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Coordinated Neuroimmune-Informed Multimodal Therapy for Refractory Post-Mastectomy Neuropathic Pain: A Case Report

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Abstract

Post-mastectomy pain syndrome (PMPS) is a persistent neuropathic condition affecting a substantial proportion of breast cancer survivors and is frequently refractory to standard pharmacologic and interventional therapies. Chronic postsurgical pain in this population is increasingly recognized as multifactorial, involving peripheral nerve injury, sustained inflammatory signaling, central sensitization, and stress-related amplification.

We report the case of a 52-year-old woman with Stage I estrogen receptor–positive breast cancer who developed severe, persistent neuropathic pain following bilateral mastectomy complicated by postoperative infection, sepsis, tissue expander removal, delayed reconstruction, impaired wound healing, and upper-extremity lymphedema. Her symptoms remained poorly controlled despite opioid therapy, topical agents, structured rehabilitation, and multiple pain-management consultations. She expressed a desire to discontinue opioid analgesics and avoid further invasive procedures.

Approximately eight months after surgery, a coordinated neuroimmune-informed multimodal regimen was initiated, combining thymosin alpha-1, low-dose naltrexone, and sublingual THC/CBD alongside structured supportive interventions. The intervention was implemented as a 12-week adjunctive program within routine clinical care. This strategy was selected to address overlapping inflammatory, neuroimmune, and stress-related contributors to persistent pain.

The patient experienced sustained and clinically meaningful improvement, including substantial reduction in neuropathic pain intensity, decreased tactile allodynia, improved sleep continuity, enhanced functional capacity, and sustained opioid discontinuation without observed adverse effects. Symptom stabilization was maintained during two months of structured post-intervention follow-up prior to patient-directed transition back to her primary oncology and medical teams.

Although causality cannot be established in a single case, this observation suggests that coordinated, mechanism-informed multimodal strategies may warrant systematic investigation for refractory PMPS within breast cancer survivorship care.

Keywords: Post-mastectomy pain syndrome; Neuropathic pain; Chronic postsurgical pain; Breast cancer survivorship; Thymosin alpha-1; Low-dose naltrexone; Cannabinoids; Neuroinflammation; Opioid-sparing therapy; Integrative oncology

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Introduction

Chronic neuropathic pain following mastectomy, commonly referred to as post-mastectomy pain syndrome (PMPS), remains a significant survivorship challenge in breast cancer care [1]. Contemporary systematic reviews estimate that persistent neuropathic pain after breast surgery affects approximately 25–60% of patients, depending on surgical approach, follow-up duration, and diagnostic criteria [2]. Despite advances in surgical technique and earlier cancer detection, a substantial proportion of survivors' experience pain that persists beyond the expected healing period and meaningfully impairs daily function, sleep, and emotional well-being [3]. Increasing evidence supports a multifactorial pathophysiology involving interacting peripheral nerve injury,

sustained inflammatory signaling, immune dysregulation, and central sensitization rather than isolated peripheral nerve damage alone [4,5].

The clinical burden of PMPS may be amplified in the setting of postoperative complications, including infection, reconstructive revision procedures, and lymphedema [6,7]. Large database analyses demonstrate that postoperative infection is associated with increased reconstructive revision burden and prolonged recovery trajectories [8]. Lymphedema and complex reconstructive courses may further contribute to ongoing tissue stress, inflammatory activation, and functional impairment [9-11]. Collectively, these factors may sustain peripheral nociceptive input and promote central pain amplification in vulnerable patients.

Conventional management strategies for PMPS include gabapentinoids, antidepressants, opioids, regional nerve blocks, topical agents, and structured physical or occupational therapy [12,13]. Contemporary reviews emphasize multidisciplinary, individualized approaches while recognizing the limitations of single-modality pharmacologic escalation [12,13]. Despite these options, many patients achieve only partial relief or experience adverse effects that limit long-term adherence and quality of life [13]. These challenges have prompted increasing interest in mechanism-informed multimodal strategies targeting immune dysregulation, chronic inflammation, microglial activation, and maladaptive central sensitization in refractory cases [4].

Thymosin alpha-1 (Tα1) is a thymic peptide with immunomodulatory and tissue-reparative properties, including modulation of pro-inflammatory cytokines and support of immune homeostasis following infection or surgical stress [14,15]. Although direct clinical data evaluating Tα1 specifically in neuropathic pain are limited, preclinical models demonstrate attenuation of microglia-mediated inflammatory signaling and reduction of pain behaviors in inflammatory pain states [16], supporting biologic plausibility in conditions characterized by sustained postoperative inflammation.

Low-dose naltrexone (LDN) has emerged as an analgesic with mechanisms distinct from conventional opioid therapy. At doses of 1–5 mg daily, LDN has been associated with attenuation of microglial activation, modulation of toll-like receptor 4–mediated inflammatory signaling, enhancement of endogenous opioid tone, and reduction of central sensitization [17,18]. Meta-analytic evidence from randomized controlled trials suggests potential benefit in chronic pain populations, particularly centralized pain syndromes, with a favorable safety profile [18,19]. These mechanisms are relevant to PMPS, where neuroinflammatory processes and central amplification are recognized contributors to pain persistence.

Cannabinoid-based therapies combining tetrahydrocannabinol (THC) and cannabidiol (CBD) modulate nociceptive signaling through CB1 and CB2 receptor activation, TRPV1 channel modulation, and enhancement of endogenous endocannabinoid tone [20,21]. Systematic reviews and position statements from major pain societies acknowledge modest evidence supporting cannabinoid-based medicines in selected chronic neuropathic pain populations while emphasizing careful patient selection and monitoring [22,23]. In addition to analgesic effects, cannabinoids may support sleep continuity and reduce anxiety—factors known to influence chronic postoperative pain experiences in breast cancer survivors.

Complementary mind–body and supportive interventions, including mindfulness-based stress reduction and heart rate variability–based autonomic regulation, have been associated with improvements in pain-related distress, sleep quality, and functional outcomes when integrated alongside conventional treatment [24-26]. Such modalities offer a patient-centered framework for addressing the multidimensional nature of PMPS within survivorship care.

This case report describes the coordinated use of Tα1, LDN, and sublingual THC/CBD in a breast cancer survivor with severe, refractory PMPS following a complicated surgical and reconstructive course. Rather than escalating isolated therapies sequentially, these agents were implemented concurrently to address interacting peripheral, central, and immune contributors to persistent pain. This report contributes to ongoing clinical discussion regarding multimodal, neuroimmune-informed strategies for chronic neuropathic pain in breast cancer survivorship [27].

Case Presentation

A 52-year-old woman with Stage I estrogen receptor–positive breast cancer was diagnosed following routine mammography and confirmatory biopsy. After multidisciplinary consultation, she elected to undergo bilateral mastectomy with immediate tissue expander placement and axillary sentinel lymph node dissection. Adjuvant endocrine therapy with anastrozole was initiated without complication, and she remained under ongoing surveillance by medical oncology, surgical oncology, and plastic surgery teams [28].

Within one week of surgery, she developed high-grade fever (maximum 103°F) accompanied by shaking chills. Presentation to the hospital was delayed for approximately three days due to severe weather conditions and lack of transportation during a regional snowstorm. She presented to the emergency department on the fourth postoperative day after symptom onset. Evaluation revealed polymicrobial infection involving the breast surgical site and bloodstream, with cultures positive for *Escherichia coli* and *Pseudomonas aeruginosa*. Broad-spectrum intravenous antibiotics were initiated following infectious disease consultation, and she underwent urgent operative removal of bilateral tissue expanders. She remained hospitalized for one week for intravenous antimicrobial therapy.

Following discharge, her surgical incision reopened within approximately ten days, requiring re-evaluation and operative re-closure. Over the subsequent months, she developed severe left upper-extremity lymphedema, clinically attributed to axillary lymph node dissection in combination with repeated infectious and inflammatory complications [1,7,9]. Despite structured physical therapy and lymphatic management, lymphedema persisted. Postoperative complications of this nature—including infection, reconstructive challenges, and lymphatic disruption—have been associated with prolonged recovery and increased risk of persistent pain following breast surgery [11]. The combination of repeated surgical intervention, polymicrobial infection, and sustained lymphatic impairment likely contributed to a prolonged pro-inflammatory postoperative environment.

Approximately six months after the initial mastectomy, delayed silicone implant reconstruction was performed. This procedure was again complicated by postoperative wound infection and dehiscence, followed by eventual healing. Subsequent capsular contracture and adhesive scar formation developed, and additional reconstructive surgery, including consideration of deep inferior epigastric perforator

(DIEP) flap reconstruction, was recommended. The patient declined further surgical intervention [10,29].

