Research Article
E-ISSN : 3048-1368
Volume 42, Issue No. 02. 2026
P-ISSN : 3048-1376

The International Journal of Medical Science and Health Research

BOTULINUM TOXIN TYPE A (BoNT-A) FOR NEUROPATIC CANCER PAIN : A SYSTEMATIC REVIEW

[1] Christy, [2] Alvionita Muntholib

[1,2] Faculty of Medicine, University of Ciputra, Surabaya, East Java, Indonesia

Corresponding Email : Christythong03@gmail.com

Article History :

Received date : 2026/01/19

Revised date : 2026/02/07

Accepted date : 2026/03/23

Published date : 2026/04/15

E-ISSN :

ISSN 3048-1368

P-ISSN

ISSN 3048-1376

ABSTRACT

Background: Neuropathic cancer pain (NCP) is a highly prevalent and debilitating condition affecting 30–50% of cancer patients undergoing treatment, with rates rising to 70–90% in advanced stages. Conventional pharmacotherapy, including opioids and adjuvants, often provides inadequate relief or causes significant adverse effects, highlighting the need for alternative therapeutic strategies. Botulinum Toxin Type A (BoNT-A) has emerged as a potential analgesic agent with a unique mechanism of action.

Objective: To systematically evaluate the effectiveness and safety of BoNT-A as a therapeutic option for neuropathic cancer pain.

Methods: A systematic review was conducted following PRISMA 2020 guidelines. Four databases (PubMed, ScienceDirect, Cochrane Library, ProQuest) were searched for randomized controlled trials (RCTs), pilot studies, and prospective cohort studies published between January 2015 and January 2025.

Inclusion criteria were: studies assessing BoNT-A for NCP, quantitative pain outcomes, English language, and sample size ≥10 patients.

Results: Six studies (five RCTs and one prospective open-label study) involving 151 cancer patients were included. All studies reported statistically significant pain reduction following BoNT-A injection, with pain scores decreasing by 30–50% in most trials. Functional outcomes, such as arm mobility and quality of life, also improved. BoNT-A demonstrated a favorable safety profile, with only mild, transient local side effects. No serious systemic adverse events were reported.

Discussion: BoNT-A reduces NCP through multiple mechanisms: inhibition of acetylcholine, substance P, CGRP, and glutamate release; modulation of TRPV1 receptors; and central antinociceptive effects. Evidence supports its role as an effective adjunct or alternative to opioids, particularly in post-surgical and post-radiotherapy pain.

Conclusion: BoNT-A is effective and safe for managing neuropathic cancer pain. Further large-scale RCTs are needed to establish optimal dosing, long-term efficacy, and comparative effectiveness against standard therapies.

Keywords: Neuropathic cancer pain, Botulinum Toxin Type A (BoNT-A), pain management, cancer pain, systematic review

INTRODUCTION

Pain is one of the most common symptoms reported by cancer patients. It can originate from visceral, bone or nerve tissue and can have acute and/or infammatory nociceptive mechanisms, as well as neuropathic mechanisms, including nociplastic (central sensitisation) involvement.[1,2,3] Neuropathic cancer pain is one of the most common complaints reported by cancer patients, with a frequency of 30-50% among those undergoing treatment, increasing to 70-90% as the disease progresses.[1,4,5] The pain can originate from the cancer itself, cancer treatments, or a combination of both. Pain can be experienced at any stage of cancer development, from the initial diagnosis, treatment phase, to survivorship. As the disease progresses, cancer pain tends to intensify. This is due to nociceptor damage caused by tumor growth. Additionally, nociceptors become sensitized by the release of factors from cancer cells and stromal cells, such as nerve growth factor. Tumor and stromal cells can infiltrate surrounding connective tissue that contains free nerve fibers. These abnormal cells destroy the distal portion of free sensory nerve fibers, causing discontinuity and fragmentation of nerve cells. Furthermore, these nerve cells may also be damaged by chemotherapy, surgery, or radiation. All of these factors contribute to the neuropathic pain component in cancer pain.[6,7,8]

