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TIME COURSE OF BOTULINUM TOXIN ANALGESIA IN PERIPHERAL NEUROPATHIC PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Endang Ulupi Khoirunnisa[1*], Yessi Mekarsari[2], Sih Reka Prawidya[3]

***Correspondence**: drnisakcm@gmail.com*
[1]Catur Medika Clinic, Sukoharjo, Indonesia
[2]Waluyo Jati Primary Clinic, Surakarta, Indonesia
[3]Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

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ABSTRACT

Background: Peripheral neuropathic pain (PNP) is frequently refractory to systemic therapies. Botulinum toxin (BTX) has emerged as a targeted option, but its time course of analgesic effect remains incompletely defined.
Objective: To characterize the onset, peak, and durability of BTX analgesia in PNP.
Methods: A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted according to PRISMA guidelines. A search was performed on December 19, 2025, covering studies published from 2006 to 2025. Included etiologies comprised diabetic neuropathy, trigeminal neuralgia, postherpetic neuralgia, and other PNP conditions. Pain outcomes were synthesized across predefined time windows: early (≤4 weeks), intermediate (6–12 weeks), and late (≥24 weeks). Random-effects meta-analyses using standardized mean differences (SMDs) were conducted at approximately 4 and 12 weeks.
Results: Eighteen RCTs were included (n=916); four (n=129) and three (n=99) contributed to the 4- and 12-week meta-analyses, respectively. BTX-A significantly reduced pain versus placebo at 4 weeks (SMD −2.79, 95% CI −4.67 to −0.90; I^2 = 93%) and 12 weeks (SMD −2.54, 95% CI −4.55 to −0.53; I^2 = 92%). Analgesia began within 1–2 weeks and peaked at 6–12 weeks. Excluding one outlier reduced heterogeneity from I^2 = 92% to 55% while preserving significance. Evidence beyond 24 weeks was limited.
Conclusion: BTX-A demonstrates a time-dependent and etiology-specific analgesic effect, with onset within 1–4 weeks, peak at 6–12 weeks, and waning after 12–16 weeks. These findings inform patient counselling and reinjection planning, typically at approximately 3-month intervals.

Keywords: botulinum toxin, pain intensit, peripheral nerves, peripheral neuropathic pain, time-course analgesic response

Introduction

Peripheral neuropathic pain (PNP) is a prevalent and disabling chronic pain condition caused by injury or dysfunction of the peripheral nervous system.[1] Common etiologies include diabetic neuropathy (DN), postherpetic neuralgia (PHN), trigeminal neuralgia (TN), and post-surgical or post-traumatic nerve injury.[2–5] Although these conditions differ in pathophysiology, they share mechanisms including peripheral sensitization, ectopic neuronal activity, and neuroinflammation.[6–10] Despite multiple pharmacological options, systemic therapies, such as anticonvulsants, antidepressants, and opioids, often provide incomplete relief and cause dose-limiting adverse effects.[5] Consequently, interest has grown in targeted, non-systemic interventions with more favorable tolerability profiles.[11]

Botulinum toxin (BTX), a neurotoxic protein produced by the anaerobic bacterium Clostridium botulinum, comprises seven serotypes (A–G), among which BTX-A is the most widely used in clinical practice and has emerged as a promising targeted option for PNP.[12] Beyond its neuromuscular blocking effects, BTX-A inhibits the release of neurotransmitters and neuropeptides such as glutamate, substance P, and calcitonin gene-related peptide (CGRP). By cleaving synaptosomal-associated protein 25 (SNAP-25), BTX-A disrupts vesicular exocytosis at peripheral nerve terminals, reducing peripheral sensitization and nociceptive signaling. These mechanisms provide a rationale for its use across multiple neuropathic pain etiologies. The delayed onset of analgesia reflects the underlying biological processes at peripheral nerve terminals, including toxin internalization, SNAP-25 cleavage, and subsequent modulation of neuronal activity.[11–13]

Clinical and experimental evidence suggests that BTX analgesia begins within 1–2 weeks, peaks at 6–12 weeks,[14] and may persist for several months.[15,16] However, treatment response varies across neuropathic pain etiologies and injection protocols, and the lack of a clearly defined response timeline complicates clinical decision-making, particularly in scheduling repeat injections and setting patient expectations. Previous systematic reviews and meta-analyses assessed BTX efficacy across heterogeneous outcomes and follow-up periods,[15,17–21] but did not systematically characterize the time course of analgesic response using predefined intervals. Rather than establishing a universal timeline across all PNP conditions, this study aimed to identify shared time-course patterns of BTX analgesia while accounting for etiology-specific variation using predefined early (≤4 weeks), intermediate (6–12 weeks), and late (≥24 weeks) follow-up windows.

