

REVIEWS

PHARMACOLOGICAL POTENTIAL OF CONOTOXINS: FROM MARINE VENOM TO A NEW GENERATION OF ANALGESICS

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ABSTRACT

INTRODUCTION: Conotoxins are disulfide-rich peptide neurotoxins from marine cone snails that selectively modulate ion channels and receptors involved in nociceptive signalling. Their subtype selectivity has established them as valuable pharmacological tools and promising leads for analgesic drug development.

AIM: This review evaluates the pharmacological potential of conotoxins as analgesic candidates and examines the main barriers limiting their clinical translation.

MATERIALS AND METHODS: A structured narrative literature review was conducted using PubMed, Scopus, Web of Science, and Google Scholar. Publications addressing conotoxin pharmacology, structural biology, chemical modification, preclinical analgesic activity, and clinical translation were included, whereas non-analgesic marine peptides and studies without relevance to pain-associated targets were excluded.

RESULTS: The strongest available evidence concerns ω -conotoxin MVIIA (ziconotide), a selective N-type voltage-gated calcium channel blocker approved for the intrathecal treatment of severe refractory chronic pain. α -Conotoxins such as Vc1.1 and Rg1A have shown antinociceptive effects in neuropathic pain models, partly through GABAB receptor-mediated inhibition of CaV2.2 channels. μ -Conotoxins targeting neuronal sodium channels, particularly NaV1.7, represent additional promising lead structures for analgesic development. Chemical modification strategies, including backbone cyclisation, disulfide replacement, and residue substitution, have improved peptide stability and pharmacological performance in preclinical studies.

CONCLUSION: Conotoxins represent a pharmacologically validated class of analgesic candidates whose clinical translation remains limited. Further progress depends on improved peptide stability, systemic delivery, human-target selectivity, therapeutic-window definition, and well-designed clinical trials.

Keywords: conotoxins, conopeptides, analgesics, neuropharmacology, peptide therapeutics, ziconotide

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1. INTRODUCTION

Chronic pain constitutes one of the most prevalent and economically burdensome conditions in contemporary medicine. Epidemiological data indicate that neuropathic pain alone affects approximately 7–8% of the general population in Europe, and the societal cost of chronic pain in the United States has been estimated to exceed USD 560 billion

annually [1]. Current pharmacological management relies predominantly on opioid analgesics, anticonvulsants such as gabapentin and pregabalin, tricyclic antidepressants, and non-steroidal anti-inflammatory drugs [2]. A systematic review and meta-analysis by Finnerup et al. demonstrated that these agents achieve meaningful pain relief in fewer than half of patients [3]. They are also frequently associated with adverse effects that compromise long-term tolerability. In the case of opioids, their use is further limited by significant risks of dependence and misuse. This therapeutic limitation creates a persistent need for analgesic agents with distinct structural and pharmacological profiles.

The genus *Conus* comprises an estimated 700–1,000 species of predatory marine gastropods distributed predominantly in tropical and subtropical coastal waters [4,5]. Each species employs a venom apparatus consisting of a specialised gland that synthesises a complex and species-specific mixture of peptide neurotoxins, collectively designated conotoxins or conopeptides. Individual venom profiles contain over 100 distinct peptides, and the total estimated diversity of conotoxin sequences across the genus exceeds 200,000 [6]. Despite this diversity, less than 0.1% of existing conotoxin sequences have been functionally and structurally characterised, indicating that this peptide family remains a largely unexplored source of pharmacological activity [7].

Conotoxins are characterised by their compact size (typically 10–45 amino acids), disulfide-rich frameworks, and extensive post-translational modifications including hydroxylation, glycosylation, γ -carboxylation, and C-terminal amidation [8]. Their structural diversity supports a corresponding pharmacological diversity: individual conotoxin families target voltage-gated calcium channels (VGCCs), voltage-gated sodium channels (VGSCs), voltage-gated potassium channels (VGKCs), nicotinic acetylcholine receptors (nAChRs), N-methyl-D-aspartate (NMDA) receptors, G-protein-coupled receptors, and monoamine transporters [9]. Gene-superfamily classification, based on signal-peptide sequence similarity, currently recognises more than 20 major superfamilies [10,11]. This systematic classification framework facilitates the annotation of newly discovered sequences and the prediction of putative targets.

The translational relevance of conotoxins is best exemplified by ziconotide (Prialt®), a synthetic equivalent of ω -conotoxin MVIIA isolated from *Conus magus*. Ziconotide was approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as an intrathecal analgesic for severe refractory chronic pain [12–14]. Its clinical approval provides proof of concept that a marine-derived peptide neurotoxin can be developed into a safe and effective analgesic drug, although its use requires a specific and technically demanding route of administration. Several additional conotoxin-derived candidates, including α -conotoxin Vc1.1 (ACV1), conantokin-G (CGX-1007), and contulakin-G (CGX-1160), have entered early-phase clinical evaluation, though none has progressed to regulatory approval [15].

Nevertheless, the strength of evidence differs substantially among targets. CaV2.2 blockade is clinically validated through ziconotide, whereas NaV- and nAChR-targeting conotoxins are still supported mainly by preclinical, electrophysiological, and pharmacological data.

The pharmacological interest in conotoxins as analgesic candidates stems from three principal properties. First, their evolutionary refinement over millions of years has optimised them for high potency and selectivity toward defined ion-channel subtypes, enabling discrimination between closely related isoforms with distinct roles in pain processing. Second, the structural compactness of conotoxins makes them amenable to solid-phase peptide synthesis and rational chemical modification. Third, several conotoxin classes act on validated analgesic targets, including CaV2.2, NaV1.7, NaV1.8, and $\alpha 9\alpha 10$ nAChRs, for which the genetic evidence from human pain disorders provides strong biological rationale [16].

