%) were related to skin conditions, 4.26 billion (22.8%) were related to dermatologic procedures, and 1.52 billion (8.17%) were profession-specific.

Out of 231 unique user profiles that accounted for the 360 top dermatology-related posts, 70 (30.3%) were patients, 66 (28.57%) were medical professionals, and 11 (4.76%) were estheticians (Table 1).

BCD and dermatology residents made up 15 (6.49%) and 7 (3.03%) of the top dermatology-related content creators, respectively. In the queried hashtags, verified BCD and dermatology residents created 13.89% (50/360) and 8.89% (32/360) of the top posts, respectively.

Out of the identified top posts, 46.67% (168/360) were educational, 27.50% (99/360) were self-promotional, 13.89% (50/360) were non-paid product placements, and 0.83% (3/360) were advertisements.

A total of 29.76% (50/168) and 70.24% (118/168) of educational posts were created by nonmedical and medical professionals, respectively; specifically, BCD created 20.83% (35/168) and dermatology residents created 18.45% (31/168). BCD were responsible for only 30% of the profession-specific hashtag-identified posts (Table 2).

Table 1. Medical professionals versus nonmedical professionals who created top dermatology-related TikTok videos (total unique creators: N=231).

<table>
<thead>
<tr>
<th>Category</th>
<th>Self-identified, n (%)</th>
<th>Residency or board-certified status confirmed, n (%) of total unique creators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical professionals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatologists</td>
<td>15 (6.49)</td>
<td>13 (5.63)</td>
</tr>
<tr>
<td>Dermatology residents</td>
<td>7 (3.03)</td>
<td>7 (3.03)</td>
</tr>
<tr>
<td>Physicians in other specialties</td>
<td>21 (9.09)</td>
<td>16 (6.93)</td>
</tr>
<tr>
<td>Nurse practitioners</td>
<td>6 (2.6)</td>
<td>4 (1.73)</td>
</tr>
<tr>
<td>Physician’s assistants or associates</td>
<td>2 (0.87)</td>
<td>2 (0.87)</td>
</tr>
<tr>
<td>Registered nurses</td>
<td>4 (1.73)</td>
<td>2 (0.87)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>11 (4.76)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>All medical professionals</td>
<td>66 (28.57)</td>
<td>44 (19.05)</td>
</tr>
<tr>
<td><strong>Nonmedical professionals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>70 (30.3)</td>
<td>N/Aa</td>
</tr>
<tr>
<td>Estheticians</td>
<td>11 (4.76)</td>
<td>N/A</td>
</tr>
<tr>
<td>Verified account (brand or influencer)</td>
<td>12 (5.19)</td>
<td>N/A</td>
</tr>
<tr>
<td>Other</td>
<td>72 (31.17)</td>
<td>N/A</td>
</tr>
<tr>
<td>All nonmedical professionals</td>
<td>165 (71.43)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

aN/A: not applicable.

Table 2. Users responsible for the top 10 videos under each profession-specific hashtag.

<table>
<thead>
<tr>
<th>Users</th>
<th>Hashtag, n</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#dermatology</td>
<td>#derm</td>
</tr>
<tr>
<td>Board-certified dermatologist</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dermatology resident</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Internal medicine physician</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Registered nurse</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Esthetician</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Discussion

Our results suggest that most of the popular dermatology-related content on TikTok is created by individuals without verifiable medical training. This highlights a space for BCD to showcase their profession and prevent the spread of health misinformation. As the use of social media platforms like TikTok continues to grow, BCD have an opportunity to increase their presence as a credible source for the public to acquire dermatologic knowledge.
The use of hashtags explicitly related to dermatology by users who are not BCD or dermatology residents may mislead TikTok users. Transparency regarding professional health care credentials on TikTok may improve credibility. There is currently no way to verify professional credentials on TikTok; a feature to distinguish medical professionals from nonmedical professionals can add to the visibility of BCD and help users make informed decisions regarding their source of health information online.

Conflicts of Interest
RKS is a scientific advisor for LearnHealth, Arbonne, and Codex Labs Corp and a consultant for Burt’s Bees, Novozymes, Nutrafol, Incyte, Fotona, Biogena, Image Skincare, Bristol Myers Squibb, Novartis, Pfizer, AbbVie, LEO Pharma, UCB, Sun, Sanofi, and Regeneron Pharmaceuticals.

References
6. Certification Matters. URL: https://www.certificationmatters.org/ [accessed 2023-10-06]

Abbreviations
BCD: board-certified dermatologists

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Hyaluronidase for Dermal Filler Complications: Review of Applications and Dosage Recommendations

George Kroumpouzos1,2, MD, PhD; Patrick Treacy3, MD
1GK Dermatology, PC, South Weymouth, MA, United States
2Department of Dermatology, Warren Alpert Medical School at Brown University, Providence, RI, United States
3Ailesbury Clinics Ltd, Dublin, Ireland

Corresponding Author:
George Kroumpouzos, MD, PhD
GK Dermatology, PC
541 Main St
Suite 320
South Weymouth, MA, 02190
United States
Phone: 1 7818121078
Fax: 1 7818122748
Email: gk@gkderm.com

Abstract

Background: Hyaluronidase (Hyal) can reverse complications of hyaluronic acid (HA) fillers, which has contributed substantially to the popularity of such procedures. Still, there are differing opinions regarding Hyal treatment, including dosage recommendations in filler complication management.

Objective: We aimed to address unanswered questions regarding Hyal treatment for HA filler complications, including timing and dosage, skin pretesting, properties of various Hyals and interactions with HA gels, and pitfalls of the treatment.

Methods: PubMed and Google Scholar databases were searched from inception for articles on Hyal therapy for filler complications. Articles were evaluated regarding their contribution to the field. The extensive literature review includes international leaders’ suggestions and expert panels’ recommendations.

Results: There are limited controlled data but increasing clinical experience with Hyal treatment. The currently used Hyals provide good results and have an acceptable safety profile. Nonemergent complications such as the Tyndall effect, noninflamed nodules, and allergic or hypersensitivity reactions should be treated with low or moderate Hyal doses. Hyal should be considered with prior or simultaneous oral antibiotic treatment in managing inflammatory nodules. Hyal may be tried for granulomas that have not responded to intraleisional steroids. Emergent complications such as vascular occlusion and blindness require immediate, high-dose Hyal treatment. Regarding blindness, the injection technique, retrobulbar versus supraorbital, remains controversial. Ultrasound guidance can increase the efficacy of the above interventions.

Conclusions: Hyal is essential in aesthetic practice because it can safely treat most HA filler complications. Immediate Hyal treatment is required for emergent complications. Aesthetic practitioners should be versed in using Hyal and effective dosage protocols.

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KEYWORDS
hyaluronidase; hyaluronic acid; filler; complications; nodule; vascular occlusion; therapy; treatment; application; dosage; management; skin; data; inflammatory nodule; inflammatory; injection

Introduction

Fillers are classified into three major classes based on their longevity in the tissues, which in turn depends on their structure and composition: (1) temporary, lasting less than 18 months; (2) semipermanent, lasting greater than 18 months; and (3) permanent, lasting longer than 24 months. It is generally believed that permanent fillers are nonbiodegradable and nonreversible, and therefore, complications with the inflammatory process are more likely to occur with permanent...
fillers. Dermal fillers have gained popularity over the past 2 decades despite the large spectrum of complications associated with their use, including nodule formation, misplacement, migration, infection, and vascular occlusion [1-3]. Hyaluronic acid (HA) fillers are temporary or semipermanent and remain the most used filler type [4]. Fillers that cannot be dissolved by hyaluronidase (Hyal), such as poly-l-lactic acid, calcium hydroxylapatite, and polymethylmethacrylate, are not discussed here. The ease and efficacy of Hyal in reversing HA gels’ (HAG’s) complications have contributed to such fillers’ popularity [5]. Performing Hyal injections under high-frequency ultrasound (HFUS) guidance, a recent advance in soft tissue augmentation, allows for higher accuracy and efficacy of the treatment, thereby maximizing the benefits [6].

Still, there has been a small number of well-designed randomized controlled trials (RCTs) on Hyal injections in aesthetics. Borzabadi-Farahani et al [7-11] found only 5 RCTS evaluating the effectiveness of Hyal in removing uncomplicated HA nodules. Dosing recommendations are often based on the suggestions of leading authorities and assessment by expert panels. The objective of this review is to discuss the aesthetic applications of Hyal injections and provide an updated assessment of dosing recommendations, including dosage (international units [iu]), treatment sessions, and incremental dose adjustments (titration). We discuss gaps and present our experience with Hyal treatments.

Methods

We have completed a narrative review, as a systematic review is not feasible due to the high heterogeneity of articles on this broad topic. We searched PubMed and Google Scholar databases from inception for articles on Hyal therapy for filler complications. Complication is an adverse effect emphasizing direct causality between the filler procedure and the adverse outcome or event [1]. Key terms in the search included “complication OR adverse event,” “safety,” “prevention,” “management OR treatment OR intervention,” “hyaluronidase,” and “filler.” We performed separate searches for important complications using the terms “reaction,” “granuloma,” “nodule,” “infection OR biofilm,” “vascular occlusion OR vascular compromise,” and “skin necrosis.” A separate search for using ultrasound (key term “ultrasound”) in filler procedures was performed. We searched the reference lists of relevant articles. We included expert opinions, panel recommendations, and professional body guidance.

Results and Discussion

Principal Findings

We review the findings of publications relevant to Hyal action [12-23], products available [14,18,19,21-23], reconstitution and storage [1,18,20,21,24,25], dosage considerations [5,9-11,16,18,21,26-30], skin pretesting [18,21,24,31-33], use in the management of filler complications [1,2,5-8,16,18,21,24,34-75], and the pitfalls of Hyal treatment [1,13,19,24,37,76-79].

Action of Hyal

Hyal is an endoglycosidase that can depolymerize HA leading to its degradation into monosaccharides by hydrolyzing the disaccharides at hexosaminidic β-1 through β-4 linkages [12]; however, it also breaks down to some extent other polysaccharides in the connective tissue [13,14]. In humans, 6 Hyals have been identified (HYAL-1, -2, -3, -4, HYALP1, and PH-20) [15]. Hyal has an immediate effect and a half-life of 2 minutes with the duration of action being 24 to 48 hours [16,17]. However, it is effective for a longer time period which may be related to the fact that a low number of iu is required to have a clinically significant effect; thus, even when the Hyal has mostly degraded, its action continues [18]. Commendably, Hyal breaks cross-links in the HA filler, which behaves like native HA in the skin, which has a half-life of 24 to 48 hours [15]. Hyal dissolves native HA, but the body restores native HA in 15-20 hours [19]; therefore, there are no detrimental long-term effects of Hyal on skin quality.

Hyal is a tissue permeability modifier and is indicated as an adjuvant in subcutaneous fluid administration for achieving hydration, increasing the dispersion and absorption of other injected drugs such as anesthetics and in subcutaneous urography for improving resorption of radiopaque agents [20]. Hyal is used off-label in aesthetics.

Available Hyals

Hyalys are derived from mammals (obtained from the testes), hookworms or leeches, and microbes [19]. Animal origin Hyals have been used clinically for almost 80 years [21]. Hyals that are currently available are of either animal origin or human recombinant (Table 1). Food and Drug Administration -approved Hyals include bovine (Amphadase), ovine (Vitrase) products, and recombinant human (Hylenex) products. Still, in many countries, only 1 Hyal type is available—Hylase “Desau” in Germany and “Hyalase” in the United Kingdom require reconstitution (product should be used within 6 hours) [14,22]. Recombinant human Hyal has a purity 100 times higher than some of the bovine preparations [23]. The recombinant type is thought to have a lower incidence of allergic reactions than animal-derived products that are more immunogenic, but long-term data are lacking [18,21].

https://derma.jmir.org/2024/1/e50403
The Hyal products approved by the Food and Drug Administration (Table 1) should be stored at cool temperatures (2 °C-8 °C) to maintain the quality of the product over a long period of time [18,21]. The Hyal vial should be stored unopened in a refrigerator [20]. If Hyal is stored at room temperature (25 °C), the stability is only guaranteed for 12 months [18]. The provider should follow the product guidelines for storage. The product should be injected immediately after preparation.

**Hyal Dosage**

**Considerations**

The Hyal dosage required depends on the indication (emergent vs nonemergent complication), location, volume, physical properties of the HAG to be dissolved, and patient factors [9,26]. The use of Hyal often involves a titration approach, where the practitioner assesses the response after each injection. Incremental adjustments of Hyal dosage are recommended—smaller doses and a gradual approach allow for fine-tuning, minimizing the risk of excessive filler degradation.

Vascular complications require larger doses than nonemergent (overcorrection, misplacement, and inflammatory reaction). Thinner skin (e.g., lower lids and infraorbital areas) should be treated with lower Hyal doses. Larger filler volumes, larger particle size, higher concentrations of the filler, higher amount of cross-linking, and higher amount of G-prime contribute to increased durability of the filler requiring higher Hyal dosage for dissolution [9,26]. Also, monophase (without distinct particles) HA formulations are more resistant to degradation than biphasic (particles suspended in gel) [26].

**Physical Properties of HAGs**

HA fillers have different physical properties that influence their degradation by Hyal in a time- and dose-dependent manner [21]. In an in vivo study using recombinant Hyal, Juve’derm Voluma required higher doses of Hyal than Restylane-L and Juve’derm Ultra for dissolution [11]. Therefore, Juve’derm Voluma may require repeat doses of Hyal for complete reversal. A study by Rao et al [27] demonstrated Restylane (Galderma Laboratories) dissipated most and Belotero (Merz

### Table 1. Some of the commercially available Hyal products.

<table>
<thead>
<tr>
<th>Trade name, country of origin</th>
<th>Source</th>
<th>Product details</th>
<th>Reconstitution required</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphadase, United States&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Bovine</td>
<td>150 IU/mL in 2 mL vial; contains thimerosal</td>
<td>No</td>
<td>2 °C-8 °C</td>
</tr>
<tr>
<td>Hydase, United States&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Bovine</td>
<td>150 IU/mL in 2 mL vial</td>
<td>No</td>
<td>2 °C-8 °C</td>
</tr>
<tr>
<td>Hylenex, United States&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Human recombinant</td>
<td>150 IU/mL in 2 mL vial; contains human albumin</td>
<td>No</td>
<td>2 °C-8 °C</td>
</tr>
<tr>
<td>Vitrase, United States&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ovine</td>
<td>200 IU/mL in 2 mL vial; contains lactose</td>
<td>No</td>
<td>2 °C-8 °C</td>
</tr>
<tr>
<td>Hylase “Desau,” Germany</td>
<td>Bovine</td>
<td>150, 300, 1500 IU/mL in vial</td>
<td>Yes</td>
<td>25 °C±2 °C; 60% relative humidity</td>
</tr>
<tr>
<td>Hylase, United Kingdom</td>
<td>Not specified</td>
<td>1500 IU/mL in vial</td>
<td>Yes</td>
<td>≤25 °C</td>
</tr>
</tbody>
</table>

<sup>a</sup>Pregnancy category C.

<sup>b</sup>Food and Drug Administration–approved.

---

**Reconstitution and Storage**

Hyal is reconstituted in bacteriostatic normal saline, which is less painful upon injection than water and has additional anesthetic properties [18]. Bacteriostatic normal saline contains benzyl alcohol to prevent bacterial contamination. An aseptic technique should be used during the reconstitution process. One should gently swirl or mix the vial to dissolve the Hyal powder in the saline and avoid vigorous shaking to prevent foaming. The volume of the diluent depends on the indication and surface area to be treated, and a range of 1 to 10 mL has been evidenced in clinical practice [1]. Increased volumes of diluent or subsequent dilutions of a fraction of the reconstituted Hyal are needed if a small number of Hyal units are injected. These authors reconstitute 1500 IU Hyal (Hylase) in 1 mL bacteriostatic saline and subsequently dilute fractions of the reconstituted Hyal product to achieve the desired number of units per 0.1 mL.

There is a theoretical concept that using a lower dilution (higher Hyal concentration) might provide a more focused effect, especially when targeting specific areas like nodules.

While a lower dilution may theoretically lead to more localized effects, it is crucial to balance this with the risk of excessive filler degradation by Hyal which can result in a complete loss of the aesthetic benefit of the filler procedure.

Some authors suggested diluting Hyal in lidocaine to decrease pain in cases of vascular occlusion [24]. However, this has not gained wide support as the enzymatic action of Hyal can be affected by pH and the pH of low lidocaine concentrations is not ideal for Hyal [18]. Additionally, there is a risk of widespread, increased systemic absorption of the anesthetic and potential complications. No evidence supports using lidocaine, with or without epinephrine, solvent to reduce bruising. In a report, a patient presented with soft blue nodules post-HA filler in bilateral infraorbital areas. The lesions were treated with 75 IU Hyal (reconstituted in 1 mL 1% lidocaine with epinephrine); lidocaine with epinephrine was selected to reduce bruising but was ineffective [25].
Pharmaceuticals) was most resistant to degradation. The authors showed that responses were similar for Vitrase and Hylenex, suggesting that these products can be used interchangeably. However, a subsequent study showed that Belotero was the fastest to degrade and Juvederm Voluma (Allergan) and Restylane Lyft were the slowest, with the authors concluding that a high concentration of HA, larger particle size, and increased cross-linking increase filler durability [9]. Jones et al [28] showed that Restylane and Prevelle (Mentor Corp) displayed greater sensitivity to ovine Hyal than Juvederm Ultra and contributed to the degradation resistance of Juvederm Ultra to higher HA content and level of cross-linking.

**Drug Interactions**

Drug interactions of Hyal should be considered. Salicylates, anti-inflammatories, cortisone, herbal meds, heparin, vitamin C, estrogens, and antihistamines make tissues resistant to Hyal [5,18]. One should consider a higher Hyal dosage or repeated injections in such cases. Therefore, having a thorough drug history before injecting Hyal is extremely important.

**Dosage Recommendations for Nonemergent Complications**

Regarding dosing, there are no accepted standardized guidelines. However, the rule of thumb for treating uncomplicated nodules is 5 IU Hyal for 0.1 mL HAG 20 mg/mL [16]. In the study by Zhang-Nunes et al [11] a cross-linked filler (Juve´derm Voluma, 20 mg/mL) required higher Hyal doses for dissolution, that is, more than 20 IU Hyal per 0.2 mL filler. In another study, in vivo degradation of cross-linked, highly cohesive HA fillers required 30 IU Hyal [29]. Woodward et al [30] recommended 30 IU to dissolve 0.1 mL. However, a study showed no statistical difference between using 20 or 40 IU Hyal in degrading 0.2 mL of various fillers (4-6 mg HA) [9]. Alam et al [10] showed that, although small Hyal doses (1.5-9 IU) can remove HA fillers, slightly higher doses often result in more rapid resolution.

Hyal dose for reversing overcorrection depends on the location and quantity of filler—in such cases, one may inject 15-30 IU in nasal or perioral areas, 3-4.5 in the periorbital area, 10-15 in the infraorbital area, and 1.5 in the lower [5]. However, even lower Hyal doses may be effective in reversing excessive augmentations. More resistant HAGs require higher Hyal doses of repetitive injections [21].

**Skin Pretesting**

As detailed in the section “Pitfalls” below, allergic reactions to Hyal are uncommon in aesthetics; they have been mainly reported in cases of peribulbar injection in the ophthalmology practice [31,32]. Therefore, no pretest is warranted in emergencies, such as vascular occlusions, as the risks of delaying the therapeutic intervention outweigh the potential benefit from pretesting [18,21]. However, bedside availability of epinephrine is required. Skin pretesting is considered optional when treating nonemergency complications of HAGs, such as overcorrection, superficial implantation, or inflammatory reactions. No pretesting is required for recombinant Hyal but may be considered for ovine, bovine, or compounded Hyals.

The testing consists of intradermal injection of 0.02-0.05 mL Hyal (to achieve a bleb of 5 mm) followed by observation for local wheal and flare within 5 minutes [21,24]. It is positive if such a reaction persists for 20-30 minutes. There is a lack of consistency regarding the optimal Hyal dose or concentration for pretesting. Doses 5-16 IU have been chosen [21,24], with the proponents of the higher doses indicating that lower doses may be unreliable since the drug causes an irritant reaction that could be misinterpreted as an allergy.

Before injecting Hyal, one should check for possible or confirmed allergy to bee and wasp stings; such allergies pose a significant risk of cross-reactivity [24,33]. There are no standard precautions for using Hyal in patients allergic to bee and wasp stings [21]. In nonemergency filler complications, when a history of a large, localized reaction or anaphylaxis to bee or wasp stings exists, an intradermal test by an allergist is recommended. In emergent complications requiring Hyal in such a patient, the risks and benefits of not performing a skin pretest should be weighed [21].

**Managing Filler Complications**

**Overview**

This section reviews the elective use of Hyal for complications such as the Tyndall effect, noninflamed nodules resulting from overcorrection or misplacement of HA filler, inflammatory nodules, and allergic or immunogenic reactions to HA filler (Table 2). It also details the emergency use of Hyal in managing vascular occlusion to prevent tissue necrosis and blindness from periocular emboli. We discuss Hyal dosing for such complications and present our experience with Hyal treatments.
Table 2. Hyaluronidase dosage and considerations for treating complications of facial filler injections.

<table>
<thead>
<tr>
<th>Aesthetic indication</th>
<th>Hyal dosage&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Hyal dosage (authors’ experience)</th>
<th>Considerations&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyndall effect</td>
<td>10-75 iu&lt;sup&gt;c&lt;/sup&gt; [2,34]</td>
<td>≤150 iu</td>
<td>• Nature of HA&lt;sup&gt;d&lt;/sup&gt; filler (eg, cross-linked)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patient’s wish to maintain cosmetic benefit of filler injection</td>
</tr>
<tr>
<td>Noninflammatory nodules (overfilling or misplacement)</td>
<td>5-150 iu [21,25]</td>
<td>≤300 iu or more, depending on severity and filler type and volume</td>
<td>• Nature and location of filler</td>
</tr>
<tr>
<td>Asymmetry or contour irregularities</td>
<td>As above</td>
<td>≤225 iu</td>
<td>• Volume of filler to be degraded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• As above</td>
</tr>
<tr>
<td>Inflammatory nodules</td>
<td>500 iu every 48 hours to be administered after OAB&lt;sup&gt;e&lt;/sup&gt; have been tried for ≥2 weeks [39]; 30-300 iu combined with OAB [40]</td>
<td>Variable; often in conjunction with other treatments</td>
<td>• Results of skin biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Results of microbiology testing (if nodule fluctuant or abscess)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Nature of HA filler (eg, cross-linked)</td>
</tr>
<tr>
<td>Vascular occlusion</td>
<td>450-1500 iu total (high-dose protocol) [60] in up to 4 Hyal cycles; 35-50 iu under HFUS&lt;sup&gt;f&lt;/sup&gt; guidance (low dose protocol) [6]</td>
<td>300-1000 iu or more, depending on size of ischemic area</td>
<td>• Nature of HA filler (eg, cross-linked)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Size of ischemic area</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Embolus size</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Timing of intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patient factors (eg, scar in the area)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• HFUS imaging availability</td>
</tr>
</tbody>
</table>

<sup>a</sup>Multiple Hyal sessions are often required, and the provider may use incremental dose adjustments depending on the response.