Methods

Research design

This systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and registered prospectively in PROSPERO (ID: 1276475). All data are included in this article and its supplementary materials.

Search Strategy

A systematic search of PubMed and Scopus was conducted on December 19, 2025, covering studies published from January 2006 to December 2025. The search combined Medical Subject Headings (MeSH) and keywords related to peripheral neuropathic pain (e.g., DN, PHN, TN, post-surgical neuropathy) and botulinum toxin (e.g., BTX-A/B). Additional relevant studies were identified through manual screening of other sources. Only English-language studies were included; grey literature was excluded.

Study Selection and Eligibility Criteria

Records were imported into Zotero and duplicates removed. Two reviewers (EUK and YM) independently screened the studies for eligibility, with disagreements resolved by a third reviewer (SRP). Eligible studies were RCTs enrolling adults (≥18 years) with PNP of any etiology. Interventions comprised any formulation of BTX, regardless of route or dose. Comparators included placebo/sham, systemic analgesics, local anesthetics, or other interventional pain treatments. The primary outcome was pain intensity, measured using validated scales.

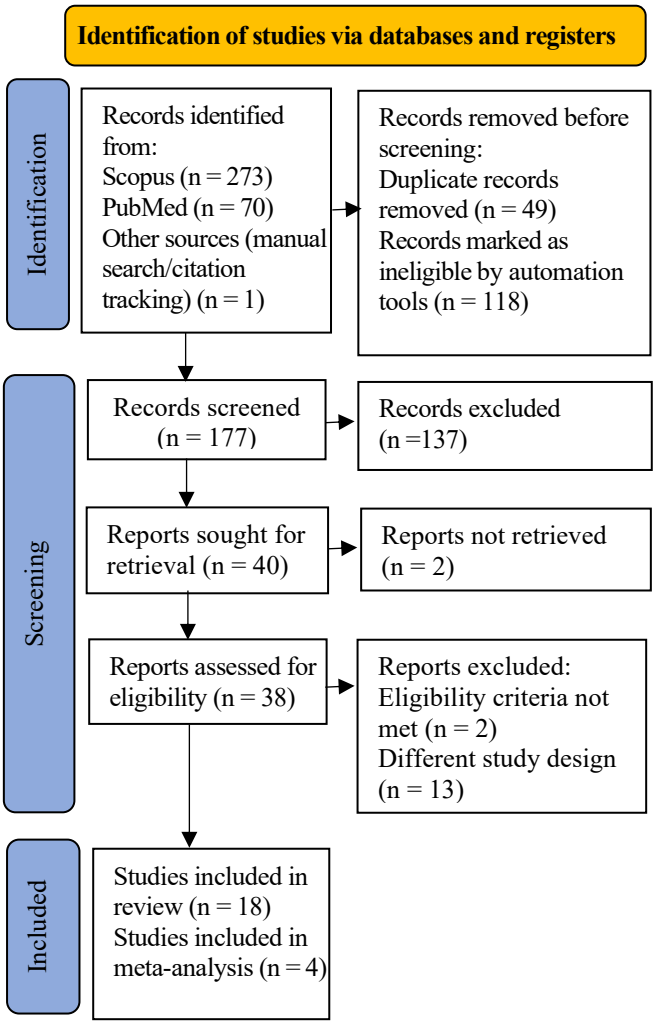

Figure 1. PRISMA 2020 flow chart

Data Extraction

Two reviewers independently extracted study characteristics, patient populations, interventions, injection sites, outcomes, and follow-up. Discrepancies were resolved by the third reviewer. Unavailable numerical data were digitized from figures at prespecified time points.

Risk of Bias Assessment

Risk of bias was assessed using the Cochrane RoB 2 tool across five domains. Each domain was rated as low risk, some concerns, or high risk.

Data Synthesis

Outcomes were synthesized across predefined time windows: early (≤4 weeks), intermediate (6–12 weeks), and late (≥24 weeks). Meta-analysis was conducted when ≥2 studies reported comparable outcomes; otherwise, findings were summarized narratively.

Statistical Analysis

Random-effects meta-analyses were conducted using standardized mean differences (SMDs) with 95% confidence intervals (CIs). Quantitative synthesis was performed at 4 and 12 weeks. Heterogeneity was assessed using I^2 and τ^2. Sensitivity analyses were performed by sequential trial exclusion. All analyses were conducted using Review Manager 5.4.1.

