STATISTICAL ANALYSIS
UDC: 615.9.03.07:615.11(4)

Botulinum Neurotoxins in dermatology and interdisciplinary medicine: pharmacology, European regulation, clinical applications, and future directions

Mihail Mihaylov[1,3] Orcid ID 0009-0001-3673-7392
Kire Stojkovski[2] Orcid ID 0000-0002-9903-0036
Nona Lazova[1,4] Orcid ID 0009-0008-9948-4661

1 Medical Center OBLIQ, Sofia, Bulgaria
2 PSI-CRO – Sofia, Bulgaria
3 Faculty of Public Health "Prof. Dr. Tzecomir Vodenitcharov", Medical University of Sofia, Bulgaria
4 Faculty of Medicine, Medical University of Sofia, Sofia, Bulgaria

Article received: 14.09.2026
Article revised: 18.09.2026
Article accepted: 22.09.2026

DOI: https://www.doi.org/10.59710/oaijoaru264366pm

Abstract

Background: Botulinum neurotoxin (BoNT) has evolved from a cause of foodborne paralysis into a precisely dosed biologic used in aesthetic medicine and multiple therapeutic specialties. Objective: To review its pharmacology, European regulatory landscape, established clinical uses, emerging applications, immunogenicity, health-economic concepts, and contemporary procedural epidemiology. Methods: A structured narrative review was updated through 24 September 2026. The original manuscript was used as the conceptual starting point; scientific claims were checked against PubMed-indexed reviews and systematic reviews, regulatory claims against European Medicines Agency documents, and procedural statistics against the International Society of Aesthetic Plastic Surgery (ISAPS) Global Survey 2024. Results: BoNT inhibits neurotransmitter release through serotype-specific proteolysis of SNARE proteins. European products include both centrally and nationally authorised formulations, and their units are not interchangeable. Established uses include focal hyperhidrosis and several neurological and urological indications. Evidence for temporomandibular disorders, rosacea, scar modulation, chronic pruritus, and psychiatric applications is promising but heterogeneous and generally off-label or investigational. ISAPS reported 7,887,955 botulinum toxin procedures in 2024, 17.4% fewer than in 2023 but 26.9% more than in 2020. Conclusion: Future progress will depend on formulation innovation, comparative trials, standardized outcome measures, long-term pharmacovigilance, and precise separation of regulatory status from clinical evidence.

Keywords: botulinum neurotoxin; botulinum toxin A; botulinum toxin E; pharmacology; European regulation; hyperhidrosis; aesthetics; immunogenicity; rosacea; scars

European regulatory snapshot

Product / substance	Serotype	EU regulatory route/status	Relevant point
Vistabel / Bocouture / Azzalure	A	National/MRP pathways	Established aesthetic indications; product-specific units/SmPCs

Nuceiva (prabotulinumtoxinA)	A	EU-wide MA, 27 Sep 2019	Glabellar lines in adults under product-specific indication
Relfydess (relabotulinumtoxinA)	A	National/DCP records	Ready-to-use liquid formulation
NeuroBloc (rimabotulinumtoxinB)	B	EU MA withdrawn 9 Dec 2022	Withdrawal requested by MAH for commercial reasons
Boey (trenibotulinumtoxinE)	E	EU-wide MA, 15 Jul 2026	First EU-authorised serotype E; glabellar lines

1. INTRODUCTION

Botulinum neurotoxin (BoNT) has undergone a distinctive transition from a cause of foodborne paralysis to a precisely dosed biologic used across neurology, dermatology, urology, ophthalmology and aesthetic medicine. Early observations by Justinus Kerner in the nineteenth century described the paralytic effects of “sausage poison”, while van Ermengem subsequently linked botulism to an anaerobic bacillus. Therapeutic development accelerated in the twentieth century, including Alan Scott’s use of BoNT for strabismus and the later recognition of facial aesthetic applications. The report by Carruthers and Carruthers in 1992 established treatment of glabellar lines as an important aesthetic application [1–4].