<sup>b</sup>Considerations are crucial to decision-making and building an individualized approach to Hyal therapy.

<sup>c</sup>i: international unit.

<sup>d</sup>HA: hyaluronic acid.

<sup>e</sup>OAB: oral antibiotics.

<sup>f</sup>HFUS: high-frequency ultrasound.

**Tyndall Effect**

When particulate HA fillers are inappropriately injected too superficially, a bluish discoloration (Tyndall effect) can result and may persist for a long time [1]. Treatment with 30-75 iu Hyal can be effective [34]—a smaller number (10-20 iu) may be used if a small amount of HA needs to be degraded [2]. This will often lead to complete resolution of the complication within 24 hours, although occasionally, a second Hyal treatment may be required [24]. The focus of the provider is on degrading the superficially placed filler. Also, Hyal dosage depends on whether the patient requests the filler to be completely removed or just eliminate the Tyndal effect [35]. The practitioner should follow up with the patient in 3-4 days to check whether additional Hyal is needed. Hyal may be used at any time and has been effective 63 months after the initial injection of HA [36].

**Noninflamed Nodules**

Noninflamed nodules result from overcorrection, filler misplacement, or migration (Figures 1 and 2). HFUS imaging is a first-line tool to identify the filler, assess its size, and exclude a soft tissue neoplasm (peer-reviewed by Kroumpouzos et al [1]). It may also help identify severe distant filler migration. Treatment of noninflamed nodules is warranted if painful, aesthetically bothersome, or associated with prolonged edema (ie, malar edema for >4 weeks). Hyal is delivered to the skin and subcutaneous tissue by directly infiltrating the visible or palpable HA depot [21]. Massage is recommended to mix the enzyme with HA and promote filler degradation. One may treat with a low dose, that is, 5-15 iu Hyal, and reassess in 1 week. However, higher doses (up to 150 iu) have been reported as effective [21,25]. As mentioned above, the volume and properties of the filler to be dissolved should be considered when deciding the dose to inject. A prospective trial included 8 participants who received 3 injections with 0.2 mL HA, and after 3-5 days each site was injected with 10, 20, or 30 iu Hyal. There were no differences among Hyal doses [8]. However, the study is limited by the small size and not including higher Hyal doses (ie, >50 iu).
The location of the filler should be considered as areas with thin skin, such as the eyelids, require low Hyal dosage (1.5-3 iu). Injecting a low dose helps prevent the loss of the HAG treatment effect. A retouch of another 1.5-3 iu 2-3 days later can be considered. Precautions to prevent ecchymosis should be taken when injecting the eyelids and infraorbital areas, especially as Hyal has been reported to spread the ecchymosis in these areas [37]. One should use a thin needle (30 G or thinner) and a single needle insertion point that helps minimize tissue trauma from the injection.

Undesired Aesthetic Outcomes

To prevent suboptimal aesthetic outcomes, the injector should consider patient characteristics, choose an appropriate filler for the area to be injected, avoid overfilling, and inject with a knowledge of anatomy. Overfilling can result in nodule formation and filler migration. Still, asymmetries, nodules, and other contour irregularities can occur even when patients are injected by experienced providers. Hyal is an appropriate therapy for such complications caused by HA fillers. The dosage approach is like that detailed for noninflamed nodules above. One should consider the amount of filler that needs to be degraded and titrate the Hyal dosage according to the response. These authors have used 150-300 iu Hyal for such complications (Table 2).

Inflammatory Nodules

Inflammatory nodules are often red and may feel warm to the touch. They can be associated with tenderness or pain. Inflammation may result from an immune response to the filler material, infection, or other complications [1]. Delayed-onset nodules (DONs) are usually inflammatory (ie, immune response to filler material), granulomatous (on histology), or related to infection or biofilm [1]. DON formation has a 0.5% incidence, a median time of onset of 4 months, and a median time to resolution of 6 weeks [38]. A subsequent retrospective study reported an incidence of 1% [39]. A skin biopsy and microbiologic testing should rule out granuloma formation and infection. A culture test of a draining or fluctuant lesion can aid in antibiotic selection. If an infection is suspected, oral antibiotic therapy should be administered, and the nodule should undergo incision and drainage if fluctuant. The American Society of Dermatologic Surgery recommended that noninflamed DONs without suspicion of infection might be treated initially with oral steroids for 1 to 2 weeks, rather than Hyal, should the retention of the aesthetic filler effect be desired [40]. The addition of antibiotics (doxycycline or minocycline) can be considered for anti-inflammatory and antimicrobial properties.

Regarding inflamed DONs, an expert panel recommended that high Hyal doses (ie, 500 iu every 48 hours until resolution) be
administered after oral antibiotics have been tried for at least 2 weeks [41]. The panelists indicated that Hyal may break down the bacterial biofilm, thus facilitating the spread of infection; therefore, it should not be used as first-line therapy for inflammatory DONs. Another expert panel favored administering Hyal injection (30-300 iu) as first-line therapy with oral antibiotics [42]. Participating experts recommend a watchful approach of 48 hours to 2 weeks after starting antibiotic therapy, unless a more resistant HA (ie, Vycross) has been injected, in which case Hyal must be given as early as possible. Vycross technology has a 1% to 4% DON risk [40]. Highly cross-linked fillers may require higher doses and more sessions of Hyal for effective degradation due to their resilient nature. Early intervention with Hyal is preferred to prevent the development of more persistent complications. The above dose recommendations were made while also acknowledging that the Hyal dose depends on the size of the nodule, location (eg, tear troughs require a lower dose than midface), and filler properties [41,42]. The clinical practice supports injecting Hyal into the center of the nodule with a low gauge (18 or 21 G) needle to disrupt an encapsulated (filler) organization by allowing more penetrations [42]. Subsequent dissolution via Hyal with increasing dosages should be repeated after 2-3 weeks; however, Hyal injections should be limited to 2-3 cycles if there has been no response [42].

HFUS-guided injection can increase the likelihood of response of a nodule or granuloma to Hyal [16]. The inflamed nodule or granuloma has a “capsule” (ie, prominent chronic inflammatory and granulomatous reaction at the periphery); in such case, ultrasound can show in real time that the needle or cannula injecting the medication has penetrated the “capsule” before Hyal is injected [1].

Granuloma is a rare complication (0.01%-1%) of fillers and appears after a latent period, which can be several months to years postinjection [43,44]. Granulomas caused by HAs appear as cystic granulomas [45]. Encapsulation occurs at advanced stages, and histology shows palisaded granulomatous tissue mainly composed of giant cells and macrophages. Biofilm formation has been a suggested trigger [46]. Granulomas can be treated with Hyal dosed up to 150 iu [47]. Multiple Hyal sessions are often required. Granulomas with conspicuous fibrosis and abundant giant cells may not respond to Hyal. Still, most authors suggest using as first-line therapy high-concentration intralesional steroids, such as 20-40 mg/mL of triamcinolone or a combination of intralesional triamcinolone 10 mg/mL, 5-fluorouracil 50 mg/mL, and lidocaine [48]. Intralesional steroids interfere with the activities of fibroblasts, macrophages, giant cells, and collagen synthesis [45]. Intralesional steroids should be considered when inflammation is a significant component of the granulomatous reaction and 5-fluorouracil when there is excessive tissue growth associated with the granuloma. Treatment should be repeated every 3 to 4 weeks until resolution [48]. Surgical excision should be the last resort.

Allergic and Hypersensitivity Reactions
Most reactions to HA fillers are localized and manifest with edema, induration, and erythema at the injection site, pruritus, pain or tenderness, and eruption as early as a few days and as late as years after injection [49,50]. There have been no reports of type II or III reactions. Type I hypersensitivity reactions, such as localized angioedema, are uncommon as are type IV (delayed) reactions that are noted in less than 1% of cases [51]. Type IV reactions can manifest with painful erythematous nodules [50]. A delayed onset facial edema may be caused by type IV reaction and can develop several days to weeks after filler injection [52].

Type I reactions typically respond to oral antihistamines with or without intraleosional or oral steroids [1,48,50]. Epinephrine should be administered in systemic reactions such as anaphylaxis or other severe cases. Providers should have an emergency kit containing epinephrine pens, oral steroids, and antihistamines in the treatment room [1]. Type IV reactions may not respond to antihistamines. Degradation of the filler depot with Hyal can be considered when an allergic or hypersensitivity reaction does not improve with a course of antihistamines or systemic corticosteroids. If the reaction is considered moderate or severe, oral corticosteroids should be taken before Hyal use to manage or prevent the potential initial worsening of symptoms due to increased antigens as the HA is broken down [52]. Hyal can be an alternative treatment for delayed facial edema as it does not carry the risks associated with prolonged systemic steroid treatment [52]; however, multiple treatment sessions are typically required, and Hyal can lead to at least partial loss of the filler treatment effect that may not be acceptable by the patient. COVID-19 vaccines have been reported to cause delayed reactions to HA fillers [53]. Two cases of COVID-19 vaccine-triggered delayed inflammatory reaction to HA filler were treated with Hyal [54,55].

Vascular Compromise and Skin Necrosis
The incidence of impending necrosis following dermal filler treatment was estimated at 0.001% (1 in 100,000 cases) in 2013 [56] and increased to 0.009% in 2020 [57]. Vascular occlusion associated with filler injection may be due to intravascular embolism, extravascular compression, and vascular spasm [1]. Pain is the earliest symptom, and coolness, blanching (immediate; may be transient), and livedo pattern are the earliest signs (Figure 3) [57]. A delayed capillary refill (normal, 1-2 seconds) is noted within minutes. A blue-gray appearance follows within tens of minutes to hours due to deoxygenated blood in the tissue. Skin breakdown is noted within days, and the following repair phase lasts days to weeks [57,58].
Figure 3. (A) Vascular compromise after embolization of the angular artery with HA injected in the nasolabial fold manifested with a livedoid pattern over the right nasolabial fold, lateral upper cutaneous lip, and nose. (B) Resolution of the complication is shown 2 days after treatment with 700 iu Hyal and vigorous massage.

Vascular compromise requires immediate treatment. However, there is no consensus regarding the Hyal protocol in this complication [7]. Hyal should be administered as soon as possible, optimally within 4 hours [5]. The number of Hyal sessions depends on the severity of the complication and how quickly the intervention occurs. An animal study showed a significant reduction of the ischemic areas within 4 hours of Hyal treatment but no improvement after 24 hours [59]. In a series of patients with impending nasal skin necrosis related to the nose and nasolabial fold augmentation with HA fillers, full resolution of the complication occurred when Hyal treatment was administered within 2 days [60]. In a systematic review, Hyal failed to eliminate the large area of necrosis but played a moderate role in earlier recovery in limited necrosis [61].

A high-dose (total of 450-1500 iu in up to 4 Hyal cycles) pulsed Hyal protocol should be adopted [18,21,62]. Delorenzi suggested a simplified determination of Hyal dosage in the high-dose protocol considering the size of the ischemic area [62]. For a “single area” (eg, one-half of the upper lip) low-volume vascular event (by definition, <0.1 mL of filler embolus) Hyal dose should be about 450 iu; if a second area is affected, such as the nose, then the dose would be 900 iu. Hyal should be infiltrated diffusely into the ischemic tissues, including the vessel’s course. Perivascular Hyal will permeate vascular walls. Delorenzi showed ex vivo that cross-linked HA contained within the intact artery is susceptible to hydrolysis by Hyal found outside the vessel in its immediate surroundings [63]. Hyal injections should be followed by warm compresses and vigorous massage of the areas to improve drug diffusion and enhance blood flow. Then one should observe and reassess skin color and capillary refill after 60 minutes [62]; however, other authors recommend assessment every 15-20 minutes [24]. If vascular compromise persists, repeat Hyal treatment for up to 4 cycles should be administered [18,62]. Daily follow-up should occur, and more Hyal treatment performed until there is a satisfactory resolution. If treatment is completed within 72 hours of the onset of ischemia, success is possible [62].

An important study by Schelke et al [6] showed that when Hyal is injected under HFUS guidance, lower dosages (35-50 iu) than those in current “high dose” protocols (>500 iu) can be used. This is due to the higher accuracy of Hyal injections performed under HFUS guidance. Also, the study showed that a single Hyal injection yields a full resolution of the vascular complication compared to hourly injections over several hours in the current, high-dose protocol.

The patient should be kept under observation in the clinic for any adverse reactions—which anaphylaxis to Hyal occurs, it is usually within minutes, but there have been cases of delayed onset [18]. All patients should be warned about allergic or
anaphylactic response symptoms and instructed to seek medical attention promptly.

**Vision Loss**

This is a rare but severe complication. A literature review by Beleznyay et al [64] identified 146 cases in 2019. In recently reported cases, the nasal region (56.3%) was at the highest risk, and HA filler was the most common (81.3%) cause of this complication. Blindness due to periocular embolism of HA is instant and associated with excruciating ocular pain. The mechanism of action of blindness after filler injection is thought to involve intra-arterial injection of filler followed by subsequent retrograde embolization into the ophthalmic artery system [64]. The retinal circulation needs to be restored within 60 to 90 minutes if the retina is to survive. Blindness is an emergency; the patient should be transferred immediately to the nearest hospital ophthalmology department [65].

Currently, there is no evidence-based, accepted standard of care for treating visual compromise caused by filler [64]. Treatments that have been used vary widely and successful attempts are rare. If an HA filler was used, Hyal should be injected into the skin at the injection site and along the path of anastomosing arteries. Retrobulbar Hyal (RBH) injection (150-200 iu in 2-4 mL of diluent) into the inferolateral orbit should be considered by practitioners who have appropriate experience and competence while waiting for an ambulance [66]. A total of 3 cases experienced partial or complete vision recovery after treatment with RBH, although only 1 case directly attributed success to the RBH [64]. In that case, full vision restoration was achieved with Hyal (450 iu as retrobulbar injections and 300 iu to surround the supraorbital and infraorbital foramina) in a patient who received HA fillers in the midface [67]. RBH did not improve vision in other reports [68,69], Zhu et al [68] failed to show any improvement in visual loss following 1500 to 3000 iu RBH in 4 patients. The authors indicated that Hyal is ineffective at recanalizing the retinal artery occlusion or improving the visual outcome after 4 hours of the onset of blindness.

However, other authors have challenged the RBH approach because Hyal did not demonstrate the ability to cross the dural sheath of the optic nerve and reach an occlusion of the central retinal artery [70,71]. In a cadaver model, Hyal could not cross the optic nerve’s dura into the space where it could bathe the central retinal artery [70]. Most importantly, hardly 5 mm of the ophthalmic artery is exposed in the orbit that is not covered with dura. An alternative approach was suggested, injecting into the supraorbital or supratrochlear artery. In the supraorbital method, Hyal is injected into the supraorbital artery in the supraorbital foramen [72]. The supraorbital approach is less invasive than the retrobulbar and can be effective in cases where the blood vessel blockage is closer to the skin’s surface. This technique has resulted in 2 cases of immediate vision recovery [72,73]. This approach requires no special skills compared to retrobulbar injections which are technically difficult procedures even for a competent ophthalmological surgeon. Still, other authors have challenged the feasibility and practicality of the supraorbital approach as the supraorbital and supratrochlear arteries are difficult to cannulate [64,74]. However, ultrasound guidance may facilitate this approach [75].

**Limitations**

Pitfalls include the loss of HAG treatment effect and adverse effects of Hyal such as allergic reactions. High Hyal doses can result in complete loss of the HAG effect. In a retrospective review of 20 patients with lower eyelid edema post-HA filler injection, Hyal 20-75 iu (injected 0.2-0.5 mL) per region was administered. All patients responded to treatment without recurrence. However, in 2 cases, all injected HA was degraded, resulting in a loss of treatment effect [76]. To prevent loss of the HAG effect, most authors recommend multiple treatment sessions with smaller Hyal doses in nonemergent filler complications, such as noninflammatory nodules, with reassessment after each session. The patient should be consulted regarding at least partial filler effect loss when Hyal is injected.

Adverse effects of Hyal injections are mainly local and include pruritus, burning sensation, swelling, erythema, ecchymosis limited to the injection site, spread of infection, and allergic reactions [1,24,77]. A total of 3 cases of ecchymosis away from the Hyal injection site in the infraorbital area were reported by this author who suggested that Hyal may facilitate the spread of ecchymosis on thin skin [37].

The overall allergy rates are low, reported 0.03%-0.13% with peribulbar injections [24]. Immunoglobulin E-mediated type I hypersensitivity with the Hyal doses administered in aesthetic medicine is rare (incidence about 0.1%), but it is quoted high (33%) with large intravenous doses (>200,000 iu) [13,24]. Delayed hypersensitivity (type IV reaction) to Hyal has been rarely reported in aesthetic practice [77-79]. A case report described delayed hypersensitivity after Hyal treatment of granulomatous HA reaction [78]. In case of severe allergy caused by exogenous Hyal, autologous serum may be considered in nonacute cases requiring accelerated removal of HA filler [19].

This narrative literature review is limited by the sole inclusion of studies published in English available in PubMed and Google Scholar, which may have excluded studies unavailable in English or indexed in other databases. There is a limited number of controlled studies. Many studies included small sample sizes and reported descriptive outcomes. There is controversy regarding the most effective Hyal protocol for managing HA filler-associated vision loss.

**Conclusions**

Properly used Hyal can resolve nonemergent HA filler complications. The physical properties of the HA filler influence its degradation by Hyal and higher Hyal doses are required for HAGs resistant to degradation. Emergent complications such as vascular occlusion with impending skin necrosis should be treated promptly with high Hyal doses flushed into ischemic tissues. Hyal treatment of vision loss has met limited success, and the injection technique, retrobulbar versus supraorbital, remains controversial. More sufficiently powered controlled studies are needed. Hyal treatment has an acceptable safety profile, with allergic or hypersensitivity reactions uncommon in aesthetic practice.
Declaration of Patient Consent

The patient has given informed consent for the patient's images and other clinical information to be published in a medical journal. The patient understands that the patient's name and initials will not be published and due efforts will be made to conceal their identity, but complete anonymity cannot be guaranteed.

Conflicts of Interest

None declared.

References


Abbreviations
DON: delayed onset nodule
HA: hyaluronic acid
HAG: hyaluronic acid gel
HFUS: high-frequency ultrasound
Hyal: hyaluronidase
iu: international units
RBH: retrobulbar Hyal
RCT: randomized controlled trial

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Worldwide Distribution and Extracutaneous Manifestations of Henoch-Schönlein Purpura in Adults: Narrative Review

Blair W Harris¹, DO; Luke Maxfield¹, DO; Abigail Hunter¹, DO; Mandy Alhajj², DO; Byung Ban³, DO; Kayd J Pulsipher¹, DO

¹Department of Dermatology, Sampson Regional Medical Center, Campbell University, Clinton, NC, United States  
²Department of Dermatology, Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH, United States  
³Department of Rheumatology, MedStar Georgetown University Hospital, Washington, DC, United States

Corresponding Author:  
Kayd J Pulsipher, DO  
Department of Dermatology  
Sampson Regional Medical Center  
Campbell University  
607 Beaman Street  
Clinton, NC, 28328  
United States  
Phone: 1 4355356888  
Email: kpulsipher@sampsonrmc.org

Abstract

Background: Henoch-Schönlein purpura (HSP), a leukocytoclastic small vessel vasculitis, exhibits both cutaneous and systemic manifestations. While predominantly observed in childhood, it may manifest in adults with more pronounced systemic involvement. Furthermore, HSP is a global phenomenon showcasing epidemiological and systemic variances.

Objective: This study aims to scrutinize extracutaneous manifestations in adults with HSP, discerning distinctions according to geographical regions on a worldwide scale.

Methods: A comprehensive search encompassing PubMed, Embase, Cochrane Library, and Web of Science was executed, covering papers published from January 1, 1970, to December 1, 2019. Keywords used included “Henoch-Schönlein purpura,” “Henoch Schönlein purpura+adult,” “IgA vasculitis+adult,” “HSP+adult,” and “IgAV.” A total of 995 publications were identified, from which 42 studies encompassing 4064 patients were selected, with a predominant focus on cases reported in Asia, Europe, and the Americas.

Results: Among adults afflicted with HSP, European patients exhibited a higher propensity for male predominance (P<.001), gastrointestinal involvement (P<.001), and musculoskeletal complications (P<.001). Conversely, patients from the Americas were least likely to experience genitourinary involvement (P<.001).

Conclusions: HSP demonstrates a variance in distribution and extracutaneous manifestations within distinct geographical boundaries. In the adult population, European patients exhibited a higher prevalence of male gender and gastrointestinal and musculoskeletal involvement. Asian patients were more predisposed to genitourinary involvement when compared to their American counterparts. The establishment of prospective studies using standardized reporting measures is imperative to validate the relationships unveiled in this investigation.

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Keywords: extracutaneous manifestations; HSP; Henoch-Schönlein purpura; immunoglobulin A vasculitis; IgAV; IgA vasculitis; narrative review

Introduction

Henoch-Schönlein purpura (HSP), also known as immunoglobulin A vasculitis (IgAV), stands as the most prevalent form of vasculitis in childhood [1]. This condition exhibits a considerable disparity in incidence between children and adults, with palpable purpura constituting a hallmark feature in both populations [1-7]. Approximately 90% (135/150) of
HSP cases manifest within the first decade of life. Notably, the United States reports an annual incidence in children ranging from 6.1 to 20.4 cases per 100,000. In the United Kingdom and France, children aged 17 years or younger demonstrate an annual incidence of approximately 20 to 70 cases per 100,000. It is noteworthy that Asian studies have documented an even higher incidence, reaching 56 cases per 100,000 [2,3,7-14].

In contrast, the annual incidence of HSP in adults exhibits a lower prevalence, estimated to range from 1.4 to 5.1 cases per 100,000, with a heightened frequency observed during the fifth and sixth decades of life [8-11]. In both pediatric and adult populations, HSP has been reported to display a male predilection, barring exceptions identified in 2 Korean studies [11-13].

Despite individual investigations focusing on the correlation between cutaneous manifestations and systemic involvement, no prior studies have undertaken a comprehensive assessment of the global geographical disparities concerning extracutaneous manifestations in adult patients. Our primary aim, therefore, is to meticulously scrutinize the existence and distribution of extracutaneous manifestations in adult patients with HSP, stratified by geographic regions across the world.

Methods

Search Parameters

To comprehensively assess extracutaneous manifestations in adults with HSP, an exhaustive review of the literature was conducted. This review encompassed the databases PubMed, Embase, Cochrane Library, and Web of Science, scrutinizing papers published from January 1, 1970, through December 1, 2019. A search was facilitated using the following keywords: “Henoch-Schönlein purpura” OR “henoch schonlein purpura+adult,” “IgA vasculitis+adult,” “HSP+adult,” and “IgAV.” A total of 995 publications were initially identified.

