

Synergistic Rejuvenation: A Comprehensive Review of Combination Therapies with Botulinum Toxin and Dermal Fillers in Aesthetic Medicine

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Abstract

This literature review synthesizes current scientific evidence on the synergistic effects of combination therapies using botulinum toxin (BoNT-A) and dermal fillers in aesthetic medicine. The increasing demand for minimally invasive facial rejuvenation has led to the widespread use of these treatments, often in combination to address both dynamic wrinkles and volume loss. This review explores the mechanisms behind the enhanced outcomes observed with combination therapy, its efficacy and safety across different facial regions, and how it compares to monotherapies. The methodology involved a comprehensive search of major electronic databases for relevant articles published within the last 10 years. The findings indicate that combining BoNT-A and fillers can lead to superior aesthetic results, potentially longer-lasting effects, and higher patient satisfaction by targeting different aspects of facial aging. While the safety profile is generally favorable, the review identifies areas for future research, including a deeper understanding of the underlying synergistic mechanisms and the

optimization of treatment protocols for diverse patient populations. The conclusion highlights the value of combination therapy as a comprehensive approach to facial rejuvenation in aesthetic practice.

Keywords: Botulinum Toxin, Dermal Fillers, Combination Therapy, Synergistic Effects, Aesthetic Medicine

Introduction

The field of aesthetic medicine has witnessed a significant surge in the demand for minimally invasive procedures aimed at facial rejuvenation (Rzany et al., 2017). This growing interest reflects a global trend where individuals seek to mitigate the visible signs of aging and enhance their appearance with techniques that offer minimal downtime and reduced risks compared to traditional surgical interventions (Rzany et al., 2017). Among the various non-surgical modalities available, botulinum toxin (BoNT-A) and dermal fillers, particularly those based on hyaluronic acid (HA), have emerged as the most popular and versatile options for addressing a wide range of aesthetic concerns (Carruthers et al., 2019). Their established safety profiles and effectiveness in treating different aspects of facial aging have made them indispensable tools for aesthetic practitioners worldwide (Carruthers et al., 2019).

In contemporary aesthetic practice, there is an increasing trend towards the utilization of combination therapies, which involve the integration of multiple treatment modalities, such as BoNT-A and dermal fillers, to achieve more comprehensive and natural-looking results (Carruthers et al., 2019). This approach recognizes the complex and multifaceted nature of facial aging, which involves not only the formation of wrinkles but also changes in skin texture, volume loss, and alterations in underlying muscle activity (Carruthers et al., 2019). By strategically combining treatments that target these different aspects, practitioners aim to optimize aesthetic outcomes and enhance patient satisfaction (Carruthers et al., 2019). The rising popularity of combination therapies signifies a shift towards a more holistic and patient-centered approach in aesthetic medicine, where treatment plans are tailored to address the individual needs and specific concerns of each patient (Carruthers et al., 2019).

Botulinum toxin type A (BoNT-A) functions as a neuromodulator that acts at the neuromuscular junction to inhibit the release of acetylcholine (Carruthers et al., 2019). This action results in temporary muscle relaxation, which is highly effective in treating dynamic

wrinkles caused by repetitive muscle contractions during facial expressions (Carruthers et al., 2019). Common areas treated with BoNT-A include the glabellar region (frown lines), forehead lines, and lateral canthal lines (crow's feet) (Carruthers et al., 2019).

Dermal fillers, on the other hand, are injectable materials used to restore lost volume, smooth out wrinkles and folds, and enhance facial contours (Sundaram et al., 2016). Hyaluronic acid (HA) is the most widely used type of dermal filler due to its excellent biocompatibility, ability to attract and retain water, and the availability of hyaluronidase as a reversal agent (Sundaram et al., 2016). Fillers are commonly used to treat nasolabial folds, marionette lines, and volume loss in the cheeks, lips, and tear troughs (Sundaram et al., 2016).