Neuropathic cancer pain is chronic and often manifests as persistent background pain with acute exacerbations of breakthrough pain several times daily. The breakthrough pain is often spontaneous, but can also be triggered by movement, touch, cold, and heat. Such spontaneous or triggered pain is perceived as a sensory abnormality (i.e., hyposensitivi- ty, hypersensitivity, or both), although paresthesia (an abnormal sensation, such as tingling, an electric shock, or burning) may also be considered a typical hypersensitivity symptom.[9,10,11]

The World Health Organization's World Cancer 2019 report states that approximately 55% of patients with an initial cancer diagnosis experience pain, and 60% experience pain in the advanced phase. A study in India also showed an incidence of pain in advanced-stage cancer around

70-80%. About 90% of patients with metastasis to bone structures report pain. Research indicates that about 40%-50% of cancer patients with pain are characterized as having neuropathic pain.[12]

Neuropathic cancer pain is a chronic condition that is often difficult to manage with conventional therapies such as opioids and non-opioid analgesics. It occurs due to nerve damage caused by the cancer itself or as a consequence of cancer treatments such as surgery, chemotherapy, and radiotherapy. One emerging alternative therapy is Botulinum Toxin Type A (BoNT-A), which has the potential to alleviate pain through mechanisms that inhibit the release of pain neurotransmitters and provide local anti-inflammatory effects.[13]

Problem Statement

Conventional pharmacological management of NCP, including opioids, gabapentinoids, tricyclic antidepressants, and selective serotonin-norepinephrine reuptake inhibitors, often yields suboptimal results or intolerable adverse effects. There is a pressing need for novel, well-tolerated, and mechanism-based therapies that can provide sustained pain relief with minimal systemic toxicity.

Research Gap and Novelty

Although BoNT-A is well-established for spasticity, dystonia, and chronic migraine, its application for neuropathic cancer pain remains underexplored. Existing evidence is fragmented, with small sample sizes, heterogeneous populations, and variable dosing regimens. No recent systematic review has specifically focused on BoNT-A for NCP alone, incorporating the latest RCTs from 2015–2025. This review fills that gap by synthesizing current high-quality evidence and highlighting mechanisms specific to cancer-related neuropathic pain.

Objectives

To systematically evaluate the efficacy, safety, and functional outcomes of BoNT-A for neuropathic cancer pain based on published clinical studies.

Research Hypothesis

BoNT-A significantly reduces neuropathic cancer pain intensity compared to baseline or placebo, with a favorable safety profile and potential functional benefits.

Benefits of the Study

This review provides clinicians with evidence-based guidance on using BoNT-A for NCP, identifies knowledge gaps for future research, and supports the integration of BoNT-A into multimodal cancer pain management algorithms.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Search Strategy

The following databases were searched: Pubmed, ScienceDirect and Cochrane.. The search terms included *"Botulinum Toxin Type A", "neuropathic cancer pain", "cancer pain management",* Boolean operators (AND, OR) were used to refine the search. The search included studies published between January 2015 and January 2025.