Inclusion Criteria

Stringent inclusion criteria were applied, focusing exclusively on papers presenting original data that contained pertinent information regarding gastrointestinal (GI), genitourinary (GU), and musculoskeletal (MSK) involvement. Specifically, GI involvement was delineated as the onset of abdominal pain, melena, or hematochezia; MSK involvement was defined by the emergence of new arthritis or arthralgia; and GU involvement was ascribed to the appearance of new proteinuria, hematuria, acute kidney injury, or the exacerbation of chronic kidney disease. Individual case reports and publications limited solely to pediatric patients were excluded from the analysis.

Screening Process

This meticulous screening process resulted in the inclusion of 42 eligible studies that adhered to the predefined criteria. The majority of the reported cases were drawn from 3 predominant regions, namely, Asia, Europe, and the Americas. Subsequently, patients were categorized according to their respective geographical regions, and a comparative analysis was performed to discern the number of cases and the mean involvement of the GI, GU, and MSK systems within each region. Statistical analyses, including omnibus tests and post hoc pairwise comparisons, were executed using MedCalc (version 19.1; MedCalc Software Ltd).

Results

Age and Gender by Geography

A total of 42 studies incorporating data from 4064 adult patients were included in this comprehensive analysis. These studies were divided into 23 European studies, 17 Asian studies, and 4 papers published in North and South America. Notably, the age of onset in Asian patients was significantly earlier, with an average of 29.8 (SD 7.02) years, compared to their European counterparts (mean 49.3, SD 9.14 years; P<.001) and individuals in the Americas (mean 48.6, SD 4.17 years; P<.001). In terms of gender distribution, a marked discrepancy emerged, with male patients exhibiting a higher prevalence in Europe (n=997, 62.2%), while both genders demonstrated a relatively equitable distribution in Asia and North and South America (n=135, 47.7% vs n=1120, 51.4%; P=.12).

Extracutaneous Manifestations by Geography

Furthermore, the clinical presentation of HSP exhibited noteworthy regional variations. Europeans displayed a higher propensity for GI involvement, affecting 58.2% (n=932) of patients, a percentage significantly greater than the 31.4% (n=89) observed in the Americas (P<.001) and the 44.7% (n=974) in Asian populations (P<.001). Additionally, MSK involvement was notably prevalent among Europeans, with 57.9% (n=928) of individuals manifesting such symptoms. This proportion exceeded the figures observed in the Americas (n=135, 47.7%; P<.001) and Asia (n=1034, 47.4%; P<.001). Interestingly, among adults in Asia with HSP, GU involvement was the most frequent, impacting 72.3% (n=1575) of patients, although this did not display a statistically significant difference from the 67.2% (n=1077) observed in European populations (P=.08). Conversely, individuals in North and South America exhibited the lowest likelihood of GU involvement at 47% (n=133; P<.001). A comprehensive summary of demographics and the extent of extracutaneous organ involvement can be found in Table 1.

Table 1. Age, gender, and extracutaneous involvement of Henoch-Schönlein purpura separated by geographic region (N=4064).

<table>
<thead>
<tr>
<th>Region</th>
<th>Total patients, n (%)</th>
<th>Age (years), mean (SD)</th>
<th>Male patients, n (%)</th>
<th>Female patients, n (%)</th>
<th>Gastrointestinal involvement, n (%)</th>
<th>Musculoskeletal involvement, n (%)</th>
<th>Genitourinary involvement, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>1602 (39.4)</td>
<td>49.3 (9.14)</td>
<td>997 (62.2)</td>
<td>605 (37.8)</td>
<td>932 (58.2)</td>
<td>928 (57.9)</td>
<td>1077 (67.2)</td>
</tr>
<tr>
<td>Americas</td>
<td>283 (6.9)</td>
<td>48.6 (4.17)</td>
<td>135 (47.7)</td>
<td>148 (52.3)</td>
<td>89 (31.4)</td>
<td>135 (47.7)</td>
<td>133 (47)</td>
</tr>
<tr>
<td>Asia</td>
<td>2179 (53.6)</td>
<td>29.8 (7.02)</td>
<td>1120 (51.4)</td>
<td>1059 (48.6)</td>
<td>974 (44.7)</td>
<td>1032 (47.4)</td>
<td>1575 (72.3)</td>
</tr>
</tbody>
</table>
Discussion

Pathophysiology
The etiology of HSP remains elusive; however, this systemic vasculitis is widely regarded as an immune-mediated disorder, characterized by the deposition of immunoglobulin A (IgA) complexes, which underlie the pathological alterations observed in the skin, kidneys, GI tract, and joints [15,16]. Various triggers have been postulated for the onset of HSP, encompassing recent upper respiratory infections, medications, and malignancies [13,17]. Notably, HSP appears to exhibit a seasonal predilection with a peak incidence during the winter months, while occurrences during the summer months are relatively rare [8,17].

Clinical Manifestations
HSP in the adult population is frequently associated with heightened disease severity and less favorable outcomes, particularly when it involves the integumentary system, renal function, and systemic vasculitic manifestations, in stark contrast to its typically benign and self-limiting course in children [11,16,18-20]. On rare occasions, HSP may extend its impact to include the pulmonary, cardiac, or nervous systems. The hallmark clinical features of HSP encompass the characteristic purpuric rash, joint pain, abdominal discomfort, edema, and hematuria [4,21,22].

Cutaneous manifestations of HSP commence as erythematous macules or urticarial papules, evolving into nonblanching palpable purpura, which symmetrically affect extensor surfaces, notably the buttocks and lower extremities. In some cases, involvement may extend to the trunk, face, and upper extremities [2]. Hemorrhagic bullae and vesicles appear to be more prevalent in older individuals [1,22].

There exists a divergence of evidence regarding the correlation between the severity of skin lesions and the extent of renal involvement and overall disease trajectory. Some investigations suggest that renal involvement is more frequent in individuals displaying skin direct immunofluorescence (DIF), indicative of immunoglobulin M (IgM) deposition and necrotic bullous skin lesions [1,23]. Conversely, other studies have failed to establish cutaneous IgM as a reliable indicator of renal or systemic disease in adult patients with HSP [24]. It is noteworthy that younger males presenting with generalized purpura and concurrent bowel involvement tend to experience less favorable outcomes, thus implying that the extent of skin involvement may serve as a predictive factor for the disease course and potentially guide therapeutic decisions [25].

Joint pain stands as a prevalent clinical manifestation of HSP, with its occurrence noted in over 60% of adult cases, with a higher likelihood observed in those 60 years and younger of age [26,27]. Joint disease may manifest in the form of arthritis or arthralgias, typically exhibiting a symmetric distribution, and most frequently impacting the knee and ankle joints [27]. Importantly, joint involvement typically resolves without enduring sequelae [28].

GI involvement, in conjunction with renal complications, constitutes a significant source of morbidity in adult patients with HSP [26]. Roughly two-thirds of HSP presentations include GI manifestations, most commonly manifesting as abdominal pain. Predominant abdominal symptoms encompass vomiting, diarrhea, periumbilical pain, and hematochezia. Notably, intussusception occurs in approximately 5% of patients, representing a significant GI complication. Other less frequent complications encompass bowel ischemia or infarction, necrosis, perforation, stricture formation, and GI hemorrhage [2,21,22,29].

Renal involvement is a common occurrence in HSP, yet its severity displays considerable variability. Indications of renal compromise manifest as hematuria and soft tissue edema due to proteinuria. Hematuria associated with HSP is typically macroscopic and may coincide with relapses of purpura or occur long after the resolution of extrarenal manifestations. The extent of proteinuria and the development of nephrotic syndrome exhibit a variable course, potentially leading to deterioration in glomerular filtration rate, azotemia, or end-stage renal failure. Predictors of renal involvement encompass recent infectious history, pyrexia, extension of purpura to the trunk, and biological markers of inflammation [22,23,30-32].

Notable predictors of adverse outcomes comprise renal insufficiency, hypertension, and the parameter of “young age” in adult patients [33-35]. Age at the onset of HSP has been postulated as a pivotal factor influencing disease severity and prognosis. Studies conducted by Hung et al [36] identified patients aged 20 years and older, male gender, bloody stools, and a rash persisting beyond 1 month as adverse prognostic factors for HSP. Schaier et al [37] reported that older patients with HSP presenting with renal involvement exhibited poorer outcomes than those aged 60 years and younger.

HSP nephritis stands as the most serious complication of HSP, with an incidence ranging from 20% to 80%. An adverse prognosis is particularly pronounced in patients presenting with nephrotic syndrome, renal failure, and, notably, hypertension at the time of diagnosis [38]. The presence of HSP nephritis aligns with the severity of renal histopathological changes [30-32,34].

Diagnosis
The diagnosis of HSP fundamentally relies upon clinical manifestations. In adults, biopsy is more frequently used to confirm the diagnosis, while pediatric patients typically necessitate biopsy only in cases of atypical presentations. While no specific diagnostic tests for HSP exist, a normal platelet count and coagulation studies play a crucial role in excluding other diseases that may be present with palpable purpura [8,17].

The diagnostic criteria for HSP, developed by European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society, exhibit a sensitivity of 100% and a specificity of 87%. The diagnostic criterion mandates the presence of purpura or petechiae, characterized by a lower limb predominance, along with a minimum of one of four of the following criteria [39]: (1) acute onset of diffuse abdominal pain, (2) histopathological evidence demonstrating leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant IgA deposits, (3) acute onset of arthritis or arthralgia, and (4) renal involvement, as indicated by proteinuria or hematuria.
For diagnosing the cutaneous vasculitis associated with HSP, the gold standard is a skin biopsy illustrating leukocytoclastic vasculitis in postcapillary venules, with the presence of IgA deposition, with or without eosinophils [22,40]. Notably, individuals aged 40 years and older, lacking eosinophils on skin biopsy, are reported to exhibit nearly a 3-fold heightened risk of developing renal involvement compared to those with eosinophils observed on skin biopsy [22,40].

HSP lacks specific biomarkers for diagnosis; nevertheless, certain markers hold effectiveness in monitoring disease activity and prognosis. DIF may reveal perivascular IgA and C3 deposition; however, individuals who otherwise meet clinical HSP criteria may not display IgA deposition on DIF [22]. In cases where diagnostic uncertainty exists or severe renal involvement is evident, a renal biopsy may be deemed necessary. Renal biopsies may illustrate mesangial hypercellularity (grades I through VI) and crescents on light microscopy. Characteristic of HSP nephritis is the presence of granular mesangial IgA and C3 deposition on light microscopy (with IgM and immunoglobulin G to a lesser extent) [13,22]. It is noteworthy that, on renal biopsy, the pathognomonic granular IgA and C3 deposition in the mesangium is indistinguishable from IgA nephropathy [22]. Moreover, the extent of interstitial fibrosis, the percentage of sclerotic glomeruli, and the presence of glomeruli displaying fibrinoid necrosis on renal biopsy have been associated with an unfavorable renal prognosis [27].

Treatment
The management of adult IgAV has garnered limited investigation and remains a subject of controversy [26,41]. Notably, adults often necessitate more aggressive therapeutic approaches compared to pediatric patients. The mainstay of treatment involves supportive care and corticosteroids, complemented by varying use of immunosuppressive agents and plasma exchange [42].

Corticosteroids contribute to the swift resolution of renal manifestations and serve as a valuable tool in the management of joint and abdominal pain along with the duration of skin lesions. However, their efficacy in preventing palpable purpura or complications such as glomerulonephritis, bowel infarction, or intussusception remains unproven [11,26,41-43].

Immunosuppressive agents, including cyclophosphamide, cyclosporine, and rituximab, have been subjects of study in the context of HSP treatment. In instances marked by severe organ involvement and life-threatening complications, corticosteroids and immunosuppressive drugs are often initiated. Nevertheless, the augmentation of immunosuppressant agents to corticosteroid regimens does not appear to confer additional benefits when juxtaposed with the use of corticosteroids in isolation. Piliebout et al [27], for instance, conducted a comparative analysis between corticosteroids alone and corticosteroids combined with cyclophosphamide in patients with biopsy-confirmed IgAV and discerned no discrepancy at 12 months with regard to remission rates, renal outcomes, and adverse events. However, it is noteworthy that overall survival was more favorable in the corticosteroids plus cyclophosphamide group [26,27,41]. In a study by Maritati et al [44], rituximab, a B-cell depleting antibody, exhibited safety and efficacy in the treatment of adult-onset IgAV, with 20 of 22 patients achieving remission, although 7 of those 20 experienced disease relapse [44].

An illustrative case series by Augusto et al [45] highlighted the potential benefits of combining corticosteroids and plasma exchange in the treatment of severe HSP in adults. This approach yielded swift improvements in the patient Birmingham Vasculitis Activity Score, estimated glomerular filtration rate, and proteinuria, culminating in positive long-term outcomes at 6 and 12 months [45]. Nevertheless, renal involvement can precipitate end-stage renal failure, and it may manifest rapidly, necessitating the imperative need for dialysis or renal transplant, notwithstanding the concerns surrounding disease relapse [41]. Encouragingly, in 1 case series, none of the 12 transplant recipients lost their grafts due to relapse [41]. However, it should be acknowledged that renal transplant recipients have been subject to relapses, with 1 instance suggesting a potential role for plasmapheresis in addressing disease recurrence [46].

Limitations
The primary limitation of this review is related to the simplicity of our search strategy. The volume of publications indexed in PubMed, Embase, Cochrane Library, and Web of Science in combination with the stringent screening process used limited our review to the 42 papers included in the results.

Conclusions
Our comprehensive review underscores the noteworthy observation that adults afflicted with HSP frequently manifest pronounced extracutaneous involvement, with a proclivity toward progressive renal disease. Furthermore, it highlights the prospect of regional disparities in the risk of developing extracutaneous manifestations associated with HSP. To corroborate the relationships elucidated in this investigation, there is a compelling need for prospective studies that use standardized reporting measures.

Conflicts of Interest
None declared.

References


Abbreviations

DIF: direct immunofluorescence
GI: gastrointestinal
GU: genitourinary
HSP: Henoch-Schönlein purpura
IgA: immunoglobulin A
IgAV: Immunoglobulin A vasculitis
IgM: immunoglobulin M
MSK: musculoskeletal

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REDCap as a Platform for Cutaneous Disease Management in Street Medicine: Descriptive Study

Emily Eachus1*, BSc; Kayla Schwartz1*, BSc; Taha Rasul1, MD; Daniel Bergholz1, MD; Jonette Keri1, MD, PhD; Armen Henderson1, MD
Miami Street Medicine, University of Miami Miller School of Medicine, Miami, FL, United States
*these authors contributed equally

Corresponding Author:
Emily Eachus, BSc
Miami Street Medicine
University of Miami Miller School of Medicine
Suite 1149
1600 NW 10th Avenue
Miami, FL, 33136
United States
Phone: 1 954 610 8779
Email: eeachus@med.miami.edu

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KEYWORDS
REDCap; unsheltered homelessness; street medicine; informatics; cutaneous; homeless; homelessness; data capture; data collection; skin; dermatology; vulnerable; low income; low resource; database; chart; health record; health records; EHR; electronic health record

Introduction

According to the 2022 Annual Homelessness Report to Congress, on a single night, 582,462 people experienced homelessness across the United States, and 233,832 (over 40%) of those experienced unsheltered homelessness [1]. A 2020 systematic integrative review of health and social care in people experiencing homelessness showed that this population experienced inequities in access to basic human needs, health care, and social support [2], which are compounded by poor interpersonal dimensions such as a lack of provider support and stigmatization. Altogether, people experiencing homelessness are at risk for morbidity and premature death [3,4]. People experiencing homelessness require programs that bypass social barriers to health care. The street medicine approach uses teams of health care providers and volunteers to meet patients where they are currently living on the streets of major cities, bypassing barriers such as lack of transportation, ability to pay, and lack of primary care by bringing a mobile clinic with medications, supplies, and providers directly to people experiencing homelessness [5].

Because student-led street medicine is often volunteer based and not directly affiliated with hospital systems, many lack robust electronic medical record (EMR) systems [6]. Correspondingly, the lack of efficient medical care documentation is an obstacle to providing longitudinal care to patients experiencing homelessness. REDCap is a Health Insurance Portability and Accountability Act–compliant free web application used to create databases for clinical research and projects [7,8]. However, per our evaluation of the medical literature, there are no reports of medical record keeping or using REDCap among street medicine organizations.

This retrospective descriptive study describes the use of a custom REDCap-based EMR for the management of cutaneous diseases in a Miami-based street medicine organization, Miami Street Medicine (MSM).

Methods

Ethical Considerations
The University of Miami Institutional Review Board (IRB) approved reviewing records of cutaneous disease among people experiencing homelessness (IRB ID: 20230666).

Overview
A custom REDCap-based EMR was developed in November 2020 for MSM. The MSM custom REDCap includes forms for medical notes, vitals, labs, and more. The EMR was further customized to the unique needs and circumstances of people experiencing homelessness.

Specific drop-down lists about cutaneous pathology were created. The drop-down menus allow for selecting a location...
on the body, wound characterization, whether the wound was infected, if debridement was done, and supplies used.

Between July 2021 and January 2022, patients were seen curbside in Miami once per week. Patients were assigned medical record numbers and had medical histories taken, vitals examined, and medications distributed as needed or called into a pharmacy by an attending physician. Records about skin and nail complaints were reviewed by board-certified dermatologists who made diagnoses of cutaneous conditions, recommended medical plans, and called in prescriptions. Diagnoses were not based on standard codes, but rather on clinical expertise, as all services were free and not reported to health insurance agencies.

Skin and nail pathologies were categorized by diagnosis as chronic infections, acute infections, inflammatory, wounds, miscellaneous, nail disorders, and undetermined.

Results

Among 140 patients experiencing homelessness seen from July 2021 to January 2022, 112 skin and nail diagnoses were recorded. The sample included a diverse cohort that was 50.2% (n=56) Black and 45.8% (n=51) White, with the remainder being Asian or Native American patients. Hispanic patients of any race made up 34.8% (n=39) of the sample. A total of 68.1% (n=77) of patients identified as male and 31.9% (n=35) as female. The highest morbidity lesions resulting in disability or infection were chronic wounds and ulcers requiring multiple care instances.

The most common dermatologic diagnosis outside of the miscellaneous category was acute infections, with the most common type of medication dispensed being for wound care (Multimedia Appendix 1).

Discussion

The use of a free customizable REDCap EMR system was instrumental in recording the high burden of cutaneous diseases and connecting patients with specialists and follow-up care. Charitable health care organizations can use REDCap as it provides cost-effective, modifiable, and accessible management of patient data. One of the benefits of using REDCap as an EMR for special populations is its customizability and ease of data analysis.

Limitations of using the REDCap EMR include data entry errors by volunteer scribes and the great effort required to build and maintain this system. As a transient population, we noted 71.6% (80/112) patient attrition from care. This could be improved by communication via phone or email. Further, many topical medications offered to patients were distributed without documentation; only medications specifically ordered for patients were included in this synthesis.

A REDCap-based EMR is a valuable tool for established street medicine teams and may improve the delivery of care to people experiencing homelessness.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Distribution of skin diagnosis by type. [PNG File, 42 KB - derma_v7i1e48940_app1.png ]

References


Abbreviations

EMR: electronic medical record
MSM: Miami Street Medicine
Research Letter

From the Cochrane Library: Systemic Interventions for Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and SJS/TEN Overlap Syndrome

Gaurav Nitin Pathak¹, PharmD; Thu Minh Truong¹,², PharmD; Amit Singal², BA; Viktoria Taranto³, MD; Babar K Rao¹,⁴, MD; Audrey A Jacobsen⁵,⁶,⁷, MD, MPH

¹Department of Dermatology, Rutgers Robert Wood Johnson Medical School, Somerset, NJ, United States
²Department of Dermatology, Rutgers New Jersey Medical School, Newark, NJ, United States
³Department of Dermatology, New York Institute of Technology, Glenhead, NY, United States
⁴Department of Dermatology, Rao Dermatology, Atlantic Highlands, NJ, United States
⁵Department of Dermatology, Hennepin Healthcare, Minneapolis, MN, United States
⁶Department of Dermatology, University of Minnesota, Minneapolis, MN, United States
⁷Department of Dermatology, Veterans Affairs Medical Center, Minneapolis, MN, United States

Corresponding Author:
Gaurav Nitin Pathak, PharmD
Department of Dermatology
Rutgers Robert Wood Johnson Medical School
1 World’s Fair Drive
Somerset, NJ, 08873
United States
Phone: 1 732235 9895
Email: gnp28@rwjms.rutgers.edu

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KEYWORDS
Steven-Johnson syndrome; toxic epidermal necrolysis; necrolysis; fatal; life-threatening; treatment; dermatology; skin; dermatological; SJS; TEN; corticosteroids; intravenous immunoglobulin; IVIG; etanercept; prednisolone; systematic; corticosteroid; corticoid; steroid; steroids

Introduction

Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN overlap syndrome are a spectrum of potentially life-threatening, rare, and severe cutaneous adverse reactions that are triggered by medication use typically within weeks of medication initiation. The pathogenesis of SJS/TEN is theorized to be a T lymphocyte–mediated immune response to an antigen of the offending medication causing epidermal necrosis [1]. There is limited evidence to support the use of therapies, such as glucocorticoids, intravenous immunoglobulins (IVIGs), cyclosporine, and etanercept, for the treatment of SJS and TEN [1]. We aim to summarize the key findings of a Cochrane review on the effects of systemic therapies for SJS/TEN.

Methods

To evaluate systemic therapies for SJS/TEN, a systematic review of randomized controlled trials (RCTs) and prospective observational comparative studies (up to March 2021) of patients of all ages with SJS/TEN was conducted [1]. The primary end points were disease-specific mortality (DSM) and adverse events leading to the discontinuation of systemic treatment therapy. Secondary end points included time to complete re-epithelialization, intensive care unit length of stay, total hospital length of stay, illness sequelae, and adverse events.

Results

In total, 9 studies with a total of 308 patients from across 7 countries were included in the analysis, of which 3 were RCTs and 6 were prospective observational studies; 2 studies were included in a meta-analysis. The risk of bias for the three RCTs was respectively rated as high, moderate, and low; all the prospective comparative studies were rated as having a high risk of bias. The interventions that were assessed included systemic corticosteroids, tumor necrosis factor-α inhibitors, and others (Table 1).