The expansion of BoNT has been driven by a common pharmacological principle: transient inhibition of neurotransmitter release at peripheral nerve terminals. At the same time, different products are not interchangeable, and their authorised indications, units, formulations and regulatory pathways differ. A contemporary review therefore requires separation of pharmacology, product-specific regulation, established indications, emerging applications and procedural epidemiology [5–7].

2. METHODS

This article was prepared as a structured narrative review updated through September 2026. The original manuscript supplied by the authors was used as the conceptual starting point. Scientific literature was checked using PubMed-indexed reviews, systematic reviews and clinical studies, while European regulatory information was checked against European Medicines Agency (EMA) product pages, assessment reports and regulatory documents. Procedural epidemiology was verified against the International Society of Aesthetic Plastic Surgery (ISAPS) Global Survey 2024. Search concepts included “botulinum neurotoxin”, “botulinum toxin A/B/E”, “SNARE”, “immunogenicity”, “hyperhidrosis”, “temporomandibular disorders”, “rosacea”, “scars”, “pruritus”, “depression”, “European Union”, “EMA”, and relevant product names. Priority was given to systematic reviews, meta-analyses, regulatory primary sources and established reviews. Because the purpose was synthesis rather than quantitative evidence pooling, no de novo meta-analysis or formal systematic-review risk-of-bias synthesis was undertaken.

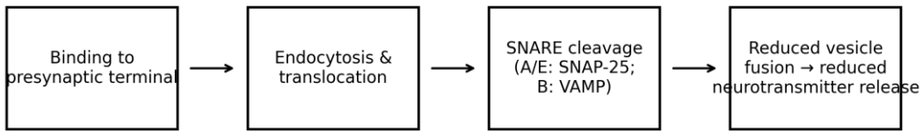
3. PHARMACOLOGY AND PHARMACODYNAMICS

BoNTs are bacterial protein toxins whose clinical effects depend on selective entry into presynaptic nerve terminals, translocation of the catalytic light chain into the cytosol, and proteolytic cleavage of SNARE proteins required for synaptic vesicle fusion. BoNT-A and BoNT-E cleave SNAP-25, whereas BoNT-B cleaves synaptobrevin/VAMP. The immediate functional consequence is reduced neurotransmitter release. At cholinergic neuromuscular junctions this produces temporary weakness; in autonomic cholinergic terminals it reduces glandular secretion. Effects on sensory and nociceptive pathways

may also contribute to analgesic or neuromodulatory effects, but these mechanisms are more complex than simple acetylcholine blockade [5,8].

The clinical duration reflects both local pharmacology and recovery of functional neurotransmission. Axonal sprouting and restoration of vesicular release contribute to recovery, so the effect is temporary rather than a permanent denervation. Formulations differ in molecular composition, potency units and clinical kinetics. Consequently, units from different products should not be treated as numerically interchangeable [6,7].

Figure 1. Simplified pharmacological mechanism of botulinum neurotoxin



Clinical effects: transient muscle weakening, reduced glandular secretion, and context-dependent sensory/neurogenic modulation

Figure 1. Simplified pharmacological mechanism of botulinum neurotoxin. Source: adapted conceptually from mechanistic reviews [5,8].

4. EUROPEAN REGULATORY LANDSCAPE

The European market contains both centrally authorised and nationally authorised or mutually recognised products. This distinction is important because “EMA approved” is not an accurate description for every BoNT product available in Europe. Vistabel, Bocouture and Azzalure are examples of products authorised through European national/mutual-recognition pathways for aesthetic indications. Nuceiva (prabotulinumtoxinA) received an EU-wide marketing authorisation on 27 September 2019 [9,10]. Relfydess (relabotulinumtoxinA) is a ready-to-use liquid BoNT-A formulation authorised through a national/decentralised pathway, with national authorisations documented in EU/EEA regulatory records [11]. Boey (trenibotulinumtoxinE) received an EU-wide marketing authorisation on 15 July 2026 for temporary improvement of moderate-to-severe glabellar lines in adults when the lines have an important psychological impact [12].

