Drugs (2026) 86:1339–1364
https://doi.org/10.1007/s40265-026-02352-8

SYSTEMATIC REVIEW

Botulinum Toxin Type A for Trigeminal and Postherpetic Neuralgia: An Umbrella Review of Systematic Reviews

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Received: 2 April 2026 / Accepted: 25 May 2026 / Published online: 1 July 2026

Abstract

Background and Objective Trigeminal neuralgia (TN) and postherpetic neuralgia (PHN) are severe peripheral neuropathic pain conditions associated with substantial functional impairment. Although pharmacological treatments are available, many patients experience insufficient efficacy or poor tolerability. Botulinum toxin type A (BoNT-A) has emerged as a potential treatment, but uncertainties remain regarding its efficacy, safety, and clinical positioning. This umbrella review aimed to synthesise evidence from systematic reviews evaluating BoNT-A in TN and PHN.

Methods A systematic search was conducted in MEDLINE, Embase, Cochrane Library, Web of Science, and CINAHL from inception to November 2025. Systematic reviews with or without meta-analysis evaluating BoNT-A in adults with TN or PHN were included. Methodological quality was assessed using AMSTAR-2, and only moderate- or high-quality reviews were included. Primary outcomes were pain intensity reduction and responder rates (≥50% pain reduction). Secondary outcomes included quality of life and adverse events.

Results Ten systematic reviews (2015–2024) met the inclusion criteria. Botulinum toxin type A was consistently associated with reductions in pain intensity and higher responder rates than placebo, particularly in TN. In PHN, evidence was more limited but supported short-term (1–3 months) improvements in pain intensity. Evidence on quality of life was scarce and inconclusive. Botulinum toxin type A was well tolerated, with mostly mild and transient adverse events.

Conclusions Botulinum toxin type A appears to provide short-term pain relief in selected patients with TN and PHN and is generally well tolerated. Current evidence supports its role as an adjunctive third-line option for focal peripheral neuropathic pain, although heterogeneity and limited long-term data warrant cautious interpretation.

1 Introduction

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as pain resulting from an injury or disease affecting the somatosensory system [1, 2]. Based on the location of the neural impairment, it can be classified as central, e.g., when it involves structures of the central nervous system, or peripheral, e.g., when it results from injury or dysfunction of the peripheral somatosensory system [3, 4]. It can present as either episodic (e.g., trigeminal neuralgia) or continuous (e.g., postherpetic neuralgia) pain. Conditions commonly associated with neuropathic pain include painful diabetic neuropathy, postherpetic neuralgia,

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Key Points

Botulinum toxin type A appears to provide short-term pain relief in trigeminal neuralgia and postherpetic neuralgia.

Evidence is stronger and more consistent in trigeminal neuralgia than in postherpetic neuralgia.

Botulinum toxin type A is well tolerated and represents a valuable third-line option for focal peripheral neuropathic pain, although standardisation and long-term data are needed.

cancer-related neuropathies and multiple sclerosis, and trigeminal neuralgia (TN) [5, 6].

Trigeminal neuralgia is widely recognized as one of the most severe pain syndromes encountered in clinical practice [7]. It is characterized by brief, unilateral, recurrent paroxysms of electric shock-like pain, often triggered by innocuous stimuli such as chewing, speaking, or light touch, with abrupt onset and termination [8, 9]. According to the International Headache Society (IHS) classification, TN is classified into classic, secondary, and idiopathic subtypes [3]. The disorder is associated with abnormal trigeminal afferent excitability and peripheral nociceptive sensitization, with possible secondary central changes contributing to allodynia and hyperalgesia [10, 11]. Trigeminal neuralgia is associated with substantial functional impairment, reduced quality of life, and psychosocial burden [12]. The reported global incidence ranges from 4 to 28.9 cases per 100,000 individuals, with higher prevalence among women and older adults [13].

Postherpetic neuralgia (PHN) is the most common chronic complication of herpes zoster and a major cause of peripheral neuropathic pain [14, 15]. It is defined as persistent pain lasting at least three months after rash onset in the affected dermatome [14, 16]. Clinically, PHN typically presents with continuous burning pain, often accompanied by mechanical allodynia and hyperalgesia [14]. The condition is associated with peripheral nociceptive injury and sensitization, with possible secondary central changes contributing to pain persistence [15]. The risk of PHN increases substantially with age, particularly after 50 years, and the condition is associated with considerable impairment in quality of life [14, 17][15].

The Neuropathic Pain Special Interest Group (NeuPSIG) guidelines recommend tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, and gabapentinoids as first-line pharmacological therapies for neuropathic pain, supported by high- to moderate-quality evidence according to GRADE framework [18, 19]. These agents act primarily by enhancing descending monoaminergic inhibitory pathways, or by reducing presynaptic release of neurotransmitters through binding to the α2δ subunit of voltage-gated calcium channels [18, 20]. Despite demonstrating superiority over placebo, only a subset of patients achieves substantial (≥ 50%) pain relief, and overall benefits remain modest, often limited by adverse effects such as dizziness and somnolence [18, 19]. Tramadol, topical lidocaine, and high-concentration capsaicin are considered second-line options, while strong μ-opioid receptor agonists are reserved as third-line options due to their unfavourable risk-benefit profile [18, 19].

In the same way, botulinum toxin type A (BoNT-A) is classified as a third-line therapy mainly in selected patients with focal peripheral neuropathic pain who do not achieve sufficient benefit from first- and second-line therapies, supported by moderate-quality evidence and a modest effect size, with a favourable tolerability profile [18, 19]. Recommended doses range from 50 to 200 units injected into the painful area, typically at three-monthly intervals. Unlike systemic therapies, BoNT-A acts primarily at peripheral nociceptive terminals [18, 19]. Through inhibition of presynaptic neurotransmitter release, BoNT-A may reduce nociceptive transmission, neurogenic inflammation, and peripheral sensitisation, with possible secondary effects on central sensitisation processes [20–23]. Adverse events are generally mild, localised, and transient, supporting its therapeutic relevance in facial neuropathic syndromes such as trigeminal neuralgia and postherpetic neuralgia.

Although the clinical application of BoNT-A has expanded in recent years, important uncertainties remain regarding the magnitude and consistency of its therapeutic effects, optimal injection protocols, and long-term safety profile, issues that are particularly relevant in conditions such as trigeminal neuralgia and postherpetic neuralgia. Moreover, the absence of standardised treatment protocols and the lack of definitive conclusions about overall efficacy and safety highlight the need for a comprehensive synthesis of the available evidence. Also, in recent years, several systematic reviews evaluating BoNT-A for trigeminal and postherpetic neuralgia have been published, often including overlapping primary studies and reporting heterogeneous findings. An umbrella review was therefore considered appropriate to critically appraise the methodological quality, consistency, and overall strength of the available review-level evidence. In this context, the present umbrella review aims to critically evaluate and integrate findings from systematic reviews of randomised controlled trials (RCTs), providing a consolidated assessment of the efficacy, safety, and clinical relevance of BoNT-A for the management of trigeminal neuralgia and postherpetic neuralgia.

2 Materials and Methods

2.1 Protocol

This comprehensive review was methodologically planned, conducted, and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations (https://www.prisma-statement.org/). The study was developed according to a review protocol that was prepared prospectively (2/10/2025) prior to data extraction and is provided as Supplementary Information 1.

2.2 Inclusion Criteria

The inclusion of studies in this review was structured according to the PICOTS approach (Population, Intervention, Comparators, Outcome, Time, and Study Design): Population (P): Adult individuals diagnosed with neuropathic pain, specifically trigeminal neuralgia and postherpetic neuralgia. Intervention (I): Treatment with botulinum toxin (any formulation). Comparators (C): Standard treatment, placebo, or other pharmacological (conventional) and non-pharmacological (surgical interventions) therapeutic approaches. Outcomes (O): The primary outcome consisted of a reduction in the intensity of neuropathic pain, measured using validated pain scales such as the Visual Analogue Scale (VAS), the Numerical Rating Scale (NRS), or equivalent instruments. Secondary outcomes included changes in pain frequency, other patient-reported clinical outcomes, and the occurrence of treatment-associated adverse events. Time (T): Outcomes were analyzed over short, medium, and long-term periods, according to the reported follow-up time. Study design (S): Only systematic reviews, with or without meta-analysis, that reported the outcomes of interest were included.

2.3 Exclusion Criteria

Narrative reports, editorials, letters to the editor, interviews, expert opinions, conference abstracts, case reports or series, duplicates, observational, cross-sectional and case-control studies, as well as in vitro studies or studies conducted in animal models, were excluded. Furthermore, publications written in languages other than English, Portuguese, Spanish, or French were also excluded. Systematic reviews classified as having low methodological quality, according to the critical appraisal tool adopted, as well as those that did not investigate the therapeutic use of BoNT-A in the treatment of trigeminal neuralgia and postherpetic neuralgia in adults, were not included in the final synthesis.

2.4 Search Strategy

A bibliographic search was conducted in the following databases: Medline (Ovid), Embase (embase.com), Cochrane Library (Wiley), Web of Science (Clarivate Analytics), and CINAHL (EBSCOhost). The last search was performed on November 24, 2025. The search strategy was developed in Medline (Ovid) in collaboration with librarians from the Karolinska Institute University Library. For each search concept, Medical Subject Headings (MeSH-terms) and free-text terms were identified. The search was then translated, in part using Polyglot Search Translator [24], for the other databases. The full search strategies were proofread by another librarian prior to execution. Databases were searched from inception and language restriction was made to English, French, Portuguese and Spanish. Deduplication was performed using Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). The full search strategies for all databases are available in the Supplementary Information 1.

2.5 Selection of Studies

The study selection process was conducted in two distinct stages using the Covidence platform (https://www.covidence.org/). Initially, titles and abstracts were analysed independently and blindly by two reviewers (MAD and TGS), and any conflicts were resolved by a third reviewer (GTC). In the second stage, the analysis of the full texts was carried out separately by the same reviewers (MAD and TGS), with any discrepancies resolved by the third reviewer (GTC). The entire selection process was documented and presented in a flowchart, in accordance with PRISMA recommendations.

2.6 Analysis of the Methodological Quality and Risk of Bias of the Included Reviews

The methodological quality and risk of bias of the included systematic reviews were assessed using the AMSTAR-2 tool (A Measurement Tool to Assess Systematic Reviews, version 2) [25]. According to the AMSTAR 2 guidelines, a review was classified as high quality when it presented no critical weaknesses and, at most, one non-critical weakness in the 16 assessment domains. High-quality reviews should adequately address all critical domains, including a clearly defined research question and inclusion criteria (PICO), a comprehensive literature search strategy, justification for excluded studies, appropriate assessment of the risk of bias in the included studies, adequate methods for meta-analysis, when applicable, and consideration of the risk of bias in the interpretation of results. Reviews that

met these criteria were considered to provide a high level of confidence in the validity and reliability of their conclusions. Data were analysed independently by two reviewers (RLP and GDC), and any discrepancies were resolved by consensus (Supplementary Information 3).

