International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
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ARTICLE TITLE	BEYOND AESTHETICS: BOTULINUM TOXIN TYPE A AS AN EMERGING ANTIDEPRESSANT STRATEGY
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5358
RECEIVED	27 March 2026
ACCEPTED	19 June 2026
PUBLISHED	30 June 2026
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BEYOND AESTHETICS: BOTULINUM TOXIN TYPE A AS AN EMERGING ANTIDEPRESSANT STRATEGY

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ABSTRACT

Major depressive disorder remains one of the most burdensome psychiatric conditions worldwide, and a substantial proportion of patients continue to suffer despite available treatments. This narrative review examines an unexpected therapeutic candidate: botulinum toxin type A (BoNT/A), a bacterial neurotoxin long used in aesthetic medicine to reduce facial frown lines, which has emerged as a promising antidepressant intervention. The review synthesises clinical evidence from randomised controlled trials and meta-analyses, alongside mechanistic data from neuroimaging and preclinical studies, to evaluate the efficacy, safety, and biological plausibility of this approach. The findings consistently indicate that a single injection of BoNT/A into the glabellar region produces meaningful and durable improvements in depressive symptoms. The proposed mechanisms are scientifically compelling: by paralysing the muscles responsible for frowning, BoNT/A disrupts a feedback loop between facial expression and emotional processing in the brain, modulates activity in key mood-regulating structures, and triggers neurochemical changes associated with recovery from depression. The treatment is well tolerated, with only mild and transient side effects. Although larger confirmatory trials are needed, BoNT/A represents a genuinely novel, accessible, and mechanistically grounded addition to the therapeutic landscape of depression.

KEYWORDS

Botulinum Toxin Type A; Major Depressive Disorder; Facial Feedback Hypothesis; Treatment-Resistant Depression; Antidepressant

CITATION

Dominika Dutkiewicz, Jacek Kowalski, Alia Echtay Yarbou, Rami Mallah, Dominika Julia Kozdroń, Michalina Weronika Nieścioruk, Paulina Szczepańska, Michał Tokarczyk, Andrzej Samujlik. (2026) Beyond Aesthetics: Botulinum Toxin Type A as an Emerging Antidepressant Strategy. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5358

Introduction

Major depressive disorder (MDD) is one of the most prevalent and disabling conditions worldwide. The World Health Organization estimates that approximately 280 million people currently live with depression. Despite decades of pharmacological research and the availability of numerous antidepressant agents, a clinically significant proportion of patients — estimated at 30–40% — fail to achieve full remission following first-line treatment [1]. This phenomenon, designated treatment-resistant depression (TRD), represents one of the most pressing unmet needs in contemporary psychiatry.

Current first-line pharmacological agents — selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) — are associated with adverse effects including weight gain, sexual dysfunction, and emotional blunting [2]. Biological therapies such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) address TRD in selected populations but remain constrained by accessibility and cost [3]. Ketamine and esketamine represent genuinely novel, non-monoaminergic mechanisms but require specialised administration settings with close patient monitoring [4]. There is therefore a persistent need for safe, accessible, and mechanistically distinct antidepressant strategies.

In this context, botulinum toxin type A (BoNT/A) has emerged as a surprising yet increasingly well-supported candidate. Originally developed for the treatment of strabismus and dystonia, BoNT/A is most widely known for its cosmetic application in the reduction of glabellar frown lines. Initial observations suggesting mood improvement in patients receiving these injections prompted the first clinical case series [5], and a substantial body of evidence has since accumulated. The present review synthesises this evidence, examines the theoretical frameworks proposed to explain the antidepressant effect, evaluates safety and tolerability, and identifies the most important outstanding questions for future research.

Methodology

This narrative review was conducted in accordance with standard practices for qualitative synthesis of clinical and preclinical literature. A comprehensive literature search was conducted using major biomedical databases, including PubMed/MEDLINE, Web of Science, and Scopus, covering publications from 1872 to 2024. The search strategy combined the following keywords: "botulinum toxin", "onabotulinumtoxinA", "depression", "major depressive disorder". Additional search terms included "facial feedback hypothesis", "amygdala", "BDNF", "serotonin", "treatment-resistant depression" and "vlPAG."