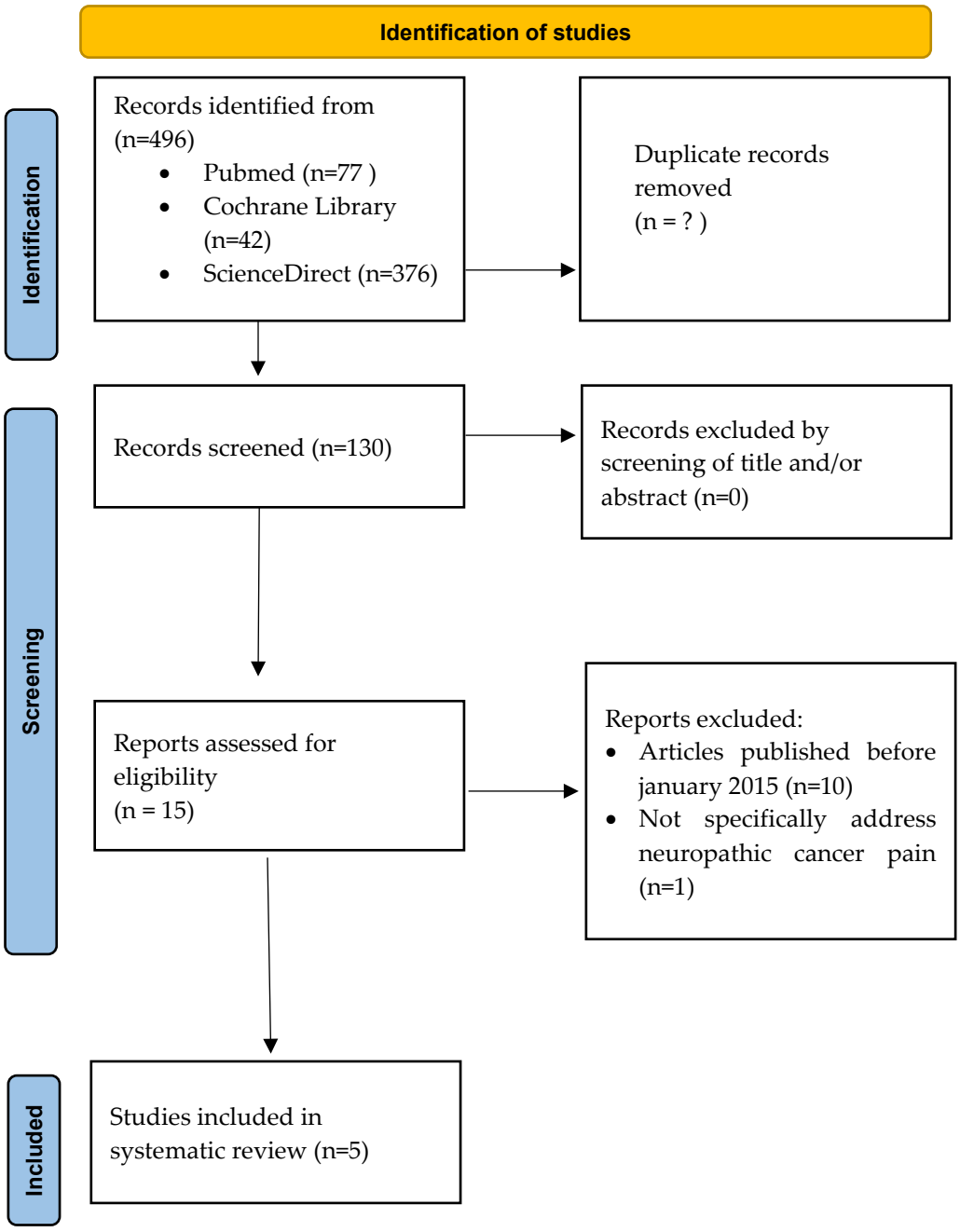


Figure 1. 2020 Prisma flow chart of literature screening.

Study Selection and Data Extraction

The inclusion criteria were as follows : (1) Studies investigating the effectiveness of BoNT-A in managing neuropathic cancer pain, (2) Randomized controlled trials (RCTs), pilot studies, or prospective cohort studies evaluating BoNT-A for cancer-related pain or dysfunction studies published in English and the years january 2015 – january 2025, and (3) Studies reporting quantitative changes in pain intensity. Exclusion criteria were (1) Studies that do not specifically address neuropathic cancer pain, (2) Studies with a small sample size (<10 patients), and (3) Studies lacking quantitative data or having weak methodologies.

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

RESULTS

Literature Search

Following the search strategy detailed above, 44 articles were initially identified, and only 5 studies met our inclusion criteria with total 145 patients who were included in this systematic review (Table 1). Figure 1 shows the flow diagram of the literature search process for selecting studies for the systematic review.