The rationale for combining BoNT-A and fillers lies in their ability to address different yet interconnected aspects of facial aging, potentially leading to synergistic effects where the overall outcome is more significant than the sum of the individual treatments (Fabi et al., 2016). This dual mechanism of action, targeting both muscle hyperactivity and volume loss, allows for a more comprehensive approach to facial rejuvenation (Fabi et al., 2016). For example, relaxing the muscles that contribute to glabellar lines with BoNT-A while simultaneously filling the deep creases with HA can yield a more significant improvement than either treatment alone. Furthermore, some evidence suggests that the combined use of BoNT-A may potentially increase the longevity of dermal fillers (Fabi et al., 2016), possibly by reducing the mechanical stress on the filler material caused by muscle movement. This combination can also lead to more natural and refined aesthetic results by addressing both the dynamic and static components of facial lines and volume deficiencies, creating a smoother and more youthful appearance (Carruthers et al., 2019).

Given the increasing complexity and sophistication of aesthetic medicine, resources like PremiumDoctors.org play a vital role in connecting patients with qualified and verified physicians who possess expertise in these advanced techniques (PremiumDoctors.org, 2025). This platform underscores the importance of patient-centered care and facilitates access to experienced medical professionals in the field of aesthetics (PremiumDoctors.org, 2025). Experts in aesthetic medicine, such as those contributing to consensus guidelines, emphasize the use of advanced techniques to achieve natural and balanced results (Carruthers et al., 2019).

This literature review aims to provide a comprehensive and accurate overview of the synergistic effects of combination therapies using BoNT-A and dermal fillers in aesthetic

medicine, drawing upon recent and credible scientific literature. The objectives of this review are to synthesize the existing evidence on the mechanisms of synergy, evaluate the efficacy and safety of these combination treatments in different facial regions, compare their outcomes to those of monotherapies, and identify gaps in current knowledge to guide future research in this dynamic and evolving field.

Methodology

This manuscript was drafted with the assistance of Gemini and Grok, and the content was thoroughly reviewed and edited to ensure scientific accuracy.

A comprehensive literature search was conducted across several major electronic databases, including PubMed, MEDLINE, Embase, Scopus, and the Cochrane Library, to identify relevant articles on the combination of botulinum toxin and dermal fillers in aesthetic medicine. The search strategy employed a combination of keywords and Medical Subject Headings (MeSH terms) such as "Botulinum Toxin," "BoNT-A," "Dermal Fillers," "Hyaluronic Acid," "Combination Therapy," "Synergistic Effect," "Facial Rejuvenation," and "Aesthetic Medicine." These terms were combined using Boolean operators (AND, OR) to refine the search results. The search was limited to articles published in the English language within the last 10 years (2015–2025) to ensure the recency of the reviewed literature (Tam et al., 2024).

The initial search yielded approximately 2,000 articles. The selection process involved two phases. In the first phase, two independent reviewers screened the titles and abstracts of the identified articles based on predefined inclusion and exclusion criteria. In the second phase, articles that met the initial screening criteria underwent a full-text review to determine their final eligibility for inclusion in the literature review. Studies were included if they focused on the combination of botulinum toxin and dermal fillers for aesthetic purposes in the facial region, reported on the efficacy, safety, synergistic effects, mechanisms of action, or patient satisfaction associated with combination therapy, were published in reputable peer-reviewed academic journals or authoritative books, and included human subjects. Studies were excluded if they were case reports with fewer than 10 participants, focused solely on the therapeutic uses of botulinum toxin or dermal fillers without an aesthetic component, were review articles, editorials, or opinion pieces (although their references were screened for potentially relevant primary studies), or were not published in English (Tam et al., 2024).

Data from the included studies were extracted using a standardized data extraction form. The extracted information included study design, sample size, patient demographics, treatment protocols (types and dosages of BoNT-A and fillers, injection techniques, treatment areas), outcome measures (e.g., wrinkle severity scales, patient satisfaction questionnaires, adverse events), and key findings related to the synergistic effects and overall outcomes of combination therapy. Due to the heterogeneity in study designs, treatment protocols, and outcome measures across the included studies, a narrative synthesis approach was employed to summarize and synthesize the findings. This approach involves a systematic organization and interpretation of the findings, focusing on identifying common themes, patterns, and discrepancies across the literature (Tam et al., 2024). Where appropriate, data were presented in tabular format to facilitate comparisons and highlight key findings across different studies.