2.7 Data Extraction

Data extraction was performed independently by two reviewers (PC and TF) using a standardised and previously tested form. Any discrepancies in data extraction were resolved through discussion with a third author acting as a referee (GDC). The extracted information included: authors, type of systematic review, year of publication, objectives, diagnostic criteria, patient age, treatment groups, number and date range of database searches, date range, number and type of studies included in each review, instruments for evaluating primary studies and their quality, methods of evidence synthesis/analysis, and outcome measures.

2.8 Data Synthesis

Data synthesis and verification were performed independently by two reviewers (NC and GDC). The results were systematically compiled into structured tables and summarised using a color-coded visualisation approach. This scheme was designed to facilitate rapid interpretation of both the direction of the effect and the certainty: green denoted favourable results and/or absence of adverse events; orange reflected absence of significant differences and/or mild adverse events; and red indicated unfavourable results and/or moderate to severe adverse events. This visual strategy was adopted to increase the clarity and comparability of efficacy and safety results, while ensuring a transparent presentation of the evidence. In addition, overlap between systematic reviews was assessed descriptively by mapping the primary RCTs included across reviews for trigeminal neuralgia and postherpetic neuralgia. A formal corrected covered area (CCA) analysis was not performed.

2.9 Meta-Analyses

The included systematic reviews presented variety in the outcomes assessed, the analytical methods used, and the units of measurement employed (such as mean difference, standardised mean difference, weighted mean difference, relative risk, and odds ratio). This diversity resulted in a limited number of reviews that could be combined in each meta-analysis. For this reason, it was decided not to perform a quantitative synthesis of the data. Therefore, the conclusions of the present umbrella review were based on a synthesis and critical appraisal of review-level evidence rather than on de novo quantitative pooling of patient-level or primary trial-level data.

3 Results

3.1 Study Selection

Across all databases, the literature search identified 2181 records. After removal of 658 duplicates, 1523 records were screened, of which 1449 were excluded for ineligibility. A total of 74 articles underwent full-text review. Following full-text assessment, 37 articles were excluded, and 37 systematic reviews were assessed for methodological quality, using the AMSTAR-2 tool. Of these, 27 systematic reviews were classified as low ($n = 14$) and critically low ($n = 13$) quality and were excluded from the umbrella review. Consequently, 10 systematic reviews, including 5 rated as high quality and 5 as moderate quality, were included in the final synthesis (Fig. 1).

3.2 Study Characteristics

The 10 systematic reviews included were published between 2015 and 2024. Most reviews included RCTs comparing BoNT-A injections with placebo (commonly saline). Some systematic reviews also included observational studies and comparisons with other pharmacological or interventional treatments. According to the included reviews, the number of primary studies ranged from 1 to 23, and the number of participants varied depending on the condition, reaching 739 individuals with TN [18, 19, 26, 27] and 125 with PHN [18, 19, 28]. Seven of the included systematic reviews conducted quantitative syntheses (meta-analyses) [26, 28–33]. The characteristics of the included systematic reviews are summarised in Table 1.

3.3 Overlap of Primary Studies Across Systematic Reviews

Considerable overlap of primary randomised controlled trials was identified across the included systematic reviews, particularly for TN. Several reviews included the same placebo-controlled BoNT-A trials, especially the studies by Wu et al. (2012), Shehata et al. (2013), Zúñiga et al. (2013), and Zhang et al. (2014) [34–37]. Overlap among PHN reviews was comparatively lower but still present, mainly involving the studies by Apalla et al. (2013) and Xiao et al. (2010) [38, 39]. To improve transparency and facilitate interpretation of the review-level evidence, the overlap of primary

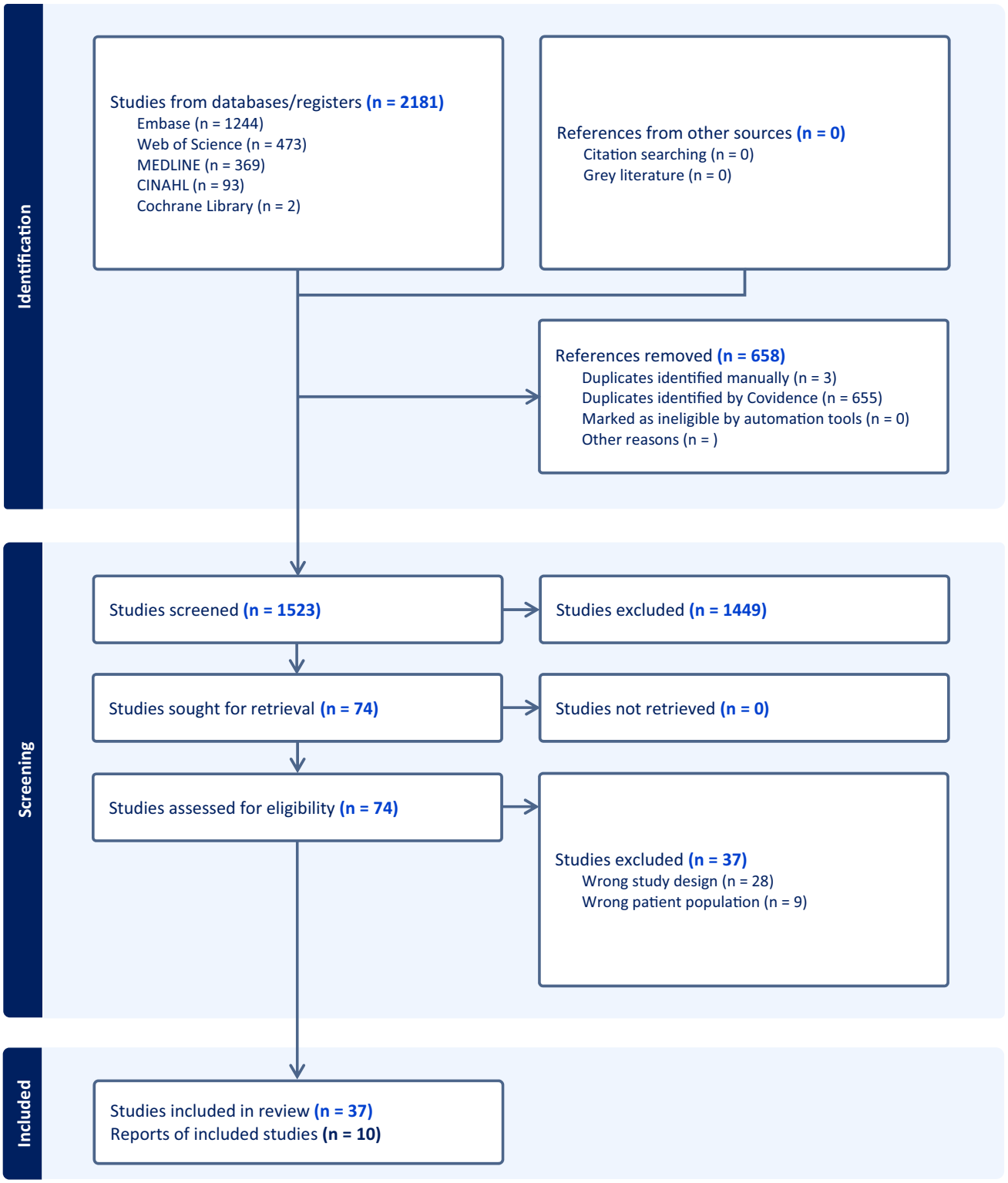

Fig. 1 Preferred reporting items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study identification, screening, eligibility assessment and inclusion for the umbrella review

Table 1 Study characteristics of the included systematic reviews

Author, year Country Type of review	Objectives of included review	Intervention (I) Control (C)	Participants details	Number of databases sourced and searched and date range of database searching	Publication date range of studies included in the review that inform each outcome of interest	Number of studies, types of studies and country of origin of studies included in each review	Instruments used to appraise the primary studies and the rating of their quality	Outcomes reported that are relevant to the umbrella review question	Method of synthesis/ analysis employed to synthesise the evidence	Comments or notes the umbrella review authors may have regarding any included study
Trigeminal neuralgia										
Bendtsen, 2019 Denmark SR	To provide evidence-based recommendations for diagnosis and pharmacological and non-pharmacological management of trigeminal neuralgia, including assessment of efficacy and safety of available therapies such as BoNT-A	**I:** Oral pharmacological interventions (Carbamazepine, Oxcarbazepine, Gabapentin, Pregabalin, Baclofen, Lamotrigine, Phenytoin), Injections of BoNT-A, RFT, BC, GR, Microvascular Decompression, Gamma Knife Radiosurgery **C:** Placebo and other treatments	**Disorder:** Classical and Secondary TN according to ICHD **N:** Not reported **% F:** Not reported **Age range:** Adults **Mean age range:** Not reported	3 From the inception of the database until Sep 2018	1970–2017	Approximately 60–70 primary studies (RCTs and observational studies) across all pharmacological and surgical interventions studies RCT, SR, Observational Studies BoNT-A vs Saline	**Primary studies:** Data extraction table **Quality:** GRADE	1. Pain intensity (VAS/ NRS) 2. Treatment response 3. Safety and tolerability 4. AE	Systematic evidence review with GRADE framework No pooled meta-analysis performed directly within guideline.	Guideline included as evidence synthesis

Table 1 (continued)

Author, year Country Type of review	Objectives of included review	Intervention (I) Control (C)	Participants details	Number of databases sourced and searched and date range of database searching	Publication date range of studies included in the review that inform each outcome of interest	Number of studies, types of studies and country of origin of studies included in each review	Instruments used to appraise the primary studies and the rating of their quality	Outcomes reported that are relevant to the umbrella review question	Method of synthesis/ analysis employed to synthesise the evidence	Comments or notes the umbrella review authors may have regarding any included study
Finnerup, 2015 Denmark SR + MA	To provide evidence-based recommendations for pharmacological treatment of neuropathic pain based on systematic review and meta-analysis of randomised controlled trials, including evaluation of efficacy and safety of botulinum toxin type A (BoNT-A)	**I:** Pharmacological treatments for neuropathic pain (antidepressants, anticonvulsants, opioids, topical agents, BoNT-A) **C:** Placebo or active comparators	**Disorder:** Neuropathic pain (including TN and PHN) according to IASP N: Not reported % F: Not reported **Age range:** Adults **Mean age range:** Not reported	3 From the inception of the database until Nov 2013	1966–2013	229 studies RCT 6 BoNT-A vs Saline	**Primary studies:** Data extraction table **Quality:** GRADE	1.Pain relief 2. NNT 3. Safety and tolerability 4. AE	Systematic evidence synthesis with meta-analysis of randomised controlled trials. Primary effect measure: NNT for ≥50% pain reduction (alternatively ≥30% pain reduction or moderate pain relief); safety assessed using NNH 95% CI derived from absolute risk differences I^2 and L'Abbé plot was used due to heterogeneous studies Publication bias was assessed using the funnel plots, Egger's and Duval and Tweedie's tests	Mixed NP review
Hary, 2022 France SR + MA	To evaluate the efficacy and safety of botulinum toxin type A (BoNT-A) in the treatment of chronic peripheral neuropathic pain, including trigeminal neuralgia and PHN	**I:** injections of BoNT-A **C:** placebo, Sham injection or standard pharmacological treatment	**Disorder:** TN, PHN, PTNP **N:** 530 % F: Not reported **Age range:** adults **Mean age range:** Not reported	5 From the inception of the database until Jun 2021	2005–2021	10 studies RCT 10 BoNT-A vs Saline	**Primary studies:** Data extraction table **Quality:** GRADE and Cochrane risk of bias tool	1. Pain intensity (VAS and NRS) 2. Quality of life 3. AE	WMD (95% CI) and RR (95% CI) for relative effect sizes I^2 was used due to heterogeneous studies; random-effects model; NNT was calculated publication bias was assessed by funnel plot asymmetry	