During this extended postoperative course, the patient developed persistent neuropathic pain involving the chest wall and axilla. She described the pain as burning, stabbing, and electric in character, accompanied by prominent tactile allodynia. These features were clinically consistent with a neuropathic pain phenotype. Symptoms initially fluctuated but progressively intensified and became continuous. By approximately eight months following the initial mastectomy, self-reported pain severity was consistently rated at 8–9/10 and had persisted well beyond the expected tissue healing period. At that time, her presentation met ICD-11 criteria for chronic postsurgical pain, defined as pain persisting for at least three months following a surgical procedure without alternative explanation [30,31].

There was no evidence of local recurrence or metastatic disease. Ongoing oncologic follow-up, including positron emission tomography (PET) imaging performed by her oncology team, was negative for recurrence.

Prior to seeking integrative management, the patient underwent multiple conventional treatment trials with limited or unsustained benefit. Early postoperative management included opioid analgesics (oxycodone and hydromorphone), which were subsequently discontinued by her treating team due to concerns regarding long-term dependence and limited functional improvement. At the time of presentation for integrative care, her regimen included lidocaine patches, gabapentin, nonsteroidal anti-inflammatory drugs, acetaminophen, tramadol, muscle relaxants, and intermittent benzodiazepine therapy. She had also participated in structured physical therapy, lymphatic drainage therapy, and multiple pain management consultations. Despite these interventions, she experienced progressive functional limitation, impaired sleep, restricted upper-body mobility, and significant emotional distress related to persistent uncontrolled pain.

Therapeutic Intervention

An individualized, time-limited, neuroimmune-informed multimodal regimen was initiated approximately eight months following the initial mastectomy, after persistent neuropathic symptoms had failed to respond adequately to conventional management. The intervention consisted of low-dose naltrexone (LDN), sublingual THC/CBD, and Thymosin alpha-1 (Tα1). The regimen was implemented as a structured 12-week adjunctive therapeutic trial with the knowledge and approval of the patient's oncology and primary care teams. She remained under active oncologic surveillance throughout this period, with routine laboratory monitoring conducted by her primary treating physicians. The integrative clinic provided biweekly in-office evaluations coinciding with Tα1 administration to assess tolerability, safety, and clinical response.

Opioid therapy had been discontinued prior to initiation of LDN, and no opioid medications were prescribed during the integrative treatment period. The therapeutic plan was developed through shared decision-making in the context of persistent symptoms, functional limitation, and limited response to conventional pharmacologic and rehabilitative strategies.

LDN was initiated at 1.5 mg nightly and titrated to 4.5 mg over four weeks. The agent was selected based on evidence suggesting modulation of microglial activation, toll-like receptor 4–mediated signaling, and endogenous opioid pathway regulation in chronic pain states [17,19], with meta-analytic data supporting potential benefit in selected chronic pain populations [18]. In the context of this patient's prolonged postoperative inflammatory and neuropathic course, LDN was incorporated to address suspected neuroinflammatory sensitization mechanisms. Treatment was well tolerated, with no reported sleep disturbance, vivid dreams, gastrointestinal adverse effects, or mood instability.

Sublingual THC/CBD therapy consisted of a state-legal, commercially available balanced 1:1 medical cannabis formulation administered at a microdose of approximately 0.25 mg THC and 0.25 mg CBD nightly (one sublingual drop). The patient elected not to increase the dose due to concern regarding potential psychoactive or cognitive effects. The formulation was selected based on literature supporting cannabinoid-mediated neuromodulation in chronic neuropathic pain and sleep disturbance [22,23,32]. The low-dose regimen was cleared by her primary care physician. Mild dry mouth was reported; no cognitive impairment, dysphoria, cardiovascular symptoms, or functional impairment were observed.

Thymosin alpha-1 was administered at 1.6 mg subcutaneously twice weekly for 12 weeks. The agent was selected based on its reported immunomodulatory properties and established clinical safety profile in inflammatory, infectious, and oncologic contexts [14,15,33,34]. Although direct clinical evidence for Tα1 in neuropathic pain remains limited, preclinical and translational data demonstrating modulation of inflammatory signaling, T-cell regulation, and restoration of immune homeostasis informed its inclusion in the context of prior polymicrobial infection and sustained postoperative inflammatory stress. Treatment was well tolerated, with no injection-site reactions, systemic adverse effects, or laboratory abnormalities observed during the monitored period.

Given the severity, chronicity, and refractory nature of symptoms, the three agents were introduced within the same treatment window to prioritize timely symptom relief and functional restoration rather than sequential pharmacologic testing. No washout period or staged monotherapy trial was performed. This coordinated multimodal approach reflects real-world integrative practice but limits attribution of clinical response to any single component and is acknowledged as an inherent methodological limitation of the design.

At the conclusion of the 12-week intervention, decisions regarding continuation, tapering, or modification of therapy were deferred to the patient's primary oncology and medical teams in accordance with the clinic's short-term, adjunctive integrative care framework.

Adjunctive Supportive Interventions

Adjunctive supportive therapies were incorporated during the integrative treatment period to address stress reactivity, functional deconditioning, and persistent lymphedema. These modalities were implemented within a broader integrative oncology framework emphasizing whole-person survivorship care rather than as primary analgesic interventions [35,36]. Their inclusion reflected recognition that chronic pain persistence often involves behavioral, autonomic, and functional contributors in addition to peripheral and neuroimmune mechanisms.

The patient continued manual lymphatic drainage and guided

movement therapy under the supervision of a certified physical therapist specializing in breast cancer–related lymphedema. Comprehensive decongestive therapy and supervised mobility restoration are recognized components of standard lymphedema management and survivorship rehabilitation [7,37]. These interventions were maintained throughout the treatment period to support tissue mobility, reduce inflammatory stasis, preserve upper-extremity function, and minimize secondary mechanical contributors to pain.

Mindfulness-based stress reduction practices were introduced to support coping capacity, pain self-regulation, and emotional resilience. Structured mindfulness interventions have demonstrated potential to reduce pain-related distress, improve neuropathic symptom perception, and modulate stress-amplification pathways in breast cancer survivors [38-40]. In this context, mindfulness training was incorporated as a supportive strategy addressing central stress reactivity rather than as a standalone analgesic modality.

Heart-rate-variability–based biofeedback was incorporated to support autonomic balance and reduce sympathetic hyperarousal, which is increasingly recognized as a contributor to chronic pain persistence and central sensitization. Systematic reviews demonstrate associations between HRV modulation, autonomic regulation, and pain outcomes in chronic pain populations [41,42]. This intervention was implemented to enhance physiologic self-regulation within the broader neuroimmune-informed framework.

Nutritional counseling emphasized anti-inflammatory, whole-food dietary patterns within an integrative framework tailored to patient preference and tolerability. While dietary modification was not implemented as a primary analgesic strategy, such approaches are increasingly incorporated into comprehensive cancer survivorship care to support systemic health, metabolic stability, and recovery [35].

Collectively, these supportive modalities were selected to complement neuroimmune-modulating pharmacologic therapy by addressing behavioral, autonomic, lymphatic, and functional factors that may amplify persistent pain states. Their integration reflected a coordinated multimodal strategy rather than reliance on any single intervention.

Clinical Outcomes and Follow-Up

Clinical outcomes were monitored longitudinally through serial in-office evaluations during the 12-week treatment period, with follow-up communication thereafter. Improvement was progressive rather than abrupt.

Within four weeks of initiating the coordinated treatment approach, the patient reported meaningful reduction in pain intensity and tactile hypersensitivity. Baseline self-reported pain had been 8–9/10. By week four, pain severity had decreased to approximately 4–5/10, accompanied by substantial reduction in electric shock–like sensations and tactile allodynia. No dose escalation of LDN, THC/CBD, or Thymosin alpha-1 was required during this interval.

By 12 weeks, pain stabilized at a functionally manageable level of approximately 2–3/10 without breakthrough flares. Although pain did not completely resolve, its intensity, neuropathic character, and functional impact were markedly reduced. The patient reported restored ability to perform routine daily activities, improved upper-extremity mobility, reduced protective guarding, and increased participation in physical therapy and lymphedema management. Improvement plateaued at this level without further escalation of pharmacologic therapy.

Sleep quality improved gradually throughout the treatment course. Prior to intervention, she reported fragmented sleep limited to 2–3-hour intervals with frequent awakenings and distressing dreams. Over time, she described the ability to sleep approximately six consecutive hours without interruption. Emotional well-being improved in parallel, with decreased anxiety and renewed engagement in social and household activities.

Opioid analgesics had been discontinued prior to initiation of the integrative treatment period and were not resumed. No adverse effects, drug interactions, cardiovascular symptoms, or interference with ongoing anastrozole therapy or oncologic surveillance were observed during the 12-week intervention.

