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REVIEW ARTICLE

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Effectiveness and safety of hyaluronic acid fillers used to enhance overall lip fullness: A systematic review of clinical studies

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Summary

Background: The majority of aesthetic treatments today are nonsurgical or minimally invasive aesthetic procedures. Soft-tissue augmentation with hyaluronic acid (HA) is one of them. Lip fullness and definition are key aesthetic factors associated with attractiveness, which is the reason that lip augmentation with HA fillers has become so popular.

Objective: To provide a systematic review of published medical literature on the effectiveness and safety of different HA fillers used to enhance overall lip fullness.

Methods and materials: The literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Twenty-two studies were included in the qualitative synthesis, 9 of them with level of evidence (LOE) 1b (randomized controlled trials), 1 with LOE 2b (individual cohort study), and 12 with LOE 4 (case series, poor-quality cohort, and case-control studies). A total number of subjects included in all studies were 3965.

Results: Hyaluronic acid fillers turned out to be an effective and safe treatment. The assessment methods (especially for efficacy) varied greatly from one study to another. Observed responses to the treatment in studies using different lip fullness scales varied between 71% and 93.2%. The most common adverse events were local reactions at the injection sites (swelling, contusion, bruising, pain, redness, and itching).

Conclusion: Based on the results of the studies included in this systematic review, HA fillers are effective and safe to use. The majority of included subjects were satisfied with the result and their looks.

KEYWORDS
efficacy, filler, hyaluronic acid, lips, safety

1 | INTRODUCTION

In recent years, aesthetic procedures have become a social phenomenon. The overwhelming majority of aesthetic treatments performed in the United States today are nonsurgical or minimally invasive aesthetic procedures.[1]

Soft-tissue augmentation with hyaluronic acid (HA) has become one of the most popular cosmetic procedures performed in the United States.[2] HA is a natural high-viscosity mucopolysaccharide found in many different parts of the human body as well as being a universal component of the spaces between the cells of the body tissues. Pure HA is inherently biocompatible and has the same chemical structure

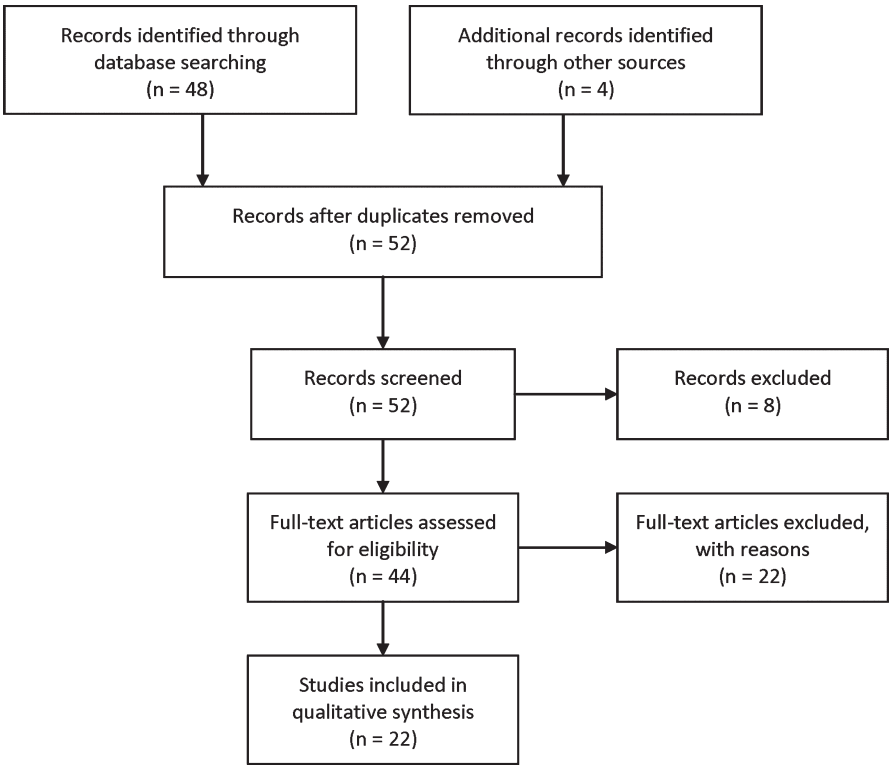

FIGURE 1 PRISMA 2009 flow diagram

in all species and all tissues. Even though the highest concentrations of HA are found in connective tissues, most HA is found in the skin.[3]

