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Narrative Review

NPM-Patch: A conceptual AI-enabled closed-loop microneedle system for tetrodotoxin delivery via Tet1-functionalized hollow silica nanoparticles in refractory cancer pain

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Abstract

Refractory cancer pain remains challenging to manage, particularly in advanced disease, in which opioid-based therapies may provide inadequate analgesia and are frequently limited by dose-related adverse effects. Tetrodotoxin (TTX), a selective blocker of voltage-gated sodium channels, represents a potential non-opioid analgesic; however, its clinical application is constrained by a narrow therapeutic window, limited tissue targeting, and the risk of systemic toxicity. This narrative review presents the NPM-Patch (Neuro-Precision Marine Patch), a conceptual drug-delivery framework integrating Tet1-functionalized hollow silica nanoparticles, a pH-responsive microneedle matrix, and an artificial intelligence–enabled closed-loop control system. Conceptually, this framework could improve neuronal targeting, facilitate controlled and sustained TTX release, and permit adaptive dose regulation based on physiological feedback. A dual-trigger release mechanism is proposed to favor localized drug release while potentially reducing systemic exposure and unintended central nervous system delivery. The integration of neuron-targeted nanocarriers, minimally invasive transdermal administration, and adaptive dose regulation may provide a basis for developing a precision-oriented approach to refractory cancer pain. However, the feasibility, pharmacokinetics, targeting specificity, analgesic efficacy, device reliability, and safety of this concept require rigorous preclinical evaluation before its potential clinical translation can be assessed.

Keywords: Cancer pain, tetrodotoxin, hollow silica nanoparticles, microneedle patch, artificial intelligence

Introduction

Cancer-related pain is among the most debilitating complications of advanced malignancy and substantially affects patients' physical functioning, psychological well-being, and quality of life. Its management becomes particularly challenging when adequate analgesia cannot be achieved with conventional therapeutic regimens. Pain has been reported in approximately 70–90% of patients with stage III-IV cancer, although estimates vary according to cancer type, disease stage, and assessment method [1]. Pharmacological management commonly includes opioids, either alone or in combination with nonsteroidal anti-inflammatory drugs and adjuvant analgesics [2,3]. Opioids remain central to cancer pain management but may provide inadequate relief and can cause constipation, sedation, respiratory depression, tolerance, and dependence [2,3]. These limitations highlight the need for safer, more targeted, and mechanistically distinct analgesic strategies for refractory cancer pain.

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Cancer pain may involve overlapping nociceptive, neuropathic, inflammatory, and ischemic mechanisms arising from tumor invasion, peripheral nerve compression, bone metastases, and treatment-related neural injury [3]. Neuropathic mechanisms and neural injury may contribute to poor analgesic responses in some patients, even after opioid dose escalation [3,4]. Systemic opioid therapy also lacks anatomical specificity and exposes both target and non-target tissues, limiting further dose escalation when adverse effects occur [2,3]. Consequently, persistent pain may coexist with treatment-related morbidity and impaired quality of life, supporting the investigation of approaches with improved anatomical and mechanistic targeting.

Voltage-gated sodium channels (VGSCs) contribute to the initiation and propagation of nociceptive signals, and altered activity of tetrodotoxin-sensitive subtypes may promote neuronal hyperexcitability and persistent pain [5-7]. Tetrodotoxin (TTX), a potent marine-derived neurotoxin, blocks several VGSC subtypes and has therefore been investigated as a non-opioid analgesic [5-7]. Randomized trials and systematic reviews suggest that carefully controlled subcutaneous TTX may provide pain relief in some patients with cancer-related or chemotherapy-induced neuropathic pain [4,8,9]. Tet1-functionalized carriers have also shown peripheral neuronal targeting in preclinical morphine-delivery models [10]. Tet1 is a 12-amino-acid neuron-targeting peptide derived from the receptor-binding region of the tetanus toxin heavy chain that preferentially binds to GT1b ganglioside receptors on neuronal membranes. Nevertheless, TTX development remains constrained by its narrow therapeutic window, potential systemic toxicity, and the absence of a validated platform for localized and temporally controlled delivery [5,11,12].