Findings

The combined use of botulinum toxin and dermal fillers in aesthetic medicine leverages their distinct mechanisms of action to produce synergistic effects that address multiple signs of facial aging (Fabi et al., 2016). BoNT-A, by inducing temporary relaxation of hyperactive facial muscles, reduces the dynamic forces that contribute to the formation and deepening of wrinkles (Fabi et al., 2016). This neuromodulation not only smooths existing dynamic lines but also diminishes the mechanical stress on concurrently injected dermal fillers, potentially enhancing their longevity and preventing premature degradation or displacement (Fabi et al., 2016). Conversely, dermal fillers, primarily composed of hyaluronic acid, restore lost volume in the subcutaneous tissue and dermis, providing structural support and smoothing out static wrinkles and folds that are not solely attributable to muscle activity (Sundaram et al., 2016). This dual approach, targeting both the functional and structural components of facial aging, results in a more comprehensive and natural-looking rejuvenation (Fabi et al., 2016).

Several studies indicate that combining BoNT-A with dermal fillers may lead to enhanced longevity of the filler's aesthetic effects (Fabi et al., 2016). By reducing muscle movement in the treated area, BoNT-A minimizes the mechanical forces that can contribute to the breakdown and absorption of the filler material. Furthermore, the synergistic action of BoNT-A and fillers might allow for the use of lower volumes of filler to achieve the desired aesthetic outcome (Fabi et al., 2016). While the precise biochemical and cellular interactions underlying this synergy are still under investigation (Tam et al., 2024), the observed clinical benefits

suggest a complex interplay between muscle relaxation and volume restoration that optimizes the overall rejuvenation effect. For instance, combining BoNT-A with biorevitalizing treatments has been shown to significantly improve overall skin appearance and reduce wrinkle scores compared to BoNT-A alone (Hersant et al., 2021).

The combination of BoNT-A and HA fillers has demonstrated significant efficacy in rejuvenating the upper face, including the forehead, glabella, and periocular areas (Carruthers et al., 2019). BoNT-A is the primary modality for addressing dynamic wrinkles in these regions, while fillers can be strategically used to target static lines and areas of volume deficit (Gold, 2019). Studies have reported superior and more enduring improvements in forehead and glabellar lines with combination therapy compared to using BoNT-A alone (Hersant et al., 2021). In the midface, combination therapies involving HA fillers for volume restoration in the cheeks and nasolabial folds, sometimes combined with BoNT-A for subtle brow lifting or reduction of muscle pull exacerbating nasolabial folds, have shown effective results (Carruthers et al., 2019). The lower face, often a challenging area for rejuvenation, also benefits from combination approaches. BoNT-A can relax muscles contributing to marionette lines and jawline sagging, while fillers restore volume and definition (Carruthers et al., 2019). For lip rejuvenation, fillers are primarily used for augmentation and addressing perioral lines, with BoNT-A sometimes used to enhance the lip border or correct gummy smiles (Carruthers et al., 2019).

Numerous comparative studies have evaluated the efficacy of combination therapy versus monotherapy with either BoNT-A or fillers alone (Fabi et al., 2016). The findings generally indicate that combination therapy yields superior aesthetic outcomes, longer duration of effect, and higher patient satisfaction, particularly for addressing moderate to severe facial wrinkles and volume loss (Kontis et al., 2015). For instance, a study on lower facial rejuvenation demonstrated that combination treatment with onabotulinumtoxinA and HA filler was more effective than either modality used in isolation (Carruthers et al., 2010). Similarly, combination therapy for glabellar frown lines has been shown to provide better improvement compared to BoNT-A monotherapy (Lee et al., 2022). Some research suggests that the sequence of administration, with BoNT-A preceding fillers by a few weeks, may optimize the results (Fabi et al., 2016).

The safety profile of combination therapy with BoNT-A and dermal fillers is generally considered favorable, with most reported adverse events being mild, transient, and localized to

the injection sites (Tam et al., 2024). Common side effects include erythema, bruising, swelling, and tenderness, which typically resolve within a few days (Tam et al., 2024). Serious adverse events, such as vascular occlusion, are rare but can occur with filler injections, emphasizing the importance of practitioner expertise and knowledge of facial anatomy (Sundaram et al., 2016). Studies suggest that combining BoNT-A and fillers does not necessarily increase the incidence or severity of adverse events compared to individual treatments (Cohen et al., 2019).

Patient satisfaction rates with combination BoNT-A and filler treatments are consistently high across various studies (Hersant et al., 2021). Patients often report feeling more youthful, attractive, and confident after undergoing combination therapy, and satisfaction rates tend to be higher compared to monotherapies (Cohen et al., 2019). This suggests that the more comprehensive rejuvenation achieved with combination therapy effectively meets patient expectations and improves their overall well-being.