The regulatory history also illustrates that authorisation status is dynamic. NeuroBloc (rimabotulinumtoxinB), previously authorised in the EU for cervical dystonia, had its marketing authorisation withdrawn on 9 December 2022 at the request of the marketing-authorisation holder, which cited permanent discontinuation for commercial reasons. This should not be interpreted as a regulatory finding that the product was withdrawn because of inferior safety or immunogenicity [13].

Figure 2. Selected European regulatory milestones for botulinum neurotoxin products

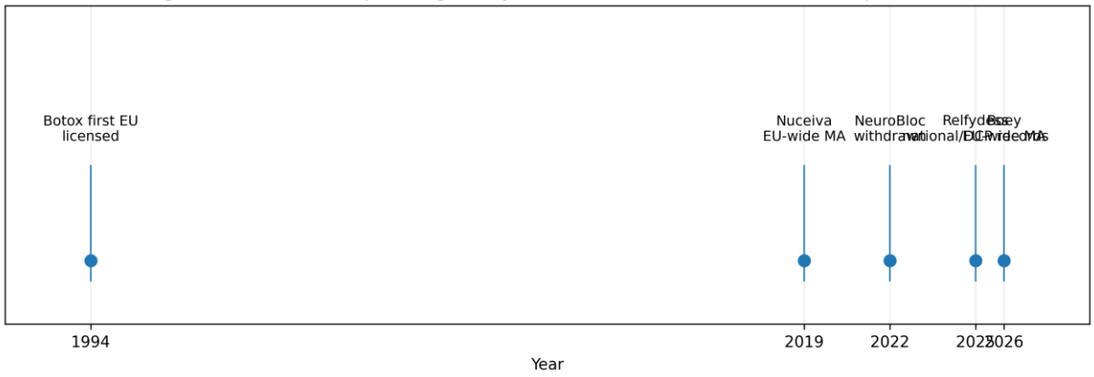


Figure 2. Selected European regulatory milestones. Sources: EMA regulatory records [9–13].

5. AESTHETIC APPLICATIONS

The best-established aesthetic use of BoNT-A is temporary reduction of dynamic facial lines caused by muscle activity. The glabellar complex, lateral canthal region and forehead are treated according to product-specific indications, anatomy and dosing instructions. Contemporary practice increasingly emphasizes preservation of natural movement rather than complete muscular immobilisation. Lower-face and neck applications require particularly careful anatomical assessment because diffusion or excessive weakening may affect oral competence, speech, swallowing or facial expression [4,7].

Ready-to-use formulations may reduce preparation steps and reconstitution variability, but they do not remove the need for product-specific storage, handling and injection protocols. The emergence of serotype E is also relevant because its shorter functional duration may be useful where reversibility and shorter treatment cycles are clinically desirable; however, claims about universal onset or duration should follow the product's approved product information rather than extrapolation between serotypes [12].

6. ESTABLISHED INTERDISCIPLINARY INDICATIONS

Primary focal hyperhidrosis is an established therapeutic indication for BoNT-A. By blocking cholinergic stimulation of eccrine glands, injections can substantially reduce sweating. Randomized evidence synthesized in a meta-analysis of eight trials involving 937 patients showed greater reductions in sweat production, disease severity and DLQI compared with placebo [14]. These findings illustrate why patient-reported outcomes are particularly relevant in dermatology: symptom reduction may translate into meaningful improvements in work, social interaction and daily functioning [15].

BoNT-A is also established in several neurological and urological disorders, although indications are product-specific. In overactive bladder, intradetrusor BoNT-A can reduce urgency and urge urinary incontinence in appropriately selected patients who remain symptomatic despite pharmacological therapy. Exact doses and injection protocols should be taken from the current SmPC of the selected product rather than presented as a universal BoNT dose [5,6,7].

7. EMERGING AND OFF-LABEL DERMATOLOGIC AND INTERDISCIPLINARY APPLICATIONS

Temporomandibular disorders and sleep bruxism are clinically relevant but evidence remains heterogeneous. An umbrella review of 18 systematic reviews found moderate evidence for pain reduction in myogenous TMD, but no consistent superiority for mandibular movement and concerns regarding adverse effects on muscle and bone. BoNT-A should therefore be described as a selected or adjunctive intervention rather than a universal first-line treatment, and fixed cross-product dosing should be avoided [16].