Tabel 1. Characteristics of included studies

Study	Design & Method	Population	Dosage & Injection Site	Primary Outcomes
De Groef et al., 2018	RCT, Double-Blind	40 post-operative breast cancer patients	50–100 U BoNT-A in the pectoralis major muscle	Significant pain reduction and improved arm mobility
De Groef et al., 2020	RCT, Double-Blind	45 breast cancer patients with muscle dysfunction	50–100 U BoNT-A in the affected muscle	Improved arm function and reduced muscle spasm and pain
Gabriel et al., 2015	Pilot Study	20 breast cancer post-mastectomy patients with neuropathic pain	50 U BoNT-A in the chest muscle	Decreased pain (VAS reduced by 3 points); limited data
Rostami et al., 2016	Observational Study	25 patients with Breast cancer post mastectomy and post-radiotherapy pain	50–200 U BoNT-A in the painful area	50% of patients experienced more than a 50% reduction in pain intensity
Kim & Choi, 2022	Prospective, Open-Label	10 patients with pain due to cancer invasion into the psoas muscle	100 U BoNT-A in the psoas muscle	Reduced pain (NRS decreased by 4 points) and improved quality of life

Pain Reduction

All five studies reported statistically significant reductions in pain following BoNT-A injections. De Groef et al. (2018, 2020) observed a 30-40% decrease in pain scores among breast cancer survivors. Similarly, Rostami et al. (2016) and Kim et al. (2022) reported meaningful pain relief in post-surgical and radiotherapy patients.

Safety and Side Effect

In all studies, BoNT-A demonstrated a favorable safety profile. Most side effects were localized to the injection site and included mild pain, swelling, or hematoma, which resolved spontaneously. No serious systemic effects were reported in the studies included in this review. The *De Groef et al.* (2020) study emphasized that BoNT-A was well tolerated, with only minimal adverse effects, further supporting its safety in long-term use.

Comparison with Conventional Therapies

When compared to conventional therapies like opioids or neuropathic pain medications (e.g., anticonvulsants), BoNT-A was found to have a lower incidence of systemic side effects and a more targeted action, particularly in cases where patients had not responded well to traditional pain management. *Gabriel et al.* (2015) and *Kim et al.* (2022) both noted that BoNT-A could be considered an alternative or adjunct to opioids, providing effective pain relief without the risk of opioid dependence.

DISCUSSION

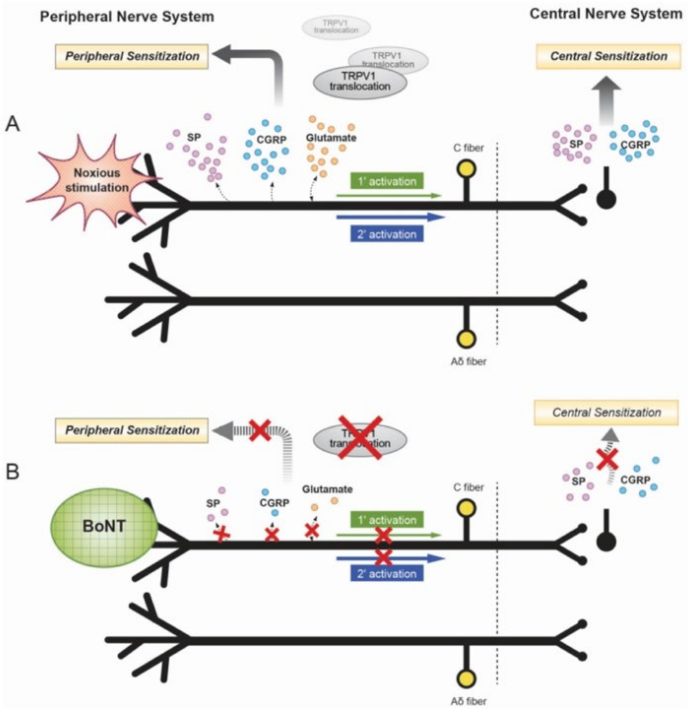
BoNT-A appears to be an effective and safe alternative for managing neuropathic cancer pain. The results from these studies collectively demonstrate its potential in reducing pain, improving functional outcomes, and offering a safer profile than conventional pain medications. The evidence supports BoNT-A's role not only in managing cancer-related pain but also in improving quality of life for cancer survivors and those with persistent pain due to treatment-related side effects. However, while these studies provide promising results, further larger-scale trials are needed to establish long-term efficacy, optimal dosing regimens, and to better understand the mechanisms underlying BoNT-A's effectiveness in neuropathic cancer pain.