At last structured follow-up contact approximately two months after completion of the active treatment period, the patient reported sustained stability of pain control and functional improvement without recurrence of severe neuropathic flares.

Methods

Study Design and Clinical Setting

This manuscript describes a single-patient clinical case report evaluating response to a coordinated, multimodal integrative treatment approach for refractory post-mastectomy neuropathic pain. Care was delivered in coordination with the patient's oncology and primary care teams as part of routine clinical practice. All therapeutic decisions, dosing adjustments, and follow-up assessments occurred within standard medical care and were not conducted under a predefined experimental protocol.

Pain severity was assessed using a patient-reported Numeric Rating Scale (0–10), and symptom progression was documented through structured longitudinal clinical follow-up during the 12-week intervention period. Functional status, sleep quality, and medication use were recorded during serial clinical encounters and through contemporaneous patient self-report.

This manuscript was prepared in accordance with CARE (Case Report) reporting guidelines [43] and contemporary surgical case reporting recommendations [44]. Given the single-patient design, no formal hypothesis testing or inferential statistical analyses were performed. Clinical interpretation relied on longitudinal symptom tracking and functional outcome assessment consistent with conceptual frameworks recognizing the multidimensional nature of pain [45].

All interventions described were administered as part of routine medical care without investigational drug use. Written informed consent for publication of de-identified clinical information was obtained from the patient.

Case Definition and Eligibility Criteria

The patient's presentation met established diagnostic criteria for chronic postsurgical neuropathic pain. Her pain developed following bilateral mastectomy, persisted for more than three months beyond the expected period of surgical tissue healing, and could not be attributed to local recurrence or alternative pathology. This clinical pattern aligns with ICD-11 classifications of chronic postsurgical pain and contemporary oncology-specific neuropathic pain guidance [12,30].

Her symptom profile included characteristic neuropathic descriptors such as burning, stabbing, and electric shock–like sensations, accompanied by prominent tactile allodynia within the surgical field. These features are consistent with validated neuropathic pain characteristics described in breast surgery populations [2] and align with current conceptualizations of sensory abnormalities as core components of neuropathic pain syndromes [5].

Her postoperative course was further complicated by infection, tissue expander removal, delayed reconstruction, and upper-extremity lymphedema—factors recognized as contributors to persistent nociceptive input and central amplification following breast cancer surgery [3,9]. The persistence and severity of symptoms despite resolution of acute surgical complications supported classification as a chronic neuropathic pain phenotype rather than an ongoing acute inflammatory process.

Prior to integrative consultation, she had experienced limited or unsustained response to guideline-based multimodal pain therapies, including opioids, gabapentinoids, antidepressants, topical agents, and rehabilitative interventions [12]. She declined additional invasive procedures, including nerve-directed interventions and reconstructive revision, electing instead to pursue conservative management within a structured shared decision-making framework [46]. Eligibility for integrative intervention was further supported by the absence of active malignancy, absence of contraindications to the proposed therapies, and ongoing clearance and monitoring by her primary oncology team.

Therapeutic Intervention Overview

An individualized multimodal regimen was implemented consisting of low-dose naltrexone (LDN), low-dose sublingual tetrahydrocannabinol: cannabidiol (THC:CBD), and Thymosin alpha-1 (Tα1). All therapies were initiated within the same treatment window in response to persistent, functionally limiting symptoms and prior limited response to conventional therapies. The approach reflected a pragmatic clinical decision to address overlapping neuroimmune and neuropathic contributors concurrently rather than sequentially.

Treatment decisions were individualized and adjusted according to patient-reported clinical response, tolerability, and functional trajectory rather than adherence to a predefined research protocol. The patient remained under concurrent oncology supervision throughout the intervention period.

Clinical monitoring included systematic assessment for adverse effects, potential drug–drug interactions, changes in pain severity, sleep continuity, mood stability, and functional capacity at each follow-up visit. No investigational agents were used, and all therapies were administered within the scope of routine clinical practice.

Low-Dose Naltrexone (LDN)

LDN was initiated at 1.5 mg orally at bedtime and titrated to 4.5 mg over a four-week period. This dosing range aligns with published literature in chronic pain populations supporting individualized titration within the 1–5 mg range [17,18,47]. The patient tolerated the regimen well, reporting no sleep disturbance, vivid dreams, gastrointestinal adverse effects, or mood instability.

THC:CBD Sublingual Therapy

A low-dose balanced 1:1 THC:CBD tincture (approximately 0.25 mg THC and 0.25 mg CBD nightly) was introduced as a state-legal medical cannabis formulation. The patient declined dose escalation due to concern regarding potential psychoactive or cognitive effects. Balanced cannabinoid formulations are supported by clinical practice guidelines for selected chronic neuropathic pain populations when initiated at conservative doses to minimize psychoactive burden [32,48]. The patient reported mild dry mouth as the only side effect, with no dysphoria, cognitive impairment, cardiovascular symptoms, or anxiety exacerbation.

Thymosin Alpha-1 (Tα1)

Thymosin alpha-1 was administered at 1.6 mg subcutaneously twice weekly for 12 weeks. This dosing is consistent with established clinical use of Tα1 in immune-modulating and inflammatory contexts [14,34]. Treatment was well tolerated, with no injection-site reactions, systemic adverse events, or laboratory abnormalities observed during the monitored period.

No modifications were made to ongoing anastrozole therapy. No clinically observed pharmacologic interactions or safety concerns were identified during the treatment period.

Integrative Supportive Modalities

In addition to pharmacologic therapy, structured non-pharmacologic interventions were incorporated within a coordinated integrative oncology framework to address stress-related amplification, functional deconditioning, and survivorship-related morbidity. These modalities were selected according to patient preference, clinical tolerance, and evolving functional needs and were documented longitudinally in treatment records. Contemporary breast cancer rehabilitation literature supports integration of manual therapy, structured movement rehabilitation, and mind–body interventions to mitigate long-term physical morbidity and functional limitation following surgical and reconstructive treatment [7,36].

Mindfulness-based stress reduction practices modeled on Kabat-Zinn protocols were introduced through guided breathing exercises, body-awareness training, and structured self-regulation techniques. Randomized and controlled data in breast cancer survivors and chronic pain populations support mindfulness interventions in reducing pain-related distress, modulating stress reactivity, and improving coping capacity [38-40]. These practices were incorporated to complement neuroimmune-targeted therapy by addressing affective and stress-related contributors to persistent pain rather than serving as standalone analgesic interventions.

Manual lymphatic drainage and soft-tissue mobilization were continued under the supervision of a certified lymphedema therapist to address postoperative edema, myofascial restriction, and tissue mobility. Comprehensive decongestive therapy and structured rehabilitation are recognized components of contemporary breast cancer survivorship care aimed at reducing long-term morbidity risk and restoring upper-extremity function [7,36].

Autonomic regulation strategies incorporating heart-rate-variability–guided biofeedback were offered to support sympathetic–parasympathetic balance, stress regulation, and sleep continuity. Systematic reviews demonstrate associations between autonomic imbalance and chronic pain states and support clinical application of HRV-based interventions in selected patients [41,42].

Nutritional counseling emphasized anti-inflammatory, whole-food dietary patterns within an integrative oncology framework tailored to patient preference and tolerability. While

dietary modification was not implemented as a primary analgesic intervention, emerging perspectives in supportive cancer care recognize lifestyle and nutritional strategies as important components of comprehensive survivorship management [35].

These supportive modalities were implemented as adjunctive measures intended to complement pharmacologic neuroimmune modulation by addressing behavioral, autonomic, lymphatic, and functional dimensions that may contribute to chronic pain persistence.

Outcome Measures

Clinical outcomes were assessed at baseline and at regular follow-up visits throughout the 12-week intervention period to evaluate longitudinal therapeutic response. Baseline documentation occurred at initiation of integrative therapy, with subsequent assessments conducted during biweekly in-office visits and follow-up communication.

Pain intensity was measured using a patient-reported Numeric Pain Rating Scale (0–10), a validated and widely used instrument for clinical pain assessment [49]. Pain ratings were obtained through direct patient self-report at each follow-up encounter. No formal neuropathic pain inventory (e.g., DN4 or NPSI) was administered. Neuropathic characteristics, including tactile allodynia, burning quality, and electric shock–like sensations, were documented through structured patient interviews and routine clinical examination findings.

Analgesic utilization was tracked through review of the patient's medication list and confirmation of opioid discontinuation prior to integrative therapy. Continued absence of opioid or breakthrough analgesic use during the intervention period was confirmed at follow-up visits.

Functional recovery was evaluated qualitatively through documented changes in upper-extremity mobility, tolerance for physical and lymphatic therapy sessions, range-of-motion progression, and return to routine daily activities. These domains are consistent with survivorship-oriented breast cancer rehabilitation frameworks that emphasize functional restoration and morbidity risk reduction [36].

