



Review Article

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# Market Dynamics – Emergence of Mesenchymal Stem Cell-Conditioned Media as a Novel Treatment for Acne

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## Abstract

Acne vulgaris and its consequential scarring inflict significant psychological and emotional burdens on those affected, profoundly impacting their overall well-being. As a chronic inflammatory condition, acne ranks as the eighth most prevalent disease globally, affecting approximately 9.4% of the population. Its incidence is escalating, affecting both adolescents and adults alike. Notably, over 85% of adolescents encounter acne, often commencing during preadolescence and persisting into adulthood. The severity of acne directly correlates with the degree of impairment and influence on an individual's life. Moreover, acne can lead to enduring physical and psychological scars.

Despite the availability of various treatment methods, there remains a persistent demand for safer and more efficacious therapies. This paper aims to delve into the market dynamics propelling innovation within the global acne treatment sector. Key factors to be explored include market size and growth, the escalating prevalence and associated costs, heightened demand for effective treatments, and the emergence of innovative therapies, such as those utilizing mesenchymal stem cell-conditioned media (MSC-CM). Addressing these market forces is Global Innovative Health Solutions, which introduces its groundbreaking therapy: SCM-Blend Acne Cream.

**Keywords:** Mesenchymal stem cell, MSC, Conditioned media, MSC-CM, Acne, Acne vulgaris, Acne cream, Treatment methods, Market dynamics

## Introduction

Acne vulgaris (hereafter referred to as acne), a global issue impacting nearly everyone at some point in their lives, carries significant mental health consequences and financial burdens. Although not life-threatening, acne can profoundly impact a patient's quality of life, self-esteem, and mental well-being [1-3]. Traditionally viewed as an adolescent condition, recent research and clinical practice over the past two decades have highlighted its prevalence among adults as well [4-9]. Moreover, acne has been linked to diminished health-related quality of life (HRQoL), with negative effects comparable to severe, life-threatening illnesses [4,10,11]. Facial acne, typically prominent on the cheeks, chin, and forehead, is characterized by erythema, post-inflammatory hyperpigmentation, and scarring [11]. Acne scarring and post-inflammatory hyperpigmen-

tation can greatly affect a person's appearance and mental well-being, including damages to self-perception, social relationships, and overall quality of life, particularly among adolescents [3,10,12-16]. Studies by *Lewis-Jones, et al.* and *Finlay, et al.* showed that patients with chronic skin diseases like acne experience greater impairment in quality of life compared to those with other skin conditions [17,18]. The more severe the acne, the greater the impairment and impact [10,19-23]. For instance, the quality of life of Malaysian adolescents was impacted proportionally to the acne severity [22]. As per *Mallon, et al.*, acne is not a trivial problem as acne patients in their study showed comparable levels of social, psychological and emotional issues to those suffered from chronic asthma, epilepsy, diabetes, and more [10]. Regional and cultural differences do not



lessen the impact of acne on both quality of life and psychological functioning as demonstrated in Egyptian patients [21].

The development of acne arises from the blockage of skin pores due to a combination of bacteria, hair follicles, sebum (skin oil), dirt, and dead skin cells, leading to inflammation. Four primary pathogenic processes contribute to the formation of acne lesions: altered follicular keratinization resulting in comedones, increased and altered sebum production controlled by androgens, colonization of follicles by *Propionibacterium acnes* bacteria, and complex inflammatory mechanisms involving both innate and acquired immunity [24,25]. Acne, a chronic inflammatory disease of the pilosebaceous unit, manifests as non-inflammatory lesions (open and closed comedones) and inflammatory lesions (papules, pustules, nodules), often resulting in varying degrees of scarring [24,26-28]. Inflammatory acne occurs when bacteria colonize closed comedones, leading to sebum breakdown and an inflammatory response by neutrophils, macrophages and lymphocytes, resulting in papules (relatively deep) and pustules (more superficial), which are erythematous lesions. Deeper and more severe forms of inflammatory acne, such as nodules and cysts, can be painful and may lead to scarring.

Obstruction and inflammation of the pilosebaceous unit, comprising the hair follicle, hair shaft, and accompanying sebaceous gland, is central to the development of acne, which primarily affects the face and upper trunk [24,26,27,29-32]. Acne lesions range from comedones to papules, pustules, nodules, and cysts, with two subtypes identified in postadolescent acne: persistent and late-onset [33]. *Capitanio, et al.* showed that 85% of patients with post-adolescent acne had mostly comedonal acne [34]. Persistent acne, continuing from adolescence into adulthood, is predominant in adult female patients, whereas late-onset acne begins after the age of 25 years [30,33].

Acne affects both men and women and is one of the most common externally visible skin diseases encountered by individuals aged 15 to 40 in the United States (U.S.) [4]. Despite being commonly associated with adolescence, many adults still grapple with acne beyond their teenage years, experiencing it differently based on various factors. Adult acne is defined by *Preneau, et al.* as onset ranging from 20-25 years [35]. The average age of adult onset was found to be 25±6 years, and one-third (33.7%) were diagnosed with acne as adults [11]. In adult women, acne pathogenesis is notably complex, with androgens playing a significant role [11,36-38]. This is evidenced by the response to hormonal treatments, notably used for hyperandrogenism disorders like polycystic ovary syndrome (PCOS), indicating the role of androgens in conditions such as acne, alongside the use of hormone-based therapies such as oral contraceptives and anti-androgen medications for managing symptoms in women with normal androgen levels [39]. PCOS is a common endocrine disorder that can cause hyperandrogenism, which is an excessive production of androgens (male hormones) in females [40]. One of the main physical manifestations of hyperandrogenism in PCOS is acne, but it's important to note that not all individuals with PCOS will experience acne, as the symptoms can vary among individuals [40]. Additionally, the absence of acne in androgen-insensitive

women and the association between rising dehydroepiandrosterone sulfate levels and acne onset in premenarchal girls and some PCOS patients further underscore the role of androgens [37,41-43].