The overall level of certainty for the parameters of interest was low, so most findings were “uncertain.” It was uncertain if corticosteroids had a higher risk of DSM versus no
corticosteroids (relative risk [RR] 2.55, 95% CI 0.72-9.03). It was also uncertain if there was a difference between IVIGs and no IVIGs in terms of DSM (RR 0.33, 95% CI 0.04-2.91), time to re-epithelialization (mean difference −2.93, 95% CI −4.4 to −1.46 d), or length of hospital stay (mean difference −2.00, 95% CI −5.81 to 1.81 d). Etanercept did not significantly reduce DSM compared to corticosteroids (RR 0.51, 95% CI 0.16-1.63; P=.72), and serious adverse events, such as sepsis and respiratory failure, occurred in treatment with both groups. It was also uncertain if there was any difference between the cyclosporine and IVIG groups in terms of the risk of DSM (RR 0.13, 95% CI 0.02-0.98). A summary of other comparator studies is included in Table 2.

### Table 1. Key characteristics of included trials.

<table>
<thead>
<tr>
<th>Study (author, year)</th>
<th>Study design</th>
<th>Sample size, n</th>
<th>Intervention</th>
<th>Outcome measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azfar et al [2], 2010</td>
<td>Prospective observational study</td>
<td>40</td>
<td>Corticosteroids (dose unknown) vs supportive care</td>
<td>Disease-specific mortality</td>
</tr>
<tr>
<td>González-Herrada et al [3], 2017</td>
<td>Prospective controlled study</td>
<td>22</td>
<td>Cyclosporine (PO³ 3 mg/kg/d or IV³ 1 mg/kg/d until re-epithelialization, then tapered off 10 mg/d every 48 h) vs IVIG² (0.75 g/kg/d for 4 d; lower dose for renal insufficiency), systemic corticosteroids (37.5- to 100-mg prednisone equivalents for 4 d), or supportive care</td>
<td>All-cause mortality, expected death rate based on SCORTEN⁴, time to stabilization of BSA⁵ involvement, time to re-epithelialization start, and time to complete re-epithelialization</td>
</tr>
<tr>
<td>Han et al [4], 2017</td>
<td>Prospective comparator study</td>
<td>28</td>
<td>Plasmapheresis (1-time dose of 1000 mL of Ringer-Locke and 2-3 L of plasma at 1 L/h) vs IVIG or corticosteroids (unknown dose)</td>
<td>Hospital length of stay</td>
</tr>
<tr>
<td>Jagadeesan et al [5], 2013</td>
<td>Prospective comparator study</td>
<td>36</td>
<td>IVIG (0.2- to 0.5-g/kg cumulative dose over 3 d and IV dexamethasone (0.1-0.3 mg/kg/d; tapered within 1-2 wk) vs IV dexamethasone (0.1-0.3 mg/kg/d; rapidly tapered within 1-3 wk)</td>
<td>Disease-specific mortality, AEs⁶ leading to discontinuation, other AEs, mean days to full skin healing, mean length of hospital stay, and illness sequelae</td>
</tr>
<tr>
<td>Kakourou et al [6], 1997</td>
<td>Prospective comparative study</td>
<td>16</td>
<td>Corticosteroids (methylprednisolone bolus 4 mg/kg/d for 2 d after fever subsided) vs supportive care only</td>
<td>Mortality</td>
</tr>
<tr>
<td>Paquet et al [7], 2014</td>
<td>Open-label randomized controlled trial</td>
<td>10</td>
<td>IV NAC® in 5% glucose over 20-h period (150 mg/kg in 250 mL over first h; then 150 mg/kg in 500 mL for 4 h; and, lastly, 150 mg/kg in 1000 mL over 15 h) and IV infliximab (5 mg/kg over 2 h) vs NAC-only regimen (same as former)</td>
<td>Disease-specific mortality</td>
</tr>
<tr>
<td>Saraogi et al [8], 2016</td>
<td>Prospective observational study</td>
<td>43</td>
<td>IV corticosteroids, IVIG, and combination of corticosteroids and IVIG vs supportive care</td>
<td>Arrest of disease progression, time to re-epithelialization, and mortality</td>
</tr>
<tr>
<td>Wang et al [9], 2018</td>
<td>Open-label randomized controlled clinical trial</td>
<td>91</td>
<td>Subcutaneous etanercept 25 mg (50 mg if &gt;65 kg) twice weekly until skin lesions healed (n=48) vs IV prednisolone 1-1.5 mg/kg/d until skin lesions healed (n=43)</td>
<td>Disease-specific mortality and other AEs</td>
</tr>
<tr>
<td>Wolkenstein et al [10], 1998</td>
<td>Double-blind randomized controlled trial</td>
<td>22</td>
<td>Thalidomide 200 mg BID⁷ PO × 5 d vs placebo at same dosing regimen</td>
<td>Disease-specific mortality</td>
</tr>
</tbody>
</table>

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³PO: per os.
⁴IV: intravenous.
⁵IVIG: intravenous immunoglobulin.
⁶SCORTEN: Score for Toxic Epidermal Necrolysis.
⁷BSA: body surface area.
⁸AE: adverse event.
⁹NAC: N-acetylcysteine.
¹⁰BID: twice per day.
### Table 2. Summary of key study findings.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of patients (number of studies)</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Certainty of evidence (GRADE(^a))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids vs supportive care</strong></td>
<td>56 (2 OS(^b)) [2,6]</td>
<td>DSM(^c): 91 per 1000 (supportive care) vs 232 per 1000 (corticosteroid); TTCR(^d): NR; ICU-LOS(^e): NR; TH-LOS(^f): NR; AE/DC(^h): NR</td>
<td>DSM: 2.55 (0.72 to 9.03); TTCR: NR; ICU-LOS: NR; TH-LOS: NR; AE/DC: NR</td>
<td>Very low</td>
</tr>
<tr>
<td><strong>IVIG(^i) and supportive care vs supportive care</strong></td>
<td>36 (1 OS) [5]</td>
<td>DSM: 55 (6 to 386) per 1000 (IVIG) vs 167 per 1000 (supportive care); TTCR: mean 10.93 d, mean difference 2.93 d lower (4.4 d lower to 1.46 d lower); ICU-LOS: NR; TH-LOS: mean 15.33 d, mean difference 2.00 d lower (5.81 d lower to 1.81 d higher); AE/DC: NR</td>
<td>DSM: 0.33 (0.04 to 2.91); TTCR: NR; ICU-LOS: NR; TH-LOS: NR; AE/DC: NR</td>
<td>Very low</td>
</tr>
<tr>
<td><strong>Etanercept vs supportive care</strong></td>
<td>No studies fit criteria</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
</tr>
<tr>
<td><strong>Cyclosporine vs supportive care</strong></td>
<td>No studies fit criteria</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
</tr>
<tr>
<td><strong>IVIG vs corticosteroids</strong></td>
<td>No studies fit criteria</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
</tr>
<tr>
<td><strong>Etanercept vs corticosteroids</strong></td>
<td>91 (1 RCT(^k)) [9]</td>
<td>DSM: 163 per 1000 (corticosteroids) vs 83 (26 to 263) per 1000 (etanercept); TTCR: NR; ICU-LOS: NR; TH-LOS: NR; AE/DC: NR</td>
<td>DSM: 0.51 (0.16 to 1.63); TTCR: NR; ICU-LOS: NR; TH-LOS: NR; AE/DC: NR</td>
<td>Low(^i)</td>
</tr>
<tr>
<td><strong>Cyclosporine vs corticosteroids</strong></td>
<td>No studies fit criteria</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
</tr>
<tr>
<td><strong>Etanercept vs IVIG</strong></td>
<td>No studies fit criteria</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
</tr>
<tr>
<td><strong>Cyclosporine vs other treatments (IVIG: n=4; corticosteroids: n=1; no specified treatment: n=1)</strong></td>
<td>22 (1 OS) [3]</td>
<td>DSM: 500 per 1000 (other treatments) vs 65 (10 to 468) per 1000 (cyclosporine); TTCR: NR; ICU-LOS: NR; TH-LOS: NR; AE/DC: NR</td>
<td>DSM: 0.13 (0.02 to 0.98); TTCR: NR; ICU-LOS: NR; TH-LOS: NR; AE/DC: NR</td>
<td>Very low</td>
</tr>
<tr>
<td><strong>Etanercept vs cyclosporine</strong></td>
<td>No studies fit criteria</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
<td>N/A(^i)</td>
</tr>
<tr>
<td><strong>N-acetylcysteine and infliximab vs infliximab alone</strong></td>
<td>10 (1 OS) [7]</td>
<td>NR</td>
<td>DSM: 2.00 (0.26 to 15.62)</td>
<td>NR(^i)</td>
</tr>
<tr>
<td><strong>Thalidomide vs placebo</strong></td>
<td>22 (1 RCT) [10]</td>
<td>NR</td>
<td>DSM: 2.78 (1.04 to 7.40)</td>
<td>NR(^i)</td>
</tr>
<tr>
<td><strong>Plasmapheresis vs other treatments</strong></td>
<td>28 (1 OS) [4]</td>
<td>NR</td>
<td>TH-LOS: mean difference −7.37 (−16.09 to 1.35) d</td>
<td>NR(^i)</td>
</tr>
</tbody>
</table>

\(^a\)GRADE: Grading of Recommendations, Assessment, Development, and Evaluation.

\(^b\)OS: observational study.

\(^c\)DSM: disease-specific mortality of Steven-Johnson syndrome and toxic epidermal necrolysis.

\(^d\)TTCR: time to complete re-epithelialization.

\(^e\)NR: not reported.

\(^f\)ICU-LOS: intensive care unit length of stay.

\(^g\)TH-LOS: total hospital length of stay.

\(^h\)AE/DC: adverse effects leading to discontinuation of Steven-Johnson syndrome/toxic epidermal necrolysis therapy.

\(^i\)IVIG: intravenous immunoglobulin.

\(^j\)N/A: not applicable.

\(^k\)RCT: randomized controlled trial.

### Discussion

The authors of the original review concluded that “etanercept (25 mg [50 mg if weight > 65 kg]) twice weekly ‘until skin lesions healed’) may reduce DSM compared to corticosteroids (intravenous prednisolone 1 to 1.5 mg/kg/day ‘until skin lesions healed’) (RR 0.51, 95% CI 0.16 to 1.63; 1 study; 91 participants; low - certainty evidence); however, the CIs were consistent with possible benefit and possible harm” [1]. Overall, data from...
the included studies were limited, with few direct clinical comparator studies for the different therapeutic agents assessed. Future multicenter large-scale studies are needed to better outline SJS/TEN medication therapy and evaluate agents of choice in disease management.

Conflicts of Interest
BR is a speaker for Incyte and Amgen. AAJ has received the Cochrane Scholarship for the original Cochrane review from the American Academy of Dermatology. All other authors have no conflicts of interest to declare.

Editorial Notice
This article is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2022, Issue 3, DOI: 10.1002/14651858.CD013130.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

References

Abbreviations
- DSM: disease-specific mortality
- IVIG: intravenous immunoglobulin
- RCT: randomized controlled trial
- RR: relative risk
- SJS: Steven-Johnson syndrome
- TEN: toxic epidermal necrolysis
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Direct-to-Patient Mobile Teledermoscopy: Prospective Observational Study

Abstract

Direct-to-patient mobile teledermoscopy is a feasible and useful adjunct to smartphone imaging for monitoring patient-identified lesions of concern, achieving comparable diagnostic and management accuracy as in-office dermatology.

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KEYWORDS

mobile teledermoscopy; teledermatology; direct-to-patient; full body skin exam; diagnostic concordance; mobile health; mHealth; dermoscopy; dermatology; dermatological; imaging; image; images; smartphone; lesion; lesions; skin; diagnostic; diagnosis; diagnoses; telehealth; telemedicine; eHealth

Introduction

Teledermoscopy is promising for improving the diagnostic accuracy of store-and-forward consultations [1]. However, few studies have explored using direct-to-patient mobile teledermoscopy to bypass in-person imaging [2-4]. Within the Veterans Health Administration system, teledermatology involves in-person visits with trained imaging technicians. Dermoscopy is not universally used. This prospective observational study evaluates a direct-to-patient mobile teledermoscopy program at the San Francisco Veterans Affairs Medical Center (SFVAMC) on its effectiveness in diagnosing and managing patient-identified lesions of concern.

Methods

Recruitment and Implementation

Adults scheduled for full-body skin exams between May and August 2022 were recruited (Figure 1) and given a Sklip mobile dermatoscope, valued at US $99.99. They were instructed to image 1-3 lesions of concern using both smartphones and dermatoscopes. A teledermatologist reviewed all images for diagnosis, management, quality, and clinical utility. Clinical utility was defined as images that increased the teledermatologist’s confidence in diagnosis and management. A dermatologist different from the teledermatologist evaluated the same lesions in-office.
Figure 1. Study participant recruitment flow diagram.

Statistical Analysis
The degree of agreement was assessed using the percentage of agreement and Cohen $\kappa$ (95% CI). Cohen $\kappa$ values were interpreted using the scale developed by Landis and Koch [5]. Excel (Microsoft Corporation) was used for data collection and analysis.

Ethical Considerations
This study was approved by the institutional review board (IRB) of the UCSF Human Research Protection Program and SFVAMC Research and Development Committee, IRB study number 21-33538. Participants provided informed consent with the option to opt out of the study. Participants were not compensated, and their data was anonymized and stored in a password-protected file.

Results
This study included 24 participants (male: n=20, 83%; mean age 65.3, SD 14.9 years). The average distance between their home zip codes and SFVAMC was 54.9 (SD 77.1) miles. A total of 12 (50%) participants had a history of skin cancer: 10 with basal cell carcinoma, 5 with squamous cell carcinoma, 4 with melanoma, and 1 with melanoma in situ.

A total of 56 lesions were imaged: 9 (17%) on the head, 1 (2%) on the neck, 8 (15%) on the posterior trunk, 16 (30%) on the anterior trunk, 15 (28%) on the arms, and 3 (9%) on the legs. The teledermatologist rated most dermoscopic images (n=37, 66%) as acceptable to good quality. There was substantial agreement between the teledermatologist and in-person dermatologist in diagnoses and management (Table 1; $\kappa=0.65$, SE 0.13, 95% CI 0.39-0.91 and $\kappa=0.67$, SE 0.11, 95% CI 0.47-0.88, respectively). Most discordant diagnoses had concordant management (n=3, 60%).

Over 85% (n=48) of lesions were diagnosed as benign neoplasms. Two participants had additional lesions suspected of malignancy identified by in-office dermatologists, one of which was biopsy-proven basal cell carcinoma. Teledermatologists considered 59% (n=33) of smartphone images to have clinical utility, while 66% (n=37) of dermoscopic images provided additional utility when used alongside smartphone images.

For 65% (n=15) of participants who responded to a questionnaire, nondermoscopy smartphone imaging was easy, whereas 52% (n=12) reported mobile teledermoscopy as easy. Most (n=18, 78%) were willing to perform mobile teledermoscopy again. Barriers to dermoscopy use included difficulty performing with nondominant hand (n=1, 4%) and requiring assistance (n=5, 22%). All dermatoscopes were returned undamaged.
# Discussion

## Principal Findings

Substantial agreement was found between the teledermatologists and in-office dermatologists, consistent with previous studies [2,6]. However, the wide CIs indicate the need for further studies with larger sample sizes and implementation improvements, especially for identifying life-threatening malignancies. We recommend providing patients’ medical history to teledermatologists. In one discordant case, a history of vitiligo could have differentiated from postinflammatory hypopigmentation. A recent study developed a checklist for mobile teledermoscopy image quality [7], which could be shared with patients to improve image quality. Because the teledermatologist had a lower threshold for biopsies, a follow-up office visit should be pursued when a procedure is recommended.

Given the high proportion of benign neoplasms in our study, teledermoscopy implementation for patient-identified lesions could lead to an increased burden for telediagnosis services. To increase the malignancy detection, we recommend providing patient education on high-risk features, such as the ABCDEs (asymmetry, border, color, diameter, and evolving) of melanoma or the 7-point checklist, before imaging [8].

## Limitations

This study is limited by its single-center design, small study population, and voluntary participation. The nonresponse rate to the initial invitation was 89% (n=399), which may be due to mail delivery issues, lack of interest, or time constraints. While premalignant lesions were identified, no malignant lesions were imaged. Future studies that involve larger cohorts, different health care settings, and more teledermatologists could elicit additional information on the efficacy of direct-to-patient mobile teledermoscopy.

## Conclusions

Substantial agreement was found between direct-to-patient mobile teledermoscopy and in-office evaluation in the diagnoses and management of patient-identified lesions. Most participants reported ease with mobile teledermoscopy use; however, most lesions were benign, indicating the need for patient education on high-risk features to ensure appropriate lesions are imaged. Providing direct-to-patient mobile teledermoscopy services may expand the reach of existing teledermatology practice.

## Acknowledgments

We would like to thank Daniel Butler, MD; Maria Wei, MD, PhD; Yiyin Chen, MD, PhD; Ruby Ghadially, MD; and Bahram Razani, MD, PhD, who participated in the study and provided in-office dermatologic care for the study population. We would also like to thank Dennis Oh, MD, PhD, for his input and review of the publication. This study received funding through the University of California, San Francisco Inquiry Office and San Francisco Veterans Affairs Medical Center Office of Education.

## Authors’ Contributions

WF wrote the original draft, developed the methodology, and supported in conceptualizing the study. GM conducted the formal analysis, led the project administration, and reviewed and edited the manuscript. AT conceptualized the study, acquired the funding, supervised the study, supported in development of the methodology, supported the project administration, and reviewed and edited the manuscript.

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**Table 1.** Distribution of diagnoses and management by the teledermatologist and in-office dermatologists.

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Teledermatologist (n=56), n (%)</th>
<th>In-office dermatologist (n=56), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>48 (85.7)</td>
<td>48 (85.7)</td>
</tr>
<tr>
<td>Premalignant</td>
<td>1 (1.8)</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Malignant</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infectious</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>7 (12.5)</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>Neoplasm of uncertain behavior</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitor</td>
<td>44 (78.6)</td>
<td>43 (76.8)</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>1 (1.8)</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Biopsy or excision</td>
<td>4 (7.1)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>1 (1.8)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Steroid/anti-inflammatory</td>
<td>6 (10.7)</td>
<td>6 (10.7)</td>
</tr>
</tbody>
</table>
Conflicts of Interest

None declared.

References


Abbreviations

ABCD(E): asymmetry, border, color, diameter, and evolving
SFVAMC: San Francisco Veterans Affairs Medical Center

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Evaluating Participation in Gender-Affirming Care: Cross-Sectional Analysis of Dermatology Program Websites in the United States

Marco Costanza¹, BS; Jeffrey Sobieraj¹, MD; Frank Wang¹,², MD

¹University of Michigan Medical School, Ann Arbor, MI, United States
²Department of Dermatology, Michigan Medicine, University of Michigan, Ann Arbor, MI, United States

Corresponding Author:
Frank Wang, MD
Department of Dermatology
Michigan Medicine
University of Michigan
1500 E Medical Center Drive
Ann Arbor, MI, 48109
United States
Phone: 1 734 936 4054
Email: fra.wang@med.umich.edu

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KEYWORDS
dermatology; gender-affirming care; transgender; dermatology residency; medical education; website; digital platform; media; gender; websites; school; resident; residencies; residency; schools; universities; universities; cross-sectional

Introduction
Transgender and gender-diverse (TGD) patients have unique dermatologic needs, including management of complications from gender-affirming hormone therapy or surgery [1]. Dermatologists play a pivotal role addressing these needs and providing services for gender-affirming care (GAC), such as laser hair removal, management of androgenetic alopecia, injectable neurotoxins, or soft tissue augmentation. To ensure culturally competent care, dermatology residency programs should provide/promote didactic and experiential training tailored to the health needs of TGD patients [2]. Additionally, prospective residents may benefit from being able to ascertain whether certain programs are involved in GAC, including education and research. We aimed to assess the current landscape of GAC participation among dermatology programs and propose strategies to enhance the visibility of such participation.

Methods
Using Doximity 2022-2023 Residency Navigator, dermatology residency programs were identified (N=141). From April to July 2023, the websites of each department, residency program, and associated institution were examined to identify participation in GAC. Next, web-based searches were conducted using department and residency program names plus the following terms: “LGBTQ health,” “gender affirming care,” “transgender healthcare,” or “transgender.” Search results were used to identify institutional multidisciplinary GAC programs, volunteer-based services/clinics participating in GAC, and participation in GAC not otherwise mentioned on program websites. Programs were independently reviewed and categorized by authors MC and JS. Interrater reliability was calculated using Cohen κ. Scores ≥0.8 were considered acceptable [3]. For discrepancies in categorization, searches were reconducted with the results discussed to reach a consensus.

Results
Among the 141 examined websites, we found that 22 (15.6%) dermatology programs mentioned providing GAC; the type of participation was variable (Table 1). The remaining programs (n=119, 84.4%) did not mention participating in dermatologic GAC. Of this group, 62 were part of institutions with multidisciplinary GAC programs, while 57 were not. Among the 22 programs participating in GAC, geographic distribution was variable, with the greatest number in the New England region (Figure 1).
Table 1. US dermatology residency programs mentioning involvement in gender-affirming care (GAC).

<table>
<thead>
<tr>
<th>Mentioning participation in GAC</th>
<th>Programs (N=141), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation in an institutional multidisciplinary GAC clinic$^a$</td>
<td>22 (15.6)</td>
</tr>
<tr>
<td>Listing a directory of SGM$^b$ health providers</td>
<td>19 (86.4)</td>
</tr>
<tr>
<td>Listing specific gender-affirming dermatologic procedures (eg, electrolysis or neurotoxins)</td>
<td>12 (54.5)</td>
</tr>
<tr>
<td>Listing GAC under a “services offered” tab</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>GAC program led by dermatology department</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Not mentioning participation in GAC</td>
<td>119 (84.4)</td>
</tr>
<tr>
<td>Multidisciplinary GAC clinic at institution but no mention of dermatology involvement</td>
<td>62 (52.1)</td>
</tr>
<tr>
<td>No mention of gender-affirming care on institutional website</td>
<td>57 (47.9)</td>
</tr>
</tbody>
</table>

$^a$Participation in a multidisciplinary clinic was defined as at least one faculty member representing the department in the clinic.

$^b$SGM: sexual and gender minority.

Figure 1. Geographic distribution of dermatology programs participating in gender-affirming care. The choropleth map shows the proportion of programs involved in gender-affirming care (GAC) per geographic region, as defined by the Association of American Medical Colleges. The number of programs with GAC out of total programs in the region are displayed, along with associated percentages and color according to the scale.

Discussion

We found that a minority of dermatology programs mentioned participating in GAC, indicating that there remains a considerable gap between the desired and current state of resident education in gender minority health [4,5]. Indeed, dermatology residents receive, on average, 75 minutes of sexual and gender minority (SGM) health education yearly [5] and report low competency and confidence in caring for TGD patients [5,6]. Furthermore, dermatology program directors report barriers to implementing SGM health training, such as lack of funding, curricular time, and experienced faculty [4].