Sleep outcomes were assessed through patient-reported nightly duration of uninterrupted rest and subjective sleep-quality feedback, consistent with single-item sleep self-report approaches commonly used in clinical settings [50]. No polysomnography or formal sleep questionnaires were performed.

Emotional and behavioral changes were documented through structured follow-up interviews addressing anxiety related to pain, coping capacity, and social engagement. No formal psychometric scales were administered. These qualitative domains reflect whole-person survivorship care principles recognized in integrative oncology models [35].

No objective biomarkers, neurophysiologic testing, or formal autonomic measurements were obtained.

Clinical Outcomes and Follow-Up

Within four weeks of initiating the combined treatment approach, the patient reported progressive improvement in pain intensity and tactile sensitivity. Baseline pain had been self-rated at 8–9/10 on a numeric rating scale. Improvement was gradual rather than abrupt. By approximately four weeks, pain severity had decreased to 4–5/10, accompanied by substantial reduction in electric shock–like sensations and tactile allodynia. No dose escalation of low-dose naltrexone, THC:CBD, or Thymosin alpha-1 was required during this period.

By completion of the 12-week intervention, pain stabilized at a functionally manageable level (approximately 2–3/10) without breakthrough flares. Although not fully resolved, both intensity and functional impact were markedly reduced. The patient reported restored participation in daily activities, improved upper-extremity mobility, reduced protective guarding, and increased tolerance for ongoing physical therapy and lymphedema management.

Sleep quality improved progressively during treatment. Prior to intervention, she described fragmented sleep limited to 2–3-hour intervals with frequent awakenings. By weeks 8–12, she consistently reported approximately six consecutive hours of uninterrupted sleep. Emotional well-being improved in parallel, with decreased anxiety related to pain and renewed engagement in social and functional activities.

Opioid analgesics had been discontinued prior to initiation of integrative therapy and were not resumed during the 12-week intervention. No adverse effects, clinically apparent drug interactions, or interference with ongoing anastrozole therapy or oncologic surveillance were observed.

Structured follow-up continued for approximately two months after completion of the 12-week intervention. During this interval, the patient reported sustained stability of pain control, continued functional improvement, and ongoing absence of opioid use. She elected to transition fully back to follow-up with her primary oncology and medical teams, who had remained concurrently involved in her care throughout the integrative treatment period. This decision reflected clinical stability, geographic convenience, and patient preference to consolidate care closer to home, as biweekly visits to the integrative clinic had become logistically burdensome. No additional structured integrative monitoring occurred beyond that time; however, the clinic remained available should she elect to return for reassessment.

Data Sources and Follow-Up

Clinical data were derived from routine in-office evaluations, structured patient interviews, and contemporaneous clinical documentation maintained during the 12-week intervention period. Follow-up visits during active treatment were conducted biweekly to coincide with Thymosin alpha-1 administration and included assessment of pain severity, functional status, sleep quality, medication use, and treatment tolerability.

Pain intensity was recorded using a patient-reported Numeric Rating Scale (0–10), a validated and widely used instrument for clinical pain assessment [49]. Neuropathic features, including tactile allodynia and electric shock–like sensations, were documented through structured clinical interviews and examination findings.

Functional changes were assessed through documented progression in upper-extremity mobility, participation in physical and lymphatic therapy, and return to routine daily activities, consistent with survivorship-oriented rehabilitation frameworks [36].

Sleep duration and subjective sleep continuity were assessed through patient self-report using single-item sleep assessment

approaches commonly employed in clinical settings [50].

Emotional and behavioral changes were documented through structured follow-up interviews addressing anxiety related to pain, coping capacity, and social engagement. These qualitative assessments reflect whole-person survivorship care models within integrative oncology [35].

Following completion of the 12-week treatment period, additional follow-up contact was conducted for approximately two months to assess durability of symptom improvement and continued opioid-free status. No formal psychometric instruments, physiologic autonomic monitoring, laboratory biomarkers, or structured medication tapering protocols were employed in this case.

Ethical and Regulatory Considerations

This case report was prepared in accordance with established principles of medical ethics and the CARE (Case Report) guideline recommendations, which provide an internationally recognized framework for transparency and completeness in single-patient clinical reporting [43].

Written informed consent was obtained from the patient for therapeutic management and for publication of de-identified clinical information. All identifying information was removed in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule to ensure protection of patient confidentiality.

The interventions described were administered as part of routine, individualized clinical care within the legal scope of medical practice. Where applicable, therapies were prescribed off-label in accordance with standard medical discretion. No investigational agents were administered, and no randomization, experimental allocation, or prospective research protocol was implemented.

Because this report describes a single clinical case arising from routine medical treatment and does not meet the definition of human subject's research under U.S. federal regulations (45 CFR 46.102), institutional review board (IRB) approval was not required.

Results

The patient demonstrated progressive and sustained clinical improvement following initiation of the coordinated multimodal treatment regimen.

Early Response (Weeks 0–4)

Within four weeks of therapy, neuropathic pain intensity decreased from a baseline of 8–9/10 to approximately 4–5/10 on the 0–10 Numeric Rating Scale. Reduction in pain severity was accompanied by decreased frequency and intensity of burning and electric shock–like sensations involving the chest wall and axilla. Improvement was gradual and consistent across follow-up visits rather than abrupt.

The patient remained opioid-free and did not require breakthrough analgesia. She reported improved mental clarity and reduced medication-related fatigue following prior opioid discontinuation.

Intermediate Response (Weeks 4–8)

Functional recovery progressed in parallel with pain reduction. Shoulder and chest wall mobility improved, protective guarding behaviors diminished, and tolerance for lymphatic massage and structured physical therapy increased. The patient resumed routine daily activities, including household responsibilities, driving, and work-related tasks.

Sleep quality improved progressively. By approximately week eight, she consistently reported 6–7 hours of uninterrupted sleep per night. Emotional well-being improved alongside physical recovery.

End-of-Treatment Status (Week 12)

By completion of the 12-week intervention, neuropathic pain stabilized at approximately 2–3/10 without breakthrough flares or reinstitution of opioid therapy. Functional capacity, sleep continuity, and psychosocial stability remained substantially improved relative to baseline.

No clinical adverse events were observed during treatment. No treatment-limiting interactions were identified with ongoing anastrozole therapy or other components of oncology management.

Post-Treatment Follow-Up

Follow-up continued for two months following completion of the active treatment period. During this interval, the patient reported sustained stability of pain control, maintained functional gains, continued opioid-free status, and no requirement for dose escalation of any component of therapy. She subsequently transitioned fully to follow-up with her primary oncology and medical teams.

Discussion

This case illustrates the potential value of a coordinated, neuroimmune-informed strategy integrating pharmacologic and structured supportive interventions in the management of refractory post-mastectomy neuropathic pain (PMPS). The patient's improvement extended beyond reduction in pain intensity to include restoration of sleep continuity, improved functional mobility, sustained opioid independence, and reduction in pain-related anxiety. The multidimensional nature of this response reflects the complex interplay of peripheral nerve injury, immune activation, central sensitization, and psychosocial amplification increasingly recognized in chronic postsurgical pain syndromes.

Notably, clinical improvement occurred well beyond the expected period of acute postoperative tissue healing. Although spontaneous recovery cannot be excluded in a single case, the delayed timing relative to surgery makes natural resolution less likely to fully account for the magnitude and tempo of symptom stabilization observed following intervention.

Low-dose naltrexone (LDN) was incorporated based on emerging evidence suggesting modulation of microglial activation, toll-like receptor–mediated inflammatory signaling, and central sensitization in chronic pain populations [47]. Neuropathic symptom stabilization occurred without dose escalation or treatment-limiting adverse effects. A balanced 1:1 THC:CBD formulation was introduced at microdose levels, consistent with contemporary guidance recommending cautious cannabinoid use in selected patients with refractory neuropathic pain [32,48]. The conservative dosing strategy permitted symptomatic benefit without psychoactive burden or functional impairment.

Thymosin Alpha-1 (Tα1) was incorporated to address potential immune dysregulation associated with prior infection, surgical stress, and persistent inflammatory signaling. Although direct evidence for Tα1 in PMPS remains limited, expanding neuroimmune research highlights the role of cytokine-mediated inflammation, microglial

activation, and immune–neural crosstalk in sustaining neuropathic pain states [51,52]. Within this framework, immune modulation represents a biologically plausible therapeutic domain in selected refractory cases. While causality cannot be inferred, the temporal association between multimodal intervention and progressive symptom improvement supports further investigation of coordinated immune and central modulation strategies.