Women have been highlighting their lips since ancient times with face paints or rouge.[4] Lip fullness and definition are key facial aesthetic factors associated with attractiveness and youth. However, lips are prone to multiple factors that can dramatically change their shape over time.[5] Temporary dermal fillers containing HA are commonly used to enhance overall lip fullness and the vermilion border, minimize perioral lines and provide lip-definition.[6] Aesthetic cosmetic procedures require an in-depth understanding of the anatomy, more specifically the surface anatomy, of the lip. The lips are complex and frequently multiple terms are used for each anatomic structure.[7]

The face is divided into thirds, with the lips comprising the key aesthetic feature of the lower third. It is the upper lip in particular that has a significant effect on the aesthetic judgement of the face.[8] At present, full and well-defined lips are the ideal in Western cultures.[9] In Caucasian women, for example, the so-called ideal ratio of upper to lower lip is 1:1.6, meaning that the lower lip is somewhat more voluminous than the upper one.[10] It is well documented that lips become thinner and less clearly defined as a result of the aging process—lips appearing full and rounded are therefore considered being youthful and beautiful.[11]

2 | OBJECTIVE

The aim of this study was to provide a systematic review of published medical literature on the use of different HA-based fillers to enhance overall lip fullness and the vermilion border. The review synthesizes different characteristics of the studies included (population, duration, study design, type of HA, efficacy (also patient satisfaction), and safety).

3 | METHODS

The literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews. The bullet list of inclusion criteria:

1. Articles (indexed in PubMed) were identified through database searching on 4 November 2017, using the following string: "(lip [tiab] OR lips [tiab]) AND (hyaluron* [tiab]) AND (*esthetic* [tiab] OR rejuvena* [tiab] OR volume [tiab] OR youthful [tiab]

TABLE 1 Different lip fullness scales

MLFS (Medicis lip fullness scale)	ALFS (Allergan lip fullness scale)	LFGS (Lip fullness grading scale)
5 = Very full	5[a] = Very marked	4 = Full
4 = Full	4 = Marked	3 = Thick
3 = Medium	3 = Moderate	2 = Moderately thick
2 = Thin	2 = Mild	1 = Thin
1 = Very thin	1 = Minimal	0 = Very thin

[a]Initial ALFS was 4-point without the "very marked" grade.

TABLE 2 Summary of literature results (sorted by year of publication/decreasing years; if two or more studies were published in the same year, they were sorted by LOE)

First author; year	N	Design	LOE	Duration	Age Mean (Range or ±SD)	Male (%)
Geronemus 2017[1]	224	Randomized, controlled, multicenter study	1b	1 y	54 (22-78)	7 (3%)
Hilton 2017[2]	60	Randomized, evaluator-blinded study	1b	1 y	41.2 (21-63)	2 (3.3%)
Yazdanparast 2017[3]	10	Nonrandomized, prospective study	4	24 w	NA (28-45)	0
Artzi 2016[4]	400	Retrospective study	4	NA	49.6 (28-70)	40 (10%)
Fisher 2016[5]	146	Report from practical experience	4	4 m	44.7 ± 14.6	2 (1.3%)
Beer 2015[6]	219	Randomized, evaluator-blinded, controlled study	1b	9 m	45.5 (18-65)	6 (3%)
Dayan 2015[7]	213	Randomized, multicenter, prospective, single-blind study	1b	3 y 4 m	49 (20-79)	9 (4.2%)
Raspaldo 2015[8]	139 142	Randomized, prospective, multicenter study	1b	3 m	48 (18-76) 49 (18-75)	4 (3%) 2 (1.4%)
Smith 2015[9]	180	Randomized, prospective, evaluator-blinded, controlled Study	1b	6 m	47.6 (18-65)	1 (1%)
Philipp- Dormston 2014[10]	62	Prospective open-label, multicenter, observational study	4	1 m	39.7 (21-75)	7 (11%)
Fagien 2012[11]	50	Multicenter, open-label study	2b	48 w	47[b] (24-68)	2 (4%)
Cartier 2012[12]	NA (44 lips)	Multicenter, open-label study	4	6 m	54.5[a] (±8.4)	2[a] (4.5%)
Eccleston 2012[13]	60	Prospective, multicenter, open-label study	4	1 y	50 (21-74)	0
Glogau 2012[14]	180	Randomized, evaluator-blinded, controlled study	1b	24 w	47.6 (18-65)	1 (1%)
Rzany 2012[15]	77 (lips 44)	Prospective, open-label, multicenter study	4	6 m	54.5 (38-71)	4 (5.2%)
Lanigan 2011[16]	57	Prospective observational study	4	5.5 m	NA (18-60+)	2 (4%)
Solish 2011[17]	21	Open-label, pilot study	4	12 w	41.1 (26-65)	3 (14%)
Carruthers 2010[18]	90	Randomized, multicenter, prospective, single-blind, parallel-group study	1b	24 w	48.1 (36.6-55.8)	0
Downie 2009[19]	79	Randomized, double-blind, single-center study	1b	12 m	NA (25-55)	0