Despite its prevalence and impact, adult acne lacks a clear age-based definition, resulting in inconsistent age demarcations in the literature [11,35]. Nonetheless, the global acne market persists in its pursuit of new treatments to enhance quality of life. This paper will explore the market dynamics driving innovation in the global acne market, such as market size and growth trends, escalating prevalence and costs, as well as the mounting demand for minimally invasive and efficacious treatments. Moreover, it will explore innovative therapies like mesenchymal stem cell-conditioned media (MSC-CM). Global Innovative Health Solutions (GIHS) emerges as a significant contributor to the expanding acne market, introducing its latest product, SCM-Blend Acne Cream. This Acne Cream is uniquely formulated with GIHS's proprietary MSC-CM, known as the SCM Blend, presenting a promising new therapeutic approach.

## Market Size and Growth Trends

The global acne treatment market is on the verge of significant growth between 2023 and 2032, primarily propelled by the high prevalence of acne-related skin conditions, rising awareness, and ongoing advancements in effective treatment options [44]. According to a market research study published by Custom Market Insights, this market is expected to achieve a Compound Annual Growth Rate (CAGR) of approximately 6.5% during 2023-2032, with a projected value of USD 18.77 Billion by 2032 [44]. Fortune Business Insights reports similar trends, forecasting a CAGR of 5.1% to 5.2% during the same period, with the market size reaching USD 17.48 billion by 2032 [45,46]. In addition, The Brainy Insights estimates a CAGR of 4.2%, projecting the market to reach USD 18.5 billion by 2032 [47]. Several factors contribute to the growth of the global acne treatment market, including the rise in the young population, increasing awareness, the development of effective treatments, and the escalating prevalence of skin problems worldwide. Despite common side effects, the demand for acne treatment remains high [44].

Acne, affecting a significant portion of the global population, has been categorized into moderate acne, mild acne, and moderate to severe acne, with the moderate acne segment holding the largest share of 43.72% in 2019 [44,48]. The 18 to 44 age group dominates the market, driven by hormonal changes and lifestyle factors [45,49]. Lifestyle changes, such as smoking, drinking, and excessive consumption of junk food, contribute to conditions like skin allergies and acne, accelerating the growth of the acne medication market [49].

Skin care clinics dominate the end-user segment, with a 38% market share in 2022, expected to grow rapidly due to increasing skin problems in urban areas [50]. Other end-users include hospitals and specialty centers. Retail pharmacies dominate distribution channels and are projected to grow significantly due to consumer preferences and rising urbanization and telemedicine [45,49].

Regionally, the Asia-Pacific market is anticipated to register the highest growth rate due to a high incidence of acne, a younger population, rising healthcare expenditure, increased government

initiatives, and the presence of numerous pharmaceutical companies [48]. However, North America leads the global acne treatment market, with a 35.9% share in 2022 and 45% in 2023, followed by Europe, due to factors such as a growing population suffering from acne, beauty-related concerns, and investments in research and development [48-50]. In North America, the U.S. market size for acne treatment was USD 5.00 billion in 2022, projected to reach USD 7.27 billion by 2030, with a CAGR of 4.7% [51]. Additionally, Canada's acne treatment market is growing due to rising awareness, access to advanced treatments, and a culture that values healthcare and wellness [52].

In conclusion, the global acne treatment market is witnessing substantial growth, fueled by increasing awareness of skin health, new product developments, and lifestyle changes. With advancements in treatment options and rising demand, the market is expected to continue its upward trajectory. GIHS aims to establish itself as a dominant player in the growing global acne market with its newly developed SCM Blend-Acne Cream, aimed at alleviating the multiple burdens of this skin disease.

### Escalating Prevalence and Costs

Acne is a widespread issue affecting individuals globally, encompassing both adolescents and adults. Acne is a common long-lasting skin condition characterized by inflammation, ranks as the eighth most prevalent disease worldwide, affecting 9.4% of the population [53]. It poses a significant concern, with nearly all adolescents aged between 15 and 17 experience some degree of acne [24,54]. Its prevalence is on the rise, particularly among adolescents, with studies indicating that 85% to 100% of adolescents experience acne, often beginning in preadolescence and continuing into adulthood [55-59].

Acne ranks among the top 10 most prevalent conditions worldwide and consistently features as one of the top three most prevalent skin conditions in large studies conducted in the UK, France, and the U.S. [53,60-62]. In Western countries, it affects 79%-95% of adolescents, while in northeastern China, 51.3% of adolescents are affected [63,64]. The Global Burden of Disease (GBD) study reports that approximately 85% of young adults aged 12-25 years are affected by acne [65]. Other studies have corroborated these findings [66,67]. Research by *Bhate, et al.* found that about 85% of individuals aged 12 to 24 experience at least minor acne [57]. Acne can occur at any life stage, persisting into one's 30s and 40s [11,30,68].