Results

A total of 344 records were identified through the literature search. After excluding non English publications, pre-2006 studies, and non original articles, 226 records remained. Deduplication yielded 177 unique records. Title/abstract screening reduced these to 40, and full text review identified 18 eligible RCTs (Figure 1). Four studies contributed to the ≤4 week meta analysis and three to the 6–12-week meta analysis. No trials reported extractable mean ± SD data beyond 24 weeks suitable for pooling.

Study Characteristics

Included trials enrolled adults with PNP of various etiologies. Pain was assessed using validated scales, and BTX was generally administered as a single intradermal (ID), subcutaneous (SC), or intramuscular (IM) injection (Table 1).

Time Course of Analgesic Response

Early analgesic effect (≤4 Weeks)

Several studies reported rapid analgesic onset within the first week.[22–30] Other studies documented onset within 2 weeks.[31–35] Two trials with single follow-up assessments reported analgesic benefit at weeks 3[36] and 4,[37] although earlier onset could not be determined due to the absence of prior measurements. Negative findings were limited to complex regional pain syndrome (CRPS), where no significant analgesic benefit was observed at 3 weeks.[38] Another study also reported no significant difference at week 4 (P = 0.29), although concurrent carbamazepine use may have influenced outcomes.[39] In subgroup analyses restricted to patients receiving carbamazepine (31 of 36 participants), differences approached but did not reach statistical significance ($P = 0.06$), indicating a possible delayed effect that became evident only at later time points.[39]

Four trials[31–34] provided pain intensity outcomes at approximately 4 weeks and were pooled in a random-effects meta-analysis. BTX-A significantly reduced pain versus placebo (SMD −2.79, 95% CI −4.67 to −0.90; P = 0.004), although heterogeneity was substantial ($I^2 = 93\%$) (Figure 2). Sensitivity analyses showed consistent results. Exclusion of Shehata et al. (2013) attenuated but preserved significance (SMD −1.38, 95% CI −2.60 to −0.15, P = 0.03; $I^2 = 90\%$), while excluding Restivo et al. (2018) increased the pooled effect (SMD −3.61, 95% CI −6.74 to −0.47; $P = 0.02$) with higher heterogeneity ($I^2 = 95\%$).[31,33] Removing two other trials preserved the direction of benefit, although confidence intervals remained wide (Supplementary Figures S1–S4).[34,32] Subgroup analyses by etiology or injection route were not performed due to insufficient studies within these categories.

Intermediate analgesic effect (6-12 Weeks)

Individual trials suggested that the intermediate phase represented maximal analgesic response to BTX. In DN, peak benefit occurred at 6 weeks,[33] 12 weeks,[22] and at both 4 and 8 weeks,[28] while another study[24] reported maximal benefit at week 4 with partial waning by week 12 despite persistent superiority over placebo. In TN, maximal benefit was observed across weeks 2–12, with peaks at 4–8 weeks,[30] 6–12 weeks,[35] and 12 weeks.[27,31] In PHN, analgesia persisted through week 12, with one study showing peak reduction at 8 weeks[32] and another demonstrating stable pain reduction from week 1 through week 24;[25] both also reported improvements in sleep. Notably, one study[26] that had shown significant benefit at week 1 reported that pain scores had risen again by week 12; nevertheless, values remained significantly lower than baseline, placebo, and lidocaine, confirming persistent yet attenuated benefit.

By contrast, a delayed effect was observed: at week 8, differences between BTX-A and placebo approached significance ($P = 0.07$), and in subgroup analyses restricted to patients receiving carbamazepine, the difference reached statistical significance ($P = 0.02$).[39] By week 12, pain reduction was significant overall ($P = 0.01$), with even stronger significance in the carbamazepine subgroup ($P = 0.007$).[39] Importantly, Safarpour et al. (2010) continued to show no analgesic benefit in CRPS at week 8, reinforcing the variability of BTX response across different neuropathic pain syndromes. [38]

Additional evidence from mixed or focal neuropathic pain populations likewise demonstrated sustained intermediate-phase benefit.[29,34] Peak analgesia was reported around weeks 12–14, while the lowest pain scores were observed at weeks 3, 4, 5, and 10, with further improvement after repeat injection at week 12.[29,34] Collectively, these findings indicate that

the intermediate period commonly captures maximal benefit, although the exact timing of peak response varies by etiology and study design.