Recent advances in nanotechnology and smart drug-delivery systems may provide strategies to address some of these limitations. pH-responsive nanocarriers, neuron-targeting ligands, and minimally invasive transdermal platforms have been investigated to improve localized delivery and reduce systemic exposure [13-15]. Closed-loop drug-delivery architectures may further support adaptive regulation based on physiological feedback, although their application to TTX remains conceptual [16,17]. Based on this background, this narrative review introduces the NPM-Patch (Neuro-Precision Marine Patch), a conceptual AI-enabled closed-loop microneedle platform integrating TTX-loaded, Tet1-functionalized hollow silica nanoparticles. The framework is proposed as a basis for investigating localized, controlled, and potentially adaptive TTX delivery for refractory cancer pain.

Tetrodotoxin (TTX) as a potential non-opioid analgesic for cancer pain

TTX is a potent marine neurotoxin naturally occurring in pufferfish of the family Tetraodontidae and several other marine organisms. It blocks tetrodotoxin-sensitive VGSCs, inhibits sodium influx, suppresses neuronal depolarization and action-potential conduction, and thereby interrupts nociceptive signal transmission [5-7]. Preclinical studies have demonstrated antinociceptive effects in models of neuropathic and cancer-related pain [5,7]. Because TTX does not act through opioid receptors, it may avoid some opioid-mediated adverse effects; however, its narrow therapeutic window and potential neurotoxicity remain major safety concerns. Systematic reviews and randomized trials indicate that subcutaneous TTX may increase the likelihood of clinically meaningful pain relief and may prolong analgesia in some patients [4,8,9]. These findings should be interpreted cautiously because the available trials are few and heterogeneous. The chemical structure of TTX and its analgesic mechanism through the blockade of TTX-sensitive VGSCs are presented in **Figure 1**.

The principal clinical studies evaluating TTX for cancer-related and chemotherapy-induced neuropathic pain are summarized in **Table 1**. Available meta-analyses suggest that TTX may increase the proportion of patients achieving clinically meaningful pain relief, although non-serious adverse events such as transient paresthesia and nausea may be more frequent [9]. No statistically significant increase in serious adverse events has been identified; however, the limited number and size of the trials preclude firm safety conclusions [9]. The analgesic effects of TTX are attributed mainly to blockade of TTX-sensitive VGSC subtypes, including NaV1.6 and NaV1.7, which are implicated in neuronal hyperexcitability and persistent neuropathic pain [5,7].

TTX may therefore represent a potential option for refractory cancer pain or chemotherapy-induced neuropathic pain, but further controlled studies are required.

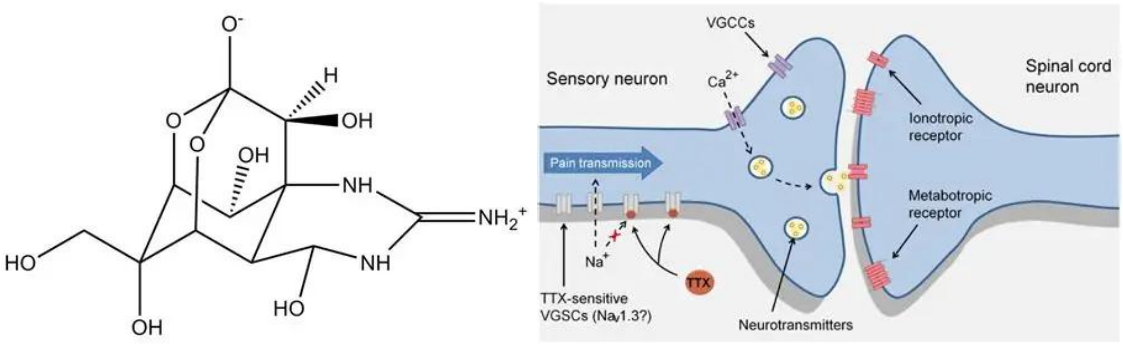

Figure 1. Chemical structure and analgesic mechanism of tetrodotoxin (TTX). TTX blocks tetrodotoxin-sensitive voltage-gated sodium channels, thereby inhibiting sodium influx, neuronal depolarization, action-potential propagation, and nociceptive signal transmission [6,7].