Rosacea and facial flushing represent another developing field. Systematic reviews report improvement in erythema and flushing, but available studies are generally small, with short follow-up and variable designs. These findings support further controlled trials rather than routine classification as an established indication [17,18].

Scar modulation is supported by a growing body of randomized evidence. Meta-analyses have reported improvements in scar scales and scar width compared with saline or no treatment, including a 2026 systematic review of 19 studies and 686 patients. Nevertheless, heterogeneity in timing, dose, anatomical site and outcome measurement remains substantial. BoNT-A is better characterized as an emerging adjunct to scar prevention or management than as a stand-alone disease-modifying therapy [19,20].

Chronic pruritus and conditions such as notalgia paresthetica remain investigational. Small trials and case series suggest possible benefit, but controlled evidence is limited and inconsistent. Proposed mechanisms include modulation of sensory neuropeptide and neurotransmitter release, yet the clinical evidence does not justify claims that BoNT permanently terminates peripheral sensitization [21,22].

Psychiatric applications, particularly major depressive disorder, are also investigational. Several randomized trials and meta-analyses have reported reductions in depressive symptom scores after glabellar BoNT-A injections, while newer systematic reviews emphasize a still-developing clinical trial landscape. The proposed facial-feedback mechanism is biologically plausible, but BoNT-A should not currently be presented as an established replacement for standard psychiatric treatment [23,24].

8. IMMUNOGENICITY AND SAFETY

Repeated BoNT treatment can lead to neutralizing antibody formation and, in some patients, secondary loss of response. A 2021 meta-analysis of 43 studies including 8,833 patients estimated an overall neutralizing-antibody incidence of approximately 1.8%, with considerable variation by indication and formulation. Dose, cumulative exposure, injection interval and formulation characteristics can influence immunogenicity. Low observed immunogenicity with some products should not be translated into a claim that antibody formation is impossible [25,26].

Clinicians should also recognize the product-wide safety issue of toxin spread: although uncommon, distant weakness, dysphagia, dysphonia, respiratory symptoms or other systemic effects have been reported and are reflected in product information. Risk assessment should therefore include medical history, anatomical injection site, dose, treatment interval and product-specific warnings [11,12].

9. HEALTH ECONOMICS AND PATIENT-REPORTED OUTCOMES

Health-economic interpretation requires separation of clinical outcomes from economic endpoints. DLQI is a validated patient-reported outcome measure for dermatologic quality of life, not a health-economic model [15]. QALY is an outcome measure used in cost-utility analysis, while the incremental cost-effectiveness ratio (ICER) expresses the incremental cost per additional unit of health outcome [27,28]. Evidence from hyperhidrosis demonstrates that BoNT treatment can improve quality of life, but cost-effectiveness depends on the indication, comparator, retreatment interval, healthcare system, productivity effects and treatment price. Therefore, a single generalized economic conclusion for all BoNT applications would not be justified [14,15].

10. PROCEDURAL EPIDEMIOLOGY

ISAPS provides useful international data on cosmetic procedures performed by plastic surgeons, but these data should not be interpreted as a census of all BoNT use. The ISAPS 2024 Global Survey reported 7,887,955 botulinum toxin procedures worldwide, compared with 9,549,245 in 2023 and 6,213,859 in 2020. Thus, the 2024 volume was 17.4% lower than in 2023 but 26.9% higher than in 2020 [29]. This pattern demonstrates why simple linear or compound-growth extrapolation can be misleading.

In 2024, botulinum toxin was most common among patients aged 35–50 years, accounting for 3,715,227 procedures, followed by 51–64 years (1,861,557), 18–34 years (1,798,454), and ≥65 years (473,277) [29]. The age-specific values are survey estimates within the ISAPS plastic-surgery reporting framework and should not be generalized to all injectors or all clinical indications.