While the causes of acne are multifactorial, including dietary, genetic, and environmental factors, the onset of puberty serves as a common trigger. Androgen production during puberty stimulates sebum production and keratinocyte hyperproliferation, partly contributing to the prevalence of acne in this population, regardless of socioeconomic status, nationality, or gender [69]. Other factors contributing to acne pathogenesis encompass genetics, as evidenced by twin studies, a family history of severe acne, and dietary factors such as glycemic index, including chocolate consumption, and dairy consumption [64,70-79]. Furthermore, environmental factors such as smoking, occlusive cosmetics, and occupational exposures contribute to acne pathogenesis [80-83].

In recent decades, the occurrence of acne in adults has been rising, particularly among women [7,68]. Despite traditionally being viewed as an adolescent condition, acne persists into adulthood. In women aged 20 to 29 years, the prevalence rate is 50.9%, compared to 26.3% in those aged 40 to 49 years. [54]. Furthermore, women are affected at higher rates than men in the same age groups, with 50.9% of women affected compared to 42.5% of men in the younger age group, and 26.3% of women affected compared to 12.0% of men in the older age group [54]. Moreover, several studies show that approximately 15% to 41% of women are affected, with environmental factors such as ultraviolet light, pollution, and lifestyle stressors contributing to its prevalence [7,11,30,68,84-88]. Women are disproportionately affected by acne compared to men, with approximately 12% to 22% of U.S. women experiencing adult acne, compared to 3% of men [7-9]. *Collier, et al.* also found that women were being more affected than men in all age groups 20 years and older [54]. Female patients account for a significant majority of dermatologist visits for acne, particularly among those older than 25 years [89,90]. Milder cases of acne may also be more prevalent in adult women [11,35].

The healthcare costs associated with acne are substantial, with an estimated financial burden of \$3 billion per year in the United States [57]. In 2013 alone, the costs related to treatment and lost productivity among individuals seeking medical care for acne surpassed \$1.2 billion, with nearly \$400 million attributed to lost productivity [48,91]. The direct cost of acne treatment in the U.S. exceeds \$1 billion annually, with over \$100 million spent on over-the-counter medications [92]. In 2013, more than 5.1 million people sought medical treatment for acne, predominantly children and young adults [91]. Furthermore, acne can result in enduring physical and psychological scars. Despite its prevalence as the most common skin condition in the U.S., finding a minimally invasive, long-lasting solution for effective acne and scar treatment remains a formidable challenge. However, companies like GIHS are pioneering efforts to address this persistent issue. Moreover, the impact of acne transcends mere financial burdens, affecting over 50 million individuals annually in the U.S. alone [45,48,51,57,93]. This significant contribution to the burden of acne treatment underscores its paramount importance within the healthcare landscape, particularly in the American market.

### Rising Demand for Better Treatments

#### Psychosocial and Emotional Distress Affecting Well-Being

The demand for an efficient and effective treatment solution for acne extends far beyond financial concerns, as it arises from the significant physical and psychosocial distress experienced by affected individuals. In a 2016 study conducted by *Hazarika, et al.*, which surveyed 100 acne patients, physical symptoms such as itch, soreness, pain, and stinging were reported by 78% of the participants [94]. Additionally, *Tasoula, et al.* and Reich et al. also observed the presence of itch symptoms in their respective studies [94-96].

While acne is not life-threatening or physically debilitating, its impact on social and psychological functioning can be severe. A large Greek survey conducted among 1,531 adolescents, with a



similar distribution of genders aged between 11 and 19, revealed a self-reported acne prevalence of 51.2%, affecting both genders equally [96]. Among them, 71.2% reported mild acne, while 28.8% reported moderate to severe acne. The survey highlighted that acne significantly affects the quality of life of young adolescents in Greece, with more severe acne associated with greater effects on self-esteem, body image, and relationships with others. The impact of acne on quality of life was significantly associated with its severity, as adolescents with moderate to severe acne experienced more profound psychosocial and emotional distress. Among those surveyed, 31.4% reported feelings of unworthiness and teasing, 21.3% made modifications to their dressing style, 19.2% experienced challenges in personal and social lives, 14% avoided swimming and other sports activities, and between 19.4% and 21.4% reported negative effects on personal activities, including hobbies and school work. Peer pressure was found to affect body image proportionally to acne severity, with feelings of embarrassment and decreased self-esteem observed in a high percentage of individuals with acne.

Findings from the Greek study were consistent with other research studies. As high as 75% of acne patients reported interpersonal problems with partner, close friends and relatives [94]. Additionally, a significant number of patients (68%) complained about the negative influence of acne on their social/leisure activities [94]. Social avoidance and withdrawal behaviour documented by *Yolac, et al.* and *Fried, et al.* can lead to the development of a permanent avoidant personality trait [97-99]. Avoidance of swimming, exercise and other sports due to acne was reported in several studies [19,100]. Between 14.4% and 25% of individuals reported difficulties in sports activities due to acne, while between 21.4% and 57% felt that acne affected their schoolwork and personal activities during holidays, including social interactions with the opposite sex [94,96,100,101]. Moreover, 69% reported avoidance behaviour, anger, and frustration affecting daily activities such as shopping, household chores, and gardening [94]. While major sleep disruption was not detected, *Tasoula, et al.* observed a significant percentage (16.6%) experienced it, higher than in the study by *Walker et al.* (6%) [19,96]. Lack of confidence, social dysfunction, and reduced employment opportunities were also documented [99,102,103]. Female adults with acne agreed that physical appeal is advantageous to getting hired and finding life partners [11,104,105]. Acne also affected adolescents' dressing styles and choices, with approximately one-fourth facing difficulty in dressing due to acne [106,107]. Social inhibition or phobia accompanying acne was evident, with nearly 20% of acne adolescents experiencing problems in relationship building due to their acne lesions [96,108]. Developmental issues of socialization, body image, and sexuality were documented [94,102]. Adolescents often resort to coping mechanisms such as avoiding eye contact, growing hair long to cover the face, or using makeup to minimize the appearance of acne lesions due to fear of scrutiny by others [109-111].