The 12-week meta-analysis confirmed the sustained analgesic benefit of BTX-A during the intermediate phase. Three RCTs (n = 99) contributed to this analysis, showing significant pain reduction versus placebo (SMD −2.54, 95% CI −4.55 to −0.53; *P* = 0.01; Figure 3); however, the heterogeneity was high (I^2 = 92%).[31,33,34] The large effect size reported in one study substantially contributed to heterogeneity, possibly owing to the highly selected population with intractable idiopathic trigeminal neuralgia and the trial's small sample size.[31] Excluding this study reduced heterogeneity from I^2 = 92% to I^2 = 55% while preserving statistical significance (SMD −0.98, 95% CI −1.70 to −0.26; P = 0.007; Supplementary Figure S7). Excluding the other two studies yielded unstable pooled estimates with persistently high heterogeneity (Supplementary Figures S5–S6)[33,34]

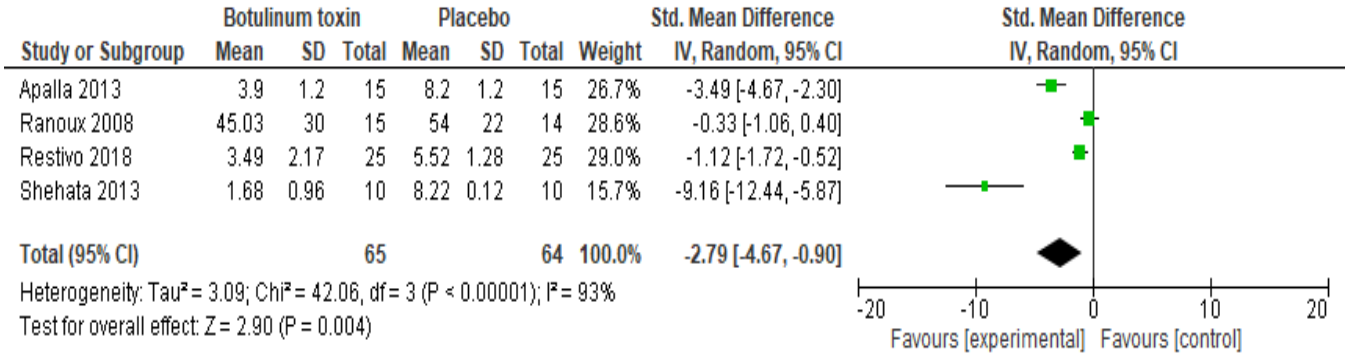

Figure 2. Meta-analysis of pain intensity in week 4

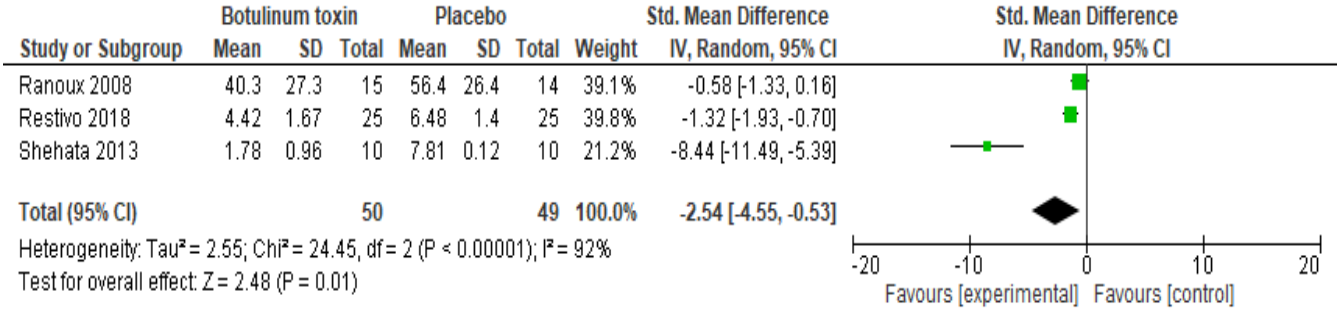

Figure 3. Meta-analysis of pain intensity in week 12

Table 1. Characteristics of the included studies

Author, Year (References)	Country	Diagnosis	Sample (n)	Intervention vs Control	Injection Site	Outcome	Frequency	Follow-up (weeks)	Drop-out
Diabetic Neuropathy (DN)									
Restivo 2018[3]	Italy	DN	50 (25/25)	BTX-A (Incobotulinumtoxin A 100 U) vs placebo	Intramuscular (IM) (gastrocnemius/foot flexor)	Brief Pain Inventory (BPI)	Single; repeat at 5 months (n=19)	1, 2, 4, 6, 8, 10, 12, 14, 16, 20	None
Gaber 2022[24]	Egypt	Painful DN	30 (10/10/10)	Duloxetine 60 mg daily vs gabapentin 300 mg BID vs BTX-A (50 U)	Intradermal (ID)	Visual Analogue Scale (VAS)	Single	1, 4, 12	None
Taheri 2020[37]	Iran	DN	141 (47/47/47)	BTX-A (150 U) one in foot vs BTX-A in both feet vs placebo	ID (sole)	VAS, Neuropathy Pain Scale (NPS)	Single	4	None
Ghasemi 2014[36]	Iran	DN	40 (20/20)	BTX-A (100 U/foot) vs placebo	ID (dorsum)	VAS	Single	3	None

Chen 2013[23]	Taiwan	DN	20 (10/10)	Onabotulinumtoxin A (50 U/foot) vs placebo	ID (dorsum of both feet)	Quantitative sensory testing (QST)	Single	1, 4, 8, 12	2