Studies were eligible for inclusion if they were peer-reviewed, published in English, and fell into one of the following categories: clinical trials, systematic reviews, or meta-analyses examining BoNT/A in MDD or depressive symptoms; preclinical studies directly relevant to its antidepressant mechanism; or pharmacoepidemiological analyses. The search was supplemented by hand-searching reference lists of identified reviews and meta-analyses. Given the narrative nature of this review, formal risk-of-bias scoring was not performed; however, methodological limitations of individual studies are discussed in context.

Results

Theoretical Frameworks for the Antidepressant Effect of BoNT/A

The Facial Feedback Hypothesis

The facial feedback hypothesis, with intellectual origins in the writings of Charles Darwin [6] and William James [7], proposes that peripheral facial muscular activity provides afferent signals to the brain that participate in the generation and modulation of emotional experience. The corrugator supercilii and procerus muscles — responsible for the glabellar frown — generate proprioceptive signals associated with negative affect. According to this hypothesis, their chemical denervation by BoNT/A interrupts this signal, reducing central amplification of negative mood states [8].

Empirical support for this hypothesis is substantial. Experimental studies have demonstrated that BoNT/A-induced paralysis of the corrugator supercilii slows the processing of emotionally negative language [9] and alters the subjective quality of emotional experience [10], effects consistent with disrupted afferent feedback from the face to the brain. Independent evidence confirms that voluntarily adopting facial expressions associated with positive affect modulates both subjective mood and autonomic responses [11], while theoretical work has established facial muscular activity as a constitutive — rather than merely expressive — component of emotion [12]. Taken together, these findings support the proposition that selectively eliminating the capacity for negative facial expression through BoNT/A injection attenuates the internal experience of negative affect [8].

Neuroimaging Evidence: The Face–Amygdala Axis

Neuroimaging studies provide compelling support for the facial feedback model by demonstrating that peripheral modulation of facial musculature produces measurable changes in the central circuits underlying emotional processing. A landmark fMRI investigation showed that glabellar BoNT/A injection attenuated the functional coupling between amygdala activation and brainstem autonomic responses during the imitation of angry expressions [13]. Subsequent research employing an A-B-A design further demonstrated that BoNT/A-induced paralysis of the frown musculature altered amygdala responses to emotional face perception, with full reversal of this effect upon recovery of muscular function — thereby establishing both the specificity and reversibility of the relationship [14]. Complementary evidence indicates that onabotulinumtoxinA modulates amygdala responses to both positive and negative facial expressions and additionally affects fusiform gyrus activity, suggesting that its influence extends across the broader network subserving social-emotional perception [15].

The neuroanatomical basis of this face–brain interaction has been elaborated in two complementary models. The first posits a bidirectional loop between the corrugator supercilii and the amygdala, in which amygdala activation drives corrugator contraction while corrugator denervation in turn modulates amygdala activity [16]. The second proposes a trigeminal pathway: proprioceptive afferents from facial mechanoreceptors project to the mesencephalic trigeminal nucleus, which sends ascending projections to the locus coeruleus — the brain's principal noradrenergic nucleus, with widespread efferents to the prefrontal cortex, hippocampus, and amygdala [17]. Together, these models provide a neuroanatomically coherent account of how a peripheral intervention at the level of the facial musculature can produce sustained changes in mood-regulating brain circuits.

Central Mechanisms: Retrograde Transport, vlPAG Circuitry, and Monoaminergic Effects

A neurobiologically distinct and particularly compelling mechanism proposes that BoNT/A does not act exclusively through peripheral facial denervation but undergoes retrograde axonal transport from the injection site to central neurons, where it exerts direct effects on mood-regulating circuits. The foundational evidence for this pathway was established by demonstrating that BoNT/A travels retrogradely along motor axons to neuronal cell bodies in the brainstem and subsequently undergoes transcytosis to second-order neurons [18]. This finding has since been replicated and extended: axonal transport to the spinal cord following peripheral injection has been confirmed and shown to be blocked by colchicine [19], retrograde transport and transcytosis in primary motor neurons has been independently documented [20], and a comprehensive review of preclinical and clinical data has concluded that the evidence collectively supports direct central nervous system action via this route [21].

The most direct causal evidence linking retrograde transport to antidepressant action was provided in a study using mice subjected to chronic restraint stress [22]. Combining BoNT/A injection into the whisker intrinsic musculature with viral circuit tracing and c-Fos brain mapping, the authors identified CaMKII-positive excitatory neurons in the ventrolateral periaqueductal grey (vlPAG) as key downstream targets, with their stress-induced hyperactivation significantly attenuated three weeks after injection. Crucially, chemogenetic silencing of the vlPAG-to-facial motor neuron projection reproduced the antidepressant behavioural effects of BoNT/A, while chemogenetic activation abolished them — establishing a specific and causal neural circuit mediating the antidepressant response [22].