This review evaluates the pharmacological potential of conotoxins as analgesic candidates, integrating evidence from preclinical mechanistic studies, structural biology, chemical modification studies, and available clinical data.

2. MATERIALS AND METHODS

2.1 Study Design

The present study was designed as a structured literature review. The review did not follow the PRIS-

MA framework for systematic reviews, because its primary objective was to provide a critical thematic synthesis of pharmacological evidence rather than a quantitative meta-analysis of a specific clinical question. The approach is therefore characterized as a structured review in accordance with the conventions of the field.

2.2 Database Search Strategy

The literature was retrieved from four major scientific databases: PubMed/MEDLINE, Scopus, Web of Science (Core Collection), and Google Scholar. The search was conducted in April 2026 and covered publications from 1985 to 2026, with a focus on studies published after 2000. The following Boolean search strategy was used and adapted for each database: (“conotoxin” OR “cono peptide” OR “cone snail venom”) AND (“analgesic” OR “pain” OR “neuropathic pain” OR “antinociceptive”) AND (“CaV2.2” OR “N-type calcium channel” OR “NaV1.7” OR “NaV1.8” OR “nicotinic acetylcholine receptor” OR “GABAB receptor” OR “NMDA receptor”). Secondary sources were identified by manual checking of the reference lists of key reviews and notable experimental articles.

2.3 Inclusion and Exclusion Criteria

The initial broad search identified more than 3000 records related to conotoxins and conopeptides. After refining the search strategy to include analgesic mechanisms, pain-related molecular targets, and clinical or preclinical pharmacological relevance, 351 records were reviewed by title and abstract. Forty-eight articles were assessed in full text, and 30 publications were included in the thematic synthesis.

Studies were excluded if they addressed marine peptides unrelated to *Conus* species and lacking pharmacological comparability to conotoxins. Publications were also excluded when they did not report data related to analgesic mechanisms or pain-related molecular targets. Duplicate publications and conference abstracts were not considered.

2.4 Data Extraction and Synthesis

For each included source, the following information was extracted: study type and design, class of conotoxins or specific peptide studied, molecular target(s), key pharmacological findings, and relevance to analgesic development. The extracted data were synthesized thematically and mechanistically, rather than presented in chronological order. A structured table of references was created to provide transparency regarding the evidence base of the review (Table 1).

Table 1. Publications included in the thematic synthesis of conotoxin pharmacology and analgesic development.

Author(s)/Year	Study Type	Conotoxin/Class	Biological Target	Main Pharmacological Finding
Terlau & Olivera (2004)	Comprehensive review	Multiple families	VGCCs, VGSCs, nAChRs, GPCRs	Described the structural and target diversity of cone snail peptides; laid the foundation for conotoxin pharmacology.
Lewis & Garcia (2003)	Review	ω -, μ -, α -conotoxins	Ion channels & receptors	Evaluated therapeutic potential of venom peptides; highlighted selectivity for defined channel subtypes.
Jin et al. (2019)	Comprehensive review/chemistry	All major families	VGCCs, VGSCs, nAChRs, transporters	Systematic overview of >10,000 conotoxin sequences; synthesis, structural classes, and pharmacological profiles.
Robinson & Norton (2014)	Review/bioinformatics	All gene superfamilies	Multiple	Defined the gene-superfamily classification of conotoxins based on signal-peptide homology.
Kaas et al. (2012)	Database/annotation	All classes	Multiple	Updated ConoServer database; tools for sequence classification and structural prediction.

Akondi et al. (2014)	Review/SAR	Multiple classes	VGSCs, nAChRs, VGCCs	Synthesis strategies and SAR analysis for conotoxins; identified structural determinants of selectivity.
Schmidtke et al. (2010)	Clinical review	ω -conotoxin MVIIA (ziconotide)	N-type Ca^{2+} channel (CaV2.2)	Summarised clinical evidence for intrathecal ziconotide in severe chronic pain; approved by FDA and EMA.
Lin et al. (2024)	Comprehensive review	Ziconotide	CaV2.2	Updated pharmacology, clinical pharmacokinetics, adverse-effect profile, and dosing of ziconotide.
Miljanich (2004)	Review	ω -MVIIA (ziconotide)	N-type VGCC	Described mechanism of N-type channel block and analgesic mechanism; landmark paper for the drug.
Rauck et al. (2006)	Double-blind RCT	Ziconotide	CaV2.2, spinal cord	Demonstrated significant pain reduction vs. placebo in severe chronic pain; key clinical trial.
Hannon (2013)	Review	ω -conotoxins	CaV2.2, CaV2.1	Evaluated ω -conotoxins as experimental tools and therapeutics; compared GVIA and MVIIA.
Pei et al. (2024)	Review	μ -conotoxins	NaV1.1–1.9	Comprehensive review of conotoxins targeting voltage-gated sodium channels; selectivity profiles.
McMahon et al. (2022)	Experimental/ pharmacology	μ -conotoxins SxIIIC, SmIIIA, KIIIA	hNaV1.7	Identified SxIIIC as a potent, near-irreversible hNaV1.7 inhibitor; compared selectivity of three μ -conotoxins.
Ekberg et al. (2012)	Review	μ -, μ O-conotoxins	VGSCs (NaV1.3, 1.7, 1.8)	Reviewed neuronal VGSC-targeting conotoxins with analgesic properties; discussed μ O-MrVIB selectivity.
Munasinghe et al. (2015)	Review	μ -conotoxins	NaV subtypes	Evaluated VGSC-targeting conotoxins systematically; discussed subtype selectivity requirements.
Satkunanathan et al. (2005)	In vivo/neuropathic pain	α -conotoxin Vc1.1	$\alpha 9\alpha 10$ nAChR	Demonstrated analgesic activity in rat CCI and PNL models; accelerated recovery of injured neurons.
Adams et al. (2008)	Electrophysiology/ in vivo	α -conotoxins Vc1.1, Rg1A	CaV2.2 via GABAB-GPCR	Proposed novel mechanism: α -conotoxins act as GABAB receptor agonists to inhibit CaV2.2 channels.
Castro et al. (2016)	Human DRG/ex vivo	α -conotoxin Vc1.1	GABAB receptor, CaV2.2, CaV2.3	Showed Vc1.1 inhibits human DRG neuroexcitability and reduces visceral nociception via GABAB.
Belgi et al. (2021)	Medicinal chemistry/ in vivo	Alkyne-bridged Vc1.1 analogue	GABAB/ CaV2.2	Alkyne cyclisation yielded metabolically stable analogue with dose-dependent reversal of allodynia.
Clark et al. (2010)	Peptide engineering/ in vivo	Cyclic Vc1.1	GABAB/ CaV2.2	Backbone cyclisation produced orally active analogue with superior stability to linear Vc1.1.
Frøsig-Jørgensen et al. (2023)	SAR/medicinal chemistry	Vc1.1 analogues	nAChR/ GABAB	Optimisation of Vc1.1 analogues; defined residues critical for selectivity at each receptor.
Kennedy et al. (2020)	Review/ peptidomimetics	α -conotoxins	GABAB, nAChR	Reviewed N-terminal domain of α -conotoxins; structural determinants for GABAB-mediated analgesia.