Yuan 2009[22]	Taiwan	DN	20 (10/10)	Onabotulinumtoxin A (50 U/foot) vs placebo	ID (dorsum of both feet)	VAS	Single	1, 4, 8, 12 (before cross-over)	2
Salehi 2019[28]	Iran	DN	32 (16/16)	Onabotulinumtoxin A (100 U/foot) vs placebo	ID (both feet)	VAS	Single	1, 4, 8, 12	None
Trigeminal Neuralgia (TN)									
Zhang 2017[27]	China	Classical TN	100 (50/50)	BTX-A 70–100 U single-dose vs 50–70 U repeated	ID/submucosal	VAS	Single or repeated	1, 4, 8, 12, 16, 20, 24	19
Shehata 2013[31]	Egypt	Intractable idiopathic TN	20 (10/10)	Onabotulinumtoxin A (5 U/site, 40–60 U total) vs placebo	Subcutaneous (SC) at trigger zones	VAS	Single	2, 4, 6, 8, 10, 12	None
Zunig 2013[39]	Argentina	Essential TN	36 (20/16)	Onabotulinumtoxin A (50-60 U) vs placebo	SC (branch territory)	VAS	Single	4, 8, 12	None
Wu 2012[35]	China	Classical TN	42 (22/20)	BTX-A (5 U/site, 75 U total) vs placebo	ID and/or submucosal	VAS	Single	1-12, weekly	2
Zhang 2014[30]	China	Classical TN	84 (27/29/28)	BTX-A 25 U vs 75 U vs placebo	ID and/or submucosal	VAS	Single	1-8, weekly	4
Post Herpetic Neuralgia (PHN) and Others									
Attal 2016[29]	France	Post-traumatic or postsurgical neuropathies, polyneuropathy, PHN	68 (34/34)	Onabotulinumtoxin A (up to 300 U) vs placebo	SC	Numeric Rating Scale (NRS)	Two administrations, 12 weeks apart	1-24, weekly	2
Chen 2022[25]	China	PHN	100 (50/50)	BTX-A (100 U) vs Pulsed Radiofrequency	SC multipoint injections	NRS	Single	1, 4, 12, 24 weeks	None
Apalla 2013[32]	Greece	PHN	30 (15/15)	Onabotulinumtoxin A (100 IU) vs placebo	SC in chessboard pattern	VAS	Single	2, 4, 6, 8, 10, 12, 16, 20, 24 weeks	None
Xiao 2010[26]	China	PHN	60 (20/20/20)	BTX-A (200 U) vs 0.5% lidocaine vs placebo	SC (dermatome)	VAS	Single	1 and 12 weeks	4
Ranoux 2008[34]	France	Chronic focal PNP with mechanical allodynia (PHN or posttraumatic/postoperative neuropathies)	29 (15/14)	BTX-A (20–190 U) vs placebo	ID (painful/allodynic area)	BPI	Single	1-24 weeks (weekly)	7
Safarpour 2010[38]	USA	Complex Regional Pain Syndrome (CRPS) with focal allodynia	14 (8 in RCT, 6 in open-label protocol)	Onabotulinumtoxin A (40–200 U) vs placebo	ID+ SC	BPI	Single	3 and 8 weeks	None

Late analgesic effect (≥24 weeks)