Table 1. Summary of clinical evidence on tetrodotoxin (TTX) for cancer-related and chemotherapy-induced neuropathic pain

Study	Study design	Population	TTX dose and route	Primary outcome	Key findings
Hagen *et al.*, 2017 [4]	Randomized, double-blind, placebo-controlled trial	Advanced cancer pain refractory to conventional analgesics	30 µg TTX, subcutaneous (SC), twice daily for 4 days	At least 30% pain reduction and duration of analgesic response	Higher responder rate than placebo and prolonged analgesia
Huerta *et al.*, 2023 [9]	Systematic review and meta-analysis of randomized controlled trials	Cancer-related pain	TTX, SC; regimens varied	Pain reduction and safety	Evidence of analgesic benefit; conclusions limited by few trials
Goldlust *et al.*, 2021 [8]	Randomized, double-blind, placebo-controlled dose-finding trial	Chemotherapy-induced neuropathic pain	7.5–30 µg TTX, SC	Numeric pain rating scale scores	Signals of efficacy at 30 µg twice daily; findings varied across outcomes

Tet1-hollow silica nanoparticle (Tet1-HSN) nanotechnology architecture for targeted tetrodotoxin delivery

Despite its analgesic potential, free TTX presents several delivery challenges. Its hydrophilicity limits passive penetration across lipid-rich biological barriers, and preclinical evidence suggests that nanocarrier encapsulation may improve penetration into peripheral nerves [7,11,18]. Clinical studies have generally evaluated parenteral rather than passive transdermal administration [4,8,9]. Non-targeted exposure may affect peripheral nerves, autonomic pathways, and skeletal muscle, producing dose-dependent neurological and cardiorespiratory toxicity [11,12,19]. Skin permeability may also vary according to barrier integrity and local conditions; this is relevant in patients with treatment-related skin injury [20,21]. These considerations support the investigation of carrier-based localization and controlled release. In the proposed NPM-Patch, hollow silica nanoparticles (HSNs) serve as the nanocarrier and Tet1 as the neuronal-targeting ligand. The proposed synthesis and functionalization process for the TTX-loaded Tet1-HSN nanocarrier is illustrated in **Figure 2**.

HSNs consist of a porous silica shell surrounding an internal cavity and can provide high loading capacity and controlled release [18,22-24]. In the proposed NPM-Patch, particle diameter, pore size, shell thickness, surface charge, and ligand density would need to be optimized experimentally rather than fixed a priori. Amorphous silica is attractive because its surface silanol groups permit functionalization, although biocompatibility depends on particle

characteristics, dose, purity, and manufacturing quality [22-24]. Template residues such as cetyltrimethylammonium bromide should be removed to minimize cytotoxicity [23,24]. In a preclinical study, TTX-loaded HSNs achieved 49% loading efficiency and prolonged nerve blockade from 79.5 minutes with free TTX to 274 minutes with the HSN formulation, with an improved systemic safety profile in the tested model [18]. These findings support HSNs as a candidate carrier but do not establish the safety or efficacy of the proposed transdermal system.