A notable clinical feature of this case is sustained opioid independence. Long-term opioid therapy in cancer survivors has been associated with persistent use beyond active treatment and increased risk of dependence [53,54]. In this patient, symptom stabilization occurred without reinstitution of opioid therapy, suggesting that mechanism-informed multimodal strategies may support opioid-sparing outcomes in selected individuals with chronic postsurgical pain.

Structured supportive interventions—including mindfulness-based stress reduction, manual lymphatic therapy, autonomic regulation techniques, and individualized nutritional counseling—were implemented alongside pharmacologic therapy. Survivorship frameworks increasingly emphasize whole-person, multidisciplinary approaches to address functional morbidity and psychosocial distress following breast cancer treatment [26,55]. In this case, integration of behavioral and rehabilitative modalities likely reinforced mobility restoration, reduced fear-avoidant behaviors, and supported sleep normalization.

Several limitations warrant consideration. This report describes a single patient and does not permit causal inference regarding individual components of therapy. Biomarker assessments, physiologic autonomic measurements, and controlled comparisons were not performed. The simultaneous initiation of multiple interventions precludes isolation of specific treatment effects. Additionally, structured follow-up extended for approximately two months beyond the active treatment period, limiting conclusions regarding longer-term durability.

Despite these limitations, this case demonstrates the feasibility and favorable safety profile of a coordinated neuroimmune-modulating approach in a patient with severe, refractory PMPS following a complex surgical course. The observed improvements in pain intensity, function, sleep, and opioid independence support the hypothesis that integrated strategies targeting immune, central, and behavioral contributors to pain warrant systematic evaluation within breast cancer survivorship care.

Integrated Mechanistic Rationale for Combined Use of Thymosin Alpha-1, Low-Dose Naltrexone, and THC:CBD in Post-Mastectomy Neuropathic Pain

To contextualize the clinical response observed in this case, it is important to consider the converging neuroimmune mechanisms implicated in persistent post-mastectomy neuropathic pain (PMPS) and how each component of the therapeutic regimen may have targeted complementary domains of this pathophysiology. Rather than attributing improvement to a single pathway, the interventions were selected within a systems-informed framework aimed at modulating interacting peripheral, central, and immune processes recognized to sustain chronic postoperative pain. This model is presented as biologically plausible rather than mechanistically definitive.

Persistent PMPS arises through interconnected mechanisms involving peripheral nerve injury, sustained inflammatory signaling, lymphatic disruption, central sensitization, microglial activation, and dysregulated stress physiology [1,51]. Increasing translational evidence supports a central role for microglial–immune interactions in maintaining neuropathic pain states and facilitating the transition from acute tissue injury to chronic central sensitization [52,56]. In this patient, tactile allodynia, persistent neuropathic descriptors, sleep disruption, and autonomic hyperarousal were clinically consistent with contributions from overlapping peripheral and central neuroimmune domains.

Low-dose naltrexone (LDN) was incorporated to potentially attenuate microglial activation and modulate toll-like receptor–mediated neuroinflammatory signaling, mechanisms implicated in amplification of dorsal horn excitability and persistent central sensitization [47,51]. Stabilization of neuropathic pain without dose escalation is consistent with a possible modulatory effect on central immune signaling, although causality cannot be established in an individual case.

The balanced THC:CBD formulation was introduced as adjunctive neuromodulation targeting both synaptic and immune-mediated pathways. The endocannabinoid system regulates nociceptive transmission, glial activation, cytokine signaling, and stress reactivity [57,58]. Through CB1-mediated modulation of excitatory neurotransmission and CB2-associated immune effects, cannabinoid therapy may influence both central sensitization and peripheral inflammatory signaling [32,48]. In this context, low-dose cannabinoid administration was selected to support neuromodulation while minimizing psychoactive burden.

Thymosin Alpha-1 (Tα1) was incorporated to address systemic immune dysregulation potentially associated with prior infection, surgical stress, and persistent inflammatory activation. Emerging translational data support its capacity to modulate lymphocyte activity, cytokine balance, and immune homeostasis in complex inflammatory states [16]. Although direct evidence for Tα1 in PMPS is limited, immune recalibration may represent a relevant therapeutic domain in patients whose postoperative course includes infection, tissue disruption, and prolonged inflammatory stress.

Taken together, the combined regimen was designed to provide multi-level modulation of peripheral inflammatory drivers, central neuroimmune amplification, and stress-related autonomic reinforcement loops—processes that interact dynamically in persistent postoperative neuropathic pain [1,51]. This coordinated strategy does not imply mechanistic certainty; rather, it reflects a patient-centered attempt to address overlapping neuroimmune contributors when conventional single-mechanism approaches prove insufficient.

Modulation of Peripheral Inflammation and Immune Dysregulation

Persistent postoperative inflammation is increasingly recognized as a driver of peripheral sensitization following tissue injury. Pro-inflammatory cytokines—including TNF-α, IL-1β, IL-6, and IFN-γ—along with downstream oxidative mediators, contribute to nociceptor hyperexcitability, ion channel sensitization, and amplification of peripheral pain signaling [52,59]. In the setting of prior surgical infection, lymphatic disruption, and repeated tissue stress, sustained immune activation may prolong peripheral nociceptive input and facilitate the transition from acute postoperative pain to

chronic neuropathic states. In this patient, the history of infection, reconstructive complications, and lymphedema suggested that persistent peripheral immune dysregulation may have contributed to ongoing symptom maintenance.

Thymosin Alpha-1 (Tα1) has demonstrated immunomodulatory properties, including inhibition of NF-κB–mediated inflammatory signaling [16], downregulation of pro-inflammatory cytokine production (Wei 2023), and restoration of lymphocyte balance in states of infection, sepsis, and systemic inflammatory stress [16,33]. Although direct evidence in post-mastectomy neuropathic pain remains limited, its incorporation in this case was intended to support immune homeostasis within a postoperative environment characterized by prior inflammatory burden and lymphatic disruption.

Low-dose naltrexone (LDN) may further influence peripheral immune signaling through attenuation of pro-inflammatory cytokine release and modulation of neuroimmune interactions [17]. While frequently discussed in the context of central microglial modulation, peripheral immune–neural cross-talk is increasingly recognized as relevant in neuropathic pain maintenance [51]. Modulation of these pathways may plausibly contribute to reduction of sustained nociceptor sensitization in chronic postoperative states.

The balanced THC:CBD formulation introduces complementary immunomodulatory mechanisms via the endocannabinoid system. Activation of CB2 receptors on immune cells has been associated with decreased cytokine release and attenuation of inflammatory signaling [20]. Cannabidiol may additionally enhance endocannabinoid tone through modulation of fatty acid amide hydrolase (FAAH) activity and increased availability of anandamide [57,58]. Through these mechanisms, cannabinoid therapy may support attenuation of peripheral inflammatory signaling while also modulating nociceptive transmission.

Taken together, the combined use of Tα1, low-dose naltrexone, and THC:CBD was designed to provide complementary modulation of immune-mediated contributors to peripheral sensitization. Although causality cannot be inferred from a single clinical observation, the observed reduction in tactile allodynia and progressive stabilization of neuropathic pain are consistent with a conceptual model in which attenuation of persistent peripheral inflammatory activation reduces ongoing nociceptive drive and limits downstream central amplification.

Reduction of Microglial Activation and Central Sensitization

Central sensitization refers to persistent enhancement of excitatory synaptic transmission within the central nervous system, characterized by reduced inhibitory modulation, lowered activation thresholds, and amplified dorsal horn neuron responsiveness [45]. Sustained activation of microglia and astrocytes plays a central role in this process through release of IL-1β, TNF-α, IL-6, brain-derived neurotrophic factor (BDNF), nitric oxide, reactive oxygen species, and other excitatory mediators that promote spinal hyperexcitability [51]. In patients with persistent neuropathic pain and tactile allodynia, glial–neuronal signaling may perpetuate central amplification even in the absence of ongoing peripheral tissue injury. The patient's prolonged allodynia and heightened pain sensitivity were clinically compatible with contributions from such central neuroinflammatory mechanisms.

Low-dose naltrexone (LDN) has been proposed to modulate microglial activation through antagonism of toll-like receptor 4 (TLR4), thereby attenuating cytokine production and interrupting neuroinflammatory feedback signaling [17]. Although definitive attribution cannot be made in a single case, gradual stabilization of neuropathic symptoms without escalation of analgesic therapy is consistent with possible modulation of central immune pathways.

Thymosin Alpha-1 (Tα1) has demonstrated capacity to influence inflammatory signaling cascades, including inhibition of MAPK pathways—ERK, JNK, and p38—and reduction of pro-inflammatory cytokine production [14,16]. While direct central nervous system effects cannot be established in this context, systemic regulation of inflammatory signaling may indirectly influence neuroimmune cross-talk relevant to central sensitization.