Table 1 (continued)

Author, year Country Type of review	Objectives of included review	Intervention (I) Control (C)	Participants details	Number of databases sourced and searched and date range of database searching	Publication date range of studies included in the review that inform each outcome of interest	Number of studies, types of studies and country of origin of studies included in each review	Instruments used to appraise the primary studies and the rating of their quality	Outcomes reported that are relevant to the umbrella review question	Method of synthesis/analysis employed to synthesise the evidence	Comments or notes the umbrella review authors may have regarding any included study
Hu, 2024 China SR + MA	To synthesise current evidence on the efficacy and safety of botulinum toxin type A (BoNT-A) for trigeminal neuralgia (TN), including effects on pain intensity (VAS), attack frequency, responder rate, and AEs	**I:** BONT-A **C:** Placebo (0.9% NaCl) in RCTs; baseline (pre–post) comparisons in single-arm/open-label studies	**Disorder:** TN according to ICHD-2 or IHS criteria Secondary TN excluded via clinical assessment and imaging (CT/MRI) **N:** 662 **% F:** Not reported **Age range:** Adults **Mean age range:** 45.6 to 82.6 y	5 From the inception of the database until Oct 2023	2002–2021	23 studies RCT, CCT, RT, PT 12 BoNT-A vs Saline 3 BoNT-A vs other active treatment 8 Single-arm BoNT-A pre-post designs	**Primary studies:** Data extraction table **Quality:** Cochrane Collaboration's tool	1. Pain intensity reduction (VAS/NRS) 2. Duration of analgesic effect 3. AE	SMD (95% CI) for continuous data χ^2 test and I^2 was used due to heterogeneous studies The Cohen criteria were used to determine the effect size of the computed SMD values Publication bias was assessed using the Egger test	
Morra, 2016 Egypt SR + MA	To synthesise evidence from published randomised controlled trials regarding the efficacy and safety of botulinum toxin type A (BoNT-A) as a treatment option for trigeminal neuralgia	**I:** BoNT-A **C:** Placebo (Saline)	**Disorder:** Trigeminal neuralgia (TN) **N:** 178 **% F:** Not reported **Age range:** Adults **Mean age range:** Approximately 58.1 to 66 y (reported in 3/4 RCTs)	10 From database inception to searches conducted in Oct 2015	2012–2014	4 studies RCT 4 BoNT-A vs Saline	**Primary studies:** Data extraction table **Quality:** Cochrane Collaboration's tool	1. Responder rate (> 50% pain reduction) 2. Pain intensity (VAS) 3. Paroxysm frequency per day 4. AE	Meta-analysis using RevMan 5.3 RR (95% CI) for dichotomous outcomes with Mantel–Haenszel method; MD (95% CI) for continuous outcomes; fixed-effect model used in main analyses; Heterogeneity assessed with I^2 and Chi-square Sensitivity analyses using random-effects model and exclusion of high-risk study	

Table 1 (continued)

Author, year Country Type of review	Objectives of included review	Intervention (I) Control (C)	Participants details	Number of databases sourced and searched and date range of database searching	Publication date range of studies included in the review that inform each outcome of interest	Number of studies, types of studies and country of origin of studies included in each review	Instruments used to appraise the primary studies and the rating of their quality	Outcomes reported that are relevant to the umbrella review question	Method of synthesis/ analysis employed to synthesise the evidence	Comments or notes the umbrella review authors may have regarding any included study
Siongco, 2020 Philippines MA	To evaluate the analgesic efficacy of Botulinum toxin type A (BoNT-A) in both muscle-based and non-muscle-based pain conditions and to determine whether route of administration (intramuscular vs SC/intradermal) influences clinical outcomes	**I:** BoNT-A **C:** placebo (Saline)	**Disorder:** TN (ICHD) PHN, DPN, CRPS (IASP or Budapest criteria) TMD (RDC/DC-TMD) **N:** 1434, **% F:** Not reported **Age range:** Adults (> 18 y) **Mean age range:** Not reported	4 From the inception of the database until Jan 2017	2000–2021	25 studies RCT 3 BoNT-A vs Saline	**Primary studies:** Data extraction table **Quality:** AMSTAR 2, ROBIS tool	1. Pain intensity (VAS) 2. AE	SMD (95% CI) for effect size Q test, τ^2 and I^2 was used due to heterogeneous studies Publication bias was assessed using the funnel plots, Egger's and Begg's tests	

Table 1 (continued)

Author, year Country Type of review	Objectives of included review	Intervention (I) Control (C)	Participants details	Number of databases sourced and searched and date range of database searching	Publication date range of studies included in the review that inform each outcome of interest	Number of studies, types of studies and country of origin of studies included in each review	Instruments used to appraise the primary studies and the rating of their quality	Outcomes reported that are relevant to the umbrella review question	Method of synthesis/ analysis employed to synthesise the evidence	Comments or notes the umbrella review authors may have regarding any included study
Sridharan, 2017 Fiji SR + NMA	To assess and compare interventions for refractory trigeminal neuralgia (patients not responding to conventional medical therapy)	**I:** BoNT-A, sumatriptan (SC), intranasal lidocaine, IV lidocaine, ophthalmic proparacaine and radiofrequency interventions **C:** Placebo (Saline)	**Disorder:** Refractory TN **N:** 533 **% F:** Not reported **Age range:** Adults (> 18 y) **Mean age range:** Not reported	4 From the inception of the database until Jun 2017	1994–2016	13 studies RCT 3 BoNT-A vs saline	**Primary studies:** Data extraction table **Quality:** Cochrane risk of bias tool and GRADE	1. Pain Relief (VAS)	Bayesian hierarchical network meta-analysis using a random-effects model OR with 95% CrI were estimated via logistic regression (logit link) Model fit assessed by DIC consistency evaluated with deviance plots treatment ranking based on SUCRA Analyses conducted using NetMetaXL and WinBUGS. Sensitivity and subgroup analyses performed	
Yang, 2018 China SR + NMA	To compare the efficacy/ performance of 8 drug treatments for TN and identify the optimal option using direct and indirect comparisons	**I:** BoNT-A CBZ, OXC, LDC, LTG, TIZ, PIM, PPC **C:** Placebo and other treatments	**Disorder:** TN **N: 672** **% F:** Not reported **Age range:** Adults **Mean age range:** Not reported	2 Time period not reported	1969–2014	13 studies RCT, RT 2 BoNT-A vs saline	**Primary studies:** Data extraction table **Quality:** Cochrane risk of bias tool	1. Response rate	Pairwise and Bayesian network meta-analysis estimating ORs Consistency assessed by node-splitting and heat plots Treatment ranking based on SUCRA Publication bias evaluated using funnel plots (R v3.2.3)	

Table 1 (continued)

Author, year Country Type of review	Objectives of included review	Intervention (I) Control (C)	Participants details	Number of databases sourced and searched and date range of database searching	Publication date range of studies included in the review that inform each outcome of interest	Number of studies, types of studies and country of origin of studies included in each review	Instruments used to appraise the primary studies and the rating of their quality	Outcomes reported that are relevant to the umbrella review question	Method of synthesis/ analysis employed to synthesise the evidence	Comments or notes the umbrella review authors may have regarding any included study
Post-herpetic neuralgia										
Finnerup, 2015 Denmark SR + MA	To provide evidence-based recommendations for pharmacological treatment of neuropathic pain based on systematic review and meta-analysis of randomised controlled trials, including evaluation of efficacy and safety of botulinum toxin type A (BoNT-A)	**I:** Pharmacological treatments for neuropathic pain (antidepressants, anticonvulsants, opioids, topical agents, BoNT-A) **C:** Placebo or active comparators	**Disorder:** Neuropathic pain (including TN and PHN) according to IASP **N:** Not Reported % **F:** Not reported **Age range:** Adults **Mean age range:** Not reported	3 From the inception of the database until Nov 2013	1966–2013	229 studies RCT 6 BoNT-A vs Saline	**Primary studies:** Data extraction table **Quality:** GRADE	1.Pain relief 2. NNT 3. Safety and tolerability 4. AE	Systematic evidence synthesis with meta-analysis of randomised controlled trials Primary effect measure: NNT for ≥50% pain reduction (alternatively ≥30% pain reduction or moderate pain relief); safety assessed using NNH 95% CI derived from absolute risk differences I^2 and L'Abbé plot was used due to heterogeneous studies Publication bias was assessed using the funnel plots, Egger's and Duval and Tweedie's tests	Mixed population review; PHN data extracted only
Hary, 2022 France SR + MA	To evaluate the efficacy and safety of BoNT-A in the treatment of chronic peripheral neuropathic pain, including trigeminal neuralgia and postherpetic neuralgia	**I:** injections of BoNT-A **C:** placebo, Sham injection or standard pharmacological treatment	**Disorder:** TN, PHN, PTNP **N:** 530 % **F:** Not reported **Age range:** Adults **Mean age range:** Not reported	5 From the inception of the database until Jun 2021	2005–2021	10 studies RCT 10 BoNT-A vs Saline	**Primary studies:** Data extraction table **Quality:** GRADE and Cochrane risk of bias tool	1. Pain intensity (VAS and NRS) 2. Quality of life 3. AE	WMD (95% CI) and RR (95% CI) for relative effect sizes I^2 was used due to heterogeneous studies random-effects model NNT was calculated publication bias was assessed by funnel plot asymmetry	Mixed conditions separated

Table 1 (continued)