Evidence beyond 24 weeks was limited, precluding firm conclusions about long-term durability. One study provided the strongest evidence, showing analgesic decline after week 14 but persistent superiority over placebo at week 24.[34] In PHN, one trial demonstrated maintained pain relief and improved sleep at 24 weeks compared with baseline, with effects comparable to pulsed radiofrequency.[25] By contrast, another study reported benefit versus placebo up to week 14, but not at week 16.[33] Another study showed significant pain reduction through week 12; however, scores had begun to rise by that point, and follow up did not extend beyond 12 weeks.[24] Trials with scheduled reinjection at week 12 complicate interpretation, as analgesic effect was declining before reinjection but still lower than placebo at week 12.[29]

Risk of Bias Assessment

Risk of bias assessment using the Cochrane RoB 2 tool showed predominantly moderate methodological quality across the 18 included trials (Figure 4). Most studies were rated as having "some concerns," mainly due to selective reporting issues related to limited protocol availability or insufficient details on prespecified analyses. Concerns regarding the randomization process were also identified because of incomplete reporting of allocation concealment or sequence generation. In contrast, bias from outcome measurement was generally low, reflecting the use of validated pain scales and consistent assessment procedures. One study showed the highest overall risk of bias, with high-risk judgments across multiple domains, including randomization, deviations from intended interventions, missing outcome data, and selective reporting.