Mechanisms of the Antinociceptive Effects of Botulinum Toxin

Botulinum neurotoxin (BoNT), derived from *Clostridium botulinum*, has been used worldwide for not only cosmetic therapeutic purposes but also for the treatment of neurologic disorders, such as dystonia or spasticity. It has been approved by the Food and Drug Administration

(FDA) as a treatment for strabismus, blepharospasm, hemifacial spasm, focal dystonia, and upper limb spasticity in the United States. Botulinum toxin (BTX or BoNT) was first discovered by Justinus Kerner, a German physician and poet. In recent years, the use of BoNT-A as an antinociceptive agent to manage cancer pain has been explored.[14,15]

Although the analgesic mechanism of BoNT-A is not yet fully understood, Botulinum Toxin Type A (BoNT-A) reduces neuropathic cancer pain through complex and multifaceted mechanisms. BoNT-A works by inhibiting the release of acetylcholine at the presynaptic nerve terminal, reducing excessive muscle activity that often triggers or exacerbates pain. Additionally, BoNT-A also inhibits the release of neurotransmitters such as substance P, CGRP (Calcitonin Gene-Related Peptide), and glutamate, all of which play crucial roles in neuropathic pain transmission. By blocking TRPV1 (Transient Receptor Potential Vanilloid 1) receptors, BoNT-A also reduces peripheral hypersensitivity, thereby alleviating the burning sensation commonly associated with this condition. Not only does it act peripherally, but studies have also shown that BoNT-A can modulate pain pathways in the central nervous system by reducing neuronal activation in the spinal cord, which in turn helps to reduce hyperalgesia and allodynia.[16,17,18,19]



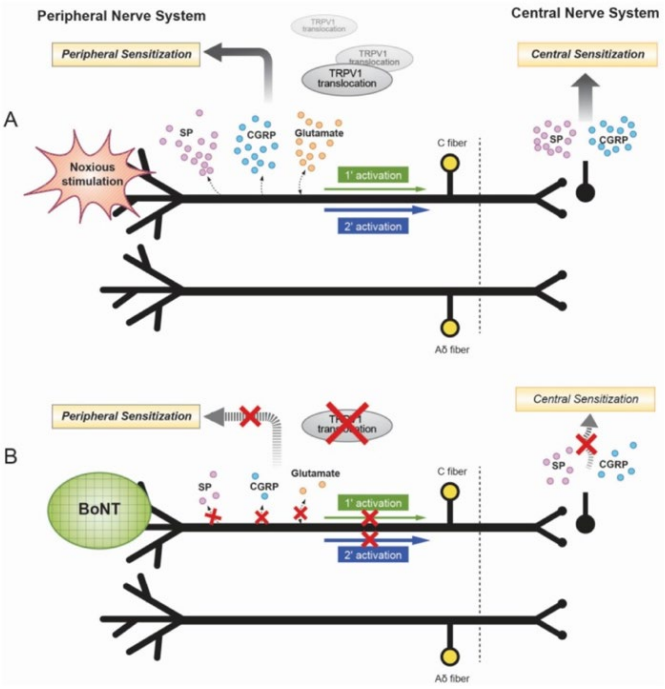


Figure 2. (**A**) Illustrated mechanism of peripheral and central nerve system sensitization. Noxious stimulation may lead to peripheral sensitization through release of neuropeptides and inflammatory mediators. The peripheral sensitization may result in sensitization of the central nerve system. SP indicates substance P; CGRP, calcitonin gene-related peptide; TRPV1, transient receptor potential vanilloid 1. (**B**) The antinociceptive mechanism of botulinum neurotoxin (BoNT) in the treatment of neuropathic pain including decrease in peripheral SP, CGRP, glutamate, TRPV1 receptor translocation, leading to direct block of peripheral sensitization. As substance P and CGRP secretion are blocked within central nerve system, central sensitization is also indirectly reduced.