We observed that over 60 dermatology programs did not mention participating in GAC but are affiliated with institutions with multidisciplinary GAC clinics. These programs may consider collaborating with providers in those clinics to improve resident education and care of TGD patients. Highlighting such collaborations may aid recruitment of SGM-identifying residency/faculty candidates, especially those interested in teaching or studying SGM dermatology.

Furthermore, it is possible that some programs actually participate in GAC but do not “advertise” it on websites. Importantly, scrutiny or legal repercussions may affect the visibility or availability of GAC services of some programs.
particularly those affiliated with pediatric hospitals. Thus, when permissible, programs can implement simple measures to highlight their efforts. Program websites could identify departmental or institutional providers passionate about providing GAC. Programs may provide information on whether they perform minimally invasive procedures for GAC, like laser hair removal, injectable neurotoxins, or soft tissue augmentation. Likewise, displaying images of providers wearing pronoun badges or “pride pins” may foster an inclusive environment for patients and providers [7]. These measures do not require curricular time or funding and are associated with improved health outcomes [1,7].

Overall, our results expand upon those of a recent study, specifically by indicating how dermatology programs participate in GAC beyond involvement in multidisciplinary clinics [8]. Our study’s limitations include using publicly available websites, which may not fully reflect TGD health content within curricula, collaborations with GAC experts, or dermatology research related to TGD patients. Future research can address these limitations by surveying program directors or multidisciplinary GAC clinics to ascertain the specifics of departmental involvement.

Our study provides insights into the various types of participation in GAC among dermatology residency programs, as well as existing challenges program directors face and potential clinical and nonclinical opportunities for improvement. Program websites may serve as a valuable and accessible resource to help TGD patients obtain GAC and to attract diverse residency and faculty candidates to a program. To cultivate a safe environment for patients and providers alike, program directors could consider, when possible/permissible, relatively easy yet impactful ways to use their program/departmental websites to enhance and advertise their participation in GAC.

Conflicts of Interest
None declared.

References

Abbreviations

GAC: gender-affirming care
SGM: sexual and gender minority
TGD: transgender and gender-diverse
Risk Factors Associated With Burden of Disease of Psoriasis From 1990 to 2019: Epidemiological Analysis

Vishnutheertha Kulkarni1, MS; David Liu2, MS; Vahram Gamsarian3, BE; Tjinder Grewal1, BS; Torunn Sivesind4, MD

1University of Queensland, Woolongabba, Australia
2University of Toledo, Toledo, OH, United States
3University of Michigan Medical School, Ann Arbor, MI, United States
4Department of Dermatology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Corresponding Author:
Vishnutheertha Kulkarni, MS
University of Queensland
The University of Queensland Diamantina Institute Level 5, West Wing, Translational Research Institute
37 Kent Street
Woolongabba, 4102
Australia
Phone: 61 7 3443 7399
Email: vishnutheertha96@gmail.com

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KEYWORDS
psoriasis; dermatology; gross domestic product; epidemiology; sociodemographic index; Global Burden of Disease; obesity; burden; skin; epidemiological; sociodemographic; chronic; noncommunicable; autoimmune; inflammation; inflammatory

Introduction
Psoriasis is a chronic inflammatory skin condition characterized by red, itchy, scaly patches that affects approximately 2% of the global population and has a significant effect on the patient’s quality of life [1]. Exploring epidemiological trends and relevant risk factors for psoriasis is vital to effectively reduce the global burden of the disease by directing efforts toward countries with the highest prevalence. This study aims to characterize trends in global rates of psoriasis and their associations with relevant risk factors.

Methods
We obtained global psoriasis data from the University of Washington Institute for Health Metrics and Evaluation Global Burden of Disease (GBD) Database and sorted it by age-standardized incidence, prevalence, and years lost to disability (YLD) rates per 100,000 people from 1990 to 2019 [2]. We further filtered these metrics by the four world regions (Asia, Africa, America, and Europe), sociodemographic index (SDI) quintiles, and the 204 countries/territories listed in the GBD database. Country-level indicator data was extracted from the World Health Organization Global Health Observatory database for possible associations with psoriasis [3]. Linear regression analyses were conducted between risk factors and incidence, prevalence, and YLD rates of psoriasis.

Ethical Considerations
This paper was conducted using publicly available databases. Therefore, no ethics approval was required.

Results
The global age-standardized prevalence rate of psoriasis per 100,000 people in 1990 was 660 (95% CI 637-681). It decreased to 504 (95% CI 487-519) in 2019. Across the world regions, psoriasis prevalence, incidence, and YLD were highest in Europe and lowest in Africa (Figure 1). Psoriasis prevalence rates were higher in the highest quintile of SDI (1990: 1256; 2019: 1073) than in the lowest quintile of SDI (1990: 338, 2019: 301) from 1990 to 2019. Similar trends were found for incidence and YLD rates.

Psoriasis incidence rates were positively associated with overweight prevalence ($R^2=0.36$), mean cholesterol ($R^2=0.21$), mental hospital admissions ($R^2=0.25$), medical doctors ($R^2=0.50$), and psychiatrists in the mental health sector ($R^2=0.58$) while being negatively associated with air pollution mortality rates ($R^2=0.40$; Table 1). Similar trends were noted for risk factor associations with psoriasis prevalence and YLD rates ($P<.001$).
Figure 1. Global age-standardized prevalence rates of psoriasis per 100,000 people by Global Burden of Disease World Region.

Table 1. Linear regression analyses of risk factors associated with incidence, prevalence, and years lost to disability (YLD) rates of psoriasis.

<table>
<thead>
<tr>
<th>Risk factors and Y value</th>
<th>Association</th>
<th>Countries, n</th>
<th>$R^2$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight prevalence (BMI $\geq 25$, age-standardized estimate; %)</td>
<td></td>
<td>182</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of psoriasis</td>
<td>Positive</td>
<td>0.26</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Prevalence of psoriasis</td>
<td>Positive</td>
<td>0.22</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>YLDS of psoriasis</td>
<td>Positive</td>
<td>0.19</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Mean total cholesterol (age-standardized estimate)</td>
<td></td>
<td>184</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of psoriasis</td>
<td>Positive</td>
<td>0.31</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Prevalence of psoriasis</td>
<td>Positive</td>
<td>0.26</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>YLDS of psoriasis</td>
<td>Positive</td>
<td>0.23</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Mortality rate attributed to household and ambient air pollution per 100,000 population (age-standardized)</td>
<td></td>
<td>182</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of psoriasis</td>
<td>Negative</td>
<td>0.40</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Prevalence of psoriasis</td>
<td>Negative</td>
<td>0.35</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>YLDS of psoriasis</td>
<td>Negative</td>
<td>N/A$^a$</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Mental hospital admissions per 100,000 population</td>
<td></td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of psoriasis</td>
<td>Positive</td>
<td>0.25</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Prevalence of psoriasis</td>
<td>Positive</td>
<td>0.21</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>YLDS of psoriasis</td>
<td>Positive</td>
<td>0.17</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Medical doctors per 100,000 population</td>
<td></td>
<td>184</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of psoriasis</td>
<td>Positive</td>
<td>0.50</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Prevalence of psoriasis</td>
<td>Positive</td>
<td>0.44</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>YLDS of psoriasis</td>
<td>Positive</td>
<td>0.41</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Psychiatrists working in mental health sector (per 100,000 population)</td>
<td></td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of psoriasis</td>
<td>Positive</td>
<td>0.58</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Prevalence of psoriasis</td>
<td>Positive</td>
<td>0.56</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>YLDS of psoriasis</td>
<td>Positive</td>
<td>0.53</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

$^a$N/A: not applicable.

Discussion

There are a few reasons why global psoriasis prevalence consistently decreased since 1990. Psoriasis may go into remission, decreasing the duration of the disease and ultimately its prevalence, especially in older individuals. Additionally, comorbidities and adverse health behaviors may lead to increased mortality rates among individuals with psoriasis,
resulting in decreased prevalence rates [4]. However, a significant global disease burden remains. Europe has the highest incidence, while Africa has the lowest. These findings were consistent with a prior study on the epidemiology of psoriasis [5]. Factors that were characteristic of wealthier countries such as high SDI, high overweight prevalence, higher mean cholesterol, and lower air pollution mortality rates were found to be associated with higher psoriasis incidence, prevalence, and YLD. Despite greater access to medical resources, high psoriasis prevalence in the highest SDI countries remains. Strong positive associations between psoriasis rates and medical doctors per 100,000 population and psychiatrists per 100,000 population further highlight this trend, underscoring the burden of psoriasis in areas more densely populated with medical professionals. Additionally, psoriasis rates are associated with mental hospital indications, indicating possible psychiatric comorbidities among patients with psoriasis. Solutions must be tailored to more complex causes of psoriasis, such as the gut-brain-skin axis’ role in skin disorders, smoking exposure, alcohol intake, specific medications, and even genetic causes [6].

Limitations of this study include underreporting in some sub-Saharan regions and potentially inaccurate modeling algorithms by the GBD website. Additionally, there may potentially be an ecological fallacy as the populations analyzed in this study may not be representative of the individual members. This study provides a unique and recent perspective on the epidemiological trends of psoriasis. To effectively reduce the burden of psoriasis in these countries, more research on the complex environmental and genetic risk factors of psoriasis should be conducted.

Conflicts of Interest

TS serves as an editorial board member-at-large for JMIR Dermatology. All other authors report no conflicts of interest. TS receives fellowship funding from Pfizer (grant 25B1519; principal investigator: Stanca Birlea) and the National Institutes of Health (grant 2T32AR00741136A1; principal investigator: Dennis Roop).

References


Abbreviations

GBD: Global Burden of Disease
SDI: sociodemographic index
YLD: years lost to disability

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doi:10.2196/48749
PMID:38358797
Introduction

Given the prevalence of keratinocyte carcinomas (KCs), it is imperative to identify accurate diagnostic tools for evaluating suspicious skin lesions [1,2]. Misdiagnosis carries significant harms, including unnecessary scarring, anxiety, and increased cost [3].

Methods

A 2018 Cochrane review [3] assessed dermoscopy as an adjunct to visual inspection (VI) for KC diagnosis among adults with skin lesions suspicious for malignancy or at risk of KC development [3]. Diagnosis was verified by histology for all malignant lesions, while clinical follow-up or histologic diagnosis was required for at least 50% of participants with benign lesions to be included in the review [3]. When these parameters were met, cancer registry and “expert opinion” were also allowed as reference standards, although this was considered less desirable [3].

Results

The review [3] included 24 studies conducted between 1987 and 2016, encompassing adult participants from North America, the Middle East, Europe, Oceania, and East Asia. Table 1 presents further information about the included studies. Among the included studies, there were a total of 8805 visually inspected lesions and 6855 lesions inspected with dermoscopy and VI. Face-to-face and teledermatology settings were evaluated separately, although no clear difference was found between settings.

For in-person basal cell carcinoma (BCC) diagnosis, the diagnostic odds ratio revealed dermoscopy and VI were 8.2 (95% CI 3.5-9.3) times more effective than VI alone (likelihood-ratio test \( P < .001 \)), supporting the predicted sensitivity difference of 14% (79% vs 93%) at a fixed specificity of 80% and predicted specificity difference of 22% (77% vs 99%) at a fixed sensitivity of 80%. The predicted values for sensitivity and specificity were estimated using summary receiver operating characteristic (SROC) curves, which were constructed based on data points derived from individual studies included in the review [4]. It is crucial to note that secondary to substantial heterogeneity between studies, the reported differences in sensitivity and specificity are illustrative examples of the values that might be achieved based on the observed data and do not necessarily reflect how the tests might perform in specific settings.

Sources of heterogeneity were unclear due to poor reporting and lack of available data, although the authors suggest that observer experience, type of dermatoscope used, and the case mix of included lesions may have contributed. Risk of bias and concerns regarding applicability were generally high or unclear

KEYWORDS
nonmelanoma skin cancer; dermoscopy; dermatoscopy; teledermatology; dermascopic; dermatoscope; oncology; skin; cancer; basal cell carcinoma; dermatology; cutaneous squamous cell carcinoma; diagnostic odds ratio; skin; lesion; diagnostic; diagnosis; keratinocyte carcinoma
across most domains assessed, particularly in participant selection, flow, and timing. Although the strength of the conclusions was limited, the addition of dermoscopy to in-person evaluations increased diagnostic accuracy on average. To estimate the impact of the predicted differences in specificity and sensitivity derived from the SROC curve for lesions inspected in person with VI alone versus VI and dermoscopy for the detection of BCC, they were applied to a hypothetical cohort of 1000 lesions. At the median prevalence of 17%, an additional 24 BCC would be identified and 183 fewer non-BCC would be treated unnecessarily with the use of dermoscopy and VI. This information is further illustrated in Table 2. Insufficient data were available for thorough analysis of cutaneous squamous cell carcinoma detection, and it could not be determined whether evaluator expertise or use of a formal algorithm improved the accuracy of KC detection.

Table 1. Quantity of evidence for target lesions.

<table>
<thead>
<tr>
<th>Setting and test (number of studies)</th>
<th>Total lesions, n</th>
<th>Total cases, n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal cell carcinoma quantity of evidence (n=21)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In person</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI (a)</td>
<td>7017</td>
<td>1586</td>
</tr>
<tr>
<td>VI + D (b)</td>
<td>4683</td>
<td>363</td>
</tr>
<tr>
<td>Image based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>853</td>
<td>156</td>
</tr>
<tr>
<td>VI + D</td>
<td>2271</td>
<td>737</td>
</tr>
<tr>
<td><strong>Cutaneous squamous cell carcinoma quantity of evidence (n=4)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In person</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>2684</td>
<td>538</td>
</tr>
<tr>
<td>VI + D</td>
<td>--- (c)</td>
<td>---</td>
</tr>
<tr>
<td>Image based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>VI + D</td>
<td>717</td>
<td>119</td>
</tr>
<tr>
<td><strong>Any skin cancer quantity of evidence (n=11)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In person</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>3618</td>
<td>2021</td>
</tr>
<tr>
<td>VI + D</td>
<td>277</td>
<td>85</td>
</tr>
<tr>
<td>Image based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>517</td>
<td>124</td>
</tr>
<tr>
<td>VI + D</td>
<td>1526</td>
<td>847</td>
</tr>
</tbody>
</table>

\(a\) VI: visual inspection.

\(b\) VI + D: visual inspection and dermoscopy.

\(c\) Not applicable.
Table 2. Extrapolation of estimated sensitivity and specificity differences applied to a hypothetical cohort of 1000 lesions.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>True negative, n</th>
<th>False negative, n</th>
<th>True positive, n</th>
<th>False positive, n</th>
<th>True negative, n</th>
<th>False negative, n</th>
<th>True positive, n</th>
<th>False positive, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>207</td>
<td>693</td>
<td>79</td>
<td>21</td>
<td>207</td>
<td>693</td>
<td>79</td>
<td>21</td>
</tr>
<tr>
<td>VI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI + D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17%</td>
<td>613</td>
<td>193</td>
<td>134</td>
<td>36</td>
<td>134</td>
<td>36</td>
<td>134</td>
<td>36</td>
</tr>
<tr>
<td>VI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI + D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53%</td>
<td>390</td>
<td>122</td>
<td>158</td>
<td>12</td>
<td>158</td>
<td>12</td>
<td>158</td>
<td>12</td>
</tr>
<tr>
<td>VI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI + D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aThe dermoscopy test had a sensitivity of 79%, and the visual inspection and dermoscopy test had a sensitivity of 93%.
bBoth tests had a fixed specificity and fixed sensitivity of 80%.
cThe dermoscopy test had a specificity of 77%, and the visual inspection and dermoscopy test had a specificity of 99%.
dNot applicable.
eVI: visual inspection.
fVI + D: visual inspection and dermoscopy.

Discussion

Recent advancements in learning algorithms using dermoscopic images, particularly deep learning techniques like convolutional neural networks (CNNs), have shown promise in improving diagnostic accuracy. In a systematic review [5] of 19 studies conducted between 2017 and 2021, CNNs demonstrated comparable or improved diagnostic accuracy compared to dermatologists. However, it is important to note that these studies primarily focused on melanoma due to its significant risk, leaving a gap in research specifically targeting KCs. Further research dedicated to KC diagnosis is crucial for a comprehensive evaluation of these conditions.

The authors of the review [3] postulated that adjunctive dermoscopy may aid specialists in identifying BCC. However, the results should be considered suggestive rather than conclusive, given the marked heterogeneity and concerns about the methodological quality of the included studies. Further investigation is required to determine any definitive benefit of dermoscopy for BCC diagnosis. Clear identification of evaluator expertise is essential to ensure meaningful results. Moreover, additional evaluation of the use of formal algorithms may benefit clinicians in varying levels of care. The ubiquity of KCs and risks of misdiagnosis underscore the need for transparent reporting of future studies to optimize diagnostic tools and improve outcomes for patients with suspicious skin lesions.

Conflicts of Interest

RPD is a joint coordinating editor for Cochrane Skin, a dermatology section editor for UpToDate, a social media editor for the Journal of the American Academy of Dermatology (JAAD), and a podcast editor for the Journal of Investigative Dermatology (JID). He is a coordinating editor representative on the Cochrane Council. He is editor in chief of JMIR Dermatology. TES is an editorial board member at large for JMIR Dermatology. RPD receives editorial stipends (JAAD and JID), royalties (UpToDate), and expense reimbursement from Cochrane Skin.

Editorial Notice

The views expressed in this paper are those of the author(s) and in no way represent the Cochrane Library or Wiley. This article is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2018, Issue 12, DOI: 10.1002/14651858.CD011901.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

References


Abbreviations

- BCC: basal cell carcinoma
- CNN: convolutional neural network
- KC: keratinocyte carcinoma
- SROC: summary receiver operating characteristic
- VI: visual inspection
Does Male Skin Care Content on Instagram Neglect Skin Cancer Prevention?

Alexa Carboni1, BS; Olnita Martini1, MS; Jessica Kirk1, BS; Nathaniel A Marroquin1, BS; Corinne Ricci1, BS; Melissa Cheng2, BS; Mindy D Szeto3, MS; Kayd J Pulsipher4, DO; Robert P Dellavalle5,6, MSPH, MD, PhD

1College of Osteopathic Medicine, Rocky Vista University, Greenwood Village, CO, United States
2Western University of Health Sciences College of Osteopathic Medicine of the Pacific, Pomona, CA, United States
3Department of Dermatology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States
4Department of Dermatology, Campbell University at Sampson Regional Medical Center, Wilmington, NC, United States
5Dermatology Service, US Department of Veterans Affairs Rocky Mountain Regional Medical Center, Aurora, CO, United States
6Colorado School of Public Health, Aurora, CO, United States

Corresponding Author:
Nathaniel A Marroquin, BS
College of Osteopathic Medicine
Rocky Vista University
8401 S Chambers Rd
Greenwood Village, CO, 80112
United States
Phone: 1 3033732008
Email: Nathaniel.Marroquin@rvu.edu

Abstract

This research letter assesses male skin care content on social media in order to bring to light the lack of content regarding skin cancer prevention posted on Instagram for male audiences.

Keywords

men; male; male skin care; male skincare; sunscreen; sun protection; photoprotection; anti-aging; skin cancer prevention; Instagram; social media; marketing; advertising; dermatology; dermatologist; skin; man; oncology; oncologist

Introduction

Social media platforms can be efficient and engaging avenues for delivering information to target audiences [1]. A recent survey showed that 42% (n=1060) of US adults obtain health care information via social media, and 45% of respondents would take health-related actions after viewing medical content on these platforms [1]. Social media outreach regarding male skin care and sun protection may be an unrealized opportunity as an effective approach for skin cancer prevention, especially considering that men comprised most new skin cancer cases worldwide in 2020 (men: n=896,192, 59%; women: n=626,516, 41%; calculated based on data from Sung et al [2]), including cases of melanoma (men: n=173,844, 54%; women: n=150,791, 46%) and nonmelanoma (men: n=722,348, 60%; women: n=475,725, 40%) of the skin. Despite there being scientific evidence that consistent topical sunscreen use aids in the prevention of most skin cancers, the vast majority of men often neglect sunscreen compared to women, statistically [3]. Furthermore, male skin could also be more susceptible to UV damage, photoaging, and greater levels of UV exposure [4]. These patterns may be associated with a lack of tailored messaging from sources of health information [3]. Traditional advertising for male-focused skin care was mostly related to beard care, razors, and shaving products, and men historically were less likely to be receptive to targeted marketing content overall [5]. However, social media may have shifted attitudes such that influencer endorsements are now the most reliable form of outreach to both men and women [6].

Methods

We aimed to evaluate male skin care social media on Instagram (Meta Platforms) and highlight any potential gaps in content related to sun safety and sunscreen use. Independent researchers investigated the following five relevant Instagram hashtags from January through March 2023: #maleskincare, #skincareformen, #skincaremen, #skincareroutine, and
#maleSkinCareProducts. A total of 60 top posts were collected for each hashtag, after excluding posts with no likes, accounts with <20 followers, and videos. Posting dates, account names, followers, likes, and types of products advertised were recorded. A third reviewer categorized each post (N=300) by the topic or product discussed, as follows: beard/hair care, antiaging, cleansing, skin care routine, skin care educational infographics, acne, sunscreen, moisturizers, fragrance, or scar care.

## Results

Sunscreen comprised only 4.7% (14/300) of all topics or products promoted, while skin care routines were the most common (83/300, 27.7%; Table 1). The “skin care routine” category encompassed posts that focused on product lines or groups of products that could be used in a skin care routine, rather than centering on 1 product. Posts regarding beard/hair care (43/300, 14.3%), antiaging (45/300, 15%), cleansing (35/300, 11.7%), educational infographics about general skin care (31/300, 10.3%), acne (4/300, 1.3%), moisturizers (39/300, 13%), fragrance (1/300, 0.3%), and scar care (5/300, 1.7%) were also examined.

<table>
<thead>
<tr>
<th>Topic discussed</th>
<th>#maleSkinCareProducts (N=60), n</th>
<th>#SkinCareRoutinePosts (N=60), n</th>
<th>#SkinCareMenPosts (N=60), n</th>
<th>#SkinCareEducationalInfographics (N=60), n</th>
<th>#MaleSkinCareProductPosts (N=60), n</th>
<th>Posts (N=300) by topic, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beard/hair care</td>
<td>9</td>
<td>7</td>
<td>9</td>
<td>5</td>
<td>13</td>
<td>43 (14.3)</td>
</tr>
<tr>
<td>Antiaging</td>
<td>7</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td>4</td>
<td>45 (15)</td>
</tr>
<tr>
<td>Cleansing</td>
<td>6</td>
<td>9</td>
<td>6</td>
<td>4</td>
<td>10</td>
<td>35 (11.7)</td>
</tr>
<tr>
<td>Skin care routine</td>
<td>19</td>
<td>13</td>
<td>19</td>
<td>18</td>
<td>14</td>
<td>83 (27.7)</td>
</tr>
<tr>
<td>Skin care educational infographic</td>
<td>7</td>
<td>14</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>31 (10.3)</td>
</tr>
<tr>
<td>Acne</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Sunscreen</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>14 (4.7)</td>
</tr>
<tr>
<td>Moisturizers</td>
<td>9</td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>7</td>
<td>39 (13)</td>
</tr>
<tr>
<td>Fragrance</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Scar care</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5 (1.7)</td>
</tr>
</tbody>
</table>

## Discussion

While the literature has suggested that men are motivated to use sunscreen due to prior knowledge of skin cancer risk reduction and a desire to appear younger [3], Instagram content related to sunscreen failed to address these factors. Shifting the focus of male skin care advertising may lead to greater interest in preventative measures and mitigate rising rates of skin cancer morbidity and mortality in men. Coupling sun protection and sunscreen promotion with the already substantial content on antiaging products may be promising, as sunscreen is known to have antiaging benefits. Interestingly, compared to women, men were more likely to rely on straightforward messaging and the credibility of the social media influencer when considering a product’s advantages and drawbacks [6]. Credentialed dermatologists therefore could play an important role in social media outreach and recommendations to men about sunscreen use, in conjunction with exploiting the more subtle marketing tactics that demonstrated prior success with male consumers [5]. This study underscores an opening for social media users and influencers to bring greater attention to an underrepresented issue.