The balanced THC:CBD formulation introduces complementary central mechanisms. Activation of CB1 receptors within spinal and supraspinal regions has been associated with suppression of glutamatergic transmission and modulation of nociceptive signaling [60]. CB2 receptor activity may attenuate microglial activation and support immune–neural regulation [20]. The endocannabinoid system more broadly regulates neuroimmune communication and pain processing [57,58], and cannabidiol has been shown to modulate TRPV1 channels implicated in central pain amplification [21]. Through these overlapping pathways, cannabinoid therapy may contribute to stabilization of established central hyperexcitability.

Taken together, the combined regimen was selected to provide multi-target modulation of glial activation and central neuroinflammatory signaling implicated in persistent post-mastectomy neuropathic pain [51]. While causality cannot be inferred from a single case, the observed reduction in tactile allodynia and sustained pain stabilization are conceptually consistent with attenuation of central amplification processes that frequently perpetuate chronic neuropathic pain states.

Enhancement of Nerve Repair, Neuroprotection, and Cellular Homeostasis

Peripheral nerve injury following mastectomy may be accompanied by mitochondrial dysfunction, oxidative stress, impaired axonal repair, and disruption of autophagic balance—processes that contribute to persistent neuropathic pain [61]. In the setting of prolonged postoperative inflammation or infection, sustained metabolic stress within injured sensory fibers may perpetuate abnormal nociceptor signaling even after apparent structural healing. In this patient, persistent tactile allodynia raised the possibility that incomplete neuronal recovery and ongoing cellular stress contributed to symptom maintenance.

Thymosin Alpha-1 (Tα1) demonstrates immunomodulatory and cytoprotective properties in experimental and clinical contexts, including modulation of apoptotic pathways, attenuation of oxidative stress, and regulation of inflammatory cascades relevant to tissue recovery [14,16,33]. Emerging data also suggests influence on cellular stress-response pathways, including autophagy-related signaling and maintenance of cellular homeostasis [62]. Although direct evidence for peripheral nerve regeneration in PMPS is lacking, Tα1 was incorporated with the intent of supporting immune-regulated tissue stability within a postoperative environment characterized by prior inflammatory and metabolic stress.

Low-dose naltrexone may contribute indirectly to neuronal

stabilization through modulation of inflammatory signaling and neuroimmune interactions [17]. While primarily discussed in the context of microglial regulation, attenuation of sustained inflammatory activity may secondarily reduce cellular stress within injured peripheral nerves.

Cannabinoid therapy provides complementary mechanisms relevant to neuronal excitability and oxidative balance. Activation of CB1 receptors has been associated with suppression of excitatory neurotransmitter release, while cannabidiol demonstrates antioxidant properties and modulation of ion channels implicated in nociceptor hyperexcitability, including TRPV1 [21,63]. These mechanisms may contribute to reduction of ectopic firing and stabilization of hyperexcitable sensory neurons characteristic of neuropathic pain.

Taken together, coordinated modulation of inflammatory stress, oxidative burden, and neuronal excitability may help stabilize metabolically vulnerable peripheral nerves in persistent postoperative pain states [61]. While direct nerve regeneration cannot be inferred from a single clinical observation, the sustained reduction in allodynia and functional improvement observed in this patient are compatible with attenuation of maladaptive peripheral nerve signaling following complex surgical and inflammatory insult.

Improvement of Lymphatic Function, Wound Healing, and Tissue Microenvironment

Lymphedema, postoperative fibrosis, and chronic wound inflammation can alter both the mechanical and biochemical environment of the surgical field, contributing to persistent nociceptive input in post-mastectomy neuropathic pain [2,7,9]. Tissue stiffness, fibrotic remodeling, and potential nerve entrapment may coexist with sustained local cytokine signaling and inflammatory stasis, creating conditions favorable to peripheral nerve sensitization. In this patient, postoperative infection, expander removal, delayed reconstruction, and upper-extremity lymphedema likely disrupted lymphatic flow and tissue homeostasis, contributing to a pro-inflammatory microenvironment capable of sustaining nociceptive signaling.

Thymosin Alpha-1 (Tα1) has demonstrated immunomodulatory effects in inflammatory and postoperative settings, including modulation of lymphocyte trafficking, attenuation of pro-inflammatory cytokine signaling, and promotion of immune resolution processes [64,65]. Translational data further suggest potential roles in supporting organized tissue repair and immune-mediated remodeling dynamics [14,34]. Although direct evidence in post-mastectomy lymphedema is limited, Tα1 was incorporated with the aim of supporting immune recalibration and stabilization of the local tissue microenvironment following prior infectious and inflammatory stress.

Low-dose naltrexone may complement these processes through attenuation of sustained neuroimmune signaling and reduction of inflammatory amplification loops that perpetuate peripheral sensitization [17,66]. By modulating persistent immune activation, LDN may indirectly reduce ongoing nociceptive drive arising from chronically inflamed or fibrotic tissue.

Cannabinoid therapy provides additional mechanisms relevant to nociceptive modulation and tissue stress. Activation of CB1 and CB2 receptors has been associated with regulation of inflammatory signaling and sensory neuron excitability [20], while cannabidiol exhibits antioxidant and endothelial-protective effects in oxidative stress models, including radiation-associated injury [21,67]. These pathways may contribute to stabilization of vascular integrity and attenuation of inflammatory sensitization within the affected tissue bed.

Taken together, modulation of immune resolution, inflammatory tone, and local tissue stress may reduce peripheral nociceptive input arising from a disrupted postoperative microenvironment [2,7]. While structural reversal of lymphedema or fibrosis cannot be inferred from a single case, the patient's progressive reduction in pain sensitivity and improved functional tolerance are compatible with attenuation of peripheral contributors to neuropathic pain within a previously inflamed and mechanically altered tissue landscape.

Neuroendocrine, Affective, and Sleep-Related Modulation of Pain

Chronic pain is frequently intensified by dysregulated stress responses, affective distress, and sleep disruption—domains that disproportionately affect breast cancer survivors [68,69]. Alterations in hypothalamic–pituitary–adrenal (HPA) axis activity, sympathetic overactivation, and fragmented sleep architecture can amplify nociceptive processing and facilitate central sensitization. In this patient, prolonged sleep fragmentation, heightened pain-related anxiety, and emotional fatigue were prominent early features, suggesting bidirectional amplification between stress physiology and pain perception.

Thymosin Alpha-1 (Tα1) has demonstrated immunomodulatory effects that may influence interactions between inflammatory signaling and stress-responsive pathways [64,65]. While direct endocrine modulation cannot be inferred in an individual case, attenuation of chronic inflammatory signaling may indirectly reduce stress-mediated amplification of pain processing.

Low-dose naltrexone may contribute to affective modulation through transient opioid receptor blockade followed by compensatory upregulation of endogenous opioid signaling, including β-endorphin and enkephalin pathways [19]. Enhanced endogenous opioid tone has been associated with improved coping capacity and modulation of centralized pain states. In this case, improvements in emotional stability paralleled pain stabilization and sustained opioid discontinuation, findings that are consistent with possible normalization of endogenous pain-regulatory systems.

Cannabinoids may further influence affective and sleep-related dimensions of pain through CB1-mediated modulation of limbic circuitry, serotonergic interactions—including 5-HT1A signaling—and effects on sleep continuity [32,48,57,58]. THC has been associated with reduced sleep-onset latency in selected clinical contexts, while cannabidiol demonstrates anxiolytic properties and may support sleep stability. The patient's transition from fragmented 2–3 hour sleep intervals to sustained 6–7 hour periods of uninterrupted rest occurred alongside reductions in pain intensity and anxiety, consistent with stabilization of reciprocal sleep–pain interactions.

Taken together, modulation of inflammatory stress signaling, endogenous opioid tone, mood regulation, and sleep continuity provides a coherent framework for understanding improved pain coping and emotional resilience in this case. Rather than implying direct correction of discrete endocrine pathways, this model aligns

with established stress–pain amplification paradigms in which stabilization of affective and sleep domains may attenuate central amplification of persistent nociceptive input.

Integrated Neuroimmune Modulation Across Peripheral and Central Pathways

Although each component of the therapeutic regimen demonstrates independent biologic activity, their concurrent implementation was intended to address the interdependent neuroimmune processes that sustain persistent neuropathic pain. Thymosin Alpha-1 (Tα1) modulates systemic and peripheral inflammatory signaling [14], low-dose naltrexone attenuates microglial-mediated neuroinflammatory amplification [17], and THC:CBD influences nociceptive transmission at peripheral, spinal, and supraspinal levels [20]. Rather than targeting isolated pathways, this coordinated approach sought to modulate overlapping inflammatory and neural mechanisms that contribute to pain chronification.