Product of HA- filler	Efficacy assessment	Subject satisfaction (efficacy)	Safety (AEs)
JUV_{XV}, RES_L	ALFS, GAIS	FACE-Q questionnaire, 11-point scale (hydration and natural look)	Swelling (94.8% vs 98.0%), firmness (91.6% vs 94.1%), and lumps/bumps (91.6% vs 90.2%)
RES_L, JUV_{XV}	LFGS, GAIS	Satisfaction Questionnaire	Implant side pain (8%), implant side papules (15%), implant side swelling (5%)
HK	MLFS, 5-point Investigator's Global Assessment	VAS	Pain (50%), swelling (10%), bruising (70%), firmness (30%), lump/bump (10%)
JUV_{XV}	NA	NA	Prolonged and recurrent inflammatory cutaneous reactions
BEL	5-stage scale for assessing naturalness and evenness, Merz scale, GAIS	6-stage scale, VAS for pain	Swelling (67.1%), erythema (23.3%), hematoma (15.1%)
RES_L	MLFS, independent photographic review, GAIS	GAIS	First vs. second treatment Lip disorder (5% vs <1%), lip pain (10% vs 7%), lip swelling 43% vs 53%), pain (8% vs 3%), contusion (44% vs 31%)
JUV_X	ALFS	NA	First vs. second treatment Swelling (95% vs 94.2%), bruising (93.3% vs 91.3%), firmness (89.6% vs 88.3%)
JUV_{XV}, RES_L	Subjects: FACE-Q (23-Item Recovery Early Life Impact, 17-Item Recovery Early Symptoms) Investigator: LFS (with 3D images), 11-point scale of overall satisfaction	FACE-Q (22-item satisfaction with lips, 10-item satisfaction with outcome	Swelling (91% vs 98.5%), tenderness (88.15% vs 95.5%), firmness (82.8% vs 95.5%), bruising (77.6% vs 88.8%), lumps (76.9% vs 90.3%), redness 76.1% vs 88.1%), pain (68.7% vs 88.8%), itching (21.6% vs 53%), discoloration (17.9% vs 43.3%)
RES_L	4-point Lip Assessment Scale (texture, firmness, symmetry)	NA	NA
JUV_{XV}	Injector Satisfaction scale (improvement in lips, natural look)	Subject Satisfaction scale (improvement in lips, natural look, feel of the lips)	Bruising (1.6%-5%), swelling (61.3%-64.7%)
JUV_{XV}	LFS	11- point scale	Swelling (94% of subjects), bruising (92%), and tenderness (88%)
HA_{EL}	LFGS, 3D analyses	Subject satisfaction questionnaire	Bruising, erythema, lump/bump, swelling, pain, pruritus
JUV_{XV}	iALFS	11-point overall satisfaction scale	Injection site bruising (51.7%), injection site swelling, and lumps (8.3%)
RES_L	LFS, independent photographic review, GAIS	NA	Swelling (58%), bruising (44%) tenderness (22%), pain (21%), erythema (17%); 4 severe AE
HA_{EL}	GAIS, LFGS	Satisfaction questionnaire	Bruising, erythema, lumps and bumps, edema and swelling, pain and tenderness, pruritus. [a](4-point severity scale)
JUV_X	Injector Patient Case Assessment Form	Patient Questionnaire	NA
RES_L	MLFS, GIAS	NA	Bruising (79%), redness (58%), swelling (95%), pain (58%), tenderness (90%), itching (21%), mass (37%)
JUV_X, JUV_{X+}	Cosmetic Improvement Scale, GAIS, Fullness assessment	NA	Pain from swelling at treatment site (3.3%), cold sore (3.3%)
PER_L	CKC scale using 2D images, 3D stereophotogrammetry	5-point rating scale	Cold sore (22%), dry lips (4%)