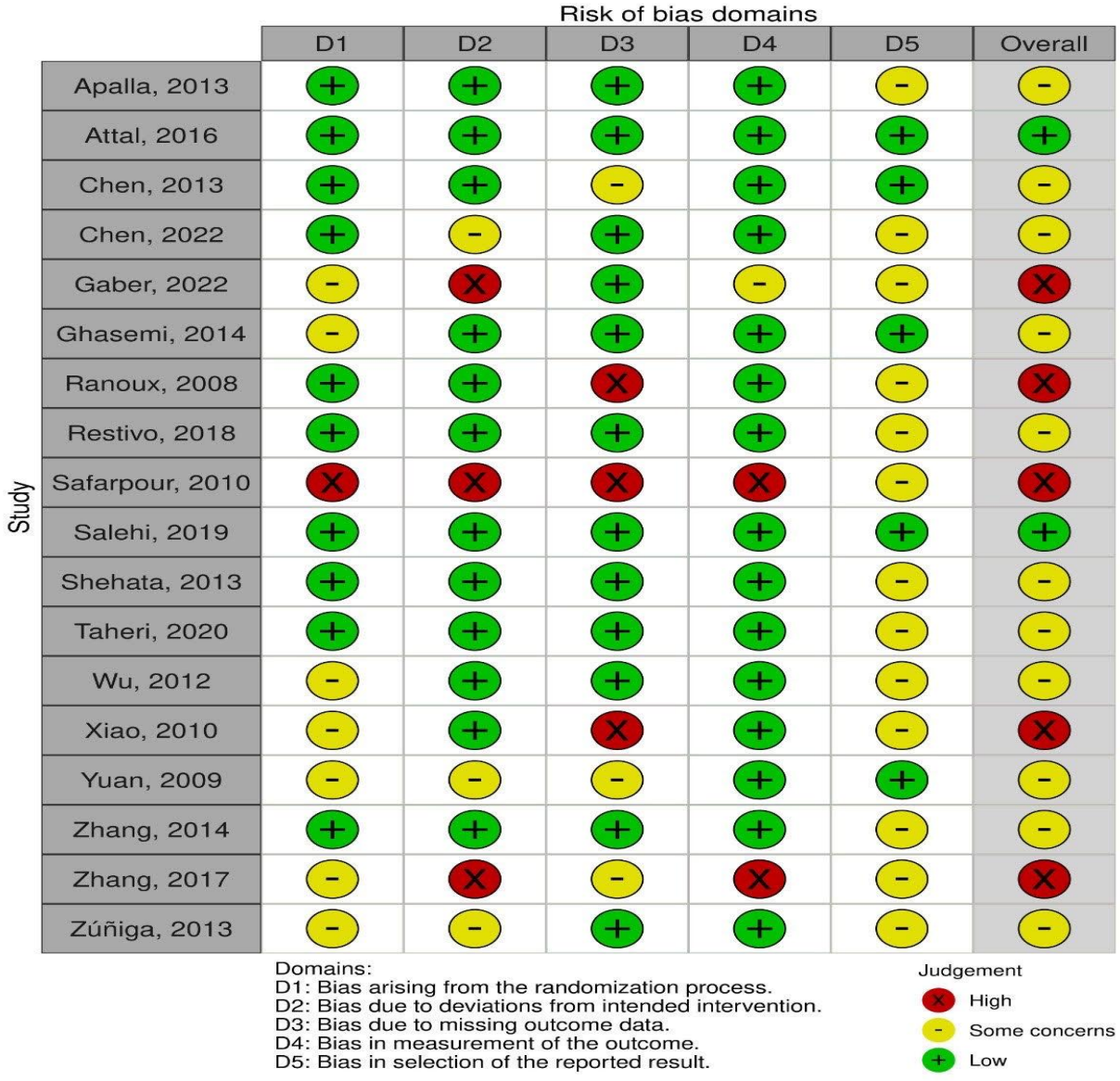

Figure 4. Risk of bias assessment using RoB 2

Discussion

This systematic review demonstrates a characteristic time-course pattern of analgesic response to BTX in PNP, with onset within 1–4 weeks, peak effect most commonly observed during the intermediate phase (6–12 weeks), and limited evidence regarding durability beyond 24 weeks. All trials meeting the inclusion criteria investigated BTX-A; no studies of other serotypes were identified. Although BTX-A is best known for its neuromuscular effects, clinical observations that pain relief may precede motor effects support a direct sensory mechanism.[40,41] The analgesic effects of BTX-A are primarily attributed to SNAP-25 cleavage and subsequent inhibition of nociceptive neurotransmitter release at peripheral sensory terminals.[11,12] By reducing the release of glutamate, substance P, and CGRP, BTX-A decreases peripheral sensitization and neuroinflammatory signaling relevant to TN, DN, and PHN.[11,13] Additional mechanisms, including modulation of transient receptor potential vanilloid-1 (TRPV1), retrograde transport, and microglial anti-inflammatory effects, may contribute to sustained analgesia.[13,42,43]

Across etiologies, the clinical signal was most evident in DN, TN, and PHN; by contrast, CRPS showed little or no benefit. The negative findings in CRPS were attributed by the authors to the complex pathophysiology of CRPS-related allodynia, the predominance of severe and advanced cases, and methodological factors including limited sample size, mixed study design, broad dosing ranges (40–200 units), and predominantly ID injection.[38] Although accumulating evidence suggests that BTX-A may also modulate central sensitization through retrograde transport and microglial effects,[44] the multifactorial mechanisms of CRPS including central sensitization, neuroinflammation, and autonomic dysregulation may contribute to greater variability and reduced treatment responsiveness compared with other neuropathic pain conditions.[45]

The early follow-up window generally demonstrated favorable analgesic responses to BTX-A, although the effect magnitude varied across studies and etiologies. Most trials reported clinically meaningful pain reduction within 1–2 weeks, and meta-analysis at approximately 4 weeks confirmed significant benefit versus placebo despite substantial heterogeneity. Beyond placebo-controlled trials, BTX-A also demonstrated clinically competitive efficacy versus active comparators. In one three-arm trial comparing BTX-A with duloxetine and gabapentin, all groups showed significant pain reduction by week 12, but only BTX-A demonstrated significant improvement at all follow-up time points, including the early phase.[24] BTX-A also showed analgesia comparable to pulsed radiofrequency for PHN while offering a substantial cost advantage,[25] and produced greater pain reduction than lidocaine during early follow-up, further supporting superiority over short-acting local anesthetics.[26] Taken together, these findings suggest that BTX-A analgesia may emerge within the first 4 weeks and remain clinically competitive with commonly used pharmacological and interventional therapies.

During the intermediate follow-up window (6–12 weeks), analgesic effects generally reached their peak, although timing and magnitude varied across studies and etiologies. Individual trials in DN, TN, and PHN demonstrated peak or sustained pain reduction within this period, with analgesic effects often maintained through week 12 despite some variability in peak timing. Even in the study where partial waning was observed by week 12, pain scores remained significantly lower than baseline and control comparators.[26] Importantly, the 12-week meta-analysis confirmed that BTX-A remained significantly more effective than placebo, with sensitivity analyses supporting persistence of analgesic benefit despite heterogeneity. Together, these findings suggest that the intermediate window captures the peak and sustained analgesic effects of BTX-A. Supporting this time-course pattern, a double-blind crossover study in painful diabetic polyneuropathy[23] demonstrated that ID onabotulinumtoxinA significantly improved tactile and mechanical pain thresholds on quantitative sensory testing from week 1 through week 12 versus saline, suggesting that modulation of peripheral sensory function may contribute to sustained analgesia during the intermediate phase.