Preclinical and translational evidence demonstrates bidirectional communication between inflammatory cytokine activity and the endocannabinoid system within immune and neural tissues [57,58]. Inflammatory states may alter endocannabinoid tone and receptor expression, while endocannabinoid signaling can influence cytokine production and immune-cell behavior. Although these interactions were not directly measured in this case, simultaneous modulation of inflammatory and endocannabinoid pathways provides a biologically plausible framework for understanding how combination therapy may stabilize neuroimmune cross-talk without requiring escalation of individual agents.

Cannabinoid-mediated effects on limbic and autonomic circuitry [32,48] further illustrate the integration of neural, immune, and behavioral domains in chronic pain. Improvements in sleep continuity and emotional regulation occurred alongside reductions in pain intensity and sustained opioid independence, findings that are consistent with dynamic coupling between affective regulation and nociceptive processing.

Taken together, this case demonstrates the feasibility of a systems-informed, multi-domain therapeutic strategy targeting peripheral inflammation, central sensitization, and stress-related amplification simultaneously. While individual contributions cannot be isolated in a single-patient report, coordinated modulation of peripheral, central, and systemic processes offers a coherent explanatory model for the breadth and durability of the observed clinical response. This framework aligns with contemporary understanding of chronic pain as a network-level disorder rather than a single-pathway phenomenon (Table 1) (Figure 1).

Clinical Implications for Refractory Post-Mastectomy Neuropathic Pain

The clinical course described in this case highlights the potential value of a coordinated, multimodal strategy for patients with refractory post-mastectomy neuropathic pain (PMPS) who do not achieve adequate relief from standard pharmacologic or interventional approaches. Contemporary reviews emphasize that PMPS remains challenging to manage, with a substantial proportion of survivors experiencing persistent neuropathic symptoms despite conventional therapy [6,11,12]. In this patient, meaningful reduction in pain intensity, attenuation of tactile allodynia, restoration of sleep continuity, functional recovery, and sustained opioid discontinuation suggest that addressing overlapping biologic and behavioral contributors to pain may be clinically relevant in carefully selected cases.

Rather than relying solely on sequential symptom-based pharmacologic escalation, this case illustrates how a coordinated framework integrating pharmacologic, rehabilitative, and supportive interventions may facilitate more comprehensive recovery. Sustained opioid avoidance without symptom destabilization is particularly notable in the context of survivorship care, where long-term opioid exposure carries risks of dependence, tolerance, and impaired quality of life. Broader chronic pain and integrative oncology literature supports the principle that mechanism-informed, multimodal strategies may reduce opioid reliance while improving functional outcomes [26,55]. In chronic postsurgical pain populations, successful tapering or sustained avoidance of opioid therapy represents a meaningful clinical milestone.

From a survivorship perspective, this patient's postoperative complications—including infection, delayed reconstruction, and lymphedema—represent recognized risk factors for persistent neuropathic pain following breast cancer treatment [1,12]. Rehabilitation and integrative oncology frameworks emphasize coordinated, multidisciplinary approaches to address complex symptom clusters and long-term functional morbidity in this population [35,36]. A structured whole-person model may therefore be particularly relevant for patients whose pain is sustained by interacting inflammatory, neural, and psychosocial contributors.

Importantly, the non-invasive and opioid-sparing characteristics of this approach align with survivorship priorities focused on long-term function, quality of life, and minimization of treatment-related

Table 1: Integrated Mechanistic Actions of Thymosin Alpha-1, Low-Dose Naltrexone, and THC: CBD in Post-Mastectomy Neuropathic Pain.

Mechanistic Domain	Thymosin Alpha-1 (Tα1)	Low-Dose Naltrexone (LDN)	THC:CBD Cannabinoids
Inflammation & Cytokine Modulation	↓ TNF-α, IL-1β, IL-6 via NF-κB suppression; shifts Th1/Th17 to regulatory state (64)	↓ TNF-α, IL-6, IL-1β; TLR-4 blockade dampens immune-driven pain (17).	CB2 activation ↓ inflammatory cytokines; ↑ endocannabinoid tone via FAAH inhibition (20)
Microglial & Glial Activation	↓ microglial signaling and MAPK activity (ERK/JNK/p38) (16)	TLR-4 antagonism reduces microglial cytokine output and central sensitization (17).	CB1/CB2 modulation decreases glial-mediated neuroinflammation (20)
Nerve Repair & Neuroprotection	Anti-apoptotic (↑Bcl-2, ↓Bax), mitochondrial stabilization, improved autophagy (34).	OGF–OGFr axis supports cellular repair and neural recovery (70)	TRPV1/TRPA1 channel modulation decreases ectopic firing and neuropathic symptoms (71).
Central Sensitization Control	↓ dorsal horn excitability via glial down-regulation (64).	↓ NMDA/AMPA activity, ↓ synaptic wind-up, and spinal excitability (60).	CB1 ↓glutamate & substance P release and improves descending inhibition (63).
Immune & Lymphatic Recovery	Enhances T-cell balance, lymphocyte trafficking & tissue resolution after sepsis/lymphedema (64).	↓ chronic inflammatory microenvironment in postsurgical tissues (17).	↓ scar & radiation related inflammation and nociception (21)
Mood, Sleep & Stress Pathways	Stabilizes HPA-axis and cortisol signaling (Besman 2024).	↑ endogenous endorphins & improved emotional coping (66).	5-HT1A activation & sleep improvement reduce affective pain amplification (71).
Opioid-Sparing & Safety Advantages	Enhances immune environment and cannabinoid response (65).	↓ opioid load via endogenous analgesia (66).	↓ opioid reliance via non-opioid analgesic pathways (63)

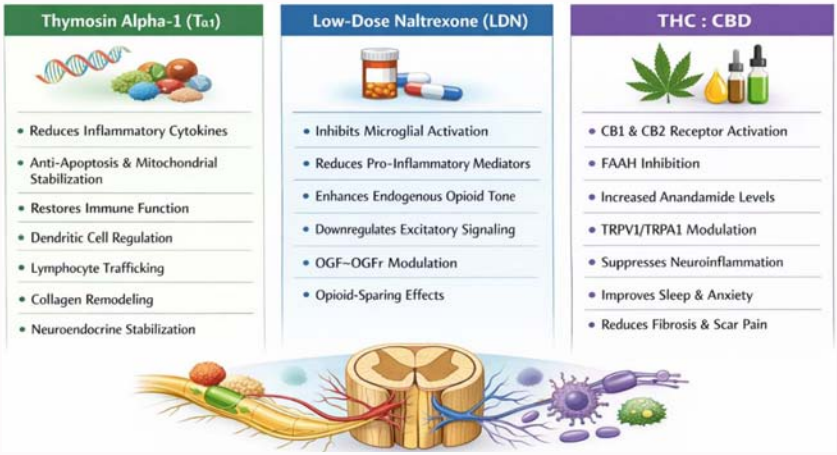

Figure 1: Integrated mechanisms of thymosin alpha-1, low-dose naltrexone, and THC:CBD in post-mastectomy neuropathic pain.
This graphical abstract illustrates how three mechanistically distinct therapies—thymosin alpha-1 (Tα1), low-dose naltrexone (LDN), and THC:CBD cannabinoids—may act synergistically to reduce post-mastectomy neuropathic pain through coordinated modulation of peripheral, central, and immune pathways.
The left panel highlights Tα1's proposed actions in reducing inflammatory cytokine signaling, promoting anti-apoptotic and mitochondrial stabilization pathways, restoring immune homeostasis following surgical or inflammatory stress, regulating dendritic cell function, modulating lymphocyte trafficking, and supporting extracellular matrix remodeling and neuroendocrine stability [14,16].
The central panel depicts LDN's inhibition of microglial activation and toll-like receptor–mediated neuroinflammatory signaling, reduction of pro-inflammatory mediators, enhancement of endogenous opioid tone, downregulation of excitatory neurotransmission, modulation of the OGF–OGFr axis, and opioid-sparing effects [17,47].
The right panel illustrates THC:CBD-mediated mechanisms, including CB1 and CB2 receptor activation, FAAH inhibition with increased endocannabinoid (anandamide) signaling, modulation of TRPV1/TRPA1 and related ion channels, suppression of neuroinflammation, improvement in sleep and anxiety, and reduction of fibrosis- and scar-associated pain [20,48,57].
Collectively, these therapies target key drivers of neuropathic pain, including peripheral inflammation and immune dysregulation, microglial activation and central sensitization, impaired nerve repair, and wound-healing abnormalities. Their combined effects may contribute to a coordinated reduction in neuropathic pain across peripheral, central, and systemic domains.
This figure represents a biologically plausible, hypothesis-generating framework that integrates mechanisms described in the text rather than direct mechanistic measurement.

morbidity [35,36]. While findings from a single case cannot establish efficacy or generalizability, this experience offers a hypothesis-generating model suggesting that coordinated neuroimmune-informed care may warrant systematic evaluation in refractory PMPS populations.