Brady et al. (2013)	Review/drug design	Multiple classes	VGCCs, nAChRs	Described peptidomimetic strategies (Type I–III), cyclisation, and non-peptide mimetics of conotoxins.
Craik and Adams (2011)	Chemistry review	Conopeptides (general)	Ion channels	Reviewed residue substitution, backbone cyclisation, and disulfide modification to improve conotoxin stability.
Dutertre et al. (2014)	Venom proteomics	Multiple, Conus geographus	Ion channels	Distinguished predatory from defensive venom components; showed context-dependent venom deployment.
Nguyen, Craik & Kaas (2023)	Bibliometric review	All conotoxins	All targets	Quantitative analysis of 2000–2022 conotoxin literature; identified research trends and gaps.
Essack et al. (2012)	Review	CGX-1007, ACV1, Xen2174	NMDA-R, nAChR, NET	Reviewed conotoxins in clinical trials; summarised indications, mechanisms, and development status.
Finnerup et al. (2015)	Systematic review/meta-analysis	(Analgesic pharmacotherapy context)	NaV, Ca ²⁺ channels	Established evidence base for neuropathic pain pharmacotherapy; contextualises need for new analgesics.
Zhao et al. (2026)	Computational/in vivo	μ -conotoxins KIIIA, CnIIIC, SxIIIC	NaV1.7	Engineered mutants R10EKIIIA and R20WCnIIIC showed enhanced analgesic activity vs. wild-type in vivo.
Sanchez-Campos et al. (2022)	Patent analysis	Multiple classes	Multiple	224 conotoxin patents analysed; majority academic; Prialt only approved product; highlights translational gap.

3. RESULTS

The literature searches and thematic screening identified 30 key publications that formed the evidence base of this structured narrative review. These sources included clinical trials and clinical reviews, preclinical in vivo studies, electrophysiological investigations, medicinal chemistry studies, database and bibliometric analyses, and contextual pharmacotherapy reviews. The included publications are summarised in Table 1.

3.1 Structural Classification and Pharmacological Diversity of Conotoxins

The most widely adopted classification framework divides conotoxins into gene superfamilies on the basis of signal-peptide sequence similarity, with more than 20 distinct superfamilies currently recognised [4,5]. Within each superfamily, peptides are further grouped into pharmacological families according to their cysteine framework and molecular target. This hierarchical system provides a practical framework for predicting target associations and guiding the annotation of newly sequenced venom components [10,11].

Several conotoxin families have established relevance to analgesic pharmacology. The ω -conotoxins, which belong to the O-superfamily, block N-type and

P/Q-type VGCCs. The μ -conotoxins, from the M- and O-superfamilies, block VGSCs by occluding the outer vestibule of the pore. The α -conotoxins, belonging to the A-superfamily, antagonise nAChRs and may also inhibit N-type calcium channels through indirect mechanisms. Additional relevant classes include the conantokins, also referred to as con-conotoxins or conG peptides, which block NMDA receptors, and the contulakins, which act at neurotensin receptors [4,5,9]. Disulfide-rich conotoxins share a cysteine scaffold stabilised by intramolecular disulfide bonds. The connectivity of these bonds determines the three-dimensional fold and strongly influences receptor-binding geometry [6,8].

Post-translational modifications represent a distinctive feature of native conotoxins that profoundly influences their pharmacological activity. γ -Carboxylation of glutamate residues is characteristic of conantokins and is essential for Ca²⁺-dependent NMDA receptor interaction. Glycosylation, observed in contulakins and some κ -conotoxins, modulates receptor subtype selectivity. Hydroxylation of proline and 4-trans-hydroxyproline incorporation affect conformational stability and proteolytic susceptibility [5,8]. These modifications complicate total synthesis but also provide rational opportunities

for analogue design aimed at improving stability or selectivity.

The combinatorial diversity arising from the combination of more than 20 gene superfamilies, multiple cysteine frameworks, variable inter-cysteine loop sequences, and extensive post-translational modifications accounts for the estimate that the genus *Conus* encodes more than 200,000 unique conotoxin sequences [5]. A bibliometric analysis of the conotoxin literature from 2000 to 2022 by Nguyen et al. identified a progressive increase in the number of conotoxin sequences deposited in databases such as ConoServer, driven largely by high-throughput transcriptomics and proteomics [17]. However, the same analysis confirmed that structural and pharmacological characterisation has consistently lagged behind sequence discovery, leaving the overwhelming majority of identified sequences without assigned biological activity.