The downstream neurochemical consequences of this central action have been characterised in a series of preclinical studies. A single facial BoNT/A injection in chronically stressed mice produced marked increases in serotonin (5-HT) concentrations in the hippocampus, hypothalamus, and prefrontal cortex, and upregulated brain-derived neurotrophic factor (BDNF) expression together with the BDNF/ERK/CREB signalling cascade across multiple limbic regions [23] — the same molecular targets engaged by conventional antidepressants. Elevations in norepinephrine in the striatum and serotonin in the hypothalamus following facial injection have been additionally documented [24], and a systematic neurochemical characterisation has further demonstrated differential modulation of dopamine, noradrenaline, and serotonin across sensory, limbic, and motor brain regions [25]. Together, these findings delineate a mechanistic chain extending from peripheral injection through retrograde transport and vlPAG circuit modulation to broad neurochemical changes that closely parallel the molecular signature of antidepressant drug action.

The Social Feedback Hypothesis

Another socially mediated mechanism proposes that the cosmetic consequence of BoNT/A injection — a more relaxed or positive facial appearance — alters the quality of social interactions, generating positive environmental feedback that reinforces mood improvement. The positive influence of glabellar BoNT/A injections on observers' first impressions has been experimentally demonstrated [26]. This mechanism may contribute to sustained antidepressant effects beyond the pharmacological duration of the toxin, and is consistent with the broader literature on the role of social interaction in depression maintenance and recovery.

Clinical Evidence

Pioneer Case Series

Clinical investigation was initiated by a case series of 10 patients with MDD treated with onabotulinumtoxinA (29 U) to the glabellar region [5]. At two months, 9 of 10 patients no longer met DSM-IV criteria for MDD, with the remaining patient reporting substantial improvement. While uncontrolled, this study provided the impetus for randomised investigation and explicitly framed the corrugator supercilii as a therapeutic target via the facial feedback mechanism.

Randomised Controlled Trials

Table 1 summarises the key randomised controlled trials of BoNT/A in depression. Six RCTs have been published to date, encompassing a cumulative sample of more than 450 randomised patients.

Table 1. Summary of Randomised Controlled Trials of Botulinum Toxin Type A in Major Depressive Disorder

Study	n	Preparation & Dose	Injection Site	Scale	Primary Outcome
Finzi & Wasserman [5]	10	OnabotulinumtoxinA 29 U	Glabellar	DSM-IV	9 of 10 patients no longer met MDD criteria at 2 months
Wollmer et al. [27]	30	OnabotulinumtoxinA 29 U	Glabellar	HDRS	47.1% vs. 9.2% reduction; p = 0.002; d = 1.28
Finzi & Rosenthal [28]	74	OnabotulinumtoxinA 29 U	Glabellar	HDRS	Response rate 52% vs. 15% (p < 0.001)
Magid et al. [29]	30	OnabotulinumtoxinA 40 U	Glabellar	MADRS	Significant reduction sustained at 24 weeks; d = 0.83
Brin et al. [30]	258	OnabotulinumtoxinA 29 U	Glabellar	HDRS-17	Significant improvement vs. placebo in adult females (Phase 2)
Ceolato-Martin et al. [31]	58	OnabotulinumtoxinA 29 U	Glabellar vs. crow's feet	MADRS/ HDRS	Glabellar superior; shorter illness duration and higher agitation predicted response

Note. HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = Major Depressive Disorder; U = units of onabotulinumtoxinA.

The first double-blind, randomised, placebo-controlled trial enrolled 30 patients with treatment-refractory MDD [27]. At six weeks, HDRS scores had declined by 47.1% in the treatment group versus 9.2% in the placebo group (p = 0.002; Cohen's d = 1.28). These findings were extended in a larger sample of 74 patients, reporting a response rate of 52% versus 15% in placebo (p < 0.001) [28]. A 24-week study demonstrated sustained MADRS reductions (d = 0.83) considerably exceeding the pharmacological action of the toxin [29]. The largest RCT to date (n = 258) confirmed significant HDRS-17 improvements in adult females with MDD [30]. Most recently, a randomised trial directly comparing glabellar and crow's feet injection sites in 58 patients with TRD found superiority of the glabellar protocol and identified shorter illness duration and higher psychomotor agitation as predictors of treatment response [31].