Author, year Country Type of review	Objectives of included review	Intervention (I) Control (C)	Participants details	Number of databases sourced and searched and date range of database searching	Publication date range of studies included in the review that inform each outcome of interest	Number of studies, types of studies and country of origin of studies included in each review	Instruments used to appraise the primary studies and the rating of their quality	Outcomes reported that are relevant to the umbrella review question	Method of synthesis/ analysis employed to synthesise the evidence	Comments or notes the umbrella review authors may have regarding any included study
Siongco, 2020 Philippines MA	To evaluate the analgesic efficacy of Botulinum toxin type A (BoNT-A) in both muscle-based and non-muscle-based pain conditions and to determine whether route of administration (intramuscular vs SC/intradermal) influences clinical outcomes	**I:** BoNT-A **C:** Placebo (Saline)	**Disorder:** TN (ICHD) PHN, DPN, CRPS (IASP or Budapest criteria) TMD (RDC/DC-TMD) **N:** 1434, **% F:** Not reported **Age range:** Adults (> 18 y) **Mean age range:** Not reported	4 From the inception of the database until Jan 2017	2000–2021	25 studies RCT 3 BoNT-A vs Saline	**Primary studies:** Data extraction table **Quality:** AMSTAR 2, ROBIS tool	1. Pain intensity (VAS) 2. AE	SMD (95% CI) for effect size Q test, $\tau 2$ and I^2 was used due to heterogeneous studies Publication bias was assessed using the funnel plots, Egger's and Begg's tests	High clinical heterogeneity
Soliman, 2025 UK SR + MA	To update pharmacological and neuromodulation treatment recommendations for neuropathic pain based on randomised controlled trials	**I:** Pharmacological treatments (including BoNT-A) and non-invasive neuromodulation interventions **C:** Placebo or sham-controlled comparators depending on intervention type	**Disorder:** Neuropathic pain conditions including PHN **N:** 48,789 **% F:** 45.11% **Age range:** Adults (> 18 y) **Mean age range:** Not reported	4 From the inception of the database until Jan 2024	2013–2024	313 studies RCT 11 BoNT-A vs saline	**Primary studies:** Data extraction table **Quality:** Cochrane risk of bias tool 2 and GRADE	1. Treatment response (pain reduction) 2. Treatment withdrawal due to AE	Random-effects meta-analysis using risk differences as effect estimates NNT and NNH were calculated from pooled effects Risk of bias assessed with Cochrane RoB 2 Certainty of evidence evaluated using GRADE	Guideline-type evidence synthesis

Table 1 (continued)

Author, year Country Type of review	Objectives of included review	Intervention (I) Control (C)	Participants details	Number of databases sourced and searched and date range of database searching	Publication date range of studies included in the review that inform each outcome of interest	Number of studies, types of studies and country of origin of studies included in each review	Instruments used to appraise the primary studies and the rating of their quality	Outcomes reported that are relevant to the umbrella review question	Method of synthesis/ analysis employed to synthesise the evidence	Comments or notes the umbrella review authors may have regarding any included study
Wen, 2020 China SR + NMA	To compare the efficacy of different interventional therapies, including botulinum toxin type A, for the treatment of postherpetic neuralgia and determine the most effective treatment using direct and indirect comparisons.	**I:** BoNT-A, PRF, Nerve Block, SC or local infiltration, Stellate ganglion block, Ozone **C:** Placebo, Standard Oral Pharmacological therapy, Other interventional therapies, Sham procedure	**Disorder:** PHN **N:** 702 **% F:** Not reported **Age range:** Adults **Mean age range:** 57.06 to 73.53 y	3 From the inception of the database until Oct 2020	2010–2017	12 studies RCT 1 BoNT-A vs saline 1 BoNT-A vs Saline vs lidocaine	**Primary studies:** Data extraction table **Quality:** Cochrane risk of bias tool	1. Pain intensity (VAS and NRS)	MD (95% CI and 95% CrIs) for effect sizes I^2 was used due to heterogeneous studies DerSimonian–Laird (DL) random effects (RE) model was used for the paired meta-analysis Node-splitting method and Inconsistency factor analysis was used for consistency assessment	Direct PHN evidence

AE adverse event, *BoNT-A* botulinum toxin type A, *CI* confidence interval, *CrI* credible interval, *CTR* control, *GRADE* Grading of Recommendations Assessment, Development and Evaluation, *IASP* International Association for the Study of Pain, *MA* meta-analysis, *MCID* minimally clinically important difference, *MD* mean difference, *NMA* network meta-analysis, *NeuPSIG* Neuropathic Pain Special Interest Group, *NNH* number needed to harm, *NNT* number needed to treat, *NRS* numerical rating scale, *OR* odds ratio, *PGIC* patient global impression of change, *PHN* post-herpetic neuralgia, *RCT* randomised controlled trial, *ROBIS* risk of bias in systematic reviews, *RR* risk ratio, *SC* subcutaneous, *SMD* standard mean difference, *SR* systematic review, *SUCRA* surface under cumulative ranking curve, *TN* trigeminal neuralgia, *VAS* visual analogic scale, *WMD* weighted mean difference

Table 2 Descriptive overlap assessment of primary randomised controlled trials for trigeminal neuralgia across included systematic reviews

Original BoNT-A study Disorder	Type	Number of subjects	Age	BoNT-A type, dose (dose/side)	Injection p/muscle	Control	Outcome	Included in studies (n)	Included in studies (authors)
Wu, 2012 China Classical TN	RCT Parallel, double-blind	42 23F, 19M	30-88 y Mean 58.6 y	BoNT-A (Lanzhou Biological Products Institute, China) 75 U affected trigeminal branch (V1–V3) 5 U per point	Single session 15 points intradermal/submucosal injections in trigger zones	Saline solution	Pain (VAS) Attack frequency Responder ≥ 50% PGIC	6	Hu 2024; Siongco 2020; Sridharan 2017; Yang 2018; Morra 2016; Finnerup 2015
Shehata, 2013 Egypt Idiopathic TN	RCT Double-blind	20 11F, 9M	27–72 y Mean 45.95 y	Botox® 40–60 U affected trigeminal branch (V1-V3) 5 U per point	Single session Subcutaneous "follow-the-pain" 8 points (40 U) to 12 points (60 U)	Saline solution	Pain (VAS) Paroxysm frequency QoL scale Medication use	3	Hu 2024; Siongco 2020; Morra 2016
Zúñiga, 2013 Argentina Essential TN	RCT Double-blind	36 17F, 19 M	BTX: 42–90 y; mean 64.5 y PBO: 44–93 y; mean 66.06 y	Botox® 50 U affected trigeminal branch (V1–V3) +10 U masseter muscle (V3 involvement)	Single session SC injections in various sites 1 cm apart along involved branch(es) + IM masseter if V3 Number of points NR	Saline solution	Pain (VAS) Attack frequency SF-36 QoL	3	Hu 2024; Siongco 2020; Morra 2016
Zhang, 2014 China Classical TN	RCT Double-blind	84 48F, 36M	31–89 y Mean 59.8 y	BoNT-A (Lanzhou Biological Products Institute, China) 25 U or 75 U distributed across affected trigeminal branches (V1–V3)	Single session Multiple 20 intradermal/submucosal injection points in painful areas (V1–V3 distribution)	Saline solution	Pain (VAS) Responder rate PGIC	4	Hu 2024; Siongco 2020; Yang 2018; Morra 2016

BoNT-A botulinum toxin type A, *F* female, *IM* intramuscular, *M* male, *NR* not reported, *PBO* placebo, *PGIC* patient global impression of change, *QoL* quality of life, *SC* subcutaneous, *SF-36* 36-item Short Form Survey, *RCT* randomised controlled trial, *TN* trigeminal neuralgia, *U* units, *VAS* visual analogic scale

Table 3 Descriptive overlap assessment of primary randomised controlled trials for postherpetic neuralgia across included systematic reviews

Original BoNT-A study Disorder	Type	Number of subjects	Age	BoNT-A type, dose (dose/side)	Injection p/muscle	Control	Outcome	Included in studies (n)	Included in studies (authors)
Apalla, 2013 Greece PHN	RCT Double-blind, placebo-controlled Parallel	30 BoNT-A: 8M, 7F PBO: 10M, 5F	NR range BoNT-A mean 73.2 y PBO mean 77.5 y	Botox® 100 U affected dermatomes 5 U per injection site	Single session 40 SC injections (≥ 1 cm apart) over painful dermatome	Saline solution	Pain (VAS) Sleep score Maintenance of pain reduction	5	Wen 2020; Hary 2022; Siongco 2020; Soliman 2025; Finnerup 2015
Xiao, 2010 China PHN	RCT Double-blind, placebo-controlled Parallel	60 32F, 28M	42–84 y Mean 68 y	BoNT-A (Lanzhou Biological Products Institute, China) Up to 200 U total injected across affected dermatome(s) Dose adjusted according to allodynia area	Single session SC injections mapped to painful dermatome Number of injection points NR	Saline solution lidocaine active control	Pain (VAS) Sleep duration Opioid use	4	Wen 2020; Hary 2022; Siongco 2020; Finnerup 2015

BoNT-A botulinum toxin type A, *F* female, *IM* intramuscular, *M* male, *NR* not reported, *PBO* placebo, *PHN* post-herpetic neuralgia, *QoL* quality of life, *RCT* randomized controlled trial, *SC* subcutaneous, *U* units, *VAS* visual analogue scale

Only primary randomised controlled trials that could be clearly identified within the included systematic reviews were mapped

randomised controlled trials across included systematic reviews was mapped descriptively (Tables 2, 3).

3.4 Doses and Injection Protocols

Botulinum toxin type A was administered using variable dosing regimens and injection protocols depending on the neuropathic pain condition and study design. Overall, total doses ranged from approximately 15–300 U per treatment session [18, 19, 26, 28]. Across the included studies, both fixed-site and "follow-the-pain" approaches were used, reflecting variability in injection patterns, number of sites, and total dose administered. Different BoNT-A formulations were reported across studies [26, 28].

In TN, BoNT-A was most administered in single-session protocols using doses typically ranging from 25 to 100 U, although higher doses of up to 200 U were also reported [18, 19, 26, 27]. Injections were performed subcutaneously or intradermally along the distribution of the affected trigeminal branches, following a multi-point injection technique. The number of injection sites varied across studies, generally ranging from a few targeted points to approximately 15–25 sites, with 2.5–5 U per injection point [18, 26, 27].

In PHN, BoNT-A was typically injected within the affected dermatomal area using multi-point injection approaches. Total doses ranged from 100 to 300 U depending on the size of the painful area, with up to 40 injection sites reported in some studies [18, 19, 28]. Both single-session and repeated injection protocols were described, with follow-up intervals of approximately 12 weeks in studies including multiple treatment sessions [18, 19, 28].

3.5 Quantitative Findings

Most of the included systematic reviews investigated the pain-reducing effects of BoNT-A for the assessed conditions using the Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS). Several reviews also evaluated treatment response, typically defined as a ≥ 50% reduction in pain intensity, whereas fewer reviews assessed quality-of-life outcomes. Adverse events associated with BoNT-A treatment were reported in most of the included systematic reviews. A quantitative presentation of these outcomes is shown in Tables 4, 5, 6, 7, 8, 9, 10 and 11.