The ISAPS 2025 survey had not yet been officially released at the time of this review; therefore, an estimated 2025 value is deliberately not substituted for observed data. Likewise, unsupported market-revenue forecasts have been excluded from the present review. Future quantitative forecasting should use transparent assumptions, uncertainty intervals and a clearly defined data-generating population.

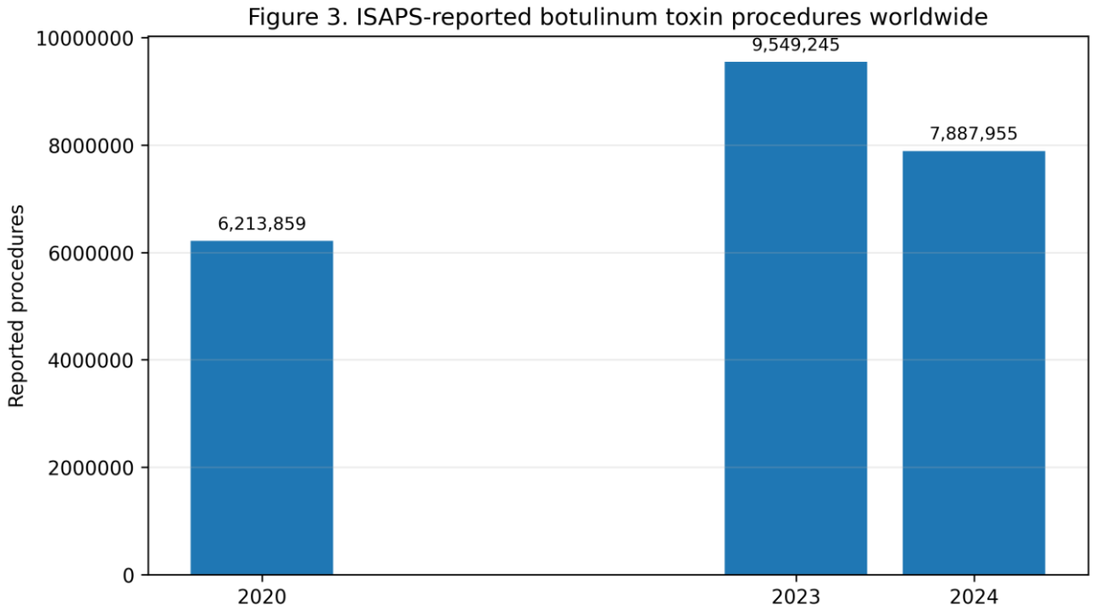


Figure 3. ISAPS-reported botulinum toxin procedures worldwide in 2020, 2023 and 2024. Source: ISAPS Global Survey 2024 [29].