## Conflicts of Interest

RPD is the editor-in-chief of JMIR Dermatology, an editor of Cochrane Skin, a dermatology section editor for UpToDate, a social media editor for the Journal of the American Academy of Dermatology (JAAD), and a Cochrane Council cochair. RPD receives editorial stipends (JMIR Dermatology), royalties (UpToDate), and expense reimbursement from Cochrane.

## References


Letter to the Editor

Strengthening TikTok Content Analysis in Academia Using Follower Count and Engagement

Serena Ramjee1, MBBS; Zeeshaan-ul Hasan2, MBBS, BSc

1Urology Department, Darent Valley Hospital, Dartford, United Kingdom
2Dermatology Department, Barts Health NHS Trust, London, United Kingdom

Corresponding Author:
Serena Ramjee, MBBS
Urology Department
Darent Valley Hospital
Darenth Wood Road
Dartford, DA2 8DA
United Kingdom
Phone: 44 1322 428100
Email: serena.ramjee1@nhs.net

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KEYWORDS
social media; skin of color; skin of colour; representation; TikTok; atopic dermatitis; dermatology; dermatologist

Letter

We read with great interest Abdelnour et al’s paper titled “Skin of color representation for atopic dermatitis on TikTok: cross-sectional analysis” [1] and express our gratitude for the findings.

Using the search term #eczema in July 2022, the study evaluated the representation of patients with skin of color (SoC) and the quality of atopic dermatitis videos on TikTok. A review of 119 eligible videos revealed that physicians produced significantly higher-quality content than nonphysicians but may underrepresent SoC. Viewer count was a secondary measure, with its mean value lower for physicians compared to nonphysicians, though the difference was not significant. The authors noted that this lower viewer count may limit the impact of better SoC representation in physicians’ videos. However, we believe that this conclusion cannot be made without further analysis.

Using the viewer count, one may infer that physician content is less popular. However, in instances where there is an insignificant difference in viewer count between sources, this measure alone provides limited information. On TikTok, a view is “counted” within the 3 seconds of playback, meaning a user does not have to view the entire video. Additionally, the viewer count corresponds to the number of times a video has been played rather than unique views [2]. These factors, coupled with TikTok automatically replaying its videos once they finish, mean the viewer count does not reflect the number of individuals that have viewed a video.

Follower count and engagement (likes, saves, shares, and comments) provide additional context. These measures, alongside viewer count, enable the calculation of a video’s engagement rate and reach percentage (view rate). Engagement rate estimates the percentage of viewers that engage with a video (engagement×100/viewer count) [3], whereas reach percentage estimates the percentage of a source’s followers that view a video (viewer count×100/followers) [2]. Marketing companies suggest a “good” engagement rate lies between 1% to 5% [3] and define the average reach percentage as 14.49% [2]. To demonstrate the application of these formulas, we reviewed the results from Pagani et al [4] below.

This cross-sectional study screened the top 50 videos when searching “slugging” (defined as thickly coating the skin with a petrolatum-based ointment like Vaseline and can form the final step of a nighttime skincare routine [4]) on TikTok and analyzed their upload source, content, and quality. Videos were categorized by source into health care providers, influencers, and others. Assessing follower count and engagement (likes and comments) revealed that although influencers have a nonsignificantly lower median viewer count than health care providers (94,500 vs 102,150), their videos had a greater reach percentage (65.3% vs 24.9%) and engagement rate (8.1% vs 4.3%). These values suggest that influencers created more
engaging content, which may be better promoted by TikTok’s algorithm and result in a higher viewer count long term.

We observe that TikTok content analysis is becoming a prevailing means of understanding public dermatology-related information, an unsurprising trend since the platform’s video-based format favors dermatology’s visual nature, and believe follower count and engagement aid this analysis. Regarding the work of Abdelnour et al [1], these measures may assist in determining the impact of improved SoC representation in physician-produced atopic dermatitis videos. If these measures are low, targeted recommendations for improving engagement and reach can be suggested, such as integrating popular trends or cross-promoting content.

Conflicts of Interest
None declared.

Editorial Notice
The corresponding author of “Skin of Color Representation for Atopic Dermatitis on TikTok: Cross-Sectional Analysis” declined to respond to this letter.

References

Abbreviations
SoC: skin of color

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An Unusual Case of Anderson-Fabry Disease: Case Report

Alpana Mohta¹, MD; Achala Mohta², MBBS; Pramila Kumari³, MD

¹Department of Dermatology, Venereology and Leprosy, Sardar Patel Medical College, Bikaner, India
²Department of Preventive and Social Medicine, Sardar Patel Medical College, Bikaner, India
³Department of Dermatology, Era's Lucknow Medical College, Lucknow, India

Corresponding Author:
Alpana Mohta, MD
Department of Dermatology, Venereology and Leprosy
Sardar Patel Medical College
SP Medical College Rd
Bikaner, 334001
India
Phone: 91 8769036292
Email: dralpanamohta10@gmail.com

Abstract

Angiokeratoma is a group of capillary malformations characterized by the formation of variably sized dark red hyperkeratotic papules. Initially, it was believed that angiokeratoma corporis diffusum was a telltale sign of Anderson-Fabry disease; however, current consensus states that it is also seen in various other lysosomal enzymatic deficiencies. In this report, we present the case of a 12-year-old boy who developed angiokeratoma corporis diffusum with sensorineural deafness, acroparesthesias, and renal involvement.

Case Report

A 12-year-old boy with average intelligence presented to us with multiple pinhead-sized dark red papular eruptions all over his body since the age of 6. The lesions first appeared on the legs and gradually increased over several years, involving bilateral limbs and trunks, with clustering over the genitalia (Figure 1A, 1B, and 1C). Upon examination, discreet and grouped nonblanchable angiomatous papules were observed, distributed symmetrically across the entire body, with relative sparing of the face, palms, soles, and mucosa. There was the presence of hyperkeratosis over some of the angiomatous papules.

The patient confirmed that the lesions would bleed when scratched. The patient also reported experiencing generalized asthenia and a low-grade fever 4 months prior. On further inquiry, the patient revealed that he had shooting pains starting from the back and radiating to bilateral lower limbs for the past 3 months. However, until his current visit, his family had not sought any treatment for his condition.
The child had no history of seizures, visual disturbances, hearing loss, or atypical facial features. There was no history of similar skin lesions or associated features in any family members. The child also had bilateral cervical lymphadenopathy. On pure tone audiometry, there was sensorineural hearing loss in both ears. No ocular abnormalities were detected on the slit lamp and fundus examination. Lab investigations revealed microcytic hypochromic anemia, thrombocytopenia, and hypoproteinemia. On further biochemical analysis, the child’s leukocyte α-Galactosidase A activity was very low (0.1 nmol/h/mL). The child’s galactosidase alpha gene study revealed a missense mutation in α-Galactosidase A. The remaining investigations and imaging (ie, electrocardiogram, high-resolution computed tomography, ultrasonography, and chest x-ray) were unremarkable.

Due to the patient’s low socioeconomic status, a genetic study could not be carried out for the rest of the family members.

Upon histopathological evaluation, thin-walled ectatic capillaries having vacuolated endothelial cells were observed in the upper dermis. The epidermis had elongated rete ridges and hyperkeratosis (Figure 2A and 2B). Enzyme assay could not be done due to resource limitations and financial constraints. A diagnosis of angiokeratoma corporis diffusum was made. The course and prognosis of the disease were explained to the patient and his family. The large angiokeratomas were removed using radiofrequency ablation, and the patient is currently being managed with a multidisciplinary approach, including intravenous α-Galactosidase A enzyme replacement therapy infusion. The case is still being followed up with a measure of improvement in his acroparesthesia following 3 months of treatment.

Figure 1. (A) discreet angiokeratoma over trunk; (B) clustered angiokeratoma over umbilicus; (C) clustered angiokeratoma over genitalia.
Angiokeratoma corporis diffusum was described for the first time in 1898. Although Angiokeratoma corporis diffusum has often been used interchangeably with Anderson-Fabry disease, the latter may be associated with lysosomal defects, including fucosidosis, mannosidosis, sialidosis, Kanzaki disease, and monosialotetrahexosylganglioside gangliosidosis [3,4].

Anderson-Fabry disease is an X-linked disorder. In this disease, there is a deficiency in the enzyme α-Galactosidase A, which is responsible for glycosphingolipid catabolism. This deficiency leads to the accumulation of glycosphingolipids, chiefly globotriaosylceramide (GL3) and a metabolite of GL3 called globotriaosylsphingosine (lyso-GL3) in various cells. This accumulation predominantly affects the kidney, heart, and nervous system, contributing to systemic involvement [5].

Fabry disease mutations are observed in around 1 in 22,000-40,000 male individuals, whereas atypical presentations are linked to approximately 1 in 1000-3000 male and 1 in 6000-40000 female individuals [6].

This condition can be categorized into 2 main types: a severe classical form, typically observed in men with no residual enzyme activity, and a milder nonclassical form. Classical Fabry disease is associated with neuropathic pain, cornea verticillate, and angiokeratoma. Over time, it can lead to issues like cardiac rhythm problems, hypertrophic cardiomyopathy, progressive renal failure, and stroke.

On the other hand, nonclassical Fabry disease, also known as late-onset or atypical Fabry disease, displays a more variable progression. Patients with this form are generally less severely affected, and their symptoms may be confined to 1 organ. Despite its X-linked inheritance pattern, women can also experience Fabry disease symptoms, but their condition is typically less severe than that of men due to X-inactivation patterns in women [7].

Often, acroparesthesia in Anderson-Fabry disease is precipitated by emotional or physical stress, febrile illness, and prolonged temperature variation [8]. In our patient, acroparesthesia was triggered by an episode of febrile illness.

Our patient also had hypoalbuminemia, an indicator of renal disease. Kidneys are one of the most commonly involved organs in Anderson-Fabry disease, often resulting in end-stage renal disease and a high mortality rate in untreated patients. Manifestations often mirror diabetic nephropathy’s progression—initial hyperfiltration, followed by albuminuria, heavy proteinuria, and gradual kidney function decline. Tubular manifestations, though rarer, involve renal tubular acidosis, Fanconi syndrome, and impaired urine concentration. Renal involvement is attributed to GL3-induced inflammation and oxidative damage to the glomeruli and podocytes in the kidneys [9].

Fabry disease has no complete cure. To manage it, enzyme replacement (α-Galactosidase A) is initiated upon diagnosis, irrespective of symptoms in affected male patients or those on renal therapy. Female carriers and male patients with low α-Galactosidase A levels receive enzyme replacement only if they exhibit kidney, neurological, or heart issues. Patients with a history of long-term dialysis also receive enzyme replacement. Hypertension is managed with medications like angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Enzyme infusions (alpha or beta) are administered every 2 weeks based on body weight [6].

Discussion

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Conclusions

This report highlights the high reliability of a thorough clinical evaluation for diagnosing atypical and unusual variants of genodermatoses, including Anderson-Fabry disease. Angiokeratoma is a reliable clinical indicator when screening patients for Anderson-Fabry disease. Early identification of these lesions aids in early detection of the disease, enabling timely treatment.

Declaration of Patient Consent

The patient’s parent has given informed consent for the patient’s images and other clinical information to be published in a medical journal. The patient’s parent understands that the patient’s name and initials will not be published and due efforts will be made to conceal his identity, but complete anonymity cannot be guaranteed.

Data Availability

The data that support the findings of this series are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

References


Abbreviations

GL3: globotriaosylerosylceramide
Reflecting on Decades of Data: The Global Burden of Disease–Cochrane Project

Madeline Adelman1*, MD; Isaac Weber2*, MD

1Department of Dermatology, University of Colorado, Aurora, CO, United States
2Mercy Hospital St. Louis, St. Louis, MO, United States
*all authors contributed equally

Corresponding Author:
Isaac Weber, MD
Mercy Hospital St. Louis
615 S New Ballas Rd
St. Louis, MO, 63141
United States
Phone: 1 (314) 251 6000
Email: isaac.weber@mercy.net

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KEYWORDS
Global Burden of Disease; Cochrane Library; review; trachoma; onchocerciasis; vitamin A deficiency; data; glaucoma; macular degeneration; vision loss; disorders; disease burden

Introduction

The Global Burden of Disease (GBD) 2010 study was a systemic epidemiological collaboration between seven institutions to quantify health loss due to diseases, injuries, and risk factors [1]. Its purpose was to develop a platform to compare the magnitude of these health metrics across age groups, countries, sexes, and times, producing comparative metrics for hundreds of causes of premature death and disability. Participating institutions included the “Institute for Health Metrics and Evaluation as the coordinating center, the University of Queensland School of Population Health, the Harvard School of Public Health, the Johns Hopkins Bloomberg School of Public Health, the University of Tokyo, Imperial College London, and the World Health Organization (WHO)” [1].

This project set out to broadly expand the previous GBD 1990 study, conducted primarily by researchers at the World Health Organization and Harvard, to include nearly 500 experts from around the world [2]. In addition, it generated estimates for more than double the number of diseases and sequelae, and improved methods for estimating disability weights. GBD 2010 resulted in estimated disease risk factors, morbidity, and mortality for 291 diseases and injuries and 1160 sequelae [2].

The Cochrane Database of Systematic Reviews (CDSR) is the leading resource for systematic reviews in health care. The GBD-Cochrane project maps the cause-specific disease burden as established by the GBD study to associated systematic reviews of interventions evaluating the same diseases in CDSR. There are seven completed GBD-Cochrane projects and three active projects [4].

Methods

The GBD 2010 study used all available data on cause of death from 187 countries; this included data on vital registration, verbal autopsy, mortality surveillance, censuses, surveys, hospitals, police records, and mortuaries. This data was used to quantify disease burden, disability-adjusted life years, and years of life lost to premature mortality [3].

The GBD-Cochrane project maps the cause-specific disease burden as established by the GBD study to associated systematic reviews of interventions evaluating the same diseases in CDSR. There are seven completed GBD-Cochrane projects and three active projects [4].

Results

These projects provide high-quality data on systematic reviews and help determine if they poorly or strongly correlate with disease burden. For example, a review of ophthalmologic conditions showed that trachoma, onchocerciasis, vitamin A deficiency, and refraction and accommodation disorders were all underrepresented in the CDSR, while glaucoma, macular degeneration, and other vision loss disorders were overrepresented [5]. Other completed projects have shown poor representation of tropical diseases, while mental health and behavioral conditions are overrepresented [6,7].
Discussion

There are a plethora of reasons a condition might be overrepresented in the CDSR. Overrepresentation might reflect the high prevalence of these conditions and, therefore, greater availability for randomized clinical trials. Alternatively, overrepresentation may reflect a disparity in funding, the disparity in research in high- versus low-income countries, or the prioritized interest of the public and pharmaceutical companies. Underrepresentation may reflect a decreasing disease burden, existing effective interventions for those conditions, or a lack of researchers in low- and middle-income nations where certain conditions are more prevalent.

The active GBD-Cochrane projects include conditions in the realm of heart disease, cancer, and infectious disease. As the GBD-Cochrane project continues to map systematic reviews and protocols against disease burden, we will continue to identify research gaps and opportunities to make informed decisions with future research.

Acknowledgments

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Conflicts of Interest

None declared.

References

2. GBD history. The Institute for Health Metrics and Evaluation. URL: https://www.healthdata.org/gbd/about/history [accessed 2023-06-28]

Abbreviations

CDSR: Cochrane Database of Systematic Reviews
GBD: Global Burden of Disease
Potential Use of ChatGPT in Responding to Patient Questions and Creating Patient Resources

Kelly Reynolds¹, MD; Trilokraj Tejasvi¹, MBBS
Department of Dermatology, University of Michigan, Ann Arbor, MI, United States

Corresponding Author:
Trilokraj Tejasvi, MBBS
Department of Dermatology
University of Michigan
1500 East Medical Center Drive
Ann Arbor, MI, 48109
United States
Phone: 1 7349364054
Fax: 1 7346476593
Email: ttejasvi@med.umich.edu

Abstract

ChatGPT (OpenAI) is an artificial intelligence–based free natural language processing model that generates complex responses to user-generated prompts. The advent of this tool comes at a time when physician burnout is at an all-time high, which is attributed at least in part to time spent outside of the patient encounter within the electronic medical record (documenting the encounter, responding to patient messages, etc.). Although ChatGPT is not specifically designed to provide medical information, it can generate preliminary responses to patients’ questions about their medical conditions and can precipitately create educational patient resources, which do inevitably require rigorous editing and fact-checking on the part of the health care provider to ensure accuracy. In this way, this assistive technology has the potential to not only enhance a physician’s efficiency and work-life balance but also enrich the patient-physician relationship and ultimately improve patient outcomes.

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KEYWORDS
artificial intelligence; AI; ChatGPT; patient resources; patient handouts; natural language processing software; language model; language models; natural language processing; chatbot; chatbots; conversational agent; conversational agents; patient education; educational resource; educational

Introduction

ChatGPT (OpenAI) is an artificial intelligence (AI)–based natural language processing model that leverages data via complex deep learning algorithms to generate human-like text responses to user-generated prompts [1,2]. This tool is able to quickly, and often remarkably and accurately, generate responses to complex prompts across an infinite array of topics [1,2]. Since the rollout of ChatGPT in November 2022, it has garnered a significant amount of attention for its ability to create remarkably astute prompts for complex inquiries, making it an incredible tool not only for personal use but also for professional and commercial use [1-3].

It is difficult to overstate how the application of ChatGPT and other AI assistive technologies will revolutionize so many aspects of our day-to-day lives. Specifically for health care providers, it seems that there are myriad ways in which this writing-assistant technology has the potential to not only enhance a physician’s efficiency and work-life balance but also enrich the patient-physician relationship and ultimately improve patient outcomes. The advent of this assistive technology has come at a dire time for health care providers, as burnout is at an all-time high [4]. A study funded by the Agency for Healthcare Research and Quality found that the electronic medical record (EMR) is a key player in promoting stress and physician burnout, specifically time spent in the EMR outside of the patient encounter. The Agency for Healthcare Research and Quality [5] has proposed a variety of interventions to mitigate this issue, including offloading of physicians’ workload as well as implementation of simplified, standardized, and automated workflow operations within the EMR, and preliminary applications of AI in these processes have shown promise [6]. Specifically, we propose that ChatGPT may be a promising tool to help reduce time spent outside of the patient encounter for dermatologists and other outpatient health care providers.
Providers by helping to generate first drafts of written information for patients—for example, instructions for patients and responses to questions in the “patient portal”—which seems to be a relatively underexplored application of this technology.

Although there is a buzz of excitement regarding the application of ChatGPT and other algorithmic or AI technologies in science and medicine [2,7], this excitement is balanced by important concerns about the limitations of this technology or fears about these algorithmic technologies outperforming or replacing health care providers. Importantly, although algorithms have their rightful place in the practice of medicine, the use of algorithms does not substitute for clinical judgment and does not capture the nuances of individualized medicine. This speaks to the importance of the patient-physician relationship, which is based on subtleties in human interactions that AI technologies cannot capture [6]. There are also important ongoing conversations regarding the ethical, privacy, and regulatory concerns about the use of AI technology in health care, although an in-depth conversation on these apprehensions is beyond the scope of this paper [6,7].

An obvious but important caveat is that ChatGPT in its current form is not designed to provide medical information. If, as a patient, you ask a medical question, ChatGPT implements a stock phrase: “As an AI language model, I am not authorized to provide personalized medical advice or recommendations. It is important to consult with a qualified healthcare professional...” [1]. This new technology is still “learning” and may occasionally “hallucinate,” that is, make up false information. Additionally, in generating its responses, ChatGPT may reference poor-quality studies or those with disproven conclusions and may not account for recently published research. This potentially dangerous limitation has been a focus of many critics of this technology, as ChatGPT-generated false medical information could be misleading, and broader dissemination thereof has the potential to create widespread confusion and potentially foster distrust of medical providers [6]. While solely relying on AI-generated health information without human oversight does indeed have dangerous potential, we propose that if ChatGPT-generated responses are edited and fact-checked by a human health care provider, the ChatGPT-based synthesis of information can be an incredibly useful tool to generate a first draft for patient-based resources.

For example, a patient sends a message to his dermatologist inquiring about whether he should stop his bexarotene for treatment of his cutaneous T-cell lymphoma after having been diagnosed with COVID-19. Inputting this question into ChatGPT generates an accurate response; of course, the caveat is that the chatbot is “not authorized to give medical advice.” Adding more specificity to the prompt specifying that the response should be at a “fifth-grade reading level” or should “cite scientific papers” creates an even better response (Textbox 1 [1]).

After reviewing and making edits to the ChatGPT output, this thorough response may be as good or superior to the response that many dermatologists would have been able to generate de novo.

This same approach can also be applied to drafting written resources for patients. For example, prompting ChatGPT to “create a resource for a patient at a fifth-grade reading level regarding the special considerations of topical steroid application in patients with autism” yields a response (Textbox 2 [1]) in seconds, which would have otherwise required a fair amount of effort to create from scratch.

**Textbox 1.** ChatGPT’s response to a patient question regarding the discontinuation of bexarotene in the setting of active COVID-19 infection.

> If you have been diagnosed with COVID-19, it’s important to talk to your doctor before stopping any medication. There is currently no scientific evidence suggesting that bexarotene should be stopped if you have COVID-19.

A study published in the Pharmacological Research journal found that bexarotene may have antiviral effects against COVID-19 [8]. However, more research is needed.

In conclusion, if you have been diagnosed with COVID-19 and are taking bexarotene, it’s important to talk to your doctor before stopping the medication. There is currently no scientific evidence suggesting that bexarotene should be stopped if you have COVID-19, and it may even have some potential benefits.”
Title: Understanding Topical Steroid Application in Patients with Autism

Introduction: If you or a loved one has autism and needs to use topical steroids, there are a few things you should know. Topical steroids are medicines that are applied to the skin to reduce inflammation and itching. This resource will explain the special considerations that people with autism should keep in mind when using topical steroids.