(Continues)

TABLE 2 (Continued)

First author; year	N	Design	LOE	Duration	Age Mean (Range or ±SD)	Male (%)
De Arruda 2008[20]	33	Prospective study	4	3 m	55 (30-55)	
Jacono 2008[21]	66	Nonrandomized, open-label, prospective case series	4	2 y	45.8 (20-76)	4 (6%)
Bosniak 2004[22]	1446	Nonrandomized, retrospective interventional case series	4	6 y	50.5 (±10.2)	417 (29%)

AEs, Adverse events (related to treatment and injection site reactions); ALFS, Allergan Lip Fullness Scale; BEL, Belotero; CKCS, Catherine Knowles-Clark scale; FACE-Q, patient-reported outcome instrument designed to measure outcomes among facial aesthetic patients; GAIS, Global Aesthetic Improvement Scale; HA_{EL}, HA_E LIPS-Emervel; HK, Hyamax Kiss; JUV_X, Juvederm Ultra; JUV_{X+}, Juvederm Ultra Plus; JUV_{XV}, Juvederm Volbella; LFGS, Lip Fullness Grading Scales; LOE, level of evidence; m, months; MLFS, Medicis Lip Fullness Scale; N, number of patients; NA, not available; NRS, Numerical Rating Scale; PD, Perfectha Derm; PER_L, Perlane; RES_K, Restylane Kysse; RES_L, Restylane; SD, standard deviation; VAS, Visual Analogue Scale; w, weeks; y, years.
[a]Data for group with augmentation treatment of their lips.
[b]Median, not average.

OR augmentation*[tiab]) AND (safety [tiab] OR efficac* [tiab] OR effective*[tiab] OR satisfac* [tiab]) AND (english [la])."
2. The following article types were selected: clinical trial, randomized controlled trial, case report, clinical trial phase II, clinical trial phase III, clinical trial phase IV, comparative study, controlled clinical trial, and multicenter study.
3. The limitation based on years was set from 2000 until 2017.

The search returned 48 articles. First, the duplicates were excluded. The abstracts of identified eligible studies were manually reviewed by the second author to remove publications related to topics other than aesthetics or where lips were not one of the examined anatomic areas. Studies where the method of application was topical were also excluded. The inclusion criteria of every individual study were not relevant for inclusion in our review. The selection procedure is presented in Figure 1. In the end, 22 studies were included in the qualitative synthesis. Each included study was labeled with appropriate level of evidence by the Oxford Centre for Evidence-Based Medicine.[12] Individual randomized controlled trials were labeled with 1b, individual cohort studies were labeled with 2b, and case series (and poor-quality cohort and case-control studies) were labeled with 4.

4 | RESULTS

After the database search and article selection, the results of the literature extraction were summarized (see Table 2). When preparing the results, few major points (described in more detail below) were analyzed with special interest: efficacy and assessment methods that were used, satisfaction of the patients, incidence, severity, and amount of anticipated adverse events (AE) and differences between filler types.

In the case of a few studies, the investigators did not exclusively focus on the lips. In those cases, we only included the part presenting the results concerning the lips. The population size ranged from 10 to 1446. A total number of subjects included in all studies were 3965. Less than half of the included studies (only nine) were randomized. The duration of the follow-up ranged from 1 month to 6 years. The average age of the study population was between 40 and 55 years. The majority of patients were women. The percentage of males was between 0 and 29.

The main challenge in synthesizing results was the heterogeneity of the assessment methods (particularly efficacy) used in the studies. There was also a wide variety of how the results were reported. Only a few scales used in the studies were validated: Medicis Lip Fullness Scale (MLFS), Allergan Lip Fullness Scale (ALFS), Lip Fullness Grading Scale (LFGS), the Catherine Knowles-Clark scale (CKCS), and FACE-Q. Non-validated scales included the widely accepted Global Aesthetic Improvement Scale (GAIS), Visual Analogue Scale (NRS), and many other different unnamed point scales of improvement and patient satisfaction. The most commonly used assessment scale was the photonumeric Lip Fullness Scale (LFS). Three different LFS were used: Medicis LFS,[13-16] Allergan LFS,[6,17,18] and Lip Fullness Grading Scale .[19-22] For the number of points on the scales and its descriptive definitions, see Table 1.