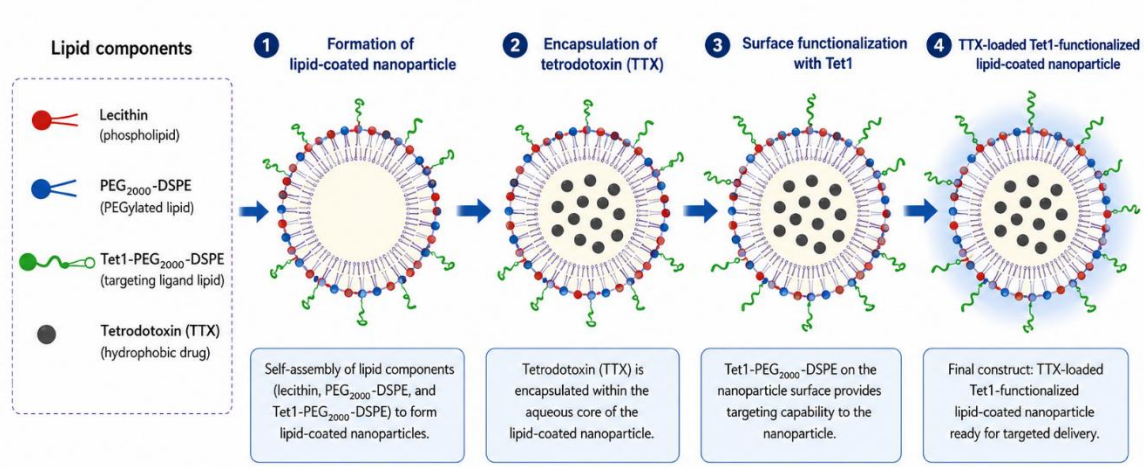

Figure 2. Proposed synthesis and functionalization of the tetrodotoxin (TTX)-loaded Tet1-hollow silica nanoparticle (Tet1-HSN) nanocarrier.

To improve neuronal localization, the proposed carrier is functionalized with Tet1, the Tet1 peptide (HLNILSTLWKYRC) that should not be confused with the TET1 enzyme. Tet1 recognizes neuronal gangliosides, including GT1b, and has been investigated as a ligand for peripheral nerve targeting [10,25,26]. In morphine-loaded lipid nanoparticle models, Tet1 functionalization increased neuronal uptake and dorsal root ganglion accumulation and reduced brain exposure relative to free morphine [10]. The same platform prolonged analgesia in a chronic constriction injury model [10]. These findings support the targeting principle but cannot be directly extrapolated to TTX, HSNs, transdermal administration, or human cancer pain. The proposed structure of the TTX-loaded Tet1-HSN nanocarrier and its neuronal-targeting mechanism are illustrated in **Figure 3**.

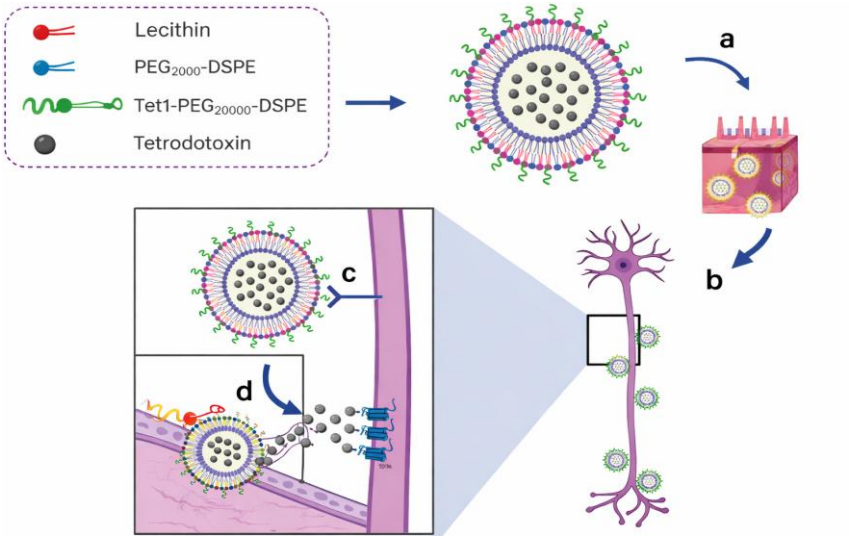

Figure 3. Proposed structure and mechanism of action of the tetrodotoxin (TTX)-loaded Tet1-hollow silica nanoparticle (Tet1-HSN) nanocarrier.

However, neuronal uptake and retrograde axonal transport create a theoretical safety concern. GT1b gangliosides are present in peripheral and central nervous tissues, and tetanus-

toxin-derived targeting pathways can facilitate neuronal internalization [25,26]. An intact carrier-payload complex could therefore potentially transport TTX toward central structures. TTX poisoning can cause progressive paralysis, respiratory failure, and death; lethal doses in adults have been reported in approximately the 1–2 mg range [19]. The proposed design incorporates an acid-labile hydrazone element and an esterase-cleavable element to favor release before prolonged neuronal transport. Hydrazone and oxime linkers can undergo acid-catalyzed cleavage [27], and the skin exhibits a pH gradient from an acidic surface toward near-neutral viable layers [28]. However, whether this gradient would produce sufficiently rapid and spatially selective TTX release after microneedle insertion is unknown. Linker kinetics must therefore be evaluated directly against neuronal uptake, retrograde transport, systemic exposure, and central nervous system toxicity.