What are Topical Steroids? Topical steroids are medicines that are applied to the skin to reduce inflammation and itching. They are often used to treat skin conditions like eczema, psoriasis, and allergic reactions. Topical steroids come in many forms, including creams, ointments, and lotions.

Special Considerations for People with Autism: If you or your loved one has autism and needs to use topical steroids, here are some things to keep in mind:

Communication: People with autism may have difficulty communicating their symptoms or the effects of the medication. It is important to communicate any changes in symptoms or side effects to your doctor.

Sensory Issues: People with autism may be sensitive to touch, texture, or smell. They may have difficulty with the feel or smell of the medication. Talk to your doctor about any sensory issues you or your loved one may have.

Routine: People with autism often thrive on routine. Applying medication at the same time each day can help establish a routine and make the medication easier to manage.

Education: Educate yourself and your loved one about the medication. Explain why the medication is necessary and what it is intended to do. Use simple language and visuals if needed.

Conclusion: Topical steroids can be a helpful treatment for skin conditions, but special considerations need to be taken for people with autism. If you or your loved one has autism and needs to use topical steroids, communicate any changes in symptoms or side effects to your doctor, address any sensory issues, establish a routine, and educate yourself and your loved one about the medication. Talk to your doctor if you have any questions or concerns.

In conclusion, ChatGPT is a tool that may show promise in assisting dermatologists and other outpatient health care providers in generating information for patients to address their questions and concerns, which may help patients better understand and manage their condition and ultimately may help to promote treatment compliance and enhance the patient-physician relationship. The use of ChatGPT has important implications as it pertains to reducing physician burnout by assisting with and automating tasks outside of the patient encounter. Although there are important limitations to this technology, by ensuring the prompt is specific and using this output as a “first draft” and editing for accuracy, this technology can be used to generate exceptionally high-quality patient resources. Importantly, ensuring the accuracy and appropriateness of the medical information generated by ChatGPT requires rigorous evaluation and validation against trusted sources as well as adherence to current regulatory guidelines. There are seemingly endless ways in which natural language processing tools such as ChatGPT may be used to streamline health care providers' workflow, thereby reducing burnout. However, more research is needed regarding patients’ perceptions of chatbot-generated resources as well as the potential implications of AI on the patient-physician relationship.

Conflicts of Interest
None declared.

References

Abbreviations

AI: artificial intelligence
EMR: electronic medical record
Readability and Health Literacy Scores for ChatGPT-Generated Dermatology Public Education Materials: Cross-Sectional Analysis of Sunscreen and Melanoma Questions

Katie Roster¹, MS; Rebecca B Kann¹, BA; Banu Farabi², MD; Christian Gronbeck³, MD; Nicholas Brownstone⁴, MD; Shari R Lipner⁵, MD, PhD

¹New York Medical College, New York, NY, United States
²Dermatology Department, NYC Health + Hospital/Metropolitan, New York, NY, United States
³Department of Dermatology, University of Connecticut HealthCenter, Framington, CT, United States
⁴Department of Dermatology, Temple University Hospital, Philadelphia, PA, United States
⁵Department of Dermatology, Weill Cornell Medicine, New York, NY, United States

Corresponding Author:
Shari R Lipner, MD, PhD
Department of Dermatology
Weill Cornell Medicine
1305 York Ave 9th Floor
New York, NY, 10021
United States
Phone: 1 646 962 3376
Email: shl9032@med.cornell.edu

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KEYWORDS
ChatGPT; artificial intelligence; AI; LLM; LLMs; large language model; language model; language models; generative; NLP; natural language processing; health disparities; health literacy; readability; disparities; disparity; dermatology; health information; comprehensible; comprehensibility; understandability; patient education; public education; health education; online information

Introduction
A study of 402 randomly selected Medicaid enrollees reported an average of a 5th-grade reading level, which is lower than the average 8th-grade level of US adults [1,2]. Therefore, the American Medical Association (AMA) recommends developing health materials at a 6th-grade reading level or lower [3]. However, a 2018 systematic review of 7891 health websites reported that educational health materials are often at 10th- to 15th-grade reading levels [4].

In a study evaluating ChatGPT-generated materials for 14 dermatological diseases, content was at a 10th-grade reading level [5]. We hypothesized that ChatGPT could be prompted to generate rewritten health materials at a lower grade level and in line with AMA recommendations. The readability of ChatGPT-generated dermatology information and public educational resources on the American Academy of Dermatology Association’s (AAD) website was assessed and determined whether strategic prompting would enhance the material’s readability.

Methods
We inputted the AAD website’s sunscreen and melanoma FAQs individually into ChatGPT, then compiled corresponding outputs, with the supplemental prompts: “I don’t understand, please clarify” and “I still don’t understand, please clarify.” We used well-established readability and health literacy assessment tools and a single web-based readability calculator to calculate 7 different scores [6,7], and computed an “average readability” score with these grade level outputs. A 2-sample t test was used for comparisons (P<.05). To determine information accuracy before and after prompting, 3 dermatology residents blindly evaluated the education materials using a numerical scale: 1 (not accurate), 2 (somewhat accurate), and 3 (accurate).

Results
The AAD’s sunscreen FAQs and melanoma FAQs had Flesch Reading Ease scores of 60.9 (standard/average) and 56.2 (fairly difficult), respectively. The initial ChatGPT output had readability scores of 60.5 (standard/average) and 46.5 (difficult) for sunscreen and melanoma questions, respectively. Subsequent prompting resulted in readability levels of 69.4
The AAD’s sunscreen FAQs and melanoma FAQs had readability levels of 9.2 and 9.4 (both 9th grade), respectively, and the original ChatGPT sunscreen and melanoma output readability levels were 9.6 and 10.4 (9th grade and 10th grade), respectively, with no differences in readability between AAD and ChatGPT for both question sets (P=.32 and P=.15, respectively). The first and second prompting of the sunscreen FAQs output generated material at lower reading levels than AAD-generated material (6.0, P=.005; 4.4, P<.001, respectively). Melanoma FAQs, after prompting, achieved lower reading levels versus AAD material, with scores of 8.0 (8th grade; P=.08) and 7.4 (7th grade; P=.007) (see Table 1).

The AAD material scored an average of 2.82 in accuracy, while the original ChatGPT material scored 2.89. All of the material (42/42, 100%) averaged within the 2-3 range. Initial and secondary prompting resulted in generated material with average scores of 2.63 and 2.62, respectively. Of the 42 materials generated from prompting, 42 (95.2%) averaged within the 2-3 range.

Discussion

The AAD’s sunscreen FAQs and melanoma FAQs had readability scores below the recommended threshold of 80 (Flesch Reading Ease scale) and above the recommended 6th-grade reading level, consistent with a study showing that 27 subungual melanoma websites had poor readability overall, with only 22% having readability lower than the 7th-grade reading level [8]. Taken together, these findings emphasize the need to enhance readability of dermatology public education information.
Our study demonstrated that ChatGPT may be a solution to this problem. Prompting ChatGPT following initial inputs improved health information readability versus AAD materials and was closer to or within recommended guidelines. Our findings are similar to a 2023 study assessing 9 uveitis web pages with an average Flesch-Kincaid Grade Level of 11.0 (SD 1.4); ChatGPT improved the readability, with a mean Flesch-Kincaid Grade Level of 8.0 (SD 1.0) [9]. Therefore, the use of ChatGPT to adapt output to enhance readability might have applicability in dermatology and other medical fields.

Most of the ChatGPT-generated material was rated as accurate to somewhat accurate. However, additional prompting resulted in a slight trend toward less accuracy, with 2 responses below the 2-3 (accurate to somewhat accurate) range. This observation may highlight a potential limitation to the applicability of ChatGPT in this context. Additionally, only a small number of questions were assessed. We analyzed the ChatGPT-3.5 version, which includes information up until September 2021.

In conclusion, ChatGPT could be used to enhance the readability of dermatology health information and lower it to the 6th-grade reading level recommended by the AMA. Larger studies are needed to corroborate our data and evaluate the utility of ChatGPT for dermatology public education materials.

Conflicts of Interest
SRL has served as a consultant for Eli Lilly, Ortho Dermatologics, Moberg Pharmaceuticals, and BelleTorus Corporation.

References
7. Readable. 2023 Jun. URL: https://readability-score.com/ [accessed 2023-02-14]

Abbreviations
AAD: American Academy of Dermatology Association
AMA: American Medical Association
Assessing the Utility of Multimodal Large Language Models (GPT-4 Vision and Large Language and Vision Assistant) in Identifying Melanoma Across Different Skin Tones

Katrina Cirone, Mohamed Akrout, Latif Abid, Amanda Oakley

Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

AIPLabs, Budapest, Hungary

Department of Computer Science, University of Toronto, Toronto, ON, Canada

Department of Dermatology, Health New Zealand Te Whatu Ora Waikato, Hamilton, New Zealand

Department of Medicine, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand

Corresponding Author:
Katrina Cirone, HBSc
Schulich School of Medicine and Dentistry
Western University
1151 Richmond Street
London, ON, N6A 5C1
Canada
Phone: 1 6475324596
Email: kcirone2024@meds.uwo.ca

Abstract
The large language models GPT-4 Vision and Large Language and Vision Assistant are capable of understanding and accurately differentiating between benign lesions and melanoma, indicating potential incorporation into dermatologic care, medical research, and education.

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KEYWORDS
melanoma; nevus; skin pigmentation; artificial intelligence; AI; multimodal large language models; large language model; large language models; LLM; LLMs; machine learning; expert systems; natural language processing; NLP; GPT; GPT-4V; dermatology; skin; lesion; lesions; cancer; oncology; visual

Introduction
Large language models (LLMs), artificial intelligence (AI) tools trained on large quantities of human-generated text, are adept at processing and synthesizing text and mimicking human capabilities, making the distinction between them nearly imperceptible [1]. The versatility of LLMs in addressing various requests, coupled with their capabilities in handling complex concepts and engaging in real-time user interactions, indicates their potential integration into health care and dermatology [1,2]. Within dermatology, studies have found LLMs can retrieve, analyze, and summarize information to facilitate decision-making [3].

Multimodal LLMs with visual understanding, such as GPT-4 Vision (GPT-4V) [4] and Large Language and Vision Assistant (LLaVA) [5], can also analyze images, videos, and speech, a significant evolution. They can solve novel, intricate tasks that language-only systems cannot, due to their unique capabilities combining language and vision with inherent intelligence and reasoning [4,5]. This study assesses the ability of publicly available multimodal LLMs to accurately recognize and differentiate between melanoma and benign melanocytic nevi across all skin tones.

Methods
Our data set comprised macroscopic images (900 x 1100 pixels; 96-dpi resolution) of melanomas (malignant) and melanocytic nevi (benign) obtained from the publicly available and validated MClass-D data set [6], Dermnet NZ [7], and dermatology textbooks [8]. Each LLM was provided with 20 unique text-based prompts that were each tested on 3 images (n=60 unique image-prompt combinations) consisting of questions about “moles” (the term used for benign and malignant lesions), instructions, and image-based prompts where the image was...
annotated to alter the focus. Our prompts represented potential users, such as general physicians, providers in remote areas, or educational users and residents. The chat content was deleted before each submitted prompt to prevent repeat images influencing responses, and testing was performed over a 1-hour timespan, which is insufficient for learning to take place. Prompts were designed to either involve conditioning of ABCDE (asymmetry, border irregularity, color variation, diameter \(>6\) mm, evolution) melanoma features or to assess effects of background skin color on predictions. Conditioning involved asking the LLM to differentiate between benign and malignant lesions where one feature (eg, symmetry, border irregularity, color, diameter) remained constant in both images to determine whether the fixed element was involved in overall reasoning. To assess the impact of color on melanoma recognition, color distributions of nevi and melanoma were manipulated by decolorizing images or altering their colors.

### Results

Analysis revealed GPT-4V outperformed LLaVA in all examined areas, with overall accuracy of 85% compared to 45% for LLaVA, and consistently provided thorough descriptions of relevant ABCDE features of melanoma (Table 1 and Multimedia Appendix 1). While both LLMs were able to identify melanoma in lighter skin tones and recognize that dermatologists should be consulted for diagnostic confirmation, LLaVA was unable to confidently recognize melanoma in skin of color nor comment on suspicious features, such as ulceration and bleeding.

| Table 1. Performance of Large Language and Vision Assistant (LLaVA) and GPT-4 Vision (GPT-4V) for melanoma recognition. |
|-----------------|-----------------|-----------------|
| Feature         | LLaVA           | GPT-4V          |
| Melanoma detection | Melanoma identified—referenced shape and color | Melanoma identified—referenced the other ABCDEs of melanoma |
| **Feature conditioning** | | |
| Asymmetry       | Melanoma identified—referenced size and color | Melanoma identified—referenced the other ABCDEs of melanoma |
| Border irregularity | Melanoma identified—referenced size and color | Melanoma identified—referenced the other ABCDEs of melanoma |
| Color           | Melanoma identified—incorrectly commented on color distribution | Melanoma identified—referenced the other ABCDEs of melanoma |
| Diameter        | Melanoma missed—confused by the darker color | Melanoma identified—referenced the other ABCDEs of melanoma |
| Color + diameter | Melanoma missed—confused by the darker color and morphology | Melanoma identified—referenced morphology, complexity, color, and border |
| Evolution       | Melanoma identified—referenced size and color | Melanoma identified—referenced the other ABCDEs of melanoma |
| **Color bias**  | | |
| Benign—darkened pigment | Darkened lesion classified as melanoma, became confused about other melanoma features | Darkened lesion classified as melanoma, became confused about other melanoma features |
| Melanoma—darkened pigment | Darkened lesion classified as melanoma, became confused about the other ABCDEs of melanoma | Darkened lesion classified as melanoma, became confused about the other ABCDEs of melanoma |
| Melanoma—lightened pigment | Unable to recognize malignancy and to identify that the image had been altered | Melanoma identified—referenced the other ABCDEs of melanoma and recognized that the altered image had been lightened |
| **Skin of color** | | |
| Melanoma detection | Diagnostic uncertainty—unsure of lesion severity and diagnosis | Melanoma identified—referenced the other ABCDEs of melanoma |
| Suspicious features | Did not identify suspicious features | Identified suspicious features and recommended medical evaluation—ulceration, bleeding, and skin distortion |
| **Image manipulation** | | |
| Visual referring | Tricked into thinking the annotations indicated sunburned skin | Correctly identified that the annotations were artificially added and could be used to monitor skin lesion evolution or to communicate concerns between providers |
| Rotation        | Tricked into thinking an altered image orientation constituted a novel image | Correctly indicated it could not differentiate between the 2 images and accurately referenced the ABCDEs of melanoma |

\(\text{ABCDE}: \text{asymmetry, border irregularity, color variation, diameter }>6\ \text{mm, evolution.}\)
Discussion

Across all prompts analyzing feature conditioning, GPT-4V correctly identified the melanoma, while LLaVA did not, when color, diameter, or both were held constant (Figure 1). This suggests these features influence melanoma detection in LLaVA, with less importance placed on symmetry and border. Both LLMs were susceptible to color bias, as when a pigment was darkened with all other features held constant, the lesion was believed to be malignant. Alternatively, when pigments were lightened, GPT-4V appropriately recognized this alteration, while LLaVA did not. Finally, image manipulation did not impact GPT-4V’s diagnostic abilities; however, LLaVA was unable to detect these manipulations and was vulnerable to visual referring associated with melanoma manifestations. The red lines added around the nevus’s edges were identified as sunburned skin when presented to LLaVA, while GPT-4V correctly recognized these annotations as useful for monitoring lesion evolution or communicating specific concerns between health care providers.

Figure 1. Melanoma detection when conditioned on color and diameter. GPT-4V: GPT-4 Vision; LLaVA: Large Language and Vision Assistant.

Although limitations are present, GPT-4V can accurately differentiate between benign and melanoma lesions. Performing additional training of these LLMs on specific conditions can improve their overall performance. Despite our findings, it is critical to account for and address limitations such as reproduction of existing biases, hallucinations, and visual prompt injection vulnerabilities and incorporate validation checks before clinical uptake [9]. Recently, the integration of technology
within medicine has accelerated, and AI has been used in dermatology to augment the diagnostic process and improve clinical decision-making [10]. There is an urgent global need to address high volumes of skin conditions posing health concerns, and the integration of multimodal LLMs, such as GPT-4V, into health care has the potential to deliver material increases in efficiency and improve education and patient care.

Conflicts of Interest
None declared.

Multimedia Appendix 1
The 20 unique text-based prompts provided to GPT-4 Vision and Large Language and Vision Assistant and the responses of both large language models depicted side by side.

[DOCX File, 5509 KB - derma_v7i1e55508_app1.docx ]

References

Abbreviations

ABCDE: asymmetry, border irregularity, color variation, diameter >6 mm, evolution
AI: artificial intelligence
GPT-4V: GPT-4 Vision
LLaVA: Large Language and Vision Assistant
LLM: large language model
Atrophic Postacne Scar Treatment: Narrative Review

Enas Attia¹,², MD

¹Department of Dermatology, Venereology, and Andrology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
²Department of Dermatology, Ain Al Khaleej Hospital, Abu Dhabi, United Arab Emirates

Corresponding Author:
Enas Attia, MD
Department of Dermatology, Venereology, and Andrology, Faculty of Medicine
Ain Shams University
Abbasiya square
Cairo, 11566
Egypt
Phone: 20 224346709
Fax: 20 224346709
Email: annosah1974@yahoo.com

Abstract

Acne scarring is a frequent complication of acne. Scars negatively impact psychosocial and physical well-being. Optimal treatments significantly improve the appearance, quality of life, and self-esteem of people with scarring. A wide range of interventions have been proposed for acne scars. This narrative review aimed to focus on facial atrophic scarring interventions. The management of acne scarring includes various types of resurfacing (chemical peels, lasers, and dermabrasion); the use of injectable fillers; and surgical methods, such as needling, punch excision, punch elevation, or subcision. Since the scarred tissue has impaired regeneration abilities, the future implementation of stem or progenitor regenerative medical techniques is likely to add considerable value. There are limited randomized controlled trials that aimed to determine which treatment options should be considered the gold standard. Combining interventions would likely produce more benefit compared to the implementation of a single method.

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KEYWORDS

acne; atrophic scars; treatment; acne scarring; scars; scarring; well-being; psychosocial well-being; psychosocial; physical well-being; self-esteem; face; facial scarring; implications; skin; dermatology; dermatologist

Introduction

Atrophic scars present clinically as indentations in the skin due to destructive inflammation in the deep dermis as a result of delayed or inadequate acne treatment. Atrophic postacne scars are further classified into ice-pick scars (V-shaped epithelial tracts with a sharp margin that can extend deeper in the skin), boxcar scars (a round-to-oval scar with sharp vertical sides that can extend deeper in the skin), and rolling scars (irregular scars with a rolling or undulating shape) [1]. Atrophic postacne scar risk assessment depends on the worst-ever severity of acne, the duration of acne, family history of atrophic postacne scars, and lesion manipulation behaviors. This provides a dichotomous outcome: lower versus higher risk of developing scars [2].

Early effective treatment of acne is the best strategy to prevent or limit postacne scarring. Different factors influence the treatment choice for acne scars, for example, color, texture, distensibility, and morphology. For example, the selection of the chemical peeling agent and concentration depends on the patient’s skin type and severity of scarring. Moreover, considering the flexibility and low cost, chemical peels, in general, play an important role in the management of all grades of acne scars. However, trichloroacetic acid (TCA) chemical peeling carries the risk of postinflammatory hyperpigmentation (PIH), particularly in darker skin phototypes [3]. Regarding lasers, choosing the type and appropriate settings while taking into consideration the depth of the scar, skin type, and tendency to develop PIH is of utmost importance [4]. Nevertheless, severe scars are poorly treated and do not improve greatly with resurfacing procedures, where punch excision and punch elevation can be tried instead [3].

Preprocedure considerations include the acne-free period, isotretinoin-free period, history of skin infections (eg, herpes virus), history of general or local skin disorders affecting healing, history of keloids or hypertrophic scarring, history of tanning, skin phototype, and sun exposure habits, as well as
management of acne scarring includes various types of resurfacing (chemical peels, lasers, and dermabrasion); the use of injectable fillers; and surgical methods, such as needling, subcision, punch excision, or punch elevation [6].

This narrative review aimed to focus on facial atrophic scarring interventions in brief. The outcomes, including adverse events, participant satisfaction, and postprocedure downtime, are reviewed.

Methods

A PubMed literature review was conducted, and the search keywords included a combination of the following keywords: “acne,” “scars,” and “treatment.” The synonyms “management,” “modalities,” and “therapy” were also considered, along with the names of different modalities such as “laser,” “radiofrequency,” “needling, microneedle, micro needling or microneedling,” “dermaroller,” “dermabrasion, microdermabrasion or micro dermabrasion,” “chemical peel, chemical peeling or chemical peels,” “platelet rich plasma,” “stem cells,” “fillers,” “subcision,” “punch,” “growth factor,” “ozone,” and “botulinum toxin.”

The articles regarding clinical trials, meta-analyses, and systematic reviews with at least an English abstract that were published before June 1, 2023, were included. Articles discussing interventions for nonfacial or other types of scars were excluded.

Results

Scars-Associated Erythema Management

Treating scars-associated erythema (SAE) can be an initial and dramatic step toward improving acne scarring. Pulsed dye laser (PDL) is the gold standard. It uses selective thermolysis to destroy vascular components of the dermis, leading to clinical improvement of erythema. The major chromophore is oxyhemoglobin, which absorbs light in the yellow and green range, with peaks at 418, 542, and 577 nm. The long-pulsed PDL (595-600 nm) slowly heats target vessels with less risk of postprocedure purpura. In addition to treating SAE, PDL also induces collagen remodeling, thus improving the depressed appearance of scars [7].

Other laser and light devices include the potassium titanyl phosphate laser, also known as the frequency-doubled neodymium-doped yttrium aluminum garnet (Nd:YAG) laser; 1550-nm erbium-doped fractional laser (EDL); and intense pulsed light (IPL) [8]. The use of the potassium titanyl phosphate laser leads to significant improvement in the vascular component without significant effects on collagen remodeling [9].

In addition to being a frontline agent for atrophic scars, the 1550-nm wavelength emitted by EDL penetrates approximately 1000 μm into the skin to target tissue water, allowing for the improvement of erythema through microvascular destruction of vessels deeper in the dermis [10].

IPL does not typically produce purpura, and larger spot sizes allow for a greater surface area to be treated deeper and more quickly. However, given the range of wavelengths that may be used; adjacent, competing chromophore absorption peaks; and poor specificity, drawing conclusions regarding efficacy in treating SAE with IPL is difficult. Moreover, care must also be taken to avoid postinflammatory hypopigmentation and PIH in darker skin phototypes [7].