Severe acne has been associated with increased anxiety, depression symptoms, and overall impact on patients' lives [112]. Studies have shown a heightened prevalence of mood disorders, psychiatric hospitalizations, school absenteeism, unemployment, and even

suicidal ideation among individuals with severe acne [113,114]. Moreover, anxiety and depression were prevalent among acne patients, with up to 9% reporting suicidal ideation [115-118]. However, *Magin, et al.* found that feelings of unworthiness due to negative peer appraisal were more prominent than anxiety and depression, leading to impairment of self-esteem and self-image [96,99,119]. Furthermore, *Singam, et al.* demonstrated that patients with co-existent acne are more likely to experience primary hospital admissions for various mental health disorders, including depression, schizophrenia, and substance use disorders, compared to those without acne [59,113].

Though prevalent among acne adolescents, with almost half experiencing an impact on their self-esteem, embarrassment and self-esteem issues were felt by adults as well [10,94,112,120]. Studies have highlighted acne's particularly troublesome impact on patients between 20 and 40 years old, including distress related to their appearance compared to younger age (16-19 years old) groups [111,121-123]. Emotional effects and quality of life did not differ between males and females, with both genders equally affected by their skin problems [96,124-126]. However, studies from different regions showed varying impacts, possibly due to cultural differences [21,117,127]. Overall, acne significantly affects quality of life, leading to disturbances in body image, emotional stress, and social isolation [122,128-131]. Given the severe impacts of acne on individuals, there is an urgent need to develop more effective acne treatments.

#### Acne Scars Diminishing Well-Being

Acne scars, a persistent complication, represent a daunting consequence due to their potential to cause facial disfigurement and psychological distress, particularly when located on the face after lesions have healed [67,132,133]. This issue significantly impacts patients' quality of life [134-136]. Acne lesions typically manifest on the cheeks and forehead and can lead to permanent scarring, which tends to worsen with age due to natural lipoatrophy, further accentuating the scars [26,137]. Scarring often occurs early in acne and may affect up to 95% of patients, with its severity linked to both the severity of acne and delay before treatment [138]. Adults with acne demonstrate a higher prevalence of acne scars (59%) compared to the non-adults (32%) [139]. Despite varying degrees of scar formation, scars remain a significant concern for individuals due to their impact on appearance and psychological well-being [140].

Scar formation in acne can be categorized into two main stages: excessive tissue formation leading to keloid or hypertrophic scars, and tissue loss or damage resulting in atrophic scars [26,141]. Among these, facial atrophic scars are the most common [89,142-144]. These scars are crucial considerations in acne management and treatment due to their significant impact on physical and emotional well-being. Atrophic scars, which account for more than 80% of acne scars, are primarily of the ice pick (~60%), boxcar (~25%), or rolling (~15%) types [66,145-147]. Atrophic acne scars are a consequence of inflammation that damages deep dermal structures, resulting in irregular collagen synthesis and breakdown, causing skin indentation due to tissue contraction [142]. Acne scars

are enduring outcomes of acne, with prevalence rates as high as acne itself, affecting 47% of acne sufferers [139]. Main risk factors include male gender, family history of acne, and acne severity [139]. Genetic factors, such as *SELL* and *TGFB2*, have been implicated in scarring, further highlighting a genetic influence [148]. Acne scars are prevalent across all levels of acne severity, with severe acne particularly prone to scar formation due to intense skin inflammation [139,149]. Geographical variations in acne scar prevalence have been noted, with Africa (31%) demonstrating lower rates compared to Asia (52%) and Europe (51%) [139,150]. Despite dark-skinned individuals' heightened susceptibility to keloid and hypertrophic scars, they are less prone to atrophic acne scars, possibly due to genetic factors [150-152]. In addition, traditional observations suggest a higher prevalence of acne scars in men (58%), potentially due to hormonal and glandular differences [89,153,154]. Early intervention and comprehensive acne management are crucial in mitigating the risk of scarring, considering the multifaceted nature of acne scars influenced by genetic predisposition, acne severity, and gender differences.

#### **Current Treatment Methods with Side Effects: Non-Surgical vs. Surgical**

Facial acne scars prompt a range of treatment methods, including both surgical and non-surgical approaches. Non-surgical options involving topical medications and non-invasive procedures show promise, while surgical options like punch excision and subcutaneous excision address deeper scars. Even mild acne demonstrates a significant prevalence of scars, emphasizing the importance of treating all forms of acne to prevent scarring [139]. Due to their significant impact and difficulty in treatment, acne scars are gaining more attention. Risk factors for scarring include severe acne, duration of acne, family history of atrophic scars, and lesion manipulation [155]. Although treatments like laser resurfacing, micro-needling, chemical peels, and fillers exist, completely eliminating acne scars remains challenging. Various post-acne scar treatments exist, each with differing efficacy, side effects, and downtime. While recent advancements offer promising options, it's essential to consider associated risks and potential adverse effects before treatment initiation. Current methods include traditional approaches like skin abrasion, chemical peeling, and micro-needle therapy, as well as newer options like mesenchymal stem cells (MSC) and laser therapy. Laser therapy, categorized as ablative and non-ablative fractionated lasers, offers effective treatment, although associated with potential short-term adverse reactions, including pain, erythema, and inflammation [156].