From an analgesic drug-discovery perspective, this structural diversity is relevant only when it can be linked to reproducible modulation of pain-associated molecular targets. Therefore, the subsequent sections focus on conotoxin classes for which mechanistic or translational evidence connects target engagement with antinociceptive activity.

3.2 ω -Conotoxins and Voltage-Gated Calcium Channels: The Paradigm Case of Ziconotide

The ω -conotoxins are the best-characterised conotoxin class with respect to analgesic mechanisms and clinical translation. These peptides, members of the O-superfamily, selectively block VGCCs of the CaV2 family (N-type, P/Q-type, and R-type) by binding to the outer vestibule of the channel pore [18]. Their analgesic relevance derives from the role of N-type (CaV2.2) channels in presynaptic neurotransmitter release at nociceptive synapses. CaV2.2 channels are abundantly expressed on the central terminals of primary afferent nociceptors in the superficial laminae of the dorsal horn. At this site, they gate the calcium influx required for the release of substance P and glutamate.

Ziconotide (SNX-111), the synthetic equivalent of ω -MVIIA from *Conus magus*, is a 25-amino-acid peptide that binds CaV2.2 with high affinity and in a voltage-independent, state-independent manner [14]. Its pharmacological mechanism, namely inhi-

bition of presynaptic calcium influx and consequent reduction of nociceptive neurotransmitter release in the spinal dorsal horn, provides a pharmacological basis for the antinociceptive and analgesic effects observed in animal models and clinical studies.

In a randomized, double-blind, placebo-controlled trial conducted by Rauck et al., 220 adults with severe chronic pain were randomized to intrathecal ziconotide ($n = 112$) or placebo ($n = 108$). The study population was clinically severe and highly treatment refractory, with a mean baseline VASPI score of 80.7 mm, a mean pain duration of approximately 14–15 years, and prior exposure to intrathecal morphine in approximately 90% of patients [19]. Ziconotide was initiated at 0.1 $\mu\text{g}/\text{hour}$ (2.4 $\mu\text{g}/\text{day}$) and titrated slowly over three weeks in increments of 0.05–0.1 $\mu\text{g}/\text{hour}$, reaching a mean dose of 0.29 $\mu\text{g}/\text{hour}$ (6.96 $\mu\text{g}/\text{day}$) at study termination. The primary endpoint was the mean percentage change in VASPI score from baseline to Week 3. Ziconotide produced a statistically significant mean improvement in VASPI compared with placebo at Week 3 (14.7% versus 7.2%; $P = 0.036$), with significant analgesic separation already observed at Week 1 (16.6% versus 5.0%; $P = 0.0026$). However, the proportion of patients achieving at least 30% improvement in VASPI did not differ significantly between groups (16.1% versus 12.0%; $P = 0.39$), indicating that the magnitude of clinical response was modest despite statistical significance.

The clinical evidence was further synthesised by Schmidtco et al. in *The Lancet*, who reviewed three randomized, double-blind, placebo-controlled trials of intrathecal ziconotide in severe chronic pain [12]. Across these trials, ziconotide demonstrated statistically significant analgesic efficacy in distinct refractory pain populations, including cancer- or AIDS-associated pain, chronic non-malignant pain, and severe chronic pain of mixed etiology. In the two fast-titration trials, ziconotide reduced VASPI scores by 51.4% versus 18.1% with placebo in patients with cancer- or AIDS-associated pain and by 31.2% versus 6.0% in patients with chronic non-malignant pain, with both comparisons reaching $p < 0.001$.

The primary therapeutic limitation of ziconotide is its route of administration. Its poor ability to cross the blood-brain barrier, combined with its susceptibility to systemic proteolysis, necessitates

intrathecal delivery via an implanted pump system. This requirement restricts its use to patients with sufficiently severe pain to justify invasive spinal access and technical infrastructure, limiting its applicability to a specialist clinical context. The comprehensive review by Lin et al. documented the adverse-effect profile associated with intrathecal ziconotide, including neurological and neuropsychiatric reactions such as dizziness, confusion, hallucinations, and nystagmus, attributable to off-target activity at CaV2.2 channels expressed in the central nervous system outside the dorsal horn [13]. The therapeutic index of the drug is narrow, and dose titration must be gradual and carefully monitored. Despite these constraints, the clinical validation of ziconotide confirms the pharmacological viability of N-type calcium channel blockade as an analgesic strategy and establishes the ω -conotoxin scaffold as a structurally proven starting point for further drug development.

Other ω -conotoxins of pharmacological interest include GVIA from *Conus geographus* and CVID (AM336) from *Conus catus*. GVIA irreversibly blocks CaV2.2 and has been widely used as a pharmacological tool. CVID preferentially blocks N-type over P/Q-type channels and has demonstrated potent antinociception in rodent models following intrathecal administration [18]. CVID progressed to Phase II clinical trials but was discontinued without public disclosure of reasons, illustrating the translational uncertainty inherent to this compound class.

3.3 μ -Conotoxins and Voltage-Gated Sodium Channels

Voltage-gated sodium channels are the molecular determinants of action-potential initiation and propagation in nociceptive neurons. The nine mammalian isoforms (NaV1.1–NaV1.9) differ in biophysical properties, pharmacological profiles, and tissue distribution, with NaV1.7, NaV1.8, and NaV1.9 preferentially expressed in peripheral nociceptors [20]. Gain-of-function mutations in SCN9A (encoding NaV1.7) cause primary erythromelalgia and paroxysmal extreme pain disorder, while loss-of-function mutations result in congenital insensitivity to pain [16]. This genetic evidence strongly supports NaV1.7 as a pain-associated target for analgesic development.