The primary efficacy endpoint was an increase in lip fullness for at least one grade on MLFS, ALFS, or LFGS. The observed response to treatment in studies[6,13-20,22] that used those scales varied between 71% and 93.2%. At 12 months, the response rate varied between 48.3% and 60%. There was always a statistically significant difference ($P < 0.001$) between treatment and no treatment. In many studies (see Table 2), patient satisfaction was also one of the endpoints. It was measured with non-validated questioners, unnamed scales with different points or simply "satisfied/not satisfied." The majority of studied subjects were satisfied with their lip improvement. The percentage of satisfied patients depended on the duration of the follow-up. Bosniak et al[3] showed that almost 61% of all patients with HA filler treatment remained satisfied with their results after 9 months. Eccleston et al[6] reported 96.9% of subjects being satisfied after one month and 80% after twelve months; 79.7% of subjects were satisfied after six months in the Rzany et al study.[20]

Product of HA- filler	Efficacy assessment	Subject satisfaction (efficacy)	Safety (AEs)
PD	NA	Poll questionnaire (9 items) + EEG	NA
RES_L	NA	5-point satisfaction scale	Transient erythema (NA), infrequent bruising (NA).
RES_L	Clinical observations; before/after photos (0-3 scale for volume and contour characteristics)	3-level scale of satisfaction	Transient erythema and infrequent bruising

There was a wide range of anticipated adverse events (AE), but the most common ones were local reactions at the injection sites (swelling, contusion, bruising, pain, redness, and itching). The main deficiency was that some of the studies did not report those kinds of AEs although they are expected with filler injections.[23] Only one study[24] describes (in 4.25% of patients) prolonged (up to 11 months) and recurrent (average: 3.17 episodes) late (average onset: 8.41 weeks after injection) inflammatory cutaneous reactions, but the incidence might vary between different products. The authors also believe that the prevalence of such reactions is higher and influenced by several parameters including the number and volume of HA-based gel injections, the nature of the product injected as well as possible individual factors.[24]

In four randomized controlled studies,[13,14,17,18] the authors defined severity and duration of AEs. Most subjects reported treatment-related AEs as mild (range 71%-88%) or moderate (range 11%-16%) in severity. Most of them resolved in less than 60 days (majority in 2 weeks).

In some studies,[6,18,22,25] Fitzpatrick skin type was also taken into account when analyzing results. Dayan et al[17] showed that subjects with Fitzpatrick skin types IV/V/VI tended to have a lower incidence of AEs than those with types I/II/III.

Some of the studies were comparative and some non-comparative. Three randomized controlled studies compared two different HA fillers with lidocaine: Juvederm Volbella (produced using a novel crosslinking process based on Vycross technology (Allergan plc, Dublin, Ireland) which combines low- and high-molecular weight HA[18] and Restylane (nonanimal stabilized HA filler [3]). Two studies[18,26] found less AEs and higher efficiency in the group treated with Juvederm Volbella; however on the contrary, the third study[19] was in favor of Restylane.

As a large amount of aesthetic injection procedures involves botulinum toxin, one study should be highlighted.[27] Its aim was to compare combined treatments of onabotulinumtoxin A and a 24-mg/mL smooth, cohesive HA gel filler with either treatment on its own. Combination therapy was superior to either modality used alone. All treatment regimens were well-tolerated, and the frequency of AEs considered to be definitely or probably related to treatment did not differ between groups.

5 | DISCUSSION

5.1 | Summary of main results and comparison with other reviews

There is only one systematic review with a similar field of research. Cohen et al[1] prepared a systematic review of trials dealing with efficacy and safety of small- and large-gel-particle HA injectable fillers. Effective treatment was demonstrated for the nasolabial folds, glabella, hands, and lips. The overall safety profiles were mostly similar for the different treated areas. The lips were more extensively examined in five studies.