The substantial heterogeneity (>90%) observed across pooled analyses likely reflects important differences in neuropathic pain pathophysiology and patient populations among included studies. TN represents a highly localized neuropathic pain syndrome confined to the trigeminal nerve distribution,[46] whereas DN typically involves diffuse, length-dependent peripheral nerve dysfunction,[47] and PHN involves localized dermatomal nerve injury caused by herpes zoster virus reactivation.[48] These differences in anatomical distribution and underlying mechanisms may influence toxin distribution, nociceptive processes, and responsiveness to BTX-A, particularly given the limited diffusion of botulinum toxin from the injection site (approximately 30–45 mm),[49] which may have differential implications for localized versus more widespread neuropathic pain conditions. Heterogeneity may also reflect variation in injection techniques (ID, SC, IM), dosing regimens, and injection sites.

A key contributor to this heterogeneity was the study.[31] The marked influence of this trial on pooled estimates highlights the impact that individual studies

may exert in meta-analyses with limited sample sizes. The exceptionally large effect size observed in this study (SMD −9.16) may reflect its highly selected population of patients with intractable idiopathic trigeminal neuralgia and small sample size. Sensitivity analysis excluding this study reduced heterogeneity from I^2 = 92% to I^2 = 55% while preserving statistical significance, suggesting that the overall analgesic benefit of BTX-A during the intermediate phase remained evident despite attenuation of pooled effect magnitude. Notably, findings from the supplementary analyses similarly demonstrate that, after exclusion of this outlier, the remaining trials show a more homogeneous and moderate analgesic effect, supporting a more stable estimate of treatment benefit. Accordingly, the pooled estimates should be interpreted with caution and are likely to reflect general trends rather than precise effect sizes.

Evidence regarding the long-term durability of BTX-A analgesia beyond 24 weeks remains limited, as few placebo-controlled trials reported outcomes at this time point. Available data suggest that although BTX-A effects tend to decline after the intermediate phase, pain relief may persist up to 24 weeks in selected patients, with some studies showing continued superiority over placebo[34] or comparable efficacy to pulsed radiofrequency.[25] However, earlier attenuation of benefit, limited follow-up, and scheduled reinjection complicate interpretation. Overall, while BTX-A analgesia may extend up to 24 weeks in some patients, the durability of a single injection remains uncertain and warrants further investigation.

This time-course pattern aligns with the known pharmacodynamics of BTX-A. The peak clinical effect occurring between 6 and 12 weeks parallels maximal SNAP-25 cleavage and suppression of neuropeptide exocytosis.[16,40] Effects generally decline thereafter, likely reflecting the reversible action of BTX-A and compensatory neuronal sprouting.[14,15,50,51] Nevertheless, evidence from PHN and focal neuropathic pain suggests that some patients may sustain analgesia to 24 weeks or beyond, possibly reflecting downstream modulation of inflammatory pathways or central sensitization.[25,34] These mechanistic considerations may help explain the sustained analgesic response observed in selected patients despite overall attenuation over time.

This review has several limitations, including small sample sizes, heterogeneity in etiology, dosing, and follow-up, limited long-term data, and methodological concerns reflected by RoB 2 assessments. The absence of studies investigating BTX-B or other serotypes further limits generalizability beyond BTX-A. In addition, reliance on discrete time points may obscure finer variations in analgesic response across follow-up periods. Despite these limitations, this systematic review provides a structured synthesis of the time course of BTX-A analgesia across PNP conditions. By using predefined early, intermediate, and late windows, the analysis offers a pragmatic framework for anticipating treatment response, counseling patients, and planning reinjection intervals. Future studies should enroll larger and more diverse populations and use standardized protocols with narrower dosing ranges. Head-to-head trials comparing injection techniques (ID, SC, and IM) are needed to define optimal delivery strategies. Finally, longer-term studies beyond 24 weeks are essential to evaluate durability and long-term safety across neuropathic pain conditions.

Conclusion

Botulinum toxin type A demonstrates a time-course profile of analgesic effect that is both time-dependent and etiology-specific in peripheral neuropathic pain, with onset within 1–4 weeks, peak efficacy at 6–12 weeks, and waning after 12–16 weeks. These findings have important clinical implications for managing patient expectations and planning repeat injections, which are typically administered at approximately 3-month intervals. Analgesic benefit was observed in conditions such as trigeminal neuralgia, postherpetic neuralgia, and diabetic neuropathy, whereas no clear efficacy was demonstrated in complex regional pain syndrome. Future studies should prioritize standardized administration protocols, including injection technique and dosing tailored to specific etiologies, to reduce heterogeneity and optimize treatment outcomes.

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Declaration of Interests

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

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