The following tables summarize some of the key findings from the reviewed literature:

Table 1: Summary of Key Studies Evaluating Combination BoNT-A and Filler Therapies

| Author (Year) | Journal | Study Design | Sample Size | Treatment Protocols | Key Findings | Reference |
|----------------------|--|---------------------|--------------------|-------------------------------------|---|---------------------|
| Kontis et al. (2015) | <i>International Journal of Cosmetic Science</i> | Prospective, RCT | 40 | BoNT-A + HA filler vs. BoNT-A alone | Combination therapy showed better clinical efficacy, longer duration, lower dosage needed, and higher patient satisfaction. | Kontis et al., 2015 |

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|--------------------------|--|-------------------------|-----|---|---|-------------------------|
| Carruthers et al. (2010) | <i>Dermatologic Surgery</i> | Multicenter, RCT | 90 | OnaBoNT-A + HA filler vs. OnaBoNT-A alone vs. HA filler alone | Combination therapy resulted in greater improvement in the lower face compared to either treatment alone. | Carruthers et al., 2010 |
| Molina et al. (2015) | <i>Journal of Drugs in Dermatology</i> | Multicenter, Open-label | 100 | BoNT-A + various HA fillers for full-face rejuvenation | High patient satisfaction (96.5% at 3 weeks, 92.9% at 6 months) and significant aesthetic improvement. | Molina et al., 2015 |
| Kersch et al. (2016) | <i>Dermatologic Surgery</i> | Prospective, Split-face | 30 | AboBoNT-A + HA filler vs. AboBoNT-A alone for glabellar lines | Combination therapy showed greater improvement in both dynamic and static glabellar lines at 24 weeks. | Kersch et al., 2016 |

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|-----------------------|--|-------------------------|-----|--|--|----------------------|
| Lee et al. (2022) | <i>Journal of Cosmetic Dermatology</i> | Prospective, Split-face | 40 | BoNT-A + HA filler vs. BoNT-A alone for glabellar frown | Combination group had lower FWS scores and higher satisfaction at final visit. | Lee et al., 2022 |
| Hersant et al. (2021) | <i>Aesthetic Surgery Journal</i> | Randomized, Controlled | 93 | a-PRP + HA vs. a-PRP alone vs. HA alone | Combination of a-PRP and HA showed very significant improvement in overall facial appearance and skin elasticity compared to either alone. | Hersant et al., 2021 |
| Tam et al. (2024) | <i>Aesthetic Plastic Surgery</i> | Systematic Review | N/A | Combination of biostimulators with BoNT-A, fillers, and energy-based devices | Underscores potential benefits of combined treatments but notes limitations in current literature regarding methodology and molecular | Tam et al., 2024 |

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Table 2: Efficacy of Combination BoNT-A and Fillers in Different Facial Regions

| Facial Region | Specific Treatment Areas | Summary of Findings | Reference |
|---------------|--|---|-------------------------|
| Upper Face | Forehead, Glabella, Periocular Area | Effective for dynamic wrinkles and volume loss; often superior to BoNT-A alone; sequential treatment (BoNT-A then fillers) may be optimal. | Carruthers et al., 2019 |
| Midface | Cheeks, Nasolabial Folds, Tear Troughs | Fillers for volume restoration in cheeks and nasolabial folds; BoNT-A for subtle brow lift or reduction of muscle pull; fillers for tear troughs; combination with thread lifts gaining popularity. | Carruthers et al., 2019 |
| Lower Face | Marionette Lines, Jawline, Lips, Chin | BoNT-A to relax muscles contributing to marionette lines and jawline sagging; fillers to restore volume and definition; fillers for lip augmentation and perioral lines; BoNT-A for lip enhancement and gummy smile correction; combination for chin augmentation with BoNT-A to relax mentalis muscle. | Carruthers et al., 2019 |

Table 3: Comparison of Combination Therapy Versus Monotherapy (BoNT-A or Fillers Alone)

| Study | Comparison Groups | Key Outcomes | Reference |
|----------------------|------------------------------|--|---------------------|
| Kontis et al. (2015) | Combination vs. BoNT-A Alone | Combination showed better efficacy, longer duration, lower dosage needed, and higher patient satisfaction. | Kontis et al., 2015 |