In our study, the systematic search conducted according to the PRISMA guidelines identified 22 eligible articles, nine of which were randomized controlled studies. Hyaluronic acid fillers (different products) turned out to be an effective and safe treatment in all of the included studies. The assessment methods (especially for efficacy) used in the studies included in both reviews and the way how the results were reported differed a lot from one study to another. Only few scales were validated. The primary efficacy endpoint was an increase in lip fullness for at least one grade on different lip fullness scales (MLFS, ALFS, or LFGS). Observed responses to the treatment in studies[6,13-20,22] using those scales varied between 71% and 93.2%. At 12 months, the response rate varied between 48.3% and 60%. In Cohen's review, the validated MLFS has been used in one out of five studies with observed responses of 70% after 6 months.

The most common AEs in both reviews were local reactions at the injection sites (swelling, contusion, bruising, pain, redness, and itching), and duration of AEs varied considerably while being mild in severity.

The main difference between Cohen's review and ours was the number of publications providing highest-quality evidence. There were only two randomized studies with a 1b level of evidence. The authors of the review concluded that safety and efficacy data for lips exist but are considerably more limited. In our review, nine out of 21 studies were randomized with a 1b level of evidence. Cohen's review took place in 2013. As the aesthetic procedures in recent years are more and more popular, the number of studies published in the last 5 years is also much higher and we can make more reliable conclusions.

5.2 | Source of bias and limitations of included studies

When reviewing the articles,[18,27] one can notice that the overall volumes (initial visit and touch-up) of injected HA filler are much higher than in everyday clinical practice. Consequently, extended longevity of the effect (approx. 60% responder rate in the lip fullness scale at 1 year) is remarkable as prior clinical experience suggests that most HA fillers do not last for more than 6 months in this highly mobile area. But what does the aesthetic and financial relevance of the outcomes with such volumes mean to everyday clinical practice? It is aesthetically inappropriate and beyond the financial ability of most patients to use, for example, 3 mL of filler in the lips.[28]

Another limitation was the wide use of non-validated scales for efficacy assessment and lack of precise outcome definition. Only few of the scales used in the studies were validated: Medicis Lip Fullness Scale (MLFS), Allergan Lip Fullness Scale (ALFS), Lip Fullness Grading Scales (LFGS), the Catherine Knowles-Clark scale, and FACE-Q.

Sample sizes were consistently small in some studies,[15,16,29] and only few[13,30] of the studies performed sample size calculation. Potentially, insufficient sample sizes might have compromised the statistical precision, leading to wide confidence interval estimates and absence of statistical significance.[31]

5.3 | Limitations of this review

One of the potential limitations of this review might be that the search, inclusion of studies, and synthesis were performed by a single researcher.

Another limitation is the search strategy, because it included only published literature. Trials with positive results are more likely to be published and more quickly compared to trials with negative results, which may be subject to publication bias.[31] Because the majority of included studies evaluated only short-term outcomes, long-term effects remain unclear.

There was also a lack of homogeneity in the included studies, resulting in the lack of a quantitative synthesis of effect sizes with enhanced statistical precision.

5.4 | Ideas for future research and clinical practice

The aesthetic anatomic proportions (for example the volume of the lips) play a significant role in aesthetic cosmetic practice. On the other hand, however, psychological variables also play a crucial role. The majority of studies performed in the field of aesthetic practice focus on physiological and anatomical outcomes. As was shown in this systematic review, the subject's satisfaction can be a very important and relevant endpoint. It would be interesting to prepare a systematic review of published literature on more detailed psychological outcomes (eg, self-confidence). Another idea for future research could be a study on the impact of social media on the increase in the number of aesthetic procedures. Nowadays, social media, such as Instagram, represent the largest pool of before and after photographs. Plastic surgeons are known to have several thousands of Instagram followers with only one purpose: to bring in new and younger clients. The influence of social media is enormous and has a high potential for research.

6 | CONCLUSION

The main conclusion based on the results of the studies included in this systematic review is that HA fillers are effective and safe to use for lip augmentation. The majority of included subjects were satisfied with the result and their looks. The main challenge in synthesizing results is the heterogeneity of the assessment methods (specially efficacy) used in the studies. There is also a wide variation of how the results are reported. The most common adverse events are local reactions at the injection sites, serious AEs are uncommon. More high-quality clinical studies with similar assessment methods are needed to be able to perform a meta-analysis of effectiveness and safety of HA fillers.

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