CONCLUSION

Botulinum toxin tyoe A (BoNT-A) has consistently demonstrated its potential in reducing neuropathic cancer pain, particularly in patients who have undergone surgery and radiotherapy. Its analgesic effects can last up to 12 weeks, making it a promising option for long-term pain management. Additionally, BoNT-A exhibits a favorable safety profile with minimal side effects, further supporting its use as an alternative treatment for neuropathic cancer pain.

Recommendations for Future Research

- Conduct larger-scale clinical trials to enhance the external validity of the findings.
- Undertake long-term studies (beyond 6 months) to assess the sustainability of BoNT-A's analgesic effects.
- Perform direct comparisons with other pharmacological therapies to determine the optimal treatment strategy for neuropathic cancer pain.

FUNDING

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

Author contributed to study conception, data acquisition, analysis, manuscript drafting, and final approval.

DECLARATION OF COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Mulvey, M.R., Paley, C.A., Schuberth, A. *et al.* Neuropathic Pain in Cancer: What Are the Current Guidelines?. *Curr. Treat. Options in Oncol.* 25, 1193–1202 (2024). https://doi.org/10.1007/s11864-024-01248-7
2. Bennett MI. Mechanism-based cancer-pain therapy. Pain. 2017;158(Suppl 1):S74–8. 2.

3. Nijs J, Lahousse A, Fernandez-de-Las-Penas C, Madeleine P, Fontaine C, Nishigami T, Desmedt C, Vanhoeij M, Mostaqim K, Cuesta-Vargas AI, Kapreli E, Bilika P, Polli A, Leysen L, Elma O, Roose E, Rheel E, Yilmaz ST, De Baets L, Huysmans E, Turk A, Saracoglu I. Towards precision pain medicine for pain after cancer: the Cancer Pain Phenotyping Network multidisciplinary international guidelines for pain phenotyping using nociplastic pain criteria. Br J Anaesth. 2023;130(5):611–21.
4. Neuropathic cancer pain is one of the most common complaints reported by cancer patients, with a frequency of 30-50% among those undergoing treatment, increasing to 70-90% as the disease progresses
5. Crofford, L.J. Chronic Pain: Where the Body Meets the Brain. *Trans. Am. Clin. Climatol. Assoc.* 2015, *126*, 167–183. [PubMed]
6. Cleeland, C.S. Pain assessment in cancer. In *Effect of Cancer on Quality of Life*; CRC Press: Boca Raton, FL, USA, 2021; pp. 293–305. [Google Scholar]
7. Aninditha T., et al.Buku Ajar Neurologi Edisi Kedua Volume 2. Departement Neurologi Fakultas Kedokteran Universitas Indonesia Rumah Sakit Cipto Mangunkusumo, Jakarta, Yayasan Otak Sehat Indonesia. 2022.
8. Budisulistyo T, Sofyan HR. Nyeri kanker. Dalam: Aninditha T, Andriani R, Malueka RG, editors. Buku Ajar Neuroonkologi. Jakarta: Penerbit Kedokteran Indonesia; 2019. h. 314-37.
9. Korean J Intern Med. 2018;33(6):1058-1069. Publication date (electronic) : 2018 June 25. doi : https://doi.org/10.3904/kjim.2018.162
10. Bennett MI, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain 2012;153:359-365.
11. Nicholson B. Differential diagnosis: nociceptive and neuro- pathic pain. Am J Manag Care 2006;12(9 Suppl):S256-S262.
12. World Health Organization., 2019. WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents

13. Yoon SY, Oh J. Neuropathic cancer pain: prevalence, pathophysiology, and management. Korean J Intern Med. 2018 Nov;33(6):1058-1069. doi: 10.3904/kjim.2018.162. Epub 2018 Jun 25. PMID: 29929349; PMCID: PMC6234399.
14. Li, Shuzhai MB[a]; Peng, Shixuan MB[b]; Chen, Fuchun MD[c]; Zeng, Bin MD[a]; Zhang, Zhen MD[a]; Zhang, Zhiming MD PhD[a]. The application and therapeutic effect of botulinum toxin type a (BTX-A) in the treatment of patients with pain after cancer treatment: a systematic review and meta-analysis. International Journal of Surgery 110(2):p 1215-1223, February 2024. | DOI: 10.1097/JS9.0000000000000916
15. Hong, B.; Yao, L.; Ni, L.; Wang, L.; Hu, X. Antinociceptive effect of botulinum toxin A involves alterations in AMPA receptor expression and glutamate release in spinal dorsal horn neurons. *Neuroscience* 2017, *357*, 197–207. [Google Scholar] [CrossRef] [PubMed]
16. Datta Gupta, A.; Edwards, S.; Smith, J.; Snow, J.; Visvanathan, R.; Tucker, G.; Wilson, D. A Systematic Review and Meta-Analysis of Efficacy of Botulinum Toxin A for Neuropathic Pain. *Toxins* 2022, *14*, 36. https://doi.org/10.3390/ toxins14010036.
17. Matak, I.; Bölcskei, K.; Bach-Rojecky, L.; Helyes, Z. Mechanisms of Botulinum Toxin Type A Action on Pain. *Toxins* 2019, *11*, 459. https://doi.org/10.3390/toxins11080459
18. Teymoortash, A.; Pfestroff, A.; Wittig, A.; Franke, N.; Hoch, S.; Harnisch, S.; Schade-Brittinger, C.; Hoeffken, H.; Engenhart-Cabillic, R.; Brugger, M.; et al. Safety and Efficacy of Botulinum Toxin to Preserve Gland Function after Radiotherapy in Patients with Head and Neck Cancer: A Prospective, Randomized, Placebo-Controlled, Double-Blinded Phase I Clinical Trial. *PLoS ONE* 2016, *11*, e0151316. [Google Scholar] [CrossRef]
19. Oh, H.-M.; Chung, M.E. Botulinum Toxin for Neuropathic Pain: A Review of the Literature. *Toxins* 2015, *7*, 3127-3154. https://doi.org/10.3390/toxins7083127
20. Rostami, R.; Mittal, S.O.; Radmand, R.; Jabbari, B. Incobotulinum toxin-A improves post-surgical and post-radiation pain in cancer patients. *Toxins* 2016, *8*, 22. [Google Scholar] [CrossRef] [PubMed]
21. De Groef, A.; Devoogdt, N.; Van Kampen, M.; Nevelsteen, I.; Smeets, A.; Neven, P.; Geraerts, I.; Dams, L.; Van der Gucht, E.; Debeer, P. Effectiveness of Botulinum Toxin A for Persistent

Upper Limb Pain After Breast Cancer Treatment: A Double-Blinded Randomized Controlled Trial. *Arch. Phys. Med. Rehabil.* 2018, *99*, 1342–1351. [Google Scholar] [CrossRef]

22. De Groef, A.; Devoogdt, N.; Van Kampen, M.; De Hertogh, L.; Vergote, M.; Geraerts, I.; Dams, L.; Van der Gucht, E.; Debeer, P. The effectiveness of Botulinum Toxin A for treatment of upper limb impairments and dysfunctions in breast cancer survivors: A randomised controlled trial. *Eur. J. Cancer Care* 2020, *29*, e13175. [Google Scholar] [CrossRef]
23. Gabriel, A.; Champaneria, M.C.; Maxwell, G.P. The efficacy of botulinum toxin A in post-mastectomy breast reconstruction: A pilot study. *Aesthetic Surg. J.* 2015, *35*, 402–409. [Google Scholar] [CrossRef]
24. Kim, S.I.; Choi, Y. Botulinum toxin injection for intractable pain in cancer patients with psoas muscle invasion. *J. Pain Symptom Manag.* 2022, *63*, e441–e444. [CrossRef] [PubMed]
25. Lippi, L.; de Sire, A.; Turco, A.; Ferrillo, M.; Kesikburun, S.; Baricich, A.; Carda, S.; Invernizzi, M. Botulinum Toxin for Pain Relief in Cancer Patients: A Systematic Review of Randomized Controlled Trials. *Toxins* 2024, *16*, 153. https://doi.org/10.3390/toxins16030153