Different types of laser treatment are utilized for acne scar management. Ablative lasers, such as 10600 nm CO<sub>2</sub> and 2940 nm pulsed Er: YAG lasers, vaporize the skin surface, promoting tissue removal and forming scabs post-treatment [140,157]. Several studies on ablative lasers have yielded mixed clinical efficacy results [158-161]. Despite being effective, CO<sub>2</sub> lasers can lead to short-term adverse reactions like erythema and pigmentation [162-164]. Non-ablative lasers, including pulsed dye, 1320 nm Nd: YAG, 1450 nm diode, and 1550 nm erbium glass lasers, are effective in reducing boxcar-type atrophic acne scars [165]. For instance, 675 nm

lasers stimulate collagen resynthesis, resulting in significant scar improvement without adverse reactions [165-167]. Studies also show the effectiveness of 1320 nm Nd: YAG lasers in treating atrophic acne scars, especially in younger patients [168-170]. Combining 1550 nm fractionated lasers with tretinoin has proven more effective than laser monotherapy for ice-pick-type scars, illustrating combination therapy often yields optimal results [170].

Other non-surgical treatments for acne scarring include chemical peels, fillers, micro-needling, and thread lifting. However, thread lifting has the least evidence regarding its clinical efficacy for acne scarring [171,172]. It involves inserting barbed threads under the skin to lift tissues and stimulate collagen synthesis [173]. Initially using non-absorbable threads, now semi-permanent absorbable threads are preferred due to lower infection risk, despite a shorter duration [171-173]. Minor complications may include mild erythema, small hemorrhage, small ecchymosis, transitory esthesia, and mild tumefaction [173]. Research using absorbable polydioxanone (PDO) threads showed improvement in boxcar scars without adverse events, but larger studies are needed to further assess effectiveness and safety [174].

Micro-needling therapy involves creating tiny holes in the skin to promote collagen production and skin regeneration, effectively improving rolling and boxcar scars with minimal side effects [175-177]. However, it is less effective for ice-pick scars and does not cause pigment deposition [178-182]. Combining micro-needling with other treatments like platelet-rich plasma (PRP) or chemical peels can enhance results, offering a versatile and safe approach to acne scar treatment [180,181,183-186]. Nevertheless, side effects such as erythema, edema and pain are commonly reported [187].

Skin fillers are a common method to address atrophic acne scars by injecting medical materials into depressed areas to level them with the surrounding skin. These fillers come in short-acting, semi-permanent, and permanent types, each with varying durations and biodegradability [188,189]. Short-term fillers like hyaluronic acid (HA) and exogenous collagen last 6 to 18 months, providing immediate volume increase and long-term collagen synthesis stimulation [190-193]. Semi-permanent fillers like poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA) stimulate collagen production but may cause adverse reactions [194-198]. Permanent fillers such as polymethylmethacrylate (PMMA) offer long-lasting results but require careful monitoring for complications [188,199].

Chemical peels utilize acids like alpha-hydroxy acids (AHAs) such as glycolic and lactic acid, beta-hydroxy acids (BHAs) like salicylic acid, and trichloroacetic acid (TCA) to promote skin exfoliation and collagen production [200,201]. Emerging agents like pyruvic acid and mandelic acid are also increasingly used for this purpose [171,200]. Different peeling strengths can address various skin issues, including acne scars, photoaging, dyschromia, and precancerous lesions [202]. Combining acids like salicylic and mandelic peels (SMPs) has proven effective for acne scar treatment [203-206]. Deeper scars, especially ice-pick scars, may require stronger agents like TCA (>50%) [165,204,205]. Chemical peels offer fast recovery, are cost-effective, and can be used alone or with other treatments to address various scar types [200,204,207-211].

Dermabrasion, a first major advanced treatment for scarring, involves controlled abrasion of superficial skin layers to stimulate re-epithelialization and collagen production [138,171,212,213]. While effective for shallow rolling and boxcar scars, it is less so for ice pick scars and may cause complications like pain and dyschromia [26,66,143,206,214-216]. Despite its historical effectiveness, dermabrasion is gradually being replaced by alternatives like chemical peels and lasers, which offer comparable or superior results with shorter recovery times [206].

Punch excision treatments, including punch elevation, excision, and grafting, involve using a circular blade to reach subcutaneous tissue [66]. These approaches effectively target deep ice pick and boxcar scars resistant to other treatments [182]. While punch elevation lifts scars without damage, excision may lead to visible ring scars and uneven texture if not done optimally [182,205,217-220]. Laser treatment can improve resulting uneven texture and linear scars [171,180,182,219,220]. Punch grafting offers a last resort for deep scars by inserting graft tissue into the punch site [171,221]. Despite being effective for specific scar types, punch techniques haven't seen recent advancements apart from adjunct laser therapies [171].

Subcutaneous excision, a surgical technique devoid of incisions, effectively targets atrophic acne scars and wrinkles, especially rolling scars, boasting improvement rates of up to 100% in standardized grading systems [222]. However, its efficacy is limited for boxcar scars, and complications such as nerve and blood vessel damage can lead to side effects like hematoma formation and excessive pigmentation [223-225]. Despite advancements in surgical instruments, complications remain a concern. Combining subcutaneous excision with treatments like micro-needling therapy, laser therapy, or hyaluronic acid injections enhances efficacy [222-224]. Studies highlight improved outcomes when combining subcutaneous excision with procedures like CO2 fractional laser or PRP [161,224,227,228]. Nonetheless, achieving optimal results necessitates careful surgical technique and a comprehensive understanding of facial anatomy.