NPM-Patch: A pH-responsive smart microneedle system

A dissolving microneedle patch provides a minimally invasive transdermal interface by traversing the stratum corneum and depositing the payload within viable skin [29,30]. Hyaluronic acid is widely used in dissolving microneedles because it dissolves in interstitial fluid and can support rapid release after insertion [30]. Chitosan can exhibit pH-dependent protonation, swelling, and permeability [31]. The proposed HA-chitosan matrix is therefore intended to combine rapid insertion-site dissolution with pH-responsive modulation. Although extracellular pH may be lower in some tumor tissues [32], the skin at the intended application site may not provide a consistent trigger. Release behavior should therefore be characterized across physiological and disease-relevant pH conditions.

The proposed system has two release phases: an early phase driven by hyaluronic acid microneedle dissolution and a sustained phase mediated by HSNs. Rapid hyaluronic acid dissolution may support initial delivery [30], whereas HSN porosity may permit higher loading and slower release [18,22-24]. A separate animal study of gelatin-functionalized mesoporous silica nanoparticles reported pharmacodynamic activity for up to 21 days [33]. However, this evidence does not establish a 21-day TTX release profile or justify a weekly replacement schedule for NPM-Patch. Release duration, dose reproducibility, and replacement intervals require empirical determination. The proposed targeted delivery of Tet1-HSN nanoparticles through the microneedle is illustrated in **Figure 4**.

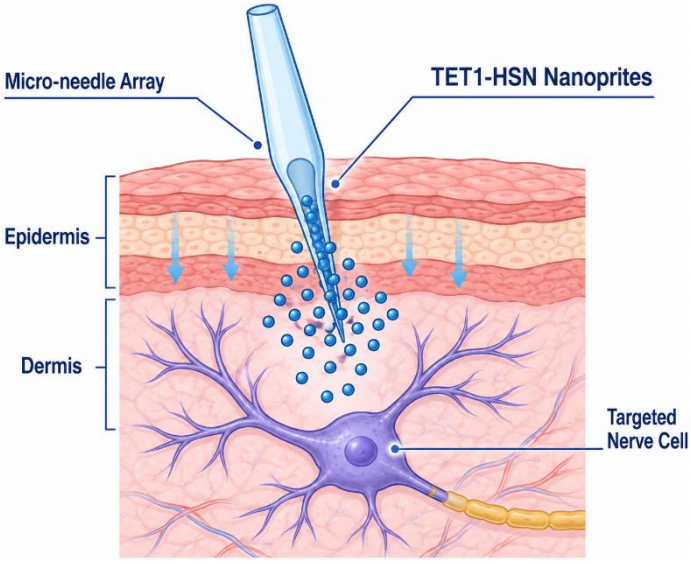

Figure 4. Proposed targeted delivery of Tet1-hollow silica nanoparticle (Tet1-HSN) nanoparticles through a microneedle array.

Integrated AI-based logic and closed-loop control architecture in the NPM-Patch

The management of refractory cancer pain is dynamic because of tumor progression, neuroinflammatory processes, and interindividual variability in analgesic response. Fixed dosing

schedules may therefore fail to accommodate temporal changes in pain intensity and treatment tolerance. Closed-loop systems integrate sensing, computational control, and actuation to adjust delivery according to physiological feedback [16,17]. In the proposed NPM-Patch, sensors would monitor skin temperature, impedance, and, if technically feasible, biochemical correlates of nociceptive activity. These measures are indirect and would require validation against patient-reported pain, neurological status, and TTX exposure. The architecture should therefore be considered conceptual rather than clinically deployable. The principal sensing, computational control, actuation, and feedback components of the proposed closed-loop system are illustrated in **Figure 5**.

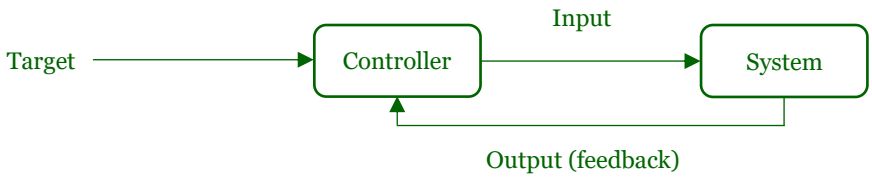

Figure 5. Basic elements of a closed-loop control system [34].