Limitations

This report describes single-patient clinical observation and cannot establish causality or generalizability. The individual contributions of each therapeutic component cannot be isolated, and the relative impact of pharmacologic versus supportive interventions remains uncertain. These constraints are inherent to case-based methodology and should guide cautious interpretation in accordance with CARE guideline principles for single-patient reporting [43].

Objective biomarkers of immune or neuroinflammatory activity were not obtained, and advanced neurophysiologic or neuroimaging assessments were not performed. Pain intensity, sleep quality, and emotional well-being were assessed primarily through patient-reported measures rather than standardized psychometric instruments or polysomnographic evaluation. Although clinically meaningful, reliance on self-report introduces potential reporting and recall bias.

The temporal relationship between intervention and symptom improvement does not exclude the possibility of natural recovery, regression toward the mean, or delayed postoperative stabilization independent of treatment effects. Additionally, structured follow-up extended for approximately two months beyond the 12-week intervention period; longer-term durability beyond this timeframe cannot be confirmed.

Selection bias must also be considered. The patient was highly motivated, engaged in integrative care, and willing to participate in structured supportive interventions—characteristics that may not be representative of the broader population of individuals with refractory post-mastectomy neuropathic pain.

Contextual and expectancy effects inherent to integrative care models may have contributed to symptom improvement. Therapeutic alliance, structured clinical attention, and meaning responses are recognized contributors to analgesic outcomes in chronic pain. The multidisciplinary and supportive nature of care provided in this setting may therefore have influenced both subjective and functional outcomes.

While these limitations preclude definitive mechanistic conclusions, the sustained and multidimensional clinical response observed, including opioid avoidance without symptom destabilization—underscores the need for structured prospective investigation. Sustained opioid reduction represents a clinically meaningful endpoint in chronic pain populations [70-72]. Controlled studies will be required to determine reproducibility, isolate component effects, and clarify mechanistic pathways.

Future Directions

Future research should extend these observations through a structured prospective investigation that incorporates predefined clinical endpoints and mechanistic measures. Prospective case series and controlled pilot studies evaluating multimodal, neuroimmune-

informed strategies for refractory post-mastectomy neuropathic pain (PMPS) are warranted and should build on emerging clinical and conceptual frameworks in this domain [73,74]. Particular attention may be directed toward patients with complex postoperative courses, including infection, delayed reconstruction, radiation exposure, or lymphedema—where overlapping inflammatory and central sensitization mechanisms may contribute to persistent symptom burden.

Integration of objective biologic measures could enhance mechanistic clarity and improve patient stratification. Exploratory translational biomarkers may include inflammatory cytokine profiling, immune cell phenotyping, and assessment of autonomic function. Preclinical and translational research highlights microglial activation and immune–neural crosstalk as central contributors to chronic neuropathic pain, and emerging molecular and imaging approaches may offer avenues for future biomarker development [51,56,75]. Although these methodologies remain largely investigational, incorporating biologic correlates alongside standardized clinical outcomes could strengthen causal inference and refine therapeutic targeting.

Comparative studies evaluating coordinated combination strategies versus single-agent approaches may help clarify relative contributions, optimal sequencing, and dosing considerations. Randomized pilot designs or adaptive trial frameworks could be particularly informative in determining whether multimodal strategies offer additive or synergistic benefits. Rigorous assessment of opioid-sparing endpoints, sleep restoration, and functional recovery would be especially valuable in survivorship-focused research, where long-term quality-of-life outcomes are central. Despite increasing support for multimodal frameworks in the broader chronic pain literature, high-quality studies specific to PMPS remain limited, representing a meaningful opportunity for advancement.

Broader investigation of neuroimmune-modulating strategies may also be relevant to other chronic postsurgical neuropathic pain conditions characterized by persistent inflammation and central sensitization [76]. However, extension beyond PMPS should proceed cautiously and be guided by condition-specific pathophysiology and carefully designed clinical trials.

Ultimately, systematic validation of coordinated neuroimmune modulation will require stepwise translational research integrating clinical endpoints, biologic correlates, and long-term functional outcomes. This case serves as a hypothesis-generating example intended to inform the design of such structured investigation, consistent with prior integrative and mechanism-oriented approaches to complex post-mastectomy complications [73].

Conclusion

This case report describes clinically meaningful and sustained improvement following coordinated use of Thymosin Alpha-1, low-dose naltrexone, and sublingual THC:CBD in a breast cancer survivor with severe, refractory post-mastectomy neuropathic pain. Reduction in pain intensity, restoration of sleep continuity, functional recovery, and durable opioid avoidance were observed within a conceptual framework consistent with integrated modulation of inflammatory, neuroimmune, and stress-related contributors to chronic postsurgical pain.

As a single-patient observation, these findings cannot establish

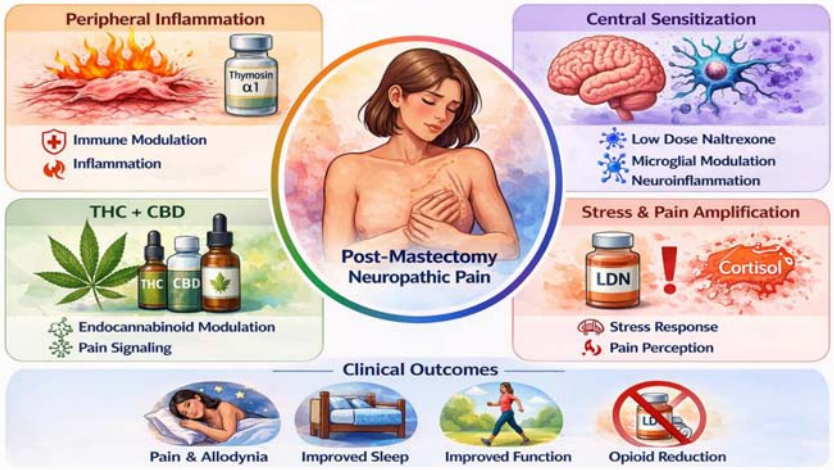

Figure 2: Integrated neuroimmune-informed multimodal strategy for refractory post-mastectomy neuropathic pain.
This conceptual schematic illustrates a multimodal, neuroimmune-informed therapeutic framework targeting key biological mechanisms implicated in persistent post-mastectomy neuropathic pain, including peripheral inflammation, central sensitization, and stress-related amplification pathways [1,51]. These interrelated processes are increasingly recognized as central contributors to chronic postsurgical pain through sustained neuroimmune dysregulation and maladaptive signaling within peripheral and central nervous system pathways.
Thymosin alpha-1 (Tα1) is depicted as supporting immune homeostasis and attenuating peripheral inflammatory signaling, thereby potentially modulating cytokine-driven neuroimmune activation [14,16]. Low-dose naltrexone (LDN) is represented as influencing microglial activation and toll-like receptor–mediated neuroinflammatory pathways associated with central sensitization and amplification of pain signaling [17,47]. A balanced THC:CBD formulation is illustrated as modulating nociceptive transmission and neuroimmune cross-talk through effects on the endocannabinoid system, with potential downstream effects on both peripheral and central pain processing pathways [20,48,57].
Together, these interventions are proposed to act on complementary and interacting domains within the neuroimmune axis, contributing to reduction in neuropathic pain intensity and tactile allodynia, improvement in sleep continuity and functional capacity, and facilitation of sustained opioid avoidance.
This integrated model highlights the potential importance of targeting multiple converging biological pathways rather than isolated mechanisms in the management of refractory post-mastectomy pain. The schematic represents a biologically plausible, hypothesis-generating framework derived from the present case and supported by existing literature, rather than direct mechanistic measurement, and is intended to inform future translational and clinical investigation of integrative neuroimmune-targeted therapeutic strategies.

causality or generalizability. Rather, this case serves as a hypothesis-generating example suggesting that mechanism-informed, multimodal strategies targeting interconnected peripheral and central processes may warrant structured investigation in carefully selected survivorship populations. Contemporary integrative oncology and survivorship models emphasize patient-centered, coordinated approaches to persistent neuropathic pain following cancer treatment [35,74,77].

Prospective and controlled studies will be required to clarify component-specific effects, validate mechanistic pathways, and determine reproducibility across broader patient cohorts. Systematic evaluation of coordinated neuroimmune-informed care may contribute to the refinement of future therapeutic frameworks for refractory post-mastectomy neuropathic pain.

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The authors express appreciation to the patient described in this report for her willingness to share her clinical experience to contribute to medical understanding of post-mastectomy neuropathic pain. The authors also acknowledge the broader community of breast cancer survivors whose experiences continue to inform efforts to improve survivorship care and symptom management (Figure 2).

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