Combined therapy for acne scars, utilizing multiple treatment methods simultaneously, has garnered attention for its ability to comprehensively address scars and enhance treatment efficacy. Common combinations, such as laser therapy with PRP injections, have demonstrated superior outcomes compared to laser therapy alone [229,230]. Studies have also highlighted the efficacy of PRP in combination with techniques like subcision and micro-needling therapy [186,224,231]. Combination therapy, integrating both surgical and non-surgical methods, is often utilized for optimal scar improvement. Further research is necessary to identify the most effective combinations among the wide array of available treatment options.

Each treatment modality presents unique benefits and risks, necessitating personalized approaches considering patient-specific factors like genetics, age, and skin type [171,232]. While experimental treatments hold potential, careful planning and consideration of efficacy, safety, patient preferences, and cost are crucial for optimal outcomes in treating acne scars.

### Topical vs. Oral: Retinoids and Antibiotics

As antibiotic resistance continues to rise, acne treatment approaches have shifted away from widespread antibiotic use toward more limited usage, favoring isotretinoin for moderate to severe cases. However, due to the ongoing need for innovative therapies to address acne's widespread occurrence, effective patient counseling and regular evaluations are paramount [32]. Additionally, there is a growing demand for effective treatments to manage this globally prevalent condition.

Topical retinoids like adapalene, tretinoin, and tazarotene effectively treat acne by preventing comedone formation and reducing inflammation [233,234]. They are preferred for all types of acne, minimizing scarring and discoloration [235,236]. Patients usually start with low concentrations due to potential side effects like dryness and irritation, gradually increasing as tolerated. Oral isotretinoin, a systemic retinoid, is safe and effective for severe acne, also recommended for moderate cases resistant to treatment [25]. It reduces sebum production, acne lesions, and scarring, without increasing depression risk, though rare mood exacerbation cases have been reported [237-252]. Isotretinoin doesn't associate with inflammatory bowel disease, but its safety and efficacy remain uncertain [25,67,253]. Treatment must consider reproductive plans, monitored through the iPLEDGE program, established by the FDA in 2006, mandating contraception use for fertile women, to prevent pregnancies while on isotretinoin therapy due to its severe teratogenic effects, including craniofacial, cardiac and thymic malformations [254-258]. Despite the strict monitoring, a noncompliance rate of 29% was reported [259]. Nonetheless, isotretinoin remains a cornerstone treatment.

Topical antibiotics are effective against acne but face challenges due to emerging resistance, especially with erythromycin and clindamycin. [25,236,260-264]. Combining them with benzoyl peroxide is recommended to combat resistance [25,236,260,264-267]. Oral antibiotics like tetracyclines, preferred for moderate to severe cases, should be used cautiously to prevent resistance [25,236,264]. Antibiotic resistance affects over 2.8 million people in the US, with common side effects like nausea, vomiting, and diarrhea reported in around 7% of tetracycline users and 4% of macrolide users [25,45,262]. Minocycline and doxycycline are contraindicated during pregnancy due to the risk of tooth and bone discoloration, while their use during breastfeeding is generally considered safe [25,257,268-272]. Minocycline may cause fewer gastrointestinal side effects but can lead to tinnitus, dizziness, and skin pigmentation [25, 272]. Doxycycline is associated with sun sensitivity and stomach upset, primarily metabolized by the liver and safe for patients with kidney problems [25]. Limiting oral antibiotics may reduce risks like inflammatory bowel disease and infections [273-275]. Certain antibiotics like penicillin, erythromycin, and cephalosporin are considered safer during pregnancy, though caution is advised due to potential fetal cardiac malformations and hepatotoxicity [268,276-279]. Penicillin and cephalosporin are safe for use during breastfeeding but rarely used for acne due to uncertain effectiveness and potential side effects such as allergic reactions, nausea and diarrhea [25,268]. The effects of these antibiotics on



oral contraceptive pills are uncertain, with limited evidence suggesting a potential risk of contraceptive failure [280-285]. However, other antibiotic classes are discouraged unless tetracyclines or macrolides (e.g., erythromycin) are contraindicated, and switching antibiotic classes should be approached cautiously to avoid promoting bacterial resistance [25,264,286].

Women over 25 years old often experience treatment failure, with a significant portion failing multiple courses of antibiotics or even isotretinoin [32,241,242,287,288]. Treating acne in adult women requires individualized approaches, considering patient preferences and reproductive factors. Screening for depression before and after isotretinoin initiation is recommended [289]. Despite advancements, the lack of a standardized acne grading system complicates treatment efficacy assessments, highlighting the need for further research in this area [25,290].

The prescription medicines segment, including antibiotics, retinoids, and other products commanded a market share of approximately 57% in 2022 [47]. Retinoids led among therapeutic classes, capturing about 29% of the market share in the same year, owing to their efficacy against moderate to severe acne by unclogging pores [47]. Equally dominant in 2022 was the antibiotics segment, driven by their approval for acne treatment and effectiveness in managing exudates [45,46]. In 2023, the topical segment emerged as the dominant force and is expected to maintain its lead due to increased product availability and patient preference for easy application [45]. Conversely, the oral segment is projected to grow due to rising acne prevalence and new product launches. Patients prioritize effective, comfortable, and easy-to-use acne treatments, regardless of whether antibiotics or retinoids dominate the market. However, this dominance comes with product limitations and suboptimal efficacy, necessitating a personalized medicine approach. In response to this demand, GIHS is launching its SCM-Blend Acne Cream, offering an enhanced acne treatment option that can be used either alone or in combination therapy.