Table 4 Table presenting quantitative findings regarding the effect of BoNT-A treatment on pain intensity in trigeminal neuralgia

Author, year	Outcome intervention(s)	No. studies/no. participants	Results/findings	Heterogeneity
Hu et al, 2024	Pain intensity BoNT-A vs placebo/baseline, 1mo	4/178	Significant reduction [MD −2.36 (95% CI −3.86, −0.87), $p = 0.002$]	$I^2 = 0\%$, $p = 0.416$
	Pain intensity BoNT-A vs placebo/baseline, 2 mo	4/178	Significant reduction [MD −2.54 (95% CI −4.13, −0.95), $p = 0.002$]	$I^2 = 11.6\%$, $p = 0.335$
	Pain intensity BoNT-A vs placebo/baseline, 3 mo	4/178	Significant reduction [MD −4.05 (95% CI −6.13, −1.97), $p = 0.002$]	$I^2 = 2.0\%$, $p = 0.002$
	Pain intensity BoNT-A	13/484	Significant reduction [MD −5.19 (95% CI −6.05, −4.33), p?]	$I^2 = 89.6\%$, $p = 0.001$
	Pain intensity BoNT-A, up to 6 mo follow-up	4/NR	Mean pain reduction [MD −5.88 (95% CI −8.37, −3.39), p?]	$I^2 = 96.8\%$, $p < 0.001$
	Pain attack frequency BoNT-A, 3–6 mo	8/279	Significant reduction [MD −17.85 (95% CI −23.36, −12.34), $p < 0.001$]	$I^2 = 72.1\%$, $p < 0.001$
Hary, 2022	Pain intensity BoNT-A vs placebo, 1 mo	9/505	Moderate-quality evidence [MD −1.87 (95% CI −2.91, −0.83), p?] NNT = 3	$I^2 = 90\%$
	Pain intensity BoNT-A vs placebo, 3 mo	6/505	Moderate-quality evidence [MD −1.38 (95% CI −1.95, −0.81), p?] NNT = 7	$I^2 = 0\%$
Morra, 2016	Pain intensity BoNT-A vs placebo, 1 mo	3/114	Significant reduction [MD −2.89 (95% CI −4.66, −1.12), $p = 0.001$]	$I^2 = 20\%$, $p = 0.29$
	Pain intensity BoNT-A vs placebo, 2 mo	4/150	Significant reduction [MD −2.47 (95% CI −3.96, −0.99), $p = 0.001$]	$I^2 = 22\%$, $p = 0.28$
	Pain intensity BoNT-A vs placebo, 3 mo	3/98	Significant reduction [MD −3.43 (95% CI −5.21, −1.64), $p = 0.0002$]	$I^2 = 48\%$, $p = 0.14$
	Pain attack frequency BoNT-A vs placebo, end of follow-up (≈2–3 mo)	2/62	Significant reduction [MD −29.79 (95% CI −38.50, −21.08), $p < 0.00001$]	$I^2 = 36\%$, $p = 0.21$
Siongco, 2020	Pain reduction BoNT-A vs placebo (neuropathic pain MA incl. TN) ≤3 mo	Not reported	Significant reduction favouring BoNT-A [SMD −0.5463, $p < 0.001$]	$I^2 = 67.3\%$

BoNT-A botulinum toxin type A, *CI* confidence interval, *MA* meta-analysis, *MD* mean difference, *NR* not reported, *SMD* standard mean difference, *TN* trigeminal neuralgia

Table 5 Table presenting quantitative findings regarding the effect of BoNT-A treatment on responder rate and clinical improvement in trigeminal neuralgia

Author, year	Outcome intervention(s)	No. studies/no. participants	Results/findings	Heterogeneity
Finnerup, 2015	Pain relief ≥50% reduction (neuropathic pain including TN) BoNT-A vs placebo)	6/137 (BoNT-A trials assessed for risk of bias)	Clinically meaningful pain relief favouring BoNT-A; pooled NNT 1.9–2.5 for ≥50% pain reduction	Not reported
Hu et al, 2024	Responder rate (≥50% pain reduction) BoNT-A, end of treatment period (≈3–6 mo)	10/672	Response proportion 70.7% [(95% CI 0.653–0.761), $p = 0.003$]	Not reported
Morra, 2016	Responder rate (>50% pain reduction) BoNT-A vs placebo, end of follow-up (2–3 mo)	2/122	Significant improvement [RR 2.87 (95% CI 1.76–4.69), $p < 0.0001$]	$I^2 = 4\%$, $p = 0.31$
Yang, 2018	Response rate BoNT-A vs placebo (pairwise MA), short-term follow-up	2/126	Significant improvement [OR 3.57 (95% CI 1.85–7.14), p?]	N/A
	Response rate BoNT-A vs placebo (network meta-analysis), mixed follow-up	13/672	BoNT-A superior to placebo [OR 14.0 (95% CI 3.9–56.0), p?]	
Sridharan, 2017	Adequate pain relief BoNT-A vs placebo	11/not reported	Low-quality evidence [OR 10.24 (95% CI 4.60–25.14), p?] No significant difference	N/A (Bayesian MTC)

BoNT-A botulinum toxin type A, *CI* confidence interval, *MA* meta-analysis, *MTC* mixed treatment comparison, *N/A* not applicable, *NNT* number needed to treat, *OR* odds ratio, *RR* risk ratio, *TN* trigeminal neuralgia

Table 6 Table presenting quantitative findings regarding the effect of BoNT-A treatment on quality of life in trigeminal neuralgia

Author, year	Outcome Intervention(s)	No. studies/no. participants	Results/findings	Heterogeneity
Hary, 2022	Sleep score BoNT-A vs placebo, 1 mo	3/134	Moderate-quality evidence [SMD −0.75 (95% CI −2.02, 0.52), *p*?]	$I^2 = 91\%$
	Sleep score BoNT-A vs placebo, 3 mo	2/104	Moderate-quality evidence [SMD −0.04 (95% CI −0.43, 0.34), *p*?]	$I^2 = 0\%$

BoNT-A botulinum toxin type A, *SMD* standard mean difference

Table 7 Table presenting quantitative findings regarding the effect of BoNT-A treatment on AEs in trigeminal neuralgia

Author, year	Outcome intervention(s)	No. studies/no. participants	Results/findings	Heterogeneity
Finnerup, 2015	AEs/tolerability	6/137 (BoNT-A trials assessed for risk of bias)	Low risk of treatment discontinuation due to AEs; NNH ≈ 83 based on pooled absolute risk differences	Heterogeneity assessed using I^2 statistics and L'Abbé plots (numerical I^2 not reported)
Hary, 2022	Pain during injection BoNT-A vs placebo	Not reported	High-quality evidence [RR 0.99 (95% CI 0.89–1.10), $p = 0.86$]	$I^2 = 0\%$
Hu, 2024	Injection-related AEs	4/178	Facial asymmetry, oedema (3.70%), haematoma (2.78%); mild/transient	N/A
Morra, 2016	Injection-related AE	4/178	Facial asymmetry and oedema/haematoma at injection site; mild and transient; no serious AEs reported	N/A
Bendtsen, 2019	Clinical tolerability recommendation	Guideline	BoNT-A acceptable add-on therapy; very-low certainty evidence	N/A

AE adverse event, *BoNT-A* botulinum toxin type A, *CI* confidence interval, *NNH* number needed to harm, *N/A* not applicable, *RR* risk ratio

3.5.1 Effect of BoNT-A Treatment on Pain Intensity in TN and PHN

Evidence on TN pain intensity reduction showed variable heterogeneity across studies (Tables 4, 5, 6, 7, 8, 9, 10, 11). Most systematic reviews evaluated changes in pain intensity following BoNT-A injections compared with baseline or placebo. The overall findings generally favoured BoNT-A treatment, with reductions in pain intensity consistently reported after treatment [26, 28–30]. Follow-up evidence from 1–3 months further indicated that BoNT-A was associated with improvements in pain intensity over time [26, 28–30]. Across the included meta-analyses [26, 29, 30], BoNT-A was consistently associated with reductions in pain intensity in patients with TN. These findings were observed both in comparisons with baseline and in randomised comparisons with placebo. Pooled analyses also indicated reductions in attack frequency following BoNT-A treatment in TN. The magnitude of the effect varied across studies, with considerable heterogeneity reported [26, 29] (Tables 4, 5, 6, 7, 8, 9, 10, 11). Reported pooled effect estimates for pain reduction ranged approximately from MD −1.38 to −5.88 across different follow-up periods, whereas heterogeneity varied from low to substantial (I^2 ranging from 0 to 96.8%).

Postherpetic neuralgia pain intensity reduction showed variability across studies (Table 8). Most systematic reviews evaluated BoNT-A against placebo, consistently reporting greater reductions in pain intensity following BoNT-A administration [28, 30]. Evidence from one network meta-analysis showed higher diminution of pain intensity after BoNT-A injections compared with subcutaneous infiltrations of lidocaine; however, direct comparative data between BoNT-A and active interventions were limited and inconsistent with other interventional and pharmacological treatments [26, 32]. The overall findings generally favoured BoNT-A treatment, with reductions in pain intensity reported after treatment. Pooled analyses [28, 30], supported by evidence from interventional network meta-analysis [32], indicated short-term (1–3 months) improvements in pain intensity following BoNT-A administration. However, effect estimates varied across studies, with moderate to high heterogeneity observed [28, 30] (Tables 4, 5, 6, 7, 8, 9, 10, 11). Reported heterogeneity in pooled PHN analyses ranged up to 98%, reflecting variability in study design, injection protocols, and outcome assessment.

Table 8 Table presenting quantitative findings regarding the effect of BoNT-A treatment on pain intensity in post-herpetic neuralgia

Author, year	Outcome intervention(s)	No. studies/no. participants	Results/findings	Heterogeneity
Wen, 2020	Pain intensity BoNT-A vs other pharmacological treatments, 1 wk	2/90 direct BoNT-A trials; network total 12/702	Significant reduction favouring BoNT-A [MD −3.81 (95% CrI −5.28, −2.35), *p*?]	N/A (Bayesian NMA)
	Pain intensity BoNT-A vs nerve block, 1 wk		Significant reduction favouring BoNT-A [MD −2.55 (95% CrI −4.21, −0.98), *p*?]	
	Pain intensity BoNT-A vs pulsed radiofrequency (PRF), 1 wk		Significant reduction favouring BoNT-A [MD −1.61 (95% CrI −3.22, −0.05), *p*?]	
	Pain intensity BoNT-A vs stellate ganglion block, 1 wk		Significant reduction favouring BoNT-A [MD −3.78 (95% CrI −5.67, −1.86), *p*?]	
	Pain intensity BoNT-A vs other pharmacological treatments, 1 mo		Significant reduction favouring BoNT-A [MD −6.92 (95% CrI −9.96, −3.79), *p*?]	
	Pain intensity BoNT-A vs nerve block, 1 mo		Significant reduction favouring BoNT-A [MD −6.81 (95% CrI −10.18, −3.35), *p*?]	
	Pain intensity BoNT-A vs pulsed radiofrequency (PRF), 1 mo		Significant reduction favouring BoNT-A [MD −5.10 (95% CrI −8.35, −1.82), *p*?]	
	Pain intensity BoNT-A vs stellate ganglion block, 1 mo		Significant reduction favouring BoNT-A [MD −6.43 (95% CrI −10.06, −2.73), *p*?]	
Hary, 2022	Pain intensity BoNT-A vs placebo (peripheral neuropathic pain incl. PHN), 1 mo	9/505	Moderate-quality evidence [MD −1.87 (95% CI −2.91, −0.83), *p*?] NNT 3;	$I^2 = 90\%$
	Pain intensity BoNT-A vs placebo (peripheral neuropathic pain incl. PHN), 3 mo	6/219	Moderate-quality evidence [MD −1.38 (95% CI −1.95, −0.81), *p*?]; NNT 7;	$I^2 = 98\%$
Siongco, 2020	Pain reduction BoNT-A vs placebo (neuropathic pain MA incl. PHN), mixed follow-up	Not reported	Significant reduction favouring BoNT-A, [SMD −0.5463; *p*?]	$I^2 = 67.3\%$, $p = 0.000$