Although human genetic data strongly validate NaV1.7 as a pain-associated target, the clinical devel-

opment of selective NaV1.7 inhibitors has been challenging, indicating that target validation alone is insufficient to ensure analgesic efficacy.

μ -Conotoxins are small, highly basic peptides (16–26 amino acids) that block VGSCs by occluding the outer pore vestibule through interaction with the turret region adjacent to the selectivity filter. The first member of this family characterised, GIIIA from *C. geographus*, preferentially inhibits the skeletal-muscle isoform NaV1.4 and has been used extensively to study VGSC topology [14]. Of greater therapeutic interest are μ -conotoxins with selectivity toward neuronal isoforms implicated in pain. The review by Pei et al. provided a comprehensive assessment of μ -conotoxin pharmacology at all nine human NaV isoforms, identifying a clear preference for tetrodotoxin-sensitive subtypes (NaV1.1–1.4, NaV1.6, NaV1.7) over tetrodotoxin-resistant subtypes (NaV1.8, NaV1.9) [16].

McMahon et al. conducted a systematic electrophysiological comparison of μ -conotoxins SxIIIC, SmIIIA, and KIIIA at human NaV channel isoforms expressed in mammalian cells [21]. Their data revealed substantially different selectivity profiles among peptides that are highly similar in primary sequence: SmIIIA inhibited hNaV1.7 with an IC₅₀ of 41 ± 4 nM, compared with 152 ± 22 nM for SxIIIC and 379 ± 43 nM for KIIIA. Crucially, SxIIIC displayed near-irreversible inhibition of hNaV1.7, a kinetic property that may confer prolonged pharmacological activity and distinguish it pharmacodynamically from reversible blockers. The structural basis of the observed selectivity differences among these closely related peptides remains to be fully defined, but these findings indicate that small sequence variations in the inter-cysteine loops of μ -conotoxins exert substantial effects on isoform selectivity.

Computational and in vivo work by Zhao et al. demonstrated that rational engineering of μ -conotoxin residues can enhance analgesic activity beyond that of the parent peptides [22]. Using molecular dynamics simulations and patch-clamp electrophysiology, the authors identified critical basic residues at the C-terminus of KIIIA and CnIIIC that determine channel-binding geometry. Engineered mutants (R10EKIIIA and R20WCnIIIC) demonstrated significantly enhanced analgesic activity in

vivo relative to their wild-type counterparts, providing direct evidence that structure-guided modification of μ -conotoxins can improve pharmacological performance.

The μ O-conotoxin MrVIB from *Conus marmoreus* represents a structurally distinct subtype that selectively inhibits NaV1.8, the predominant VGSC isoform in unmyelinated nociceptive C-fibre neurons. Ekberg et al. reviewed evidence that intrathecal administration of MrVIB produced selective analgesia without motor deficits in rodent pain models, attributable to the peripheral restriction of NaV1.8 expression [20]. This isoform selectivity is pharmacologically advantageous because NaV1.8 has limited expression in cardiac muscle and the central nervous system, thereby reducing the risk of adverse cardiovascular and neurological effects that complicate non-selective sodium channel blockers [23].

3.4 α -Conotoxins, Nicotinic Acetylcholine Receptors, and GABAB-Mediated Calcium Channel Inhibition

α -Conotoxins are among the largest and most pharmacologically diverse conotoxin families. These peptides act as competitive antagonists at nAChRs. Their biological activity and therapeutic relevance are largely related to selective inhibition of defined receptor subunit combinations expressed in pain-processing neurons [24]. Among the α 9 α 10 nAChR-selective α -conotoxins, Vc1.1 (from *Conus victoriae*) and Rg1A (from *Conus regius*) have attracted particular attention following the demonstration of their antinociceptive properties in rodent models of neuropathic pain.

The mechanistic interpretation of Vc1.1 has evolved over time. Initial studies focused on α 9 α 10 nAChR antagonism, whereas subsequent electrophysiological and ex vivo data implicated GABAB receptor activation and downstream inhibition of CaV2.2 currents. This shift in mechanistic understanding is important because it affects both target selection and translational extrapolation from rodent models to human pain states.

Satkunanathan et al. provided the first in vivo evidence of analgesic activity for Vc1.1 [25]. The peptide produced dose-dependent suppression of mechanical hyperalgesia in the chronic constriction injury (CCI) and partial nerve ligation (PNL) rat mod-

els. These effects persisted for up to one week after cessation of treatment and were accompanied by evidence of accelerated functional recovery of injured nociceptive neurons. These findings were replicated for Rg1A, which produced a comparable reduction of CCI-induced hyperalgesia. The mechanistic basis of this analgesic activity was subsequently clarified by Adams et al., who demonstrated through electrophysiological experiments in rat dorsal root ganglion (DRG) neurons that neither the nAChR antagonism nor direct CaV2.2 blockade was the primary pharmacological mechanism [26]. Instead, Vc1.1 and Rg1A act as agonists at GABAB receptors, coupling through inhibitory G-proteins to suppress CaV2.2 (N-type) calcium channel currents in sensory neurons. This indirect mechanism of CaV2.2 inhibition via a G-protein-coupled receptor accounts for the analgesic activity of these peptides while distinguishing their pharmacological profile from direct calcium channel blockers such as ziconotide.

The translational relevance of the GABAB-mediated mechanism was further supported by Castro et al. [27]. They demonstrated that Vc1.1 inhibits the excitability of human DRG neurons in a GABAB receptor-dependent manner. The same study also showed reduced nociceptive signalling from colonic afferents in a mouse model of chronic visceral hypersensitivity. The enhanced antinociceptive effect observed under hypersensitivity conditions relative to baseline is of particular clinical interest, as it suggests that the analgesic efficacy of Vc1.1 may be potentiated in pathological pain states.