At the computational level, a simplified digital-twin-inspired model is proposed to represent the temporal evolution of the patient's pain-related state. Reinforcement-learning and closed-loop approaches have been explored for adaptive drug delivery, but their performance depends on model validity, reliable sensor input, and externally defined safety constraints [34,35]. The proposed state equation is: $dH(t)/dt=\alpha H(t)+\beta B(t)-\gamma T(t)$, where $dH(t)/dt$ is the rate of change in pain-related burden over time; $H(t)$ is a composite representation of pain intensity, neural excitability, and functional impairment; α is the disease-progression coefficient; $B(t)$ is a time-dependent pain-associated biomarker, such as substance P or calcitonin gene-related peptide; β is the biomarker-sensitivity coefficient; $T(t)$ is the effective TTX dose delivered by the NPM-Patch; and γ is the treatment-response coefficient. Higher values of $H(t)$ indicate greater pain-related burden.

Dose recommendations could be generated using an actor-critic reinforcement-learning framework [34,35]. Within this framework, the actor would propose bounded dose adjustments, whereas the critic would estimate the expected analgesic benefit and safety of each action. Translating a digital command into controlled TTX release would require a validated actuator capable of modifying release from the microneedle-nanocarrier system; such an actuator has not yet been demonstrated for NPM-Patch. The controller should therefore be regarded as a conceptual decision-support architecture rather than an established autonomous dosing system.

Any future controller should impose hard constraints on dose magnitude, rate of change, and cumulative exposure [16,17,34]. Automated anomaly detection and safe-mode activation should suspend adaptive control when sensor failure or unexpected physiological changes are detected. The interface should display sensor trends, model predictions, dosing history, and uncertainty to support clinician review. Interpretability and human oversight are essential, and algorithmic control should support rather than replace clinical judgment [17,34].

Economic evaluation considerations

The economic value of the NPM-Patch cannot be determined until its clinical effectiveness, safety, manufacturing costs, device lifespan, monitoring requirements, and effects on healthcare utilization have been established. A future economic evaluation should compare the NPM-Patch with the current standard of care, including opioid-based therapy, adjuvant analgesics, nerve blocks, and relevant neuromodulation approaches. The assessment should consider healthcare-system and societal perspectives, direct and indirect costs, quality-adjusted life-years, budget impact, and uncertainty in key model parameters. The proposed elements, outcomes, data sources, and analytical approaches for a future economic evaluation of the NPM-Patch are summarized in **Table 2**.

Liestyadi et al. Narra Review 2026; 2 (2): e28 - http://doi.org/10.52225/narrarev.v2i2.28

Table 2. Proposed framework for the future economic evaluation and cost-effectiveness assessment of the NPM-Patch

Evaluation component	Measure or focus	Description	Potential data source or method
Intervention and comparators	NPM-Patch	AI-enabled microneedle system for targeted TTX delivery	Future preclinical and clinical studies
	Standard of care	Opioids, adjuvant analgesics, and interventional pain procedures	Clinical guidelines and routine-care data
	Alternative therapies	Neuromodulation and other advanced pain interventions	Comparative literature
Perspective	Health-care system	Costs to hospitals and payers	Cost-of-illness studies
	Societal	Productivity loss and caregiver burden	Societal costing studies
Time horizon	Short term	6-12 months for early pain-control outcomes	Trial-based analysis
	Long term	Multiyear or lifetime horizon for chronic pain management	Decision-analytic modeling
Direct medical costs	Device acquisition	Cost per patch and supporting hardware	Future manufacturer and procurement data
	Application and monitoring	Staff time, sensor monitoring, and clinical oversight	Time-and-motion and hospital costing
	Hospitalization	Potential changes in pain crises and admissions	Claims and hospital data
	Medications	Potential changes in opioid and adjuvant use	Pharmacy data
Indirect costs	Productivity loss	Work absence and reduced productivity due to pain	Work Productivity and Activity Impairment questionnaire or comparable instruments
	Caregiver time	Informal care burden	Patient and caregiver surveys
Effectiveness outcomes	Pain reduction	Change in validated pain scores, such as the Brief Pain Inventory	Clinical studies
	Quality-adjusted life-years	Utility-weighted survival	Utility measurement and modeling
Incremental analysis	Incremental cost	Cost difference versus standard of care	Economic model
	Incremental effectiveness	Difference in quality-adjusted life-years versus standard of care	Model output
Cost-effectiveness	Incremental cost-effectiveness ratio	Incremental cost per quality-adjusted life-year gained	Primary decision metric
Budget impact	Annual budget impact	Financial consequences of population-level adoption	Payer simulation
Uncertainty	Sensitivity analyses	One-way and probabilistic analyses of parameter uncertainty	Scenario and Monte Carlo analyses
Policy considerations	Willingness-to-pay threshold	Country-specific decision threshold	Policy references
	Access and affordability	Availability across health-care settings and patient groups	Health-equity analysis
Interpretation	Cost-effectiveness conclusion	Value-based assessment to inform, not determine, policy decisions	Integrated economic analysis