Ablative Laser Resurfacing

Traditional ablative laser resurfacing removes the epidermis and part of the dermis of the scars, allowing collagen remodeling and re-epithelialization. Ablative 10,600-nm carbon dioxide (CO₂) lasers and 2940-nm erbium-doped yttrium aluminum garnet (Er:YAG) lasers are the most commonly used ablative lasers for acne scars. CO₂ lasers cause denaturation and thermal stimulus in the tissues surrounding ablation, promoting wound healing and the production of myofibroblasts and matrix proteins [11]. Adverse effects include persistent erythema, hypopigmentation, PIH, infection, scarring, and a relatively long recovery period (weeks) [12].

Fractional laser resurfacing acts, as the name indicates, on regularly spaced arrays over a fraction of the skin surface to induce thermal ablation of microscopic columns of epidermal and dermal tissue. Microscopic columns of light or microthermal zones (MTZs) leave the intervening skin unaffected and minimize damage to the epidermis. The skin adjacent to sites of laser injury remains intact, allowing for rapid postprocedural re-epithelialization due to the migration of intact cells into the damaged microcolumns [13]. This approach provides a faster recovery when compared with conventional ablative resurfacing [14].

Fractional 10,600-nm CO₂ laser; 2940-nm Er:YAG laser; 2790-nm erbium-doped yttrium scandium gallium garnet laser; 1540-nm erbium glass (Er:glass) laser; and 1550-nm EDL produce comparable rates of improvement in atrophic acne scars after multiple treatments. The least responsive scar type is ice-pick scars [7]. Adverse effects include erythema that lasts for days to weeks, PIH that lasts for weeks, and procedural discomfort. These lasers are safer in darker skin phototypes, with less dyschromia than ablative lasers. Lower densities have been associated with less risk for hypopigmentation [15]. The deeper penetration of the laser might lead to contraction of the underlying muscle, so lower energy and densities should be used on the periorcular region [7]. Fractional 1540 - nm Er:glass laser treatment for 3 sessions at 4 - week intervals improved scar texture and severity [16].

Nonablative Laser Resurfacing

Nonablative laser resurfacing, such as the short- and long-pulsed and Q-switched Nd:YAG lasers and diode lasers, produces dermal thermal injury while preserving the epidermis; this promotes collagen remodeling, which leads to improvement in scarring [17]. Results are accordingly modest (20%-30%), and multiple treatment sessions are required to achieve typically less impressive results. Postprocedure side effects are minimal, with erythema lasting less than 2 hours and no reports of pain, swelling, oozing, or scarring. Using the 532-nm Nd:YAG laser...
for an average of 3 treatments improved scars by an average of 53.6%, with a range from 10% to 90% [18]. The use of the nonfractional, nonablative Q-switched 1064-nm Nd:YAG laser (4 sessions at 4 - week intervals) resulted in a more than 50% improvement in 3 out of 32 patients with acne scarring [19].

The picosecond 755-nm Alexandrite laser delivers shorter pulse durations with lower fluences of energy and, therefore, leads to fewer adverse effects. With the aid of a diffractive lens array, which delivers pulses 500 μm apart, it permits the treatment of a greater surface area, improving the appearance and texture of atrophic rolling scars similar to fractional ablative lasers. This technology has a favorable safety profile for darker skin phototypes; the mean pain score is mild; and downtime is minimal, with transient erythema and edema and no exfoliation, vesiculation, crusting, scarring, hypopigmentation, or PIH [20].

Radiofrequency
Nonablative radiofrequency (RF) treatments deliver a current through the dermis that stimulates dermal remodeling. With traditional unipolar or monopolar RF, a single electrode allows for penetration deep into the dermis, but this is associated with increased pain and discomfort [21]. Bipolar RF allows for the delivery of a more focused current to the dermis. Fractional RF uses an array of electrodes to create zones of thermal wounds that stimulate dermal remodeling. Microneedles can be used to deliver RF to a particular depth within the dermis. Microneedle bipolar RF and fractional RF treatments offer the best results for acne scarring, particularly ice-pick and boxcar scars [22]. Needling and ablative fractional lasers are tolerable and safe procedures with no significant difference in the treatment of skin scars in 60% of previous studies [23]. The adverse reactions associated with RF include transient erythema, and scabbing that resolve within days [7]. Zhang et al [24] found that fractional RF sessions resulted in comparable improvement of acne scars after fractional lasers, with no PIH observed on the areas treated with fractional RF.

Skin Needling
Skin needling procedures may diminish the appearance of acne scars. A needling device is rolled over the surface of the skin to form numerous perforations in the epidermis and dermis, with the goal of stimulating new collagen [25]. The advantages of skin needling include low cost, a relatively short recovery period (2-3 days), and a very low risk for PIH [26].

Skin needling treatment is well tolerated by most people and the pain is minimal. The full result may take 8 to 12 months as the deposition of new collagen takes place slowly [25].

One important advantage is that the epidermis remains intact, eliminating most of the risks of chemical peeling or laser resurfacing. Furthermore, microneedling provides a clear channel for the efficient absorption of topical agents, including platelet-rich plasma (PRP), which can improve cosmetic results [27].

Dermabrasion and Microdermabrasion
Dermabrasion involves the use of tools (eg, high - speed brush, diamond cylinder, fraise, or silicon carbide sandpaper) to remove the epidermis or the epidermis and part of the dermis. An advantage of the procedure is that it allows the clinician to target scar edges precisely without thermal injury. It may be effective for some acne scars but is usually not used for ice-pick or deep boxcar scars. Adverse effects include significant pain, a considerable recovery time, scarring, pigment alterations, and milia formation [28].

Microdermabrasion (MDA) is a minimally invasive epidermal resurfacing procedure, in which abrasive crystals are propelled against the skin under the control of a handheld vacuum system. The crystals cause gentle mechanical abrasion to the skin, which ultimately removes the stratum corneum layer of the epidermis. As part of the wound healing process, new epidermis forms with enhanced cosmesis [29]. Half-side comparison between combined MDA plus aminolevulinic acid–photodynamic therapy (PDT) versus combined MDA plus placebo - PDT for 5 sessions (4 - week intervals) showed more improvement of scarring on the combined MDA plus aminolevulinic acid–PDT split - face than the combined MDA plus placebo - PDT split - face using the Physician’s Global Assessment of Acne Scarring scale [30].

Chemical Peels
Chemical peels (using glycolic acid, lactic acid, salicylic acid, mandelic acid, TCA, or phenol) are used in treating small, depressed scars but not ice-pick or deep boxcar scars [31,32]. They induce injury to the skin that stimulates collagen remodeling and are categorized as superficial, medium, and deep based on the depth of the injury [7].

Superficial peels, such as lactic acid, salicylic acid, glycolic acid, Jessner solution, and 10% to 20% TCA, only affect the epidermis. Medium depth peels, such as combined Jessner solution with 25% to 35% TCA, affect the epidermis and papillary dermis. Deep peels, such as 50% or higher TCA and phenol (carbolic acid), injure skin to the midreticular dermis. Complications, including prolonged erythema, infection, PIH, and scarring, are more common in darker skin phototypes, deeper peels, and sun exposure. Phenol has been associated with cardiac toxicity related to systemic absorption [7].

Serial biweekly application of glycolic acid peels with different concentrations in a gradually increasing manner (2 - week intervals) is better than 15% glycolic acid cream applied daily for 24 weeks [33]. The chemical reconstruction of skin scars (CROSS) chemical peeling method applied twice every 12 weeks had comparable results to the use of the 1550-nm Er:glass fractional laser for 3 sessions (6 - week intervals) [34]. Four sessions (4 - week intervals) of chemical peeling using full - strength TCA (100% TCA) CROSS showed equivalent improvement as 4 sessions (4 - week intervals) of skin needling using a dermaroller, with reported transient PIH in the peeling group [35]. Six sessions (4 weeks apart) of chemical peeling with 20% TCA combined with skin needling showed comparable improvement as 6 sessions (4 weeks apart) of fractional nonablative 1540-nm Er:glass laser treatment, with more than 50% improvement in acne scars [36]. Ultrapulsed CO2 fractional laser combined with 30% supramolecular salicylic acid has better efficacy in the treatment of acne scars than laser alone, and according to patient self-assessment, the combined treatment has a greater degree of improvement in acne scars and does not increase patient pain scores and related...
adverse reactions [37]. Four sessions (6 - week intervals) of chemical peeling with 20% TCA combined with skin needling is superior to deep peeling using a non-hydro-alcoholic solution of oil phenol in 60% concentration formula [38].

**PRP and Stem Cell Therapy**

Autologous PRP can enhance wound healing by accelerating tissue repair through the release of growth factors, cytokines, and chemokines from their granules. Intradermal injections of PRP were first noted to improve acne scarring when used for skin rejuvenation. Topical PRP has a synergistic effect with skin needling in atrophic acne scars, as skin needling creates a way for PRP absorption and allows platelets to contribute to wound healing. PRP as both an intradermal injection and topical application in fluid or gel form after fractional ablative CO₂ laser therapy enhanced the recovery of laser-damaged skin and improved the clinical appearance of acne scars [39-41].

Mesenchymal stem cells (MSCs) are capable of differentiation into various cell lineages and have been shown to promote wound healing [42]. MSCs can be isolated from umbilical cord blood and expanded [43]. In contrast to umbilical cord MSCs, adipose tissue-derived MSCs are relatively easy to obtain. One injection of autologous adipose tissue-derived adult stem cells is as effective as 3 sessions of fractional CO₂ laser in the treatment of atrophic acne scars [44].

**Filler**

Injectable fillers have been proposed to improve the appearance of atrophic acne scars, including collagen, autologous fat transfer, and artificial injectable fillers [45]. Hyaluronic acid (HA) fillers typically last for a few months, making repeated treatments necessary, which increases cost [7]. Semipermanent fillers can last up to 2 years and are biostimulatory; they include poly-ι-lactic acid and calcium hydroxyapatite [46,47]. Permanent fillers comprise larger particles that cannot be phagocytosed. They can last from several years to lifelong but can be displaced over time due to changes in the adjacent connective tissue. Silicone is relatively cheap and is stable for 10 to 20 years. Polymethylmethacrylate is a synthetic permanent filler suspended in bovine collagen and lidocaine [7]. Solomon et al [48] injected 96 patients with acne scars with polymethylmethacrylate, resulting in 99.0% improvement, high patient satisfaction, and a good safety profile.

O’Daniel [49] implemented an individualized multimodal approach in patients with atrophic acne scars and aging. Resurfacing techniques were used to correct surface irregularities, long-lasting dermal fillers were used addressed the volume loss resulting from acne scars, and subsuperficial musculoaponeurotic system face-lift procedures were used to counter the soft tissue laxity and ptosis associated with aging. In the author’s clinical practice, multimodal approaches incorporating fractionated laser, injectable poly-L-ι-lactic acid, and subsuperficial musculoaponeurotic system face-lift procedures have achieved optimal aesthetic outcomes, high patient satisfaction, and durability of aesthetic effect over time.

Autologous fat grafting, PRP, and stromal vascular fraction are effective and safe for the treatment of acne scars. Autologous fat grafting and stromal vascular fraction may be a better treatment for acne scars than PRP. However, this hypothesis still needs to be tested in the future in large randomized controlled trials [50].

**Individual Atrophic Scars Surgical Management**

Punch excision may be an effective treatment for ice-pick scars and small (<3 mm) boxcar scars. A punch biopsy instrument of equal or slightly greater diameter than the scar is used to incise the tissue to the subcutaneous fat layer and excise the scar. Some authors espouse punch excision followed by secondary intention healing, in which a scar is created but is less noticeable because of change at the depth of the base. It has been associated with good results, but secondary widening of the scar may occur [28]. The defect should be closed by sutures along relaxed skin tension lines. Placing a single nonabsorbable suture for punch holes 2.5 mm or larger might facilitate wound healing and minimize spreading [7]. For scars larger than 3.5 mm, elliptical excision may be more favorable than punch excision [51].

Punch elevation is best suited for boxcar scars. The scar border is excised, leaving the deepest part of the scar that is adherent to the fat layer. The scar is raised higher than the surrounding skin; it then retracts during healing to become level with the surface [28].

Fractional CO₂ laser preceded by punch elevation produced a more than 50% improvement in acne scars after 2 sessions [52].

Subcision is used for the management of rolling or depressed scars; a blade inserted parallel to the skin surface is used to cut fibrotic strands tethering the scar to the underlying tissue [53]. Reported adverse effects include bruising, swelling, bleeding, and infection [54]. RF-assisted subcision was found to be comparable to conventional subcision with no risk of hematoma, but entry point burn can occur [55]. Using microplasma RF technology combined with subcision to treat depressed scars obtained relatively satisfactory results with no adverse effects [56].

It is of note that blunt cannula subcision is more effective than Nokor needle subcision for acne scars treatment [57]. Injectable fillers showed comparable results to 18 - gauge Nokor needle subcision [58], yet bruising from subcision was significantly worse than that from injection, whereas lumpiness from fillers was significantly worse than that from subcision. Significant and persistent improvement of acne scars, without considerable complications, was noted after the combined protocol of subcision, followed by HA filler initially, and then followed by fractional CO₂ laser 2 weeks later [59]. Subcision combined with HA or threads could offer a more significant, clinical improvement of acne scars than subcision alone [60].

Subcision with autologous fat grafting showed better yet nonsignificant results versus subcision with PRP injection in the treatment of postacne scars [61]. However, one study comparing subcision with PRP injection versus normal saline showed similar efficacy, denoting that subcision, similar to the mechanical effect of injecting solution, is more important than the nature of the solution in the treatment of atrophic acne scars [62].
Other Treatments

Treatment with topical epidermal growth factor after ablative fractional CO\textsubscript{2} laser is safe and improves the clinical appearance of atrophic acne scars. Epidermal growth factor may help decrease skin pigmentation after laser treatment [63].

Botulinum toxin type A microtoxin, when injected intradermally as microdroplets, can be used to reduce pore size, sebum production, rosacea, acne, scars, and fine lines. Intradermal injection can also be used for the safe prevention and management of scars [64].

Ozone has been gaining greater visibility for its possible antioxidant effects when used in human dermatological pathologies, including skin scarring. However, more studies with better methodological standards and longer-term assessments of side effects should be conducted to achieve better standards and safety in ozone therapy for dermatological conditions [65].

The main treatments for atrophic postacne scars discussed in this review are summarized in Table 1.
Table 1. Procedures for atrophic postacne scars.

<table>
<thead>
<tr>
<th>Procedure and techniques</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular lasers or light</strong></td>
<td>Improve SAE$^e$ and may induce collagen remodeling</td>
<td>PIH$^f$</td>
</tr>
<tr>
<td>PDL$^a$, KTP$^b$, EDL$^c$, and IPL$^d$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ablative lasers</strong></td>
<td>Remove epidermis and part of the dermis, allowing collagen remodeling and re-epithelialization</td>
<td>Persistent erythema, hypopigmentation, PIH, infection, scarring, and long recovery period</td>
</tr>
<tr>
<td>Ablative CO$_2$$^g$ and Er:YAG$^h$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fractional ablative lasers</strong></td>
<td>Faster recovery, safer in darker skin phototypes, and less dyschromia</td>
<td>Poor results for ice-pick scars, erythema, PIH, and procedural discomfort</td>
</tr>
<tr>
<td>Fractional CO$_2$, 2940-nm Er:YAG, 2790-nm Er:YSGG$^i$, 1540-nm Er:glass$^j$, and 1550-nm EDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nonablative lasers</strong></td>
<td>Dermal thermal injury while preserving epidermis; minimal side effects: short erythema and minimal pain, swelling, oozing, scarring, or downtime</td>
<td>Results are modest and less impressive</td>
</tr>
<tr>
<td>Q-switched Nd:YAG$^k$, diode, and picosecond 755-nm Alexandrite</td>
<td></td>
<td></td>
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<tr>
<td><strong>RF</strong></td>
<td>Create zones of thermal wounds to stimulate dermal remodeling; microneedle bipolar RF and fractional RF offer the best results for ice-pick and boxcar scars with no PIH</td>
<td>Transient pain, erythema, and scabbing</td>
</tr>
<tr>
<td>Fractional RF +/- needling</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Needling</strong></td>
<td>Low cost, well tolerated, increase transepidermal absorption of topical agents, short recovery period, and low PIH</td>
<td>The full result may take 8 to 12 months as the deposition of new collagen takes place slowly</td>
</tr>
<tr>
<td>Needling device rolled over skin</td>
<td></td>
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<tr>
<td><strong>Dermabrasion and microdermabrasion</strong></td>
<td>Mechanical resurfacing procedures target scar edges precisely without thermal injury</td>
<td>Not effective for ice-pick or deep boxcar scars</td>
</tr>
<tr>
<td>High-speed brush, diamond cylinder, fraise, silicon carbide sandpaper, and abrasive crystals</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemical peels</strong></td>
<td>Induce chemical injury to the skin that stimulates collagen remodeling</td>
<td>Prolonged erythema, infection, PIH, and scarring in darker skin phototypes, deeper peels, and sun exposure; phenol has cardiac toxicity related to systemic absorption</td>
</tr>
<tr>
<td>Glycolic acid, lactic acid, salicylic acid, mandelic acid, TCA$^{m}$, and phenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PRP and stem cell therapy</strong></td>
<td>Enhance wound healing through the release of growth factors, cytokines, and chemokines</td>
<td>Better when combined with skin needling or fractional laser</td>
</tr>
<tr>
<td>Autologous PRP$^o$, MSCs$^p$, and adipose tissue–derived MSCs</td>
<td></td>
<td></td>
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<tr>
<td><strong>Filler</strong></td>
<td>Address the volume loss resulting from atrophic acne scars</td>
<td>Lumpiness and temporary results, making repeated treatments necessary, which increases cost</td>
</tr>
<tr>
<td>HAP$^q$ fillers, PLL$^r$, and CaHA$^s$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Individual atrophic scars surgical management</strong></td>
<td>Suitable for ice-pick scars and small (&lt;3 mm) boxcar scars +/- sutures along relaxed skin tension lines</td>
<td>Secondary widening of the scar may occur</td>
</tr>
<tr>
<td>Punch excision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elliptical excision</td>
<td>More favorable than punch excision in larger scars</td>
<td>Secondary scar may occur</td>
</tr>
<tr>
<td>Punch elevation</td>
<td>For boxcar scars</td>
<td>Better when followed by fractional CO$_2$ laser</td>
</tr>
<tr>
<td>Subcision</td>
<td>A blade is used to cut fibrotic strands tethering the scar</td>
<td>Bruising, swelling, bleeding, and infection</td>
</tr>
<tr>
<td>RF-assisted subcision</td>
<td>Comparable to convention subcision with no hematoma</td>
<td>Entry point burn</td>
</tr>
<tr>
<td>Microplasma RF technology combined with subcision</td>
<td>Satisfactory results with relatively no adverse effects</td>
<td>Short-term pain, edema, erythema, scaling, and effusion</td>
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</tbody>
</table>

$^a$PDL: pulsed dye laser.

$^b$KTP: potassium titanyl phosphate.

$^c$EDL: erbium-doped fractional laser.

$^d$IPL: intense pulsed light.

$^e$SAE: skin actinic elastosis.

$^f$PIH: postinflammatory hyperpigmentation.

$^g$CO$_2$: carbon dioxide.


$^i$YSGG: yttrium–scandium–gallium–garnet.

$^j$Er:glass.


$^l$RF: radiofrequency.

$^m$TCA: trichloroacetetic acid.

$^n$PRP: platelet-rich plasma.

$^{o}$MSC: mesenchymal stem cell.

$^{p}$Adipose tissue–derived MSCs.

$^q$HAP: hydroxyapatite.

$^r$PLL: poly-L-lactic acid.

$^s$CaHA: calcium hydroxylapatite.
Discussion

Principal Findings

Acne scarring is a frequent complication of acne. Early effective treatment of acne is the best strategy to prevent or limit postacne scarring.Treating SAE is the gold-standard, initial, and dramatic step toward improving acne scarring.

The management of acne scarring includes various types of resurfacing (chemical peels, lasers, and dermabrasion); the use of injectable fillers; and surgical methods, such as needling, punch excision, punch elevation, or subcision. There are limited randomized controlled trials that aimed to determine which treatment should be considered the gold standard.

Less invasive, less traumatizing procedures are more appreciated with less side effects and less downtime. Injectable fillers improve atrophic acne scars; however, the impermanence of their effect and their minimal utility for fine, shallow, and sharply depressed scars should be also considered.

The Energy-Based Devices for the Treatment of Acne Scars: 2022 International Consensus Recommendations considered energy-based devices to be a first-line treatment for a variety of acne scar types and stated that patients without access to these treatments may not be receiving the best available care for optimal cosmetic results [66]. The consensus recommended future high-quality research and updated international treatment guidelines and reimbursement schemes to reflect this status.

Combining interventions likely produce more benefit compared with the implementation of a single method. Since the scarred tissue has impaired regeneration abilities, the future implementation of stem or progenitor regenerative medical techniques is likely to add considerable value. One readily available strategy is PRP, which appears to be a safe and effective treatment for various types of atrophic scars. In addition, when added to ablative lasers or microneedling, it seems to considerably add to the efficacy of treatment and reduce the side effects [67]. Platelet-rich fibrin (PRF), a second-generation platelet concentrate, was developed for the purpose of overcoming the limitations of PRP. PRF can produce a higher cumulative release of growth factors than PRP. The therapeutic response was significantly higher in PRF than PRP either alone or combined with needling [68].

Conclusions

Early effective treatment of acne is the best strategy to prevent or limit postacne scarring. Treating SAE is the gold-standard, initial, and dramatic step toward improving acne scarring. Combining less invasive, less traumatizing procedures is more beneficial and more appreciated with less side effects and less downtime.

Future studies should recruit sufficient participants for blinded trials and include combined therapies versus placebo. Trials should collect baseline variables (participant demographics, acne lesions and extent, skin phototype, scar duration, and depth of scars) to ensure that they are balanced. Trials outcomes should be assessed by both participants and investigators, including adverse events, participant satisfaction, and quality of life, as well as cost and postprocedure downtime.

Conflicts of Interest

None declared.

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Abbreviations

CO2: carbon dioxide  
CROSS: chemical reconstruction of skin scars  
EDL: erbium-doped fractional laser  
Er glass: erbium glass  
Er YAG: erbium-doped yttrium aluminum garnet  
HA: hyaluronic acid  
IPL: intense pulsed light  
MDA: microdermabrasion  
MSC: mesenchymal stem cell  
MTZ: microthermal zone  
Nd YAG: neodymium-doped yttrium aluminum garnet  
PDL: pulsed dye laser  
PDT: photodynamic therapy  
PIH: postinflammatory hyperpigmentation  
PRF: platelet-rich fibrin  
PRP: platelet-rich plasma  
RF: radiofrequency  
SAE: scars-associated erythema  
TCA: trichloroacetic acid

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