A critical translational challenge for Vc1.1 and related α -conotoxins is the discrepancy between their potency at rat and human α 9 α 10 nAChRs. Vc1.1 inhibits rat α 9 α 10 nAChRs heterologously expressed in *Xenopus* oocytes with IC₅₀ values in the range of 19–109 nM, whereas its potency at human α 9 α 10 nAChRs is substantially lower (IC₅₀ 320–1000 nM) [28]. This species difference complicates the extrapolation of preclinical analgesic efficacy to human therapeutic outcomes and underscores the need for pharmacological characterisation of conotoxin candidates specifically at human receptor isoforms before clinical development is considered.

3.5 Conantokins and NMDA Receptor Modulation

Conantokins are unusual conopeptides that lack disulfide bonds, contain multiple γ -carboxyglutamate (Gla) residues, and adopt α -helical conformations in the presence of calcium ions. Their primary molecular target is the NMDA receptor, specifically NR2B-containing subtypes, where they act as antagonists. Conantokin-G (Con-G) from *Conus geographus* was advanced into clinical evaluation as CGX-1007 for refractory epilepsy, on the basis of its NR2B-selective NMDA antagonism and demonstrated antiepileptic activity in animal models [15]. The primary clinical indication for CGX-1007 was epilepsy rather than pain. However, NMDA receptor antagonism is a recognised mechanism contributing to central sensitisation and chronic pain maintenance. Therefore, conantokins represent a pharmacologically relevant class within the broader context of analgesic neurotoxin development.

3.6 Preclinical Evidence and the Translational Pipeline

The preclinical evidence base for conotoxin analgesic activity encompasses multiple rodent models, diverse administration routes, and different classes of compounds. The strength of this evidence base varies considerably across compound classes. For ziconotide, the preclinical-to-clinical translation was successful, supported by robust mechanistic data, pharmacokinetic characterisation, and three pivotal controlled clinical trials. For α -conotoxins including Vc1.1, preclinical analgesic efficacy in CCI and PNL models is well established [17]. However, clinical development remains at an early stage. This may partly reflect the discontinuation of Vc1.1 (ACV1) during Phase II trials, which has been associated in the literature with species-specific receptor pharmacology and formulation-related challenges.

An analysis of conotoxin patents by Sanchez-Campos et al. identified 224 conotoxin-related patents filed up to the time of their review [29]. The authors noted that the vast majority originated in academic institutions rather than commercial pharmaceutical entities. Only one product, ziconotide (Prialt®), has reached market authorization. This finding highlights the persistent gap between the richness of the preclinical pharmacological literature and actual

therapeutic development, and reflects the combined challenges of peptide delivery, patent commercialisation, and clinical-trial investment.

Among investigational conotoxin-derived compounds that have entered clinical evaluation, contulakin-G (CGX-1160) is a neurotensin receptor subtype-1 agonist that was tested intrathecally for severe chronic pain, and Xen2174 (Mr1A) from *Conus mar-moreus*, a norepinephrine transporter (NET) inhibitor, underwent Phase II evaluation for post-surgical pain [27]. Neither progressed to regulatory approval. These discontinued programmes illustrate the difficulty of achieving clinical efficacy with novel peptide analgesics and the limitations of intrathecal delivery outside the specific clinical niche currently occupied by ziconotide.

3.7 Chemical Modification Strategies for Improved Pharmacological Properties

Native conotoxins have several important pharmacokinetic limitations, including susceptibility to proteolytic degradation, short plasma half-life, and limited ability to cross the blood-brain barrier after systemic administration. These limitations have motivated substantial chemical engineering efforts aimed at producing analogues with improved stability and bioavailability while retaining or enhancing biological activity [23,24].

Backbone cyclisation, in which the N- and C-termini are joined by a peptide linker, represents the most extensively validated modification strategy. Clark et al. demonstrated that head-to-tail cyclisation of Vc1.1 using a GGAAGG hexapeptide linker produced a cyclic analogue, cVc1.1 [30]. Compared with the linear peptide, cVc1.1 showed superior stability to proteolysis and enhanced potency as a GABA_B receptor-mediated CaV2.2 inhibitor. It also demonstrated oral analgesic activity in the CCI rat model. This constituted the first demonstration that a conotoxin-derived compound could produce analgesic effects following oral administration, a finding with substantial pharmacological and translational significance.

Belgi et al. reported that replacement of the disulfide bond in Vc1.1 with a metabolically stable alkyne bridge, using on-resin alkyne metathesis, yielded a structurally modified analogue [31]. Despite its substantially different backbone topography, this an-

analogue retained potent and selective GABAB receptor agonism. It also dose-dependently reversed mechanical allodynia in a rat neuropathic pain model. The alkyne bridge confers resistance to thiol-disulfide exchange and oxidative degradation, two processes that compromise native disulfide-containing peptides under physiological conditions.

Craik and Adams reviewed a broad range of chemical modification strategies applicable to conotoxins, encompassing residue substitution with non-natural amino acids, dicarba bridge formation as a disulfide surrogate, lipidation to improve membrane permeability and pharmacokinetic properties, and glycosylation modifications [6]. Each approach carries trade-offs: residue substitutions may improve target selectivity or stability but can also disrupt the binding pharmacophore; backbone cyclisation improves stability but may alter the three-dimensional

fold and modify receptor-binding geometry; lipidation improves bioavailability but can introduce off-target effects.