Implementation and stakeholder considerations

Translation of the NPM-Patch from a conceptual framework into a testable medical platform would require coordinated contributions from government, academia, industry, community and media, and environmental stakeholders. Government institutions would provide regulatory oversight, policy support, and research funding; academia would lead preclinical and clinical validation; industry would support manufacturing, quality control, and scale-up; community and media stakeholders would contribute to public engagement and health literacy; and environmental stakeholders would address ethical and sustainable sourcing of marine-derived TTX. The proposed roles of these stakeholder groups are summarized in **Table 3**, and their relationships within the penta-helix framework are illustrated in **Figure 6**.

Figure 6. Proposed penta-helix framework for NPM-Patch development and clinical translation. The framework highlights the complementary roles of government, academia, industry, community and media, and environmental stakeholders in supporting regulation, scientific validation, manufacturing, public engagement, and sustainable resource use.

Table 3. Proposed penta-helix stakeholder framework for NPM-Patch development

Stakeholder sector	Core role	Potential inputs	Potential outputs	Intended contribution
Government	Governance and funding	Public-health need for safer pain management and ethical oversight	Regulatory pathways, research funding, and precision-medicine policies	Could provide legal, safety, and funding frameworks for development.

Stakeholder sector	Core role	Potential inputs	Potential outputs	Intended contribution
Academia	Research and validation	Scientific questions, preclinical evidence, and methodological expertise	Peer-reviewed evidence, validation studies, and a skilled workforce	Could provide scientific credibility and technical expertise.
Industry	Scale-up and translation	Validated prototypes, regulatory requirements, and market needs	Scalable manufacturing, quality assurance, and distribution systems	Could translate validated prototypes into accessible products.
Community and media	Social integration	Patient priorities, lived experience, and public concerns	Health communication, patient engagement, and improved health literacy	Could build trust and support informed adoption.
Environment	Sustainability and ethics	Marine biodiversity, sourcing constraints, and environmental risks	Sustainable sourcing standards, environmental assessment, and ethical guidance	Could reduce ecological harm and support responsible TTX sourcing.

Conclusion

NPM-Patch is a conceptual framework rather than an established treatment for refractory cancer pain. It integrates TTX-mediated VGSC blockade, Tet1-guided neuronal targeting, HSN nanoencapsulation, a proposed dual-trigger HA-chitosan microneedle matrix, and an AI-enabled closed-loop control layer. These components could support localized and adaptive delivery, but their combined pharmacology, manufacturability, sensor validity, actuator performance, and safety have not been demonstrated. Future studies should prioritize formulation characterization, dermal release kinetics, neuronal targeting, systemic and central nervous system exposure, retrograde transport, dose-response relationships, device reliability, and preclinical analgesic and toxicological outcomes before clinical translation is considered.

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Competing interests

Nothing to declare.

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Underlying data

No new data were generated or analyzed in this narrative review.

Declaration of artificial intelligence use

The artificial intelligence tool, ChatGPT, was used for language editing and refinement, including improvement of grammar, sentence structure, and readability. The authors confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were made solely by the authors.

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