BoNT-A botulinum toxin type A, *CI* confidence interval, *MA* meta-analysis, *MD* mean difference, *N/A* not applicable, *NMA* network meta-analysis, *NNT* number needed to treat, *PHN* post-herpetic neuralgia, *SMD* standard mean difference

Table 9 Table presenting quantitative findings regarding the effect of BoNT-A treatment on responder rate and clinical improvement in post-herpetic neuralgia

Author, year	Outcome intervention(s)	No. studies/no. participants	Results/findings	Heterogeneity
Finnerup, 2015	Responder rate (≥50% pain reduction) (neuropathic pain incl. PHN) BoNT-A vs placebo	6/137 (BoNT-A trials assessed for risk of bias)	Significant pain relief favouring BoNT-A; NNT 1.9–2.5 for ≥50% pain reduction based on pooled absolute risk differences	Not reported
Soliman, 2025	Pain relief responders (refractory peripheral neuropathic pain incl. PHN), ≥3-wk follow-up	6/pooled sample size not explicitly reported	Moderate certainty [SMD 0.5 (0.2–0.9); NNT 2.7 (1.8–5.1), *p*?]	Heterogeneity not separately reported for BoNT-A subgroup

BoNT-A botulinum toxin type A, *NNT* number needed to treat, *PHN* post-herpetic neuralgia, *SMD* standard mean difference

Table 10 Table presenting quantitative findings regarding the effect of BoNT-A treatment on quality of life in post-herpetic neuralgia

Author, year	Outcome Intervention(s)	No. studies/no. participants	Results/findings	Heterogeneity
Hary, 2022	Sleep score BoNT-A vs placebo (peripheral neuropathic pain incl. PHN), 1 mo	3/134	Moderate-quality evidence [SMD −0.75 (95% CI −2.02, 0.52), *p*?]	$I^2 = 91\%$
	Sleep score BoNT-A vs placebo (peripheral neuropathic pain incl. PHN), 3 mo	2/104	Moderate-quality evidence [SMD −0.04 (95% CI −0.43, 0.34), *p*?]	$I^2 = 0\%$

BoNT-A botulinum toxin type A, *CI* confidence interval, *PHN* post-herpetic neuralgia, *SMD* standard mean difference

Table 11 Table presenting quantitative findings regarding the effect of BoNT-A treatment on AEs in post-herpetic neuralgia

Author, year	Outcome intervention(s)	No. studies/no. participants	Results/findings	Heterogeneity
Finnerup, 2015	Adverse events/tolerability	6/137 (BoNT-A trials assessed for risk of bias)	Low risk of treatment discontinuation due to AEs; NNH ≈ 83 based on pooled absolute risk differences	Heterogeneity assessed using I^2 statistics and L'Abbé plots (numerical I^2 not reported)
Hary, 2022	Pain during injection BoNT-A vs placebo	3/111	High-quality evidence [RR 0.99 (95% CI 0.89–1.10), $p = 0.86$]	$I^2 = 0\%$
	Neurological AEs BoNT-A vs placebo	2/133	[RR 1.72 (95% CI 0.73–4.09), *p*?]	$I^2 = 0\%$
	Digestive AEs BoNT-A vs placebo	2/133	[RR 0.41 (95% CI 0.04–3.97), *p*?]	$I^2 = 57\%$
Soliman, 2025	Withdrawals due to AEs (refractory peripheral neuropathic pain incl. PHN), ≥ 3 wk	8/317	Moderate certainty [NNH 216.3 (23.5–∞), *p*?]	Not reported
Wen, 2020	AEs	Not reported	Safety outcomes described narratively; no pooled PHN-specific quantitative estimates available	N/A (MA not performed)

AEs adverse events, *BoNT-A* botulinum toxin type A, *CI* confidence interval, *LLLT* low-level laser therapy, *MA* meta-analysis, *MCID* minimally clinically important difference, *MD* mean difference, *MMO* maximal mouth opening *NNH* number needed to harm, *PHN* postherpetic neuralgia, *RCT* randomized controlled study, *RR* risk ratio, *SMD* standard mean difference, *SR* systematic review, *TMD* temporomandibular disorders, *WMD* weighted mean difference

3.5.2 Responder Rate and Clinical Improvement in TN and PHN

For TN, most systematic reviews evaluated responder rates (≥ 50% pain reduction) following BoNT-A injections compared with placebo. The overall findings generally favoured BoNT-A treatment, with higher responder rates consistently reported [18, 26, 29] (Table 5). Follow-up assessments, typically ranging from 2 to 3 months, indicated sustained treatment response over time [26, 29]. Across the included meta-analyses and network meta-analyses, BoNT-A was associated with improved responder rates in patients with TN [26, 29, 31]. Reported responder rates for ≥ 50% pain reduction generally ranged from approximately 70% in pooled analyses, with odds ratios favouring BoNT-A over placebo ranging from 2.87 to 14.0 across reviews. However, the magnitude of treatment response varied across studies, and some analyses reported low-certainty evidence or inconsistent findings [33] (Tables 4, 5, 6, 7, 8, 9, 10, 11).

Treatment response in PHN was reported by a limited number of the included reviews (Table 9). Generally, compared with placebo, BoNT-A treatment showed higher response rates [18, 19]. Follow-up data were limited but suggested short-term (1–3 months) improvements after treatment. However, heterogeneity was not consistently reported in the included meta-analyses, limiting the interpretation of between-study variability (Tables 4, 5, 6, 7, 8, 9, 10, 11).

3.5.3 Effect of BoNT-A Treatment on Quality of Life in TN and PHN

Evidence on quality-of-life outcomes after BoNT-A treatment for TN and PHN was limited (Tables 6 and 10). Only one systematic review with meta-analysis assessed

Table 12 Summary of evidence regarding botulinum toxin A (BoNT-A) treatment in orofacial neuropathic pain conditions

Summary of evidence regarding Botulinum toxin A (BoNT -A) treatment in orofacial neuropathic pain conditions		
a-1. Effect of BoNT-A treatment on pain intensity in ***trigeminal neuralgia***		
Author, year	**Outcome**	**BoNT-A vs placebo or other treatments**
Hary, 2022	Pain intensity	BoNT-A showed significant reductions in pain intensity compared with placebo at both short-term follow-ups
Hu et al., 2024	Pain intensity	BoNT-A showed significant reductions in pain intensity and pain attack frequency compared to placebo across multiple follow-up periods
Morra, 2016	Pain intensity	BoNT-A showed significant reductions in pain intensity and attack frequency compared with placebo at short-term follow-up
Siongco, 2020	Pain intensity	BoNT-A showed significant improvements in pain reduction across neuropathic pain conditions including trigeminal neuralgia
a-2. Effect of BoNT-A treatment on pain intensity in ***post-herpetic neuralgia***		
Author, year	**Outcome**	**BoNT-A vs placebo or other treatments**
Hary, 2022	Pain intensity	BoNT-A showed significant improvements compared with placebo at short-term follow-ups
Siongco, 2020	Pain intensity	BoNT-A showed significant pain reduction compared with placebo across neuropathic pain conditions including post-herpetic neuralgia
Wen, 2020	Pain intensity	BoNT-A demonstrated significant reductions in pain intensity compared with several interventional treatments
b-1. Effect of BoNT-A treatment on responder rate in ***trigeminal neuralgia***		
Author, year	**Outcome**	**BoNT-A vs placebo or other treatments**
Finnerup, 2015	Responder rate (≥50% pain reduction)	Clinically meaningful pain relief favouring BoNT-A compared with placebo
Hu et al., 2024	Responder rate (≥50% pain reduction)	BoNT-A demonstrated high responder rates
Morra, 2016	Responder rate (≥50% pain reduction)	BoNT-A showed significantly higher responder rates compared with placebo
Sridharan, 2017	Responder rate	BoNT-A showed improved pain relief compared with placebo, although the certainty of evidence was low
Yang, 2018	Responder rate	BoNT-A demonstrated higher response rates compared with placebo in network meta-analysis
b-2. Effect of BoNT-A treatment on responder rate in ***post-herpetic neuralgia***		
Author, year	**Outcome**	**BoNT-A vs placebo or other treatments**
Finnerup, 2015	Responder rate (≥50% pain reduction)	Clinically meaningful pain relief favouring BoNT-A compared with placebo
Soliman, 2025	Pain relief responders	BoNT-A demonstrated clinically meaningful pain relief compared with placebo
c-1. Effect of BoNT-A treatment on quality of life in ***trigeminal neuralgia***		
Author, year	**Outcome**	**BoNT-A vs placebo or other treatments**
Hary, 2022	Sleep score	BoNT-A showed improvements in sleep-related outcomes, although results were not statistically significant
c-2. Effect of BoNT-A treatment on quality of life in ***post-herpetic neuralgia***		
Author, year	**Outcome**	**BoNT-A vs placebo or other treatments**
Hary, 2022	Sleep score	BoNT-A showed improvements in sleep-related outcomes, although results were not statistically significant

Table 12 (continued)

d-1. Table summarizing the evidence from quantitative research synthesis regarding the effect of BoNT-A on adverse events in ***trigeminal neuralgia***		
Author, year	**Outcome**	**BoNT-A vs placebo or other treatments**
Bendtsen, 2019	Adverse events	BoNT-A acceptable add-on therapy with very low certainty evidence
Finnerup, 2015	Adverse events	Low risk of treatment discontinuation due to adverse events
Hary, 2022	Adverse events	Adverse events were generally mild and comparable to placebo
Hu, 2024	Adverse events	Adverse events (facial asymmetry, edema, hematoma) were few and generally mild and transient
Morra, 2016	Adverse events	Injection-related adverse events were mild and transient with no serious complications reported

d-2. Table summarizing the evidence from quantitative research synthesis regarding the effect of BoNT-A on adverse events in ***post-herpetic neuralgia***		
Author, year	**Outcome**	**BoNT-A vs placebo or other treatments**
Finnerup, 2015	Adverse events	Low risk of treatment discontinuation due to adverse events.
Hary, 2022	Adverse events	Adverse events were generally mild and comparable to placebo
Soliman, 2025	Adverse events	Low risk of treatment withdrawal due to adverse events
Wen, 2020	Adverse events	Safety described narratively; no pooled PHN-specific quantitative estimates.

Green color indicates a positive outcome in the synthesis. For treatment outcome that indicates an effect favouring BoNT-A in comparison to either placebo or other treatments of trigeminal and post-herpetic neuralgia. When it comes to adverse events that indicates that there is a low risk for adverse events.