Brady et al. further described peptidomimetic design strategies in which the pharmacophore of a conotoxin is displayed on a non-peptidic scaffold, thereby addressing both stability and bioavailability constraints [32]. These type III peptidomimetic approaches have been applied to ω -GVIA, generating small-molecule N-type channel inhibitors with micromolar affinity. However, the binding affinity and selectivity of peptidomimetic analogues have generally been inferior to those of the parent peptides, reflecting the difficulty of recapitulating the precise three-dimensional pharmacophore geometry of folded disulfide-rich peptides in a non-peptidic molecular framework.

Table 2. Chemical modification strategies used to improve conotoxin drug-like properties.

Strategy	Example	Intended Benefit	Main Limitation	Translational Status
Backbone cyclisation	Cyclic Vc1.1	Improved proteolytic stability; possible oral activity	May alter peptide conformation and receptor-binding geometry	Advanced preclinical
Alkyne bridge/disulfide replacement	Alkyne-bridged Vc1.1 analogue	Increased metabolic stability; resistance to disulfide exchange	Synthetic complexity; limited clinical validation	Preclinical
Dicarba bridge formation	Disulfide surrogate analogues	Improved redox stability	Risk of altered folding and reduced potency	Preclinical/optimisation
Residue substitution	Non-natural amino acid analogues	Improved selectivity, potency, or stability	May disrupt pharmacophore residues	Discovery/preclinical
Lipidation	Lipid-modified conotoxin analogues	Improved membrane interaction and pharmacokinetics	Possible off-target effects and altered distribution	Early preclinical
Glycosylation modification	Glycosylated conopeptide analogues	Modulation of stability, solubility, or receptor interaction	Complex synthesis; unpredictable activity changes	Early preclinical
PEGylation	PEG-modified analogues	Prolonged circulation time and reduced renal clearance	Possible loss of receptor affinity due to steric effects	Early-stage concept
Peptidomimetics/small-molecule mimetics	ω -GVIA-derived mimetics	Improved drug-like properties and oral development potential	Often reduced affinity and subtype selectivity compared with parent peptides	Early discovery

The main chemical modification strategies used to improve the drug-like properties of conotoxins, together with their intended benefits, limitations, and current translational status, are summarised in Table 2. Overall, the available evidence indicates that chemical modification strategies have not progressed equally in terms of translational relevance. Backbone cyclisation currently appears to be the most advanced approach, because it directly addresses proteolytic instability and has produced orally active Vc1.1 analogues with retained antinociceptive activity in vivo. Disulfide-bond replacement strategies, including alkyne and dicarba bridges, are also pharmacologically attractive because they reduce susceptibility to thiol-disulfide exchange and oxidative degradation while preserving the constrained peptide topology required for receptor recognition. However, these approaches remain largely at the preclinical optimisation stage. Lipidation, glycosylation, PEGylation, and other pharmacokinetic modifications may improve systemic exposure or membrane interaction, but their effect on receptor selectivity and off-target pharmacology requires careful evaluation. Peptidomimetic and small-molecule approaches offer the greatest theoretical potential for oral bioavailability and commercial development, yet they have generally struggled to reproduce the high affinity and subtype selectivity of native disulfide-rich conotoxins. Thus, the most promising translational strategy may not be complete replacement of the peptide scaffold, but rational stabilisation of bioactive conotoxin frameworks combined with route-specific delivery optimisation.

4. DISCUSSION

4.1 Current State of Knowledge and Strength of Evidence

The pharmacological literature reviewed here establishes that conotoxins represent a structurally diverse and mechanistically validated class of analgesic candidates. The available evidence is strongest for ω -conotoxins acting on CaV2.2 channels, where ziconotide has achieved a full translational arc from molecular target identification to clinical drug approval [12–14,19]. For other classes of compounds, including α -conotoxins and μ -conotoxins with neuronal VGSC selectivity, the evidence is largely pre-

clinical and mechanistic, with limited and largely unsuccessful clinical validation to date [15,17].

A major challenge in conotoxin pharmacology is that, despite the existence of numerous selective ligands relevant to pain pathways, this molecular diversity has resulted in only one approved analgesic drug.

The clinical approval of ziconotide represents a remarkable achievement in the field. This approval confirms that cone snail venom peptides can be developed into clinically useful analgesics and supports N-type calcium channel blockade as a therapeutic strategy for severe pain. However, the therapeutic application of ziconotide remains narrowly limited [7,8].

4.2 Mechanistic Insights and Therapeutic Implications of α -Conotoxins

Adams et al. found that the α -conotoxins Vc1.1 and Rg1A achieve analgesia through activation of the GABAB receptor, rather than exclusively through nAChR antagonism [26]. This discovery represents a significant advance in conotoxin pharmacology over the past two decades. It resolves a previously existing discrepancy in the literature regarding the relationship between nAChR pharmacology and in vivo analgesic activity and establishes a plausible mechanism for the peripheral analgesic effects of these peptides. Furthermore, it identifies the GABAB receptor as a target for the development of analgesics using conotoxin-derived scaffolds, expanding the pharmacological options beyond direct ion channel blockade.

Subsequent confirmation of this mechanism in human DRG neurons and in a mouse model of visceral pain by Castro et al. strengthened the translational case for Vc1.1 [27]. The species differences reported for human versus $\alpha 9\alpha 10$ nAChRs raise important questions regarding the direct extrapolation of rodent pharmacology to human clinical outcomes. The therapeutic relevance of nAChR antagonism versus GABAB agonism in the overall analgesic profile of Vc1.1 in vivo remains incompletely understood, and the relative contribution of each mechanism under different pain conditions has not been systematically compared.