## Opportunities for Novel Therapies

### Mesenchymal Stem Cells-Derived Conditioned Media (MSC-CM) as an Emerging Therapeutic

Managing post-acne scars poses significant challenges. Novel therapies utilizing mesenchymal stem/stromal cell conditioned media are being explored for acne scars, wound healing, and other skin conditions such as scalp psoriasis [160,291-301]. Recent research emphasizes that the therapeutic effects of mesenchymal stem cells (MSCs) stem from their secretion of paracrine factors, which trigger antiapoptotic events and facilitate tissue repair by maintaining an increased paracrine factor environment, thus making conditioned media derived from MSC cultures (MSC-CM), also known as the secretome of MSCs, a promising avenue for various regenerative therapies [302]. The stromal/stem cell secretome, comprising proteins, microRNA, growth factors, antioxidants, proteasomes, and exosomes, plays a pivotal role in therapeutic efficacy [303]. Conditioned media (CM) containing the secretome, serve as a rich source of paracrine factors, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like

growth factor-1 (IGF-1), IGF-2, and stromal cell-derived factor 1 (SDF-1), which promote tissue repair and regeneration [304-307].

Tissue regeneration and improvement in skin appearance quality may be facilitated by the presence of growth factors, chemokines, and cytokines in MSC-CM. Previous studies indicate that paracrine factors from MSCs in the CM play a pivotal role in wound healing [308,309]. Adipose-derived stem cell (ADSC)-CM has been shown to stimulate collagen synthesis, dermal fibroblast migration, and wound healing in animal models [310]. MSC-CM has also demonstrated efficacy in promoting skin burn wound recovery in rats, with factors like basic fibroblast growth factor (bFGF) being implicated in tissue regeneration [311,312]. Comparative studies suggest that wound healing with bone marrow-derived mesenchymal stem cell (BMMSC)-CM surpasses that with fibroblast-CM [308]. Stem cell-derived CM presents a viable alternative for cell-based therapies, given its effectiveness in healing various wounds [306,308,309,313]. MSC-CM's properties vary depending on factors such as cell source, culture conditions (hypoxic vs. normoxic), and timing of collection [314-318]. For example, hypoxic treatment, commonly used to enhance CM, has been shown to reduce oxygen levels and improve cellular functions [319]. CM obtained from MSCs cultured under hypoxic conditions has been shown to enhance cell proliferation and self-renewal capacities [319-322]. Allogenic MSC-CM has demonstrated superior healing rates compared to xenogenic MSC-CM, particularly under hypoxic conditions [319-321,323,324].

Differentiating MSC-CM from culture media alone is vital, as the former demonstrates superior efficacy in wound healing and scar reduction [321,325,326]. MSC-CM has shown greater hypertrophic scar reduction compared to culture media alone, with topical application post-laser treatment resulting in less erythema and pigmentation, suggesting that the observed effects of MSC-CM in these conditions are likely attributable to its secretome rather than the culture media alone [160,327-330]. Despite its potential, CM necessitates more frequent administration compared to MSC due to shorter half-lives of cytokines and growth factors [306].

Combining MSC-CM with conventional therapy may yield better outcomes, with various routes of administration showing promise, particularly topical and subcutaneous methods, which are the least invasive [299,300,331-333]. MSCs primarily isolated from adipose tissue, bone marrow, and umbilical cord blood have been utilized, with MSC-CM also showing potential benefits in atrophic scars and hypertrophic scars, particularly when combined with botulinum toxin type A (botox) [160,291-293,322,327-329,334,335]. Micro-needling combined with topical stem cell products, like amniotic fluid-derived mesenchymal stem cell-conditioned media (AF-MSC-CM), offers a novel approach for scar treatment. In a study comparing efficacy, significant improvement was noted with AF-MSC-CM compared to microneedling alone [292]. Similarly, the application of human stem cell-conditioned media following fractional CO2 laser procedure demonstrated atrophic scar improvement [293]. However, mixed results were observed with topical stem cell-conditioned medium after fractional carbon dioxide laser (FCL) compared to combined FCL and PRP or FCL alone for treating

atrophic acne scars [291]. While SC-CM may enhance FCL efficacy, PRP seems to be the preferable option [291]. While adverse events are more commonly associated with laser therapy than MSC-CM treatment, further clinical studies are needed to fully assess the effects of MSC-CM on scar improvement. Nonetheless, combined therapy with laser therapy has shown promise in reducing acne scars [160,291-293].

**Innovative Treatment Approach: GIHS's SCM-Blend Acne Cream**

Emerging therapies for acne scars, such as stem cells and cytokines, including MSCs, growth factors, and conditioned media, show promise in improving outcomes and reducing scars. Despite this progress, treating acne and its resultant scars remains challenging due to their prevalence and the absence of a universal solution.

According to a patient study published in the Journal of International Medical Research in November 2022, over 45% of patients discontinued therapy prematurely due to unresponsiveness and side effects associated with acne treatment products [51]. Additionally, Fortune Business Insights reported that approximately 37% of patients discontinued using acne treatment products due to side effects [51].