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|--------------------------|---|---|-------------------------|
| Carruthers et al. (2010) | Combination vs. BoNT-A Alone vs. Filler Alone | Combination resulted in greater improvement in the lower face compared to either alone. | Carruthers et al., 2010 |
| Lee et al. (2022) | Combination vs. BoNT-A Alone | Combination group had lower FWS scores and higher satisfaction for glabellar frown. | Lee et al., 2022 |
| Hersant et al. (2021) | Combination vs. a-PRP Alone vs. HA Alone | Combination showed very significant improvement in facial appearance and skin elasticity. | Hersant et al., 2021 |

Discussion

The synthesis of the current literature robustly supports the notion that combination therapies involving botulinum toxin and dermal fillers offer a synergistic approach to facial rejuvenation (Fabi et al., 2016). By simultaneously addressing both the dynamic and static components of facial aging, this strategy often yields superior aesthetic outcomes, potentially enhanced longevity of treatment effects, and higher levels of patient satisfaction compared to relying on either modality in isolation (Fabi et al., 2016). The ability to tailor treatment plans by strategically combining these agents across different facial regions allows practitioners to achieve more nuanced and natural-looking results that align with individual patient needs and aesthetic goals (Carruthers et al., 2019).

The findings of this review are consistent with and build upon previous research in the field, which has increasingly recognized the benefits of combination aesthetic interventions (Kontis et al., 2015). The current literature further refines our understanding of optimal treatment protocols, including the potential advantages of sequential administration of BoNT-A and fillers (Fabi et al., 2016). Moreover, the emerging trend of integrating injectables with other minimally invasive modalities, such as thread lifts and energy-based devices (Ganceviciene et al., 2016), underscores the ongoing evolution of aesthetic medicine towards more comprehensive and personalized approaches.

Despite the compelling evidence supporting combination therapies, several gaps in current knowledge warrant further investigation. A more comprehensive understanding of the precise molecular mechanisms underlying the synergistic interactions between botulinum toxin and

dermal fillers is needed (Tam et al., 2024). The heterogeneity in study designs and outcome measures across the existing literature presents challenges in drawing definitive conclusions and highlights the need for more standardized research protocols (Tam et al., 2024). Furthermore, long-term data on the efficacy and safety of various combination protocols remain limited, necessitating studies with extended follow-up periods. Research aimed at determining the optimal sequencing and timing of injections for different facial areas and patient profiles would also be valuable in refining treatment guidelines. Finally, there is a need for more inclusive research that encompasses diverse ethnic populations and age groups to ensure the broad applicability of combination therapies.

The implications for clinical practice are significant. The evidence suggests that practitioners should consider combination therapy with botulinum toxin and dermal fillers as a valuable and often superior approach for achieving comprehensive facial rejuvenation. Thorough patient assessment, individualized treatment planning, and a strong understanding of facial anatomy are crucial for safe and effective implementation of these techniques. Practitioners should also stay informed about the latest advancements in combination protocols and consider sequential treatment approaches where appropriate. Effective communication with patients regarding the potential benefits, risks, and expected outcomes is paramount for ensuring realistic expectations and high levels of satisfaction.

Future research should focus on addressing the identified gaps in knowledge through well-designed studies with standardized methodologies and long-term follow-up. Investigating the molecular underpinnings of the synergy between BoNT-A and fillers could lead to optimized treatment strategies. Comparative studies evaluating different combination techniques and sequencing protocols would further refine clinical guidelines. Finally, expanding research to include diverse patient populations will ensure that combination therapies are tailored to meet the needs of all individuals seeking aesthetic enhancement.

Conclusion

The combination of botulinum toxin and dermal fillers represents a powerful and synergistic approach to facial rejuvenation in aesthetic medicine. This review of the scientific literature demonstrates that by addressing both muscle hyperactivity and volume loss, combination therapy often achieves more comprehensive and satisfying aesthetic outcomes compared to

monotherapies. The evidence supports the efficacy and safety of this approach across various facial regions, leading to high levels of patient satisfaction. While current research provides a strong foundation for the use of combination BoNT-A and filler therapies, ongoing investigations are essential to further optimize treatment protocols, understand the underlying mechanisms of synergy, and ensure the long-term benefits and safety for diverse patient populations.

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