4.3 NaV Channel Selectivity: A Critical Challenge

The development of μ -conotoxins as analgesic leads depends not only on achieving high efficacy across pain-related sodium channel isoforms, but also on establishing a sufficiently wide margin of selectivity across NaV subtypes for safety. NaV1.7, NaV1.8, and NaV1.9 are strongly implicated in nociceptive signaling, while inhibition of NaV1.4 can lead to skeletal muscle toxicity and inhibition of NaV1.5 can carry cardiac risk. Furthermore, activity at central neuronal isoforms, such as NaV1.1 and NaV1.2, can contribute to adverse effects on the central nervous system. Therefore, for μ -conotoxins, selectivity should not be determined solely by efficacy at NaV1.7 or NaV1.8, but by a complete separation between engagement of the analgesic target and inhibition of safety-related isoforms.

The findings reported by McMahon et al. illustrate both the potential and the limitations of this approach [21]. Closely related μ -conotoxins can exhibit markedly different potency and kinetic profiles across human NaV isoforms, indicating that relatively small sequence changes can significantly affect channel recognition. However, efficacy at hNaV1.7 alone is insufficient as a translational criterion. A clinically useful analgesic derived from μ -conotoxin would require a profile in which inhibition of pain-related isoforms is achieved at concentrations that remain clearly separated from those affecting skeletal muscle, heart, or central neuronal sodium channels.

The nearly irreversible inhibition of hNaV1.7 by SxIIIC is particularly important in this context. Prolonged on-target residence could theoretically prolong the duration of analgesia, which may be an advantage for the control of chronic pain. However, the same kinetic property could also raise safety concerns if the compound displays incomplete isoform selectivity or if off-target sodium channel inhibition is observed. Therefore, kinetic selectivity, reversibility, and recovery from channel blockade should be considered in conjunction with conventional potency parameters such as IC₅₀.

The findings of Zhao et al. demonstrated that rational engineering of specific μ -conotoxin residues can enhance analgesic activity and alter channel binding properties [22]. However, converting

such engineered analogs into clinically viable analgesics will require more than improved activity in preclinical pain models. Future studies should systematically compare the leading μ -conotoxins and their analogs across all human NaV isoforms, assess state- and use-dependent channel block, determine the reversibility of inhibition, and integrate these pharmacological data with in vivo safety assessment. Without this broader framework for selectivity and safety, μ -conotoxins may remain valuable pharmacological tools rather than clinically competitive analgesic candidates.

4.4 Limitations of Existing Studies

Several methodological limitations restrict direct clinical extrapolation of the existing literature on conotoxin pharmacology. First, the majority of preclinical analgesic studies have been conducted in rodent models using peripheral nerve injury paradigms (CCI, PNL), which model certain aspects of neuropathic pain but do not capture the full heterogeneity of clinical chronic pain conditions. Inflammatory, visceral, and cancer pain models, as well as models of central sensitization, are less well represented in the conotoxin literature. Second, the majority of pharmacological studies have characterised conotoxin activity at rodent receptors and channels. As shown for Vc1.1 at $\alpha 9\alpha 10$ nAChRs, species differences can be pharmacologically relevant, necessitating systematic characterization of lead compounds at human receptor isoforms.

Third, pharmacokinetic characterization is incomplete for most conotoxin candidates other than ziconotide. Plasma half-life, volume of distribution, metabolic stability, and central nervous system penetration have not been reported for the majority of α - and μ -conotoxins studied under systemic administration conditions. This information gap limits the ability to assess whether systemic delivery can achieve adequate drug concentrations at spinal or supraspinal targets. It also remains unclear whether the analgesic effects observed after local intrathecal or peripheral injection in rodents would be reproducible with a clinically viable systemic route of administration.

Fourth, long-term safety data are scarce. The adverse reaction profile of intrathecal ziconotide in humans is well characterised, but comparable data

for conotoxin-derived candidates are largely lacking. Chronic analgesic therapy requires a safety profile compatible with months to years of continuous treatment, but the available preclinical toxicology data for most potential conotoxins extend at most to days to weeks.

4.5 Research gaps and future directions

One of the most significant gaps in the current literature on conotoxin pharmacology is the limited number of clinical trials involving conotoxin candidates other than ziconotide. Among the compounds studied here (Vc1.1, Xen2174, CGX-1007, CGX-1160) all entered early-phase clinical evaluation, but none progressed to Phase III or regulatory review. The underlying reasons for the termination of these programmes are poorly documented in the published literature, limiting the ability of the scientific community to learn from these failures and develop more successful strategies for clinical translation.

5. CONCLUSION

Conotoxins represent a pharmacologically validated, structurally characterised, and highly diverse class of marine-derived analgesic candidates. Their development potential is supported by the clinical approval of ziconotide for the intrathecal treatment of severe refractory chronic pain. In addition to ziconotide, several other classes of conotoxins remain pharmacologically relevant for the development of analgesics. These include ω -, μ -, and α -conotoxins, which exhibit selective activity at CaV2.2 channels, neuronal NaV isoforms, nAChRs and GABAB receptors. Their target selectivity offers the possibility of developing analgesic agents that act via pathways different from those of current pharmacotherapy.

Available evidence indicates that preclinical analgesic activity is well established for several conotoxin classes beyond ziconotide. Chemical modification strategies can also improve the pharmacokinetic and pharmacodynamic properties of natural peptides. However, the application of these preclinical findings to clinical analgesic development has been largely unsuccessful, reflecting the combined challenges of peptide delivery, species-specific pharmacological differences, narrow therapeutic windows, and incomplete safety characterisation.

Realizing the full therapeutic potential of conotoxins as a new generation of analgesics requires the

integration of structure-guided peptide engineering, comprehensive pharmacokinetic characterisation, refinement of systemic delivery technologies, and carefully designed clinical trials in patient populations with specific pain phenotypes. Despite these challenges, conotoxins provide a strong pharmacological rationale for continued research.

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