In response to these challenges, GIHS offers a unique and effective solution: SCM-Blend Acne Cream. GIHS, a technology company with a vision of building a 'Foundation for the Future,' focuses on

innovation in regenerative medicine, particularly stem cell therapeutics, to address human diseases. Led by Dr. Jonathan Lakey, a renowned researcher in stem cells and islet transplant for diabetics, GIHS aims to bring health and happiness to people through scientific innovation. Dr. Lakey's recent publication on Neurocream, with MSC-CM as the therapeutic agent, showed a 50% reduction in foot pain, tingling, and swelling in diabetic patients using the Neurocream, highlighting the potential benefits of stem cell therapeutics beyond diabetes [336]. As the Chief Scientific Officer and Co-Founder of GIHS, Dr. Lakey's expertise in stem cells is integral to the development and commercialization of stem cell therapeutics, including the SCM-Blend Acne Cream for acne patients.

Currently, GIHS is conducting a pilot study on the SCM-Blend Acne Cream (Table 1), with preliminary results showing visible improvement in acne for treated patients (Figures 1,2). No adverse effects have been reported so far, indicating the cream's safety and efficacy. Patient adherence to topical agents like the SCM-Blend Acne Cream is crucial for treatment success. Studies have shown that over 75% of patients adhere to topical agents, surpassing the average adherence rates of 50% to 60% [337-339]. Given the preference for non-invasive topical treatments in the acne treatment market, GIHS is well-positioned to drive market growth with its SCM-Blend Acne Cream. By offering a comfortable and effective solution, GIHS aims to make impactful changes and improve patients' quality of life with its new creation, the SCM-Blend Acne Cream.

**Table 1:** Use Instructions and Ingredients for the SCM-Blend Acne Cream for Daily Application.

| <b>SCM-Blend Acne Cream with 0.25% Salicylic Acid for Daily Usage</b>   |   |
|---|---|
| <p style="text-align: center;"><b>Directions for use:</b></p> <p>For daily use acne treatments, start with a clean face. Apply a small amount of the product evenly over the affected areas. If irritation occurs, consider reducing usage or consulting a dermatologist.</p>   | <p style="text-align: center;"><b>ADVERSE REACTION STATEMENT</b></p> <p>If you experience any adverse reactions or discomfort while using Acne Cream, it is important to discontinue use immediately and follow these instructions:</p> <ol style="list-style-type: none"> <li>1. Wash the affected area gently with mild soap and lukewarm water to remove any remaining cream.</li> <li>2. Pat the area dry with a clean, soft towel.</li> <li>3. Avoid scratching or further irritating the affected area.</li> <li>4. If the reaction involves redness, itching, or rash, you may consider applying a hypoallergenic, over-the-counter topical hydrocortisone cream to help relieve symptoms, following the manufacturer's instructions.</li> <li>5. Monitor the reaction closely. If it worsens or persists for more than 24 hours, seek medical attention or consult a healthcare professional.</li> <li>6. If you believe the reaction is severe or potentially life-threatening (such as difficulty breathing, swelling of the face, lips, tongue, or throat, or other signs of anaphylaxis), seek immediate medical assistance by calling emergency services.</li> <li>7. Once the reaction has subsided, discontinue using permanently and consult with a healthcare professional or dermatologist for further guidance on alternative products or treatments.</li> </ol> |
| <p style="text-align: center;"><b>Ingredients</b></p> <p>Water, Coconut Oil*, SCM BLEND, Salicylic Acid, Apricot Kernel Oil, Glycerin, Stearic Acid, Cetearyl Alcohol, Polysorbate 60, Phenoxyethanol, Vitamin E, Glycolic Acid, Tartaric Acid, Malic Acid, Aloe Barbadensis Leaf Juice*, Shea Butter*, Mango Butter, Sugarcane*, Bilberry Fruit Extract*, Maple Syrup*, Orange Peel Extract*, Lemon Peel Extract*, Cranberry Fruit Extract*, Bladderwrack Extract*, Green Tea Extract*, White Willow Bark Extract*, Neem Seed Oil*, dimethicone, Rosemary Leaf Extract*, Alcohol*, Xanthan Gum, Tetrasodium Glutamate Diacetate.</p> |   |
| <p><b>Note:</b> Remember to keep the original packaging and any information related to the cream to share with healthcare professionals if needed. Your safety and well-being are our top priorities, and discontinuing use in the event of a reaction is a precautionary step to ensure your health.</p>   |   |





Figure 1: Patient 1 result, before and after treatment with the SCM-Blend Acne Cream.



Figure 2: Patient 2 result, before and after treatment with the SCM-Blend Acne Cream..

### Conclusion

Early intervention is crucial to prevent worsening acne and scar formation, emphasizing the importance of prompt and effective acne treatment. Facial acne not only affects physical appearance but also disrupts emotional and social functioning. Although adult acne tends to be mild or moderate, its predominantly inflammatory nature can make it resistant to conventional treatments like anti-

biotics and isotretinoin, leading to increased scarring [241,242]. Overall, acne is a multifaceted condition that imposes significant burdens on both individuals and society. Its far-reaching effects underscore the importance of developing effective treatment strategies and providing support for those affected by this common dermatological condition [59,113]. New therapies for treating acne are constantly being researched and developed due to various market dynamics, including market size and growth trends, increasing

prevalence and awareness, and the demand for better treatments. Many of these treatments are still undergoing testing, but early studies indicate promising results, such as GIHS's SCM-Blend Acne Cream. To offer an effective solution to the acne problem, GIHS proposes a novel treatment with its SCM-Blend Acne Cream. GIHS offers a new treatment option to patients by providing effective and customizable modalities tailored to their individual needs. This facilitates advancements in personalized medicine within both clinical and cosmetic dermatology.

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