Orange color indicates an uncertain outcome in the synthesis. For treatment outcome that indicates an effect that does not favour BoNT-A but can be similar to either placebo or other treatments of trigeminal and post-herpetic neuralgia. When it comes to adverse events it indicates moderate risk for adverse events.

Red color indicates an absence of or very low effect outcome in the synthesis. For treatment outcome that indicates an effect that does not favour BoNT-A but instead favours either placebo or other

Green colour a positive outcome in the synthesis. For treatment outcome that indicates an effect favouring BoNT-A in comparison to either placebo or other treatments of trigeminal and PHN. When it comes to AEs that indicates that there is a low risk for AEs

Orange colour indicates an uncertain outcome in the synthesis. For treatment outcome that indicates an effect that does not favour BoNT-A but can be similar to either placebo or other treatments of trigeminal and PHN. When it comes to AEs it indicates moderate risk for AEs

Red colour indicates an absence of or very low effect outcome in the synthesis. For treatment outcome that indicates an effect that does not favour BoNT-A but instead favours either placebo or other treatments of trigeminal and PHN. When it comes to adverse events it indicates high risk for AEs

AEs adverse events, *BoNT-A* botulinum toxin A, *PHN* post-herpetic neuralgia

these outcomes, focusing exclusively on sleep-related measures [28]. Botulinum toxin type A showed reductions in sleep disturbance scores and increases in sleep duration, with some findings significant versus baseline or placebo [28]. However, pooled analyses did not demonstrate statistically significant differences between BoNT-A and placebo for these outcomes [28] (Tables 4, 5, 6, 7, 8, 9, 10, 11).

3.5.4 Adverse Events of BoNT-A Treatment in TN and PHN

For TN, AEs were generally mild and transient. The most reported events were injection-related reactions, including facial asymmetry, oedema, and haematoma at the injection site. Some analyses also reported pain during injection, although the frequency of these events was comparable between BoNT-A and placebo (Table 7).

Regarding PHN, AEs were also mild and transient and were reported by a limited number of systematic reviews with meta-analysis. The most reported AEs were local injection-related reactions, including oedema and haematoma at the injection site (Table 11).

Overall, BoNT-A treatment is generally well tolerated in patients with TN and PHN.

3.6 Synthesis of Evidence

Table 12 summarises the evidence from the quantitative research synthesis regarding the effects and AEs following BoNT-A treatment. Overall, quantitative evidence indicates generally favourable effects of BoNT-A compared with placebo for TN and with placebo or other active treatments for PHN across pain intensity, attack frequency, and responder rate outcomes. The included meta-analyses reported reductions in pain intensity following BoNT-A treatment when compared to placebo/short-term follow-ups 1–3 months) for both TN and PHN [26, 28–30, 32]. It was reported that attack frequency was also reduced following BoNT-A treatment when compared to placebo in short-term follow-ups (1–3 months) [26, 29]. Responder rate outcomes also suggested meaningful reductions in pain intensity following BoNT-A treatment, with higher response rates generally reported among patients receiving BoNT-A compared with placebo or other interventions for TN and PHN. Evidence on quality-of-life outcomes was limited and derived from a single systematic review, which reported improvements in sleep-related outcomes that were not statistically significant. Reported AEs were generally mild and transient, and the risk of treatment discontinuation due to AEs was low. Overall, although heterogeneity across studies was observed, the available evidence suggests that BoNT-A is a safe treatment that may provide beneficial effects in the management of TN and PHN pain.

4 Discussion

This umbrella review synthesises evidence from moderate- to high-quality systematic reviews on the use of BoNT-A for trigeminal neuralgia and PHN, two clinically important models of peripheral neuropathic pain. Overall, the available evidence indicates that BoNT-A may provide short-term reductions in pain intensity, attack frequency, and increased responder rates, while maintaining a favourable safety profile. However, the magnitude and consistency of effect varied across reviews, particularly in PHN, reflecting substantial heterogeneity at several levels. Clinical heterogeneity included differences in patient phenotypes, disease chronicity, and pain characteristics. Intervention heterogeneity involved variation in BoNT-A formulations, doses, dilution protocols, injection depth, and injection-site strategies. Methodological heterogeneity was related to differences in study design, risk of bias, and duration of follow-up, whereas outcome heterogeneity reflected the use of different pain scales, responder definitions, and patient-reported outcomes. Taken together, these findings support BoNT-A as a clinically relevant option in carefully selected patients, while also highlighting the need for better standardisation and longer-term data especially in terms of its effects on attack frequency in TN.

The clinical effects observed in this review should be interpreted in light of the pathophysiology of TN and PHN. In TN, focal demyelination at the trigeminal root entry zone, most commonly related to neurovascular compression, promotes ectopic impulse generation, high-frequency discharges, and ephaptic transmission between adjacent fibres [7, 12]. This results in the characteristic paroxysmal pain attacks and may also facilitate peripheral sensitisation, with secondary central amplification over time. In PHN, by contrast, varicella-zoster virus-induced damage to primary afferents and dorsal root ganglion neurons leads to persistent peripheral nociceptor dysfunction, spontaneous activity, deafferentation, and central sensitisation [14, 15]. Although the initiating lesions differ, both disorders involve abnormal peripheral input that can sustain central nociceptive gain. This shared feature is important because it provides a biological rationale for local BoNT-A treatment, particularly in focal neuropathic pain states [40].

A key point is that the analgesic effect of BoNT-A is not explained solely by muscle atrophy. Experimental work indicates that, after uptake into peripheral sensory terminals, BoNT-A cleaves SNAP-25 and interferes with vesicular exocytosis, thereby reducing the release of glutamate, substance P, and calcitonin gene-related peptide (CGRP). This reduces peripheral sensitisation and neurogenic inflammation, mechanisms that are especially relevant in neuropathic pain characterised by allodynia and hyperalgesia [21, 40]. This peripheral mode of action is probably the most clinically relevant explanation for the benefits seen in TN and PHN, where treatment is delivered directly into the painful territory. This provides a coherent mechanistic explanation for the clinical effects observed in this review.

In addition, mechanistic studies suggest that BoNT-A can modulate nociceptor function more broadly by affecting pronociceptive signalling pathways in primary afferents. Of particular interest for neuropathic pain, experimental data indicate downregulation of pronociceptive ion-channel expression in sensory ganglia, including Nav1.7 and Transient Receptor Potential Vanilloid 1 (TRPV1), together with suppression of inflammatory mediators. This is mechanistically attractive in TN, where sodium-channel dysregulation is thought to contribute to ectopic firing in injured trigeminal

fibres and is one of the reasons why systemic sodium channel blocking medications such as carbamazepine have such low number-needed-to-treat statistics [7, 40, 41]. However, this point should be presented with some caution: although altered sodium-channel expression may be part of the downstream biology associated with BoNT-A analgesia, direct sodium-channel blockade does not appear to be established as its principal mechanism, and recent preclinical work has suggested that the analgesic effect may even be sodium-channel independent [42]. Thus, it may be more accurate to state that BoNT-A can modulate ion channel-related excitability rather than to claim a direct sodium-channel blocking action.

The work by Matak and colleagues is particularly useful for framing these mechanisms. Their studies support the view that BoNT-A shows selectivity for sensitised nociceptive systems rather than for normal acute nociception, and that TRPV1-expressing, capsaicin-sensitive afferents are important targets. They also provide evidence for cleaved SNAP-25 in central terminals after peripheral application, supporting axonal transport from the periphery to the trigeminal nucleus caudalis or dorsal horn [21, 43]. These observations suggest that at least part of the central effect may arise from reduced transmitter release from primary afferent terminals after peripheral uptake.

From a clinical interpretation standpoint, the peripheral effect is likely the dominant one in TN and PHN. This matters because it helps explain why BoNT-A may be particularly attractive in focal peripheral neuropathic pain, where a treatment delivered into the painful field can reduce nociceptive input without the systemic adverse effects associated with oral therapies. Any central effects of BoNT-A are best regarded as complementary or secondary, potentially contributing to attenuation of central sensitisation once abnormal peripheral input has been reduced. Experimental literature supports retrograde transport and reduced activity in central nociceptive structures, but the relative clinical importance of these central effects in humans currently remains less certain than the peripheral actions [21, 40, 43]. This distinction is clinically relevant, as it supports the rationale for targeting localised neuropathic pain conditions with peripherally delivered treatments.

The present findings are also clinically relevant when viewed against current treatment recommendations. The Neuropathic Pain Special Interest Group (NeuPSIG) of IASP continues to place BoNT-A as a third-line treatment option for neuropathic pain, with use mainly in peripheral neuropathic pain conditions [18, 19]. In the 2025 update, this remained a weak recommendation based on moderate-certainty evidence, balancing efficacy, safety, accessibility, and cost [19]. This positioning is consistent with the present umbrella review: BoNT-A is not yet a first-choice treatment, but it represents a valuable option in selected patients with focal peripheral neuropathic pain, particularly when first- and second-line treatments are insufficient, poorly tolerated, or contraindicated.

The efficacy results in this umbrella review should therefore be interpreted cautiously and in the context of heterogeneous study designs and outcome measures. Reductions in pain intensity, attack frequency, and higher responder rates were observed most consistently in TN, whereas the PHN evidence base was smaller and more heterogeneous. This difference may reflect not only the smaller number of studies in PHN, but also biological variability related to disease chronicity, extent of deafferentation, and the balance between peripheral and central drivers of pain. If BoNT-A acts primarily by suppressing abnormal peripheral input, it is plausible that patients with a stronger peripheral sensitisation phenotype may benefit more than those with more established centralisation or severe deafferentation pain [19, 40]. This remains an important hypothesis for future stratified clinical research.

In terms of safety, the present review aligns with the broader neuropathic pain literature in showing that BoNT-A is generally well tolerated. Adverse events were mostly local and transient, such as injection-site discomfort, oedema, haematoma, or temporary facial asymmetry, with very low discontinuation rates. For clinicians, this favourable tolerability profile is highly relevant, particularly in older patients and in those who cannot tolerate dizziness, sedation, cognitive blunting, or drug interactions associated with systemic agents [18, 19]. Thus, even when efficacy is modest on average, BoNT-A may still offer an advantageous risk-benefit balance in selected patients.

Several implications for future research emerge from this review. First, future trials should better standardise BoNT-A dose ranges, dilution protocols, injection depth, number of injections, injection site selection, re-treatment intervals, and formulation equivalence, since substantial intervention heterogeneity remains a major barrier to interpretation and clinical implementation. Similar concerns regarding standardisation and translation of BoNT-A into routine clinical practice have also been highlighted in recent discussions on chronic orofacial pain management [44]. Second, future studies should distinguish more clearly between TN phenotypes and between PHN patients with predominantly evoked pain versus ongoing spontaneous pain, as these may reflect different mechanisms and treatment responsiveness. Third, studies with longer follow-up and repeated treatment cycles are needed to determine durability, cumulative benefit, and optimal retreatment intervals. Finally, mechanistic clinical studies linking sensory phenotyping to treatment response may be especially informative, given that current preclinical data suggest that BoNT-A acts preferentially on sensitised nociceptor populations [19, 21, 40, 43].