Meta-Analyses and Systematic Reviews

Table 2 summarises findings from the three principal meta-analyses published to date.

Table 2. Summary of Meta-Analyses and Systematic Reviews of Botulinum Toxin Type A in Depression

Study	Studies Included	Effect Size	Main Conclusion
Qian et al. [32]	4 RCTs	Significant superiority over placebo	BoNT/A significantly reduces depression scores vs. placebo at 6 weeks across all included trials
Schulze et al. [33]	5 RCTs	d = 0.98	Large pooled effect; robust across patient populations, doses, and assessment instruments
Demchenko et al. [34]	21 studies (471 pts)	Significant across all diagnoses	Benefits confirmed in MDD, bipolar depression, BPD, and SAD; adverse events mild and reversible

Note. BD = bipolar disorder; BoNT/A = botulinum toxin type A; BPD = borderline personality disorder; MDD = major depressive disorder; pts = patients; SAD = social anxiety disorder.

A systematic review and meta-analysis of all available RCTs confirmed significant superiority of BoNT/A over placebo at the primary six-week endpoint [32]. An updated analysis with an additional trial reported a pooled effect size of d = 0.98 — a large effect robust across subgroup analyses [33]. The most comprehensive systematic review to date encompassed 21 studies involving 471 patients across multiple psychiatric diagnoses, with significant antidepressant effects observed in all disorders studied, including MDD, bipolar depression, borderline personality disorder, and social anxiety disorder, and adverse events consistently mild and reversible [34]. A further narrative review concluded that the accumulated evidence justifies consideration of BoNT/A for TRD, noting the favourable cost profile relative to branded antidepressants given the infrequent administration schedule [35].

Interpretation of the pooled evidence requires attention to several methodological considerations. The included trials have differed substantially in sample size, patient selection criteria, BoNT/A preparation and dose, injection technique, outcome instruments, and follow-up duration, resulting in considerable clinical heterogeneity across the meta-analytic datasets. All three meta-analyses have been limited by the small number of eligible RCTs and the correspondingly modest total patient numbers, constraining the statistical power of subgroup analyses. The risk of publication bias cannot be excluded, as positive trials may be more likely to reach publication than null findings. Furthermore, the consistent use of onabotulinumtoxinA across trials limits conclusions about the class effect of BoNT/A preparations more broadly. Despite these limitations, the magnitude and consistency of the pooled effect — with Cohen's d ranging from 0.83 to 0.98 across independent analyses — is notable, and compares favourably with the pooled effect sizes typically reported for SSRIs and SNRIs in similarly designed meta-analyses [1].

Predictors of Treatment Response

The identification of clinical predictors of treatment response represents an important emerging area of research. In the most recent RCT, Ceolato-Martin et al. [31] reported that shorter illness duration and higher baseline levels of psychomotor agitation were independently associated with greater antidepressant response to glabellar BoNT/A injection. These findings are clinically intuitive: shorter illness duration may reflect less established neurobiological chronicity, while psychomotor agitation — involving heightened facial musculature tension — may indicate greater baseline activity in the corrugator-amygdala feedback loop targeted by the intervention. Additionally, the superiority of the glabellar over the crow's feet injection site observed in the same trial suggests that precise anatomical targeting of the corrugator supercilii and procerus muscles is critical to therapeutic efficacy, consistent with the facial feedback mechanistic framework. Replication of these predictors in independent cohorts and their incorporation into future trial designs would substantially advance the precision medicine application of BoNT/A in depression.

Administration Protocol, Safety, and Tolerability

Across published RCTs, the standard intervention has involved a single injection session targeting the glabellar complex — specifically the bilateral corrugator supercilii and the procerus muscle — using onabotulinumtoxinA at doses of 29 U or 40 U. The onset of antidepressant effect typically becomes apparent within two to four weeks of injection, and the duration of benefit frequently extends beyond 16 weeks — considerably exceeding the pharmacological duration of the toxin — with effects persisting up to 24 weeks in some trials [29]. This temporal dissociation between pharmacological action and clinical benefit suggests that BoNT/A initiates neuroplastic changes that outlast the period of muscle paralysis, a hypothesis supported by preclinical BDNF data [23]. Outcome assessment across trials has employed diverse instruments including the HDRS, MADRS, Beck Depression Inventory (BDI), and Patient Health Questionnaire-9 (PHQ-9); this heterogeneity complicates direct trial-to-trial comparisons and meta-analytic synthesis, and standardisation of outcome instruments in future trials is recommended.