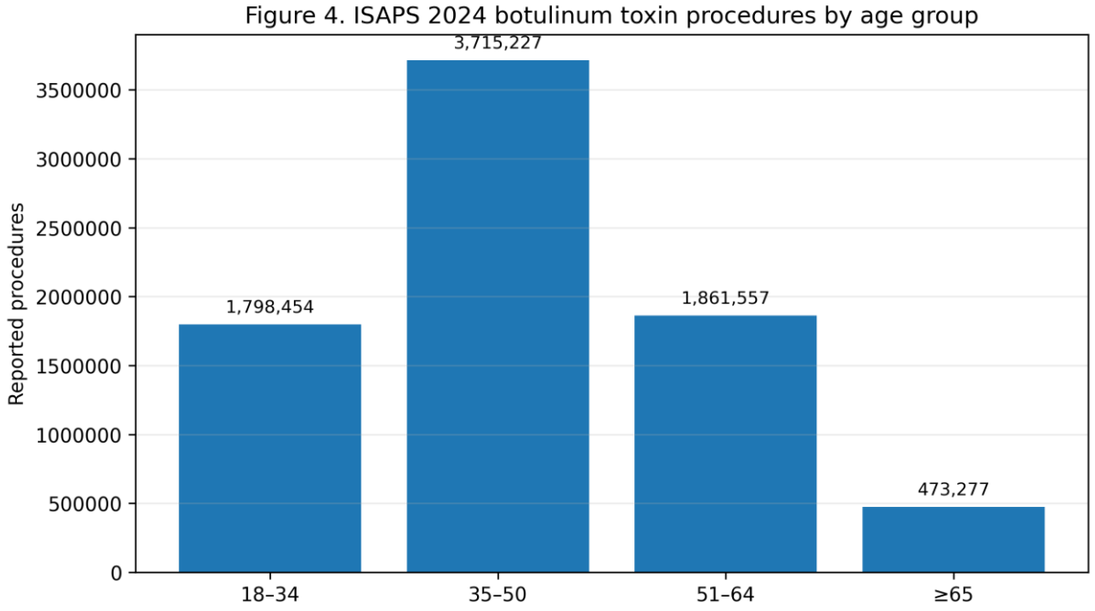


Figure 4. ISAPS 2024 botulinum toxin procedures by age group. Source: ISAPS Global Survey 2024 [29].

11. FUTURE DIRECTIONS

Future development is likely to focus on formulation engineering, pharmacological control of duration, immunogenicity reduction, simplified administration and expansion into conditions with mechanistically plausible but incompletely proven indications. Ready-

to-use liquid formulations may improve workflow, while alternative serotypes may allow different onset-duration profiles. However, technological novelty should not be equated with clinical superiority.

Priority research questions include head-to-head comparative trials, standardized dosing terminology, long-term safety surveillance, validated patient-reported outcomes and adequately powered randomized trials for emerging dermatologic indications. For aesthetic practice, prospective studies should also evaluate patient-reported naturalness, functional outcomes and retreatment intervals rather than relying solely on investigator-rated wrinkle scales.

12. CONCLUSION

BoNT has evolved into a versatile biologic platform with established therapeutic and aesthetic applications and a rapidly developing research pipeline. Its contemporary interpretation requires three distinctions: pharmacological effects are serotype- and formulation-dependent; European regulatory status differs among products and authorisation routes; and procedural volume is not equivalent to clinical or market utilization.

The strongest evidence currently supports established indications such as focal hyperhidrosis and several neurological and urological disorders, while applications in TMD, rosacea, scars, chronic pruritus and psychiatric disease remain at different stages of evidence development. Future progress should therefore combine formulation innovation with rigorous comparative trials, transparent regulatory reporting and clinically meaningful outcome assessment.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ACKNOWLEDGEMENTS

The authors acknowledge the administrative and technical support provided during literature compilation and manuscript preparation.

REFERENCES

1. Rizo J, Sudhof TC. The history of botulinum toxins in medicine: a thousand year journey. Aesthet Surg J. 2017;37(Suppl 1):S4–S11. doi:10.1093/asj/sjw284.
2. van Ermengem E. Classics in infectious diseases. A new anaerobic bacillus and its relation to botulism. Rev Infect Dis. 1979;1(4):701–719. doi:10.1093/clinids/1.4.701. Originally published in 1897.
3. Scott AB. Botulinum toxin injection of eye muscles to correct strabismus. Trans Am Ophthalmol Soc. 1981;79:734–770. PMID:7043872.
4. Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with C. botulinum-A exotoxin. J Dermatol Surg Oncol. 1992;18(1):17–21. doi:10.1111/j.1524-4725.1992.tb03295.x.
5. Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum neurotoxins: biology, pharmacology, and toxicology. Pharmacol Rev. 2017;69(2):200–235. doi:10.1124/pr.116.012658.
6. Scaglione F. Conversion Ratio between Botox®, Dysport®, and Xeomin® in Clinical Practice. Toxins (Basel). 2016;8(3):65. doi:10.3390/toxins8030065.
7. Brin MF, Nelson M, Ashourian N, Brideau-Andersen A, Maltman J. Update on Non-Interchangeability of Botulinum Neurotoxin Products. Toxins (Basel). 2024;16(6):266. doi:10.3390/toxins16060266.
8. Montecucco C, Schiavo G. Mechanism of action of tetanus and botulinum neurotoxins. Mol Microbiol. 1994;13(1):1–8. doi:10.1111/j.1365-2958.1994.tb00396.x.