From a practical clinical perspective, BoNT-A should be viewed as an adjunctive treatment for focal peripheral neuropathic pain rather than as a replacement for established first-line therapies. In TN and PHN, it may be especially useful in patients with localised pain, mechanical allodynia, inadequate response to oral medication, or poor tolerability of systemic treatment. Its mechanism of action, centred primarily on peripheral nociceptive terminals with possible secondary central consequences, makes it conceptually different from conventional oral agents and may partly explain why some otherwise treatment-refractory patients still obtain benefit. Therefore, BoNT-A should currently be regarded as an adjunctive and selectively applied treatment rather than a broadly applicable routine therapy for neuropathic pain.

4.1 Limitations and Strengths

Despite these strengths, the present umbrella review has limitations. It depends on previously published systematic reviews and therefore inherits limitations of the underlying primary studies, including small sample sizes, variable risk of bias, and non-standardised outcome reporting. The follow-up periods were predominantly short, and patient-centred outcomes such as functioning and quality of life were insufficiently reported. In addition, grey literature sources were not systematically searched, and publication bias therefore cannot be excluded. Furthermore, several included systematic reviews shared overlapping primary RCTs, particularly in trigeminal neuralgia. Although overlap was assessed descriptively, a formal corrected covered area analysis was not performed. Therefore, the apparent consistency of findings may partly reflect repeated inclusion of the same primary studies. Nevertheless, by restricting inclusion to moderate- and high-quality reviews, this study aimed to provide a more methodologically robust synthesis of the currently available evidence. However, this approach may have reduced comprehensiveness and excluded parts of the broader evidence landscape, particularly findings from reviews with lower methodological quality.

5 Conclusion

Botulinum toxin type A appears to provide short-term pain relief with a favourable tolerability profile in selected patients with trigeminal neuralgia and PHN, with evidence supporting reductions in pain intensity and responder rates. Although heterogeneity in treatment protocols and limited long-term data preclude definitive conclusions regarding optimal use, current evidence supports BoNT-A primarily as an adjunctive third-line option for selected patients with focal peripheral neuropathic pain, and the available findings should therefore be interpreted cautiously.

Within the current therapeutic landscape, BoNT-A should be regarded as a clinically relevant and mechanism-based adjunct for patients who do not achieve sufficient benefit from first- and second-line treatments, particularly in selected patients with localised pain presentations. Future high-quality trials are essential to standardise treatment protocols, identify responder phenotypes, and define the long-term role of BoNT-A in neuropathic pain management.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-026-02352-8.

Acknowledgements The authors would like to thank Emma-Lotta Säätelä and Lovisa Liljegren, librarians at Karolinska Institutet, for developing the search strategy and performing the literature search.

Funding Open access funding provided by Karolinska Institute. No funding was received for this systematic umbrella review.

Declarations

Conflict of interest Authors declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval Not applicable.

Consent (participation and publication) Not applicable.

Code availability Not applicable.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions Giancarlo De la Torre Canales and Nikolaos Christidis had the main idea for the article. However, all authors contributed to the study conception and design. Giancarlo De la Torre Canales, Marie-Amélie Dureisseix, and Thiago Germano dos Santos performed the literature search with help from the university library at Karolinska Institutet. Selection of papers was performed by Marie-Amélie Dureisseix, and Thiago Germano dos Santos. The protocols for data extraction and the risk of bias were developed by Giancarlo De la Torre Canales, Glauce Crivelaro do Nascimento, Rodrigo Lorenzi Poluha, and Nikolaos Christidis. Data extraction was done by Pedro Miguel Teixeira Carvas Cebola and Tatiana Foscaldo. Analysis of risk of bias was performed by Glauce Crivelaro do Nascimento, Rodrigo Lorenzi Poluha. The synthesis of the results was performed by Giancarlo De la Torre Canales and Nikolaos Christidis. Further, both Giancarlo De la Torre Canales and Nikolaos Christidis double checked all parts of the data extraction, assessment of risk of bias and certainty of evidence. Giancarlo De la Torre Canales and Nikolaos Christidis drafted the first manuscript that was critically revised by Justin Durham. After that, all authors commented on the revised version of the manuscript. Finally, all authors read and approved the final manuscript.

References

1. McDonough P, et al. Neuropathic orofacial pain: cannabinoids as a therapeutic avenue. Int J Biochem Cell Biol. 2014;55:72–8.
2. Nisbet G, Sehgal A. Pharmacology in the management of chronic pain. Anaesth Intensive Care Med. 2019;20(10):555–8.
3. Olesen J, Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211.
4. Val M, et al. Is botulinum toxin effective in treating orofacial neuropathic pain disorders? A systematic review. Toxins (Basel). 2023;15(9):541.
5. Health, N.I.f. and C. Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings. London: National Institute for Health and Care Excellence (NICE); 2020.
6. Kumar S, et al. Pain in trigeminal neuralgia: neurophysiology and measurement: a comprehensive review. J Med Life. 2013;6(4):383–8.
7. Gambeta E, Chichorro JG, Zamponi GW. Trigeminal neuralgia: an overview from pathophysiology to pharmacological treatments. Mol Pain. 2020;16:1744806920901890.
8. Vivanco-Estela A, et al. Sex-related differences in cannabidiol's antinociceptive efficacy in a trigeminal neuralgia rodent model. Pain. 2025;166(10):e336–50.
9. Di Stefano G, et al. Triggering trigeminal neuralgia. Cephalalgia. 2018;38(6):1049–56.
10. Shankar Kikkeri N, Nagalli S. Trigeminal neuralgia [Updated 2022 Jul 9]. StatPearls [Internet]. Treasure Island: StatPearls Publishing, 2023.
11. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. Lancet Neurol. 2014;13(9):924–35.
12. Obermann, M, Recent advances in understanding/managing trigeminal neuralgia. F1000Res. 2019;8.
13. Ostrowski H, Roszak J, Komisarek O. Botulinum toxin type A as an alternative way to treat trigeminal neuralgia: a systematic review. Neurol Neurochir Pol. 2019;53(5):327–34.
14. Johnson RW, Rice AS. Clinical practice. postherpetic neuralgia. N Engl J Med. 2014;371(16):1526–33.
15. Mallick-Searle T, Snodgrass B, Brant JM. Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. J Multidiscip Healthc. 2016;9:447–54.
16. Gruver C, Guthmiller KB. Postherpetic neuralgia. StatPearls [Internet]. StatPearls Publishing; 2023.
17. Forbes HJ, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. Pain. 2016;157(1):30–54.
18. Finnerup NB, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162–73.
19. Soliman N, et al. Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: a systematic review and meta-analysis. Lancet Neurol. 2025;24(5):413–28.
20. Dolphin AC. Voltage-gated calcium channels and their auxiliary subunits: physiology and pathophysiology and pharmacology. J Physiol. 2016;594(19):5369–90.
21. Matak I, et al. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019. https://doi.org/10.3390/toxins11080459.
22. Chamani G, et al. Botulinum toxin type A for the prevention of migraines: an umbrella review of systematic reviews. Toxins (Basel). 2026. https://doi.org/10.3390/toxins18010033.
23. 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.
24. Clark JM, et al. Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. J Med Libr Assoc. 2020;108(2):195–207.
25. Shea BJ, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
26. Hu X, et al. Efficacy and safety of Botulinum Toxin Type A in the treatment of trigeminal neuralgia: an update on systematic review with meta-analyses. Clin J Pain. 2024;40(6):383–92.
27. Bendtsen L, et al. European Academy of Neurology guideline on trigeminal neuralgia. Eur J Neurol. 2019;26(6):831–49.
28. Hary V, Schitter S, Martinez V. Efficacy and safety of botulinum A toxin for the treatment of chronic peripheral neuropathic pain: a systematic review of randomized controlled trials and meta-analysis. Eur J Pain. 2022;26(5):980–90.
29. Morra ME, et al. Therapeutic efficacy and safety of Botulinum Toxin A therapy in trigeminal neuralgia: a systematic review and meta-analysis of randomized controlled trials. J Headache Pain. 2016;17(1):63.
30. Siongco PRL, et al. Botulinum neurotoxin injections for muscle-based (dystonia and spasticity) and non-muscle-based (neuropathic pain) pain disorders: a meta-analytic study. J Neural Transm (Vienna). 2020;127(6):935–51.
31. Yang F, et al. Efficacy of 8 different drug treatments for patients with trigeminal neuralgia: a network meta-analysis. Clin J Pain. 2018;34(7):685–90.
32. Wen B, et al. Efficacy of different interventions for the treatment of postherpetic neuralgia: a Bayesian network meta-analysis. J Int Med Res. 2020;48(12):300060520977416.
33. Sridharan K, Sivaramakrishnan G. Interventions for refractory trigeminal neuralgia: a Bayesian mixed treatment comparison network meta-analysis of randomized controlled clinical trials. Clin Drug Investig. 2017;37(9):819–31.
34. Wu C-J, et al. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia. 2012;32(6):443–50.
35. Shehata HS, et al. Botulinum toxin-type A: could it be an effective treatment option in intractable trigeminal neuralgia? J Headache Pain. 2013;14(1):92.
36. Zúñiga C, et al. Acute treatment of trigeminal neuralgia with Onabotulinum toxin A. Clin Neuropharmacol. 2013;36(5):146–50.
37. Zhang H, Lian Y, Ma Y, Chen Y, He C, Xie N, et al. Two doses of botulinum toxin type A for the treatment of trigeminal neuralgia: observation of therapeutic effect from a randomized, double-blind, placebo-controlled trial. J Headache Pain. 2014;15(1):65. https://doi.org/10.1186/1129-2377-15-65.
38. Apalla Z, et al. Botulinum toxin A in postherpetic neuralgia: a parallel, randomized, double-blind, single-dose, placebo-controlled trial. Clin J Pain. 2013;29(10):857–64.

39. Xiao L, et al. Subcutaneous injection of Botulinum toxin A is beneficial in postherpetic neuralgia. Pain Med. 2010;11(12):1827–33.
40. Bagues A, et al. Neurobiological mechanisms of Botulinum neurotoxin-induced analgesia for neuropathic pain. Pharmacol Ther. 2024;259:108668.
41. Yang KY, et al. Antinociceptive effects of Botulinum toxin type A on trigeminal neuropathic pain. J Dent Res. 2016;95(10):1183–90.
42. Kesdogan AB, et al. Analgesic effect of Botulinum toxin in neuropathic pain is sodium channel independent. Neuropharmacology. 2024;253:109967.
43. Matak I, Rossetto O, Lackovic Z. Botulinum toxin type A selectivity for certain types of pain is associated with capsaicin-sensitive neurons. Pain. 2014;155(8):1516–26.
44. Val M, Manfredini D, Guarda Nardini L. Is botulinum toxin the future of orofacial pain management? Evidence and perspectives. Dent Med Probl. 2025;62(3):405–7.