The safety profile of glabellar BoNT/A injection in published depression trials has been consistently favourable. The most frequently reported adverse effects are local and transient: eyelid ptosis (typically resolving within four to six weeks), localised bruising, and transient headache. No serious systemic adverse events have been reported across the psychiatric trials, and the doses employed (29–40 U onabotulinumtoxinA) fall within the standard range used in cosmetic practice, where decades of postmarketing surveillance provide strong reassurance regarding long-term tolerability. A methodological concern specific to this intervention, however, is the potential for cosmetic unblinding — the possibility that participants correctly identify their treatment allocation based on the visible reduction in glabellar wrinkling, thereby introducing expectation bias. Future trials should incorporate validated blinding-success assessments and explore the use of diluted active BoNT/A as a cosmetically active comparator to address this limitation.

Discussion

The evidence reviewed in this paper converges on a consistent and clinically meaningful conclusion: a single glabellar injection of BoNT/A produces a significant antidepressant effect in patients with MDD, with pooled effect sizes (d = 0.83–1.28) that compare favourably with — and in some analyses exceed — the effect sizes reported for conventional antidepressants in placebo-controlled trials (d = 0.3–0.5) [1]. The consistency of findings across independent research groups in multiple countries, across different sample sizes, outcome instruments, and follow-up durations, strengthens confidence in the robustness of the phenomenon.

The mechanistic picture that has emerged is perhaps the most intellectually compelling aspect of this body of work. The convergence of multiple lines of evidence — from the social psychology of facial expression and embodied emotion [11, 12], through the functional neuroimaging of the face-amygdala circuit [13, 14, 15], to the molecular neurobiology of BDNF and serotonin in preclinical depression models [23, 24, 25], and most recently the causal circuit-level evidence from chemogenetic manipulation of the vlPAG [22] — constitutes a mechanistic account of remarkable coherence for a relatively young field. The finding that chemogenetic silencing of CaMKII-positive vlPAG neurons projecting to facial motor neurons reproduces the antidepressant effects of BoNT/A is particularly significant, as it establishes a causal neural circuit and suggests a new target for pharmacological intervention entirely independent of conventional monoaminergic mechanisms [22].

Several important limitations of the existing evidence base must nonetheless be acknowledged. The total number of patients randomised across all published RCTs remains modest, and the risk of publication bias cannot be excluded. The methodological heterogeneity across trials in terms of patient selection criteria, dose, outcome instruments, and follow-up duration limits the precision of meta-analytic synthesis. The cosmetic unblinding problem is a persistent challenge that has not been fully resolved. The majority of RCT participants have been patients with chronic or treatment-resistant depression, limiting generalisability to first-episode or treatment-naive populations.

From a clinical translation perspective, several questions require resolution before BoNT/A can be considered for routine psychiatric practice. The optimal dose, injection protocol, and treatment frequency have not been definitively established. Whether BoNT/A is most appropriately used as monotherapy, augmentation of existing pharmacotherapy, or specifically in TRD has not been systematically investigated. The predictors of treatment response identified in the most recent RCT [31] — shorter illness duration and higher psychomotor agitation — require replication. The potential transdiagnostic application of BoNT/A also warrants attention; preliminary evidence suggests benefits in bipolar depression, borderline personality disorder, and social anxiety disorder, pointing to broader therapeutic relevance beyond MDD [34].

Conclusions

Botulinum toxin type A has traversed a remarkable conceptual journey — from a cosmetic agent to a mechanistically grounded antidepressant candidate supported by converging clinical and preclinical evidence. The accumulated data demonstrate that a single glabellar injection produces significant, durable improvements in depressive symptoms, with effect sizes that compare favourably with those of established pharmacological treatments, and a safety profile that is consistently benign.

What distinguishes BoNT/A from other candidate antidepressants is not merely its efficacy but the coherence of its mechanistic rationale: multiple independent lines of evidence — behavioural, neuroimaging, circuit-level, and neurochemical — converge on a biologically plausible account of how a peripheral facial intervention modulates central mood-regulating systems. This mechanistic depth sets a strong foundation for further clinical development.

The path to routine psychiatric use requires definitive large-scale trials, standardised outcome measures, and pharmacoeconomic evaluation. Whether BoNT/A ultimately secures a place in the psychiatric armamentarium will depend on the research community's willingness to pursue these steps — but the existing evidence makes a compelling case that it should.

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