9. European Medicines Agency. Nuceiva (botulinum toxin type A): EPAR. Marketing authorisation issued 27 September 2019. EMA.

10. European Medicines Agency. Botulinum toxin A products: regulatory information and nationally authorised medicinal products. EMA; current regulatory records.

11. European Medicines Agency. Botulinum neurotoxin type A (150 kDa), free from complexing proteins: PSUSA/00009084/202412; list of nationally authorised medicinal products and Relfydess product information. EMA; 2025.

12. European Medicines Agency. Boey (trenibotulinumtoxinE): EPAR. EU marketing authorisation issued 15 July 2026. EMA.

13. European Medicines Agency. NeuroBloc (botulinum toxin type B): EPAR. EU marketing authorisation withdrawn 9 December 2022 at the request of the marketing-authorisation holder for commercial reasons. EMA.

14. Nawrocki S, Cha J. Botulinum toxin versus placebo: a meta-analysis of treatment and quality-of-life outcomes for hyperhidrosis. Dermatol Surg. 2021;47(4):e1–e7. PMID:33619611.

15. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–216. doi:10.1111/j.1365-2230.1994.tb01167.x.

16. De la Torre Canales G, et al. Botulinum toxin-A for the treatment of myogenous temporomandibular disorders: an umbrella review of systematic reviews. Drugs. 2024;84(7):779–809. doi:10.1007/s40265-024-02048-x.

17. Faghihi G, et al. Use of botulinum toxin in treating rosacea: a systematic review. Dermatol Ther. 2021. PMID:33958886.

18. Alshami MA, et al. The efficacy and safety of botulinum toxin A for the treatment of rosacea: a systematic review. Cureus. 2023;15(12):e51304. doi:10.7759/cureus.51304.

19. Li MY, et al. Effectiveness of botulinum toxin type A injection on scars: a systematic review and meta-analysis of randomized controlled trials. Plast Reconstr Surg. 2022;150(6):1249e–1258e. doi:10.1097/PRS.0000000000009742.

20. Chávez-Goicochea AP, et al. Efficacy and safety of botulinum toxin type A for pathological scar prevention: a systematic review and meta-analysis. Plast Reconstr Surg. 2026;158(1):53e–64e. doi:10.1097/PRS.0000000000012631.

21. Kocatürk E, et al. How does botulinum toxin inhibit itch? J Cosmet Dermatol. 2022. PMID:36287970.

22. Botulinum toxin treatment of notalgia paresthetica—a critical review and update. 2026. PMID:41591196.

23. Demchenko I, et al. Botulinum toxin injections for psychiatric disorders: a systematic review of the clinical trial landscape. Toxins (Basel). 2024;16(4):191. doi:10.3390/toxins16040191.

24. Qian T, Shao S, Lenahan C, Shao J, Li Y. Efficacy and safety of botulinum toxin vs. placebo in depression: a systematic review and meta-analysis of randomized controlled trials. J Affect Disord. 2021. PMID:33343429.

25. Albrecht P, et al. Immunogenicity to botulinum toxin type A: a systematic review with meta-analysis across therapeutic indications. Aesthet Surg J. 2021. doi:10.1093/asj/sjab058.

26. Jankovic J, et al. Immunogenicity of botulinum toxin formulations: potential therapeutic implications. Toxins (Basel). 2021. PMID:34515975.

27. Drummond MF, et al. Methods for the Economic Evaluation of Health Care Programmes. 4th ed. Oxford University Press; 2015.

28. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-Effectiveness in Health and Medicine. Oxford University Press; 1996.

29. International Society of Aesthetic Plastic Surgery. ISAPS International Survey on Aesthetic/Cosmetic Procedures Performed in 2024. Global Survey 2024. Published 2025.
30. European Medicines Agency. Product information and safety communications for authorised botulinum toxin products. EMA; accessed 24 September 2026.